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# Introductory Chapter: Immunogenetics

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## 1. Major histocompatibility complex (MHC): the master system for self-/nonself-recognition

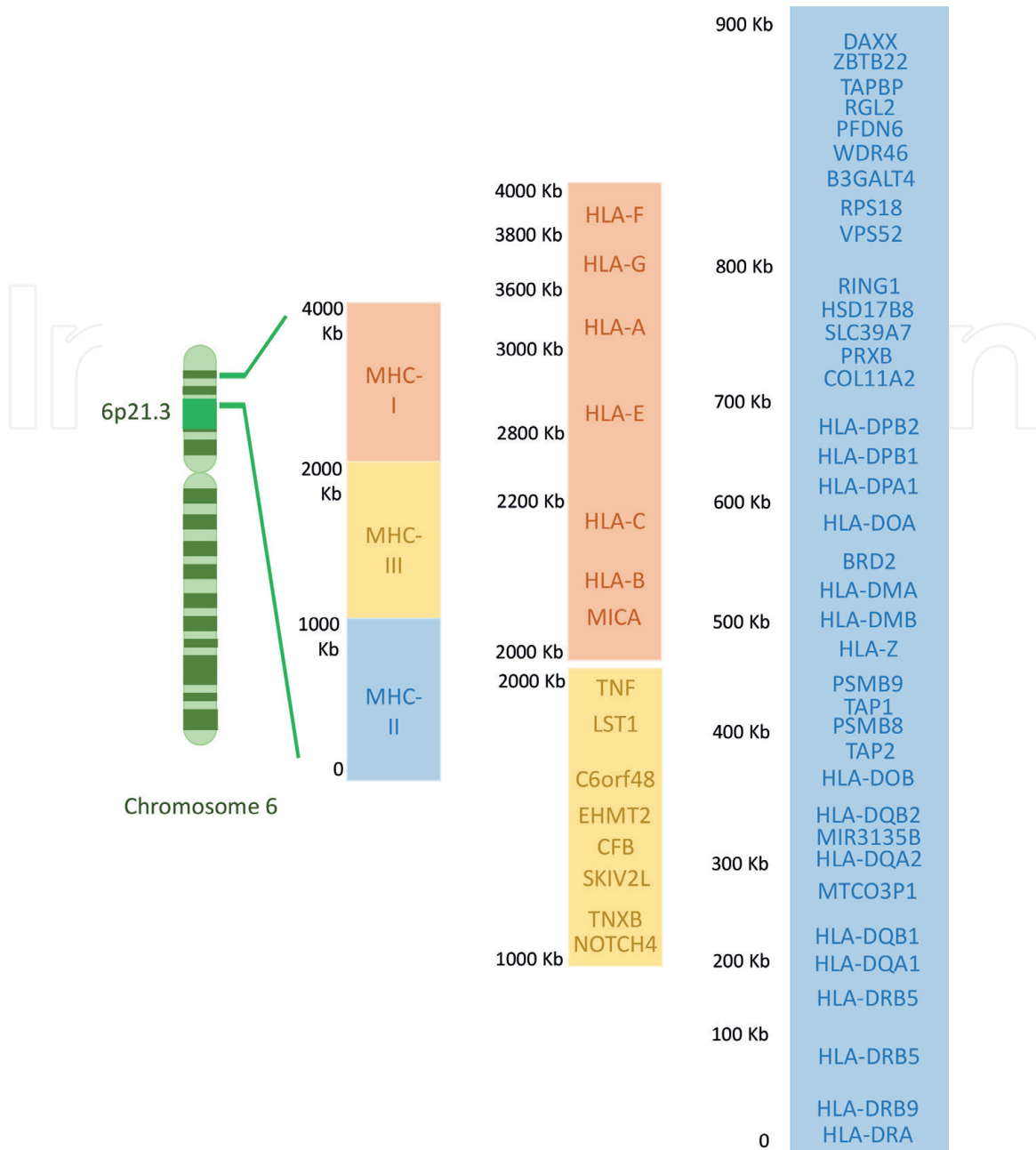
It is a gene family found in many vertebrates. In humans, the “HLA” is interchangeably used with MHC. The MHC gene family is composed of three main subfamilies clustered near one another on chromosome 6. As shown in **Figure 1**, MHC class III genes space between MHC class I and class II genes. Glycoproteins encoded by MHC class I genes are present on the surface of all nucleated somatic cells, while the expression of MHC II glycoproteins is largely restricted to the specialized antigen-presenting cells (APCs) such as dendritic cells, macrophages, and B cells. Both have extracellular domains that form the peptide-binding region. Those of MHC class I molecules govern the presentation of peptide (antigen) primarily derived from intracellular sources (endogenous) to CD8<sup>+</sup> cytotoxic T lymphocytes (CTLs), while those of MHC class II molecules are particularly effective at presentation of peptide primarily originated from extracellular sources (exogenous) to CD4<sup>+</sup> helper T (T<sub>H</sub>) cells. In the following, the specific mechanisms of action appear:

