

## Possible Critical Role of Latent Chronic *Toxoplasma gondii* Infection in Triggering, Development and Persistence of Autoimmune Diseases

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**Conflict-of-interest statement:** The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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**Received:** September 12, 2018

**Revised:** September 27, 2018

**Accepted:** September 29, 2018

**Published online:** December 21, 2018

### ABSTRACT

*T. gondii* is globally distributed with a high proportion of the world population estimated to be seropositive, and in the U.S. the parasite is responsible for approximately million infections each year. *T. gondii* tachyzoites infect almost all nucleated cells and their intracellular multiplication and lifelong persistence in the host cells play an important role in triggering and development of autoimmune diseases (ADs). Latent chronic *T. gondii* infection may be associated with iron, iodine, and folic acid deficiencies that facilitate development and/or

progression of ADs. The oral route is the natural portal of entry for the parasite and gastrointestinal manifestations are frequently reported in patients with ADs. Prolactin was found to bind to tachyzoites and this process impairs their adhesion and penetration into the host cells. Hyperprolactinemia (HPRL) demonstrated in patients with different ADs may therefore reflect host defense against *T. gondii* infection, and several antipsychotic drugs that induce HPRL also have antitoxoplasmatic activity. Leptin and obesity play an important role in triggering and maintenance of inflammation and autoimmunity. *T. gondii* infection causes a significant increase in leptin levels and there is a significant positive association between the parasite seropositivity and obesity. Nitric oxide (NO) acts as a proapoptotic as well as an antiapoptotic biomodulator, and have a variety effects on autophagy. Overproduction of NO during *T. gondii* infection causes dysfunction of both these processes and therefore hinders cleaning service of the apoptotic/autophagic cell-derived antigenic remnants, finally leading to triggering and development of ADs. Damage of the olfactory system associated with chronic latent *T. gondii* infection may affect olfactory bulb volume and various olfactory functions, being therefore at least in part responsible for the smell impairment in ADs. The potent proinflammatory response of macrophages to infection with *T. gondii* type II may explain the ability of the strain to cause pathology after oral infection. The parasite also triggers the secretion of antiinflammatory cytokines, such as IL-10, TGF- $\beta$ , and generation of reactive nitrogen intermediates, thus suppressing the development of the T<sub>H</sub>1 immune responses and deactivating macrophages. *Toxoplasma* chronic infection-induced cytotoxic T lymphocyte exhaustion leads to development of ADs because of decreased polyfunctionality, cytotoxic capability, cytokine production, proliferative capacity, and metabolic deficiency. The process of CD4<sup>+</sup> and CD8<sup>+</sup> T-cell immune exhaustion inhibits the immune response, thus facilitating pathogen persistence. Systemic *T. gondii* infection triggers a rapid and persistent decrease in the size of naïve CD4<sup>+</sup> T lymphocyte pool, and a long-term thymic atrophy and output due to destruction of the thymic epithelium. Chronic parasite infections characterized by lower pathogen burden usually restricted to tissues, suggest alternative driving forces in the induction of T cell exhaustion, such as parasite encystations. A significantly lower occurrence of antibodies to persistent viral infections reported in patients with some ADs compared with controls may be due to

suppressed (exhausted) function of host B cells. Both *T. gondii*- and viral-associated inflammatory processes may be mutually overlapping which lead to worsening or improving clinical course of ADs depending on final temporary or stable proinflammatory/antiinflammatory cytokine constellations. Dual-affinity T cell receptors may partly be responsible for frequently observed coinfections of *T.gondii* with some viruses and bacteria. Commonly reported comorbidities in ADs may at least in part be explained by liver damage caused by the pathogen. Vitamin D deficiency is often found in patients with ADs and there is vast evidence that the vitamin has an important beneficial impact on both innate and acquired immunity. Moreover, vitamin D exerts toxoplasmodic effects and therefore should find a firm place in treatment regimens used in ADs.

**Key words:** Autoimmune diseases; *Toxoplasma gondii*; *H. pylori* infection; Viral infections; Autoantibodies; Hyperprolactinemia; Leptin; Obesity; Cytokines; Nitric oxide; Cysteine cathepsins; T and B cells immune exhaustion; Apoptosis; Autophagy; Liver damage; Olfactory dysfunction; Vitamin D deficiency

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Prandota J. Possible Critical Role of Latent Chronic *Toxoplasma gondii* Infection in Triggering, Development and Persistence of Autoimmune Diseases. *International Journal of Neurology Research* 2018; 4(1): 379-463 Available from: URL: <http://www.ghmet.org/index.php/jnr/article/view/2430>

## INTRODUCTION

### Autoimmune diseases (ADs)

ADs are the third most common category of disease in the United States after cancer and cardiovascular disease, affecting approximately 14.7-23.5 million people (5-8% of the population) with at least one autoimmune condition<sup>[1]</sup>, and about 78% (or 6.7 million) of the persons are women<sup>[2-4]</sup> (**Table 1**).

Autoimmune thyroid diseases are the most common ADs, affecting approximately up to 10% of the world population<sup>[14,15]</sup>. Collectively, ADs are the fifth leading cause for death in women before age 65<sup>[16]</sup>. Recent estimates of NIH indicated that actual number of these clinical entities ranged from 80 to as many as 120 diseases, and affected population could be as high as ~50 million Americans. The direct health care costs of these diseases are > \$100 billion per year<sup>[17,18]</sup>.

### *T. gondii* infection

Toxoplasmosis is a neglected, opportunistic disease and the intracellular parasite is highly pathogenic especially for immunocompromised subjects<sup>[19-21]</sup>. At present, in immunocompetent persons *T. gondii* infection is believed to be asymptomatic<sup>[20,21]</sup>, but a steadily increasing body of literature data strongly suggests that the pathogen is emerging as a neglected global health threat<sup>[19,22-27]</sup>, also in immunocompetent individuals<sup>[24]</sup>.

Worldwide, over six billion people have been infected with *T. gondii*<sup>[23,28]</sup> and IgG seroprevalence against the parasite varied from 6.7% in Korea<sup>[29]</sup>, 47% in France<sup>[30]</sup>, to 98% in some regions<sup>[31]</sup>. In the United States, *T. gondii* is responsible for approximately million infections each year, and the overall antibody seroprevalence among individuals ≥ 6 yrs of age in 2011-2014 was 11.14% (95% CI 9.88% - 12.51%)<sup>[32]</sup>. The frequency of infection increased significantly with age in persons aged 66-75 years<sup>[28,33]</sup>. The parasite is omnipresent, and exposure to kittens and raw or uncooked foods were the main risk

factors for *T. gondii* infection in the United States<sup>[34]</sup>. Contamination of drinking water with the parasite oocysts also contributed to their widespread dissemination<sup>[35]</sup>.

Among women of childbearing age (15-44 yrs of age) the overall seroprevalence was 9.1% indicating that over 90% of women were susceptible to congenital transmission of the parasite during pregnancy<sup>[32]</sup>. In pregnant women, the seroprevalence of anti-*T. gondii*-specific IgG antibodies varied from 6.1% in Mexico to 75.2% in Democratic Republic of Sao Tome and Principe (**Table 2**)<sup>[32,36]</sup>.

The global annual incidence of congenital toxoplasmosis was estimated to be 190 100 cases (95% CI: 179 300-206 300), equivalent to a burden of 1.20 million Disability Adjusted Life Years (DALYs) (95% CI: 0.79-1.90)<sup>[22]</sup>. Recent review by Torgerson *et al*<sup>[37]</sup> revealed that foodborn toxoplasmosis (10.3 million cases, 95% Uncertainty intervals (UI) 7.40-14.9 million) was the second most common foodborn parasitic disease, and this ailment with 825,000 DALYs (95% UI 561,000-1.26 million) resulted in one of the highest burdens in this term, mainly due to years lived with disability. At present, approximately 100 diseases and clinical entities probably have been associated with this neglected parasitic infection, including several ADs<sup>[24]</sup>.

## INFECTIONS AND AUTOIMMUNITY

Viruses, number of bacteria and parasites are different preceding infections known as frequent environmental triggers that induce development of several ADs, and more than one pathogen can induce the same disease through similar pathomechanism(s) (e.g. “molecular mimicry”, inflammation, antigen competition, superantigens)<sup>[38-43]</sup> (**Tables 3 and 4**). Epidemiological and clinical studies suggested also a protective or limiting role of parasitic helminth infections on human autoimmune and allergic disorders<sup>[40,44-47]</sup>.

Root-Bernstein & Fairweather<sup>[42,50]</sup> proposed few theories having the common assumption that there is a genetic predisposition to ADs<sup>[51]</sup>, and that such inclination requires environmental triggers<sup>[52,53]</sup>,

**Table 1** ADs in the United States by prevalence rate, dominant chemokine profile, and percentage of female patients (acc. to Seli & Arici [5], Ackerman [6]; with own modification).

Autoimmune disease	Prevalence rate per 100,000	Dominant chemokine profile	Female patients (%)
Hashimoto's thyroiditis	792	Th2	95
Sjögren's syndrome	14	Th2	94
Addison's disease	5	Th1 <sup>a</sup>	93
Scleroderma	4	Th2	92
Systemic lupus erythematosus	24	Th2	89
Primary biliary cirrhosis	3	Th1 <sup>b</sup> (IL-12/Th1 and IL-23/Th17)	89
Graves' disease	1152	Th2	88
Rheumatoid arthritis	860	Th1	75
Myasthenia gravis	5	Th1 <sup>c</sup>	73
Polymyositis/ Dermatomyositis	5	Th1 (Th17/IL-17) <sup>d</sup>	67
Multiple sclerosis	58	Th1	64
Vitiligo	400	Th1 <sup>e</sup>	52
Insulin-dependent diabetes mellitus	192	Th1	48

<sup>a,b,c,d,e</sup> Adapted from Refs [7-11], respectively. Namazi [11] suggested that the Th1-promoting effects of dehydroepiandrosterone (a naturally occurring adrenal steroid derived from cholesterol) can provide an explanation for the stronger Th1-immune response of women because it is a critical up-regulator of IL-2 generation, and induces the production of mature DCs with possible Th1-skewing potential [12,13].

especially focusing on infections (Table 4).

Accumulating body of evidence suggests that *T. gondii* infection in humans has been implicated in a number of autoimmune disorders (Table 5). These associations are probably related to host/pathogen antigen(s) homology<sup>[91-93]</sup>, because during its life cycle the parasite

**Table 2** Seroprevalence of anti-*T. gondii*-specific IgG antibodies in pregnant women in a selected number of countries (acc. to Elsheitka [36], Jones *et al* [32]; with own modification).

Study location	Year	Prevalence (%)
Mexico	2006	6.1
UK <sup>a</sup>	2005	9.1
USA	2010	9.1
Norway	1998	10.9
Bangladesh	1997	11.18
India	1999	11.6
Thailand	1998	13.1
Sweden	1999	14
Finland	1992	20.3
Denmark	1993	27.4
Turkey	2005	30.1
The Netherlands	2004	40.5
Switzerland	1995	46.1
France	1996	54.3
West Indies	2006	57
Germany	1999	63.2
DRSTP <sup>b</sup>	2007	75.2

<sup>a</sup>UK, United Kingdom; <sup>b</sup>DRSTP, Democratic Republic of Sao Tome and Principe.

**Table 3** Infectious agents associated with ADs in humans in the years 2004-2005 (acc. to Fairweather & Rose [38]; Samarkos & Vaiopoulos [39]; with own modification).

Disease	Infectious agent
Multiple sclerosis	EBV, measles virus
Diabetes mellitus type 1	Coxsackie virus B4, rubella virus, CMV, mumps virus
Graves' disease	<i>Yersinia enterocolitica</i>
Rheumatoid arthritis	<i>Escherichia coli</i> , <i>Mycobacterium tuberculosis</i> , EBV, HCV
Reactive arthritis	<i>Enterobacteriaceae</i> , <i>Chlamydia trachomatis</i>
Spondyloarthropathies	<i>Enterobacteriaceae</i> , <i>Klebsiella spp.</i>
Polyarteritis nodosa	HBV, HCV, HIV
Leśniowski-Crohn's disease <sup>a</sup>	<i>Mycobacterium paratuberculosis</i>
Celiac disease	Adenoviruses
Systemic lupus erythematosus	EBV, retroviruses
Psoriasis	Retroviruses, <i>Streptococcus</i>
Myocarditis	CB3, CMV, <i>Chlamydia</i>
Rheumatic fever/myocarditis	Group A <i>Streptococcus haemolyticus</i>
Chagas' disease/myocarditis	<i>Trypanosoma cruzi</i>
Myasthenia gravis	HSV, HCV
Guillain-Barre syndrome	CMV, EBV, <i>Campylobacter spp.</i>
Henoch-Schönlein purpura	<i>Streptococcus β-hemolyticus</i>
Immune hemolytic anemia	EBV, <i>Mycoplasma pneumoniae</i>
Kawasaki disease	<i>Staphylococcus aureus</i> , <i>Streptococci</i> , <i>Yersinia pseudotuberculosis</i>

CB3, Coxsackie virus B3; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSV, Herpes simplex virus. <sup>a</sup>Polish surgeon Antoni Leśniowski in 1904 was the first to provide description of *ileitis terminalis* known as Crohn's disease [48, 49].

**Table 4** Theories of how infections could cause ADs (acc. to Root-Bernstein & Fairweather [42, 50]; with own modification).

Theory	Description	Refs
Hidden/cryptic antigen	Tissue damage releases hidden antigens	[54]
Epitope spread	Multiple epitopes against self needed before AD develops	[55-57]
Anti-idiotypic	Cellular receptor targets induce cross-reactive autoantibodies	[58, 59]
Molecular mimicry	Accidental crossreactivity	[60-63]
Bystander or adjuvant effect	Microbial or cytokine activation of pre-existing autoreactive immune cells	[63-65]
Dual-affinity T cell receptors (TCR)	Non-specific activation of 2 <sup>nd</sup> TCR	[60, 66]
Antigenic complementarity <sup>a</sup>	Multiple infections by microbes that share antigenic complementarity/crossreactivity	[67-70]
Co-infection (or co-exposure)	Releases self tissue and activate immune response (inflammasome activation), may involve crossreactivity or antigenic complementarity	[71-75] <sup>b</sup>
- Viral/parasite persistence	Repeated activation drives epitope spread	[71,76-80]
- Cytokine dysregulation	Increased Th17 allows AD	[56,80-85]
- Disrupt immune regulation	Increased Treg allow AD	[80,86,87]

<sup>a</sup>Innate TLR4/inflammasome activation can increase proinflammatory Th1- and Th17-type immune responses, which are frequently associated with development of AD in animal models [83], especially that damaged and dying host cells release nuclear particles that activate toll-like receptors (TLRs) [88]. <sup>b</sup>It should be noted that TLR2, TLR4 and the inflammasome were important in the pathogenesis of multiple sclerosis [73], and otherwise it is known that both these TLRs (and TLR9) played a marked role in the host defense against *T. gondii* infection through their activations by the glycosylphosphatidylinositol-anchored proteins dominating the surface of the parasite tachyzoites [89,90].

**Table 5** ADs associated with *T. gondii* infection (acc. to Flegr, Prandota, *et al* [24]; with own modification).

Clinical entity	Refs
Multiple sclerosis	[97]
Systemic sclerosis	[98-101]
DM types 1 and 2	[102-104]
Hashimoto thyroiditis, Graves' disease; thyroid autoimmune diseases	[15,98,101,105,106]
Rheumatoid arthritis, Still's disease	[98,107-111]
Myocarditis, chronic heart failure, rheumatic fever/myocarditis	[112,113]
Autism spectrum disorders	[93,114-119]
Inflammatory bowel disease	[101,120, 121]
Leśniowski-Crohn's disease	[120]
Ulcerative colitis	[120]
Celiac disease	[122-128]
Primary biliary cirrhosis, biliary atresia, cholestatic disorders	[129-131]
Hepatitis, liver cirrhosis	[132-140]
Systemic lupus erythematosus	[141-143]
Ocular toxoplasmosis (retinochoroiditis, uveitis, retinitis pigmentosa)	[144-146]
Epilepsy	[147-152]
Antiphospholipid syndrome	[98,101,153-155]
Polymyositis, dermatomyositis	[113,156-162]
Autoimmune bullous disease (pemphigus and bullous pemphigoid)	[101,163]
Polyarteritis nodosa	[164]
Wegener's granulomatosis; other vasculitides	[98,101,154]
Kawasaki disease	[164]
Cryoglobulinemia	[98, 154]

interacts with approximately 3000 host genes and/or proteins<sup>[93]</sup>. It was proposed that antibodies raised to the pathogen may contribute to autoimmunity *via* the parasite/host protein mimicry (pentapeptides to heptapeptides or longer) that were identical to those within proteins expressed by numerous viruses, bacteria and parasites<sup>[94,95]</sup>. In a recent study, Zemkova *et al*<sup>[96]</sup> found that both unicellular and multicellular parasites used a significantly lower number of different pentapeptides than free-living controls and suggested that T-cell receptors mostly recognize the five amino acids-long part of peptides that are presented in the groove of major histocompatibility complex (MHC) molecules.

Cytokines generated in the host during infection with the parasite play a pivotal role in triggering, regulation, persistence, and treatment of these processes<sup>[84]</sup>. Given that *T. gondii* infection can induce variable immunomodulatory effects, according to the 'hygiene hypothesis'<sup>[46,165]</sup> it may also exert beneficial actions and protect against development of some ADs<sup>[166]</sup>. The effects of acute and chronic Coxackie virus B3 and two protozoan *T. gondii* and *T. cruzi* infections on the changes in the proinflammatory/antiinflammatory T<sub>H</sub>1, T<sub>H</sub>2, T<sub>H</sub>17, and T regulatory (Treg) cell final patterns of cytokine immune responses in the host may at least in part explain the molecular basis of such beneficial or harmful actions that influence clinical course of coinfections (**Table 6**). This scenario may be strongly supported by the finding that several released inflammatory cytokines downregulated expression of major hepatic cytochromes P450 and other biotransformation enzymes responsible for the metabolism of many endogenous (*e.g.* steroids, vitamins, prostaglandins, leukotrienes, thromboxanes) and exogenous (nutritional compounds, drugs and their metabolites, pesticides, environmental agents) substances<sup>[167-174]</sup> that finally affect various biochemical processes and thereby clinical course of ADs in genetically predisposed persons persistently exposed to harmful environmental factor(s).

The aim of this work was to review and analyze available literature data suggesting that there is a link between acute and chronic *T. gondii* infection and development of ADs, which includes the idea of a common origin for these diseases<sup>[175]</sup>, and to provide possible clinical, physiopathological and molecular explanations for several underlying pathomechanisms associated with these disturbances.

## LATENT CHRONIC *T. gondii* INFECTION MAY BE ASSOCIATED WITH IRON, IODINE AND FOLIC ACID DEFICIENCIES THAT FACILITATE DEVELOPMENT AND/OR PROGRESSION OF ADs

*T. gondii* must acquire nutrients from its host to survive and ensure its proliferation<sup>[176]</sup>. The parasite is an auxotroph for iron<sup>[177,178]</sup>,

**Table 6** Regulation of cytokine gene expression in the course of acute and chronic viral and two protozoan infections (acc. to Teixeira *et al* [80]; with own modification).

T cell response	Cytokine	Regulation of expression					
		Coxackie virus B3		<i>T. gondii</i>		<i>T. cruzi</i>	
		Acute	Chronic	Acute	Chronic	Acute	Chronic
T <sub>H</sub> 1	IFN-γ	↑	↑	↑	↓↑	↑	↑
	TNF-α	↑	↑→	↑→	↑↓→	↑	↑→
	IL-2	↓↑	↑	↓↑	↑	→	↓→
	IL-12	↑	↑	↑↓→	↑↓→	↑↓→	↑
T <sub>H</sub> 2	IL-4	↑↓	↑	↑	↑	↑	↑↓→
	IL-5	↓	↑	↑	↑	↑	↑
	IL-6	↑	↑	↓	↑	↑	↑
	IL-10	↑↓	↑	↑↓	↑↓	↑	↑↓→
	IL-13	↑	NF	NF	NF	↑	↑→
T <sub>H</sub> 17 <sup>a</sup>	IL-17	↑	↑	NF	↓↑	↑	↑
Treg	TGF-β	↑	↑	↑	↑	↑	↑

NF, not found; ↑, superexpression; ↓, underexpression; →, no alteration. Multiple arrows mean that different results were reported in the literature. Treg, T regulatory cell. <sup>a</sup>The source of IL-17A cytokine are CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells, neutrophils, and eosinophils [85].

cholesterol<sup>[179,180]</sup>, tryptophan<sup>[181]</sup>, arginine<sup>[177,182]</sup>, polyamines<sup>[183]</sup>, purines<sup>[184]</sup>, and other essential nutrients<sup>[185]</sup>. Nutritional deficiencies may favor inducing and/or progression of ADs.

**Iron.** Worldwide, over 40% of children who have iron deficiency anemia are frequently associated with infection<sup>[186]</sup>. Iron plays a critical role in normal immune function, because of its growth promoting and differentiation-inducing properties for immune cells and its interference with cell-mediated immune effector pathways, and cytokine and enzymatic activities. In addition, relative iron deficiency is associated with mild immunosuppression (**Table 7**)<sup>[187-189]</sup>.

In children with iron deficiency anemia Hassan *et al*<sup>[198]</sup> found markedly lower serum IgG levels, IL-6, decreased phagocytic activity, and oxidative burst of neutrophils compared with controls. They also showed a significant positive correlation between serum iron and IL-6 levels<sup>[198]</sup>. The presence of transferrin receptor on immature, proliferating thymocytes and the inhibition of thymocyte proliferation and differentiation by anti-transferrin receptor antibody highlight the importance of iron to T cell development. Iron regulates T-lymphocyte sensitivity to the IFN-γ/STAT1 signaling pathway<sup>[199]</sup>. There is an association of the iron transporter NRAMP1 (natural resistance-associated macrophage protein 1; this protein plays an important role in resistance to infection and macrophage function<sup>[200]</sup>) with several autoimmune disorders along with evidence that iron can catalyze the production of cryptic epitopes of several autoantigens, and establishes a potential role for iron in the development of

**Table 7** Changes in immune function associated with iron deficiency (acc. to Baker & Ghio [189]; with own modification).

Immune function	Effect of iron deficiency	Refs
T-lymphocyte proliferation	Decreased blastogenesis and mitogenesis	[190-193]
T-cell numbers	Decreased Th and Tc cells in blood	[194]
Immunoglobulin levels	Lower serum levels of IgG4	[191]
Neutrophil and macrophage function	Decreased bactericidal activities	[190,191]
TNF and IL-2 secretion	Reduced production by activated cells	[190,194,195]
IFN-γ, IL-12, IL-2, IL-6 and IL-10 serum levels	Decreased concentrations	[191,194,196]
Serum macrophage MIF and MCP-1 levels	Increased susceptibility to infection	[197]
Humoral, cell-mediated and non-specific immunity	Decreased responsiveness to functional tests of immune function	[191]

MIF, migration inhibitory factor; MCP-1, monocyte chemoattractant protein-1.

autoimmunity<sup>[187]</sup>.

ADs often present with abnormal iron homeostasis<sup>[189]</sup>. Nutritional deficiencies are important determining factors for fetal growth, body composition and childhood development. For example, Dosman *et al*<sup>[201]</sup> showed that among 33 children with autism spectrum disorders (ASD) 77% had restless sleep at baseline which improved significantly with iron therapy, suggesting a relationship between sleep disturbance and iron deficiency. Similar prevalence of iron deficiency was found in 69% of preschoolers and 35% of school-aged children indicating that children with ASD require iron monitoring and its supplementation, especially that there was a correlation between low ferritin and more severe impairment in those children<sup>[202]</sup>. Deficient in iron body stores of the autistic individuals could be associated with chronic infection due to *T. gondii* because additional requirements for this ion are necessary for proliferation of the pathogen. This suggestion may be supported by the finding of Dimier & Bout<sup>[178]</sup> that intracellular *T. gondii* replication was iron-dependent, suggesting that IFN- $\gamma$ -treated enterocytes inhibited the parasite replication by limiting the availability of intracellular iron to this apicomplexan. In addition, children with ASD and chronic toxoplasmosis have overproduction of IFN- $\gamma$  and NO<sup>[114]</sup>, and it was shown that NO intercepts iron before incorporation into ferritin and indirectly mobilizes iron from ferritin in a glutathione-dependent manner<sup>[203]</sup>.

In model animals with SLE, both iron deficiency and iron supplementation affected disease manifestations<sup>[204]</sup>. Patients with SLE have inadequate nutritional status and food intake<sup>[205]</sup>. In one study of 170 women with SLE, inadequate iron intake was present in 36.7% of patients aged between 19 and 50 yrs old and 12.5% of individuals aged between 50 and 59 yrs<sup>[205]</sup>. In SLE, hematological abnormalities are frequent, and anemia was found in about 50% of patients, with anemia of chronic disease being the most common form<sup>[206]</sup>. In addition, impaired erythropoietin response and presence of antibodies against erythropoietin may contribute to the pathogenesis of this type of anemia. Moreover, autoantibodies, T lymphocytes, and disturbed balance in the cytokine network can also affect bone marrow erythropoiesis, leading to anemia<sup>[206]</sup>. Importantly, it was suggested that significantly increased serum levels of cytokine IL-6 may be responsible for development of anemia in this disease because there was an inverse correlation between IL-6 concentrations and hemoglobin in SLE patients<sup>[207]</sup>. It must be emphasized that chronic *T. gondii* infection was also associated with increased production of proinflammatory cytokines including IL-6<sup>[117]</sup>, and this cytokine was found to promote the intracellular multiplication of the parasite in mice<sup>[208]</sup>.

In patients with active rheumatoid arthritis (RA) anemia of chronic disease (ACD) is often present, and the prevalence of iron deficiency is up to 50-70%<sup>[209]</sup>. Weber *et al*<sup>[210]</sup> found that mucosal uptake of iron was markedly decreased in patients with active RA, with and without iron deficiency. Inflammatory cytokines, particularly TNF- $\alpha$ , IL-1, IFN- $\gamma$  and IL-6 were thought to contribute to the pathogenesis of ACD in RA, possibly by inhibiting erythropoietin production and macrophage iron release<sup>[211-213]</sup>. Moreover, TNF- $\alpha$ , IFN- $\gamma$  and IL-1 changed iron movement by reducing the concentration of transferring receptor on the cell surface, increasing synthesis of ferritin for metal storage and activating NO systems to reduce intracellular iron<sup>[190]</sup>. At present, it is believed that IL-6 is involved in the pathogenesis of RA by altering the balance between T<sub>H</sub>17 cells and Treg, and acts on inducing the production of hepcidin (a master regulator of iron homeostasis) which causes iron-deficient anemia, and its release is stimulated by the cytokine IL-6<sup>[214,215]</sup>. Important role of IFN- $\gamma$ ,

TNF- $\alpha$ , and IL-6 marked increases generated during chronic *T. gondii* infection is in line with the aforementioned reasoning. IL-6 also frequently participates in the pathology of ocular diseases associated with infections caused by this parasite, including ADs<sup>[216,217]</sup>.

In summary, iron deficiency may have important implications in ADs, particularly in individuals with chronic *T. gondii* infection. On the other hand, limiting the availability of intracellular iron plays an antimicrobial role in human macrophage activity against this pathogen<sup>[218]</sup>.

## Iodine

**A.** Thyroid dysfunction is common, over two billion people worldwide are at risk for iodine deficiency and 30-70% will be hypothyroid<sup>[219]</sup>. Mooij *et al*<sup>[220]</sup> demonstrated that an insufficient dietary iodine intake in normal nonautoimmune female rats was capable to induce a thyroid autoimmune reactivity. A higher incidence of antithyroglobulin antibodies has been demonstrated in iodine deficiency regions<sup>[221]</sup>. Kabelitz *et al*<sup>[222]</sup> found the prevalence of anti-thyroid peroxidase antibodies and autoimmune thyroiditis in children and adolescents in an iodine replete area. Iodine deficit influenced development of thyroid autoimmunity especially in elderly people, and thyroid autoantibodies are common in old age<sup>[223,224]</sup>. Patients with endemic goiter<sup>[225]</sup> and endemic cretinism<sup>[226]</sup> showed to have increased serum IgG that affect the growth of thyrocytes *in vitro*. Thyroids of iodine-deficient goiter patients contain aggregates of epithelial cells and DCs (the antigen-presenting cells)<sup>[227]</sup>, which are capable of transferring autoimmune thyroiditis in experimental animals<sup>[228]</sup>, and the aberrant MHC class II expression on thyrocytes in Graves' disease may be relevant for autoimmunity<sup>[229]</sup>. It must be noted that recently iodine deficiency has also been reported in autistic children and their mothers, and it was inversely related to disease severity<sup>[230,231]</sup>. Statistically significant lower concentrations of free triiodothyronine, free thyroxine and higher levels of thyroid stimulating hormone were found in the autistic groups as compared with the control groups. Interestingly, urinary iodine was markedly lower among patients with ASD and their mothers as compared with respective controls (both  $p < 0.001$ ), and this may reflect a sparing effect of their bodies due to iodine deficiency.

**B.** Several authors suggested that there is a relationship between iodine deficiency and *T. gondii* infection<sup>[220,232,233]</sup>. Impaired thyroid function was found in murine toxoplasmosis<sup>[234]</sup>. Studies of Stahl *et al*<sup>[234,235]</sup> performed on female mice infected intraperitoneally with cysts of *T. gondii* Cornell strain, demonstrated hypothalamic dysfunction associated with decline of serum thyroxine (T<sub>4</sub>) concentrations and atrophy in the thymus, ovaries and uterus. In humans, Kankova *et al*<sup>[106]</sup> found that pregnant women (9-12<sup>th</sup> gestational weeks) with latent toxoplasmosis had a decrease in serum thyroid stimulating hormone (TSH) levels ( $p < 0.049$ ), and a positive correlation was found between free thyroxine levels and the index of positivity for anti-*T. gondii* IgG antibodies ( $p = 0.033$ ). Moreover, the infected pregnant women often had more highly elevated thyroid peroxidase antibodies (a serum marker of autoimmune thyroid diseases) than the *Toxoplasma*-negative participants ( $p = 0.004$ )<sup>[106]</sup>. Singh *et al*<sup>[233]</sup> analyzed 194 school students aged 10-18 yrs and showed a significant difference in the seroprevalence of *T. gondii* infection in children with grade II goiter as compared with individuals having grade I goiter or no goiter (46.1% vs. 31.8 and 26.5%, respectively,  $p < 0.05$ ). Finally, Wasserman *et al*<sup>[105]</sup> demonstrated in sera of 1807 pregnancies in 1591 women that prior infection with *T. gondii* was associated significantly with the elevation of thyroid peroxidase antibodies.

C. Thyroid cells are capable to produce many cytokines and other factors that play an important role in development of host autoimmunity (Table 8)<sup>[236]</sup>.

The expression of ICAM-1 and LFA-3 by thyroid cells is enhanced by IFN- $\gamma$ , TNF and IL-1<sup>[237]</sup>. It must be noted that *T. gondii* infection also triggers production of proinflammatory (e.g. IFN- $\gamma$ , IL-12, TNF- $\alpha$ , IL-1 $\beta$ , IL-6), antiinflammatory cytokines (IL-10, IL-4, TGF- $\beta$ , IL-6), and NO<sup>[238,239]</sup>. Inflammation induced by the parasite and/or other pathogens can therefore modify cell signaling pathways and influence T cell activity and cytokine secretion profiles by thyroid cells sometimes leading to autoimmunity. Interestingly, *T. gondii* secretes a pore-forming protein (TgPLP1) that is crucial for rapid parasite exit from host cells<sup>[240]</sup>, and thyroid cell destruction is mediated by perforin containing cells (mainly NK cells and CD8<sup>+</sup> T cells) which accumulate in the thyroid and by Fas dependent mechanism<sup>[241,242]</sup>. One cannot exclude that at least in part TgPLP1 present in these cells contribute to thyroid tissue destruction observed in Hashimoto's (goitrous) thyroiditis (HT). This may be supported by the finding of *T. gondii* transmission from infected DCs to NK cells<sup>[243]</sup>.

Wide varieties of cytokines were detected in thyroid tissues from patients with autoimmune thyroid disease (ATD), hyperthyroid Graves' disease (GD), and HT<sup>[237,244-248]</sup>, and several lines of evidence suggested that they play an important role in the pathogenesis of these clinical entities through modulation of iodine uptake by thyroid follicular cells, in addition to affecting their growth and function<sup>[247]</sup>. In this context, it should be emphasized that TSH increased both sodium iodide symporter (NIS) gene expression (NIS is essential for iodide uptake by the thyroid gland and the formation of thyroid hormones) and iodide uptake in primary thyroid follicular cell cultures in a dose-dependent manner, and this induction was modulated by cytokines<sup>[247,249,250]</sup>. It was reported that cytokines IL-1 $\alpha$ , TNF- $\alpha$  and IFN- $\gamma$  at concentrations of 0.1, 1, 10, 50 and 100 mU/L inhibited TSH-induced NIS gene expression and iodide uptake (both TNF- $\alpha$  and, to a lesser extent IL-1 $\alpha$ , inhibited basal and induced NIS expression, but IFN- $\gamma$  exerted similar activity only in 1000 mU/L concentration and inhibition ranged from 40 to 65%<sup>[247]</sup>. Ozawa *et al*<sup>[249]</sup> showed that prolonged administration of TNF- $\alpha$  to mice resulted in a dose-dependent decrease in serum concentrations of triiodothyronine (T<sub>3</sub>) and T<sub>4</sub>, while in healthy volunteers induced changes in TSH and thyroid hormones resembling those found in non-thyroidal illness observed in patients with infections, in whom production of this cytokine is a feature<sup>[250]</sup>. Furthermore, other cytokines, such as IL-6 and IL-1 $\beta$  have been found to decrease NIS mRNA expression in TSH-stimulated FRTL-5-cells (Fisher rat thyroid cell line), and IL-1 $\beta$  suppressed iodide accumulation<sup>[251]</sup>. TNF- $\beta$  and IFN- $\gamma$ , separately and added together with IL-1 $\beta$  affected function of cultured human thyroid cells<sup>[252,253]</sup>, and IL-6 was found to inhibit human thyroid peroxidase gene expression<sup>[254]</sup>. These reports are in line with the finding of different cytokine mRNA profiles in GD, HT, and nonautoimmune thyroid disorders<sup>[255]</sup>, as well as with the higher levels of NIS mRNA in GD compared with multinodular goiter tissue samples<sup>[247]</sup>, and with the enhanced production of IFN- $\gamma$  by thyroid-derived T cell clones observed in patients with HT<sup>[256]</sup>. Nb. IFN- $\gamma$  was found to induce MHC class II expression by thyroid epithelium<sup>[257]</sup>. It should be noted that in humans, iodine uptake is not exclusive to the thyroid gland, as other organs also can accumulate this ion, including the salivary gland, stomach, placenta, lactating mammary gland, and probably intestine<sup>[255,256,258,259]</sup>. Finally, it must however be added that iodine deficiency may also reflect a host defense against development of Hashimoto's thyroiditis because in

**Table 8** Biomolecules generated by thyroid cell that interplay with the immune system (acc. to Saranac *et al* [236]; with own modification).

Cytokines	IL-1, IL-6, IL-12, IL-13, IL-15, IL-17, and IL-18
Growth factors	IGF-1, IGF-2, EGF, and VEGF
Adhesion molecules	ICAM-1 and LFA-3
Inflammatory mediators	NO, prostaglandins

ICAM-1, intercellular adhesion molecule-1; LFA-3, lymphocyte function-associated antigen-3; VEGF, vascular endothelial growth factor; IGF-1, insulin-like growth factor 1 or 2; EGF, epidermal growth factor.

one study it appeared that after iodine prophylaxis the incidence of this clinical entity was 4-fold higher than in other subgroups with this disorder<sup>[260]</sup>.

Together, increased production of proinflammatory cytokines play an important role in the pathogenesis of thyroid dysfunction, ATD, GD and HT. Chronic *T. gondii* infection should be taken into consideration as a potential environmental trigger of ADs associated with the thyroid gland because of frequent iodine deficiency and worldwide distribution of the parasite.

