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EDITORIAL

Regulatory T Cells and Histamine in Allergic Contact Dermatitis

Masahiro Seike[1]

1. Masahiro Seike, Department of Food and Nutrition Science, Sagami Women's Junior College, 2-1-1 Bunkyo Minamiku Sagamihara Kanagawa, 252-0383, Japan.

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Correspondence to: Masahiro Seike, Department of Food and Nutrition Science, Sagami Women's Junior College, 2-1-1 Bunkyo Minamiku Sagamihara Kanagawa, 252-0383, Japan.
Email: m-seike@star.sagami-wu.ac.jp
Telephone: +81-42-749-4784

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ABSTRACT

Regulatory T cells (Tregs) are crucial in preventing excessive immune responses and autoimmunity. Tregs elicit a direct or indirect response on target cells (such as lymphocytes, dendritic cells, monocytes, and mast cells). In allergic contact dermatitis and its animal model contact hypersensitivity, Tregs suppress sensitization and elicitation of delayed-type hypersensitivity responses to allergens. Chronic allergic contact dermatitis (CACD) induced by repeated exposure of the skin to the same allergen bears clinical, histological and immunological similarities with those of atopic dermatitis. Allergic responses of CACD are ameliorated as a result of infiltration of Tregs and elevation of IL-10 and transforming growth factor-beta1 (TGF-β1) levels. In CACD, histamine suppresses Tregs infiltration and IL-10 production by decreasing the TGF-β1 levels through histamine H1 and H4 receptors. As a result, histamine amplifies eczema and maintains allergic reactions in CACD.

Key words: Regulatory T cell; Chronic allergic contact dermatitis; Histamine; IL-10; Transforming growth factor-beta1

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REGULATORY T CELLS

Regulatory T cells (Tregs) play an important role in the immune system. Tregs are involved in the prevention of autoimmune diseases, allergies, infection-induced organ pathology, transplant rejection and graft versus host disease via suppression of effector T cells and other immune cells[1]. In certain conditions, Tregs protect against cancer by controlling cancer-associated inflammation[2]. Conversely, they also decrease immune responses against various types of cancer[3, 4]. Therefore, Tregs are a subject of intense investigations.

Tregs are divided into natural Tregs (nTregs) and induced Tregs (iTregs)[5]. nTregs are known as thymus-derived Tregs (tTregs), and they express the transcription factor forkhead box P3 (FoxP3). nTregs acquire stable phenotypic and genetic characteristics during thymus selection and maturation and mainly induce immune tolerance to autoantigens[6]. nTregs express CD4, CD25, and FoxP3, with low CD127 expression[7]. CD4+CD25+Tregs account for 5%-10% of mature human or mouse CD4+T cells[6]. iTregs are derived from the peripheral lymphoid tissue. Naïve conventional T cells are transformed after coming in contact with an antigen and in the presence of immature transforming growth factor (TGF)-dendritic cells, IL-10, and interferon (IFN)-γ[8]. There are three types of iTregs: CD4+CD25+FoxP3+iTregs, expressing FoxP3; CD4+CD25^{low}FoxP3+Th3 cells, mainly secreting TGF-β; and CD4+CD25^{low}FoxP3-type1 regulatory T (Tr1) cells, secreting high level of IL-10[5]. The iTregs suppress the immune response induced by autoantigens and regulate the immune response induced by external antigens[5]. Th3 cells secrete TGF-β and IL-10 to mediate the suppression mechanism, while Tr1 cells secrete IL-10 to suppress T cell proliferation[6].

Tregs exist in all lymphoid tissues and include approximately 10% of all T cells in the normal skin, with a high proportion remaining in a resting state, especially in pilous follicles[9]. Few can be found in

the interfollicular dermis, while majority is located near the follicular epithelium[10].

SUPPRESSIVE MECHANISMS OF REGULATORY T CELLS (FIGURE 1)

Tregs show two different mechanisms of suppressing immune cells. They can either elicit a direct response on target cells or an indirect effects, in which third party cells or molecules are triggered and in turn suppress the target cells[11].