## 2. MHC class I

T-cell receptor (TCR) on the surface of CTLs interacts with peptide-MHC class I complex. It has the ability to discriminate self from foreign. CTLs are stimulated upon TCR recognition of foreign peptides. Stimulated CTLs promote T-cell proliferation and lysis in peptide-pulsed target cells. Also MHC class I molecules interact with NK cell receptors, e.g., killer-immunoglobulin-like receptors (KIRs), thereby controlling effector functions of NK cells that can damage self-components, for example, cell cytotoxicity and excessive inflammation [1]. In this manner, MHC I molecules induce self-tolerance via a NK cell-dependent mechanism as well.

## 3. Class I MHC restriction of CTLs

Because both self and foreign peptides can bind to class I MHC molecules, so a question to ask is what would happen to class I MHC molecules loaded with self-peptide. The answer lies within the process by which T lymphocytes are selected in the thymus. Thereby, CTLs can enter circulation if their surface TCR is reactive to self-class I MHC molecules loaded with foreign, not self, peptides. This reaction is known as class I MHC restriction of CTLs, because it occurs only in the presence of self-class I MHC molecules (for review see [2]). As if, class I MHC molecules act as parent to CTLs. Two possibilities arise [3]. First, self-class I MHC compatibility is necessary for sensitizing of the foreign peptide and thereby for binding and lysis of the target cell



**Figure 1.**  
The genetic architecture of human major histocompatibility complex (MHC).

by CTLs. In this case, there might be specific MHC gene products and the interactions between them that function to distinguish self from foreign. Second, self-components undergo changes in composition on encountering foreign antigen, so that their recognition is not possible unless a compatible class I MHC system is available.

## 4. MHC class II

### 4.1 Macrophages

Extracellular peptides or pathogens are engulfed by phagocytosis into macrophages and assembled into a vesicle, called phagosome. Lysosomes combine with the phagosome to digest substances in order to extract their antigens. MHC class II molecules orient antigens to the outer surface of cell membrane, where T<sub>H</sub> cells stand ready to bind and assist with recognition of antigens. Recognition of a foreign antigen by T<sub>H</sub> cells would force more macrophages to phagocytose pathogens.

## 4.2 B lymphocytes

Immunoglobulins are attached to the surface of B cells. Binding of a foreign antigen to these immunoglobulins induces the engulfment of that particular antigen by B cells. B cells prepare ingested antigen for presentation by MHC class II molecules. Peptide-MHC II complex would engage T<sub>H</sub> cells that promote proliferation of antibody-producing plasma cells. Antibodies produced by plasma cells enter the circulation and form complex with matching antigens. Matching antigen-antibody complexes are susceptible to cleavage.

In this manner, MHC class I and class II molecules are very important in the initiation of cell-mediated and antibody-mediated immune responses. As a result, they have always been in the center of attention of immunogeneticists.

## 5. The genetic architecture of human MHC

**Figure 1** shows three main MHC classes of genes. Occupying about 0.1% of the human genome [4], the MHC ranks as the most gene-dense region in the human genome. Two hundred and twenty-four MHC loci have been so far isolated from humans, among which 20–30% [5] are associated with a known or putative function in innate and adaptive immune responses [4], while the rest act as mediators of growth, development, mating, reproduction, odor, and olfaction [6]. This would imply that MHC is working on contextually different aspects of the evolution. As in mammalian genome, some MHC genes related to adaptive immune system are present in invertebrate genomes. This would tell us that the origin of the adaptive immune system dates back to at least 400 million years ago [7].