**Folic acid.** Natural CD25<sup>+</sup>CD4<sup>+</sup> Treg cells constitutively express high amounts of folate receptor 4 (FR4), a subtype of the receptor for folic acid, compared with other activated or naïve T cells before and after antigenic stimulation, and FR4 is functionally essential for their maintenance because its blockade was sufficient for reducing natural Treg cells *in vivo*<sup>[261]</sup>. It is therefore likely that Treg cells are highly dependent on folic acid and FR4 may enable them to bind and incorporate folic acid efficiently, and it was suggested that depletion of these cells can evoke severe immune responses to self antigens, in addition to enhancing immune responses to nonself antigens<sup>[261]</sup>. It must be noted that thyroid dysfunction is frequently observed in autism and recently Frye *et al*<sup>[262]</sup> suggested that this abnormality may be related to blocking folate receptor  $\alpha$  autoantibodies that are prevalent in ASD.

Massimine *et al*<sup>[263]</sup> provided morphological and biochemical evidence that *T. gondii* has a specific protein transporter exposed at the parasite surface, with high affinity for folic acid, which is responsible for the acquisition and salvaging of exogenous folate compounds. Transport of folic acid across the parasite plasma membrane was rapid, biphasic, temperature-dependent, bidirectional, concentration dependent and specific. Methotrexate, a folate analog, was found to be internalized by the protozoan pathogen to the mitochondrion<sup>[263]</sup>. These findings may further support the suggestion that *T. gondii* infection was associated with development of Down syndrome<sup>[118]</sup>, especially that the simultaneous dietary restriction and infection with the parasite were able to induce DNA damage in the peripheral blood cells of infected mice<sup>[264]</sup>, as well as affect brain levels of folate and disrupt cognitive function<sup>[265]</sup>.

## VASCULAR ENDOTHELIAL CELLS ARE SUSCEPTIBLE TO PERSISTENT INFECTION WITH *T. GONDII* TACHYZOITES AND THEREFORE MAY PARTICULARLY FAVOR DEVELOPMENT OF ADs

The endothelial cells are critically important for the delivery of nutrients and oxygen throughout the body, but they also contribute to pathology including the triggering and persistence of inflammation<sup>[266]</sup>. Tropism of different pathogens for particular cell types and/or specific tissue sites was a long-recognized biological phenomenon<sup>[267]</sup>. *T. gondii* is disseminating in the body in a Trojan

horse-manner in various eukaryotic cells, including endothelial cells and macrophages, and division rate of intracellular unprimed *T. gondii* tachyzoites in endothelial cells, monocyte-derived macrophages, peritoneal, or alveolar cells is rapid (Table 9)<sup>[268]</sup>.

Canedo-Soares *et al*<sup>[285]</sup> analyzed invasion kinetics of two *T. gondii* strains, RH (virulent) and ME49 (nonvirulent) in two human vascular endothelial cell types, HMEC-1 (skin microvasculature) and HUVEC (umbilical cord vein vasculature) and established that surprisingly the less virulent strain invaded a greater proportion of cells than the more aggressive RH strain. Similar results were obtained by Lachenmaier *et al*<sup>[286]</sup> who showed *in vitro* that RH tachyzoites invaded lower proportion of rat brain microvascular endothelial cells than those of ME49 strain. Thus, it appeared that *T. gondii* virulence relied more on its replication speed than on its invasion efficiency<sup>[285]</sup>.

Smith *et al*<sup>[267]</sup> found that retinal vascular endothelium cells have enhanced susceptibility to infection with *T. gondii* tachyzoites in comparison with aorta (55% more), umbilical vein (33%), and dermal endothelial cells (34%). Free tachyzoites had the ability to transmigrate a stimulated human retinal endothelium monolayer<sup>[287]</sup>. Tachyzoites crossed *in vitro* retinal endothelium assisted by intercellular adhesion molecule-1 (ICAM-1) (the cell surface IgG immunoglobulin superfamily member), and ICAM-1 blockade significantly inhibited the parasite migration across stimulated human retinal, but not choroidal vascular endothelium<sup>[287]</sup>. There has been interest in the heterogeneity of vascular endothelium, not only between arteries and venous types<sup>[288]</sup>, but also between same type vessels located within different organs or within different tissues in the same organ<sup>[289,290]</sup>. An intracellular environment low in ROS or RNI and/or high in iron or tryptophan facilitate tachyzoite proliferation<sup>[274,279,283]</sup>.

## AUTOIMMUNITY AND GASTROINTESTINAL TRACT DISORDERS

### Underestimated role of oral *T. gondii* infection in development of gastrointestinal manifestations frequently reported in ADs

Gastrointestinal manifestations are often documented in many systemic ADs including SLE, RA, Sjögren's syndrome, Behçet disease, progressive systemic sclerosis, polyarteritis nodosa, inflammatory muscle disorders, antiphospholipid antibody syndrome, thyroid diseases, primary biliary cirrhosis, and ASD<sup>[291-294]</sup>.

*T. gondii* exposure is the well-documented risk factor for schizophrenia<sup>[295,296]</sup>, inflammatory bowel disease, ulcerative colitis, celiac disease, autism, and Leśniowski-Crohn's disease<sup>[120]</sup>. Interestingly, in a large sample of 23 471 primary care patients (mean age 51.4 yrs, 66.1% female) studied recently it was found a significantly increased prevalence of ADs in functional gastrointestinal tract disorders not explained by differences in age and gender<sup>[297]</sup>. This may support a notion that *T. gondii* infection play a much more important, but so far neglected, role in the pathogenesis of ADs<sup>[120]</sup>.

The oral route is the natural portal of entry for *T. gondii*. Enterocytes are the first cells to be invaded by the parasite when ingested pathogens are released from cysts or oocysts within the gastrointestinal tract<sup>[178,298]</sup>. The intestinal epithelium constitutes a unique lymphoid compartment of the gut mucosa immune system with the presence of intraepithelial lymphocytes that have the ability to lyse *T. gondii* infected enterocytes and to synthesize IFN- $\gamma$  in infected mice<sup>[299]</sup>. The intestinal epithelium and the underlying mucosal tissues, as well as local lymph nodes with lymphatic endothelial cells (LECs) are heavily populated with immune system

**Table 9** Division rate of intracellular *T. gondii* tachyzoites in primary human cells *in vitro* (acc. to Channon *et al* [268]; with own modification).

Cell type	Parasite division rate Unprimed	IFN- $\gamma$ primed	Mechanism	Refs
<b>Hemopoietic</b>				
Lymphocyte	S			[268]
Neutrophil	S			[268-270]
Adherent monocyte	S		ROS; not TS	[270-275]
Nonadherent monocyte	R	R		[268,272]
Dendritic cell	R			[268]
Alveolar macrophage	R	S	Partly TS	[275]
Peritoneal macrophage	R	S		[276]
Monocyte-derived macrophage	R	S	ROS; not RNI	[274-277]
<b>Nonhemopoietic</b>				
Neuron	S			[278]
Foreskin fibroblast	R	S	TS	[279,280]
Umbilical vein endothelial cell	R	S	TS or ROS; not RNI	[274,281]
Retinal pigment epithelial cell	R	S	TS	[282]
Fetal astrocyte	R	S	RNI	[278,283]
Fetal microglial cell	R	R		[284]

R, rapid; S, slow; RNI, reactive nitrogen intermediates; ROS, reactive oxygen species; TS, tryptophan starvation.

that can make rapid contact with the parasite following intestinal penetration, and there was a protective mucosal T<sub>H</sub>2 immune response against *T. gondii* by murine mesenteric lymph node DCs<sup>[300]</sup>. Lymphatic vessels are key routes for the recirculation of fluid and cells that enter tissues from blood vessels<sup>[301]</sup>. LECs line the afferent and efferent lymphatic vessels, the medullary sinuses, and both the ceiling and floor of the lymph nodes<sup>[302]</sup>. The gaps between LECs are so large that bacteria and other cells can enter along with the fluid. DCs, macrophages, and lymphocytes enter lymphatics, but neutrophils and erythrocytes generally do not<sup>[301]</sup>. Recently, it was demonstrated that LECs have antigen presenting cell properties because they express MHC I and MHC II molecules on the cell surface, and frequently they are presumed to be the first that encounter peripheral antigens, cytokines and immune cells<sup>[302]</sup>. LECs are also important for CD4<sup>+</sup> T cell tolerance by acting as a storage for antigens that are not directly presented on their own MHC II, but transported to DCs for MHC II presentation<sup>[303]</sup>. LECs probably are able to directly present antigens to CD8<sup>+</sup> T cells during the early phases of inflammation and indirectly by DCs through archiving of antigens<sup>[304,305]</sup>. Enlarged mesenteric lymph nodes frequently seen at imaging in patients with inflammatory bowel disease, children with abdominal pain, and in asymptomatic children<sup>[306-308]</sup> may be due to *T. gondii* infection<sup>[120]</sup>. This suggestion is supported by the finding that DCs can move to Peyer's patches and mesenteric lymph nodes where they interact with naïve lymphocytes and initiate adaptive immune response that result in activation of T and B memory cells, and proliferative response and cytokine release, finally leading to gastrointestinal tract inflammation<sup>[120,309]</sup>. Thus, it seems that tachyzoites released during *T. gondii* oral infection may also attack LECs and at least in part participate in development of these immunopathological events, including lymphoid nodular hyperplasia in the colon of children with autism<sup>[310]</sup>, and gastrointestinal disorders and manifestations in several other ADs<sup>[120]</sup>.

## T. GONDII, VIRUSES AND BACTERIA UTILIZE HEPARAN SULFATE (HS) PROTEOGLYCANS AS RECEPTORS FOR INFECTION, INVASION, AND COLONIZATION

### Impaired sulfation of sugars on the surface of host cells is beneficial for defense against infection with the parasite

Parasites, viruses (HBV, HCV, HEV, HSV- and -2, CMV, HIV-1, HPV, HTLV1)<sup>[311]</sup> and bacteria (*H. pylori*, *Chlamydia*, *Streptococcus*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Mycobacterium tuberculosis*, *Borrelia burgdorferi*, *Yersinia enterocolitica*)<sup>[311-313]</sup> use HS as receptors for infection, invasion, and colonization of host cells and tissues<sup>[314,315]</sup>. HS proteoglycans are present on the cell surface, within the extracellular matrix, as soluble molecules in tissues and blood, and in the cell nucleus, in which they control many cellular functions such as cell cycle and proliferation, transcription machinery, chromatin structure modification, and transport cargo to the nucleus<sup>[316,317]</sup>. *T. gondii*, like viruses, also binds to sialic acid residues on the host cell surface<sup>[92,318]</sup>. The parasite contact with the cell surface in fibroblasts is mediated by laminins on the pathogen surface, which bind to host  $\beta 1$  integrins<sup>[319]</sup>, and laminin chains are implicated as autoantigens in several ADs<sup>[320]</sup>.

Proteoglycans are important host cell receptors, and the tachyzoite surface antigens SAGs are key ligands<sup>[321-323]</sup>. Proteoglycans are built of glycosaminoglycan (GAG) chains in which HS is the main component<sup>[324]</sup>. Tachyzoites SAG3 binds HS proteoglycans on CHO cells<sup>[323]</sup>, and the parasite lectin is also capable of binding to sulfated proteoglycans<sup>[325]</sup>. The ability of tachyzoites to infect a number of different cell lines has been correlated with the surface expression of sialic acid residues<sup>[326]</sup>.

The tachyzoite form of *T. gondii* can efficiently invade and rapidly multiply in almost every type of nucleated mammalian cell<sup>[327-329]</sup>, and it was suggested that HS facilitates parasite replication postinvasion<sup>[330]</sup>. *T. gondii* expresses a surface antigen SAG3 that binds to HS<sup>[323]</sup>. HS is a GAG polymerized from N-acetylglucosamine and glucuronic acid attached to protein core of a proteoglycan<sup>[330]</sup>. It was shown that: a) HS was necessary for extensive *T. gondii* infection of several cell types, b) efficient infection depended on N sulfation of subsets of N-acetylglucosamine chains, c) the surface antigen SAG3 of the parasite probably binds to glycoconjugates terminating in sialic acid<sup>[326]</sup>, which are as abundant on the cell surface as HS<sup>[330]</sup>, and d) HS facilitated replication of the parasite in the cytoplasm of mammalian cells within a self-made membrane-bound compartment – the parasitophorous vacuole<sup>[323,326,330]</sup>. Several studies documented that altering HS altered infection<sup>[325,331]</sup>, and it was demonstrated *in vitro* that the parasite required N sulfation of HS initiated by N-deacetylase/N-sulfotransferase-I because mammary tumors lacking this enzyme(s) exhibited markedly reduced *T. gondii* infectivity<sup>[330]</sup> (**Table 10**).

Hyaluronan, a major non-protein GAG component of the extracellular matrix and the major polysaccharide involved in atherosclerotic process of the blood vessel wall, plays a crucial role acting as a modulator of all inflammatory stages, affecting the behavior of both endothelial and smooth muscle cells<sup>[343]</sup>. In addition, GAGs and proteoglycans possess the properties essential for lipid retention, immune system activation, SMVCs proliferation, and macrophage recruitment<sup>[343]</sup>.

*T. gondii* tachyzoites are able to infect several types of cells. Mutant cells, which present few or no surface-exposed sialic acid

**Table 10** Glycoconjugate glycans as viral and *T. gondii* receptors (acc. to Olofsson & Bergström [332]; with own modification).

Virus type	Receptor	Refs
HCV	Heparan sulfate (HS)	[333]
HSV types 1 and 2	HS (chondroitin sulfate)	
CMV	HS	[334-336]
HHV types 6 and 7	HS	
HHV type 8	HS	[337]
HIV-1	HS (chondroitin sulfate); Sulfatide; fucose on DC. Galactosylceramide: receptor for transcytosis through the mucosa. Glycosaminoglycan (GAG): contributing to brain invasion	[338-341]
<i>T. gondii</i> <sup>a</sup>	HS	[314,315,323,329,330]
	Hyaluronan	[342]

<sup>a</sup>Cell surface HS and glycans containing sialic acid, have been shown to act as adhesins and potential receptors for *T. gondii* [330]. Other parasites, viruses and bacteria, also utilize HS as receptors for infection, invasion, and colonization of host cells and tissues [314,315].

residues were infected to a lower extent. Similar effects were obtained if sialic acid residues were removed by previous neuraminidase treatment<sup>[326]</sup>. Addition of sialic acid residues to surface-exposed glycoconjugates using fetuin as a sialic acid donor rendered the cells easily infected by *T. gondii*. These findings indicated that surface-exposed carbohydrate residues of the host cell were involved on the process of *T. gondii*-host cell recognition<sup>[326]</sup>.

Ortega-Barria & Boothroyd<sup>[325]</sup> found a sugar-binding activity (lectin) in tachyzoites of *T. gondii* that plays an important role in human endothelial cells and fibroblasts infection. Binding of *T. gondii* to host cells is partially mediated by interaction with sulfated GAGs<sup>[331]</sup>. Interestingly, infectivity of tachyzoites for human foreskin fibroblast cells that are commonly used *in vitro* to grow *T. gondii* was increased by low concentrations of the sulfated glycoconjugate, whereas high concentrations of soluble GAGs decreased the attachment of parasites to human host cells from a variety of lineages, including monocytic, fibroblast, endothelial, epithelial, and macrophages cells<sup>[325,331]</sup>. The inhibition of parasite attachment by GAGs was observed with heparin and HS and also with chondroitin sulfates, indicating that the ligands for attachment are capable of recognizing a broad range of GAGs (**Table 11**).

It was also found that addition of excess soluble GAGs blocked parasite attachment to serum-coated glass, thereby preventing gliding motility of extracellular parasites (**Table 12**)<sup>[331]</sup>. A significant proportion of cytokines bind to GAGs such as heparin, a highly sulfated HS. GAGs are involved in signaling, stabilization and/or storage of several cytokines including IL-8, monocyte chemoattractant protein-1, VEGF, G-CSF, basic fibroblast growth factor, and hepatocyte growth factor<sup>[344]</sup>. Ishiwa *et al*<sup>[345]</sup> demonstrated that dextran markedly inhibited *T. gondii* infection, and particularly low molecular weight dextran (10 kDa) most effectively both *in vitro* and *in vivo* slowed the growth of the parasite inside host cells. Interestingly, this preparation recently administered intravenously inhibited acute *T. gondii* infection in pigs<sup>[346]</sup>.

It must be noted that inhibition of GAGs biosynthesis and sulfation on the host cells reduced *Toxoplasma* infectivity, and tachyzoites showed a reduced ability to infect epithelial cell mutants deficient in the biosynthesis of surface proteoglycans<sup>[325]</sup>. The importance of sulfated proteoglycan recognition was supported by the demonstration that GAG-deficient mutant host cells, and wild-



**Table 11** Inhibition by soluble GAGs of *T. gondii* attachment to various mammalian cells<sup>a</sup> (acc. to Carruthers *et al* [331]; with own modification).

Cell line	Cell type	Heparin	CSC	IC <sub>50</sub> (mg/mL) <sup>a,CSA</sup>	Dextran sulfate	Dextran	Fucoidin
HFF	Fibroblast	4.8 ± 2.0	4.1 ± 1.4	7.3 ± 1.7	2.2 ± 0.4	> 20	> 20
HEp-2 <sup>b</sup>	Epithelial	5.5 ± 1.6	4.5 ± 0.4	6.3 ± 2.3	5.7 ± 2.3	14.1 ± 2.1	19.5 ± 0.2
HUV-EC-C <sup>b</sup>	Endothelial	1.8 ± 0.2	1.6 ± 0.4	2.9 ± 1.5	1.0 ± 0.4	9.7 ± 3.4	4.1 ± 1.8
U373 <sup>b</sup>	Glial or astrocyte	3.0 ± 1.9	3.0 ± 0.8	1.1 ± 0.4	2.1 ± 0.4	7.4 ± 3.8	16.0 ± 3.7
U937 <sup>b</sup>	Macrophage	2.0 ± 0.3	1.8 ± 0.8	2.6 ± 1.5	6.7 ± 2.6	7.0 ± 2.7	13.2 ± 4.9
G361 <sup>b</sup>	Melanocyte	4.0 ± 0.3	2.0 ± 0.1	3.0 ± 1.9	4.6 ± 0.4	8.8 ± 4.7	0.3 ± 0.1
Average <sup>c</sup>		3.5 ± 1.4	2.8 ± 1.1	3.9 ± 2.2	3.7 ± 2.1	11.2 ± 4.6	11.7 ± 6.2

<sup>a</sup> IC<sub>50</sub>, 50% inhibitory concentration; Numbers are means ± SE; n = 2 or 3; <sup>b</sup> The cells obtained from the American Type Culture Collection; <sup>c</sup> Average values (± SE) for all cell lines tested; CSA, chondroitin sulfate A; CSC, chondroitin sulfate C; fucoidin, a sulfated L-fucose oligosaccharide; GAGs, glycosaminoglycans.

**Table 12** Effects of increasing concentrations of soluble GAGs on trail lengths produced by gliding *Toxoplasma* (acc. to Carruthers *et al* [331]; with own modification).

Compound	Trail length <sup>a</sup> at GAG concn <sup>b</sup> of:			
	0	6.25	12.5	25
Dextran	9.7	9.1	9.2	8.8
Dextran sulfate	9.6	8.5	8.3	4.2 <sup>c</sup>
Heparin	10.2	9.3	7.9	4.7 <sup>c</sup>
Heparan sulfate	9.2	8.3	7.8	4.4 <sup>c</sup>
CSA	9.4	8.8	8.2	4.6 <sup>c</sup>
CSC	9.5	8.8	8.4	4.6 <sup>c</sup>

<sup>a</sup> Mean trail length in parasite body length (approximately 5-7 μm);

<sup>b</sup> In mg/mL; <sup>c</sup> Significantly different from control (p ≤ 0.05, Student's *t* test); CSA, chondroitin sulfate A; CSC, chondroitin sulfate C; GAGs, glycosaminoglycans.

type cells treated enzymatically to remove GAGs, were partially resistant to parasite invasion<sup>[331]</sup>. In this context, one may suggest that metabolic abnormalities, such as the impaired sulfation and sulfoxidation found in patients with autism may reflect a defense of the host cells against invasion of the parasite. Moreover, the significantly decreased platelet sulfotransferase activity due to elevated estrogen levels found during pregnancy or in the control females on estrogen-containing oral contraceptive pills associated with impairment in sulfation capacity<sup>[347]</sup> may be consistent with the notion of host cell defense. The adverse influence of pregnancy upon sulfation may represent a long-lasting, epigenetic enzymatic adaptation of pregnant women defending the fetus against *T. gondii* infection. The same reasoning may be applied to poor sulfation and sulfoxidation found in the patients with primary biliary cirrhosis<sup>[348-350]</sup> because the parasite can initiate a pathogenic process that may eventually result in clinically overt autoimmunity<sup>[129,131]</sup>. It should be emphasized that for example steroid sulfation or desulfation pathways have both been implicated in improving and/or worsening metabolic outcomes associated with type 2 diabetes and obesity, and in the healthy brain, colon, adrenal, and kidney predominate sulfation, while desulfation dominates in the breast, ovary, prostate, testis, placenta, and uterus<sup>[351]</sup>.

In summary, *T. gondii* infection of almost all nucleated cells, rapid or slow intracellular multiplication and life-long persistence of the pathogen in the host cells, use of HS proteoglycans and sialic acid as the parasite, viral and/or bacterial receptors for infection, invasion, colonization, and control of many cellular functions of human host cells from a variety of lineages and different tissues, may play an important role in triggering and development of several ADs. Impaired sulfation and sulfoxidation processes reported in some patients with ADs may represent defense reactions of the host cells against infection with the parasite.

## POSSIBLE LINK BETWEEN THE INCREASED SERUM AUTOANTIBODIES AGAINST LAMININ IN PATIENTS WITH SEVERAL ADs AND CHRONIC *T. GONDII* INFECTION

### Important role of laminin in development of reproductive function disturbances

#### ADs

Autoimmunity against laminins has been described in several ADs including vasculitis, connective tissue diseases, mucous membrane pemphigoid, and antilaminin  $\gamma 1$  pemphigoid, cutaneous lupus erythematosus, scleroderma, and psoriasis, and all these diseases were found to be associated with pathogenic role of antilaminin  $\gamma 1$  autoantibodies<sup>[320,352,353]</sup>.

Laminins are a family of glycoproteins present in the extracellular matrix and the major constituents of basement membranes, and integrins ( $\alpha\beta$  transmembrane receptors) act as receptor for laminins. The  $\alpha 6\beta 1$  integrin is the major leukocyte laminin receptor on macrophages, neutrophils, endothelial cells of large blood vessels, and T cells<sup>[354]</sup>. Cell adhesion molecules, integrin  $\alpha 6\beta 1$  and intercellular adhesion molecule (ICAM)-1 were implicated in tachyzoite binding to host cells. Soluble host laminin can associate with the surface of extracellular parasites. This adherent laminin is then available to interact with integrin  $\alpha 6\beta 1$ , creating a molecular bridge between parasite and host cell<sup>[319]</sup>. Human ICAM-1 recognizes the parasite adhesive microneme protein MIC2 that is liberated onto the surface of the parasite prior to host cell invasion<sup>[355]</sup>. Smith *et al*<sup>[356]</sup> showed that human retinal endothelial cells contained relatively high levels of transcripts encoding ICAM-1 and the integrin  $\alpha$  v subunit; this subunit is capable of binding laminin when complexed with integrin  $\beta 3$  as a receptor complex on microvascular endothelial cells<sup>[357]</sup>.

***T. gondii* infection.** Furtado *et al*<sup>[358]</sup> found that laminin, an extracellular matrix protein, increased *T. gondii* attachment to the murine macrophage cell line J774 in a dose-dependent fashion. It was also demonstrated that tachyzoites bearing surface laminin bind to multiple laminin receptors in attaching to different target cells, including human foreskin fibroblasts and Chinese hamster ovary cells<sup>[319]</sup>, and may therefore be responsible for the etiology of ovarian dysfunction<sup>[359]</sup> and uterine atrophy in chronic murine toxoplasmosis due to ovarian dysfunction<sup>[360]</sup>. These suggestions may be supported by the report that among 413 patients with inner ear disorders of unknown etiology, serum antilaminin antibodies were found in 68% of individuals with sensorineural hearing loss<sup>[361]</sup>. Other authors also documented that toxoplasmosis was associated with sensorineural hearing loss in children<sup>[362]</sup>. Similar associations

were found between the increased titers of serum autoantibodies against laminin in patients with systemic sclerosis<sup>[363]</sup>, and in individuals with SLE<sup>[364]</sup>, and the elevated serum IgG against *T. gondii* in these two clinical entities<sup>[98,99,141]</sup>. It must be noted that serum anti-toxoplasma antibodies were markedly increased also in patients with antiphospholipid syndrome<sup>[98]</sup>, and endothelial cells appeared to be the target for antiphospholipid antibodies, likely leading to a procoagulant state<sup>[365]</sup>. Nb. human endothelial cells are known to be activated by IFN- $\gamma$  to inhibit *T. gondii* replication<sup>[210]</sup>. In addition, an association of IgG antilaminin-1 autoantibodies with endometriosis in infertile patients, and with women having recurrent miscarriages, have been reported<sup>[366-368]</sup>, and *T. gondii* infection is known to impair reproductive function in animals<sup>[319,359,360,369,370]</sup>. The above-presented arguments are very important and may be supported by the significantly increased levels of antilaminin autoantibodies in nonautoimmune individuals with acute parasitic infections (**Table 13**), frequently reported problems with infertility in persons suffering from various ADs<sup>[371-377]</sup>, pregnancy loss and endometriosis<sup>[368]</sup>, and *T. gondii* worldwide dissemination in animal and human populations.

## ANTIRIBOSOMAL P AUTOANTIBODIES FOUND IN A SUBSET OF PATIENTS WITH SLE MAY BE AT LEAST IN PART GENERATED BY THE CONCOMITANT LATENT CHRONIC TOXOPLASMOSIS

### Patients with SLE

Ribosomal P (Rib-P) proteins comprise a family of acidic phosphoproteins that are critical for regulation of cell cycle, differentiation, proliferation, and responses to stress<sup>[379-382]</sup>. Ribosomal proteins account for 12-15% of the total cellular protein in an eukaryotic cell<sup>[383,384]</sup>. The Rib-P consists of three phosphoprotein components of the 60S ribosomal subunit, designated P0 (m.w. 38 kDa), P1 (19 kDa), and P2 (17 kDa)<sup>[385]</sup>, directed mainly against their carboxy 22 amino acids<sup>[386]</sup>. The prevalence of antibodies to Rib-P in patients with SLE ranged from 10 to 40%, being highest in Chinese (35%) and Japanese (28%) individuals and markedly lower in Brazil (10%) and Canada (8%)<sup>[387]</sup>. It was found that anti-Rib-P IgG antibodies are highly specific for SLE<sup>[386,388]</sup>, were more frequently found in juvenile-onset SLE than in adult-onset disease<sup>[389]</sup>, and Rib-P protein P0 was even suggested to be a candidate for the target antigen of antiendothelial cell antibodies in mixed connective tissue disease<sup>[390]</sup>. Their presence in serum frequently showed correlation with a concomitant development of other diseases, such as hepatitis<sup>[391-393]</sup>, and nephritis<sup>[392,394]</sup>. It is also very interesting that anti-Rib-P antibodies exist in a masked state in virtually all healthy adults<sup>[395]</sup>, and can be unmasked and detected only after treatment of serum with immobilized Rib-P antigens<sup>[395-397]</sup>. One cannot exclude that these "healthy adults" suffered from subclinical *T. gondii* infection.

### *T. gondii* infection

The parasite ribosomal protein promoters and knockdown revealed molecular pathways associated with proliferation and G1 cell-cycle arrest<sup>[398]</sup>. Analysis of DNA sequences from the 5' end of 239 directionally cloned *T. gondii* RH strain tachyzoite-derived cDNAs showed significant similarity to several classes of genes/proteins, including 24 ribosomal proteins<sup>[399]</sup>. Similarities with human ribosomal proteins (all with significant matches) represented about 12% of the total *T. gondii* expressed sequence tags (ESTs), and five

**Table 13** The prevalence of significantly elevated autoantibodies in nonautoimmune individuals with acute parasitic infections (acc. to Berlin *et al* [378]; with own modifications).

Infection/autoantibody	Parasitic (n = 17)	Control (n = 80)	p-value
Annexin-V	8 (47.1%)	3 (3.8%)	0.001
LMN	4 (23.5%)	1 (1.3%)	0.003
aPT	4 (23.5%)	1 (1.3%)	0.003
aPL	3 (17.6%)	2 (2.5%)	0.036

LMN, antilaminin antibodies; aPT, antiprothrombin antibodies; aPL, antiphospholipid antibodies.

were sequenced more than once leaving a total of 24 independent ribosomal protein ESTs (**Table 14**).

During the screening of the parasite cDNA expression library with monoclonal antibodies (mAb), an expressed cDNA clone Tg621 (a polypeptide of 313 amino acids) was detected, that reacted with 38 kDa protein localized in the cytoplasm of tachyzoites<sup>[400,401]</sup>. Ahn *et al*<sup>[402]</sup> demonstrated that mAb Tg621 bind ribosomal P protein (RPP) of *T. gondii* (TgRPP), and the expressed and purified TgRPP assayed in western blot with the sera of patients with toxoplasmosis resulted in the 74% of positive reactions as compared with 8% in control individuals. The antibody formation against TgRPP in those patients was therefore regarded as specific and suggested a potential autoantibody<sup>[402]</sup>. Because of quite frequent significant similarities between the expressed sequence tags of *T. gondii* tachyzoite clones (and probably also bradyzoite clones) and human ribosomal proteins (**Table 14**), it seems that chronic toxoplasmosis is at least in part responsible for the increased production of anti-Rib-P autoantibodies in patients with SLE. The worldwide dissemination of the parasite, the fact that these autoantibodies are present in a masked state also in healthy individuals<sup>[396,397]</sup>, and the findings that they bind to T lymphocytes<sup>[403]</sup> and other human cells<sup>[404]</sup>, and penetrate into live hepatic cells causing cellular dysfunction in culture<sup>[405]</sup>, may support this suggestion.

Several authors reported an association of anti-Rib-P with neuropsychiatric manifestations of SLE<sup>[406-409]</sup>, in particular psychotic depression<sup>[386,388,410]</sup>. It must be emphasized that an increasing body of evidence suggested a significant relationship between *T. gondii* infection and development of mood disorders<sup>[411-413]</sup>. Moreover, damage of the olfactory system associated with smell defects in patients with many neurodegenerative diseases<sup>[414]</sup> and/or autoimmune disturbances including SLE and MS, was probably due to *T. gondii* infection<sup>[93,97,98,101,143,415]</sup>. Thus, it seems that chronic toxoplasmosis strongly participates in the generation of anti-Rib-P autoantibodies and development of neuropsychiatric manifestations in several ADs.

## HYPERPROLACTINEMIA (HPRL) IN ADs MAY REFLECT THE HOST DEFENSE AGAINST *T. GONDII* INFECTION

**Several antipsychotic medications induce HPRL and have antitoxoplasmatic activity**

### Prolactin, HPRL and ADs

Prolactin (PRL) is a hormone produced by the pituitary, the decidua, the myometrium, the mammary gland and leukocytes<sup>[416]</sup>. PRL regulates the differentiation of secretory glands, including the mammary gland, ovary, prostate, submaxillary and lacrimal glands, liver, and pancreas, as well as proliferation in different cell types, such as mammary epithelium, astrocytes, adipocytes, pancreatic beta cells, and T lymphocytes<sup>[417,418]</sup>.

PRL acts as an immunomodulator which may interfere with lymphocyte activation and cytokine production<sup>[419-421]</sup>. Activation of T lymphocytes mediated by the interaction of PRL, PRL-R, JAK2/STAT5 pathways led to generation and release of several cytokines including IL-1, IL-4, IL-5, IL-6, IL-10, IFN- $\alpha$ , which stimulate activated B cells to proliferate and differentiate<sup>[422,423]</sup>. In human T cells obtained from blood of healthy people, PRL in physiological concentrations significantly increased TNF- $\alpha$  and IFN- $\gamma$  producing CD4<sup>+</sup> and CD8<sup>+</sup> cells and IL-2 producing CD8<sup>+</sup> cells<sup>[424]</sup>.

Brand *et al*<sup>[421]</sup> showed that PRL at physiological concentrations during pregnancy, anesthesia and medication, selectively and significantly enhanced IL-12 and TNF- $\alpha$  synthesis *via* NF- $\kappa$ B and interferon regulatory factor-1, at LPS-stimulated human immune cell cultures, in a dose-dependent manner. It was suggested that PRL at these elevated concentrations may strongly initiate an immune response, and then antigen-presenting cells may abnormally stimulate an immune response, finally leading to autoimmune reactivity<sup>[421]</sup>. In humans, HPRL was associated with abnormalities in T-cell function and phenotype, abnormal T-cell proliferation<sup>[425,426]</sup>, inhibition of NK cells<sup>[427]</sup>, decreased neutrophil chemotaxis<sup>[428]</sup>, and increased activity of antigen-presenting cells<sup>[429]</sup>. Importantly, at high concentrations, PRL may inhibit the proinflammatory activation of T helper cells<sup>[430]</sup>.

PRL has been shown to stimulate T and B cells<sup>[431,432]</sup>, NK cells, macrophages, neutrophils, CD34<sup>+</sup> hematopoietic cells, and antigen-presenting DCs<sup>[418,433,434]</sup>. The hormone promoted proliferation in T lymphocytes, protected against apoptosis, and enhanced cell survival<sup>[417,418,435]</sup>.

PRL generation was stimulated *in vitro* by the cytokines IL-2 and IL-6, and inhibited by IL-1<sup>[436-438]</sup>. PRL appeared to be necessary for IL-2 receptor expression and T-cell proliferation<sup>[431]</sup>, and may also modulate B-cell expansion<sup>[432]</sup>. On the other hand, it was established that in T lymphocytes both IL-2 and IL-4 reduced PRL mRNA levels to 25 and 28% of control values, respectively, while IL-1 $\beta$  decreased PRL mRNA levels to 58% of control values<sup>[416]</sup>.

PRL receptors are present in a wide range of peripheral cells of the immune system including T and B lymphocytes, NK cells, and intestinal epithelial cells<sup>[421,439,440]</sup>. The PRL receptor, a member of the cytokine receptor superfamily, including IL-2, IL-2 and IFN receptors, was found on lymphocytes, monocytes, neutrophils, NK cells, and thymic epithelial cells<sup>[439,440]</sup>.

HPRL was demonstrated in various ADs, particularly in SLE, MS, SS and Sjögren's syndrome<sup>[441]</sup> (**Table 15**). HPRL is also a common finding among patients with psychiatric disease, and antipsychotic drugs-induced HPRL occurs overall in up to 70% of patients with schizophrenia, depending on the medication used<sup>[443-445]</sup>. All antipsychotic drugs block dopamine D<sub>2</sub> receptors and thus delete the inhibitory effect of dopamine on PRL secretion<sup>[446]</sup>. Boerrigter *et al*<sup>[447]</sup> in 165 patients with schizophrenia or schizoaffective disorder found an overall decrease in the antiinflammatory IL-2 mRNA levels in serum ( $p < 0.006$ ) and an increase in cytokines IL-6 ( $p = 0.01$ ), IL-8 ( $p = 0.024$ ) and TNF- $\alpha$  ( $p < 0.001$ ) compared to healthy controls.

Haga & Rygh<sup>[448]</sup> established that patients with primary SS had moderately increased serum PRL levels compared with matched controls (271.5 vs. 205.9 mIU/L;  $p < 0.02$ ), especially evident in those diagnosed before the age of 45 yrs and with active disease. Interestingly, these authors suggested that the disease may be preceded by HPRL for many years<sup>[448]</sup>. This recommendation is in line with the recent findings that *T. gondii* infection may participate in development of this clinical entity<sup>[98,99]</sup>.

In several ADs the level of cortisol was found to be subnormal. The reduced corticosteroid concentration had a permissive effect in

**Table 14** Significant matches of *T. gondii* (RH strain tachyzoite-derived cDNAs) expressed sequence tags (ESTs) with database sequences from human ribosomal proteins (acc. to Wan *et al* [399]; with own modification).

