

## HLA Loci and Respiratory Infectious Diseases

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### ABSTRACT

The HLA system harbour a wide set of genes that plays an important role in the regulation and action of the immune system against invading pathogens, making them natural candidates for research on the genetic susceptibility for respiratory infections. Thus, along past decades, this topic has been subject to intense research and, consequently, several alleles of those loci have been implicated in the ability, more or less effective, to tackle and control invading pathogens in the respiratory system. Current editorial introduce, revise, summarize and comment the major advances in the role of HLA genes for the development of, and protection against, respiratory infectious disease. A general picture is drawn and new challenges on the field are relocated, especially those that might enlighten respiratory diseases aetiology and, thus, contribute in advances for diagnosis and treatment.

**Key words:** HLA; MHC; Susceptibility; Association; Respiratory system; Infectious disease

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### INTRODUCTION

Respiratory disease is a broader concept that includes any pathology affecting airways or any of its structures and organs<sup>[1]</sup>. Also, the pathologies affecting human respiration have a wide range on its aetiologies, from environmental, namely viral or bacterial infections and different sources and sorts of pollution or allergens, until genetic causes, together with a more or less complex admixture of both<sup>[2,3,4]</sup>. Contributing as well for its conceptual amplitude is the extensive gradient of severity levels that the multiple respiratory diseases assume, from simple flu and cough to chronic and severe pathologies. Accordingly to the World Health Organization, chronic respiratory diseases affect hundreds of millions worldwide, being asthma, with 300 millions, and chronic obstructive pulmonary disease (COPD), with 210 millions, the most prevalent<sup>[5]</sup>. However, lower respiratory infection diseases are one of the leading causes of death on the world, assuming the fourth position, after COPD, with the responsibility for 3.1 million lives lost in 2012<sup>[6]</sup>.

Since it is an outside open system, respiratory tract is a privileged way to pathogens entry into the body. However, despite this vulnerability and mostly because of it, one of the immune system defence first lines is precisely located in the respiratory system, especially in epithelium airways, in order to protect it, and the entire organism, from infections. When the inhaled foreign organisms contact with the airway epithelium they are confronted with a protective arsenal that ranges from physical barriers and antimicrobial compounds until immune receptors, which lead to the production of cytokines and chemokines that may affect microorganisms directly but also recruit immune cells<sup>[7]</sup>. On the development of respiratory infectious diseases, host genetics play an important role. In fact, since the organism ability to oppose to any outside aggression is greatly influenced by its genetic characteristics, especially those defining the immune system structure and function, the susceptibility to viral or bacterial respiratory infections would be, at least partially, defined by its genome<sup>[8,9]</sup>. Despite often providing conflicting results, several studies identified and evaluated hundreds of candidate-genes for respiratory infectious disease susceptibility and, among those, several genetic markers were confirmed has been positively associated<sup>[10,11]</sup>.

## THE HLA SYSTEM

Since the human Major Histocompatibility Complex (MHC), known also as the Human Leukocyte Antigen (HLA) region, harbours a wide set of genes that play an important role in the regulation and action of the immune system against invading pathogens, it is not surprising that several alleles of those loci have been implicated in the ability, more or less effective, to tackle and control infections in the respiratory system<sup>[12,13,14]</sup>. The HLA system is located in the short arm of chromosome 6 (6p21.3), along approximately 4 megabases, and it constitutes an intricate and interrelated cluster of genes involving more than 300 loci, from which at least 160 are functional genes<sup>[15,16]</sup>. These functional genes are considered the most polymorphic of the human genome and about 40% of them have an important role in the regulation and action of the immune system<sup>[12,17]</sup>. Accordingly to the structure and function of its genes, the human MHC has been classified in three main regions: class I, class II and class III; and despite it is known as HLA system, most of the genes enclosed in each region are non-HLA. The class I are located on the most telomeric region of the human MHC and, besides a majority of non-HLA genes, it includes 3 high polymorphic HLA genes, known as classical (Class Ia: HLA-A, HLA-B and HLA-C) and 3 low polymorphic HLA genes, known as non-classical (class Ib: HLA-E, HLA-F and HLA-G), besides a dozen of HLA pseudogenes and one HLA non-coding gene<sup>[18]</sup>.