T-lymphocytes

Tregs suppress CD4+ T cell activation and proliferation through contact-dependent and contact-independent mechanisms[12]. They generate immunosuppressive adenosine or transfer cAMP to T lymphocytes. Tregs rapidly suppress T lymphocyte receptor-induced Ca^{2+}, nuclear factor of activated T cells, and nuclear factor kuppa-B (NF-κB) signaling. In addition, they produce immunosuppressive cytokines (IL-10, IL-35, TGF-β), suppress target cells through IL-2 consumption or induce effector cell death via granzyme and perforin[12]. Furthermore, Tregs suppress T lymphocyte indirectly by downregulating co-stimulatory molecules on dendritic cells via cytotoxic T-lymphocyte antigen 4 (CTLA-4)[12]. Tregs also influence proliferation, activation and apoptosis of CD8+ T cells[13, 14]. As a result, the induction of effector and memory CD8+ T cells is reduced[15].

B-lymphocytes

Tregs have the potential to suppress autoreactive B cells in an antigen-specific manner and to prevent the production of harmful autoantibodies. This suppression requires PD-1 expression on autoreactive B cells and expression of the two PD ligands on Treg[16]. Furthermore, Tregs destroy B cells by releasing granzyme B and perforin[17].

Dendritic cells

Tregs interact with dendritic cells in a leukocyte function-associated antigen-1 dependent manner[18] and down-regulate the expression of CD80/86 on target cells through CTLA-4[15]. Tregs express LAG3, a homolog of CD4 receptor. It binds to MHC-II with a higher affinity than CD4, and mediate the activation of PI3K/AKT, p42/44ERK, and p38MAPK pathways[19]. As a result, dendritic cells exhibit an increased expression of co-stimulatory molecules and reduced capacity to capture the antigens[15]. Tregs disrupt the microenvironment of the immunological synapse provided by dendritic cells, which are essential for T cells proliferation. In detail, Tregs function either by reducing the limiting enzyme for glutathione synthesis or by consuming extracellular cysteine[20, 21].

Monocytes

Tregs act on monocytes by inhibiting their cytokine secretion, differentiation and antigen presenting function. Monocytes exhibit classical features of M2 macrophages such as increased expression of CD206 and CD163. They reduce the capacity to respond to pro-inflammatory stimuli as demonstrated by decreased production of IL-6 and tumor necrosis factor-α (TNF-α) and decreased NF-κB activation, following co-culture with Tregs[22]. In addition, monocytes co-cultured with expanded Tregs reduce their capacity to increase detrimental IL-17 producing T-cells when compared to freshly isolated Tregs[23].

Granulocytes

Tregs limit granulocytes accumulation by decreasing the expression of chemoattractant, CXCL1 and CXCL2, thus preventing aberrant skin infiltration[24]. Neutrophils co-cultured with Tregs produce more IL-10 and TGF-β and decrease IL-6 production[25]. Moreover, Tregs induce the expression of heme oxygenase-1, indoleamine 2,3-dioxygenase and the suppressor of cytokine signaling 3 molecules[25]. Conversely, recent studies show that Tregs are able to activate resting basophils by inducing their expression of CD69,