<i>T. gondii</i> clones	Human ribosomal protein identification	Accession	Length	%ID	Score
Tga024	S3a	sp: P33433	88	60	276
Tgb073	S16	sp: P17008	105	64	338
Tgc038	S16	sp: P17008	69	62	214
Tgc059	S23	sp: P39028	89	84	390
Tgc084	S26	sp: Q06722	99	61	312
Tgd029	S27a	pir: A22632	95	43	193
Tga093	S30	sp: Q05472	42	80	177
Tgd011	L7a	sp: P12970	115	51	310
Tgb056	L8	sp: P25120	40	31	171
Tga025	L38	sp: P23411	32	68	121

*T. gondii* cDNA clones of ESTs with significant BLAST score are listed with the corresponding putative identification, organism, database accession, length and percent identity of the match. Match lengths are in amino acid residues. Databases are SwissProt (sp) and Protein Information Resource (pir). It must be noted that mitochondrial genes of the parasite tachyzoite cDNA clones of NADH-ubiquinone oxidoreductase (Tga067) and cytochrome b (Tgb097) showed 94% similarity with human mitochondrial genes [399].

**Table 15** ADs associated with HPRL (acc. to Orbach & Shoenfeld [442]).

Multi-organ diseases	Organ specific diseases
Systemic lupus erythematosus	Diabetes mellitus type 1
Rheumatoid arthritis	Graves' disease
Systemic sclerosis	Hashimoto's thyroiditis
Sjögren's syndrome	Addison's disease
Reactive arthritis	Lymphocytic hypophysitis
	Celiac disease
	Multiple sclerosis
	Uveitis
	Rejection of heart transplantation

development of these clinical entities because increased PRL level may enhance immune response in patients with low cortisone levels and corticosteroids antagonize the stimulatory effect of PRL<sup>[442,449]</sup>.

**Tables 15 and 16** summarized the organ specific and multi-organ ADs associated with HPRL, and associations of HPRL with various ADs activities.

Studies of patients with HPRL of various etiologies have suggested an increased generation rate of several autoantibodies, including antinuclear and/or antithyroid antibodies, anticardiolipins, anti-dsDNA, anti-Ro, without clinical evidence of autoimmune disease<sup>[422,478-480]</sup>. PRL induced immunoglobulin synthesis and generation of anti-dsDNA by normal and SLE lymphocytes<sup>[481]</sup>. After PRL stimulation spontaneous IgG production of SLE peripheral blood mononuclear cells was markedly enhanced compared to that in healthy controls, and the physiological concentration of PRL (20 ng/mL) induced IgG production more effectively than PRL at 100 ng/mL<sup>[482]</sup>.

#### Medications and HPRL

Several drugs may cause HPRL, including antipsychotics, antidepressants, opiates and cocaine, antihypertensive medications (verapamil, methyl dopa, reserpine), gastrointestinal agents (metoclopramide, domperidone, cimetidine, ranitidine), and estrogens<sup>[441]</sup> (**Table 17**).

Perkins<sup>[485]</sup> found that risperidone (mean dose 4-7.6 mg/day) was associated with the greatest elevation of plasma PRL levels after 4-8 weeks of treatment as compared with haloperidol (5-12.9 mg/

**Table 16** Autoimmune disease activities associated with HPRL (acc. to Shelly *et al* [450]; with own modification).

Disease	Association of HPRL with disease activity	Refs
SLE (HPRL in 15-33% of the patients)	HPRL was related to neurological, renal, and hematological involvement, serositis, anti-double stranded DNA, and hypocomplementemia	[451-454]
Rheumatoid arthritis	HPRL was found in children with ANA seropositive JRA	[455-459]
Sjögren's syndrome (HPRL in 3.6-45.5% of the patients)	HPRL was not associated with hormonal status but rather reflects disease pathology	[460]
Systemic sclerosis	PRL-receptors and S100A6 protein were detected in these patients	[461-473]
Multiple sclerosis (HPRL in 30% of the patients)	PRL level was found to be related to the secondary-progressive type of disease	[464]
Thyroid diseases	To be further investigated in large studies	[465]
Chronic hepatitis C (HPRL in 10.1% of the patients)	There was an association between HPRL and the infection with HCV genotype 3 ( $p < 0.01$ ).	[466]
Celiac disease	PRL may play a part in immune modulation in the intestinal damage of the disease	[467,468]
Uveitis	Not correlating	[469,470]
Peripartum cardiomyopathy	Present	[471-473]
Behçet's disease	Possible role in expression and pathogenesis of the disease	[474,475]
Psoriasis vulgaris	HPRL may have a role in the pathogenesis of this disease, and in the hyperproliferation of keratinocytes	[476,477]

ANA, antinuclear antibody; JRA, juvenile rheumatoid arthritis.

**Table 17** Effects of psychotropic drugs on serum PRL levels (acc. to Molitch [441]; with own modification).

	Medications	Increase in PRL <sup>a</sup>
Antipsychotics	Typical	
	Phenothiazines (chlorpromazine, fluphenazine, thioridazine)	+++
	Butyrophenones (haloperidol)	+++
	Thioxanthenes (thiothixene)	+++
	Atypical	
	Risperidone	+++
	Molindone	++
	Quetiapine	+
Antidepressants	Tricyclics	
	Amitriptyline	+
	Desipramine	+
	Clomipramine	+++
	Monoamine oxidase inhibitors	
	Pargyline	+++
	Clorgyline	+++

<sup>a</sup> +, PRL increase to abnormal levels in small percentage of patients; ++, increase to abnormal levels in 25% to 50% of patients; +++, increase to abnormal levels in more than 50% of patients. Interestingly, in one study the use of 1,25-dihydroxyvitamin D3 for 7 days caused serum PRL levels to double in five healthy men [483]. On the other hand, lithium carbonate (a drug used in schizophrenia and schizoaffective disorders) appeared to decrease PRL levels by about 40% [484].

day; almost 100 ng/mL end point PRL concn), olanzapine (10-17.5; approximately 30 ng/mL), ziprasidone (160 mg/day), quetiapine (307 mg/day), and aripiprazole (30 mg/day), which caused the smallest increase (nearly 10 ng/mL)<sup>[485]</sup>.

It appeared that several other groups of medicaments also caused HPRL, including prokinetic drugs (metoclopramide, domperidone), antihypertensive (reserpine, verapamil, alpha-methyl dopa), opiates (morphine), H<sub>2</sub>-receptor antagonists (cimetidine, ranitidine), anticonvulsive drugs, estrogens, cholinomimetics. In addition, HPRL has been demonstrated during conditioning and after blood stem-cell transplantation, as well as following blood marrow transplantation<sup>[486]</sup>, and it must be noted that *T. gondii* infection has frequently been detected in such patients<sup>[487-490]</sup>.

### *T. gondii* infection and PRL.

**PRL bound to the parasite tachyzoites impairs the process of their adhesion and penetration into the host cells, as well as the replication abilities**

PRL stimulated T cell proliferation<sup>[491]</sup> and the release of

proinflammatory cytokines, which efficiently control the course of *T. gondii* infection<sup>[492-494]</sup>. The action of PRL may thus be bidirectional, *i.e.* the hormone may limit the proliferation of the parasite *via* surface host cell receptors and increased release of various protective cytokines, and *via* *Toxoplasma* tachyzoites by inhibiting their ability for penetration of the host cell<sup>[495]</sup>.

PRL was capable of inhibiting multiplication of *T. gondii* in murine microglial cell cultures<sup>[493]</sup>, and restricted intracellular growth of the parasite in mice and human cell lines<sup>[495,496]</sup>. Dzitko *et al*<sup>[495]</sup> demonstrated that *in vitro* preincubation of *T. gondii* BK strain (type I) tachyzoites with recombinant human PRL (rhPRL) caused a significant decrease in the replication of tachyzoites in one murine (L929) and two human (HeLa and Hs27) cell lines (**Table 18**).

Moreover, it was reported that serum human PRL was bound to live RH tachyzoites (type I) and ME49 (type II) strains in a specific way and the binding was concentration-dependent<sup>[497]</sup>. Inhibitory effect of the hormone on the parasite proliferation has been found in the peripheral blood mononuclear cells from patients with HPRL<sup>[496]</sup>. It was also demonstrated that women with HPRL had lower *T. gondii* seroprevalence<sup>[498]</sup>. The physiological increase in serum PRL levels during pregnancy may thus markedly reduce the risk of the parasite proliferation in the expecting mother and its transfer to the fetus<sup>[496]</sup>. Dzitko *et al*<sup>[495]</sup> found that rhPRL did not exert any cytotoxic effect toward the parasite or host cells, and suggested that PRL may affect *T. gondii* adhesion to the host cells and penetration of parasites into the host cells as demonstrated by the reduced number of infected cells<sup>[495,498]</sup>. It must be noted that women with HPRL had lower anti-*T. gondii* IgG seroprevalence than those with normal PRL level (33.9% and 45.58%, respectively;  $p < 0.025$ )<sup>[498]</sup>. It appeared that in the group of women with high PRL serum level (*i.e.* > 86 ng/mL) seroprevalence (12.5%) was markedly lower ( $p < 0.004$ ) than in the controls, and this finding suggested that HPRL may be an important factor preventing *T. gondii* infection in women<sup>[498]</sup>. Recently, it was reported that sheep PRL binds to live tachyzoites of RH (type I) and ME49 (type II) strains<sup>[497]</sup>. Dzitko *et al*<sup>[497]</sup> demonstrated the high similarity of two PRL receptor domain regions (2-37 aa and 127-162 aa) with some *T. gondii* proteins (42% and 37% of amino acid identities, respectively, suggesting that certain proteins of the parasite may function as PRL receptors. Thus, the PRL bound to the parasite may affect the process of adhesion and then effective parasite's penetration of the host cell.

In 1953, the large study of Kozar<sup>[499]</sup> performed in Poland was

first to show that the patients with schizophrenia had a significantly higher positive antibody skin test against *T. gondii* compared with healthy controls (52% vs. 25%;  $p < 0.0001$ ;  $n = 495/961$  vs. 170/681, respectively). Further investigations confirmed that the parasite may be responsible for the development of this clinical entity<sup>[500-503]</sup>. It must be emphasized that several medications successfully used in the treatment of various neurological and psychiatric disorders, including schizophrenia and epilepsy, showed to have antitoxoplasmatic activity in cell culture (Table 19).

It seems that the elevation of serum PRL concentration plays an important role in modulating the host defense reaction against *T. gondii* infection<sup>[492,493]</sup>. This notion is consistent with the findings that PRL and TNF- $\alpha$  upregulated expression of intracellular adhesion molecule -1 and production of endogenous IL-6 (this cytokine plays a dual role in  $T_H1/T_H2$  differentiation<sup>[511]</sup> and enhances *T. gondii* intracellular replication<sup>[208]</sup>) and IL-3 by microglia<sup>[493,512]</sup>. In addition, PRL increased indoleamine 2,3-dioxygenase (IDO) expression in CD14<sup>+</sup> cells<sup>[513]</sup> and peripheral monocytes<sup>[514]</sup>, the mechanisms that enhances antitoxoplasmatic activity and/or impairs defense of the parasite<sup>[515-519]</sup>. The hormone also stimulated IFN- $\gamma$  and other  $T_H1$ -type cytokine production during *T. gondii* infections<sup>[520]</sup>, thus probably reflecting the host's vigorous defense against the parasite. Subsequent finding that the women with HPRL had markedly lower seroprevalence of *T. gondii* antibodies than those with normal PRL levels (33.9 vs. 45.58%,  $p < 0.025$ )<sup>[498]</sup> strongly supported this suggestion.

IgG antiendothelial cell antibodies (AECA) have been reported in sera from patients with various systemic autoimmune-inflammatory diseases, including SLE and vasculitis<sup>[521]</sup>. Krause *et al*<sup>[522]</sup> found elevated presence of microvascular and macrovascular AECA in the sera from 19/25 (76%) women with HPRL, as well as increased titers of anticardiolipin and low levels of anti-dsDNA antibodies. Interestingly, inhibition studies showed that the affinity purified AECAs bound the endothelial cell antigens in a dose-dependent manner. Although none of the studied patients had clinical manifestations of autoimmune disease, the presence of autoantibodies suggested that they may represent an increased risk for development of these entities<sup>[521,522]</sup>. It should be emphasized that vascular endothelial cells are particularly susceptible to infection with *T. gondii* tachyzoites, and their intracellular division rate is rapid<sup>[268]</sup>. The parasite adhesion to vascular endothelium was observed even during disturbed blood flow characteristic for atherosclerosis<sup>[523-525]</sup>.

## T. GONDII CHRONIC INFECTION-INDUCED CYTOTOXIC T LYMPHOCYTE EXHAUSTION LEADS TO DEVELOPMENT OF ADs BECAUSE OF DECREASED FUNCTIONALITY, INCLUDING PROLIFERATIVE CAPACITY, CYTOKINE PRODUCTION, CYTOTOXIC CAPABILITY AND METABOLIC DEFICIENCY

### Induction of exhaustion may however also reflect a host cell defense reaction in autoimmune and inflammatory diseases

Mutually overlapping immunosuppressive effects caused by concomitant intracellular *T. gondii* and chronic viral infections play a key role in development and persistence of several ADs mainly via pathogen/host protein mimicry<sup>[93,98,378,526,527]</sup>. Chronic *T. gondii* infection exerts also a stimulating effect on the host immune control of viral infections in patients with ADs and *vice versa*<sup>[528-530]</sup>. The

**Table 18** Inhibition of the *in vitro* proliferation rate (%) of *T. gondii* BK strain (type I) tachyzoites pre-incubated with the rhPRL before infection of the murine L929 and human HeLa and Hs27 cells (treatment before infection) (acc. to Dzitko *et al* [495]; with own modification).

rhPRL (ng/mL)	Pre-incubation time (min)			
	0	30	60	180
<b>L929 cells</b>				
2	1.38 $\uparrow$ $\pm$ 8.88	4.03 $\pm$ 5.26	2.41 $\pm$ 8.48	3.88 $\pm$ 10.88
5	5.24 $\uparrow$ $\pm$ 4.09	12.37 $\pm$ 9.50	8.98 $\pm$ 8.83	7.39 $\pm$ 8.76
20	9.72 $\pm$ 8.47	19.87* $\pm$ 4.28	19.66** $\pm$ 5.73	26.76** $\pm$ 3.02
100	9.57 $\pm$ 9.84	23.66* $\pm$ 10.99	25.53** $\pm$ 3.19	27.00** $\pm$ 2.50
<b>HeLa cells</b>				
2	3.02 $\pm$ 6.94	9.46 $\pm$ 5.74	3.48 $\pm$ 10.72	3.91 $\pm$ 7.02
5	0.83 $\uparrow$ $\pm$ 7.07	8.76 $\pm$ 7.68	7.47 $\pm$ 4.94	8.66 $\pm$ 5.53
20	3.53 $\pm$ 7.20	20.81** $\pm$ 4.21	19.05** $\pm$ 2.63	21.14** $\pm$ 5.62
100	6.32 $\pm$ 4.44	21.93** $\pm$ 5.48	23.01** $\pm$ 5.93	36.15** $\pm$ 11.53
<b>Hs27 cells</b>				
2	1.76 $\pm$ 3.59	1.09 $\pm$ 5.23	2.22 $\pm$ 3.48	4.80 $\pm$ 5.87
5	0.50 $\pm$ 6.06	2.37 $\pm$ 7.01	4.66 $\pm$ 5.32	3.48 $\pm$ 4.23
20	2.07 $\pm$ 3.69	23.05** $\pm$ 4.97	27.71** $\pm$ 7.42	29.64** $\pm$ 6.23
100	10.60 $\pm$ 2.36	31.74** $\pm$ 5.79	31.71** $\pm$ 7.06	32.12** $\pm$ 3.53

The results from 12 evaluations were shown as a percentage of replication intensity as compared to the control lacking rhPRL (100%)  $\pm$  SD).  $\uparrow$ , increased intensity of the parasite proliferation. \*  $p < 0.05$ , \*\*  $p < 0.01$ . rhPRL, recombinant human PRL.

**Table 19** Drugs tested for *in vitro* activity against *T. gondii* (acc. to Jones-Brando *et al* [504]; with own modification).

Drug	Solvent	ID <sub>50</sub> <sup>a</sup> ( $\mu$ g/mL)	TD <sub>50</sub> <sup>b</sup> ( $\mu$ g/mL)	TI <sup>c</sup>
Valproic acid	ethanol	4.5	62.4	13.9
Sodium valproate	ethanol	4.1	52	12.7
Carbamazepine	ethanol	72	100	1.3
Lithium carbonate	1 N HCl	> 100	> 100	
Haloperidol	ethanol	5.6	103	18.4
9-OH-Risperidone	tartaric acid	20.1	134	6.7
Risperidone	tartaric acid	74	129	1.7
Fluphenazine HCl	Toxo CGM	3.5	17.9	5.1
Clozapine	ethanol	5.8	20	3.4
Olanzapine	DMSO	33.2	100	3
Chlorpromazine HCl	DMSO	2.6	6	2.3
Quetiapine fumarate	DMSO	18.6	33	1.8
Trimethoprim	DMSO	5.3	63.8	12.1

<sup>a</sup> Median inhibitory dose, a measure of tachyzoite inhibition. <sup>b</sup> Median toxicity dose, a measure of cytotoxicity. <sup>c</sup> Therapeutic index, a measure of efficacy determined by TD<sub>50</sub>/ID<sub>50</sub> ratio. DMSO, dimethylsulfoxide; Toxo CGM, *Toxoplasma* cell growth medium. Valproic acid at a concentration of 1 mg/mL inhibited 7% of the tachyzoites and trimethoprim at 3.2 mg/mL produced 2% inhibition, but the combination of these two compounds at those concentrations resulted in a potentiating effect inhibiting 55% of the tachyzoites. Fond *et al* [505] reported that also other antipsychotic drugs, such as amisulpride, cyamemazine, levopromazine, loxapine, tiapride and zuclopenthixol *in vitro* exerted antitoxoplasmatic activity in the range of 0.19 to 1  $\mu$ M concentrations. The 50% inhibitory concentration (IC<sub>50</sub>) for the last preparation was 8  $\pm$  1.8  $\mu$ M while its serum levels varied from 0.01-0.12  $\mu$ M [506], but antipsychotic drugs usually achieve much higher and persistent concentrations in the brain tissue [507]. In human fibroblast cell cultures, IC<sub>50</sub> for fluphenazine, thioridazine, and trifluoperazine against developing tachyzoites of the parasite RH strain was 1.7, 1.2 and 3.8  $\mu$ M, respectively [508]. Recently, Murata *et al* [509] found that *in vitro* hydroxyzine (an antihistamine and anxiolytic compound) reduced parasite replication (IC<sub>50</sub> value for *T. gondii* tachyzoites was 1.0 mM) and had no effect on host cell viability. Importantly, the drug also reduced the number of *in vitro*-induced bradyzoites [509], and it should be noted that bradyzoites within mature tissue cysts are dynamic and replicating entities *in vivo* [510].

**Table 20** Specific *T. gondii* molecules that manipulate host innate immunity responses (acc. to Pollard *et al* [531]; with own modification).

<i>T. gondii</i> molecule	Host target	Effect in host	Refs
Profilin	TLR11	IL-12 production through MyD88	[532,533]
GPI	TLR2 and TLR4 <sup>a</sup>	Induction of TNF- $\alpha$ through NF- $\kappa$ B	[89,534]
Cyclophilin	CCR5	IL-12 generation through CCR5	[535]
Lipoxygenase	Unknown	Downregulation of CCR5; decrease in IL-12	[535]
ROP16	Unknown	<i>T. gondii</i> type I and type II strains induce STAT3/6; decrease in IL-12	[536]
ROP18	Unknown	Infections by strains carrying type I and type II allele results in increased mortality	[537-539]
HSP70	Unknown	Can inhibit NF- $\kappa$ B nuclear translocation and iNOS	[540]

TLR, Toll-like receptor (TLRs are important for the recognition of intracellular pathogens and protection of the host because binding of a ligand to its TLR stimulates proinflammatory activity). <sup>a</sup> TLR2 and TLR4 play a pivotal role in the development of ADs [541]; *T. gondii* inhibits TLR4 ligand-induced mobilization of intracellular TNF- $\alpha$  to the surface of neutrophils infected with the parasite, thus revealing an immunosuppressive activity [534]; The parasite hijacks STAT3 signaling, and IL-10/STAT3 signaling cascade is a crucial pathway involved in controlling IL-12 and TNF [542]. MyD88, myeloid differentiation factor 88, an adaptor molecule; GPI, glycosylphosphatidylinositol; HSP70, heat shock protein 70; iNOS, inducible NO synthase; ROP, *T. gondii* rhoptry proteins excreted during parasite invasion to host cells; CCR5, a transmembrane receptor expressed by multiple cell types including DCs that transmit signals through G-like proteins [535].

parasite exploits multiple strategies to downregulate the host's defense responses, including subverting intracellular signaling pathways in infected cells to evade immunity<sup>[9]</sup>. *T. gondii* manipulate the expression levels of key host microRNAs<sup>[93,527]</sup> to favor its own growth while avoiding immune control, in order to survive and proliferate. Several parasite biomolecules that stimulate or manipulate host immune responses and their effects on various host cell functions are presented in **Table 20**<sup>[531]</sup>.

*T. gondii* manipulate immune system favoring T<sub>H</sub>2 lymphocyte reactions over T<sub>H</sub>1 responses in the host<sup>[535,543]</sup>, and therefore may exert at the same time a triggering and a protective role in several ADs. The pathogen triggers the secretion of antiinflammatory cytokines, such as IL-10 and TGF- $\beta$  thereby suppressing development of the T<sub>H</sub>1 immune responses and deactivating macrophages<sup>[544-548]</sup>. Another pathomechanism that the parasite uses to suppress host immunity is the induction of apoptosis in selected cell lineages. It was found that following *T. gondii* invasion, CD4<sup>+</sup> splenocytes underwent programmed cell death. Fas-FasL interaction has been implicated in this process as demonstrated for apoptosis of Peyer's patch T cells in perorally infected mice<sup>[549,550]</sup>. Similarly, the microbe caused induction of apoptosis in monocytes<sup>[551]</sup>.

During chronic infection, *T. gondii* has evolved several strategies to avoid or to interfere with potentially efficient antiparasitic immune responses of the host. Such immune evasion included: a) altering the expression and secretion of immunomodulatory cytokines or by altering the viability of immune cells, and b) interference with intracellular signaling cascades, thereby abolishing a number of antimicrobial effector mechanisms of the host<sup>[552]</sup> (**Table 21**).

Infection of different host cell types from humans and mice with *T. gondii* blocks apoptosis induced by diverse proapoptotic stimuli<sup>[552]</sup> (**Table 22**).

## CONCOMITANT VIRAL AND *T. GONDII* INFECTIONS MODULATE INFLAMMATORY RESPONSES AND AFFECT CLINICAL OUTCOME OF ADs

### Important role of CD4<sup>+</sup> and CD8<sup>+</sup> T cell immune exhaustion during persistent infections

Recent estimates suggest that during lifetime approximately 8-12 chronic infections are harboring in each of us and comprise what is referred to as our virome. Several viruses, such as HIV, hepatitis B or C viruses (HBV, HCV), Epstein-Barr virus, cytomegalovirus,

papilloma virus, and adenovirus can negatively impact human health by causing chronic disease and establishing latency (HIV, EBV, CMV, papilloma virus)<sup>[587]</sup>.

Normal T cell immune response against intracellular microbes exhibits polyfunctionality, rapid proliferative potential, and low apoptosis<sup>[588]</sup>. During acute infections, T cells clear the pathogen, ultimately leading to the development of robust antigen-independent memory T cells characterized by the ability to mount rapid recall response and reactivate functional effector mechanisms upon antigen re-exposure<sup>[589]</sup>. In contrast, during the chronic stage, antigen-specific T cells become functionally impaired and even get physically deleted<sup>[590]</sup>. Persistence of antigen-specific T cells exhibiting impaired effector functions, poor recall response and suboptimal antigen-independent homeostatic proliferation is referred to as exhaustion. In various chronic viral models of infection such as lymphocytic choriomeningitis virus (LCMV), HBV, HCV, it has been demonstrated that CD8 T cells gradually lose their function, and finally become exhausted<sup>[588]</sup>.

Acute exposure to foreign antigen results in persistent antigen-specific cellular immunity, but during chronic viral infection persistent antigen exposure may exhaust that response<sup>[591]</sup>. This exhausted CD8 T-cell phenotype may itself be defined by a distinct transcriptional signature, and signatures of CD4 T-cell help and CD8 exhaustion predict clinical outcome in autoimmunity<sup>[591,592]</sup>. It must be noted that T cells maintain an exhausted phenotype also after antigen withdrawal and population reexpansion<sup>[593]</sup>. McKinney *et al*<sup>[591,592]</sup> showed that the same signature found in chronic viral infection can be seen in chronic self-antigen exposure during autoimmunity, with one exception: whereas exhaustion results in viral persistence it predicts favorable outcome in autoimmunity. These authors demonstrated that the CD8 exhaustion signature in autoimmunity is inversely correlated with that of concurrent CD4 help and can be robustly identified in mixed cell population<sup>[591,592]</sup>.

Multiple factors such as antigen load, duration of infection, CD help, regulatory T cells, and type of antigen presenting cell affect the intensity of CD8 T cell exhaustion<sup>[594,595]</sup>. The occurrence of T cell exhaustion in viral models has been associated with concomitant high viral load and persistent antigen levels, loss of CD4<sup>+</sup> T-cell help, suppressive cytokines IL-10 and TGF- $\beta$ , and DCs as well as Treg cells that are the major sources of the immunosuppressive cytokines IL-10 and TGF- $\beta$ <sup>[589,596,597]</sup> (**Table 23**). In contrast, chronic parasite infections are characterized by lower pathogen burden usually restricted to tissues, suggesting alternative driving forces in the induction of T cell exhaustion, such as for example parasite

**Table 21.** Downregulation of cell-mediated immune responses after infection with *T. gondii* (acc. to Lang *et al* [552]; with own modification).

Evasion strategy	Consequence(s)	Molecular mechanism(s)	Parasite effect	Refs
Induction of IL-10	Decreased T <sub>H</sub> 1 response;		Indirect	[540,553]
	Deactivation of macrophages	Independent of PGE <sub>2</sub>	Indirect	
Induction of TGF- $\beta$	Reduced TNF- $\alpha$ production by macrophages; reduced IFN- $\gamma$ production by NK cells	Antagonizes IL-12	Indirect	[545,547,554]
IFN- $\alpha$ / $\beta$ upregulation	Reduced IFN- $\gamma$ levels and splenocyte proliferation		Indirect	[555]
Inhibition of TNF- $\alpha$ and IL-12 production	Deactivation of macrophages; inhibition of T <sub>H</sub> 1 responses	Reduced phosphorylation of p65/RelA; defective nuclear import of NF- $\kappa$ B; IL-10-independent STAT3 phosphorylation	Direct	[543, 556-559]
Decreased IL-12 production by DCs <sup>a</sup>	Inhibition of T <sub>H</sub> 1 responses	LXA <sub>4</sub> -mediated downregulation of CCR5	Indirect	[548,560]
Blockade of MHC class II upregulation	Defective antigen presentation to CD4 <sup>+</sup> T cells	Reduced activity of CIITA and IRF-1 promoters	Direct	[561-563]
Inhibition of NO production	Defective antiparasitic activity	Inhibition of iNOS transcription	Direct	[564,565]
Inhibition of NO production in microglia	Reduced antiparasitic activity	Secretion of PGE <sub>2</sub> , IL-10 and TGF- $\beta$	Indirect	[566,567]
Inhibition of p47 GTPases		Reduced transcription		[568]
Significant suppression of IL-2, IFN- $\gamma$ (but not IL-10). Markedly lower levels of IgG1, IgG2a, IgG2b, IgG3, IgA, IgM	Suppressed cytokine and immunoglobulin secretions by murine splenic lymphocytes		Indirect	[569]

CIITA, master regulator of major histocompatibility complex class II transcription; CCR5, CC chemokine receptor; DCs, dendritic cells; iNOS, inducible nitric oxide synthase; IRF-1, interferon regulatory factor-1; LXA<sub>4</sub>, lipoxin A<sub>4</sub>; MHC, major histocompatibility complex molecules; PGE<sub>2</sub>, prostaglandin E<sub>2</sub>; TGF- $\beta$ , transforming growth factor- $\beta$ . <sup>a</sup>*T. gondii* preferentially invades immature CD8 $\alpha^+$  DCs, failing to activate them in the process, and rendering them insensitive to subsequent activation by TRL ligands or CD40L signal [557]. Proliferation of *T. gondii* in inflammatory macrophages was associated with diminished ROS production in host cells [570]. In young children with congenital toxoplasmosis specific T cell response to the parasite antigens was impaired and such hyporesponsiveness has been restored during childhood. The acquisition of functional T cell response was disease-unrelated and indistinguishable in terms of strength, epitope specificity, and cytokine profile from the corresponding responses in immunocompetent adults with asymptomatic acquired *T. gondii* infection [571]. In pregnant mice, *T. gondii* infection caused a decrease of CD4<sup>+</sup>CD25<sup>+</sup>-regulatory T cells [572].

**Table 22** Suppression of immune responses to *T. gondii* by parasite-triggered modulation of host cell apoptosis (acc. to Lang *et al* [552]; with own modification).

Evasion strategy	Consequence(s)	Molecular mechanism(s)	Parasite effect	Refs
Apoptosis of CD4 <sup>+</sup> cells	T-cell unresponsiveness	Cell death by neglect	Indirect	[549]
Apoptosis of leukocytes <sup>a</sup>	Unrestricted parasite replication and host death	Upregulation of Fas and FasL; TNF-dependent mechanisms	Indirect	[550,573,574]
Inhibition of apoptosis in parasite-positive cells	Blockade of host cell suicide; avoidance of CTL- and NK-mediated cytotoxicity	Inhibition of cytochrome c-release; upregulation of antiapoptotic molecules	Direct	[575-579]
		Interference with caspase activation; degradation of PARP (?)		[580]

CTL, cytotoxic T lymphocyte; Fas, receptor; FasL, Fas ligand (a cell surface molecule belonging to TNF family and death factor, which binds to its receptor Fas, thus inducing apoptosis of Fas-bearing cells); NK, natural killer cells; PARP, poly(ADP-ribose) polymerase. <sup>a</sup>*T. gondii* delayed neutrophil apoptosis by inducing granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor secretion by the parasite-infected human fibroblasts. Although neutrophils are unable to kill *T. gondii*, this can retard their division time from the usual 6-8 hrs cycle to a 24 hrs cycle and this enhanced neutrophil survival may contribute to the robust proinflammatory response elicited in the pathogen-infected host cells [581]. Interference in the normal process of apoptosis may cause some health disturbances such as ADs, neurodegenerative disorders, and cancers [582-586]. Besides the harmful effects, activation-induced cell death may serve as a mechanism for elimination of activated T cells, reducing damage to hosts [582].

encystation and latency<sup>[596]</sup>.

A chronic infection is usually caused when the host is unable to fully clear the microbe (impaired cleaning service), and this may be a result of host immune dysfunction or immune evasion by the pathogen or both<sup>[588]</sup>. During T cell exhaustion, loss of function appears to occur in a hierarchical manner: CD8 T cells undergoing exhaustion first lose the capacity for IL-2 secretion followed by marked decreases in their potential for proliferative expansion and ability to exert cytotoxic function. In extreme cases, exhausted CD8 T cells lose the capacity to secrete TNF, followed by IFN- $\gamma$ , and are ultimately deleted physically from the host<sup>[607-609]</sup>. These progressive declines in T cell activity and survival translate in to

deficiencies in pathogen control by the host<sup>[608]</sup>. Thus, CD8 T-cell exhaustion is associated with impaired clearance of chronic pathogen infection, driven both by persistence of foreign antigen(s) and by the lack of accessory “help” signals, especially during concomitant infections<sup>[591,592,610]</sup> (Tables 24-27).

T cell dysfunction that occurs during chronic viral infections is distinct from the state of T cell anergy (a condition of long-lasting, partial or total unresponsiveness contributing to peripheral T-cell tolerance)<sup>[611,612]</sup>. CD4<sup>+</sup> and CD8<sup>+</sup> anergic T cells induced by IL-10-treated human DCs displayed antigen-specific suppressor activity caused mainly by the increased surface and intracellular expression of cytotoxic T-lymphocyte antigen-4 molecule<sup>[613]</sup>. IL-10 also directly

**Table 23** Immune clearance and tolerance changes and clinical manifestations of chronic HBV-infected patients (acc. to Ye *et al* [597]; with own modification).

Status	Immunological characteristics	Immunological effects	Clinical manifestations	Refs
Immune clearance	IL-12↑↑, IL-18↑↑, IFN-γ↑, IFN-α↑, IL-10↓	Inflammatory response, cell infiltration (T cell, NK, NKT cell and monocytes), complete or partial virus deletion	Active hepatitis B, liver damage, elevated ALT level	[598-604]
Immune tolerance	IL-10↑, TGF-β↑, PD-1↑, CTLA-4↑, Treg↑	Exhaustion, apoptosis, persistent HBV replication	Low-grade inflammation, normal or low level of ALT	[598,599,604-606]

HBV, hepatitis B virus; ALT, alanine aminotransferase; PD-1, programmed cell death-1; CTLA-4, cytotoxic T-lymphocytes-associated antigen-4; Tregs, T-regulatory cells; NK, natural killer cells.

**Table 24** Differences between T cell anergy and T cell exhaustion (acc. to Rodrigues *et al* [596]; with own modification).

Unresponsive state	Differentiation state affected	Driving forces	General characteristics of the unresponsive state
T cell anergy	Naïve/Effector	Impaired antigen presentation	Impaired activation and proliferation
		Reduced costimulation	Defective differentiation and functions
		Expression of immunomodulatory molecules (IDO, CD73, CD39)	Apoptosis
		Regulatory cytokines (IL-10, TGF-β)	
T cell exhaustion	Effector	Antigen persistence, chronic activation	Progressive impairment of effector function
		Regulatory cytokines (IL-10, TGF-β)	Exhausted T cells present high and sustained expression of inhibitory molecules such as PD-1, TIM-3, and LAG-3
		Suboptimal priming (while in the naïve state)	Decreased expression of common γ chain cytokine receptor
			Apoptosis

IDO, indoleamine 2,3-dioxygenase; LAG-3, lymphocyte-activated gene-3; PD-1, programmed death-1; TIM-3, T-cell immunoglobulin, and mucin domain-containing protein-3.

**Table 25** Progressive exhaustion of CD8 T cell effector response capabilities associated with increasing viral load level and time in chronically infected host (acc. to Kahan *et al* [615]; with own modification).

CD8 T cell effector	Functional	Partial exhaustion		Severe exhaustion	
	CD4 help decreasing →	Viral load increasing →			
IL-2	++	-	-	-	-
TNF-α	+++	+/-			
IFN-γ	+++	++	+	-	-
Cytotoxicity	+++	+			
Inhibitory receptors	+	+	++	+++	+++
Proliferative potential	+++	++	+	-	-
Apoptosis	-	+/-	+/-	++	++++

inhibits CD8<sup>+</sup> T cell function by enhancing N-glycan branching to decrease antigen sensitivity<sup>[614]</sup>. One essential difference between anergy and exhaustion is the differing mechanisms of induction of these types of T cell dysfunction. Anergy is induced when T cells do not receive all the necessary signals for T cell activation, while T cell exhaustion during chronic viral infection is associated with initially normal effector differentiation followed by a progressive loss of function over time<sup>[584,592,593]</sup> (Table 24).

CD8 T cells can adapt a spectrum of exhausted states, and the levels of viral antigen and availability of CD4 T cells are key determinants of the extent of CD8 T cell exhaustion. CD4 T cells also succumb to exhaustion, which may lead to further deterioration of the antiviral CD8 T cells response<sup>[587,615]</sup>. The most severely exhausted CD8 T cells develop under conditions of high viral loads and ineffective CD4 T cell help<sup>[616]</sup>. CD8 T cell exhaustion is characterized by the gradual loss of effector capabilities, the sustained upregulation of inhibitory receptors (e.g. PD-1), and the loss of self-renewal abilities, which compromise viral control. Severely exhausted T cells may undergo apoptosis and become deleted from the chronically infected host<sup>[587,615]</sup> (Tables 24-26). T

cells dysfunction can be reversed at early stages of exhaustion, but it becomes more permanent as exhaustion progresses and the cells become more terminally differentiated<sup>[587,595]</sup>.