HLA class I loci express molecules composed by a heavy chain that bound non-covalently to a light chain, a  $\beta$ -2 microglobulin encoded by B2M gene located on chromosome 15. The heavy chain is structured in three domains ( $\alpha$ 1,  $\alpha$ 2 and  $\alpha$ 3) together with a membrane-spanning region and a cytoplasmic tail<sup>[19]</sup>. Classical HLA class I genes express cell-surface glycoprotein molecules on almost all nucleated cells, playing an important role in “self” and “non-self” immune recognition. These molecules display at cell surface small protein fragments almost originated in the cytosol. Their interaction with inhibitory or activating receptors from the surface of Natural Killer (NK) or cytotoxic CD8+ T-cells modulates the lytic activity. As a result, when a cell expresses foreign proteins, due to a viral infection, or shows a different expression pattern, due to an oncogenesis process, HLA class I signals those changes through its own binding to the resulting peptides and, after recognition by NK or CD8+ T cells, an immune response is triggered<sup>[20,21,22]</sup>. This same immune mechanism is responsible for allograft rejection when HLA compatibility between donor and recipient is missing<sup>[23]</sup>. HLA-B is the most polymorphic classical class I gene, with 4077 alleles indentified to date in the different human populations, followed by HLA-A (3285 alleles) and HLA-C (2801 alleles) (IMGT/HLA Database, release 3.22.0, 2015-10-10). Despite each HLA variant has a singular structure in its peptide-binding groove, the number of small peptides that can bind to each one is large<sup>[24]</sup>. Additionally, the high polymorphism that classical class I HLA shows improves the ability of the immune system to recognise a wider range of pathogens. As so, since heterozygosity at any of the classical class I loci are associated with positive outcomes during immune infections, these polymorphisms have been driven by selection to improve the efficacy of the immune system<sup>[25,26,27]</sup>.

Non-classical class I loci (HLA-E, HLA-F and HLA-G) are best known for their participation on the regulation of the innate immunity but they can also play a role in regulating adaptive responses. HLA-E, -F and -G co-express in the placenta trophoblast cells and several studies have shown a poor prognosis associated to their higher expression in different types of malignant tumours, facts that

emphasize their role in immune modulation and protection against NK lysis<sup>[28,29]</sup>. In opposition to the ubiquitous expression of classical class I, these non-classical loci tend to be conditional and tissue or organ specific<sup>[30]</sup>. HLA-E molecules act on both the innate and adaptive immune system playing a key role in their modulation<sup>[31,32]</sup>. HLA-E is represented by only 7 non-synonymous alleles (IMGT/HLA Database, release 3.22.0, 2015-10-10) and, even so, only two of them (E\*01: 01 and E\*01: 03) have been show to express relevant molecules for the immune function<sup>[33]</sup>. These HLA-E molecules are broadly expressed on all cells<sup>[34]</sup>, presenting in the healthy cells surface a limited set of highly conserved peptides derived from classical HLA class I<sup>[35]</sup>. HLA-E molecules and its binding peptides constitute complexes that act as ligand for both inhibitory (NKG2A/CD94) and stimulatory (NKG2C/CD94) receptors in NK cells and in a subset of CD8+ T cells<sup>[36,37]</sup>. Through this mechanism, NK cells monitor the HLA expression that is occurring inside the cell and, thus, evaluate its health status<sup>[38]</sup>. A change in the complexes constituted by HLA-E and its binding peptides prevent the connection with the NK inhibitory receptor (NKG2A/CD94), which triggers a cytotoxic response against the unhealthy cell<sup>[39]</sup>. HLA-F is also a very low polymorphic locus with only 4 proteins expressed (IMGT/HLA Database, release 3.22.0, 2015-10-10) and its expression and function patterns still under investigation. Despite expressing at cell surface at specific conditions and in particular cells, namely in activated lymphocytes, its most common expression is cytoplasmic<sup>[40,41]</sup>. HLA-F seems to be expressed in the first moments of the activation of an immune response and the evidences of its unusual properties, e.g., independent pathway to reach cell surface<sup>[42]</sup> and ability to bind bigger peptides<sup>[43]</sup>, point out for a different biological function than that of other class I molecules. HLA-G is better studied and despite its low polymorphism it's higher than other non-classical class I. With 51 alleles found worldwide, HLA-G locus expresses 17 distinct functional proteins and, due to alternative splicing, can assume membrane-bound and soluble isoforms (IMGT/HLA Database, release 3.22.0, 2015-10-10)<sup>[44]</sup>. Its functions are oriented towards immune inhibition and tolerance and one of its most known implications is on the prevention of maternal-foetal rejection<sup>[45]</sup>. Cells from placenta migrate into the maternal uterus and produce both membrane and soluble HLA-G isoforms, which will inhibit maternal immune response against foetal foreign antigens through interaction with inhibitory receptors in maternal leukocytes, establishing an immune privilege<sup>[30]</sup>. This mechanism of inhibition and tolerance mediated by HLA-G has revealed to be involved in tumour escape from the immune system and, in fact, a higher expression has been significantly correlated with poor prognosis in patients with solid tumours<sup>[46,47,48]</sup>.

Among the tens of non-HLA genes located on class I region, is worth mentioning the two functional MIC (MHC class I-related chain) genes (MICA and MICB). MICA and MICB are located between HLA-B and the centromeric end side of the class I region and, despite showing low homology with classical HLA genes, they are also highly polymorphic and express as membrane bound glycoproteins or soluble forms. In opposition to HLA, these glycoproteins don't combine with  $\beta$ 2-microglobulin, do not bind peptides and are not expressed on normal circulating lymphocytes<sup>[49]</sup>. MICA and MICB are ligands of the natural killer (NK) and T cells receptor NKG2D (natural-killer group 2, member D), and both express under stress conditions to activate an immune response<sup>[50]</sup>.