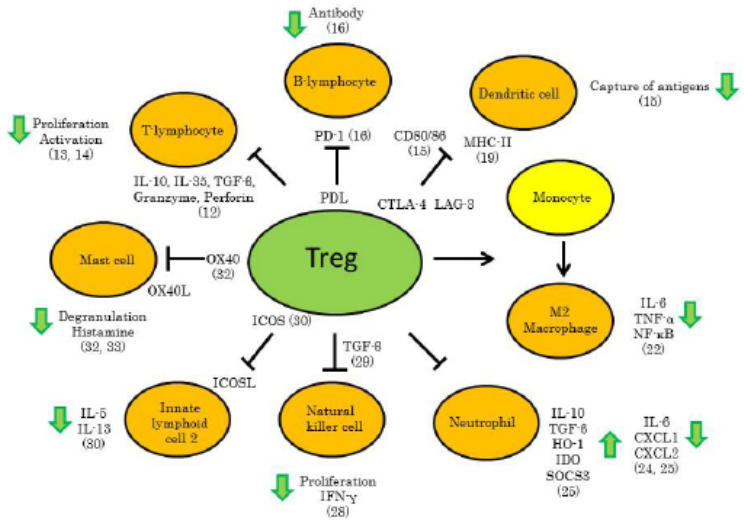

Figure 1 Suppressive mechanisms of regulatory T cells. Regulatory T cells (Tregs) suppress T lymphocyte activation and proliferation. Tregs also generate immunosuppressive cytokines and induce T lymphocyte death via granzyme and perforin. Tregs prevent the production of antibodies through PD-1/PD ligands. Dendritic cells reduce the capacity to capture the antigens through CD80/86/CTLA-4 and LAG-3/MHC-II. M2 macrophages decrease the production of IL-6 and TNF-α, and the activation of NF-κB. Neutrophils produce more IL-10 and TGF-β, and decrease IL-6. Furthermore, Tregs induce the expression of heme oxygenase-1 (HO-1), indoleamine 2,3-dioxygenase (IDO), and the suppression of cytokine signaling molecule (SOCS3). Natural killer cells suppress the proliferation and secretion of IFN-γ via TGF-β. Innate lymphoid cell 2 decreases the secretion of IL-5 and IL-13 via ICOS/ICOSL. Mast cells inhibit degranulation and the secretion of histamine via OX40/OX40L.

CD203c, and CD13. In addition, activated basophils are able to release IL-4, IL-8 and IL-13[26].

Innate lymphoid cells

During pregnancy, Tregs suppress natural killer cells to create a tolerable environment favoring implantation[27], while in tumors, Tregs have the potential to block natural killer cells, thereby generating an immune-suppressive environment, which favors cancer cell survival[28]. Tregs prevent natural killer cells from proliferating, secreting IFN-γ and enhancing missing self-recognition[28]. They suppress natural killer cells via membrane bound TGF-β[29].

Induced Tregs, but not thymus-derived Tregs, have the ability to suppress innate lymphoid cell 2 function by preventing the secretion of both IL-5 and IL-13 in an ICOS/ICOSL dependent manner[30].

Mast cells

Tregs also negatively regulate mast cells by suppressing their degranulation and anaphylactic response[31, 32]. The induction of allergen-specific tolerant T cells in a murine model of bronchial asthma causes a decrease in circulating histamine after challenge[33]. In mast cells, Tregs directly inhibit degranulation *in vitro* and *in vivo* through OX40/OX40L reverse signaling[32].

ALLERGIC CONTACT DERMATITIS AND REGULATORY T CELLS

Allergic contact dermatitis, one of the most common skin diseases, is affecting 15-20% of the general population worldwide[34]. Allergic hypersensitivity is associated with both immunoglobulin (Ig) E and T helper 2 (Th2) responses to environmental allergens. In allergic individuals, priming of allergen-specific CD4+Th2 cells by antigen-presenting cells results in the production of Th2 cytokines, which are responsible for initiating B cell production of allergen-specific IgE. IgE binds to the high-affinity IgE receptor on mast cells and basophils. Allergen cross-linking of the cell surface-bound allergen-specific IgE leads to the release of allergic mediators such as histamine, which are stored in granules, as well as to the secretion of de novo synthesized prostaglandins, cysteinyl leukotrienes, cytokines and chemokines[32]. Granule stored-allergic mediators are the key to immediate allergic reactions such as wheal and flare responses of the skin[35], whereas de novo synthesized mediators are more important for the late phase of allergic response[32].

Allergic contact dermatitis and its animal model contact hypersensitivity (CHS) are T cell-mediated skin inflammatory diseases caused by delayed-type hypersensitivity responses to environmental allergens[36-38]. Small organic compounds that rapidly penetrate the skin and bind to proteins in the dermis comprise an important group of contact allergens[39]. Small organic compounds activate keratinocytes and mast cells directly or indirectly through the innate immune system. The activated keratinocytes and mast cells produce various chemical mediators, which activate dendritic cells. The activated dendritic cells capture antigens, mature, and migrate to the draining lymph nodes via afferent lymphatics. The migrated dendritic cells present antigens to naïve T cells in the draining lymph nodes. Antigen-specific clones differentiate and proliferate into effector T cells[40]. During this sensitization process, the transfer of Tregs suppresses CHS. Tregs in lymph nodes acquire an activated phenotype through ATP. The activated Tregs establish gap junctions with dendritic cells in the lymph nodes, which causes a reduction in the capacity of dendritic cells to stimulate CD8+ T cells[41]. When Tregs are depleted during sensitization, it causes higher effector CD4+ and CD8+ T cell induction and leads to enhanced and prolonged ear swelling. The results indicate that endogenous Tregs contribute to the control of sensitization[42].