T cell exhaustion associated with chronic infection was initially reported in viral models as specific CD8 T cells that failed to produce cytokines<sup>[613]</sup>, and a similar pattern has been reported for chronic parasitic infections, including *T. gondii*<sup>[588,594,596,617]</sup>. *Toxoplasma* is a strong inducer of antigen-specific CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes, indicating that pathogen peptides are efficiently targeted to the appropriate cellular pathways of antigen presentation during infection<sup>[239]</sup>. Both CD4 and CD8 T cells have been reported to act synergistically to supervise *T. gondii* infection<sup>[618]</sup>, but CD8 T cells are considered pivotal for control of chronic toxoplasmosis<sup>[619]</sup>. The synergistic effect of CD4 T cells is mainly restricted to their helper role in the maintenance of a long-lived CD8 T cell response<sup>[620]</sup>. However, systemic *T. gondii* infection triggers a rapid and persistent decrease in the size and function of naïve CD4<sup>+</sup> T lymphocytes, and causes a long-term thymic atrophy and output due to destruction of the thymic epithelium<sup>[621]</sup>. Khan *et al*<sup>[549]</sup> demonstrated that activation-induced CD4<sup>+</sup> T cell transient unresponsiveness occur during acute *T. gondii* infection in mice, and may be important in immune downregulation and parasite persistence in the infected host. This immunosuppression can be induced through stimulation and production of IL-10, TGF-β, and the RNI<sup>[622,623]</sup>. IL-10 inhibits parasite killing and NO production by IFN-γ-activated macrophages<sup>[622]</sup>. Immunosuppressive activity due to RNI generation was observed particularly during the early phase of infection with the pathogen<sup>[623]</sup>. Associated with suppression of immune response was also a decrease in the production of IL-2<sup>[624]</sup> and IFN-γ<sup>[625]</sup>. In addition, acute *T. gondii* infection induced CD4<sup>+</sup> T cell apoptosis (CD4<sup>+</sup> T cells exhibited DNA fragmentation pattern) as a long-term consequence to T cells rendered anergic<sup>[549]</sup>. Manipulation of the mechanisms regulating apoptosis<sup>[626]</sup>, as well as the balance between generation of pro- and anti-inflammatory cytokines<sup>[627,628]</sup> may have direct/indirect effects on the APCs involved in processing



**Table 26** T cell functionality during acute versus chronic viral infections with some examples of CD8 virus-specific T cells (acc. to Virgin *et al* [587]; with own modification).

Acute infection	Highly polyfunctional memory T cells characteristics					
Antigen cleared. Low inflammation	IFN- $\gamma$	TNF	CTL	IL-2	Proliferative potential	Apoptosis
	+++	+++	+++	+	+++	-
Chronic infection. Antigen persists, inflammation persists	Hierarchical loss of T cell function during chronic infections					
CMV	+++	++	++/-	+/-	++	-
EBV	++	+	+	-	+	-
HIV, HCV, HBV	+/-	+/-	+/-	-	+/-	+/-
Chronic LCMV	+/-	-	-	-	-	++
Apoptotic T cell						++++

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HIV, human insufficiency virus; HCV, hepatitis C virus; HBV, hepatitis B virus; LCMV, lymphocyte choriomeningitis virus.

**Table 27** *Toxoplasma*-specific CD8<sup>+</sup> lymphocytes in the course of acute and chronic infection (acc. to Długonska & Grzybowski [636]; with own modification).

Characteristics	Acute/early chronic infection	Late chronic infection
CD8 <sup>+</sup> lymphocytes	Functional (naïve → activated)	Exhausted
Polyfunctionality degree <sup>a</sup>	High	Low
<i>T. gondii</i> antigen load	High → low	High
Recall <i>T. gondii</i> antigen reaction	High	Low
Inhibitory receptors (e.g. PD-1)	Low	High
Transcription factors (T-bet, Eomes)	Low	High
Apoptosis	Low	High

PD-1, Programmed death protein-1. T-bet and Eomes are the key transcription factors regulating NK cell maturation and function, and act as important drivers of other immune cell development and cytolytic function. <sup>a</sup> Polyfunctionality, one of the hallmarks of robust CD8 response, is the capacity of a single T cell to display multiple functions. CD8<sup>+</sup> lymphocytes simultaneously display cytotoxicity (granzym B) and enhanced generation of proinflammatory cytokines (IFN- $\gamma$ , TNF- $\alpha$ ).

and presentation of antigens from apoptotic cells, and in switching the immune system on or off<sup>[629]</sup>. Several reports confirmed that *T. gondii* infection inhibits the maturation of professional APCs<sup>[563,630]</sup>, but recently Dupont *et al*<sup>[631]</sup> suggested that, on the contrary, infection induces DC maturation, probably depending on other accessory cells present in the experiments.

Chronic parasite persistence also has a strong impact on the effector function of specific T cells, inducing their step-wise loss of cytotoxic and/or helper activities<sup>[589]</sup>. Exhausted T cells present high and sustained expression of inhibitory molecules such as PD-1, TIM-3, LAG-3, and T cell immunoglobulin<sup>[589]</sup>. It must be noted that PD-1 inhibitory receptor regulates bioenergetic insufficiencies early and late during infection, and early exhausted T cells exhibit suppressed glycolysis, oxidative phosphorylation, and mitochondrial metabolism<sup>[632]</sup>.

CD4<sup>+</sup> T-cell function is critical to sustain CD8<sup>+</sup> cytotoxic T-cell response during chronic viral infections (several months or longer to clear the infection)<sup>[633]</sup>. During chronic toxoplasmosis, CD4 dysfunction is more pronounced than CD8 T cells<sup>[619]</sup>. It should be noted that both *T. gondii*-positive men and women have markedly reduced lymphocyte B-cell counts<sup>[634]</sup>, and since B cells are regulating optimal CD4<sup>+</sup> T cell activation<sup>[635]</sup>, this abnormality may also at least in part contribute to the development of T cell exhaustion. Moreover, apoptosis of CD4<sup>+</sup> T cells caused during acute *T. gondii* infection in mice<sup>[550]</sup> may likewise participate in the exhaustion process. CD4 T cell exhaustion causes CD8 T cell dysfunction during chronic toxoplasmosis<sup>[619]</sup>, and there is strong evidence that CD8 T cell

exhaustion plays an important role in the reactivation of chronic toxoplasmosis<sup>[594,595]</sup>. During this stage of the disease, CD8 T cells exhibit progressive functional exhaustion, poor recall response, and elevated apoptosis<sup>[594,636]</sup>. Exhausted CD8 T cells are ineffective at clearing pathogens, and this therefore leads to establishment of a persistent chronic infection<sup>[637]</sup> (**Table 27**).

Two models – *T. gondii* and LCMV infections and their CD4 and CD8 T cell exhaustion inhibitory receptor profiles, as well as potential treatments are presented in **Table 28**<sup>[588]</sup>. It must be noted that LCMV infection clinically mimics both congenital toxoplasmosis and CMV infection<sup>[638]</sup>.

In summary, *T. gondii* chronic infection-induced cytotoxic T lymphocyte exhaustion leads to development of ADs because of decreased polyfunctionality, cytotoxic capability, cytokine production, proliferative capacity, and metabolic deficiency. The process of T-cell exhaustion inhibits the immune response, thus facilitating pathogen persistence. CD8 T-cell exhaustion is associated with impaired clearance of chronic pathogen infection, driven both by persistence of foreign antigen(s) and by the lack of accessory “help” signals, especially during concomitant infections. In chronic toxoplasmosis, CD4 T cell dysfunction is more pronounced than CD8 T cells. Functional exhaustion of CD8<sup>+</sup> T cells may cause reactivation of latent disease during later phases of chronic toxoplasmosis. In autoimmune processes where evidence of CD4 T-cell costimulation was pronounced, that of CD8 T-cell exhaustion was reduced, therefore induction of exhaustion may also reflect a host defense reaction. Chronic parasite infections characterized by lower pathogen burden usually restricted to tissues, suggest alternative driving forces in the induction of T cell exhaustion, such as parasite encystations. Both *T. gondii*- and viral-associated inflammatory processes may be mutually overlapping which lead to worsening or improving clinical course of ADs depending on the final temporary or stable proinflammatory/antiinflammatory cytokine constellations.

## DOWNREGULATION OF B AND NK CELLS, NEUTROPHILS AND MACROPHAGES DEFENSE RESPONSES DURING *T. GONDII* INFECTION

**A significantly lower occurrence of antibodies to persistent viral as well as *T. gondii* infections reported in patients with some ADs compared with controls may be due to suppressed (exhausted) function of host B cells**

**B cells.** These cells contribute to disease pathogenesis in autoimmunity and also play an immunomodulatory role in regulating

the immune response by secreting cytokines that inhibit disease onset and/or progression<sup>[640,641]</sup>. It was found that pathogenicity of *T. gondii* increases through B2 cell-mediated downregulation of host defense responses<sup>[642]</sup>, and Flegr & Striz<sup>[634]</sup> demonstrated that lymphocyte B-cell counts were significantly reduced in both males and females with toxoplasmosis as compared with controls.

B cells (also known as B2 cells) play a significant role in development of several ADs, including RA, SLE, vasculitis, myositis, MS, Sjögren syndrome, blistering skin disease, and chronic lymphocytic leukemia<sup>[643,644]</sup>. These cells positively regulate immune responses through antibody production and CD4<sup>+</sup> T cell activation<sup>[645]</sup>. B1 cells (a subclass of B cell lymphocytes) can generate regulatory B cells (B10 cells) that affect immune responses through the production of antiinflammatory cytokine IL-10 important in the pathophysiology of many ADs<sup>[645]</sup>. Regulatory B cells act as inhibitors of immune responses and inflammation. B cells and B10 cells balance immune responses during inflammation and autoimmunity<sup>[646]</sup>.

B cells can function as antibody-producing cells and they can also modulate immune responses through critical secretion of cytokines and chemokines, as well as antigen presentation<sup>[647-650]</sup>. B1 and marginal zone (MZ) B cells (innate-like B cells) are activated during *T. gondii* infection because they generated short-lived plasma cells providing a prompt antibody source, and also induce massive B cell response that leads to hypergammaglobulinemia with production of serum specific for the parasite and self and/or not related antigens<sup>[650]</sup>.

B cell exert suppressive functions in infectious diseases<sup>[651]</sup> because neutralizing antibody production by B cells and cytotoxic activity of CD8<sup>+</sup> T cells are well accepted components of the adaptive immune response of the host to viral infection<sup>[652]</sup>. Chen *et al*<sup>[653]</sup> demonstrated that B1 cells play an important role in host protection against *T. gondii* infection since high expression of both T<sub>H1</sub>- and T<sub>H2</sub>-type cytokines and a high level of NO production in *T. gondii*-infected B cell-deficient mice transferred with primed B1 cells. However, B cell-deficient mice have a decreased resistance to infection with the parasite despite unimpaired expression of IFN- $\gamma$ , TNF- $\alpha$ , and iNOS<sup>[654]</sup>. Moreover, B1 cells would also be implicated in the pathogenesis of toxoplasmosis through the production of antibodies against the HSP70 of *T. gondii* and IL-10<sup>[655]</sup> thus regulating susceptibility to *T. gondii* infection<sup>[656]</sup>. Because B cells can directly modulate also DC and T-cell subsets that affect adaptive immunity and the progression of infection<sup>[657]</sup>, they may play both a protective and a pathological role in the host.

The parasites have evolved unique ways to evade B cell immune responses inducing apoptosis of conventional mature B cells and MZ B cells<sup>[650]</sup>. Moreover, it was suggested that during many chronic infectious diseases, such as for instance HIV-AIDS, tuberculosis and malaria, immune activation and inflammation drive a large expansion of exhausted B cells (atypical memory B cells or tissue-like memory B cells) that contribute to deficiencies in the acquisition of humoral immunity<sup>[658]</sup>. Strickland & Sayles<sup>[659]</sup> found that *T. gondii* infected mice immunized with sheep red blood cells had a depression not only in the primary, but also in the secondary humoral immune response, since they showed less IgM and IgG splenic antibody-secreting cells than non-infected control animals. This indicate that the parasite not only affected development of the cells involved in antibody production but also disturbed an already established humoral response against other pathogens through memory B cells<sup>[650,659]</sup>. This reasoning may be supported by the significantly lower occurrence of antibodies against *T. gondii* and some other pathogens in the sera of diabetic patients compared with their family members or healthy controls, probably due to their impaired innate immune B cell

**Table 28** *T. gondii* and LCMV infections, and T cell exhaustion characteristics (acc. to Gigley *et al* [588]; with own modification).

Pathogen	CD4 exhaustion	CD8 exhaustion	Inhibitory receptors <sup>a</sup>	Treatment <sup>b</sup>
<i>T. gondii</i>	+	+	PD-1	(i) $\alpha$ PD-L1
LCMV chronic clone 13	+	+	PD-1, LAG-3, CD160, 2B4, Tim3	(i) $\alpha$ PD-L1 (ii) $\alpha$ PD-L1 + $\alpha$ LAG-3 (iii) $\alpha$ PD-L1 + Tim3-Ig

<sup>a</sup>Inhibitory receptor profile of T cells in the parasite and two different models of exhaustion. <sup>b</sup>Strategies to rescue T cell exhaustion by blocking inhibitory receptor interaction with it ligand *via* use of blocking antibodies ( $\alpha$ PD-L1,  $\alpha$ LAG3) or fusion proteins (Tim3-Ig). Interestingly, PD-1 deficient signaling as a result of PD-1 gene polymorphisms in humans has been associated with development of various ADs [639]. 2B4, a non-MHC binding receptor with multiple functions expressed on NK and CD8<sup>+</sup> T cells in mice and humans; CD160 is a membrane protein found on normal NK and T cells, which improve proliferation and cytotoxic activity in CD8 T cells. LAG-3, lymphocyte-activation gene-3; PD-L1, programmed death ligand 1; Tim3-Ig, T cell immunoglobulin and mucin domain 3.

capacity associated with persistent infections with these microbes (Table 29)<sup>[104]</sup>. These findings are also in line with the markedly lower levels of immunoglobulins IgG1, IgG2a, IgG2b, IgG3, IgA, and IgM secreted by murine splenic lymphocytes infected *in vitro* with *T. gondii* tachyzoites<sup>[572]</sup>. Moreover, low maternal anti-*Toxoplasma* IgG antibody was associated with increased offspring odds of autism<sup>[660]</sup>, and several parental ADs were correlated with ASD in offspring<sup>[661]</sup>.

Recently, Alvarado-Esquivel *et al*<sup>[662]</sup> reported a similar example of a lower frequency of anti-*T. gondii* IgG antibodies in female patients with various neurological diseases (8 of 213; 3.8%) as compared with female controls (23 of 213; 10.8%) (OR = 0.32; 95% CI: 0.14–0.73;  $p = 0.005$ ). The authors tried to explain this fact as a protective effect of the pathogen infection against neurological disturbances, or that *T. gondii* infection did not play an important role in neurological entities in the investigated population. It seems however that this finding may reflect impaired (exhausted) B cell functions due to persistent infection of the female patients with the parasite<sup>[651]</sup>. Similar markedly lower seroprevalence rates of *T. gondii* infection compared to controls have been reported in patients with MS<sup>[415,663,664]</sup>. Moreover, it was suggested that the parasite play a protective role in this clinical entity because patients infected with the microbe had experienced fewer relapses with lower disability scores<sup>[415]</sup>. This is not surprising because *T. gondii* infection is known to affect both proinflammatory and antiinflammatory processes in the host<sup>[535]</sup>, and markedly increased generation of antiinflammatory cytokines IL-10 and TGF- $\beta$ , and a decrease in IL-12 and IFN- $\gamma$ -secreting cells, together with induction of Tregs, can favorably alter the clinical course of MS<sup>[665,666]</sup>. Infection with the parasite is associated with similar changes in the serum cytokines, IgE and Tregs responses<sup>[300,553,554,667-669]</sup> as these caused by gastrointestinal helminths in patients with MS<sup>[665]</sup>. Furthermore, several authors found a protective effect of cat exposure during childhood on MS risk<sup>[670,671]</sup>, and otherwise it is known that *T. gondii* serotyping in cats revealed predominance of type II infections (most frequent in humans)<sup>[672]</sup>, and studies performed in different countries indicate high prevalence of the parasite, other protozoa and helminths in cat feces<sup>[673]</sup>.

It was demonstrated that vitamin D deficiency is associated with increased autoimmunity as well as an increased susceptibility to infection<sup>[674]</sup>, especially that it exerts modulatory effects on B cell differentiation<sup>[675]</sup>. Hypovitaminosis D may affect B cell function in ADs because B cells upregulate the vitamin D receptor on several immune cells upon activation, and due to regulated expression of the metabolizing enzymes CYP27B1 and CYP24A1, B cells control

the local availability of active vitamin D<sup>[676]</sup>. These findings are clinically relevant and in one study it was found that women with *T. gondii* infection had vitamin D deficiency as compared with controls<sup>[677]</sup> and otherwise it is known that estrogen dysregulated T- and B-cell balance by inducing selective T-cell hypoactivity and B-cell hyperactivity, thus increasing risk of ADs<sup>[678,679]</sup>. Moreover, vitamin D dose-dependently inhibited intracellular growth of the parasite<sup>[680,681]</sup>.

**NK cells.** These cells interact with various components of the immune system and therefore have the potential to function as regulatory cells. NK cells can assist in DC maturation and T-cell polarization, and also prevent or limit autoimmune responses<sup>[682]</sup>. There is a rapid transfer of *T. gondii* tachyzoites from infected DC to effector NK cells during infection<sup>[243]</sup>. NK cells can boost immune defense *via* their cytolytic activity and capacity to produce IFN- $\gamma$ . The cells can however also dampen immune responses to pathogens *via* secretion of the antiinflammatory cytokine IL-10<sup>[683]</sup>, and can promote T cell exhaustion during chronic infections<sup>[615]</sup>. NK cells can target and kill activated CD4 T cells during the early stages of viral infections, removing vital helper functions, thereby fostering the development of CD8 T cell exhaustion. NK cells may also directly target antiviral CD8 T cells, reducing their availability to control the infection and thus also promoting exhaustion<sup>[684,685]</sup>. The targeted depletion of NK cells can save the antiviral T cell responses and permit viral clearance<sup>[686]</sup>. It is important to note that following *T. gondii* infection of the NK cells there was reduced IFN- $\gamma$  generation, increased TGF- $\beta$  production by these cells, and downmodulation of their effector functions, *i.e.* impaired target recognition and cytokine release, two mechanisms that independently could enhance survival of the pathogen<sup>[687]</sup>. On the other hand, parasitized NK cells did not facilitate the spread of the parasite to the brain<sup>[688]</sup>. Besides of T cells, other cells such as NK cells and neutrophils might also be the source of IL-17, and an exaggerated T<sub>H</sub>17 response may lead to severe inflammatory responses and development of ADs<sup>[689-691]</sup>.

**Neutrophils.** These cells control infectious pathogens by phagocytosing and degrading microbes, releasing immunoregulatory cytokines (IL-12, TNF- $\alpha$ , IFN- $\gamma$ ) and chemokines during infection, and producing ROS<sup>[692-694]</sup>. Neutrophils play an important role during early *T. gondii* infection<sup>[695-697]</sup>. Lima *et al*<sup>[692]</sup> revealed evasion of human neutrophil-mediated host defense during *T. gondii* infection because the parasite inhibited a proinflammatory cytokine IL-1 $\beta$  production in these cells by inhibiting the activation of NF- $\kappa$ B signaling pathway and by impairing function of the inflammasome, the multiprotein complex responsible for IL-1 $\beta$  maturation<sup>[692]</sup>.

Recently, IL-17 has been identified regulating neutrophil-mediated inflammation, and suppression of this cytokine may contribute to virus-induced immunosuppression as well as to the pathogenesis of many acute and chronic inflammatory disorders<sup>[698]</sup>. Kelly *et al*<sup>[699]</sup> demonstrated that early neutrophil induction during *T. gondii* infection is dependent on IL-17-mediated signaling. A diminished response in IL-17R knockout animals was associated with a defect in the migration of polymorphonuclear leukocytes to infected sites and an impaired generation of the macrophage inflammatory protein-2 early during infection.

**Macrophages.** Recently, Dupont *et al*<sup>[631]</sup> found that *T. gondii* infected disproportionately macrophages and DCs, and it appeared that phagocytosis of parasites was not sufficient to induce immune responses of these cells. Macrophages play an important role in tissue homeostasis, presentation of foreign and self-antigens following infection, pathogen clearance, resolution of inflammation and tissue healing<sup>[700-703]</sup>. Macrophages are crucial for the host response

**Table 29** Percentages of T1DM patients, their first-degree family members (FM) and healthy controls with antibodies against *T. gondii* and some other infectious agents (acc. to Krause *et al* [104]; with own modification).

Infectious agent	T1DM	FM	Controls	P value
<i>T. gondii</i>	5.4	24.4	40	0.001
EBV-VCA (IgG anti-VCA)	82.1	92.6	92.8	0.04
EBV-EBNA (IgG anti-EBNA)	71.4	89.3	90.7	0.001
CMV	69.6	79.7	92.9	0.001
HP	55.1	78.3	80.7	0.01

CMV, cytomegalovirus; EBV, Epstein-Barr virus; EBV-VCA, EBV viral capsid antigen; EBV-EBNA, EBV nuclear antigen; HP, *Helicobacter pylori*.

**Table 30** The effect of NO (S-nitroso-glutathione, GSNO, 200  $\mu$ M, 24 hrs) on the secretion of IL-6 and IL-8 in human saphenous vein endothelial cells (HSVEC) monolayers (acc. to De Caterina *et al* [723]; with own modification).

	IL-6		IL-8	
	pg/10 <sup>5</sup> cells	Inhibition by GSNO	pg/10 <sup>5</sup> cells	Inhibition by GSNO
Control, no IL-1 $\alpha$	< 20		25.9 $\pm$ 3.0	
Control + GSNO	< 20	ND	25.8 $\pm$ 1.3	< 1%
IL-1 $\alpha$ (10 ng/mL)	286.0 $\pm$ 19.8		970 $\pm$ 31.0	
IL-1 $\alpha$ + GSNO	142.0 $\pm$ 3.3 <sup>a</sup>	50%	723 $\pm$ 46.7 <sup>a</sup>	25%

Results are mean  $\pm$  SE of protein concentration assayed in quadruplicate in medium from greater than 4 HSVEC monolayers in each control unstimulated condition and greater than 8 HSVEC monolayers for each stimulated condition. <sup>a</sup>  $p$  < 0.01 in comparison with corresponding control conditions. ND, not detected.

to infection with various pathogens because enhanced generation of ROS and RNIs endow these cells with potent antimicrobial activity<sup>[704]</sup>. These cells are also professional APCs as they efficiently process and present peptide antigens for MHC class I- and class II-restricted presentation on the cell surface. Microbial peptide-bearing macrophages activate antigen-specific CD4<sup>+</sup> and CD8<sup>+</sup> T cells and therefore are an important component in the bridge connecting innate and adaptive immunity<sup>[704,705]</sup>. Following antigen stimulation immature monocytes emigrate from blood vessels into peripheral tissues where they differentiate into mature macrophages and DCs comprising as much as 15% of total cells<sup>[702]</sup>.

*T. gondii* rhoptry proteins utilize multiple mechanisms of host manipulation to establish chronic infection of the host<sup>[706]</sup>. Several of these proteins including ROP16 and ROP18 kinases secreted into the host cell cytosol directly phosphorylate host cell proteins and thereby subvert host cytokine signaling pathways in macrophages<sup>[707-710]</sup>. Jensen *et al*<sup>[709]</sup> showed that clonal lineages of the parasite have evolved distinct ways of subverting host macrophages. *T. gondii* strain type II (most frequent) infected macrophages are classically activated (M1), while type I and III infected macrophages are alternatively activated (M2)<sup>[709]</sup>. Furthermore, macrophages are considered M1 when stimulated by IFN- $\gamma$  or LPS to release NO, important for killing *T. gondii*, and M2 when stimulated by IL-4 or IL-13 (M2a) to produce IL-10, TGF- $\beta$  and arginase-1<sup>[711,712]</sup>. TGF- $\beta$  suppressed IFN- $\gamma$ -induced toxoplasmastatic activity in murine macrophages by inhibition of TNF- $\alpha$  generation<sup>[547]</sup>. Moreover, *T. gondii* facilitated parasite replication in activated murine macrophages through reduced expression of the iNOS<sup>[552, 565]</sup>. Parasites that require T<sub>H</sub>2 immune response for effective clearance are strong inducers of M2 macrophages, however, bacteria and viruses that require T<sub>H</sub>1-type responses may induce M2 as a strategy to evade the immune system<sup>[700]</sup>. M2 may exacerbate autoimmune disease by presenting self-tissue to T cells, and cause the release of profibrotic factors

including IL-1 $\beta$ , TGF- $\beta$ , b-fibronectin and matrix metalloproteinases. Marshall *et al*<sup>[713]</sup> demonstrated that peroxiredoxin, a redox enzyme derived from *T. gondii* on murine macrophages, promoted altered macrophage function, and reduced IL-1 $\beta$  secretion and caspase-1 activity, while simultaneously increasing IL-10 release. Moreover, the *in vitro* replication of the parasite (RH strain) was enhanced when macrophages were treated with peroxiredoxin. All these activities highlight an important role for M2 macrophages in modulating immunopathology in ADs and promoting parasite replication during *T. gondii* infection<sup>[713]</sup>.

## NITRIC OXIDE (NO) ACTS AS A PROAPOPTOTIC AS WELL AS AN ANTIAPOPTOTIC BIOMODULATOR, AND HAVE A VARIETY EFFECTS ON AUTOPHAGY

***T. gondii* infection causes dysfunction of both these processes and therefore hinders cleaning service of the apoptotic/autophagic cell-derived antigenic remnants, finally leading to triggering and development of several ADs**

### NO

This potent biomediator has multiple functions in immunity and autoimmunity, being both friend and foe. Bogdan<sup>[715]</sup> reported that iNOS-derived NO is critical for defense against many microorganisms, including viral infections, intracellular bacteria and parasites. However, iNOS-mediated inflammatory tissue damage and/or disease has been demonstrated in many ADs, including inflammatory arthritis, experimental autoimmune encephalomyelitis, uveoretinitis, and immune complex glomerulonephritis<sup>[714-716]</sup>. In patients with RA and SLE several studies documented increased endogenous NO synthesis, and this mediator modulated mitochondrial events involved in apoptosis and regulated mitochondrial biogenesis in lymphocytes and other cell types. NO overproduction may perturb T cell activation, differentiation and effector responses, thus eventually contributing to the pathogenesis of autoimmunity<sup>[717]</sup>.

Mitochondria are a source of NO production<sup>[718]</sup>. Naturally produced NO circulates in plasma primarily as S-nitroso adduct of serum albumin<sup>[719]</sup>, a reservoir with which plasma levels of free NO can be regulated for the maintenance of vascular tone<sup>[714]</sup>. Importantly, iNOS-derived NO can modulate the cytokine response of macrophages, T cells, endothelial cells, and fibroblasts<sup>[720,721]</sup>. It was demonstrated upregulation of iNOS expression when naïve NK cells were cultured in the presence of recombinant IL-2, and induction of iNOS enhanced NF- $\kappa$ B binding activity in IL-2 activated NK cells<sup>[722]</sup>. Moreover, NO inhibited activation of NF- $\kappa$ B<sup>[723]</sup>. NF- $\kappa$ B is a redox-sensitive transcription factor, and the intracellular redox status of the cell is extremely important in the regulation of NF- $\kappa$ B activity<sup>[724,725]</sup>. Activated NF- $\kappa$ B has been identified in SMC, macrophages, and endothelial cells of human atherosclerotic lesions<sup>[726,727]</sup>. It must be noted that the NF- $\kappa$ B family also play an important role in the regulation of genes associated with the development of innate and adaptive responses required for the recognition and immunologic control of pathogens<sup>[728,729]</sup>.

NO is a potent oxidant produced by both endothelial cells and macrophages that appear to exert both protective and atherogenic effects, depending on the source of production. NO produced by endothelial NOS has vasodilator function and is potentially atheroprotective. In contrast, NO produced *via* the much higher capacity iNOS in macrophages, serving antimicrobial functions

based on its potent oxidative properties, is potentially atherogenic<sup>[730]</sup>. Moreover, iNOS was overexpressed in macrophage-derived foam cells so the cytotoxic amounts of NO were produced<sup>[731]</sup>. The mechanisms responsible for the atherogenic modification of low density lipoproteins may include: oxidation mediated by myeloperoxidase, 15-lipoxygenase, and/or NOS<sup>[730,732]</sup>. However, NO has also many antiatherogenic properties<sup>[723]</sup>, including reduction of platelet aggregability<sup>[733]</sup>, limitation of vascular smooth muscle cell proliferation<sup>[734,735]</sup>, inhibition of leukocyte adhesion to the endothelium<sup>[736,737]</sup>, and prevention of monocyte chemotaxis<sup>[738]</sup>. In addition, NO selectively decreased the endothelial expression of adhesion molecules E-selectin and intracellular adhesion molecule-1, and proinflammatory secreted cytokines IL-6 and IL-8 (Table 30)<sup>[723]</sup>.

Several examples of the molecular immune-system functions for NO have been presented in Table 31<sup>[715]</sup>.

A large body of evidence indicates also that cell death (apoptosis/autophagy) is a major modulating factor of atherogenesis<sup>[764,765]</sup>. Autophagy in atherosclerosis may have both protective and detrimental effects. Potential factors that stimulate autophagy in atherosclerosis included oxidized lipids, endoplasmic reticulum stress, inflammation, hypoxia and metabolic stress conditions<sup>[765]</sup>. Razani *et al*<sup>[766]</sup> found that atherosclerotic aortas had elevated levels of p62 (a protein that recognizes cellular waste), indicating that dysfunctional autophagy is characteristic of plaques. It was suggested that deficiency of autophagy was associated with proatherogenic inflammasome activation<sup>[766]</sup>. It must be also emphasized that impaired clearance of apoptotic cells promoted synergy between atherosclerosis and ADs<sup>[767]</sup>, and that atherosclerotic process was found to be accelerated in several ADs, including autoimmune rheumatic diseases and SLE<sup>[768,769]</sup>. In this context, it must be noted that *T. gondii* infection probably play an essential role in the pathogenesis of atherosclerosis<sup>[525]</sup>.

Stimulation of autophagy by inflammation in atherosclerosis<sup>[765,770]</sup> acts as an immune defense pathomechanism of the host<sup>[771,772]</sup>. Cytokines take part in modulation of autophagy<sup>[771,772]</sup>. For example, proinflammatory cytokines T<sub>H</sub>1 type immune response, such as TNF- $\alpha$  took part in autophagic smooth muscle cells death<sup>[773]</sup>, and IFN- $\gamma$  in macrophages<sup>[774]</sup> and nonimmune cells<sup>[775]</sup>, while T<sub>H</sub>2 cytokines such as IL-4 and IL-13 had the potential to act as suppressors of autophagy<sup>[771]</sup>.

### Autophagy and apoptosis

These two basic physiopathologic processes contribute to maintenance of cellular homeostasis. The host immune system uses them to clear intracellular pathogens and as a mechanism to monitor its products for evidence of pathogen invasion and cellular transformation<sup>[776]</sup>. Beyond enhancing immunity through antigen loading onto MHC class II molecules, autophagy's role is to assist the clonal expansion of B and T cells for efficient adaptive immune responses<sup>[776]</sup>. When autophagy occurs, part of the cellular constituents is sequestered in double membrane-bound vesicles called autophagosomes and subsequently degraded upon fusion with lysosomes to provide essential elements for maintaining cell metabolism<sup>[776]</sup>. Autophagy target long-lived cytosolic proteins and damaged organelles, and involves double membrane formation, elongation, vesicle maturation and finally delivery of the targeted materials to the lysosome. Apoptotic cell death is characterized by cell rounding, membrane blebbing, cytoskeletal collapse, cytoplasmic and chromatin condensation/fragmentation, nuclear pyknosis, and formation of membrane-enveloped apoptotic bodies, that are rapidly

**Table 31** Selected functions of NO in the immune-system, cells involved, effects and molecular mechanisms [acc. to Bogdan [715]; with own modification).

Category	Examples of cells producing NO	NO effects	Molecular mechanisms	Refs
Antimicrobial activity	Macrophages, neutrophils, microglia, endothelial cells, epithelial cells, microglia, astroglia, eosinophils, fibroblasts	Killing or reduced replication of infectious agents (viruses, bacteria, protozoa, fungi, helminths)	Direct and/or indirect effects of NO on pathogens	[739-741]
Antiinflammatory/ immunosuppressive effects	Macrophages “suppressor phenotype”	Inhibition of: -T and B cells proliferation; -antibody production by CD5 <sup>+</sup> B cells; -autoreactive T and B cell diversification; -inhibition of leukocyte recruitment, adhesion, extravasation, chemotaxis	-Apoptosis of T cells or APCs; -downregulation of MHC class II, costimulatory molecules or cytokines; -disruption of signaling cascades and transcription factors; -inhibition of DNA synthesis; -downregulation of adhesion molecules or chemokines	[742-752]
Modulation of the production and function of cytokines, chemokines, and growth factors (pro- and antiinflammatory effects)	Macrophages, T cells, endothelial cells, fibroblasts	Up- and downregulation of: -IL-1, IL-6, IL-8, IL-10, IL-12, IL-18, TNF, IFN- $\gamma$ ; -TGF- $\beta$ , G-CSF, M-CSF, VEGF; -MIP-1 $\alpha$ , MIP-2, MCP-1	Modulation of: -signaling cascades (e.g. G-proteins, Jak, MAP kinases, caspases, protein phosphatases); -transcription factors (e.g. NF- $\kappa$ B, AP-1, Sp1); -proteins regulating mRNA stability or mRNA translation; -latent cytokine precursor complexes; -enzymes that process cytokine precursors	[743,753-759]
T helper cell deviation	e.g. macrophages	-Induction and differentiation of Th1 cells; -suppression of Th1 (and Th2) cell responses; -suppression of tolerogenic T cell responses	1. Possible stimulation of IL-12-mediated signaling; 2. Suppression of IL-12 production	[744,749,760,761]
Tissue-damaging effects	Macrophages, microglia, astroglia, keratinocytes, mesangial cells	Necrosis and/or fibrosis of the parenchyma	-Apoptosis of parenchymal cells; -degradation of extracellular matrix; -deposition of matrix, proliferation of mesenchymal cells; -influx of inflammatory cells <i>via</i> chemokine regulation	[744,762,764]

APCs, antigen presenting cells; AP-1, activator protein-1; G-CSF, granulocyte-colony stimulating factor; Jak, Janus kinases; MAP kinases, mitogen-activated protein kinases; MCP-1, monocyte chemoattractant protein-1; M-CSF, macrophage colony-stimulating factor; MHC class II, major histocompatibility complex class II; MIP-1 $\alpha$ , macrophage inflammatory protein-1 $\alpha$ ; MIP-2, macrophage inflammatory protein-2; Sp1, stimulatory protein 1; TGF- $\beta$ , transforming growth factor- $\beta$ ; VEGF, vascular endothelial growth factor.

phagocytosed by macrophages or neighbouring cells<sup>[777]</sup>. Apoptosis can be distinguished from necrotic cells death because apoptotic cells profoundly inhibit phagocytic macrophage responses and this represents a cell-associated, dominant-acting antiinflammatory signaling activity acquired posttranslationally during the process of physiological cell death<sup>[778,779]</sup>. Necrotic cell death, on the other hand, is associated with an early loss of membrane integrity resulting in rapid cell swelling, leakage of its contents and induction of an inflammatory response<sup>[779]</sup>. The effects of both early and late apoptotic cells on signaling were dominant over those of necrotic cells<sup>[780]</sup>. Therefore, clearance of apoptotic leukocytes is implicated in the resolution of inflammation, and defective clearance of apoptotic cells contributes to development of inflammatory and ADs<sup>[781-785]</sup>. It is well established that the accumulation of apoptotic debris exacerbate symptoms of inflammation and autoimmunity<sup>[786,787]</sup>. Uptake of early apoptotic debris can have an immunosuppressive effect on the host cell that is associated with the downregulation of TNF- $\alpha$  and the upregulation of IL-10<sup>[788,789]</sup>. Uptake of apoptotic cells by DCs (the most potent antigen-presenting cells) play a significant role in the immune responses, because DCs that have ingested apoptotic cells have a reduced capacity to stimulate T cells<sup>[790,791]</sup>. The ingestion of apoptotic cells by immature DCs can inhibit their maturation and antigen presentation with suppression of the secretion of the proinflammatory cytokine IL-12<sup>[790,791]</sup>.