The HLA class II genes are located on the most centromeric region of the human MHC and it includes alpha and beta chain genes, the classical HLA-DPA, -DPB, -DQA, -DQB, -DRA and -DRB, and

also the non-classical HLA-DMA, -DMB, -DOA and -DOB, besides some pseudogenes and nonHLA genes<sup>[18]</sup>. The alpha and beta chains expressed by the classical class II genes associate each other non-covalently to compose heterodimer transmembranar molecules on the surface of a restricted set of cells that interact with CD4+ T-helper cells, predominantly antigen-presenting cells (APC) such as macrophages, dendritic cells and B lymphocytes<sup>[51]</sup>. Both alpha and beta chains contribute to form the peptide binding groove and those peptides presented by HLA class II molecules on the cell surface of APC result from internalized and processed exogenous antigens that could derive from cell surface proteins, soluble proteins or proteins from a virus, bacteria or protozoa invaders<sup>[52]</sup>. When CD4+ T-helper cells become activated, after recognizing a foreign peptide presented within the antigen binding groove of a class II molecule, they differentiate and secrete cytokines which influence the proliferation, function and differentiation of other immune cells, including other T cells, B cells and macrophages, triggering an adaptive immune response against foreign pathogens or allograft<sup>[53]</sup>. HLA-DR loci code for the DR heterodimer molecule, with the low polymorphic HLA-DRA1 gene expressing the alpha chain and the high polymorphic HLA-DRB1 gene the beta chain<sup>[18]</sup>. Besides the ubiquitous DRB1, other lowest polymorphic HLA-DRB loci could also be present in a variable number, namely -DRB3, -DRB4, and -DRB5 coding genes and several others non-coding genes (-DRB2; -DRB6; -DRB7; -DRB8 and -DRB9)<sup>[54]</sup>. HLA-DRA1, the sole gene expressing the alpha chain of DR molecules, is the less polymorphic class II locus with 7 alleles coding for only 2 different proteins. Otherwise, HLA-DRB1 is the most polymorphic class II locus with 1825 alleles that express 1335 different proteins in all human studied populations. The genes that express the other two classical class II molecules, HLA-DQ and -DP, show also a high asymmetry in the polymorphisms of alpha and beta chains. In fact, if we compare the HLA-DQA1, with 54 alleles and 32 expressed proteins, with the HLA-DQB1, with 876 alleles and 595 expressed proteins, and the HLA-DPA1, with 42 alleles and 21 expressed proteins, with the HLA-DPB1, with 587 alleles and 480 expressed proteins, this asymmetry is blatantly obvious. (IMGT/HLA Database, release 3.22.0, 2015-10-10).

The non-classical class II proteins, HLA-DM and -DO, assume the same structure described above for classical class II but lacks the ability to bind peptides. Their heterodimer molecules are also expressed by alpha and beta chain genes, HLA-DMA1 and -DMB1 for -DM molecules, and HLA-DOA1 and -DOB1 for -DO molecules<sup>[55,56]</sup>. However, in these non-classical loci, alpha and beta chain genes polymorphisms asymmetry are not evident and both show a very low number of alleles. To date, 7 alleles and 4 expressed proteins were found for HLA-DMA1, 13 alleles and 7 expressed proteins for HLA-DMB1, 12 alleles and 3 expressed proteins for HLA-DOA1, and 13 alleles and 5 expressed proteins for HLA-DOB1 (IMGT/HLA Database, release 3.22.0, 2015-10-10). Both HLA-DM and -DO molecules play a critical role in the HLA classical class II ability to functionally bind self and non-self peptides on APC, controlling the very first steps of an immune response<sup>[57]</sup>. HLA-DM molecules intermediate the process and the affinity of peptide binding to HLA classical class II glycoproteins, stabilizing otherwise short-lived transition states and promoting rapid peptide exchange processes that favours highest-affinity ligands. When classical class II molecules assemble in the Endoplasmic Reticulum (ER) the peptide binding groove is protected with an invariant chain until this complex reach the endosomal peptide loading compartment, where, in a stepwise manner, this invariant chain is degraded and HLA-DM catalyze its substitution by antigenic peptides. Also, the HLA-

DM molecules have the ability to stabilize empty class II proteins and induce dissociation of peptide-binding groove complexes, which increases the affinity between classical class II molecules and its ligands<sup>[58]</sup>. HLA-DO molecules also participate in this process influencing the repertoire of peptides presented by class II proteins. Despite the mechanism by which HLA-DO functions is unclear, it binds tightly to HLA-DM and modulates its activity. It seems that HLA-DO inhibits HLA-DM function by acting as a substrate mimic that prevents HLA class II access<sup>[59]</sup>.