Upon re-exposure to antigens, keratinocytes and mast cells are activated and produce various chemical mediators, which activate endothelial cells and cause inflammatory cell infiltration, including antigen-specific T cells. The infiltrated antigen-specific effector T cells are activated and produce pro-inflammatory cytokines and chemokines, which activate keratinocytes and cause further inflammatory cell infiltration[40]. Re-exposure of the skin to the same allergen leads to the development of a delayed-type hypersensitivity reaction mediated by T cells[38]. Neutrophils[43], natural killer cells[44], and innate lymphoid cells[45] influence the magnitude and duration of CHS responses. When Tregs are depleted during elicitation, it leads to an enhanced and prolonged ear swelling response. The results indicate that Tregs are important in the termination of inflammation[46]. The number of Tregs on the skin increases during the skin inflammation process, suggesting that Tregs have a suppressive role at the inflammatory sites[40]. Skin infiltrating T cells move from the skin to the draining lymph nodes in both steady and inflammatory conditions[46]. Additionally, Tregs migrate selectively under inflammatory conditions compared to under steady conditions. Moreover, Tregs that migrate to the draining lymph nodes have the potential to re-migrate into the skin. The skin-derived Tregs exhibit an activated phenotype with high expression of CTLA-4 and IL-10, and they show more potent suppressive activities compared to the resident Tregs in the draining lymph nodes. This suggests that skin Tregs exert their potent suppressive activities not only on the skin but also on the draining lymph nodes via circulation[40]. In addition to Tregs, regulatory B cells (Bregs) have been proposed as other regulators involved in CHS. Bregs are identified as the CD1b^{high}CD5+ B cell population[47]. Bregs represent 1%~2% of spleen B220+ cells, and they produce abundant amount of IL-10[48]. CD19-deficient mice exhibit augmented CHS responses, and the transfer of Bregs into CD19-deficient mice normalizes the extent of inflammation in CHS[49].

In addition, repeated exposure of the skin to the same allergen induces chronic allergic contact dermatitis (CACD). Atopic dermatitis bears clinical, histological, and immunological similarities with CACD[50, 51]. In CACD, a large number of Tregs infiltrate eczematous lesions, induced by repeated exposure to sensitizing agents. Interestingly, allergic responses of CACD (epidermal hyperplasia, dense infiltration of inflammatory cells, and elevated levels of inflammatory cytokines and IgE) are ameliorated during excessive, repeated exposure to the same allergen[52]. As the levels of TGF-β and IL-10 are elevated in CACD[52, 53], allergic responses are considered to be suppressed by Tregs.

MAST CELLS AND REGULATORY T CELLS IN ALLERGIC DERMATITIS

Mast cells are widely deployed to the skin and serve as powerful sentinels of the immune system. Mast cells are stimulated via high-affinity receptors for IgE, and by multiple other mechanisms, including activation by cytokines, which lead to the release a diverse spectrum of biologically active mediators, including some with pro- or anti-inflammatory functions[54,55]. Therefore, mast cells can have potentially important effector or immunoregulatory functions during inflammatory processes, such as during the sensitization and effector phases of CHS responses[39]. During the sensitization phase, mast cells are activated directly or indirectly

by haptens to release a diverse spectrum of mediators including histamine and TNF. IgE amplifies mast cell activation through antigen-independent cytokinergic effects. Direct cell-to-cell contacts between mast cells and dendritic cells and mast cell-derived TNF amplify dendritic cell migration to the draining lymph nodes, where these cells prime naïve T cells to become effector cells via antigen presentation. In moderate CHS responses, mast cells and mast cell-derived TNF amplify ear swelling, leukocyte recruitment (mainly neutrophils and CD8+ T cells), and epidermal hyperplasia. In more severe and chronic CHS responses, mast cells act as an early source of IL-10 in the skin, amplifying the recruitment of Tregs and limiting ear swelling and epidermal hyperplasia. Additionally, mast cells migrate to the draining lymph nodes and the spleen in an IgE-dependent manner, where they produce IL-2, which helps in maintaining the effector T cell: Treg ratio at the site of inflammation, and thereby contributes to limiting the severity of CHS responses[39].