**Autophagy (Greek term meaning “self-eating”).** This catabolic process in eukaryotic cells acting as a cellular housekeeper<sup>[792]</sup>,

is characterized by the formation of double-membrane vesicles 0.5-1.5  $\mu$ m in diameter in the cytoplasm of cells termed autophagosome<sup>[793,794]</sup>. Mature autophagosomes encase both cytosol as well as organelles, consistent with the early characterization of autophagy as a major pathway for protein degradation during period of starvation<sup>[795]</sup>. Autophagy contributes to the clearance of intracellular pathogens<sup>[794,796-798]</sup>, as well as the MHCII cross-presentation of endogenous antigens<sup>[799]</sup>. In T lymphocytes, autophagosomes form in human and murine T cells and can be induced in T-cell receptor-stimulated proliferating cells *in vitro*<sup>[800,801]</sup>.

NO have a variety of effects on autophagy depending upon the cell type. For example, in glioma cells when combined with hypothermia, NO donors (e.g. sodium nitroprusside, S-nitrosoglutathione) inhibited the completion of autophagy<sup>[802,803]</sup>, whereas in primary neurons, NO caused an increase in mitophagy (i.e. the selective degradation of mitochondria by autophagy)<sup>[804]</sup>. Overexpression of NOS impaired autophagosome synthesis, therefore in these systems, NO appeared to play an inhibitory role in autophagy<sup>[805]</sup>, especially that L-NAME (N<sup>G</sup>-nitro-L-arginine methyl ester), a nitric oxide inhibitor, prevented NO inhibition of autophagy<sup>[805]</sup>.

Autophagy is an important player in immune functions involved in triggering and exacerbating autoimmunity<sup>[806,807]</sup>, and its suppression has been implicated in a broad spectrum of human ADs, including rheumatic diseases<sup>[808]</sup>, neurodegenerative disorders<sup>[809]</sup>, inflammatory bowel disease<sup>[810]</sup>, vascular disorders, and atherosclerosis<sup>[811]</sup>. Peripheral inflammation take part in cell proteolysis, and autophagy

fights disease through cellular self-digestion<sup>[812]</sup>. Autophagy has an antiinflammatory function as demonstrated in a mouse model of Leśniowski-Crohn's disease<sup>[813]</sup>, and thus may also exert a protective role against the development of several neurodegenerative diseases<sup>[814,815]</sup>. Pua *et al*<sup>[794]</sup> demonstrated that autophagy may have a significant role in the clearance of mitochondria in T lymphocytes. Autophagy-deficient T cells had increased ROS production as well as an imbalance in pro- and antiapoptotic protein expression<sup>[794]</sup>, and ROS regulate activation-induced T cell apoptosis<sup>[816]</sup>.

**Apoptosis (Greek term meaning “the falling off of the leaves”).** This programmed cell death serves as a defense mechanism against viruses, bacteria and parasites<sup>[809]</sup>, and is the most efficient system to get rid of unwanted apoptotic cells (ACs) being a source of haptenated antigens, without causing inflammation<sup>[629,818]</sup>. Macrophages are considered the most efficient scavenger of these cells<sup>[818,819]</sup>. Internalization and/or binding of ACs has been shown to downregulate the responses of macrophages<sup>[820,821]</sup>, monocytes<sup>[788,789]</sup>, and DCs<sup>[791]</sup> to microbial stimuli<sup>[822]</sup>. Uptake of ACs by phagocytes is thought to suppress autoimmune responses through the release of antiinflammatory cytokines IL-10, TGF- $\beta$ , platelet activating factor, and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), and inhibition of proinflammatory cytokines IL-1 $\beta$ , TNF- $\alpha$ , IL-12, IL-18, and GM-CSF<sup>[820,823]</sup>. Monocytes/macrophages after phagocytosis of monocytes committed to apoptosis by for example viral infection, do not elicit a specific cytolytic T lymphocyte (CTL) response<sup>[824]</sup>. On the other hand, DCs pulsed with apoptotic monocytes activated *in vitro* virus-specific CTLs<sup>[824]</sup>. Therefore, depending on the scavengers involved in the clearance of ACs, the result in terms of specific immune responses may be quite different<sup>[629]</sup>.

Apoptosis plays a critical role in inhibiting the proliferation of invasive organisms thereby protecting uninfected cells and limiting damage to the host organism. This process is characterized by early condensation of nuclear chromatin, enzymatic cleavage of the DNA into oligonucleosomal fragments, loss of plasma membrane phospholipids asymmetry, and segmentation of the cells into membrane-bound “apoptotic bodies”<sup>[825,826]</sup>. Cells dying by apoptosis can be phagocytosed by macrophages without damaging nearby cells, in contrast to necrotic cells releasing proinflammatory molecules, such as HSP70<sup>[827]</sup>, uric acid<sup>[828]</sup>, and lysosomal and other enzymes causing inflammation of the surrounding cells<sup>[825,829]</sup>. Nb. it should be noted that uric acid acts as an antioxidant molecule<sup>[830]</sup>, a putative scavenger of peroxynitrite, which ameliorated the severity of EAE<sup>[831]</sup>. Moreover, uric acid produced in high quantities upon cellular injury is sufficient to induce T helper type 2 cell immune responses<sup>[830,832]</sup>, and therefore hyperuricemia and hyperuricosuria observed in autistic children<sup>[833,834]</sup>, may reflect a defense reaction of these patients against *T. gondii* infection probably responsible for development of this clinical entity<sup>[114]</sup>. Interestingly, aluminum hydroxide adjuvant boosts adaptive immunity by inducing uric acid generation and activating inflammatory DCs<sup>[835]</sup>, and it was suggested that autism may be caused by aluminum-containing vaccines widely used in children<sup>[836]</sup>.

There are two primary pathways of apoptosis that broadly respond to extrinsic (death receptor activation) and intrinsic (DNA damage) triggers<sup>[837]</sup>. The signaling pathway involve the activation of cysteine proteases (caspases) that play a crucial role in the regulation and execution of apoptotic cell death. The first pathway of caspase activation involves death receptors such as Fas or TNF receptors, which lead to activation of caspase-8 and subsequently can activate downstream caspase-3, -6, or -7<sup>[838,839]</sup>. In the second pathway, various proapoptotic signals provoke the release of apoptogenic proteins,

cytochrome c, and apoptosis-inducing factor from mitochondria into the cytoplasm<sup>[840,841]</sup>.

Apoptotic cells are removed by macrophages, without causing inflammation<sup>[819]</sup>. This was regarded as an active process mediated the production of IL-10, TGF- $\beta$ , and PGE<sub>2</sub>, because macrophages cocultured with early apoptotic cells generated these antiinflammatory mediators that suppressed the production of proinflammatory cytokines *in vitro*<sup>[788,820,842]</sup>. In contrast, Kurosaka *et al*<sup>[843]</sup> earlier showed that macrophages cocultured with very early apoptotic cells produced neither proinflammatory nor antiinflammatory cytokines, but generated a large quantity of NO to suppress an inflammatory response. Further study of this group<sup>[819]</sup> provided evidence for the involvement of NO that counteract proinflammatory cytokines, such as macrophage inflammatory protein-2 and keratinocyte-derived chemokine, in a salient cleanup of apoptotic cells<sup>[843]</sup>. It was suggested that these findings may support the idea that antiinflammatory signals including NO also participate in the process of apoptotic cell clearance to counteract the generation of proinflammatory cytokines<sup>[819]</sup>. Inhibition of neutrophil migration by a mechanism dependent on ICAM-1 and modulation of leukocyte adhesion, both induced by NO, may be at least in part responsible for this NO activity<sup>[736,844]</sup>.

It must be noted that low or physiological plasma NO concentrations prevented cells from apoptosis that was induced by LPS, TNF $\alpha$ /ActD, and Fas (death receptor)<sup>[845]</sup>. Yuyama *et al*<sup>[846]</sup> demonstrated that cytotoxicity of low physiological (10-100  $\mu$ M) concentration of NO was mediated by inhibition of mitochondrial cytochrome c oxidase and generation of ROS in mitochondria. On the other hand, persistent overproduction of NO acted as a proapoptotic modulator (through the interaction with metal ion, thiol, protein tyrosine, and ROS), *i.e.* activating caspase family proteases through the release of mitochondrial cytochrome c into cytosol, upregulation of the p53 expression (an essential indicator of NO-mediated apoptosis), and alterations in the expression of apoptotic-associated proteins, including the Bcl-2 family<sup>[816,845]</sup>.

In animal models, impaired apoptotic debris clearance leads to the development of autoimmunity<sup>[786,787]</sup>. It is believed that the onset of ADs can be linked to the inefficient removal of apoptotic cells<sup>[847]</sup>. Patients with autoimmune conditions have circulating antibodies that can react with the surfaces of dying cells. Particularly antiphospholipid autoantibodies bound to externalized phosphatidylserine on apoptotic cells (this nonspecific ligand can be also externalized on necrotic cells<sup>[778]</sup>) can have serious consequences for the outcome of apoptotic cell clearance leading to its deficiency<sup>[848]</sup>. They can opsonize apoptotic cells for recognition by macrophage Fc receptors, thus converting the antiinflammatory signaling of apoptotic cell removal to the proinflammatory signaling stimulated by Fc receptor-mediated phagocytosis<sup>[849]</sup>. The same is conceivable for other autoantibodies that recognize self-molecules displayed on the surface of apoptotic cells, and this may brake the barrier of self tolerance necessary for the generation of autoimmunity<sup>[847]</sup>.

Recent investigations have focused on the cross-talk between the autophagic and apoptotic signaling pathways<sup>[850,851]</sup>. Autophagy can be a precursor and even an initiator of apoptosis, and conversely, apoptotic signaling can lead to the activation of autophagy<sup>[852,853]</sup>.

### ***T. gondii* infection**

The parasite manipulates multiple strategies to downregulate the host's defense responses, including subverting intracellular signaling pathways in infected cells to evade immunity<sup>[531]</sup>.

**Autophagy.** Many viruses, bacteria, and parasites encode virulence

factors that impair the function of autophagy proteins<sup>[854-857]</sup>. In host cells *T. gondii* survives by avoiding lysosomal protease degradation, but autophagy can reroute the parasitophorous vacuole (PV) to the lysosomes and cause parasite killing<sup>[858]</sup>. Muniz-Feliciano *et al*<sup>[858]</sup> reported that *T. gondii* may deploy a strategy to prevent autophagic targeting to maintain nonfusogenic nature of the vacuole due to its unique composition lacking host proteins. However, Ling *et al*<sup>[798]</sup> demonstrated also vacuolar and plasma membrane stripping and autophagic elimination of the parasite in primed effector macrophages.

Large amounts of parasite products accumulated in cells induce necrosis<sup>[859,860]</sup>. It was demonstrated that proliferation of *T. gondii* suppresses host cells autophagy<sup>[851]</sup>. HeLa cells infected with *T. gondii* have strongly expressed autophagic markers, microtubule-associated protein 1 light chain (LC3) and Beclin 1 protein (concentrated near the PVs). The subsequent proliferation of tachyzoites suppressed HeLa cell autophagy, which can promote infected host cell survival and serve as a persistent source of foreign antigens, thus eventually leading to development of autoimmunity<sup>[851]</sup>.

Li *et al*<sup>[861]</sup> showed that induction of autophagy by *T. gondii* was involved in the tachyzoite to bradyzoite transformation *in vitro*. It appeared that both *TgAtg3* (a key autophagy protein) and *TgAtg8* were expressed at a significantly lower level in bradyzoites than in tachyzoites. *Atg3* was found to be essential for maintaining mitochondrial integrity and for normal intracellular development of tachyzoites<sup>[862]</sup>. Interestingly, NO was suggested to play an important role in triggering tachyzoite to bradyzoite stage conversion<sup>[863]</sup>. Nb. recently Watts *et al*<sup>[510]</sup> challenged the prevailing notion of bradyzoites as dormant nonreplicative entities in chronic toxoplasmosis, because they revealed dynamic cyclical, episodic replication of bradyzoites within mature tissue cysts *in vivo*.

Halonen<sup>[864]</sup> showed that in IFN- $\gamma$ -stimulated astrocytes, autophagy of disrupted vacuoles and/or dead parasites did not occur but rather that degradation of the pathogen occurs in the host cell cytoplasm. Delivery of *T. gondii* antigens from the cytosol to the endolysosomal compartments in the astrocytes may present these haptenated antigens *via* the MHC class II pathway and function as an antigen-presenting cell for the parasite in the brain. It must be noted that *T. gondii* tachyzoites downregulated MHC class II expression in microglia and astrocytes<sup>[865,866]</sup>.

**Apoptosis.** *T. gondii* triggers the secretion of antiinflammatory cytokines, such as IL-10 and TGF- $\beta$ , thus suppressing the development of the T<sub>H</sub>1 immune responses and deactivating macrophages<sup>[560-562]</sup>. The parasite inhibits also DC production of IL-12 through expression of endogenous lipoxin A<sub>4</sub>, a potent arachidonate-derived endogenous downregulator of IL-12 production<sup>[548]</sup>. Manipulation of apoptosis plays a critical role in the pathogenesis of several intracellular pathogens. *T. gondii* infection is known to induce host-cell apoptosis in several selected cell lineages. Nishikawa *et al*<sup>[551]</sup> found that when using a *Toxoplasma*-infected macrophage cell line, J774A.1, treatment with IFN- $\gamma$  significantly enhanced apoptosis in noninfected bystander cells while parasitized cells became relatively resistant. They established that apoptosis in bystander host cells was due to the secretion of NO and other soluble factors released by parasite-infected cells<sup>[551]</sup>. Moreover, induction of apoptosis in intestinal Peyer's patch T cells and the ocular tissue of mice infected with the parasite has also been reported<sup>[550,867]</sup>. Similarly, induction of apoptosis in monocytes has been reported<sup>[551]</sup>. In particular, supernatants from *T. gondii*-infected mouse macrophages can induce apoptosis in bystander macrophages but not in the infected cells, and NO was identified as a proapoptotic

molecule for macrophages<sup>[551]</sup>. Recently, D'Angelillo *et al*<sup>[544]</sup> found that *T. gondii* dense granule antigen 1 (GRA1) stimulated apoptosis of monocytes by interfering with the classical endogenous TGF- $\beta$  signal transduction pathway. GRA1 activated TGF- $\beta$  transcription and expression in monocytes (but not in lymphocytes) from both *Toxoplasma*-infected and uninfected individuals<sup>[544]</sup>.

Interestingly, acute *T. gondii* infection induced CD4<sup>+</sup> T cell apoptosis (the cells exhibited DNA fragmentation pattern) as a long-term consequence to T cells rendered anergic<sup>[549]</sup>. An increased apoptosis of activated T cells may contribute to transient immunologic hyporesponsiveness observed in acute *T. gondii* infection and pathogen persistence in the infected host cells. Decreased production of IL-2<sup>[624]</sup> and enhanced synthesis of IL-10 and RNI during acute stage of the parasite infection<sup>[622-624]</sup>, may have a role in the augmented level of apoptosis<sup>[582]</sup>.

Virulent strains of *T. gondii* elicited high levels of host cell apoptosis through overproduction of proinflammatory cytokines<sup>[576,577]</sup>. Type I strains owe their lethality at least in part to an abnormal over-induction of normally protective T<sub>H</sub>1 cytokines<sup>[573,574]</sup>, and may be more prevalent in particular during ocular toxoplasmosis<sup>[868,869]</sup>. However, the parasite employs several immunosuppressive responses in infected cells because, for example, intracellular macrophage infection results in resistance to multiple inducers of apoptosis, including UV irradiation, gamma irradiation, IL-2 deprivation<sup>[575,580]</sup>, through mechanisms such as reduced caspase activation, inhibition of mitochondrial cytochrome c release, and decreased activity of the poly(ADP-ribose) polymerase protein<sup>[580,870]</sup>. Moreover, apoptosis is blocked by indirect mechanisms also in uninfected bystander cells, thereby modulating the inflammatory response to the pathogen<sup>[870]</sup>. This is a survival strategy employed by the parasite to maintain host cell viability in an environment of proapoptotic mediators during infection<sup>[871]</sup>.

*T. gondii* has been shown to inhibit the apoptotic response of its host cell by interacting with multiple apoptotic regulatory systems to render the host refractory to apoptosis during critical phases of intracellular infection, including parasite invasion, establishment, and replication (**Table 32**)<sup>[872]</sup>.

*T. gondii* extensively modifies apoptosis of its own host cell and/or of uninfected bystander cells<sup>[870]</sup>. After infection, apoptosis is triggered in T lymphocytes and other leukocytes, thereby leading to suppressed immune responses to the parasite. The intriguing dual activity of *T. gondii* to both promote and inhibit apoptosis requires a tight regulation to promote a stable parasite-host interaction and establishment of persistent toxoplasmosis<sup>[870]</sup>. NO probably play a decisive role in this process because of its dichotomous function (beneficial and detrimental) during infection with the parasite<sup>[877]</sup>.

NF- $\kappa$ B plays an important role in development of innate and adaptive immunity in the host during *T. gondii* infection<sup>[558,728,729]</sup>. Signaling *via* the NF- $\kappa$ B cascade is pivotal for innate recognition of microbial products, and parasite, bacterial and viral pathogens have evolved ways to subvert this way of signaling to avoid their killing<sup>[728,729]</sup>. Molestina *et al*<sup>[578]</sup> suggested that activation of NF- $\kappa$ B plays an important role in stimulation of antiapoptotic gene expression by *T. gondii*. Many parasitic, bacterial and viral pathogens have evolved ways to subvert NF- $\kappa$ B signaling to promote their survival. In *T. gondii*-infected cells, the termination of NF- $\kappa$ B signaling was associated with reduced phosphorylation of p65/RelA, an event involved in the ability of NF- $\kappa$ B to translocate to the nucleus and bind DNA<sup>[558,728]</sup>. Payne *et al*<sup>[577]</sup> and others<sup>[878]</sup> demonstrated a profound inhibition of caspase activation and a requirement for the host transcription factor NF- $\kappa$ B function in the *T. gondii*-mediated

**Table 32** Intrinsic and extrinsic apoptotic pathways modulated by *T. gondii* (acc. to Carmen & Sinai [872]; with own modification).

Apoptotic pathways	Effect of <i>T. gondii</i> infection	Refs
1. Intrinsic pathway		
Cytochrome c release	Inhibition	[580,873]
Apoptosome	Inhibition of apoptosome activity	[579]
Caspase 9	Inhibition of caspase 9 activation	[873]
Bcl-2 family	Increased transcription: Bcl-2, Bfl-1, Bcl-xL, Mcl-1	[578,580]
Proapoptotic multidomain	Decreased Bax	[873]
Proapoptotic BH3-domain only	Decreased Bad	[873]
2. Extrinsic pathway		
Caspase 8	Inhibition of activation	[873]
Caspase 3	Inhibition of activation	[873]
IAPs	Increased expression of NAIP1 and 2, c-IAP1 and 2, and XIAP	[578]
Signaling cascades JNK	Decreased phospho-JNK following UV exposure	[873]
NF-κB	Activation of both host IKK and parasite encoded kinase ( <i>TgIKK</i> )	[578,874,875]
PI3K	Activation	[876]
Erk1/2	Activation	[876]

UV, ultraviolet light; IKK, inhibitor of kappa kinase; Bcl-2, Bcl-xL, Bfl-1, Mcl-1 (the antiapoptotic proteins); Bax, Bad (the proapoptotic proteins); IAP, (c-IAP1 and 2 inhibit caspases); IKK, I kappa kinase; *TgIKK*, *Toxoplasma gondii* IKK; JNK, c-Jun N-terminal kinase; NF-κB, nuclear factor kappa B; NAIP1, NLR family apoptosis inhibitory protein 1; XIAP, X-linked inhibitor of apoptosis protein; PI3K, phosphoinositide 3-kinase; Erk1/2, extracellular-signal regulated kinases 1/2.

blockade of host cell apoptosis. They suggested that the parasite activated the host survival response, thereby increasing the overall resistance of infected cells to apoptotic stimuli.

In mice, NO nitrosylated and inactivated proinflammatory molecules, such as NF-κBp65, and reduced TNF expression and signaling. iNOS-derived NO hampered both TNF- and T cell-mediated parasite brain invasion<sup>[879]</sup>. NO generated by iNOS is critical for defense against intracellular pathogens, including *T. gondii*, but may also mediate inflammatory tissue damage<sup>[879]</sup>. Scharton-Kersten *et al*<sup>[880]</sup> found that iNOS was essential for host control of persistent (but not acute) infection with the parasite. Production of NO by activated murine macrophages is also thought to represent an important mechanism to restrict replication of *T. gondii*. However, reduced expression of the iNOS after infection with *T. gondii* facilitated parasite replication in activated murine macrophages<sup>[579]</sup>.

Finally, Begum-Haque *et al*<sup>[525]</sup> provided evidence for the correlation of apoptosis with the host's genetic in toxoplasmosis. The authors demonstrated that following infection with the same P strain of parasite, the level of apoptosis was significantly higher in susceptible C57BL/6 mice than in resistant CBA/J animals. A higher level of activation induced cell death was found in susceptible *T. gondii* infected C57BL/6 mice than in resistant CBA/J animals. It appeared that apoptosis in T cells of susceptible mice was associated with altered induction of Bcl-2/Bax (the proapoptotic/antiapoptotic molecules, respectively) and loss of mitochondrial transmembrane potential. Although both CD4<sup>+</sup> and CD8<sup>+</sup> T cells were found to be susceptible to apoptosis, CD4<sup>+</sup> T cells were sensitive to Fas mediated death<sup>[586]</sup>, whereas CD8<sup>+</sup> T cells were insensitive to this biosignal<sup>[582]</sup>.

## LIVER AND/OR KIDNEY FUNCTION DAMAGE CAUSED BY *T. GONDII* INFECTION IS FREQUENTLY ASSOCIATED WITH DEVELOPMENT AND CLINICAL COURSE OF SEVERAL ADS

### ADs

Liver disease is a major cause of illness and death worldwide<sup>[881]</sup>. Several patients with various ADs, including SLE, systemic sclerosis (SSc), rheumatic disease, Sjögren syndrome, antiphospholipid

syndrome, polymyositis or dermatomyositis, autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), autoimmune thyroid disease, and inflammatory bowel disease, have laboratory evidence indicating liver<sup>[882-895]</sup> and/or kidney<sup>[896-899]</sup> function impairment or injury during their clinical course. It must be noted that some ADs with liver abnormalities, such as AIH, PBC, and primary sclerosing cholangitis (PSC) may develop in patients with systemic rheumatic diseases as having overlap syndromes (Table 33)<sup>[892]</sup>.

Subclinical liver involvement manifesting as elevated serum liver enzymes and sometimes associated with portal areas inflammation is frequent in SLE<sup>[882,883]</sup>. For example, Chowdhary *et al*<sup>[883]</sup> identified 40 SLE patients with liver enzyme abnormalities and biopsies performed in 20 individuals showed changes characteristic for nonalcoholic fatty liver disease (n = 8), autoimmune hepatitis (AIH) (6), primary biliary cirrhosis (3), hepatitis C (3), and cryptogenic cirrhosis (2). In another study<sup>[893]</sup>, retrospective analysis of 147 patients with SLE showed that 36 of them had liver enzyme abnormalities, and 72.3% of this group fulfilled the criteria for AIH.

### *T. gondii* infection and liver and/or kidney injury

In humans, latent chronic toxoplasmosis may lead to development of several liver diseases, including unexplained liver damage, cryptogenic liver cirrhosis, nonalcoholic steatohepatitis, and biliary cirrhosis<sup>[131,133,134,908]</sup>. Experimental *T. gondii* infection was associated with liver and kidney injury manifesting with a significant increase in serum alanine (AIAT) and aspartate aminotransferase (AspAT) activities, blood urea nitrogen level, decreased serum albumin concentration and alkaline phosphatase activity, albumin to globulin ratio, and marked abnormalities in plasma triglyceride and cholesterol levels<sup>[909-911]</sup>. Treatment with azithromycin caused normalization of serum AIAT and AspAT activities and improvement of total serum protein, albumin and globulin concentrations, and albumin/globulin ratio, in mice<sup>[910]</sup> (Tables 34-36). Nb. it must be noted that serum alkaline phosphatase as well as AIAT and AspAT activities were found to be markedly increased in pregnant women with toxoplasmosis as compared with controls<sup>[910A]</sup>. The difference in the serum alkaline phosphatase concentrations between mice and pregnant women may be explained by the route of *T. gondii* infection (intraperitoneal vs. probably oral, respectively) because this enzyme



is elevated mainly in the liver and bile duct disorders.

Acute *T. gondii* infection in mice caused a marked reduction in serum butyrylcholinesterase (BChE) activity ( $p < 0.01$ ) and liver damage, and positive significant correlations between serum BChE activity and BChE activity in liver ( $r = 0.89$ )<sup>[909]</sup>. In addition, serum albumin concentrations were markedly decreased (Tables 34-36), and previously it was reported that this biomarker is strongly correlated with BChE activity<sup>[912]</sup>. At necropsy, liver of the infected animals showed random necrosis foci combined with the presence of tachyzoites and cysts containing bradyzoites, as well as an increase in spleen size.

The above findings are very important because acetylcholinesterase (AChE) and BChE are biomarkers of low-grade systemic inflammation<sup>[913-915]</sup>, and it was suggested that the elevation of these two parameters may predict development of type 2 diabetes mellitus and Alzheimer disease<sup>[916]</sup>. These associations are in line with my earlier reports suggesting an important role of *T. gondii* infection in inducing of these two clinical entities<sup>[102,118]</sup>. BChE also serves as a marker predicting the prognosis of diseases<sup>[30]</sup> because when the serum activity of the enzyme is low, a high-risk of death must be taken into consideration<sup>[913, 917]</sup>. In middle-aged and elderly men and women Calderon-Margalit *et al*<sup>[912]</sup> showed that serum BChE activity was inversely related to age and was positively correlated with serum levels of albumin ( $r = 0.35$ ,  $p < 0.001$ ), cholesterol ( $r = 0.31$ ,  $p < 0.001$ ), and triglycerides ( $r = 0.30$ ,  $p < 0.001$ ). Moreover, the enzyme activity was associated with overweight, obesity, and body fat distribution parameters (*e.g.*, body mass index,  $r = 0.20$ ,  $p < 0.001$ ). Individuals with the lowest serum BChE activity had significantly higher mortality than those with the highest values<sup>[912]</sup>. Nb. recently, a positive association between *T. gondii* seropositivity and obesity has been demonstrated, and subjects with obesity had markedly higher *T. gondii* IgG titers than non-obese participants<sup>[918]</sup>.

Cholinesterases are enzymes present in cholinergic and noncholinergic tissues, as well as in blood and other body fluids. The AChE is a membrane-bound enzyme mainly found in the brain, muscles, erythrocytes, lymphocytes, and cholinergic neurons<sup>[919,920]</sup>, while BChE is present in the intestine, liver, kidney, heart, lung, brain, and serum<sup>[921,922]</sup>. AChE inhibits activation of macrophages and release of proinflammatory cytokines, such as IL-6, TNF- $\alpha$ , IL-1, and IL-18<sup>[923]</sup>. In rats, *T. gondii* infection was associated with a significant increase in the activity of AChE in whole blood and lymphocytes, and a positive correlation was found between the enzyme activity and number of lymphocytes ( $p < 0.01$ )<sup>[920]</sup>. The BChE is responsible for cholinergic neurotransmission<sup>[924]</sup>, immune responses<sup>[903]</sup>, cardiovascular risk and lipid metabolism<sup>[912]</sup>. Autonomic dysfunctions, characterized by lower vagal and higher sympathetic tone have been documented in chronic inflammatory diseases and aging, associated with a certain level of systemic inflammation<sup>[925-928]</sup>. A correlation between higher vagal tone as determined by increased frequency component of heart rate variability and lower proinflammatory cytokine levels has been reported<sup>[925,927]</sup>. Cholinergic modalities acting through vagus nerve and/or  $\alpha 7$  subunit-containing nicotinic acetylcholine (ACh) receptor-mediated mechanisms have been shown to suppress excessive inflammation in several experimental models of disease<sup>[925-928]</sup>. Vagal ACh binds with this receptor expressed on tissue macrophages in the monocyte-macrophage system, to inhibit the synthesis of proinflammatory cytokines such as TNF, IL-1, IL-6, IL-8, and high-mobility group box 1<sup>[925,927]</sup>. Interestingly, nicotine increased the ACh concentration in the plasma of rabbits<sup>[929]</sup>, and T and B cells, macrophages and DCs all express several components necessary for a functional cholinergic system<sup>[930]</sup>. It must be

**Table 33** Prevalence of liver disease overlap syndromes in selected rheumatic patients (acc. to Selmi *et al* [892]).

	AIH	PBC	PSC	Refs
AIH	-	4.2 to 9%	1.4 to 49.1%	[900]
SLE	2.7 to 20%	2.7 to 15%	1 case	[883,901,902]
pSS	6 to 47%	37 to 57%	11 cases	[902-904]
SSc	11 cases	51.20%	1 case	[902,905,906]

**Table 34** Serum markers of liver and kidney injury in BALB/c mice infected intraperitoneally with tachyzoites of *T. gondii* (RH strain) and examined after 5 days (acc. to Da Silva *et al* [909]; with own modification).

Serum biochemical parameters	Controls (n = 10)	Infected animals (n = 10)
AlAT (U/L)	35.21 $\pm$ 11.73	258.13 $\pm$ 84.37 <sup>a</sup>
Alkaline phosphatase (U/L)	338.44 $\pm$ 120.12	190.87 $\pm$ 78.66 <sup>a</sup>
Albumin (g/dL)	2.21 $\pm$ 0.03	1.51 $\pm$ 0.08 <sup>a</sup>
Total proteins (g/dL)	5.80 $\pm$ 0.40	4.55 $\pm$ 0.44 <sup>a</sup>
Urea (mg/dL)	69.28 $\pm$ 3.10	100.12 $\pm$ 25.75 <sup>a</sup>
Creatinine (mg/dL)	0.96 $\pm$ 0.32	0.87 $\pm$ 0.24

Results represent means  $\pm$  SD. <sup>a</sup>Statistically significant results compared with controls ( $p < 0.05$ ). AlAT, alanine aminotransferase. Nb. it must be noted that serum alkaline phosphatase as well as AlAT and AspAT activities were found to be markedly increased in pregnant women with toxoplasmosis as compared with controls<sup>[910A]</sup>. The difference in the serum alkaline phosphatase concentrations between mice and pregnant women may be explained by the route of *T. gondii* infection (intraperitoneal vs. probably oral, respectively) because this enzyme is elevated mainly in the liver and bile duct disorders.

also noted that the cholinergic antiinflammatory pathway play an important role in the neuroimmune basis of acupuncture<sup>[931]</sup>, frequently used in several neurodegenerative diseases<sup>[932]</sup> and ADs, including rheumatoid arthritis<sup>[933]</sup>, psoriasis<sup>[934]</sup>, inflammatory bowel disease, epilepsy, and migraine<sup>[932,935]</sup>.

In this context, many comorbidities reported in patients with ADs and associated with several viral and other infectious agents, including *T. gondii*, may be at least in part explained by liver damage caused by these pathogens<sup>[98,909]</sup>. The hepatic injury probably establishes a favorable local and systemic environment in the body that facilitates growth and proliferation of these infectious agents, further intensified by the impaired cholinergic modulation of systemic inflammation. In addition, patients with ADs are usually subjected to several invasive procedures, such as endoscopy, otorhinolaryngologic investigation, dental care, surgery, and frequently receive intravenous medications, fluids, blood and/or its components that all increase risk of viral, bacterial and/or parasite infections<sup>[121,936]</sup>.

Several authors reported that hepatitis with a clinical picture resembling acute viral hepatitis may result from *T. gondii* infection<sup>[937-939]</sup>. T cell function in patients with Australia antigen (AA)-associated hepatitis have shown that persistence of this antigen was related to impaired PHA-induced lymphocyte transformation<sup>[940,941]</sup>. Viral hepatitis appeared unlikely to be the sole causal agent in primary biliary cirrhosis, because AA has been demonstrated in the serum of only 15-20% of patients<sup>[942-944]</sup>. Because development and clinical course of these comorbidities are often associated with an increased production of various pro- and antiinflammatory cytokines which are overlapping with T<sub>H</sub>1 and T<sub>H</sub>2 types of cytokines generated by *T. gondii* infection, such an excess of various factors and released biomediators may exert beneficial or harmful effects on the host, depending on their final constellations. These suggestions are in agreement with recent findings that emphasized an important role of *T. gondii* in development of liver damage and *T. gondii*-related hepatitis<sup>[910,945,946]</sup>. The significant

**Table 35** Liver function damage in mice intraperitoneally infected with  $3 \times 10^6$  *T. gondii* trophozoites and treated with azithromycin (250 mg/kg/day for 3 days, p.o.) (acc. to Al-Kaysi *et al* [910]; with own modification).

Group of animals	Total serum protein concn (g/dL)	Serum albumin concn (g/dL)	AIAT (U/L)	AspAT (U/L)	Serum globulin concn (g/dL)	A/G ratio
Controls	7.42	4.86	9.6	10.6	2.56	1.89
	± 0.12	± 0.09	± 0.26	± 0.12	± 0.03	± 0.03
Infected	11.02 <sup>a</sup>	3.50 <sup>a</sup>	59.80 <sup>a</sup>	24.20 <sup>a</sup>	7.52 <sup>a</sup>	0.47 <sup>a</sup>
	± 0.22	± 0.26	± 5.71	± 1.33	± 0.19	± 0.12
Infected and treated	8.38	3.8	10.6	10	4.58	0.83
	± 0.06	± 0.05	± 0.12	± 0.16	± 0.03	± 0.02
Not infected and treated	7.44	4.88	9.2	10	2.56	1.96
	± 0.11	± 0.13	± 0.29	± 0.16	± 0.08	± 0.10

The values are means ± SE of 10 animals per group. <sup>a</sup>Statistically significant differences between respective groups were calculated using ANOVA test at  $p < 0.05$ . A/G, serum albumin to globulin concentration ratio. Nb. it must be noted that serum alkaline phosphatase as well as AIAT and AspAT activities were found to be markedly increased in pregnant women with toxoplasmosis as compared with controls[910A]. The difference in the serum alkaline phosphatase concentrations between mice and pregnant women may be explained by the route of *T. gondii* infection (intraperitoneal vs. probably oral, respectively) because this enzyme is elevated mainly in the liver and bile duct disorders.

**Table 36** Serum biochemical markers of liver and kidney damage in ewes and does with toxoplasmosis (positive serum IgM antibodies directed against *T. gondii*) (acc. to Mahboub *et al* [911]; with own modification).

Bioparameters	Controls (n = 20)	Sheeps with <i>T. gondii</i> infection (n = 15)	Controls (n = 20)	Goats with <i>T. gondii</i> infection (n = 15)
Total protein (g/dL)	4.20 ± 0.15	4.10 ± 0.37	5.44 ± 0.27	4.03 ± 0.80 <sup>a</sup>
Albumin (g/dL)	1.81 ± 0.20	1.24 ± 0.13 <sup>a</sup>	2.15 ± 0.23	0.84 ± 0.3 <sup>a</sup>
Globulin (g/dL)	2.39 ± 0.07	3.11 ± 0.28 <sup>a</sup>	3.47 ± 0.27	3.19 ± 0.63
A/G ratio	0.85 ± 0.08	0.41 ± 0.087 <sup>a</sup>	0.72 ± 0.07	0.34 ± 0.23 <sup>a</sup>
AspAT (U/mL)	58.87 ± 1.92	33 ± 2.69 <sup>a</sup>	67.23 ± 5.09	47.33 ± 3.56 <sup>a</sup>
AIAT (U/mL)	15.11 ± 0.43	22.86 ± 1.99 <sup>a</sup>	15.071 ± 0.81	14.67 ± 2.04
BUN (mg/dL)	24.35 ± 2.07	32.26 ± 2.26 <sup>a</sup>	42.50 ± 2.74	25.34 ± 5.64 <sup>a</sup>
Triglyceride (mg/dL)	17.82 ± 1.29	51.49 ± 6.65 <sup>a</sup>	25.28 ± 2.53	20.38 ± 5.95
Cholesterol (mg/dL)	41.61 ± 4.33	57.84 ± 5.17 <sup>a</sup>	84.15 ± 5.85	51.79 ± 17.80 <sup>a</sup>
CRP (mg/dL)	8.40 ± 1.70	10.71 ± 2.48	8.12 ± 2.37	12.00 ± 8.49 <sup>a</sup>

Results are means ± SE. <sup>a</sup>Statistically significant results compared with respective control values ( $p < 0.05$ ). AspAT, aspartate aminotransferase; AIAT, alanine aminotransferase. BUN, blood urea nitrogen. CRP, C-reactive protein. Nb. it must be noted that serum alkaline phosphatase as well as AIAT and AspAT activities were found to be markedly increased in pregnant women with toxoplasmosis as compared with controls[910A]. The difference in the serum alkaline phosphatase concentrations between mice and pregnant women may be explained by the route of *T. gondii* infection (intraperitoneal vs. probably oral, respectively) because this enzyme is elevated mainly in the liver and bile duct disorders.

relationship between the number of hepatic stellate cells (HSCs) (known to play an important role in development of fibrosis) and *T. gondii* antigens may represent an active role of these cells in liver pathology and the pathobiology of the parasite-related hepatitis<sup>[945]</sup>, especially that HSCs might also affect function of antigen presenting cells, such as DCs, liver macrophages, and Kupffer cells<sup>[947]</sup>.