Among the few non-HLA genes located on class II region, is worth mentioning the two TAP (transporter associated with antigen processing) genes (TAP1 and TAP2), located between HLA-DOB1 and -DMB1<sup>[18]</sup>. For each of both genes 12 alleles were found, being TAP1 and TAP2 responsible for expressing 6 and 5 different proteins, respectively (IMGT/HLA Database, release 3.22.0, 2015-10-10). The two polypeptide chains expressed by TAP genes form a complex that pumps degraded cytosolic peptides into the ER lumen to be subsequently loaded onto HLA class I molecules<sup>[60]</sup>. TAP is a member of the ATP-binding-cassette (ABC) family of transporters and each one of the two molecules that compose the heterodimer includes a transmembrane domain (TMD) and a nucleotide-binding domain (NBD)<sup>[61]</sup>. TAP translocates peptides from cytosol into ER under consumption of ATP and constitutes an important mechanism in the class I peptide-loading complex<sup>[62]</sup>.

The class III region of the MHC, located between class I and class II region, has no known HLA like genes but is the most gene-dense region in the human genome<sup>[63]</sup>. The 75 loci that constitute this region are responsible for expressing 55 different proteins, some of them molecules with an important role on modulating and regulating immune response (IMGT/HLA Database, release 3.22.0, 2015-10-10)<sup>[64]</sup>. Some of these class III genes that act as critical mediators of immunity include tumour necrosis factor (TNF), heat shock proteins (HSP), B-associated transcripts (BAT) and some complement components loci. For example, C2, CFB, C4B and C4A are the complement components genes that are located in MHC class III region, belonging to the complement system, part of the innate immune system, and made up of several plasma proteins that act against pathogens and induce inflammatory responses<sup>[65]</sup>. Also, TNF, located right in the middle of other two class III MHC cytokine genes (LTA and LTB), is an important multifunctional proinflammatory agent that triggers a cascade of inflammatory mediators<sup>[66]</sup>. Furthermore, 3 HSP genes (HSPA1L, HSPA1A and HSPA1B) are also aligned side by side and located within the class III region<sup>[67]</sup>. HSPs act as danger-signalling molecules to the innate immune system, showing a regulatory role, namely on natural killer cell response to cancer<sup>[68]</sup>. Additionally, BAT3 gene, one of the 5 BAT loci intermingled along MHC class III region, has been reported to be involved as an immune system mediator in diverse signalling pathways, emerging as a new set of immune regulatory proteins together with some HSPs and others<sup>[69,70]</sup>.

## HLA AND RESPIRATORY INFECTIOUS DISEASES

Since a wide spectrum of respiratory infectious diseases has been associated with several genetic markers located in the HLA region, we selected, to summarize, analyze and exemplify this topic, those with a better established relationship. Also, besides the strictly infectious, we included some in which pathogens are mostly opportunistic than the main cause of the disease. Thus, pulmonary tuberculosis, severe acute respiratory syndrome (SARS), pulmonary Mycobacterium avium complex (MAC) infection, idiopathic

bronchiectasis, diffuse panbronchiolitis and recurrent respiratory papillomatosis were selected to approach and analyse the role of HLA loci in respiratory infectious diseases, the aim of this editorial.

### Pulmonary tuberculosis

Pulmonary tuberculosis (TB) is a lung infection disease caused by *Mycobacterium tuberculosis* that still causes about 1.5 million deaths a year<sup>[71]</sup>. Despite environmental factors are the leading cause on the development of the disease, several studies had shown that host genetics also predispose to or protect from TB. Several HLA-DRB1 alleles have been reported to be related with risk of TB, regardless some inconsistency between different ethnic groups<sup>[72,73,74]</sup>. A recent meta-analysis that took in consideration the ethnicity of each case-control study suggests that, in Asian populations, the DRB1\*08: 03 and HLA-DRB1\*15 alleles confer an increased risk of TB, while DRB1\*03 and DRB1\*07: 01 are protective<sup>[13]</sup>. When including other populations besides Asian, namely European and South and North American, this same meta-analysis found consistent results with an increased risk of TB for individuals with DRB1\*08: 03 and HLA-DRB1\*15 alleles. However, in this non-grouping evaluation, besides DRB1\*03 and the exclusion of DRB1\*07: 01, other alleles emerged as conferring protection against TB, namely DRB1\*11, DRB1\*11: 03 and DRB1\*12: 02. Accordingly, in a population from South Africa, DRB1\*08: 03 allele has found to be strongly positively associated with drug-resistance, increase in lung damage and resurgence of TB<sup>[75]</sup>. Another recent meta-analysis including 19 case-control studies also confirmed the DRB1\*03 protection and DRB1\*08 risk effect and added DRB1\*04 and DRB1\*16 as markers associated with an increased infection occurrence, concluding also that both ethnicity and genotyping methods affect the association between several HLA-DRB1 alleles and TB occurrence<sup>[76]</sup>. Confirming DRB1\*04, DRB1\*15 and DRB1\*16, and adding DRB1\*09 and DRB1\*10 as polymorphisms that may contribute to the risk of TB, especially in East Asian, and identifying DRB1\*11 as conferring protection, a 31 studies meta-analysis fail to support a significant association between the HLA-DRB1\*01, \*03, \*07, \*08, \*12, \*13, and \*14 gene polymorphisms and TB risk<sup>[77]</sup>. Regardless the strong evidences of the association with these DRB1 alleles, it's still unknown whether if they influence directly TB susceptibility, namely through the ability to present *M. tuberculosis* antigens to CD4+ T-helper cells, or if it results from an indirect influence through other factors. From the results available, the heterogeneity that arose on the association between TB and DRB1 alleles seems to be a consequence of different effects exerted by genetic polymorphisms among each ethnicity, namely due to specific variations in gene-environment and gene-gene interactions<sup>[13,78]</sup>.