## 6. Evolution and selection of MHC polymorphisms

The MHC class I and class II genes continue as the most polymorphic genes in mammals. However, there are specific loci that exhibit a higher level of polymorphism compared with other loci studied in the same population. Mounting evidence supports that selective MHC polymorphisms might play a role in evolution, so that they will be maintained within one species or even command one species to be transformed into another [8]. Different hypotheses exist regarding profitable variations that are provided by MHC polymorphisms making them favorable to be accumulated by natural selection. For example, in the context of immunity, the overdominance hypothesis states that individuals being heterozygous for those certain MHC polymorphisms, the so-called extraordinary polymorphisms, will have an advantage over the homozygous individuals that the MHC function is more powerful in terms of types of peptides that they can bind to and recognition of more peptide types, in turn, would mean protection against a broader range of pathogens. This is known as heterozygous advantage or overdominance selection. For more information regarding other hypotheses, please see [2, 9–12].

## 7. Challenges in mapping MHC genes

MHC loci are difficult to map due to a number of reasons including:

1. There are many sequences and structural variations that can be extracted from MHC.

2. There is strong linkage disequilibrium between different loci that can influence the accuracy of analysis of the immunogenetic data.
3. There are nonadditive effects within the MHC loci and also epistatic interactions between the MHC and other genes that are able to affect total genomic variance [4].

As detailed in [5], different approaches have been developed for sequencing the MHC and discovery of potential copy-number variation (CNV) and of SNP regions. Sanger sequencing combined with next-generation DNA sequencing technologies can be used to detect SNPs, describe their characteristics, and obtain information for haplotype phasing.

Serological techniques and solid-phase immunoassays offer HLA typing with an appropriate resolution [13]. However, it is noteworthy to mention that despite about one century of effort, HLA (class I and II) typing—which is used to match donor and recipient for transplantation of the stem cells, cord blood, and kidney—might be challenging for bioinformaticians in some instances. Therefore, external proficiency testing (EPT) is performed to resolve ambiguities in HLA typing. According to a report of the Ad-Hoc Committee of the American Society for Histocompatibility and Immunogenetics, there is no need to resolve all ambiguous results [14]. The committee recommends that if there is more than one possible HLA genotype at the time of clinical decision-making, then we only need to refer to the criteria of EPT, which is attached to a list of common and well-documented (CWD) HLA alleles. For each HLA locus, e.g., HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1, HLA-DRB3/4/5, HLA-DQA1, and HLA-DPB1, CWD alleles consist of about 27–47% of the total alleles.

## **8. The international ImMunoGeneTics information system**

For almost 30 years, the international ImMunoGeneTics (IMGT) information system has been made available free on <http://imgt.cines.fr>. IMGT is composed of immunogenetic information on sequences, nucleotides, genes and their polymorphisms, and proteins of the immune system including immunoglobulins or antibodies, TCR, and MHC. It can be useful for diagnostic, therapeutic, and engineering purposes and also research in the different fields of medicine, in particular, autoimmune diseases, infectious diseases, acquired immunodeficiency syndrome (AIDS), and blood cancers. In this manner, IMGT helps operationalize the continuum between specialist and generalist databases.

## **9. Immunogenetics and inherited risk of multifactorial diseases**

### **9.1 HLA loci**

Genetic studies have provided evidence for association of loci on HLA and:

1. Autoimmune and inflammatory diseases: acute anterior uveitis, alopecia areata, asthma, atopic dermatitis, eczema, rheumatoid arthritis, Behçet's disease, celiac disease, collagenous colitis, granulomatosis with polyangiitis (Wegener granulomatosis), generalized vitiligo, IgA nephropathy, primary biliary cirrhosis, psoriasis, ankylosing spondylitis, systemic lupus erythematosus, vasculitis, type 1 diabetes, Crohn's disease, ulcerative colitis, dermatomyositis, and Graves' disease