All these data suggest that liver damage caused by latent chronic *T. gondii* infection has an important impact on both innate and acquired immunity of the host, development of various comorbidities and their clinical course, and improvement or worsening of the host's health. The prevalence of serum anti-*T. gondii* IgG antibodies in different ADs, including PBC, has been presented in **Tables 37 and 38**<sup>[98,129]</sup>.

Finally, it must be emphasized that autoantibodies play an important role in the pathophysiology of renal involvement in systemic ADs, such as SLE, systemic vasculitis, Goodpasture syndrome, and for example in Wegener's granulomatosis the current therapeutic standard is plasma exchange removing pathogenic immune complexes and antibodies<sup>[956]</sup>. These findings are in line with several reports suggesting a close relationship between *T. gondii* infection and development of renal diseases<sup>[957]</sup>, such as nephrotic syndrome<sup>[958,959]</sup>, various types of glomerulopathy<sup>[959-962]</sup>, and kidney transplant recipients<sup>[963-966]</sup>. In this context, it should be noted that many excretory/secretory protein antigens with molecular weights ranging from 19 to 110 kDa released from the purified tachyzoites/bradyzoites of *T. gondii* and various components of the parasite in

samples of human and animal sera, have been demonstrated in both animals and humans infected with the parasite<sup>[950,967]</sup>. These foreign antigens, autoantigens, antibodies, immune complexes, cytokines and other biomediators circulating in blood were filtered by the liver and kidneys, settled down in them, and thus participated in the development of their impaired function and damage.

In summary, these findings suggest that latent chronic *T. gondii* infection is one of the key pathogens responsible for liver and/or kidney damage in patients with various ADs. Abnormalities associated with these injuries may affect innate and/or acquired host immunity and participate in triggering and persistence of several ADs, especially that anti-*Toxoplasma* IgG antibodies have been found in both the sera of patients suffering from many of these clinical entities, and healthy adults<sup>[98,101,968]</sup>, which is in agreement with a cosmopolitan nature of the parasite..

## T. GONDII INFECTION AND AUTOIMMUNE CARDIOVASCULAR DISEASES

**Enhanced generation of proinflammatory cytokines and NO by the parasite is important in the pathogenesis of these disorders ADs**

The Global Burden of Disease data estimated that approximately 8.8% of the disability-adjusted life years of the world's low- and middle-income countries may be attributable to cardiovascular

diseases<sup>[969,970]</sup>. The heart and the vascular system are frequently involved in several ADs, in particular SLE, RA, systemic sclerosis, primary antiphospholipid syndrome, systemic vasculitis, and these cardiovascular disorders are associated with the premature accelerated atherosclerosis<sup>[971-974]</sup>. Inflammatory mechanisms contribute to progressive heart failure, and myocardial infiltration by lymphocytes and mononuclear cells, increased expression of proinflammatory cytokines and circulating autoantibodies are frequently observed in autoimmune myocarditis and dilated cardiomyopathy<sup>[975-977]</sup>. In animal models, activated and self-antigen loaded DCs play an important role in inducing autoimmune myocarditis and heart failure<sup>[978]</sup>.

Molecular mimicry plays an important role in the autoimmune pathogenesis of heart diseases<sup>[979]</sup>. Patients with heart failure have significantly higher levels of proinflammatory cytokines, such as IL-6 and TNF- $\alpha$ , compared with healthy controls<sup>[980-982]</sup>. Studies *in vitro* showed that interleukins TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-2 were found to be related to negative cardiac inotropic activity in a concentration-dependent manner, and mediated by NO as a result of iNOS induction *via* proinflammatory cytokines<sup>[983-986]</sup>. Interestingly, the elevated levels of proinflammatory cytokines, particularly IL-6, IL-1 $\beta$ , and TNF- $\alpha$ , have been repeatedly associated with depressive disorders<sup>[982,987-989]</sup>, even in apparently healthy men<sup>[990]</sup>. Higher levels of proinflammatory markers IL-6 and C-reactive protein have been independently linked with depressive symptoms also in patients with heart failure, even after correcting for disease severity<sup>[987]</sup>. Conversely, ADs and severe infections are considered as risk factors for mood disorders<sup>[991]</sup>. It should be noted that *T. gondii* infection was also found to be associated with mood disturbances<sup>[413,992-996]</sup>.

### *T. gondii* infection

Acquired immunity induced by *T. gondii* is characterized by strong CD4<sup>+</sup> and CD8<sup>+</sup> T cells activity because parasite peptides are efficiently presented to parasite-specific T lymphocytes and T<sub>H</sub>1 type cytokines display cytotoxic T-lymphocyte activity against the infected target cells and the ability to produce large amounts of IL-12, IFN- $\gamma$ , IL-1 $\beta$ , IL-18 and other proinflammatory mediators<sup>[239,997]</sup>. When produced in excess, proinflammatory cytokines end up damaging the host. Moreover, after priming with IFN- $\gamma$ , macrophages exposed to microbial products or TNF- $\alpha$  produce high levels of NO and RNI responsible for microbicidal and microbiostatic activities, especially during the early phase of *T. gondii* infection<sup>[998]</sup>. It is important to note that both NO and TNF- $\alpha$  could induce egress of the parasite tachyzoites from the host infected cells<sup>[999,1000]</sup>, and this may amplify earlier proinflammatory reactions. Cytokine production of CD8<sup>+</sup> immune T cells are polarized to a T<sub>H</sub>1 response following stimulation with tachyzoite-infected macrophages<sup>[1001]</sup>, and IL-15 (this cytokine shares some functions with IL-2) augments CD8<sup>+</sup> T-cell-mediated immunity against infection with the parasite<sup>[1002]</sup>. In addition, IL-17/IL-17 receptor-mediated signaling appeared to be important for generation of an optimal polymorphonuclear leukocytes response against *T. gondii* infection<sup>[1003,1004]</sup>, and otherwise it is known that T<sub>H</sub>17 cells are a subset of CD4 effector T lymphocytes, and cytokine IL-17 is involved in the pathogenesis of ADs<sup>[1005,1006]</sup>. Furthermore, Langrish *et al*<sup>[1007]</sup> established that IL-23 is one of the pivotal factors required for the expansion of a pathogenic CD4<sup>+</sup> T cell population characterized by the production of IL-17, IL-6, TNF, and other factors that induces triggering and maintenance of organ-specific inflammatory ADs. Interestingly, Munoz *et al*<sup>[1008]</sup> showed that IL-23 mediated *T. gondii*-induced immunopathology in the gut resembles key features of inflammatory process in inflammatory bowel disease in humans and in models of experimental colitis in rodents,

**Table 37** Prevalence of anti-*T. gondii* IgG antibodies in 1514 serum samples of patients with various ADs (acc. to Shapira *et al* [98]; with own modification).

Disease/Clinical entity	Anti- <i>T. gondii</i> IgG positive	Geographical region	P-value <sup>c</sup>
Antiphospholipid syndrome (APS) <sup>a</sup>	82/159 (52%)	Europe	< 0.0001
Cryoglobulinemia <sup>b</sup>	65/117 (56%)	Europe	< 0.0001
ANCA-associated vasculitis	45/68 (66%)	Europe	< 0.01
Autoimmune thyroid diseases	68/120 (57%)	Europe	< 0.0001
Systemic sclerosis	46/80 (58%)	Europe	< 0.0001
Rheumatoid arthritis	27/35 (77%)	Europe	< 0.0001
Rheumatoid arthritis	55/152 (36%)	Latin America	NS

<sup>a</sup>Including primary and secondary APS; <sup>b</sup>Including cryoglobulinemia and mixed cryoglobulinemia. <sup>c</sup>P values for the comparison with matched healthy controls of the same geographical region. In addition, the following specific ADs were associated with markedly increased serum anti-*T. gondii* IgG antibodies/autoantibodies: polymyositis [948], RA [107-109], Hashimoto's and Graves' diseases [15,105], Leśniowski-Crohn's disease [120,121], antiphospholipid syndrome [153], Wegener's granulomatosis and other vasculitides [154], autoimmune bullous disease [163], SLE [141], diabetes mellitus type 1 and 2 [102,104], optical nerve and retinal diseases with visual loss (the 22 kDa neuronal antigen found in the patients may represent *T. gondii* antigen [949, 950]).

**Table 38** Serum IgG levels of anti-infectious agents antibodies more prevalent in PBC compared with controls (acc. to Shapira *et al* [129]; with own modification).

Infectious agent	Patients with PBC	Controls	P value
<i>T. gondii</i> (IU/mL)	53.4 $\pm$ 9.1	36.4 $\pm$ 7.6	< 0.001
EBV-EA AI	1.7 $\pm$ 0.2	0.9 $\pm$ 0.2	< 0.0001

AI, antibody index. EBV-EA, Epstein-Barr virus - early antigen. Results are given as mean  $\pm$  SE. Anti-EBV-EA antibodies concentrations positively correlated with anti-*T. gondii* antibody levels in those patients (Spearman correlation  $r = 0.35$ ,  $p < 0.01$ ). A similar positive correlation was detected in PBC patients between anti-EBV-EA and cytomegalovirus antibodies levels ( $r = 0.32$ ,  $p < 0.01$ ), which may suggest a secondary origin of their generation as compared with the primary and the same *T. gondii*-related IL-21 type 1 cytokine stimulus intensity required to control chronic viral infection [951-953]. It should be added that IL-21 mediates its critical immunosuppressive effects (it decreases specific immunoglobulin production [951,954]) by inducing IL-10 through IL-6 or IL-27 [955].

independent of IL-17.

**Myocarditis.** *T. gondii* infection is common in cats, and in one study of clinically ill animals, the antibodies against the parasite were detected in 31.6% of the 12,628 cats analyzed<sup>[1009]</sup>. Some cats had chronic toxoplasmosis manifesting as myocarditis with arrhythmias, and/or other diseases<sup>[1009-1012]</sup>. The worldwide seroprevalence of toxoplasmosis was estimated to be up to 77% causing inflammatory type of cardiovascular disease, with 19% of AIDS cardiomyopathy associated with acute myocarditis<sup>[26,969,1013,1014]</sup>. Myocarditis caused by *T. gondii* infection often manifests atrial and ventricular arrhythmias, heart failure, AV block and even sudden death, and in several patients focal myocarditis was the only sequel of acute toxoplasmosis<sup>[1015-1017]</sup>. Recently, Hamidinejat *et al*<sup>[1015]</sup> found that the positivity rate of increased serum anti-*T. gondii* levels of IgG and IgM antibodies among 48 patients aged 40-55 years with acute myocardial infarction, was markedly higher than in control volunteers (**Table 39**). The ORs for the associations were 4.86 with 95% CI = 2.05-11.53 and 6.83, CI = 1.43-32.79, respectively (80.82% probability estimated according to the Bradford Hill criteria indicated a causal association). It must be noted that *T. gondii* was found to be the second after rubella among three most frequent fetal heart infections<sup>[1018]</sup>, and acute myocarditis due to the parasite was also described in newborns<sup>[1019]</sup>. Furthermore, the study of A'aziz *et al*<sup>[1020]</sup> demonstrated that 24.7% of sera from

54 women with toxoplasmosis were positive for anticardiolipin and antiphospholipid antibodies compared with no such antibodies revealed in 14 healthy controls ( $p < 0.0412$ ). In addition, in patients with APS Zinger *et al*<sup>[153]</sup> found a significantly higher seroprevalence of IgM antibodies to *T. gondii* compared with controls, which may suggest acute or chronic infection with the parasite, especially that IgM antibodies may persist for years after infection<sup>[1021]</sup>, and heart involvement is frequent in this clinical entity and SLE<sup>[1022,1023]</sup>.

Leak & Meghji<sup>[1011]</sup> reported 18 patients with *T. gondii* infection, who presented with heart disease characterized by arrhythmias (including atrial fibrillation, ventricular arrhythmias and heart block), atypical chest pain, pericarditis and cardiac failure. One of those individuals had acute toxoplasmosis and the other 17 patients had chronically increased anti-*T. gondii* titers. Azab *et al*<sup>[1024]</sup> estimated *T. gondii* antibodies in patients with cardiomyopathy and found that 21.4% of 56 studied samples were positive, mostly in individuals with ischemic disease. In another study, Sibalic *et al*<sup>[1025]</sup> showed the presence of *Toxoplasma* specific antibodies (analyzed by the Sabin-Feldman dye test, *i.e.* probably the best test available so far) in 86% of their 183 patients with cardiac diseases (74 of the patients had acute myocarditis, myopericarditis, or acute pancarditis; 83 had cardiomyopathy; and 26 had cardiac disorders of undefined type) and 21% of them had high titers, as compared with the values of two control groups (51% and 58%).

**Chronic heart failure (CHF).** Disturbances of the cardiovascular, neuroendocrine and immune systems are responsible for development of CHF. It was suggested that patients with CHF may be at increased risk of various opportunistic infections, especially *T. gondii*, due to their impaired immune status and global dissemination of the parasite<sup>[23]</sup>. Yazar *et al*<sup>[112]</sup> found that 66 of 97 patients with CHF had a significantly higher seropositivity rate for anti-*T. gondii* antibodies compared with 50 healthy volunteers (68% vs. 36%,  $p < 0.05$ ). In addition, other authors reported that patients with CHF have elevated serum IL-6 levels<sup>[1026]</sup>, and otherwise it was established that pretreatment of unelicited murine peritoneal macrophages with this cytokine enhanced intracellular multiplication of the parasite in a dose-dependent manner<sup>[208,1027]</sup>.

Persistent hypoxia in patients with CHF creates a beneficial tissue environment for the intracellular multiplication of the protozoan, because it induces production of host cell hypoxia-inducible factor 1 (HIF1), required for the parasite growth and survival, even at physiologic oxygen levels<sup>[1028-1030]</sup>. HIF1 $\alpha$  stimulated synthesis and release of proinflammatory cytokines IL-1, IL-6, IL-8, NO, and different growth factors (including TGF- $\beta$ 3) by vascular endothelial cells (**Table 40**), and intensified subclinical inflammatory reactions<sup>[1030]</sup>. Nb. impaired function of the CO<sub>2</sub>, AQP1, AQP4 gas channels caused by chronic *T. gondii* infection may also result in hypoxia and thus enhance neuroinflammation in autistic individuals<sup>[1031]</sup>. These abnormalities may at least in part be responsible for various biochemical disturbances and clinical manifestations observed in patients with CHF and some ADs, such as for example inflammatory bowel disease<sup>[120,1032]</sup>.

Vredevoe *et al*<sup>[1033]</sup> demonstrated that a subgroup of individuals with heart failure exhibited NK cell anergy to activation by cytokine stimulants such as IL-2 and IFN- $\gamma$ . NK cells, which represent about 10-15% of peripheral blood lymphocytes, is an important cytolytic component of the innate immunity. IL-6 promotes NK cell production of IL-17 during toxoplasmosis<sup>[1034]</sup>, and an exaggerated T<sub>H</sub>17 response may lead to severe inflammatory responses and development of ADs<sup>[1035,1036]</sup>. *T. gondii* can actively infect almost all nucleated cell type and preferentially invades immature DCs<sup>[563]</sup>.

**Table 39.** Frequency of seropositive anti-*T. gondii* IgG and IgM antibodies in patients with acute myocardial infarction (acc. to Hamidinejat *et al* [1015]; with own modification).

Serum anti- <i>T. gondii</i> antibodies	Patients with acute myocardial infarction (n = 48)	Controls (n = 48)
IgG (+)	32 (66.66%) <sup>a</sup>	14 (29.2%)
IgM (+)	11 (22.9%) <sup>a</sup>	2 (4.2%)

<sup>a</sup> Statistically significant results compared with respective controls ( $p < 0.05$ ).

**Table 40** Effects of hypoxia inducible gene expression [1030].

Erythropoietin
IL-1, IL-6, IL-8
Nitric oxide synthase-2
Heme oxygenase-1
Ornithine decarboxylase; hexokinase 2
Phosphofructokinase L; phosphoglycerate kinase-1
Pyruvate kinase M; glucose transporter-1, -3
Lactate dehydrogenase A
Glyceraldehyde-3-phosphate dehydrogenase
Insulin-like growth factor-2; enolase 1
Aldolase A, C; adenylate kinase 3
Pituitary adenylate cyclase-activating polypeptide
Transforming growth factor $\beta$ 3
Vascular endothelial growth factor

Persson *et al*<sup>[243]</sup> demonstrated rapid transmission of *T. gondii* from infected DCs to adjacent effector NK cells. However, the parasite fails to activate DCs in the process, and renders them resistant to subsequent activation by TLR ligands or the immune-system-intrinsic maturation signal CD40L<sup>[563]</sup>. It should be emphasized that maternal microchimerism may also play an important role in dissemination of *T. gondii* and triggering/development of some heart ADs because it was reported that maternal cells (“immigrant cells”) were identified in affected cardiac myocytes, probably being targets of the immune response (*i.e.* “allo-autoimmunity”)<sup>[1037,1038]</sup>, and therefore one cannot exclude that such cells are packed with the parasite and/or its antigens. Finally, it is important to note that extracellular vesicles also are involved in the pathogenesis of ADs<sup>[1039]</sup> and *T. gondii* antigen-pulsed DC-derived exosomes, as well as exosomes released from macrophages infected with the parasite or other intracellular pathogens induced a stimulatory proinflammatory response *in vitro* and *in vivo* against infection with intracellular microbes<sup>[1040,1041]</sup>.

The above-presented data may be supported by the recent finding of strong correlations between the prevalence of toxoplasmosis and heart diseases in a set of 88 countries, *e.g.* the highly positive correlation was found between prevalence of toxoplasmosis and the inflammatory heart disease (DALY:  $p = 0.025$ , mortality:  $p < 0.001$ )<sup>[24]</sup>. Moreover, the accelerated atherosclerotic process in ADs associated with the heart and/or vessels inflammation<sup>[768,1042,1043]</sup> probably is due to chronic *T. gondii* infection<sup>[525]</sup>.

In summary, there is a high frequency of cardiovascular diseases in patients with ADs. Studies *in vitro* showed that proinflammatory cytokines such as TNF- $\alpha$ , and IL-2 have been related to negative cardiac inotropic effects in a concentration-dependent manner, and mediated by NO. Acute and latent chronic *T. gondii* infections may seriously affect heart function and clinical course of cardiac disease leading to triggering and development of cardiovascular diseases in patients with ADs, particularly in those with impaired innate and/or acquired immunity. Increased generation of IL-12, IFN- $\gamma$ , IL-6, TNF, IL-1, and especially IL-12<sup>[1044]</sup>, IL-17 and IL-23, as well as NO

during such infections may be involved in the pathogenesis of several ADs. The accelerated atherosclerotic process frequently observed in these clinical entities may at least in part be due to *T. gondii* infection.

## POSSIBLE LINK BETWEEN LATENT CHRONIC *T. GONDII* INFECTION AND DEVELOPMENT OF RA

### Important role of the pathogen's cysteine cathepsin proteases in these processes

Several authors suggested that bacterial, viral and parasitic infections are known to induce and/or exacerbate ADs<sup>[1045-1047]</sup>, mainly by the mechanism of molecular mimicry<sup>[1046]</sup>. *T. gondii* infection has been reported to occur at increased frequency in RA<sup>[98,107,111,1048-1051]</sup>. For example, El-Henawy *et al*<sup>[1049]</sup> found a significantly higher seroprevalence of anti-*Toxoplasma* IgG antibodies among RA patients (46/60) compared to controls (29/60) (76.7% vs. 48.3%, respectively,  $p < 0.001$ ), and the anti-*T. gondii* IgG titre was markedly higher in patients (median, range = 232.940; 8.949-653.242 IU/mL) than controls (68.820; 2.450-318.945 IU/mL), respectively,  $p < 0.001$ . A positive correlation was established between disease activity and *Toxoplasma* seropositivity<sup>[1048-1050]</sup>. Recently, a meta-analysis of articles addressing the association between RA and toxoplasmosis showed that the combined OR was 3.30 (95% CI: 2.05 to 5.30) with  $p < 0.0001$ <sup>[1051]</sup>.

*T. gondii* seropositive RA patients had longer disease duration and morning stiffness, anti-cyclic citrullinated protein antibodies and rheumatoid factor (RF) than the parasite seronegative individuals<sup>[1048]</sup>. It was demonstrated that such patients develop antibodies to proteins containing citrullinated arginine residues, as essential parts of the antigenic determinants recognized by the RA autoantibodies<sup>[1052]</sup>. Citrullination (or deimination) is an enzyme-catalyzed process in which the positively charged NH<sub>2</sub>-group of arginine is hydrolyzed to a neutral oxygen group, and it is this oxygen group of peptidyl citrulline that is specifically recognized by autoantibodies in RA<sup>[1052,1053]</sup>. It must be noted that citrullination only occurs in certain specialized cell types (*e.g.* myelin basic protein in glia cells) and in certain types of dying cells<sup>[1052,1053]</sup>. Importantly, *T. gondii* share a high degree of sequence homology with human histones, and it was suggested that the same or similar histone posttranslational modifications (PTM) (*e.g.* citrullination, acetylation, methylation, phosphorylation, ubiquitination) are present in the parasite and that these PTM have similar functions in *T. gondii*<sup>[1054]</sup>. Recently, it was reported that the positivity for anti-citrullinated protein antibodies anti-CCP-2 and anti-CCP-3 provide the most specific identification of RA patients<sup>[1055]</sup>. Interestingly, cigarette smoking is not associated with the development of anti-peptidyl arginine deiminase 4 autoantibodies in RA<sup>[1056]</sup>.

*T. gondii* is an arginine auxotroph that derives its arginine requirement from the host cell cytoplasm. Fox *et al*<sup>[182]</sup> showed that arginine deprivation efficiently blocked the replication of intracellular parasite, and addition of citrulline rescued the growth defect observed in the absence of exogenous arginine. Arginine starvation was found to efficiently trigger differentiation of replicative tachyzoites (in both type I strain RH and type II strain PLK) into slow growing latent bradyzoites forms contained within stable cyst-like structures, and these same pathogens expressing bradyzoites antigens can be efficiently switched back to rapidly proliferating tachyzoites several weeks after arginine starvation<sup>[182]</sup>. *T. gondii* infection elicits a strong proinflammatory Th1 immune response, and upregulation of host arginine is an important mechanism that can deplete the

local availability of arginine and downregulate the production of NO *via* iNOS<sup>[1057]</sup>. In addition, among antiinflammatory cytokines produced by macrophages, DCs, and other cells during infection with the microbe<sup>[1058]</sup>, IL-10 is a relatively weak inhibitor of iNOS levels while TGF- $\beta$ 1 negatively regulates iNOS concentrations through multiple mechanisms<sup>[1059]</sup>. Moreover, TGF- $\beta$ 1 generation in the patients with RA plus toxoplasmosis was found to be significantly increased compared to both individuals with RA alone and controls<sup>[1060]</sup>. This causes disturbances in the homeostasis of NO generation during host-parasite interaction, especially that the pathogen inhibits also NO production induced by different macrophage-activating stimuli, as well as facilitates parasite replication in activated macrophages<sup>[565]</sup>, and inducible NO is essential for host control of persistent infection with the intracellular pathogen<sup>[880]</sup>.

Natural microchimerism existing not only in the blood of patients with RA but also in the rheumatic nodules<sup>[1061,1062]</sup>, may play an important role in both dissemination of the parasite and the pathogenesis of RA. Also, an association of acute infection by the parasite with onset of Still's disease, a juvenile form of RA, has been reported<sup>[109]</sup>. Recently, Al Kalaby *et al*<sup>[1063]</sup> found that toxoplasmosis positive aborted women were about 4.4 folds more likely to have RA (OR CI 95% = 4.4, 1.4-13.8,  $p \leq 0.01$ ). Eaton *et al*<sup>[1064]</sup> demonstrated also an inverse correlation between the prevalence of schizophrenia and RA, the finding confirmed later on by Oken & Schulzer<sup>[1065]</sup> data obtained from 1323 inpatients with schizophrenia. It was suggested that these two clinical entities share a common infectious and/or immune etiology<sup>[1066]</sup>, and recently, a seroprevalence of anti-*T. gondii* IgG antibodies in patients with schizophrenia has been reported<sup>[502]</sup>.

Mousa *et al*<sup>[108]</sup> treated 29 toxoplasmosis antibody-positive RA individuals with pyrimethamine and sulfadoxine, with some receiving spiramycin in addition, and found that clinical manifestations of RA markedly improved in 16 of them. Natural autoantibodies may also have a therapeutic potential because they exerted a protective effect in ADs, involving both cellular and humoral processes<sup>[1045,1047]</sup>. Natural autoantibodies and some immunological mediators were also found in the sera of healthy individuals<sup>[378,1066,1067]</sup>, and they were polyactive, mostly of IgM isotype and reacted with both self and non-self antigens. For example, RF was reported to be protective against the development of lupus nephritis, and a highly significant correlation was found between the presence of IgM-RF and the absence of kidney disease in the patients with SLE<sup>[1068]</sup>. It is interesting to note that coffee consumption seems to increase the risk of developing RA and type 1 diabetes mellitus. On the other hand, the beverage may exert a protective role against MS, ulcerative colitis, and primary sclerosing cholangitis<sup>[1069]</sup>.

Rheumatoid meningitis (RM) is often observed in well-controlled RA patients<sup>[1070,1071]</sup> or even manifested as the first symptom of the disease<sup>[1072-1074]</sup>, suggesting an ongoing intense inflammatory process in the CNS. On the other hand, Importantly, *T. gondii* share idiopathic intracranial hypertension associated with headaches and aseptic meningitis may be caused by reactivation of latent cerebral toxoplasmosis because *T. gondii* frequently infects plexus choroideus in the brain resulting in its inflammation and overproduction of cerebrospinal fluid<sup>[1075-1077]</sup>. Nardone *et al*<sup>[1078]</sup> presented a patient with RA history lasting for 24 years who developed headaches as well as gait and speech disturbances after treatment with adalimumab, an anti-TNF- $\alpha$  therapeutic agent. The authors suggested that this TNF- $\alpha$  inhibitor represent risk of development of cerebral toxoplasmosis. Lassoued *et al*<sup>[1079]</sup> also reported two patients who developed toxoplasmic retinochorioretinitis after antitumor

**Table 41** Selected ubiquitous cathepsins B, C and L and their functions in the immune system (acc. to Conus & Simon [1101]; with own modification).

Cathepsin	Function	Involvement in disease
Cath B	Early neutrophil, T and B cell apoptosis,	Inflammatory disorders
	TLRs signaling and TNF- $\alpha$ production,	Alzheimer's disease
	Selectors for peptide-MHC II complexes	Cancer
Cath C	Activation of granzymes A and B in NK cells and T lymphocytes	Inflammatory disorders
Cath L	TLRs signaling,	Rheumatoid arthritis
	Selectors for peptide-MHC II complexes,	Atherosclerosis
	NKT and CD4 T cells production,	Thymic pathology
	Neuronal cell death and osteoclastic bone degradation	Autoimmune diabetes <sup>a</sup>
		Cancer

MHC II, major histocompatibility class II compartments; NKT, natural killer T lymphocytes; TLR, toll-like receptors. Granzymes A and B are neutral serine proteases expressed in the granules of NK cells and activated cytotoxic T lymphocytes (*i.e.* CD8<sup>+</sup> T cells). <sup>a</sup>Cath L activity is essential for the development and progression of CD8<sup>+</sup> T cell-mediated murine autoimmune type 1 diabetes [1102, 1103].

**Table 42** Proteases characterized in *T. gondii*, their classes, function and localization (acc. to Li *et al* [1088]; with own modification).

Protease class	Specific protease	Protease function and localization	Refs
Cysteine	TgCPB/Toxopain-1	Invasion; rhostry protein processing	[1108,1109]
	TgCPCs	Growth and replication; cleavage of dipeptides from N-terminal in cytosol	[1110]
	TgCPL	Invasion; maturation of micronemal proteins; localized to the vacuolar compartment	[1111]
Metalloproteinase	Toxolysin 4	Invasion/egress; localized to the micronemes	[1112]
Serine	TgSUB1	Invasion, maturation of rhostry proteins; host cell attachment; localized to the micronemes	[1113]
	TgSUB2	Invasion; maturation of rhostry proteins; localized to the rhostry	[1114]
	TgROM2,4,5	Surface protein sheddase; localized to tachyzoite plasma membrane	[1115]

necrosis factor treatment in RA. It seems therefore that treatment regimens with TNF- $\alpha$  antagonists (infliximab, etanercept) in RA and spondyloarthropathies may cause reactivation of chronic cerebral toxoplasmosis. These biologic agents exert both anti-TNF- $\alpha$ - and anti-IFN- $\gamma$ -related inhibitory effects, which favor *T. gondii* replication in the brain and/or other tissues, thus triggering development of multiple adverse CNS and/or ophthalmologic abnormalities characteristic for chronic infection with the parasite<sup>[117,1080-1086]</sup>.

#### ***T. gondii* cysteine cathepsins may contribute to triggering, development, and/or progression of RA**

Juvenile idiopathic arthritis (JIA) is the most common childhood autoimmune rheumatic disease. Taubert *et al*<sup>[1087]</sup> characterized the expression levels of cathepsins (Cath) B, D, and L in JIA and found that expression of Cath B, D and L was on comparable levels in the synovectomy tissue of 16 hemophilic arthropathy and 12 RA patients. The following graduation of expression was established: Cath D > Cath L > Cath B. The authors suggested that this may play a similarly important role in destroying synovial tissue and cartilage matrix in the course of these clinical entities<sup>[1087]</sup>.

Cathepsins contribute to several pathophysiological processes including these characteristic for RA<sup>[1088]</sup>, such as antigen presentation in the immune system<sup>[1089,1090]</sup>, neuropeptide and hormone processing<sup>[1091]</sup>, and collagen turnover in bone and cartilage<sup>[1092]</sup>. In patients with RA or osteoarthritis, the Cath B, L, K, and S were expressed in joint cartilage and synovial cells, as well as infiltrating immune cells<sup>[1089]</sup>, thus contributing to cartilage destruction and immune response<sup>[1093]</sup>. Glycosaminoglycans predominantly expressed in bone and cartilage (chondroitin, keratan sulphates) potentially inhibit the collagenase activity of Cath L at 37°C, they stabilize the cathepsins at neutral pH (as demonstrated for Cath B), and chondroitin and dermatan sulphates were shown to dramatically increase the collagenolytic activities of Cath L and Cath S<sup>[1094]</sup>.

Cathepsins are expressed in macrophages, vascular endothelial and smooth muscle cells of atherosclerotic lesions<sup>[1095-1097]</sup>. In patients

with RA and osteoarthritis, the cathepsins are expressed in joint cartilage and synovial cells and in infiltrating immune cells<sup>[1089]</sup>. They contribute to cartilage destruction and modulate inflammation, immune responses, cellular functions, and are involved in development of several diseases<sup>[1098-1100]</sup> (**Table 41**).

*T. gondii* cathepsin proteases act classically as lysosomal hydrolases that digest endogenous and exogenous endocytosed polypeptides<sup>[1104,1105]</sup>. They function in the parasite microneme and rhostry protein maturation, host cell invasion, replication, and nutrient acquisition<sup>[1104,1106]</sup>. Cathepsins can also play a role in degradation of matrix proteins, antigen presentation, TNF- $\alpha$ -induced apoptosis, spermatogenesis, and tumor invasion<sup>[1104,1107]</sup>. *T. gondii* specific protease function and localization are presented in **Table 42**<sup>[1088]</sup>.

Cysteine proteases play a major role in invasion and intracellular survival of a number of pathogenic parasites. Que *et al*<sup>[1108]</sup> showed that the *T. gondii* Cath B (toxopain-1) was localized to rhostry (secretory organelles) and was critical for parasite invasion and rhostry protein processing. This cathepsin was found to be essential for infection in a chicken model of congenital toxoplasmosis<sup>[1109]</sup>. Furthermore, Cath B suppresses proliferation of peripheral blood mononuclear cells<sup>[1104]</sup> and therefore participates in the immunosuppressive activity of the parasite proteases finally leading to impairment of the host immune defense.

Interestingly, cigarette smoking infection of vascular endothelial cells by *T. gondii* tachyzoites may be an important source of cathepsins because the parasite genome expresses five members of the cathepsin proteases, including one Cath L-like (TgCPL), one Cath B-like (TgCPB), and three Cath C-like (TgCPC1, 2, and 3) proteases<sup>[1104,1116]</sup> (**Table 43**).

Dou *et al*<sup>[1117]</sup> showed that *T. gondii* tachyzoites ingested host cytosolic proteins and digested them using Cath L (one of the most potent mammalian collagenases and elastases expressed in most tissues and cell types, regulated by proinflammatory cytokines) and other proteases within its endolysosomal system. Both virulent type

**Table 43** Features of *T. gondii* cathepsin-like proteases (acc. to Dou & Carruthers, [1104]; with own modification).

Cathepsin protease	Mature molecular weight (kDa)	Activity	<i>T. gondii</i> stage expression
TgCPL	30	endopeptidase	tachyzoite/bradyzoite
TgCPB	28	endo/exopeptidase	tachyzoite/bradyzoite
TgCPC1	35	exopeptidase	tachyzoite
TgCPC2	44	exopeptidase	tachyzoite
TgCPC3	32	exopeptidase	sporozoite

**Table 44** Body weight and plasma leptin concentrations in rats intraperitoneally infected with *T. gondii* (acc. to Baltaci & Mogulkoc [1156], with own modification).

Study group	Body weight before the study (g)	Body weight after four weeks (g)	Plasma leptin levels (ng/mL)
Control rats (n = 10)	266.00 ± 32.81	270.50 ± 33.70	4.09 ± 1.15
Infected animals (n = 10)	263.50 ± 44.16	269.50 ± 42.78	7.53 ± 1.55 <sup>a</sup>

Results represent mean ± SD. <sup>a</sup>Statistically significant result ( $p < 0.01$ ).

I and avirulent type II strain parasites ingested and digested host-derived proteins, indicating that the pathway is not restricted only to highly virulent strains. Larson *et al*<sup>[1118]</sup> showed that TgCPL was associated with a discrete vesicular structure in the apical region of extracellular parasites but was found in multiple puncta throughout the cytoplasm of intracellular replicating parasites.

Cath Cs are critical to *T. gondii* growth and differentiation<sup>[1106]</sup>. *T. gondii* Cath Cs were required for peptide degradation in the parasitophorous vacuole (PV), as the degradation of the marker protein, E. coli  $\beta$ -lactamase, secreted into the PV of transgenic tachyzoites was completely inhibited by the Cath C inhibitor. TgCPC1 was the most highly expressed cathepsin mRNA in tachyzoites, and three cathepsins, TgCPC1, TgCPC2, and TgCPB, were undetectable in *in vivo* bradyzoites<sup>[1106]</sup>.

In summary, chronic *T. gondii* infection seems to play an important role in triggering and development of RA, osteoarthritis, occurrence of lesions in atherosclerosis, and other entities. Reactivation of cerebral toxoplasmosis together with neurological/ophthalmologic disorders observed in the patients treated with TNF blockers strongly support this suggestion. Infection of vascular endothelial cells by *T. gondii* tachyzoites may become an important source of additional cathepsins supply besides of these physiologically present in the host cells, because they expresses five members of the cysteine cathepsin proteases.