Other HLA loci were also found to be associated with risk and protection for TB. For example, in South India, besides HLA-DRB1\*15: 01, HLA-DQB1\*06: 01 were identified as conferring risk to TB, together with HLA-DPB1\*04 as a marker for protection<sup>[79]</sup>. Also, two studies in Cambodia confirmed DQB1\*06: 01 and adds DQB1\*05: 03 alleles as risk factors for TB<sup>[80,81]</sup>. Thus, up to date studies with HLA high resolution throughput, well defined disease pathogenesis, pathogen diversity, higher sample sizes, vaccination status information, environmental factors characterization, consistent statistics and sharply defined ethnicities are needed to better understand the relationship between HLA loci alleles and TB susceptibility. Also, the role played by gene-gene interactions (epistasis) in TB susceptibility level, namely with non-HLA loci as UBE3A, VDR, IL12, IL12RB1, INFG, MBL, SFTPA1/2, MCP1 and NRAMPI, could be a contribution to enlighten this subject<sup>[82]</sup>.

Since TB is the commonest opportunistic infection affecting HIV patients as also their leading cause of death, it worth mention that certain HLA polymorphisms have been identified as susceptibility factors to the infection and progress of TB in HIV<sup>[83]</sup>. HLA-B\*57, due to its ability to enhance the presentation of antigenic peptides on the surface of HIV-1 infected CD4+ cells to cytotoxic CD8+ T cells, has been commonly associated with a suppression of the disease progression<sup>[84]</sup>. In a sample of HIV infected from North India, HLA-DRB1\*13, -DRB5, -DQB1\*06 and -B\*15 allelic groups were associated with an increase in the risk for TB but -DQB1\*06 and -B\*51 with a protection effect<sup>[85]</sup>. In a similar study but with samples from South India, the HLA haplotype DRB1\*15: 02-DQB1\*06: 01-DPB1\*02: 01 revealed to increase the risk of TB in HIV infected and, in the opposite direction, the HLA-DPB1\*15: 01 allele as conferring protection<sup>[86]</sup>.

TNF locus, located in the MHC class III region and coding for an important multifunctional cytokine that triggers a cascade of inflammatory mediators, has been linked with an increase risk for TB. Two mutations in the promoter region of the TNF- $\alpha$  gene at positions -238 (G/A) and -308 (G/A) were associated with pulmonary TB in the Colombian population<sup>[87]</sup>, the former also confirmed for Iranian in two different studies<sup>[88,89]</sup>. Also, the susceptibility for a pulmonary tuberculosis infection was found to be associated with the TNF- $\alpha$  -857T/C genetic polymorphism in Asian populations<sup>[90]</sup> and, for a reduced risk, with the CD14 G(-1145)A and C(-159)T polymorphisms in Chinese Han population<sup>[91]</sup>. However, no association was observed between TNF polymorphisms and TB in several other populations, such Indian, Cambodian, Thais or Turkish<sup>[92-95]</sup>. Additionally, the use of TNF inhibitors in therapies against autoimmune diseases, such as rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, psoriatic arthritis and psoriasis, has been associated to an increase in TB risk<sup>[96,97]</sup>.

### Severe Acute Respiratory Syndrome (SARS)

The Severe Acute Respiratory Syndrome (SARS) coronavirus infection, presenting itself as an atypical pneumonia, is a highly contagious disease with high incidence and mortality rates. After SARS outbreak in Asia in the beginning of 2003, a few studies have been showing that HLA profile correlates with the infection. Right on the year of the outbreak, a study with a few dozens of SARS patients indicated an association of the HLA-B\*46: 01 allele with the severity of the infection in Taiwanese population<sup>[14]</sup>. Later, a case-control study in the same population revealed that the HLA-C\*15: 02 and -DRB1\*03: 01 alleles confer resistance against SARS infection<sup>[98]</sup>. Nevertheless, a cohort of 95 SARS-recovered patients from Guangdong, southern China, miss to show any association between the development of the disease and their HLA profile<sup>[99]</sup>, despite a study with 90 Chinese patients from Hong Kong confirmed the HLA-DRB1\*03: 01 as a protective allele and unveiled another risk allele, the HLA-B\*07: 03, despite not confirming the B\*46: 01<sup>[100]</sup>. Evidences of the SARS-HLA correlation has also been found in Vietnamese population, with the HLA-DRB1\*12: 02 allele showing to be significantly much more prevalent in the patients than in control group<sup>[101]</sup>. Regardless SARS affected several thousands of people along the year 2003, the number of samples included in the above studies were very low which, together with a suddenly decrease on the interest of the subject since the outbreak was contained, left to be explored the involvement of the HLA markers in the pathogenesis of the disease. Thus, understanding the genetic risk or protection conferred by HLA markers on the SARS infection requires enlightenment on their contribution for the control of viral



proliferation, on their participation in autoimmune pathogenesis and even if there is a link between them and other unknown determinates that influence directly the course of SARS infection and the associated lung damage<sup>[100]</sup>.