2. Infections: human immunodeficiency virus (HIV) set-point viral load (spVL), HIV-1 control, acquired immunodeficiency syndrome (AIDS) progression, chronic hepatitis B infection and viral clearance, hepatitis B, hepatitis B and C virus-related hepatocellular carcinoma, hepatitis B-related liver cirrhosis, chronic hepatitis C infection, human papillomavirus (HPV) seropositivity, dengue shock syndrome, leprosy, *M. tuberculosis* infection, malaria, resistance to enteric fever, and visceral leishmaniasis
3. Gastrointestinal diseases: Barrett's esophagus
4. Neurological disorders: Parkinson's disease, narcolepsy, juvenile myoclonic epilepsy, spinocerebellar ataxia, myasthenia gravis, and multiple sclerosis
5. Psychiatric disorders: schizophrenia and autism
6. Joint diseases: knee osteoarthritis
7. Cancers of the nasopharynx, cervix, colorectum, lung, blood cells, and bone marrow (lymphoid cancers)
8. Adverse drug reactions: Stevens-Johnson syndrome/toxic epidermal necrolysis (carbamazepine), agranulocytosis (clozapine), pancreatitis (thiopurine), and liver injury (terbinafine, fenofibrate, ticlopidine, and pazopanib)
9. Response to vaccines: hepatitis B
10. Male infertility due to nonobstructive azoospermia

## 9.2 Non-HLA loci

Generally, loci on non-HLA genes are involved in genetic predisposition to a variety of autoimmune and inflammatory disorders, among which the most associated have been identified in three genes: cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), protein tyrosine phosphatase (PTPN22), and tumor necrosis factor- $\alpha$  (TNF). In particular, it is noticeable that patients who receive hematopoietic stem cell transplantation (SCT) from matched sibling donor might develop acute graft-versus-host disease (GVHD). This reflects that non-HLA components have a part in making the immunogenetic profile that needs special attention in patients scheduled to undergo stem cell transplantation.

## 10. Immunogenetics and the spectrum of immune disorders

By engaging pattern recognition receptors (PRRs)—including Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs)—and signal-transducing molecules, e.g., interleukin-1 receptor-associated kinase 4 (IRAK4), the innate immune system forms the center of recognition of molecular patterns and therefore the first line of defense against foreign antigens. Abnormally low activity of this system causes underdetection of foreign agents that makes individuals susceptible to being infected, while the unwanted action of this system is being reactive to self-components, which is seen in autoimmune situations. In this manner, if anything hinders the proper functioning of the immune system, for example, genetic factors, then it is most likely that the body is prone to autoimmune and infectious diseases.

*Immunogenetics* aims to cover HLA and non-HLA effects for all the aforementioned categories with emphasis on autoimmune disorders and infections, two ends of the spectrum of immune disorders.

## **11. Autoimmune diseases**

### **11.1 Psoriasis**

Psoriasis was initially known as a disease of abnormal keratinocyte proliferation presented with chronic plaque in the majority of instances that can predispose patients to cardiovascular, psychiatric, and joint complications. It is already considered an immune-mediated skin disease where both innate and adaptive immunities play a role in initiating psoriatic lesions. Of note, Th1 pathway is overstimulated; there are high levels of Th1 cytokines and chemokines including IL-2, IL-12, and IFN- $\gamma$  in psoriatic plaques. T cells, natural killer cells, natural killer T cells, and, to a lesser extent, neutrophils contribute to cutaneous inflammation in psoriasis as well. More interestingly, dendritic cells through antigen presentation to T cells can lead to plaque formation.

Consistent with its different clinical facets, there is a catalog consisting more than 60 loci identified as risk genes for psoriasis. In particular, the risk allele at MHC class I gene is present in about half of patients with psoriasis. Generally, HLA and non-HLA genetic loci associated with psoriasis are important mediators of antigen presentation, Th17/IL-23 axis, T-cell function, antiviral immunity, macrophage activation, and nuclear factor- $\kappa$ B (NF- $\kappa$ B)-dependent signaling. A simple mechanism for these genetic risk alleles in pathogenesis of psoriasis is likely to be mediated through reducing the threshold for activation of the innate immunity.

### **11.2 Rheumatoid arthritis (RA)**

RA is a chronic inflammatory disease of synovial joints characterized by synovial hyperplasia, production of autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA), bone deformity, and systemic manifestations. Collectively, RA is associated with unfavorable long-term prognosis. Different cells such as macrophages, monocytes, fibroblasts, and T cells act to make an orchestra of cytokines, e.g., IL-1, IL-6, and TNF- $\alpha$ , which are central to the abnormal signaling pathways underlying this inflammatory arthritis.

RA has a long-recognized association with alleles at MHC class II gene that contain a common amino acid sequence in the HLA-DRB1 region, e.g., HLA-DRB1\*0404 and DRB1\*0401. In addition, there are non-HLA genetic loci associated with RA in ACPA-positive patients. As reviewed in [15], RA-associated genes are known to play a role in the nuclear factor- $\kappa$ B (NF- $\kappa$ B)-dependent signaling, TCR signaling, and JAK-STAT signaling.