## IMPORTANT ROLE OF LEPTIN AND OBESITY IN TRIGGERING AND MAINTENANCE OF INFLAMMATION AND AUTOIMMUNITY

***T. gondii* infection causes a significant increase in serum leptin levels in both animals and humans, and there is a significant positive association between the parasite seropositivity and obesity**

### ADs

Elevated circulating leptin levels makes obese individuals more susceptible to developing several ADs including SLE, RA, MS, psoriasis, autoimmune diabetes, autoimmune thyroiditis, and inflammatory bowel disease<sup>[1119,1120]</sup>. Matarese *et al*<sup>[1121]</sup> suggested that high serum leptin concentrations may be either a contributing factor<sup>[1122,1123]</sup> or a marker of disease activity<sup>[1124,1125]</sup>. Importantly, a surge of serum leptin preceded onset of autoimmune encephalomyelitis and correlated with development of pathogenic T cell responses<sup>[1126]</sup>. Moreover, leptin accelerated autoimmune diabetes in female NOD mice<sup>[1127]</sup>.

Leptin, the product of obese gene, is an adipocytokine

that promotes activation of and phagocytosis by monocytes/macrophages and their secretion of proinflammatory cytokines, NO, cyclooxygenase 2, and leukotriene B<sub>4</sub><sup>[1128-1130]</sup>. Moreover, leptin can induce chemotaxis of neutrophils and the release of oxygen radicals, such as hydrogen peroxide and superoxide anion<sup>[1131,1132]</sup>. Leptin receptors were found also on the endothelial cells<sup>[1133]</sup>, vascular smooth muscle cells<sup>[1134]</sup>, and macrophages and foam cells<sup>[1135]</sup>.

Structurally, leptin resembles cytokine IL-2 in particular and is a crucial T-cell growth factor<sup>[1136]</sup>. The levels of this biofactor were increased in infections and autoimmune disorders, or after exposure to inflammatory stimuli such as LPS, TNF- $\alpha$ , and IL-1<sup>[1127]</sup>. Leptin displayed proinflammatory properties that were most evident in inflammation and autoimmunity processes<sup>[1119,1137-1139]</sup>. In cultured T-lymphocytes, leptin stimulation caused shift toward T<sub>H</sub>1 population with increased production of proinflammatory cytokines like TNF- $\alpha$ , IFN- $\gamma$ , IL-2 and IL-18, and decreased generation of T<sub>H</sub>2 cytokines IL4, IL-5 and IL-18<sup>[1140,1141]</sup>.

Leptin can affect thymic homeostasis and the secretion of cytokines IL-1 and TNF- $\alpha$ <sup>[1120]</sup>, enhanced GM-CSF production in peritoneal macrophages<sup>[1142,1143]</sup> and mediated both proliferative and antiapoptotic activities in a variety of cell types, including T cells<sup>[1144]</sup> and monocytes<sup>[1145]</sup>. In human umbilical vein endothelial cells (HUVECs), human adult vein endothelial cells (HAVECs) and human microvascular endothelial cells (HMECs) leptin concentration-dependently (10-50 nM/L) reduced apoptosis by 20%, and increased expression of the apoptosis inhibitor bcl-2 by 55% (both  $p < 0.05$ )<sup>[1146]</sup>. Leptin enhanced availability of apoptotic cell-derived self-antigen in SLE<sup>[1147]</sup>; interestingly, there were also disturbances of apoptotic cell clearance in SLE<sup>[1148]</sup>. In lupus mice, leptin *via* cAMP, promoted the phagocytosis of apoptotic cell-derived self-antigen(s) by macrophages and subsequent proliferation of T cells reactive to apoptotic antigenic debris<sup>[1147]</sup>.

Leptin contributes also to atherosclerosis and to the increased risk of cardiovascular disease in obese individuals because increased human plasma concentrations of the cytokine have been independently associated with the common carotid artery *intima-media* thickness, an early marker of atherosclerosis<sup>[1134,1149,1150]</sup>. In human atherosclerotic lesions, leptin mediated atherosclerosis *in vitro* and *in vivo*, and induced (at doses 10-40 ng/mL) proliferation of the HUVECs and elevation of matrix metalloproteinases (MMPs) MMP-2 and MMP-9 expression, in a dose-dependent manner<sup>[1151]</sup>. Leptin accelerated cholesteryl ester accumulation in human monocyte-derived macrophages by increasing acyl-CoA: cholesterol acyltransferase 1 expression and cholesterol efflux from these cells<sup>[1152]</sup>, thus probably being responsible at least in part for

development of foam cells during *T. gondii* infection<sup>[526]</sup>. Finally, it must be noted that ADs are usually more prevalent in females<sup>[1153]</sup>, and females are relatively hyperleptinemic, whereas males are relatively hypoleptinemic<sup>[1154,1155]</sup>.

*T. gondii* infection. Baltaci & Mogulkoc<sup>[1156]</sup> established that rats infected with *T. gondii* had significantly increased plasma leptin levels four weeks after the intraperitoneal injection of live parasites as compared with control animals (Table 44).

Recently, Reeves *et al*<sup>[918]</sup> reported a significant positive association between *T. gondii* seropositivity and obesity ( $p = 0.01$ ). It was found that these obese individuals had a markedly higher *T. gondii* IgG titers compared to normal weight participants. Van Dielen *et al*<sup>[1157]</sup> demonstrated that in severely obese individuals increased leptin levels correlated with increased concentrations of inflammatory markers. Similarly, Aygun *et al*<sup>[1158]</sup> showed that obese prepubertal children had markedly elevated mean serum leptin concentration, and significantly increased serum IL-1 $\beta$ , IL-6, and TNF- $\alpha$  levels (Table 45). Other investigators demonstrated also increased serum NO levels in overweight/obese women<sup>[1159]</sup>, and significant amounts of iNOS and IL-6 expression in adipose tissue macrophages<sup>[1160]</sup>. Nb. it should be noted that sustained TNF production by the central nervous system infiltrating macrophages promoted progressive autoimmune encephalomyelitis<sup>[1161]</sup>, and IL-6 levels were elevated in chronic inflammatory conditions, such as RA, and some other ADs<sup>[1162-1164]</sup>.

It must be noted that many authors suggested a strong link between obesity (“the low grade inflammation state”), adipokines and several immune mediated ADs, being obesity as not a passive bystander<sup>[1165]</sup>. Because latent chronic *T. gondii* infection has a high prevalence worldwide, and 23% of the European adult population are now obese, while approximately 57% of the world’s adult population is projected to be obese or overweight by 2030<sup>[1166]</sup>, health disturbances associated with inflammation and autoimmunity due to chronic infection with the parasite may be a serious global public health hazard in development of ADs.

## OLFACTORY DYSFUNCTION WITH IMPAIRED SENSE OF SMELL FREQUENTLY REPORTED IN PATIENTS WITH ADs, NEURODEGENERATIVE DISEASES, AND DEPRESSION MAY BE CAUSED BY LATENT CHRONIC *T. GONDII* INFECTION

### ADs

The olfactory route for infectious and/or toxic agents may initiate or exacerbate autoimmune pathology, such as for example autoimmune hepatitis, or neuroinflammation, and accounts for common manifestations in a wide range of ADs and neuropsychiatric disorders<sup>[170,1167-1173]</sup>. The link between autoimmunity and impaired smell has been demonstrated in patients with several ADs including SLE, multiple sclerosis, Sjögren’s syndrome, schizophrenia, diabetes mellitus, ASD, Wegener’s granulomatosis, myasthenia gravis, neuromyelitis optica, hereditary angioedema, and polydermatomyositis<sup>[1174-1187]</sup>, and in neurodegenerative diseases, such as Alzheimer’s disease, Parkinson’s disease, and Down syndrome<sup>[414,1188-1190]</sup>. In a recent review, Chen *et al*<sup>[1191]</sup> reported that there were significant associations between maternal ADs developed during pregnancy or maternal thyroid disease and the risk of ASD in offspring. Perricone *et al*<sup>[1174]</sup> and others<sup>[1192]</sup> found that patients with SLE and disturbances in their olfactory functions

**Table 45** Serum proinflammatory cytokines and leptin concentrations in prepubertal obese children compared with controls (acc. to Aygun *et al* [1158]; with own modification).

Parameter	Obese children	Controls	P value
Leptin (ng/mL)	19.9 ± 7.4	7.9 ± 5.1	< 0.001
IL-1 $\beta$ (pg/mL)	33 ± 8.9	3.6 ± 1	< 0.001
IL-2 (U/L)	0.4 ± 0.1	0.9 ± 0.1	< 0.01
IL-6 (pg/mL)	45.2 ± 11.8	13.1 ± 3.9	< 0.001
TNF- $\alpha$ (pg/mL)	9.2 ± 2.3	3.9 ± 1	< 0.001
E-selectine (ng/mL)	78 ± 38	59 ± 29	< 0.01
hsCRP (mg/L)	4.1 ± 4.8	0.9 ± 1.5	< 0.001

Results are mean ± SD; CRP, C-reactive protein; hs, high-sensitivity.

**Table 46** Olfactory bulb volumes in patients with schizophrenia, first-degree relatives, and healthy controls (acc. to Turetsky *et al* [1183]; with own modification).

Group	Volumes (mm <sup>3</sup> )			
	Left bulb		Right bulb	
	Mean	SD	Mean	SD
Patients (n = 11)	70.82 <sup>a</sup>	11.77	70.18 <sup>b</sup>	14.11
Control individuals (n = 20)	81.62	16.91	85.97	13.75
Relatives (n = 19)	83.51	17.96	75.41 <sup>c</sup>	13.56

<sup>a</sup>Significant difference between patients and relatives (MANOVA,  $p < 0.05$ , two-tailed). <sup>b</sup>Significant difference between patients and controls ( $p < 0.05$ ). <sup>c</sup>Significant difference between relatives and controls ( $p < 0.05$ ).

**Table 47** Preferential localization of *T. gondii* ME49 strain cysts in different regions of murine brain at 2 and 6 months post inoculation (acc. to Melzer *et al* [1214]; with own modification).

Brain region	Two months after inoculation <sup>a</sup>	Six months after inoculation <sup>b</sup>
Cerebral cortex	34	57
Hippocampus	10	25
Thalamus	5	-
Hypothalamus	6	3
Amygdala	25	9
Caudate putamen	12	6
Cerebellum	8	-

<sup>a</sup>Total number of cysts observed = 67. <sup>b</sup>Total number of cysts observed = 32.

had neuropsychiatric manifestations of the disease, and otherwise Katzav *et al*<sup>[1193]</sup> in mice demonstrated that injection of human lupus anti-P ribosomal autoantibodies to the brain ventricles induced defect in smell capability and depression-like behaviour. Recently, Lucassen *et al*<sup>[1175]</sup> reviewed available literature data and established that the prevalence of olfactory dysfunction is significant in the MSC population, ranging from 20% to 45%. They also demonstrated the correlations between olfactory dysfunction and cognitive disturbances and depression in these patients.

Several authors showed that many neurodegenerative diseases are first demonstrable in the olfactory system, with loss of the sense of smell up to 10 years before the onset of cognitive or motor dysfunction<sup>[1172]</sup>. Olfactory dysfunction may affect up to 90% of early-stage Parkinson’s disease cases<sup>[1194]</sup>. Intriguingly, several studies reported that cigarette smoking may have a protective effect in this clinical entity because it was associated with a better sense of smell in such patients<sup>[1195-1197]</sup>. In addition, it was found that patients with Parkinson’s disease have multi-organ parasympathetic dysautonomia involving pupillary, cardiovascular, and gastrointestinal systems, with not entirely clear underlying pathophysiology<sup>[1198,1199]</sup>. The beneficial effects of smoking in this entity may be at least in part explained by the following facts: (a) autonomic dysfunctions, characterized



by lower vagal and higher sympathetic tone, and cholinergic modalities acting through vagus nerve and/or  $\alpha 7$  subunit-containing nicotinic acetylcholine receptor-mediated mechanisms have been shown to suppress excessive inflammation in several experimental models of disease by inhibiting overproduction of TNF and other proinflammatory cytokines<sup>[1200-1203]</sup>; and (b) possible chronic *T. gondii* infection in patients with Parkinson's disease exerted damaging effects on the peripheral autonomic system, especially enteric nervous system of the gastrointestinal tract, found in experimental animals and patients with autism, inflammatory bowel disease, Leśniowski-Crohn's disease, and other clinical entities<sup>[120,1204-1207]</sup>.

### ***T. gondii* infection**

Xiao *et al.*<sup>[1208]</sup> showed that in male mice, infection with the parasite led mainly to modulation of genes associated with olfactory function, such as downregulation of the number of olfactory receptors and dopamine receptor D4. However, general olfactory tests and sensorimotor gating were normal in both male and female infection<sup>[1208,1209]</sup>. The discrepancy between findings in rodents and impaired sense of smell reported in patients with Alzheimer's disease, as well as in the individuals with various ADs suffering from chronic *T. gondii* infection, may be at least partly explained by a much more developed *rhinencephalon* in animals (*lobus olfactorius*) than in humans (*bulbus olfactorius*), including morphometric parameters<sup>[1210]</sup>, therefore to a considerably smaller extent subjected to the olfactory tissue destruction<sup>[1211]</sup>. It must be emphasized that low olfactory bulb volumes have been found in patients with schizophrenia (left and right bulb) and their first-degree relatives (right bulb) as compared with healthy participants<sup>[1183]</sup> (Table 46). In another study, the significant hippocampal atrophy has been also reported in 43.9% of 150 patients with SLE, with progression of reduction in right and left hippocampal volumes related to disease duration ( $p < 0.001$ )<sup>[1212]</sup>. Moreover, patients with neuropsychiatric SLE had damage of the amygdala<sup>[1213]</sup>, and it must be emphasized that selective involvement of these two brain regions were preferentially and persistently invaded by the parasite (Table 47)<sup>[1214]</sup>.

In patients with Parkinson's disease, olfactory loss was considered as a marked early symptom that correlated with the progression of the disease<sup>[1215]</sup>, and parkinsonian symptoms have been observed as an initial manifestation in a Japanese patient with acquired immunodeficiency syndrome and *T. gondii* infection<sup>[1216]</sup>. Olfactory dysfunction has been also reported in HIV-infected and AIDS individuals<sup>[1217,1918]</sup>, in patients with Alzheimer's disease<sup>[1219]</sup>, in individuals with Down syndrome<sup>[1190]</sup>, in subjects with MSc<sup>[1175,1185]</sup>, in participants with systemic sclerosis (SSc)<sup>[1220,1221]</sup>, in patients with SLE<sup>[1192,1193,1221]</sup>, in patients with schizophrenia<sup>[1184]</sup> and their relatives<sup>[1220,1222]</sup>, and during several pregnancies<sup>[1223]</sup>, *i.e.* the entities with markedly increased serum anti-*T. gondii* IgG antibody levels compared with healthy controls<sup>[97,99,141,1204-1207,1224-1227]</sup>. Furthermore, the above-mentioned brain regions (Table 47) were consistently more frequently infected than other sites in animals with toxoplasmosis<sup>[1214,1228,1229]</sup>. Finally, it seems that damage of the olfactory system is at least in part responsible for development of depression<sup>[1230,1231]</sup> because it was found that *T. gondii* infection worsened mood in pregnant women<sup>[992]</sup>, female veterans<sup>[1232]</sup>, older persons<sup>[33,1233]</sup>, patients with SSc<sup>[98,99]</sup>, and individuals with schizophrenia<sup>[1234]</sup>. Higher incidence of depression preceded also the onset of Parkinson's disease<sup>[1235]</sup>, and the olfactory bulbectomized rat is usually serving as a model of depression<sup>[1236]</sup>.

In summary, damage of the olfactory system by chronic latent *T. gondii* infection may affect olfactory bulb volume and various

olfactory functions, being therefore responsible for the smell impairment in patients with several ADs and/or neuropsychiatric disorders. It must be emphasized that in rats infected with the parasite, the most remarkable change in smell function was manifested by their fatal attraction to cat odors ("playing cat and mouse") despite genetically evolved anti-predator inner fear<sup>[1209,1237-1240]</sup>. Finally, it seems that damage of the olfactory system may be at least in part responsible for development of depression in several ADs, and *T. gondii* may be a potential common significant environmental risk factor inducing many ADs and neurodegenerative diseases, as well as depression, the autoimmune disease often associated with these clinical entities<sup>[984,991,1240-1246]</sup>.

## **H. PYLORI INFECTION AND DEVELOPMENT OF ADs**

### **Surprisingly many similarities in the worldwide prevalence and molecular immune pathomechanisms of the bacterium and the parasite *T. gondii***

*H. pylori* is one of the most common chronic infectious agents which typically causes chronic gastritis and peptic ulcer disease in children and adults. This Gram-negative bacteria colonizes gastric epithelial cells and the gastric mucosal layer in 32.7-46.9% of the population in developed countries (Northern America, Western Europe) and 54.7-87.7% in developing countries (Africa, Latin America, Asia), for an estimated 4.4 billion people worldwide in 2015<sup>[1247,1248]</sup>. Among individual countries, even in Switzerland, which had the lowest reported *H. pylori* prevalence (18.9%), there were still approximately 1.6 million infected persons<sup>[1248]</sup>. In the U.S., the bacterium has a seroprevalence of approximately 37.1%<sup>[1248]</sup>. It was estimated that the rate of seropositivity for the bacterium increased from approximately 40% at age 20 yrs, to about 80% by the age of 70 yrs ( $p = 4.5 \times 10^{-24}$ )<sup>[1249]</sup>. The *H. pylori* recurrence rate was inversely related to the human development index (HDI) (3.1% to 10.9% depending on HDI) and directly related to its prevalence<sup>[1250]</sup>.

*H. pylori* infection has been implicated in the development of several both organ-specific and non-organ-specific ADs<sup>[1251-1253]</sup>, including autoimmune gastritis, RA<sup>[1254]</sup>, Sjögren's syndrome<sup>[1255]</sup>, primary biliary cirrhosis<sup>[129,1256]</sup>, Graves' disease<sup>[1257]</sup>, psoriasis<sup>[1258,1259]</sup>, immune thrombocytopenia purpura<sup>[1260,1261]</sup>, and neuromyelitis optica<sup>[1262]</sup>. *H. cinaedi*, an emerging enterohepatic pathogen, was suggested to have a close association with development of atherosclerosis in infected individuals through involving macrophage driven marked proinflammatory responses<sup>[1263,1264]</sup>, similarly as *T. gondii*<sup>[525]</sup>. Moreover, *H. pylori* is associated with an increased incidence of diabetes, especially in older individuals<sup>[1265,1266]</sup>. *T. gondii* may also be responsible for the development of this disease<sup>[102]</sup>, and the anti-*Toxoplasma* seropositivity is increasing with age<sup>[33]</sup>, similarly as *H. pylori*<sup>[1249]</sup>.

Infection with *H. pylori* causes primarily a T<sub>H</sub>1 type of T-cell response, resulting in the generation of monocyte-macrophage proinflammatory cytokines IL-1 $\beta$ , IL-6, IL-8, TNF- $\alpha$ , and IFN- $\gamma$  that promotes gastric mucosal inflammation<sup>[1251,1267,1268]</sup>. Yamanishi *et al.*<sup>[1254]</sup> demonstrated that *H. pylori* urease may be the predominant trigger that initiate autoimmune processes. The interaction between *H. pylori* and B-lymphocytes leads to uncontrolled growth and proliferation of predominantly B1 cells that produce polyreactive/autoreactive IgM and IgG3 antibodies<sup>[1269]</sup>. Chronic infection with the bacterium results in stimulation and increased survival of this subset of B lymphocytes<sup>[1254]</sup>. The antibodies produced do not however result in clearance of the pathogen and may therefore be involved

for example in the production of a major autoreactive antibodies against the gastric  $H^+K^+$ -ATPase, a marked indicator of body mucosa atrophy in chronic *H. pylori* gastritis<sup>[1270]</sup>. Several autoantibodies, including IgM rheumatoid factor, anti-single stranded DNA antibody and anti-phosphatidylcholine antibodies, were found to be generated by B cells after their activation by the bacterium components, particularly urease<sup>[1254]</sup>.

Takenaka *et al*<sup>[1271]</sup> suggested that *H. pylori* HSP60 activates NF- $\kappa$ B and induces IL-8 production through TLR-triggered pathways in gastric epithelial cells<sup>[1272,1273]</sup>. Kawahara *et al*<sup>[1274]</sup> reported that humoral immune responses to HSP60 are closely associated with gastric inflammation and play a role in the pathogenesis of mucosa-associated lymphoid tissue lymphoma<sup>[1275]</sup>. Chronic antigenic stimulation by latent *H. pylori* or *T. gondii* products may also be responsible for B-cell lymphomagenesis in infection-associated development of non-Hodgkin lymphoma<sup>[1269,1276-1280]</sup>. It must be noted that some ADs, such as RA, Sjögren's syndrome, SLE, and celiac disease are at increased risk of developing large B cell lymphomas<sup>[1281,1282]</sup>, and interestingly, in Sjögren's syndrome low levels of vitamin D have also been linked with the occurrence of lymphoma<sup>[1283]</sup>.

Toll-like receptors (TLR) are important for the recognition of exogenous pathogen-associated molecular patterns and binding with damage-associated molecular patterns produced by tissue damage or cells apoptosis. These actions result in stimulation of proinflammatory activity directed against invading microorganisms. Cell surface TRL2 and TRL4 play an essential role in the development of several ADs, including RA, SLE, systemic sclerosis, Sjogren's syndrome, psoriasis, MS, and autoimmune diabetes<sup>[1284]</sup>. Smith *et al*<sup>[1285]</sup> demonstrated that TLR2 and TLR5 are required for *H. pylori*-induced NF- $\kappa$ B activation and chemokine expression by gastric epithelial cells. Further study of Uno *et al*<sup>[1286]</sup> showed that TLR2 induced through TLR4 signaling initiated by *H. pylori* cooperatively amplified iNOS induction in gastric epithelial cells. It must be noted that TRL2 and TRL4 have also been activated by glycosylphosphatidylinositol derived from *T. gondii*<sup>[89]</sup>, and TRL2 appeared important for protective immunity against the pathogen<sup>[1287]</sup>. It was suggested that these two biomolecules regulate the balance between  $T_H1$  (to eliminate pathogen) and  $T_H2$  (to protect host from a robust uncontrolled inflammatory response) type of innate immune responses essential for the survival of the host<sup>[1288]</sup>.

*H. pylori* causes a chronic gastritis, ulcers, and gastric cancer at least in part by chronic inflammation and impaired host innate immunity, including inhibition of type  $T_H1$  response development<sup>[1289,1290]</sup>. Following chronic infection with the bacteria, PD-L1 was upregulated on DCs and gastric epithelial cells (GECs), capable of T cell activation<sup>[1289,1290]</sup>. *In vitro*, PD-L1<sup>hi</sup> GECs had reduced capacity to induce proliferation in CD4 T cells, which was reversed by blocking PD-L1<sup>[1289]</sup>. Furthermore, it was found that gastric CD4 T cells obtained during gastric biopsies from *H. pylori*-infected patients had higher levels of PD-1 expression, which correlated with density of the pathogen<sup>[1291]</sup>, and high PD-1 expression is a hallmark of dysfunctional T cell found in chronic microbial infections<sup>[1292]</sup>. Higher PD-L1 expression has also been demonstrated on T cells and a wide range of non-hematopoietic cell types including DCs during chronic *T. gondii* and viral infections<sup>[588,1293]</sup>.

Ek *et al*<sup>[1294]</sup> showed that *T. gondii* seropositivity was linked to elevated IgE, proinflammatory  $T_H1$ -IgG2, IgG3, and IgG4 responses to a concomitant infection with *H. pylori*, *i.e.* individuals with high *T. gondii* titers had reduced proinflammatory  $T_H1$ -IgG2, IgG3, and IgG4 responses to *H. pylori*. Similar inverse  $T_H1$  and  $T_H2$  cytokine

interaction has been reported between *H. pylori* infection and atopy, although this counteractive immune balance did not protect against atopic diseases<sup>[1295]</sup>. Interestingly, Cicconi *et al*<sup>[1296]</sup> reported a case of disappearance of antiphospholipid antibodies syndrome after *H. pylori* eradication. Critical analysis of the data presented in this letter to the editor of The American Journal of Medicine may however suggest that not only this pathogen was responsible for the clinical symptoms and laboratory abnormalities as well as for the final improvement in the patient's state of health, but the main microbe in charge was probably latent *T. gondii* infection. To support this opinion it must be noted that the hospitalized 33-yr-old woman had left-sided hemiparesis associated with episodic weakness of the upper extremities, history of Raynaud's phenomenon, and suffered from migraine with aura. After treatment with nimodipine, and following combined therapy with clarithromycin, metronidazole and omeprazole for one week there was a gradual resolution of the neurologic symptoms, migraine markedly improved, and the Raynaud's phenomenon disappeared. Although her serum toxoplasma markers were found to be negative (the majority of laboratory tests for *T. gondii* are however not fully specific and sensitive<sup>[967]</sup>), it must be noted that all these drugs are known to exert antitoxoplasmatic effects (nimodipine- a plasma membrane calcium channels blocker acts *via* disruption of  $Ca^{2+}$  homeostasis in parasites<sup>[1297,1298]</sup>, and autophagy modulation<sup>[1299]</sup>; omeprazole causes significant depolarization of the *T. gondii* PV membrane<sup>[1300]</sup>; and azithromycin and metronidazole disturb purine and DNA synthesis of the parasite<sup>[1301]</sup>). Moreover, *T. gondii* may be the cause of migraine and neurological disturbances reported in this patient<sup>[1077,1302]</sup>. Thus, it seems that *T. gondii* and *H. pylori* coinfection should be taken into consideration in the development of all these clinical and laboratory disturbances.

Finally, a large sample of 1785 young and middle-aged men and women seropositive for both *H. pylori* and *T. gondii* appeared to be more susceptible to development of cognitive function deficits than were participants seropositive for either *H. pylori* or toxoplasmosis alone<sup>[1303]</sup>. It must however be noted that these two infections are usually associated with development of iron deficiency<sup>[1304]</sup>, and this abnormality may at least in part explain possible pathomechanism of the cognition deficits.

## MUTUALLY OVERLAPPING IMMUNOSUPPRESSIVE EFFECTS CAUSED BY CONCOMITANT LATENT CHRONIC *T. GONDII* AND VIRAL INFECTIONS PLAY A KEY ROLE IN DEVELOPMENT AND PERSISTENCE OF SEVERAL ADs

In the years 1988-1994, mean total seroprevalence estimates and 95% confidence intervals of six infectious diseases among adults in the U.S. were the following: HAV 37.4% (35.2-39.8%), *H. pylori* 32.7 (29.9-35.8), *T. gondii* 25.4 (23.9-27.0), HSV-2 24.0 (22.0-26.1), HBV 5.6 (4.8-6.5), and HCV 2.4% (2.0-3.1%)<sup>[1305]</sup>. Recently, Rubicz *et al*<sup>[1249]</sup> studied seroprevalence of 13 common pathogens in 1227 Mexican Americans from San Antonio, TX, and found that the overall prevalence rates for HSV-1, HHV-6, CMV, EBV, HSV-2, HAV, *H. pylori*, and *T. gondii* were 82%, 82, 55, 46, 22%, 73, 57, and 9%, respectively. These data support general opinion that usually burden of infections is responsible for the induction of many ADs<sup>[1306]</sup>.

**CMV infection.** Human CMV is a widespread pathogen

(approximately 60-100% of the adult population is infected with the virus<sup>[1307]</sup>) that causes severe disease in patients with immature or impaired immune system, and establishes lifelong latency with recurrent reactivations in all infected hosts<sup>[1307,1308]</sup>. This common pathogen is spread through contact with infected bodily fluids, such as urine, saliva, semen, breast milk<sup>[1309]</sup>, and in immunocompetent individuals is associated with development of mononucleosis, Guillain-Barre syndrome, meningoencephalitis, hemolytic anemia, and thrombocytopenia<sup>[1308]</sup>.

Human CMV lytic replication in multiple tissues, the lifelong persistence through periods of latency and intermittent reactivation, the extraordinary large proteome, and extensive manipulation of adaptive and innate immunity make the virus a solid candidate for involvement in several ADs, including SLE, RA, systemic sclerosis, diabetes mellitus type 1, atherosclerosis, and various vasculopathies (especially scleroderma)<sup>[99,1310-1318]</sup>. CMV infection has been implicated as a trigger of vascular damage<sup>[1311]</sup> in ADs due to its ability to infect both endothelial and monocyte/macrophage cells, and upregulation of fibrogenic cytokines, such as TGF- $\beta$ 1, as well as triggering immune dysregulation<sup>[99,1319]</sup>, similarly as the parasite *T. gondii*. In certain populations CMV infection causes increased morbidity and mortality in patients with ADs, particularly SLE<sup>[1320]</sup>.

CMV infection causes transient but substantial immunosuppression<sup>[1321]</sup>, which in solid organ transplant recipients is associated with potentiation of superinfections due to various other pathogens<sup>[1294,1322]</sup>. Furthermore, CMV replication influence the viral load of other viruses, such as HCV<sup>[1323]</sup>, HHV-6 and HHV-7 viruses in solid organ recipients<sup>[1324]</sup>. In addition, subclinical CMV viremia has been documented in blood donors and this may increase viral load in the patients with ADs requiring blood transfusion<sup>[1325]</sup>.

During the acute phase of CMV invasion several cell types can be infected, including endothelial cells, monocytes, macrophages, epithelial cells, smooth muscle cells, fibroblasts, hepatocytes, neuronal cells, and DCs<sup>[1326]</sup>. Interestingly, cells with high levels of glutathione are resistant to CMV infection<sup>[1327,1328]</sup>, probably because glutathione is a major intracellular antioxidant<sup>[1329]</sup>. Active and latent CMV infections induce sustained systemic T<sub>H</sub>1 type proinflammatory cytokine responses *via* CD14 and TLR 2-dependent activation of NF- $\kappa$ B<sup>[1330,1331]</sup>. However, human CMV downregulates MHC expression<sup>[1332-1334]</sup> and impairs IFN- $\gamma$ -induced MHC class II-dependent antigen presentation by macrophages<sup>[1335]</sup>, and infection of cytolytic T lymphocytes and NK cells by CMV abrogate their ability to kill CMV-infected targets<sup>[1336,1337]</sup>. In all age groups, latent CMV infection is typically accompanied by a decrease in naïve T cells and the simultaneous accumulation of effector T cells (Table 48)<sup>[1307,1338-1341]</sup>. It should be noted that in healthy carriers, CMV-specific CD4<sup>+</sup> T cells are continuously driven to replicative exhaustion<sup>[1342]</sup>.

Vescovini *et al*<sup>[1343]</sup> demonstrated that CMV and EBV infections induced quantitatively and qualitatively different CD8<sup>+</sup> T-cell response in very long-term carriers, because CMV chronic infection was characterized by highly variable frequency and absolute number of CD8<sup>+</sup> T cells specific for two differently restricted epitopes that in some individuals were very expanded. In addition, the majority of anti-CMV CD8<sup>+</sup> T cells did not bear the CD28 molecule. On the other hand, EBV chronic infection seemed to be kept under control by a limited and stable number of circulating CD8<sup>+</sup>CD28<sup>+</sup> T cells, without marked individual variations<sup>[1343]</sup>.

Finally, it must be noted that CMV can be reactivated by increased serum levels of TNF- $\alpha$  released during various inflammation states, for example, in patients with atopic dermatitis<sup>[1344]</sup>, solid organs/bone marrow transplant recipients<sup>[1345-1347]</sup>, and enhanced generation of

**Table 48** Mean percentages ( $\pm$  SE) of CD8<sup>+</sup> and CD4<sup>+</sup> T-cell subsets in CMV-negative and CMV-positive healthy elderly donors (acc. to Weinberger *et al* [1307]; with own modification).

T cells	T-cell subsets	CMV-negative (n = 87)	CMV-positive (n = 164)	P value
CD8 <sup>+</sup>	CD28 <sup>+</sup> CD45RA <sup>+</sup> naïve	25.4 $\pm$ 1.4	18.0 $\pm$ 0.9	< 0.01
	CD28 <sup>+</sup> CD45RA <sup>-</sup> memory	49.4 $\pm$ 1.5	33.6 $\pm$ 1.2	< 0.01
	CD28 <sup>-</sup> effector	25.2 $\pm$ 1.6	48.4 $\pm$ 1.4	< 0.01
CD4 <sup>+</sup>	CD28 <sup>+</sup> CD45RA <sup>+</sup> naïve	32.8 $\pm$ 1.5	28.0 $\pm$ 1.1	< 0.01
	CD28 <sup>+</sup> CD45RA <sup>-</sup> memory	66.1 $\pm$ 1.5	62.9 $\pm$ 1.1	0.09 (NS)
	CD28 <sup>-</sup> effector	1.1 $\pm$ 0.1	9.2 $\pm$ 0.6	< 0.01

Mean Whitney U test was used to determine P value. NS, not significant.

**Table 49** Serum IgG levels of anti-infectious agents antibodies more prevalent in PBC compared with controls (acc. to Shapira *et al* [129]; with own modification).

Infectious agent	Patients with PBC	Controls	P value
<i>T. gondii</i> (IU/mL)	53.4 $\pm$ 9.1	36.4 $\pm$ 7.6	< 0.001
EBV-EA, AI	1.7 $\pm$ 0.2	0.9 $\pm$ 0.2	< 0.0001

AI, antibody index. EBV-EA, Epstein-Barr virus - early antigen. Results are given as mean  $\pm$  SE.

catecholamines during stress<sup>[1348,1349]</sup>. These actions favor persistence of available systemic CMV antigens in the host and development of ADs.

**EBV infection.** Most human adults are infected with EBV and carry the virus without clinical symptoms<sup>[1350]</sup>. In healthy individuals, the reported prevalence of multiple EBV infections is believed to be common, but ranges broadly from 0 to 100%<sup>[1351]</sup>.

Primary EBV infection typically occurs during childhood without apparent symptoms and evolves into an asymptomatic lifelong virus carrying latency. Rare cases of infection in early adulthood lead to infectious mononucleosis, which has been linked to increased risk of Hodgkin's lymphoma<sup>[1352]</sup> and the onset of RA, SLE<sup>[1353]</sup>, primary Sjögren's syndrome<sup>[1354,1355]</sup>, MS<sup>[1356,1357]</sup>, autoimmune thyroiditis<sup>[1358]</sup>, and primary biliary cirrhosis (PBC)<sup>[129]</sup> (Table 49).

Anti-EBV-EA antibodies concentrations positively correlated with anti-*T. gondii* antibody levels in those patients (Spearman correlation  $r = 0.35$ ,  $p < 0.01$ ). A similar positive correlation was detected in PBC patients between anti-EBV-EA and CMV antibodies levels ( $r = 0.32$ ,  $p < 0.01$ ), which may suggest a secondary origin of their generation as compared with the primary and the same *T. gondii*-related IL-21 cytokine stimulus intensity required to control chronic viral infection<sup>[951,953,1359]</sup>.

EBV can infect and activate both neutrophils and monocytes, and modulates several of their biologic functions, which results in triggering the release of many proinflammatory mediators<sup>[1360]</sup> (Table 50).

It must be noted that phagocytosis is directly involved in the clearance of invading pathogens and also represents a crucial step towards the presentation of specific antigens *via* the MHC class II pathway. EBV significantly reduced the phagocytic activity of primary phagocytes<sup>[1362]</sup>, most likely through the impairment of protein kinase C activity<sup>[1363,1364]</sup>.

Cytotoxic CD8 lymphocytes (CTLs) play a pivotal role in the control of viral infection and activated CTLs however often lose effector function during chronic infection. It has been reported that patients with SLE had elevated antibody responses to the herpesvirus EBV<sup>[1365,1366]</sup>, and that this antibody response showed cross-reactivity to nuclear self-antigens and lead to autoimmune manifestations<sup>[1367,1368]</sup>. EBV induces IFN production by plasmacytoid DCs<sup>[1369]</sup> and therefore repetitive bursts of viral replication could

**Table 50** Modulating effects of EBV on phagocytic biological functions (acc. to Savard & Gosselin [1360]; with own modification).