### Pulmonary MAC infection

The Pulmonary Mycobacterium avium complex (MAC) infection is caused by *M. avium* and *M. intracellulare*, two nontuberculous mycobacteria. Despite ubiquitous in the environment, MAC infections occur rarely in immunocompetent hosts, affecting mostly those with depressed immunity or with underlying lung diseases<sup>[102]</sup>. MAC is the most common cause of lung nontuberculosis and its rate of infection is globally increasing, especially in Japan<sup>[103]</sup>. Besides environmental risk factors, genetic susceptibility to the disease have been reported, some of them linked to MHC loci. In fact, through a genome wide case-control approach followed by functional analysis of the gene expression, MICA, a non-HLA gene located on class I region, has been selected in Japanese patients as a promising candidate that might be involved in susceptibility to pulmonary MAC disease<sup>[104]</sup>. Especially in female patients, D6S0009i MICA polymorphism (MICA-TM), and particularly its A6 allele, has been found in the above study has conferring genetic susceptibility to MAC. Also, since TNF locus, located in class III MHC region, is an important multifunctional proinflammatory agent, some therapies, especially in autoimmune diseases such as rheumatoid arthritis, uses TNF inhibitors which have been associated to an increased risk for MAC and other non-tuberculosis mycobacteriosis, besides TB mentioned above<sup>[105]</sup>. Despite with inconclusive results, other studies suggest that specific HLA alleles could be associated with the development of pulmonary MAC infection. In a 59 Japanese patients sample, the HLA-A\*33 and -DRB1\*13/14 (DR6) alleles, together with the haplotype A\*33-B\*44-DRB1\*13/14(DR6), were found to be associated with the infection<sup>[106]</sup>. Another article published in the same year (2000) with 64 Japanese patients confirms the association of the HLA-DRB1\*13/14 (DR6) alleles to a higher risk of MAC infection and adds also HLA-DQB1\*04/DQA1\*03/04 (DQ4) and -A\*26, this former especially in the deterioration of nodular-bronchiectatic MAC infection<sup>[107]</sup>. A most recent publication (2009) evaluating 48 Korean patients with MAC lung disease has found a higher susceptibility among the HLA-B\*46 carriers<sup>[108]</sup>.

These mostly inconclusive and inconsistent results on the HLA association with MAC infection could be deeply related to the low number of studies on the subject, mostly limited to Japanese population, with low sample numbers and low resolution HLA typing. To mitigate this, new studies need to be done with higher sample numbers and discriminating between immunocompetent, with depressed immunity and underlying lung diseases hosts. Also, four digits high resolution HLA typing studies for a most diverse panel of world populations, Asian and others are mandatory to enlighten the subject.

### Idiopathic bronchiectasis

Bronchiectasis is a pathological end-point of different mechanisms and describes a permanent dilation of the bronchi and bronchioles due to the destruction of the muscles and elastic tissues. This lungs condition starts with a narrowing of the bronchial tree which may lead, if it becomes chronic, to destruction of the epithelium and, with the consequent deficient mucociliary clearance, the retention of secretions giving way to recurrent infections<sup>[109]</sup>. The pathological processes leading to Bronchiectasis include infectious damage, genetic mutations, autoimmune diseases or, among others, unbalance

host defence. However, in half of the cases, the underlying aetiology is unknown (idiopathic bronchiectasis) and, in such situations, there are bilateral, predominantly lower-lobe disease and chronic rhinosinusitis<sup>[110]</sup>. Despite poorly understood, the progression of idiopathic bronchiectasis in the lungs is believed to result from an interaction between chronic bronchial infections and a deregulated process of inflammation, whatever one or another to be the responsible for triggering the process<sup>[111]</sup>.