### **11.3 Autoimmune thyroid diseases (AITDs)**

As for other autoimmune disorders, AITDs such as Graves's disease and Hashimoto's thyroiditis are of T-cell-mediated autoimmune disorders mainly characterized by production of autoantibodies against and T-cell infiltration in the thyroid gland. Thereby, the immune system cannot correctly maintain a constant battle causing the gland to malfunction, which can be manifested as hyper- or hypothyroidism. Generally, AITDs are of special importance in practice because of their comorbidities with other autoimmune diseases.

Among risk alleles for AITDs are genetic variants associated with thyroid function. However, a variety of AITDs-related genetic loci occur within immune-modulating and HLA genes, which are known to contribute to peripheral tolerance, T-lymphocyte activation, and antigen presentation. In this manner, a mechanism of immunogenetic susceptibility to AITDs is maintained through interference with central and peripheral tolerance, APCs, and subsequent activation of T cells.

#### **11.4 Primary biliary cirrhosis (PBC)**

It is a disease of small intrahepatic bile ducts regarded as an autoimmune liver disease with the presence of the antimitochondrial antibody (AMA) in all except a minority of patients (up to 10%). Supporting this is that the infiltration of auto-reactive CD4<sup>+</sup> T cells and CD8<sup>+</sup> T cell specific to AMA has increased manifold in the liver of patients with PBC. T cells along with other immune cells such as B cells, macrophages, eosinophils, and natural killer cells take part in the composition of the portal inflammation. Eventually, such a chronic inflammation would progress to the loss of biliary epithelial cells.

Genetic studies have detected HLA variants conferring susceptibility to PBC. However, there were HLA variants that seemed protective against PBC. Non-HLA loci associated with PBC mainly involve genes associated with T cells. In particular, they contribute to IL-12-JAK-STAT4, CD80/CD86, and IL7R- $\alpha$ /CD127 signaling pathways, which are known to play a role in Th1 T-cell polarization, TCR signaling, and T-cell homeostasis, respectively. Other PBC-associated non-HLA loci are related to B-cell function, TNF signaling, and NF- $\kappa$ B signaling.

#### **11.5 Type 1 diabetes mellitus (T1DM)**

T1DM is a T-cell-mediated autoimmune disorder characterized by the presence of autoantibodies against islet cells. Increasing incidence of T1DM and its potential microvascular and macrovascular complications have shed light on the need for identifying more effective prevention strategies and new treatment targets. To this end, it is essential to enhance our understanding of the pathogenesis of T1DM.

It is a polygenic disorder where the HLA class II genes account for almost half of genetic susceptibility for T1DM. Interestingly, there are loci of these genes that have also been associated with protection from T1DM. Of the so-far-identified non-HLA genes are a variable number of tandem mini-satellite repeats (VNTR) and CTLA-4.

#### **11.6 Systemic lupus erythematosus (SLE)**

It is a chronic autoimmune disease affecting multiple organ systems including the skin, heart, blood, muscle and joints, kidneys, and lungs. As if, SLE is the winner of all fights with the immune system that is not possible unless the immune tolerance against self-components is broken. Activation of innate immune responses and of inflammatory processes along with production of type I interferons and autoantibodies favors pathogenesis of SLE, while mechanisms of clearance of immune complexes such as apoptosis, neutrophil extracellular traps (NET), and nucleic acid sensing are defective. In particular, evidence indicates the multifaceted role of neutrophils in SLE. Lupus neutrophils undergo epigenetic changes causing them to produce higher levels of cytokines that would induce T- and B-cell abnormalities. Also, neutrophils directly contribute to the formation of NET, which is increased in SLE, while clearance of NET materials is impaired in SLE.