However, mast cells sustain inflammatory signals that locally inhibit Treg suppression. The cytokine IL-6, released by innate and adaptive cells on activation, is known to inhibit Treg anergy and suppression[56]. Among mast cell-associated membrane molecules, the co-stimulatory receptor OX40L can prevent de novo differentiation of Tregs and block their function[57, 58]. Tregs directly inhibit mast cell degranulation through OX40/OX40L[32] and suppress the release of histamine[59].

HISTAMINE AND REGULATORY T CELLS IN ALLERGIC DERMATITIS (FIGURE 2A, 2B)

Histidine decarboxylase (HDC) (-/-) mice lack the ability of synthesize histamine from histidine and show histamine deficiency[60]. In HDC (-/-) mice, no plasma extravasation reaction is observed after passive cutaneous anaphylaxis test[60]. In contrast to immediate-type response, there is no difference observed in CHS (delayed-type responses, observed as thickening of ear skin) between HDC (+/+) and HDC (-/-) mice[60, 61]. However, in CACD models, induced by sensitization and subsequent repeated challenge to a hapten, allergic responses of HDC (-/-) mice are moderate compared to those of HDC (+/+) mice[61, 62]. Histamine appears to be one of the mediators of CACD[62, 63]. HDC (+/+) mice have a lower number of FoxP3 (+) and CTLA-4 (+) cells and lower levels of IL-10 compared to in HDC (-/-) mice with CACD. Treatment with histamine H1 or H4 receptor antagonist increases the number of FoxP3+ cells, and the levels of IL-10 in HDC (+/+) mice. Histamine leads to the development of CACD by suppressing Tregs through histamine H1 and H4 receptors[53]. The transcription factor FoxP3 is an important regulator of inflammation because loss-of-function mutations result in an intense multi-organ inflammatory response associated with allergic airway inflammation, striking hyperimmunoglobulinemia E, eosinophilia, and dysregulated Th1 and Th2 cytokine production[64]. Injection of Tregs into animals with established CHS suppresses infiltration and functions of mast cells, and leads to decreased production of inflammatory cytokines at the contact site[65]. Assuming the role of Tregs in CHS as a reaction suppressor is similar to CACD, an increase in Treg activity will appear to suppress the infiltration of mast cells and decrease IL-4 levels in CACD eczematous lesions[53].

TGF-β is reported to increase Tregs through FoxP3 induction[66]. Tregs inhibit established CHS by suppressing the activity of effector T cells in mice[67]. The suppressive effect of Tregs is transmitted through the cell surface molecule CTLA-4, because effector T cell proliferation is suppressed by anti-CTLA-4 treatment in mice[68]. In humans, Tregs are able to inhibit effector T cells activation in individuals who are not allergic to nickel, while allergic individuals are unable to suppress nickel-specific effector T cell activation *in vitro*. This supports the conclusion that Tregs are involved in allergic contact dermatitis suppression and hapten tolerance[69]. Histamine decreases the levels of TGF-β1 in CACD eczematous lesions. Administration of TGF-β1 increases the number of Foxp3 (+) cells and the levels of IL-10 in CACD eczematous lesions, while administration of an anti-TGF-β1 antibody decreases IL-10 levels. Treatment with histamine H1 or H4 receptor antagonist increases IL-10 levels in HDC (+/+) mice. Therefore, histamine suppresses the number of Tregs and IL-10 production by decreasing the levels of TGF-β1 through histamine H1 and H4 receptors[53]. Since Tregs suppress Th2 cell-driven allergic reactions through IL-10 production in bronchial allergic reactions[70], histamine might reduce Th2 cytokines by reducing IL-10 in CACD[53].