HLA region hosts some of the candidate genes that have been the focus for genetic studies on idiopathic bronchiectasis. After HLA class I antigen deficiency due to a TAP2 gene mutation has been shown to be associated with familial bronchiectasis and that bronchiectasis affects 80% of patients with primary immunodeficiency resulting from defective TAP complex, a couple of studies have been developed considering that HLA could be in the core origin of the idiopathic cases<sup>[112,113]</sup>. A HLA class II polymorphism analysis in a UK Caucasian disease cohort showed a significant association between the haplotype HLA-DRB1\*01: 01-DQA1\*01-DQB1\*05: 01 and the development of idiopathic bronchiectasis, suggesting the implication of the CD4+ T cells in the lung damage underlying the disease<sup>[114]</sup>. Despite not confirmed in a replication study published by other authors<sup>[115]</sup>, HLA-C\*03 allelic group was found to be associated with an increased risk for idiopathic bronchiectasis in British patients, and C\*06 with a reduced risk<sup>[116]</sup>. Also, this same study found a distinct distribution of the serologically HLA-C groups 1 (Ser-77/Asn-80) and 2 (Asn-77/Lys-80), with a higher prevalence of HLA-C group 1 homozygosity among patients than controls. These findings and previous knowledge on the interplay between HLA-C and KIR genes, together with the implication of TAP deficiency syndrome, suggests a role for NK cells in Bronchiectasis pathology.

The need for further investigation in HLA implications for idiopathic bronchiectasis is evident since little has been done so far. TAP deficiencies and HLA expression needs to be evaluated as also if HLA implications for the disease influence susceptibility to specific pathogens or to self-reactivity, or both. More, large and different population studies are also needed to enlighten this subject.

### Diffuse panbronchiolitis

Diffuse panbronchiolitis (DPB) is an inflammatory disease of unknown aetiology affecting primarily the respiratory bronchioles and causing a severe and chronic obstructive pulmonary disease. DPB is commonly associated with recurrent respiratory tract infection and reach its highest prevalence among East Asians, especially Japanese, affecting males twice than females and, if left untreated, progressing to bronchiectasis, respiratory failure and death<sup>[117,118]</sup>.

Ready after it has been described and named in the 1960s, a genetic association was suspected, namely due to the identification of familial cases, and in 1990 a study with a few dozens of patients identified, by serologic means, the HLA-B\*54 allelic group (Bw54) has being strongly positively associated with the disease<sup>[119,120,121]</sup>. Since this allelic group is characteristic for Asian populations it, at least partly, explains why the disorder is found primarily in Asians, and raises the suspicion that the genetic predisposition for DPB has a major contribution from HLA or from a closely linked gene in the region. Since then, other studies confirmed and extended this association. The HLA high resolution typing revealed that the B\*54: 01 was the allele of the B\*54 group responsible for the association and that other B alleles, also belonging to the broad serologic group B22, were involved, namely B\*55: 04 and B\*56: 01<sup>[122]</sup>. Interestingly, the same study found that when taking together the alleles that code for the B22 antigen family, and even more when including the related

B7 serotype, the positive association with the disorder gets stronger. Other HLA were found to be associated, despite weakly, with the disease, namely A11 and C1 antigens with a positive association and, contrariwise, A33 and B44 antigens, and HLA-DRB1\*13: 02 allele, with a negative association. However, Keicho and colleagues (1998) note that these alleles constitute typical haplotypes observed among Japanese which, thus, may mean that these other genes associations could be only the result of their linkage disequilibrium with HLA-B\*54 and -B\*44.

An evaluation of HLA in Korean patients showed a positive and strong association of the A11 and B55 serotypes with DPB, and also with B62 and Cw4 but weaker<sup>[123]</sup>. Remarkable much stronger positive associations with the disease were found when considering haplotypes that includes A11, B55 and B62 (A11-Cw1: OR = 12.1, Cw1-B55: OR = 9.8, A11-B62: OR = 7.9) rather than each serotype itself. Similarly to Japanese population, this study with Koreans identified HLA-DR\*13 as a protective genetic marker against DPB. The rarity of the disease and the subsequent studies low sample number adds great difficulties to obtain conclusive results in others than Japanese population, but positive association with DPB were confirmed in Chinese patients for HLA-A\*11 and -B\*54<sup>[124,125,126]</sup>. Considering the data available on the association between HLA and DPB, some authors hypothesized that the candidate gene(s) responsible for the disease susceptibility should be located within HLA class I region, most probably between HLA-A and HLA-B loci<sup>[123,127]</sup>. Attempts to narrow the location of this hypothetical susceptibility gene(s) have been done and the results obtained indicate that it is probably located within a 200 kb segment located in the class I region 300 kb telomeric from HLA-B locus<sup>[128]</sup>. In this narrowed region, a mucin-like gene cluster were identified and some polymorphisms in one of its genes, the panbronchiolitis related mucin-like 1 (PBMUCL1), were found to be associated with the disorder, making it a new candidate gene for DPB susceptibility<sup>[129]</sup>.