As expected, such a complex situation involves contribution by both HLA and non-HLA genes. Several HLA genes including HLA-DRB1, HLA-DQB2,



HLA-DQA2, and HLA-DR3 have been associated with susceptibility to SLE and with the autoantibody profile (anti-dsDNA, anti-Ro, and anti-La) in patients with SLE. Genes encoding interferon regulatory factors (IRFs), STAT4, IFIH1, and osteopontin (OPN) contribute to polygenic high IFN signatures, while TREX1, STING, SAMHD1, and TRAP are known to give rise to monogenic high IFN signatures in SLE. Monogenic SLE results from mutation(s) in genes related to classical complement pathway, apoptosis, and antinucleosome antibody production. SLE-associated genes that occur in regulatory regions (e.g., exons, splice sites, introns, and intergenic sites) are TNFAIP3, TNIP1, BLK, ETS1, PRDM1, and IKZF1. Finally, there are SNPs located within the coding region of genes PTPN22 and immunoglobulin-like transcript 3 receptor (ILT3) that have been linked with SLE.

### **11.7 Systemic sclerosis (SSc)**

SSc is considered a complex multisystem disease characterized by a heterogeneous spectrum of clinical manifestations ranging from limited to diffuse cutaneous SSc. Both innate and adaptive immune systems, fibroblasts, and small vessels show abnormal function in SSc.

There is a long list of HLA genes conferring susceptibility to clinical and autoantibody subgroups of SSc. Also, some HLA genes appear to be protective of SSc. Non-HLA genes associated with SSc are known to play a role in innate immunity, interferon signature and inflammation, adaptive immune responses, B- and T-cell proliferation, survival and cytokine production, apoptosis, autophagy, and fibrosis.

## **12. Neurological diseases**

There is sufficient evidence to support the immunogenetic basis for some neurological diseases, in particular, multiple sclerosis, Alzheimer's disease, Parkinson's disease, neuromyelitis optica, myasthenia gravis, and amyotrophic lateral sclerosis. Below provides a rapid overview of the immunogenetics of MS as the prototype of such neurological diseases.

### **12.1 Multiple sclerosis (MS)**

It is the most common inflammatory disease of the CNS, which after interfering with normal myelination results in axonal degeneration. The pathologic characteristics of MS are demyelinating lesions, which can be broadly classified according to whether or not autoimmune processes precede demyelination. In this manner, there are lesions arising from T-cell-mediated and T-cell plus antibody-mediated autoimmune encephalomyelitis, while sometimes demyelination is an initial clue resulted from viruses and toxins. Generally, MS is considered a chronic autoimmune disease, which is primarily characterized by activation of CD4<sup>+</sup> autoreactive T cells and Th1 T-cell polarization and then by the production of antibodies, complement factors, and CD8<sup>+</sup> T cells damaging the CNS tissues.

Studies suggest a strong genetic component for MS; more than 100 genetic loci have been so far identified to confer MS susceptibility. HLA genes totally account for about 10% of the genetic variance of MS. In particular, MHC class II gene HLA-DRB1\*1501 is present in about 50% of patients with MS. After that, the IL-7R- $\alpha$  chain gene can explain about 30% of all cases. Also, IL-2RA is another non-HLA

gene implicated in MS. Fresh evidence emerged that supports the potential of KIR genes as a risk or protective factor in the immunogenetics of MS. Both CD4<sup>+</sup> T cells and NK cells express KIRs. CD4<sup>+</sup> T cells that express KIRs are involved in antibody production and NK cells that express KIRs mediate antiviral and antitumoral innate immune responses. Therefore, KIR polymorphisms can affect the individual's risk for MS through the impact they have on antiviral immunity and antibody production. Now there is a big hope for the future of pharmacogenomics of MS when the immunogenetic information may help to predict treatment response, but it is not fulfilled yet!

## 13. Infectious diseases

### 13.1 Human immunodeficiency virus (HIV)

There is a variable degree of immunity to HIV. Genetic factors account for about one-fourth of this variation, among which are HLA genes that through interaction with CD8<sup>+</sup> cytotoxic T and CD4<sup>+</sup> helper T cells help the initiation of anti-HIV adaptive immune responses, thereby conferring resistance to HIV. Studies have shown associations of HLA genes with accelerated disease progression, slow disease progression, protection against infection, reduced viral load levels, and increased susceptibility to infection. In addition, KIR genes have been implicated in resistance to HIV. More interesting is that the development of TB in people with HIV is, at least in part, determined by individual immunogenetic constitution.