Several studies suggest close relationship between histamine and Tregs. A mixture of lactic acid bacteria and sodium butyrate increases Treg differentiation in the mesenteric lymph nodes and the spleen tissues, and the serum IL-10 levels in atopic dermatitis murine model. However, it reduces serum histamine levels[71]. Oral administration of ferulic acid rutinoside suppresses serum levels of histamine in ovalbumin-sensitized mice and triggers the differentiation of Tregs[72]. Histamine levels in allergic rhinitis murine models sensitized with Derp1 and treated with Derp1-modified dendritic cells are lower,

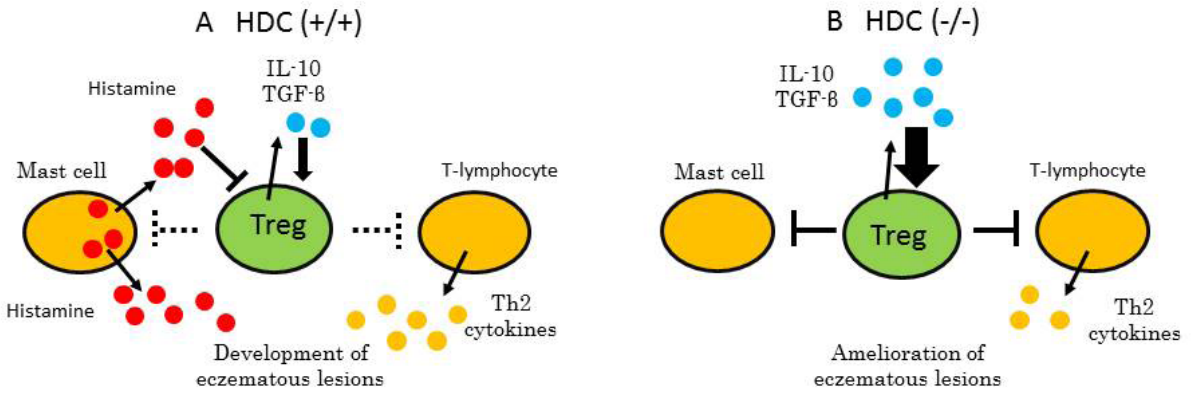

Figure 2 Suppression of Tregs and development of eczematous lesions by histamine in chronic allergic contact dermatitis. A: In histidine decarboxylase gene (HDC) (+/+) mice, mast cell derived histamine prevents Tregs from secreting IL-10 and TGF-β, which activate Tregs. Because of this change, mast cells and T lymphocytes are activated. Histamine and Th2 cytokines derived from T lymphocyte develop eczematous lesions in chronic allergic contact dermatitis (CACD). B: In HDC (-/-) mice, the deficiency of histamine increases the secretion of IL-10 and TGF-β, and activates Tregs. Because of this change, the deficiency of histamine and the decrease in Th2 cytokines ameliorate eczematous lesions in CACD.

and Treg percentage is higher, than in control models[73]. Eucheuma cottonii sulfated oligosaccharide decreases the levels of histamine and up-regulates Tregs in murine models[74]. Glycation of allergens via Maillard reaction or chemical conjugation influences the susceptibility to food-induced allergies. The ovalbumin-mannose treated mice have less histamine and more Tregs than the control mice[75]. These studies support the hypothesis that histamine levels are inversely correlated with the activity of Tregs. However, mice incubated with *Echinococcosis granulosus* and sensitized have higher histamine levels compared to healthy controls. However, there was no difference observed in the numbers of Tregs in peripheral lymph nodes between the two groups[76]. Further studies are needed to clarify the relationship between histamine and Tregs.

CONCLUSIONS

Tregs are important in the regulation and amelioration of allergic dermatitis. Mast cells are one of the inflammatory cells involved in allergic dermatitis regulated by Tregs. Since histamine, which is mainly secreted from mast cells, results in the development of allergic dermatitis by suppressing Tregs, understanding the effects of histamine against Tregs would help improve treatment of allergic dermatitis.

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