### Recurrent respiratory papillomatosis

Recurrent respiratory papillomatosis (RRP) is a rare but life-threatening disease characterized by the growth of multiple benign tumours in the larynx and other sites within the upper aerodigestive<sup>[130]</sup>. RRP is caused by human papillomavirus (HPV) infection but, despite the virus carriage rate in the oropharynx is at least 10%, few of the infected develop the disease, which indicates that other factors must contribute to the pathogenesis<sup>[131,132]</sup>. Some studies have reported an association between HLA and the development of the disease. In 1994, Bonagura and colleagues noted that HLA-DQ3 and -DR11 molecules were highly enriched in peripheral blood and that HLA class I antigens expression on papilloma tissue was markedly reduced in patients with RRP<sup>[133]</sup>. Later, they found a co-down-regulation of TAP1 and HLA class-I in respiratory papillomas compared with normal respiratory epithelial tissue and that the patients with the most aggressive and rapidly progressive disease expressed the lowest levels of TAP1<sup>[134]</sup>. Since TAP translocates peptides from cytosol into ER and constitutes an important mechanism in the class I peptide-loading complex, the authors of these studies suggest that the resultant absence of surface HLA class-I molecules would prevent the recognition of HPV peptides at the cell membrane and, consequently, an effective action of the immune system.

Also, an investigation with British patients identified an association between the presence of the HLA-DRB1\*03: 01 allele and the susceptibility to RRP, as also to its severity. This same study found preliminary evidences for an HLA-DRB1\*14 association in juvenile-

onset disease and a HLA-B\*27 association in adult-onset disease<sup>[135]</sup>. Another study confirmed the association between HLA-DRB1\*03: 01 and the severity of the disease in Caucasian patients and found also a positive association with DRB1\*01: 02, DQB1\*02: 01 and DQB1\*02: 02 and a protective effect for DQB1\*06: 02<sup>[136]</sup>. In Korean patients HLA-DRB1\*11: 01 and -DQB1\*03: 01, together with DRB1\*11: 01-DQB1\*03: 01 haplotype, were strongly associated to severe RRP<sup>[137]</sup>.

## CONCLUSION

The respiratory tract, being an outside open system, is subject to frequent contact with a wide diversity of bacteria and virus. The ability of the human respiratory system to halt the invasion and proliferation of pathogens, and prevent an infection to install is based in an all complex innate and adaptive immune system in which an extensive arsenal is involved. These immune mechanisms range from physical barriers and antimicrobial compounds to immune receptors that lead to production of cytokines and chemokines, which may affect microorganisms directly and recruit immune cells<sup>[7]</sup>. The complexity and multiplicity of the apparatus and pathways involved in the immune response are defined and organized by a highly diverse genetic basis. Thus, on the development of respiratory infectious diseases, host genetics are obviously well positioned to play an important and defining role, influencing the organism ability, more or less effective, to oppose to any outside aggression<sup>[8,9]</sup>.

To date, most studies on HLA association with respiratory infectious disease share the same handicap: a low sample number. The rarity of some of these pathologies, especially when we consider well genetically defined populations, makes difficult the enlargement of sample number. Also, increasing even more the difficulties to assemble a greater sample number is the variability of aetiologies that can be on the basis of each one of these pathologies. Despite the available conflicting results and the need for further, larger and better studies, it is evident that respiratory infectious disease susceptibility is strongly dependent on the individual and collective gene pool. Among these genetic factors, HLA loci play a central role despite, also here, research is needed to enlighten present knowledge. So far, this field has been mostly centred in studies of association which have shown a high number of HLA alleles with either risk or protective effect. The specific HLA alleles implicated in the susceptibility for respiratory infectious disease constitute a highly diverse set, varying accordingly with the pathogen involved and, for the same disorders, between different human populations. On these HLA and respiratory infectious disease associations two different pictures seem to emerge: a directly implication of the HLA alleles or an association through a close linkage with other loci that may be the direct cause. One or another could be the basis for the HLA associations that have been found in several populations, depending on the respiratory infectious disease considered. In this unclear involvement of HLA loci, gene-gene and gene-environment interactions could be present, making even more difficult a comprehensible analysis of the results obtained on the studies. Additionally, besides the influence of a more or less effectiveness of the HLA portfolio to signalling the invading pathogens, the evolution and installation of respiratory infections could also depend on immune cross-reactivity between self and non-self antigens that cause inflammatory conditions among which opportunistic pathogens proliferate.

Also, to be taken in consideration in the analysis of the high variability found for different populations on the same disease HLA association, is the possibility that this inconsistency, besides

dependent on different gene linkages, could be related to specific pathogens characteristics, gene-environment interactions or other specific pathways on the aetiology of the disease. As that, each HLA association study needs to identify, characterize and discriminate better the specific conditions in which the disease appears and develops, since it can make all the difference in the sense of the obtained data.

A new step forward on the HLA association with respiratory infectious disease demands for a much more careful approach in future studies. Besides the above considerations, HLA studies need to be done with DNA high resolution techniques in order to assure a four digits typing. However, high resolution data should be also analyzed in the context of their serologic meaning, especially grouping antigens through their families and functions. The need to enlarge the picture of possible mechanisms and pathways involved in the aetiology of the respiratory infectious disease requires the study of new DNA markers along the MHC region, including HLA and non-HLA loci as also segments showing linkage with the already identified genetic markers.

## CONFLICT OF INTERESTS

The author has no conflicts of interest to declare.

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