### 13.2 Hepatitis B virus (HBV) and hepatitis C virus (HCV) infection

Infection with HBV or HCV influences the expression of intrahepatic genes, thereby leaving patients liable to chronic liver disease, cirrhosis, and hepatocellular carcinoma. Virus-specific T-cell responses are central to the removal of infected hepatocytes, and therefore, the kinetics of these responses can aid in monitoring clinical recovery. In 1 year, about 2% of patients with chronic HBV infection will experience spontaneous viral clearance, which is characterized by HBV-specific T cells temporarily appearing in the peripheral blood. Such an experience does not occur at all in the case of chronic HCV.

Genetic factors contribute to interindividual variation in clinical course of HBV and HCV infection. GWASs have identified HLA and non-HLA that confer susceptibility to persistent HBV infection, progression of disease, and risk of HBV-related hepatocellular carcinoma. Again, both HLA and non-HLA genes have been linked with spontaneous clearance of HCV. Two genes MICA and DEPDC5 demonstrated association with HCV-related hepatocellular carcinoma.

### 13.3 Tuberculosis (TB)

*Mycobacterium tuberculosis* is recognized by innate immune receptors including TLRs, C-type lectin receptors (CLRs), and NLRs. Upon its recognition, different mechanisms by which immune cells (macrophages and T cells) and cytokines (IL-12, IFN- $\gamma$ , IL-4, TNF- $\alpha$ , IL-10, IL-6, and TGF- $\beta$ ) can mediate antimycobacterial functions are engaged. Consistently, increasing evidence supports the individual genetic contribution to the control of tuberculosis infection, severe primary tuberculosis, and pulmonary tuberculosis. Genetic risk factors for developing TB include both HLA and non-HLA genes.

## 14. Immunogenetics and immunosenescence

Immunosenescence refers to immune decline with age, which causes increased infection risk and related morbidity and mortality in the elderly. It is characterized by a chronic low-grade inflammation that arises from aberrant innate and adaptive immune responses, playing a role in a myriad of diseases including, but not limited to, atherosclerosis, obesity, type 2 diabetes, osteoporosis, osteoarthritis, neurodegenerative diseases, major depression, and malignancy. In the last four decades, immunosenescence has received great attention from geneticists. However, due to heterogeneous methodology, we are still unable to generalize the findings to all elderly people. In addition to HLA genes, non-HLA genes related to adaptive immunity and to innate immunity appear to contribute to the immunogenetic network of human longevity.

## 15. Immunogenetics of atopic diseases

The most common chronic diseases afflicting children are asthma, hay fever (allergic rhinitis), and eczema (atopic dermatitis). Due to their strong association with concurrent atopic dermatitis, both asthma and allergic rhinitis can be defined as a type of atopic diseases. In this manner, atopy can be used as an umbrella term that describes a group of diseases, e.g., asthma, allergic rhinitis, food allergy, and urticaria. Atopy is considered a result of a Th2-mediated process, where Th2 cytokines promote the production of IgE by IgE<sup>+</sup> memory B cells and plasma cells.

Genome screens show that, in general, atopic diseases are largely heritable (60%) and suggest that shared genes for atopy and other autoimmune diseases lie on the short arm of chromosome 6 where MHC gene are. In particular, the airway epithelium undergoes changes in asthma, and as a result, common genes are likely to cause asthma and other epithelial-based diseases, e.g., Crohn's disease and psoriasis. In addition, genes encoding innate immune receptors and cytokines, which are central to the initiation and progression of allergic responses, contribute to the immunogenetic network of atopy.

## 16. Vaccinomics and adversomics: immunogenetics and response to vaccination

Immune responses to vaccines vary between individuals. The main goal of vaccinomics is to deal with genes that may explain a substantial part of this variation. For example, studies estimate the variation in antibody response to hepatitis B surface antigen (HBsAg), measles virus, mumps virus, and rubella virus to be about 60, 88, 38, and 45% hereditary based. Generally, HLA and non-HLA genes encoding cytokines, cell surface receptors, and TLRs affect immune responses to vaccines, e.g., HBV, smallpox, MMR, and seasonal influenza. Moreover, there is evidence that genetic factors play a role in determining vaccine safety and adverse events, and consequently, it led to the emergence of adversomics. Overall, vaccinomics and adversomics facilitate prediction of vaccine efficacy and safety by using immunogenetic knowledge, and this in itself helps in developing more effective vaccines.

In this manner, *immunogenetics* aims to specify situations in which genetic mutations cause the immune system to be functionally imperfect and secure solutions for them.

## Acknowledgements

We apologize to all colleagues whose excellent works could not be cited due to space constraints.

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