Phagocytes	Dependent on viral adsorption	Dependent on viral protein expression/replication
Neutrophils	Induction of IL-1R-1Ra>IL-1 $\alpha$ / $\beta$ , IL-8 and MIP-1 $\alpha$ expression	Induction of cellular death by apoptosis
	Priming effect on LTB <sub>4</sub> release and superoxide production	
Monocytes	Induction of IL-6 expression	Induction of IL-1 $\beta$
	Induction of GM-CSF	Inhibition of TNF $\alpha$ and MIP-1 $\alpha$ expression
	Priming effect on LTB <sub>4</sub> and C <sub>4</sub> biosynthesis	Inhibition of PGE <sub>2</sub> biosynthesis
	Inhibition of DCs development from monocyte precursors	Inhibition of phagocytosis

DCs, dendritic cells; LTB<sub>4</sub>, leukotriene B<sub>4</sub>; GM-CSF, granulocyte-macrophage colony-stimulating factor; MIP-1 $\alpha$ , macrophage inflammatory protein-1 $\alpha$ ; PGE<sub>2</sub>, prostaglandin E<sub>2</sub> (PGE<sub>2</sub> exerted antiviral activity, regulated humoral response by increasing the immunoglobulin class switching, particularly IgE in B lymphocytes, favored Th0-like response to shift towards a Th2-like pattern, i.e. decreased IL-2 and IFN- $\gamma$  production and promoted IL-4, IL-5 and IL-10 synthesis by these cells [1360, 1361]. PGE<sub>2</sub> and LTB<sub>4</sub> inhibited NOS type 2 expression, iNOS synthesis and expression, and NO production in macrophages and hepatocytes [1302].

**Table 51** EBV and CMV infections serology in patients with inactive and active SLE (acc. to Larsen *et al* [1350]; with own modification).

	Healthy controls (n = 31)	Inactive SLE patients (n = 76)	Active SLE patients (n = 42)	P-value
Female sex (%)	27 (87%)	71 (93%)	36 (86%)	0.32
Inclusion age (yrs), median, range	33.0 (19-57)	34.3 (16-61)	34.6 (16-58)	0.92
EBV serology	29 (92%)	76 (100%)	42 (100%)	0.006 <sup>a</sup>
CMV serology	18 (58%)	58 (76%)	35 (83%)	0.035 <sup>a</sup>
Anti-EBV IgG titers <sup>b</sup> , median (RU/mL), range	10500 (2400-25400)	17900 (2900-28900)	19300 (2800-35400)	< 0.0001 <sup>a</sup>
Corticosteroid (%), median (mg/day, range)	n/a	73% 5 (0-55)	65% 7.5 (0-60)	0.49

<sup>a</sup>Healthy controls vs. all SLE patients. <sup>b</sup>Only titers from seropositive individuals were included. RU, Relative Units.

account, at least in part, for the overexpression of IFN and IFN-induced genes observed in SLE<sup>[1370,1371]</sup>. Larsen *et al*<sup>[1350]</sup> demonstrated exhausted cytotoxic control of EBV in SLE. They found that both inactive and active SLE patients had significantly elevated EBV viral loads compared to age- and sex-matched controls ( $p = 0.003$  and  $p = 0.002$ , respectively) (Table 51), and less EBV-specific CD8<sup>+</sup> T cells were able to secrete effective molecules (IFN- $\gamma$ , TNF- $\alpha$ , IL-2 and CCL4) to kill EBV-infected targets.

It is disputed whether EBV reactivation is a cause or consequence of SLE disease activity and Larsen *et al*<sup>[1350]</sup> believe that frequent EBV reactivation appears to be an aggravating consequence, rather than a cause, of SLE immunopathology. This opinion may be supported by the similarly lower anti-EBV IgG titers between inactive and active SLE patients (Table 51), and confirm that another concomitant pathogen infecting these patients (but not CMV), such as for instance, *T. gondii* play an important role in activation of this clinical entity<sup>[141]</sup>.

Plot *et al*<sup>[1372]</sup> suggested that some viral infections, may have a protective role in the etiopathogenesis of celiac disease (Table 52). The authors believed that EBV, CMV, and rubella may establish a certain immunological background that disfavors the evolution of some autoimmune conditions such as this clinical entity.

However, although B lymphocytes were reported to generate TNF- $\alpha$  in response to EBV infection<sup>[1373]</sup>, recombinant TNF- $\alpha$  was found to inhibit, in a dose-dependent manner, the proliferation and differentiation of both EBV-activated and -transformed human B cells<sup>[1374]</sup>, known to be involved in the production of antibodies. In addition, during the acute phase of viral infection, rapidly reduced cell survival associated with episodes of neutropenia and monocytopenia was observed, thus at least temporarily or persistently influencing the immune defense of the host and potentially affecting the outcome of EBV and/or other concomitant pathogen(s) infections<sup>[1360]</sup>.

Sandberg-Bennich *et al*<sup>[1375]</sup> demonstrated that the most evident risk factor for development of celiac disease was associated with neonatal infections (OR = 1.52, CI 1.19; 1.95). *T. gondii* infection may therefore play an important role in triggering development

**Table 52** The rate of positive antibodies against various infectious agents in patients with celiac disease compared with healthy controls (acc. to Plot *et al* [1372]; with own modification).

Antigen tested	Celiac patients	Controls	P value (two-sided t-test)
Antirubella IgG	79/90 (87.8%)	282/297 (94.9%)	< 0.05
Anti-CMV IgG	49/90 (54.4%)	201/297 (67.7%)	< 0.01
Anti-EBV capsid antigen IgG	71/90 (78.9%)	264/297 (88.9%)	< 0.01
Anti-EBV nuclear antigen IgG	70/90 (77.8%)	268/297 (90.2%)	< 0.01

of both diabetes and celiac disease, especially that the increased percentage of antigliadin IgG antibodies was found to be associated with type 1 diabetes mellitus (T1DM)<sup>[104]</sup>. Moreover, Rostami Nejad *et al*<sup>[122]</sup> found that amongst 827 pregnant women, 154 (31%) and 58 (7%) of them had positive total IgG and IgM for *T. gondii* serology. In addition, 27 women were simultaneously diagnosed with celiac disease, and 16 out of 27 (59%) had infection with the parasite as compared with 257 out of 800 (32%) non-celiac disease pregnant women (OR = 3.07, 95% CI 1.4-6.7) ( $p = 0.04$ ). The authors suggested that celiac disease during pregnancy increases the risk of *T. gondii* infection<sup>[122]</sup>. Critical analysis of the literature data suggests however that on the contrary, chronic latent infection with the parasite increases the risk of celiac disease development<sup>[102]</sup>. This reasoning is strongly supported by the report of Severance *et al*<sup>[123]</sup> that in mice receiving a standard wheat-based rodent chow, peroral, intraperitoneal and prenatal *T. gondii* exposure launched a highly significant generation of anti-gluten IgG antibodies in all infected animals compared to uninfected controls ( $p \leq 0.00001$ ). Perorally-infected females showed higher concentrations of anti-gluten IgG than males ( $p \leq 0.009$ ) indicating that the parasite-generated gastrointestinal infection led to a marked anti-gluten response in a sex-dependent manner<sup>[123]</sup>. These findings may be explained by the following facts: 1) transepithelial migration of *T. gondii* is linked to its active motility and virulence<sup>[1376]</sup>, 2) involves an interaction of human ICAM-1 with the parasite adhesion MIC2 resulting in its

immunoprecipitation<sup>[355]</sup>, and 3) the parasite targets the paracellular pathway to invade the intestinal epithelium and affects epithelial tight junction-associated proteins<sup>[1377]</sup>, thus finally affecting host intestinal wall permeability. The beneficial ameliorations effects of breastfeeding and human colostrum, which contains large quantities of lactoferrin, administered in neonatal autistic rats with celiac disease, may further support the above-presented reasoning<sup>[1378,1379]</sup>. In addition, recently, an increased anti-*T. gondii* IgG seroprevalence has been reported in autistic children<sup>[114]</sup>, and the pathogen may be responsible for development of some other gastrointestinal disorders<sup>[120]</sup>, including the finding of a strong association of protozoan-selected single nuclear proteins with Leśniowski-Crohn's disease loci ( $p = 0.008$ )<sup>[128]</sup>.

In summary, TNF- $\alpha$  selectively inhibits activation of human B cells by EBV. A significantly lower occurrence of antibodies to persistent viral infections reported in patients with some ADs compared with controls at least in part may be due to suppressed (exhausted) function of host B cells. IL-10-generating B cells induced in the course of microbial infections can inhibit concurrent immune responses directed towards unrelated antigens and as a consequence ameliorate the clinical course of some ADs, and this could explain how some pathogens exert protective effects in specific clinical entities<sup>[651]</sup>.

**Hepatitis B and C virus infections.** HBV and HCV infections are a marked burden on global public health. Schweitzer *et al*<sup>[1380]</sup> reported that 248 million people were chronically infected with HBV worldwide in 2010, and approximately 780 000 persons die each year due to chronic hepatitis B infection and another 130 000 from acute hepatitis B<sup>[1381]</sup>. The WHO estimates that 30–150 million people globally have chronic HCV infection, and 350 000 to 500 000 people die each year from hepatitis C related liver diseases<sup>[1382]</sup>. Age-specific prevalence varied by geographical region with prevalence below 2% in North America and Western Europe, up to 12% in Africa. In areas where the HBV is endemic, a substantial proportion of the patients are coinfecting with hepatitis C and B<sup>[1383-1385]</sup>. Occult hepatitis B infection occurs frequently in patients with chronic hepatitis C liver disease and may have clinical significance<sup>[1386]</sup>. HBV/HCV dual infection affects viral load, serum antibody response, and proinflammatory cytokine levels, differently from HBV or HCV single infection (for instance, serum TNF- $\alpha$ , IL-6, and IL-8 were markedly lower in HBV/HCV dual-infected patients)<sup>[1387]</sup>.

Both HBV and HCV are transmitted parenterally, sexually and perinatally, with perinatal and sexual transmission being more common for HBV than for HCV<sup>[1388]</sup>. HBV is spread predominantly by percutaneous or mucosal exposure to infected blood and other body fluids with multiple forms of human transmission, including sexual contact<sup>[1389]</sup>.

The liver participates in local and systemic tolerance to self and foreign antigens and this function has been attributed to resident cells expressing antiinflammatory mediators and inhibitory cell surface ligands for T cell activation<sup>[1390]</sup>. Liver cells responsible for the tolerogenic properties of the organ include the resident DCs, liver sinusoidal endothelial cells, Kupffer cells, and hepatic stellate cells. These cells mediate immunosuppression by generation of IL-10 and TGF- $\beta$ , as well as by expression of the PD-L1. IL-10 or TGF $\beta$  and/or PD-1, as well as CTLA-4, contribute to the immunosuppressive mechanisms of Tregs (CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> regulatory T cells). Hepatocytes also add to the liver tolerance effect by expression of MHC class II molecules<sup>[1390]</sup>.

Lin *et al*<sup>[1391]</sup> found that Tregs at least in part contribute to the defective functions of virus-specific exhausted CD8<sup>+</sup> T cells in

Table 53 The prevalence of anti-infectious agent antigen IgG antibodies in patients with autoimmune bullous disease (ABD) and controls (acc. to Sagi *et al* [163]; with own modification).

Infectious antigen	Patients with ABD (n = 49)	Controls (n = 99)	P value
<i>T. gondii</i>	65%	40%	0.01
Hepatitis B core	35%	7%	< 0.001
Hepatitis C	14%	0%	< 0.001
<i>H. pylori</i>	90%	31%	< 0.001
CMV	90%	75%	0.03

patients with chronic HBV infection. In such infection cellular immune responses of the host are weak or absent, which leads to a state of relative collapse of virus-specific adaptive immunity and the inability to control HBV replication<sup>[1392]</sup>. Barboza *et al*<sup>[1393]</sup> reported that increased frequencies of antigen-induced CD4<sup>+</sup>FoxP3<sup>+</sup>IL-10<sup>+</sup> Tregs correlated with viral load suggesting that antigen-induced Tregs could contribute to an inadequate response against the virus, leading to chronic infection.

It was demonstrated<sup>[1394]</sup> that NF- $\kappa$ B was significantly decreased in the HCV-infected patients, and this decrease was associated with the presence of mixed cryoglobulins and RF. Decreased expression of NF- $\kappa$ B was found to be important in the development of peripheral T-cell apoptosis, thus contributing to viral persistence and autoimmunity in these patients<sup>[1394]</sup>.

Sagi *et al*<sup>[163]</sup> demonstrated significantly increased titers of serum IgG antibodies directed against various pathogens in the sera of patients with pemphigus and bullous pemphigoid as compared with controls. This finding support the hypothesis that infections, including HBV and HCV, play an important role in triggering and development of an autoimmune response in the genetically susceptible host (**Table 53**).

High prevalence of autoimmune phenomena has been reported in HCV antibody positive patients with lymphoproliferative and connective tissue disorders<sup>[1395]</sup>. It appeared that some cases of idiopathic thrombocytopenic purpura may be linked to both HCV and HBV infection<sup>[1395]</sup>. Moreover, a significant increase of autoantibodies has been observed for HCV infection and thyroid autoimmune disorders (OR 1.6; 95% CI 1.4–1.9) as well as hypothyroidism (OR 2.9; 95% CI 2.0–4.1)<sup>[1396,1397]</sup>. Patients with HCV were found to be more susceptible than patients with HBV to autoimmune thyroid disease<sup>[1398]</sup>. It must be noted that chronic HCV infection is associated with vitamin D deficiency, but it is yet unsolved what comes first, HCV infection or vitamin D deficit<sup>[1399]</sup>.

Agmon-Levin *et al*<sup>[91]</sup> evaluated the prevalence of serum antibodies against HCV and other infectious agents in a large number of sera from patients with 18 various ADs and found that anti-HCV antibody was detected in 115/1322 (8.7%) of patients with ADs and 0.4% of matched controls (n = 236) ( $p < 0.0001$ ). The prevalence of anti-HCV antibody was significantly higher in 7 specific ADs (cryoglobulinemia, mixed cryoglobulinemia, pemphigus vulgaris, vasculitis, secondary anti-phospholipid syndrome, Hashimoto's thyroiditis, and inflammatory bowel disease) compared to controls. Patients with ADs and serum anti-HCV positivity also had an increased prevalence of antibodies against HBV core antigen, *T. gondii* and CMV as opposed to a lower frequency of serum autoantibodies<sup>[91]</sup>.

Finally, Ram *et al*<sup>[1400]</sup> suggested that for instance HBV infection may exert a protective role in some ADs because they found a low percentage of antibodies to HBcAg in patients with SLE, MS and T1DM compared with matched healthy donors. In another study<sup>[1401]</sup>, mean antibody titres to measles in patients with RA were

also significantly lower than in controls, and an inverse correlation between measles antibody levels and serum globulin concentrations was detected. Furthermore, similar markedly lower mumps virus IgG class antibody levels were found in type 1 diabetic children than in their non-diabetic siblings ( $p < 0.0005$ ) approximately 2.5 years after the mumps-measles-rubella vaccination<sup>[1402]</sup>. However, as it was discussed earlier, these findings may rather reflect decreased immune responsiveness of these patients because during many chronic infections virus-specific CD8<sup>+</sup> T cells, CD4<sup>+</sup> T cells, as well as B cells, undergo exhaustion as they gradually lose their full ability to respond to antigenic activation, and CD8 T-cell dysfunction has been well documented in several chronic human viral infections, including HBV and HCV<sup>[597,635,1403-1407]</sup>. It must be noted that for these two viruses clonal exhaustion may be a protective mechanism preventing severe immunopathology and death from an exaggerating CD8 T cell response<sup>[1408]</sup>. Moreover, during chronic viral and *T. gondii* coinfections, intracellular tachyzoites could impair capacity of lymphocytes to produce immunoglobulin and cytokine secretions<sup>[569]</sup>.

**HIV infection.** Critical bioevents of HIV-1 infection occur in lymphoid tissue and typically are associated with coinfection by other pathogens that usually worsen the clinical course of HIV disease<sup>[1409]</sup>. *T. gondii* is a common HIV copathogen that worsens the clinical course of HIV disease<sup>[1410]</sup>. Sassi *et al*<sup>[1409]</sup> examined the interaction of both these microbes in coinfecting human tonsillar tissue *ex vivo* and found that live *T. gondii* preferentially inhibited R5 HIV-1 replication (but not X4 HIV-1), because its genome encoded cyclophilin-18 from the parasite that binds to a chemokine receptor CCR5 (an inhibitor of HIV-1 cell fusion) and was able to suppress R5 HIV-1 replication in peripheral blood monocyte cells<sup>[1411]</sup>, thus eventually altering the risk of HIV-1 infection between *T. gondii*-infected and control participants. Another pathogen, HHV-7 also upon HIV-1 coinfection in lymphoid tissue *in vivo* suppressed replication of R5, but in addition downregulated CD4 (the HIV-1 receptor) on the surface of both infected and uninfected T cells<sup>[1412]</sup>.

**Measles virus infection.** Measles is sometimes a severe viral infection and one of the most infectious of communicable diseases. However, during 2000–2016 period, annual reported measles incidence decreased from 145 to 19 cases per million persons, and annual estimated measles deaths decreased 84%, from 550,100 to 89,780<sup>[1413]</sup>. In 2017, countries of the European Region reported 15,941 confirmed measles cases, and the highest incidence was recorded in Romania (252.4 cases per 1 million population); there were 20 measles deaths, including 10 registered in Romania<sup>[1414]</sup>.

Measles results in a systemic illness which causes profound immunosuppression frequently leading to serious complications. Recovery from measles produces lifelong immunity. Increased titres to MV or its genome were found in sera of patients with several ADs<sup>[1415,1416]</sup>, including SLE<sup>[1417]</sup>, ASD<sup>[1418,1419]</sup>, autoimmune chronic hepatitis<sup>[1420]</sup>, subacute sclerosing panencephalitis<sup>[1421]</sup>, inflammatory bowel disease<sup>[1422]</sup>, MS<sup>[71,1423]</sup>, type 1 diabetes<sup>[1424]</sup>. There have been also reports of paramyxovirus nucleocapsid-like structures and elevated measles antibody titers in several connective tissue disorders, such as RA, polymyositis, scleroderma, Goodpasture's syndrome, Sjogren's syndrome, and Reiter's syndrome<sup>[1425]</sup>. In one study<sup>[1401]</sup>, a subdivision of patients with RA, myasthenia gravis and primary biliary cirrhosis showed that the presence of anti-nuclear antibody (ANA) has been associated with markedly increased measles antibody concentrations compared with the ANA-negative sera. Interestingly, it was found that earlier natural infection or vaccination against measles seems to have an inhibitory effect on the development of thyroid autoantibodies<sup>[1426]</sup>.

Tishon *et al*<sup>[1427]</sup> found that CD4 T cell control primary MV infection of the CNS and regulation is dependent on combined activity with either CD8 T cells or with B cells. MV-immunosuppression represents a direct contact-mediated silencing of T cells which acquire a transient paralytic state<sup>[1428]</sup>. The immunosuppression include: a) lymphopenia<sup>[1429]</sup> (it should be noted that reduced T cell numbers and the resulting exaggerated homeostatic-type proliferation of T cells due to the increased responses to cytokine IL-2, a mediator that regulates T cell turnover, generate autoimmunity<sup>[1430]</sup>), b) a prolonged T<sub>H</sub>2 immune responses resulting in cytokine imbalance consistent with suppression of cellular immunity to secondary infections<sup>[1431]</sup>, and c) T-cell nonresponsiveness due to silencing of peripheral blood lymphocytes that fail to expand in response to *ex vivo* stimulation<sup>[1431,1432]</sup>. Lymphopenia results from depletion of T cells by mechanism also involving MV infection, and expression of the major MV receptor CD150 plays an important role for targeting these cells<sup>[1431]</sup>. Virus transfer is thought to be mediated by monocytes<sup>[1433]</sup> and DCs, which are considered as central to the induction of T-cell silencing and functional skewing. DCs were identified as initial target cells *in vivo* of MV and contribute to functional deficiency in these cells because the ability of infected DC cells to stimulate T cells is compromised<sup>[1432]</sup>. MV infection resulted in apoptosis (and/or cell cycle arrest<sup>[1434]</sup>) in DC/T-cell cocultures, which may contribute to a reduced T-cell response<sup>[1432]</sup>. In addition, MV-DCs interaction inhibits innate immunity because selective signaling through TLR4 mediates suppression of the proinflammatory cytokine IL-12 synthesis<sup>[1435,1436]</sup>.

During coinfection of MV with *T. gondii* the above-mentioned disturbances may be enhanced by malnutrition due to the parasite infection-associated iron<sup>[178]</sup>, iodine<sup>[219,232,233]</sup>, and/or folate<sup>[263]</sup> deficiency. This may result in establishment of persistent MV infection in the CNS, probably enhanced by immunosuppression associated with concomitant latent chronic *T. gondii* infection and finally leading to development of ASD<sup>[71,114]</sup>. In addition, there is evidence supporting an important role for hyperthermia and HSPs in the immune response to MV infection, which promotes MV clearance from brain in a mouse model of persistent infection<sup>[1437,1438]</sup>. These experimental findings are well in line with transient beneficial effects of fever on behavior of children with autism<sup>[1439]</sup>.

## BENEFICIAL EFFECTS OF VITAMIN D IN ADS AND *T. GONDII* INFECTION

**Vitamin D markedly decreases the proliferation of *T. gondii* tachyzoites in macrophages and reduces tissue pathology in animals infected with the parasite**

**Vitamin D.** Hypovitaminosis D affects more than one billion people to approximately 50% of population worldwide<sup>[1440,1441]</sup>, and is linked to some of the important risk factors of leading causes of death in the US<sup>[1442]</sup>. The National Health and Nutrition Examination Survey 2005 to 2006 data analyzed for vitamin D deficiency (serum 25-hydroxyvitamin D levels  $\leq 20$  ng/mL) in adult participants (n = 4495) confirmed that the overall prevalence rate was high (41.6%), with the highest rate found in blacks (82.1%), followed by Hispanics (69.2%)<sup>[1442]</sup>.

Epidemiological data show that low vitamin D status is associated with an enhanced autoimmune response in healthy individuals, and increased risk of T<sub>H</sub>1 mediated both autoimmune clinical entities and neurodegenerative diseases<sup>[1440,1443-1447]</sup>. Decreased vitamin D levels have been found in several ADs, including RA, SLE, systemic sclerosis, MS, inflammatory bowel diseases, T1DM, autoimmune thyroid diseases (Hashimoto's thyroiditis and Graves' disease),

**Table 54** Effects of 1,25(OH)<sub>2</sub>D<sub>3</sub> on innate immune system (acc. to Pelajo *et al* [1455]; Youssef DA *et al* [680]; and Szodoray *et al* [1445] with own modification).

Vitamin D actions on the immune system	References
Decreases the antigen-presenting activity of macrophages to lymphocytes; acts on phenotype and function of antigen presenting cells (monocytes, macrophages, DCs) <i>via</i> oxidative burst, production of acid phosphatase and hydrogen peroxide, and maturation of cytokines; acts on neutrophils mobility and phagocytic function; upregulates antimicrobial peptides (cathelicidins, beta-2/beta-3 defensins) in neutrophils, NK cells, monocytes, macrophages, and lymphocytes	[680, 1475, 1476]
Inhibits the maturation of monocytes into DCs	[460, 1477]
Induces the activation of Tregs and NK T cells	[1478, 1479]
Inhibits Th1 type cytokine response	[460, 1461, 1472, 1477]
Decreases IL-2, IFN- $\gamma$ , and CD4 and CD8 DNA synthesis	[460, 680, 1475-1477]
Stimulates the Th2 type cytokine dominance	[460, 1472, 1477, 1495, 1479]
Increases IL-4, IL-5, IL-10, and TGF- $\beta$ 1 <sup>a</sup> synthesis	[1462, 1476, 1477]
Inhibits the synthesis of IL-12, IL-1 $\alpha$ and IL-1 $\beta$ , IL-6 and TNF- $\alpha$	[1461, 1472, 1475, 1478]
Inhibits B cell proliferation, plasma cell differentiation, and antibody/immunoglobulin production	[460, 675, 1476, 1477, 1482, 1483]
Triggers B cell apoptosis	[680]
Increases apoptosis induced by DCs and T lymphocytes-tolerance	[1483]
Induces autophagy in human monocytes/macrophages <i>via</i> cathelicidin	[1462, 1465]
Induces NOS in a human monocyte/macrophage cell line <sup>b</sup>	[1484]

NOS, nitric oxide synthase. <sup>a</sup> This cytokine is well known for its immunosuppressive action on leukocyte cell lines [1473], and specifically was found to be an antagonist of proinflammatory cytokines TNF $\alpha$ , TNF- $\beta$ , IFN- $\gamma$  and IL-2 [545, 547, 1485]; on the other hand, however, TGF- $\beta$  belongs to biomediators favoring growth of *T. gondii* [1486]. <sup>b</sup> NO is an effector molecule of parasite killing [1587]. Interestingly, 1 $\alpha$ 25(OH)<sub>2</sub>D<sub>3</sub> suppressed growth and triggered the destruction and clearance of another intracellular pathogen *Mycobacterium tuberculosis* by activating autophagy in infected human monocytes/macrophages [1488].

mixed connective tissue disease, scleroderma, autoimmune gastritis, and autoimmune uveitis<sup>[1447-1457]</sup>. For example, Kamen *et al*<sup>[1458]</sup> showed that 67% of the 123 analyzed patients with SLE were vitamin D deficient, with mean serum concentrations markedly lower among African Americans (15.9 ng/mL) compared to Caucasians (31.3 ng/mL), and vitamin D levels < 10 ng/mL were found in 22 of the SLE cases. It must be noted that hypovitaminosis D was also reported in obese children and adolescents, and serum vitamin D was positively correlated with insulin sensitivity, which was fat mass-mediated<sup>[1459]</sup>.

Vitamin D was found to modulate both the innate and acquired immune systems<sup>[1444,1460-1463]</sup>. Generally, immunoregulatory actions of active vitamin D on various immune host cells are the following: T<sub>H</sub>1 (decrease number, suppress function), T<sub>H</sub>2 (increase number/function, suppress function), regulatory T cells (Tregs) (increase function, increase number), DCs (inhibit maturation, inhibit T<sub>H</sub>1 induction, increase T<sub>H</sub>2 induction)<sup>[1443]</sup>. Macrophages, endothelial cells, and smooth muscle cells, among others, are able to transform vitamin D (25(OH)<sub>2</sub>D<sub>3</sub>) to its active hormonal form, 1,25(OH)<sub>2</sub>D<sub>3</sub>. The active metabolite primarily mediates its effects through the intracellular vitamin D receptor (VDR)<sup>[1464]</sup>, which is expressed in most cell types of the immune system, in particular in antigen presenting cells, such as monocytes, macrophages, DCs<sup>[1465]</sup>, B cells, and CD4<sup>+</sup> and CD8<sup>+</sup> T cells<sup>[1460,1464]</sup>. DCs play a central role in orchestrating cellular immune responses to self and foreign antigens<sup>[1466]</sup>. Vitamin D induces naïve CD4<sup>+</sup> T to differentiate into Tregs producing IL-10<sup>[1446]</sup>. 1,25(OH)<sub>2</sub>D<sub>3</sub> inhibits proliferation of T<sub>H</sub>1 cells through impairing production of IL-2, TNF- $\alpha$ , and IFN, as well as T<sub>H</sub>17 cells, and thus skewing cytokine production toward a T<sub>H</sub>2 phenotype<sup>[680,1467,1468]</sup>. Moreover, this vitamin modulates human B cell differentiation<sup>[661]</sup>. Vitamin D can exert its antiinflammatory effects through regulating the biosynthesis of proinflammatory molecules in the prostaglandin pathway or through NF- $\kappa$ B enhancer of activated B cells by affecting cytokine production and inflammatory responses<sup>[1451]</sup>. Vitamin D may also prevent autoimmunity by stimulating naturally occurring Tregs<sup>[1469]</sup>.

Vitamin D facilitates also neutrophil motility and fagocytic function<sup>[1470]</sup>. Circulating vitamin D levels have a direct influence on

macrophages, increase their “oxidative burst” potential, such as for instance maturation and generation of cytokines, hydrogen peroxide, and acid phosphatase<sup>[680,1471]</sup>. Active vitamin D and corticosteroids exerted additive immunosuppressive effects on T<sub>H</sub>1 responses<sup>[1472]</sup>. All these actions finally result in a T<sub>H</sub>2 type-driven antiinflammatory state in the host<sup>[1473,1474]</sup>. A summary of multiple immunoregulatory actions of vitamin D on immune system is presented in **Table 54**.

Several of the above-presented actions of vitamin D on immune system may have beneficial effects on clinical course and outcome of patients with ADs<sup>[99,1469,1489,1490]</sup>.

***T. gondii* infection.** An infectious pathogenesis put forward that intracellular parasite infection disrupt the vitamin D regulated immune system resulting in persistent infection and chronic inflammation. Studies showed that 1,25(OH)<sub>2</sub>D<sub>3</sub> directly increased cathelicidin antimicrobial peptide CAMP gene expression which could enhance host defense against infection<sup>[1491,1492]</sup>. Vitamin D was also required for IFN- $\gamma$ -mediated antimicrobial activity of human macrophages<sup>[1462]</sup>. Moreover, it induces NOS in a human macrophage-like cell line<sup>[1493]</sup>, and NO has a strong toxoplasmacidal activity<sup>[863,998]</sup>. It should be added that NO production in macrophages, endothelial cells and hepatocytes is positively controlled by TNF- $\alpha$ , IFN- $\gamma$ , IL-2, and negatively controlled mainly by IL-10, IL-4, TGF- $\beta$ <sup>[1487]</sup>.

Finally, it must noted that vitamin D significantly decreased *in vitro* proliferation of *T. gondii* tachyzoites in macrophages (**Table 55**), increased NO generation in these cells (**Table 56**)<sup>[1494]</sup>, and diminished various tissue pathology in animals infected with the parasite (**Table 57**), possibly by acting on tachyzoites in parasitophorous vacuole<sup>[681]</sup>. Interestingly, vitamin D may also be linked to the increased susceptibility and mortality of mice infected with the pathogen, probably because of its downregulation of the T<sub>H</sub>1 type cytokine responses<sup>[1495]</sup>.

In summary, low serum levels of vitamin D are frequently reported in patients with ADs and these clinical entities have sometimes a tendency to co-occur<sup>[1496]</sup>. There is a vast evidence indicating that this vitamin may prevent, reduce the risk and/or modify the course of ADs<sup>[1497]</sup>, especially that it is beneficial in bacterial, viral and *T. gondii* infections frequently associated with these entities. It must be noted that vitamin D exerts marked antiinflammatory and toxoplasmacidal effects.

**Table 55** Effect of vitamin D<sub>3</sub> and IFN- $\gamma$  on proliferation of *T. gondii* (RH strain) tachyzoites per infected peritoneal macrophage of BALB/c mice after incubation for 96 hrs in RPMI1640 cells culture (acc. to Ghaffarifar *et al* [1494]; with own modification).

Experiment No.	Controls	Solvent <sup>a</sup>	Vit D <sub>3</sub> (1000 IU)	IFN- $\gamma$ (100 IU)	Vit D <sub>3</sub> (1000 IU) plus IFN- $\gamma$ (100 IU)
1	3.01 $\pm$ 0.14	2.93 $\pm$ 0.16	2.49 $\pm$ 0.19 <sup>b</sup>	2.6 $\pm$ 0.2 <sup>b</sup>	2.37 $\pm$ 0.19 <sup>b</sup>
2	3.15 $\pm$ 0.12	3.03 $\pm$ 0.16	2.74 $\pm$ 0.16	2.5 $\pm$ 0.15 <sup>b</sup>	2.58 $\pm$ 0.13 <sup>b</sup>
3	3.05 $\pm$ 0.15	3.04 $\pm$ 0.14	2.82 $\pm$ 0.17	2.57 $\pm$ 0.16 <sup>b</sup>	2.69 $\pm$ 0.2 <sup>b</sup>
4	3.16 $\pm$ 0.14	3.0 $\pm$ 0.14	2.39 $\pm$ 0.19 <sup>b</sup>	2.59 $\pm$ 0.2 <sup>b</sup>	2.03 $\pm$ 0.19 <sup>b</sup>

Numbers of tachyzoites are given as a mean  $\pm$  SD. <sup>a</sup> Ethanol 95. <sup>b</sup> Statistically significant differences compared with controls ( $p \leq 0.05$ ).

**Table 56** Effect of vitamin D<sub>3</sub> and IFN- $\gamma$  on NO production by peritoneal macrophages of BALB/c mice infected with *T. gondii* (RH strain) after incubation for 24 hrs in RPMI1640 cells culture (acc. to Ghaffarifar *et al* [1494]; with own modification).

Experiment No.	Controls	Solvent <sup>a</sup>	Vit D <sub>3</sub> (1000 IU)	IFN- $\gamma$ (100 IU)	Vit D <sub>3</sub> (1000 IU) plus IFN- $\gamma$ (100 IU)
1	109 $\pm$ 8.02	108.2 $\pm$ 12.45	165 $\pm$ 11.30 <sup>b</sup>	146 $\pm$ 7.22 <sup>b</sup>	187.8 $\pm$ 9.82 <sup>b</sup>
2	108 $\pm$ 9.46	108.9 $\pm$ 6.93	121.2 $\pm$ 6.68	139.5 $\pm$ 5.76 <sup>b</sup>	136.2 $\pm$ 10.21 <sup>b</sup>
3	109.6 $\pm$ 7.35	108.2 $\pm$ 4.96	139 $\pm$ 7.01 <sup>b</sup>	146 $\pm$ 4.93 <sup>b</sup>	146.9 $\pm$ 9.62 <sup>b</sup>
4	109 $\pm$ 7.03	108.6 $\pm$ 4.26	166 $\pm$ 7.01 <sup>b</sup>	146.2 $\pm$ 5.60 <sup>b</sup>	191.5 $\pm$ 9.62 <sup>b</sup>

Values are given as mean  $\pm$  SD. <sup>a</sup> Ethanol 95. <sup>b</sup> Statistically significant results compared with controls ( $p \leq 0.05$ ). NO production was estimated as a nitrite release from infected macrophages ( $\mu$ M).

**Table 57** Effect of pretreatment with 1,25(OH)<sub>2</sub>D<sub>3</sub> (0.5  $\mu$ g/kg/2 days) on tissue pathology caused by *T. gondii* avirulent ME49 strain infection with 20 cysts administered intraperitoneally in BALB/c mice (acc. to Rajapakse *et al* [681]; with own modification).

Tissue	Pathology	No treatment	Treatment with Vit D <sub>3</sub>
Lung	Alveolar macrophages	1	0
	Inflammatory foci	2	1
Liver	Inflammatory foci	3	2
	Hemorrhage	2	0
	Mitosis	1	0
Small intestine	Inflammatory infiltrates	1	0
	Necrotic mucosal cells	2	1
Brain	Presence of the parasite	2	0
Spleen	Granulocytes	2	1

Histopathologic examination of the tissues was performed 7 days post inoculation. Numbers are based on severity of the lesions (0, no lesion; 1, mild; 2, slight; 3, moderate changes) and the total was divided by the number of animals in the group. Also, *in vitro* studies with incubated intestinal epithelial cells showed a significant dose-dependent inhibition of intracellular *T. gondii* tachyzoites (RH strain, type I) proliferation at 10<sup>-7</sup> M of 1,25(OH)<sub>2</sub>D<sub>3</sub> concentration.

## CONCLUSION

All presented literature data may suggest that *T. gondii* is the chief of the criminal gang responsible for triggering, development and clinical course of several ADs. This recommendation is supported by the following facts: a) approximately 30-50% of the world population is infected with the parasite, b) the pathogen was detected in patients with various ADs, c) *T. gondii* have a plethora of antigens at its disposal that can attack host protein and carbohydrate substances resulting in development of antibodies and autoantibodies to self antigens and enhancing immune responses to nonself antigens, d) specific molecules of the microbe manipulate multiple strategies to downregulate innate and acquired defense immune responses of the host, e) *T. gondii* in the host may act in the form of tachyzoites and/or bradyzoites, being present intracellularly and/or circulating in the blood, and attacking all nucleated cells, particularly endothelial cells, as well as affecting bystander cells, thus leading to development of various organ-specific and organ-nonspecific clinical entities. Dual activity of the parasite to both promote and inhibit cell apoptosis and impaired clearance of autophagy proteins that serve as a persistent source of foreign antigens favor development of autoimmunity.

Finally, it must be emphasized that *H. pylori* and/or viral infections, although important in the pathogenesis of several ADs, have much less efficient and not such sophisticated biological armamentarium used to abnormally affect host immune responses, than the parasite *T. gondii*.

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