Chapter 7

Immunogenetics of *MHC* and *KIR* in the Leprosy

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Additional information is available at the end of the chapter

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Abstract

Several genetic polymorphisms in immune response genes have been associated to leprosy. This fact converges on the main hypothesis that genetic factors are involved in the disease susceptibility in two distinct steps: leprosy *per se* and their clinical forms. These genes play an important role in the recognition process, in the activation of the main metabolic pathway of the immune response and in the evolution of the disease. The scope of this project was to highlight the role of the immune response genes in the context of leprosy, emphasizing the participation of some of them in the signaling and targeting processes in response to bacillus infection and on disease evolution, such as HLA, *KIR* and *MIC* genes. Some environmental and genetic factors are important when the exposure to the bacillus occurs, leading to cure or not. Factors that favor a cellular or humoral immune response may influence the clinical manifestations after the infection inducting to one of extreme poles. Furthermore, some genetic factors were associated to the type of reaction that some individuals present during the disease development. Thus, it is very important to highlight the participation of some genetic factors in the immunopathogenesis of leprosy.

Keywords: leprosy, *HLA* genes, *MICA* genes, *KIR* genes, genetic predisposition, genetic polymorphism

1. Introduction

Leprosy is a chronic infectious granulomatous disease caused by the obligate intracellular bacillus *Mycobacterium leprae* (*M. Leprae*). Dermatoneurological signs and symptoms, such as skin and peripheral nerve lesions, are common manifestations of the disease and occasionally, it may affect respiratory tract, eyes, lymph nodes, nasal structures, testicles and internal organs [1, 2].

Leprosy is an important endemic disease, considered as a serious public health and social problem worldwide, as it leads to neural impairment or physical disability. Thus, special attention is needed, due to the consequences in the socioeconomic life of the patients or even their possible sequels in those who are cured. Worldwide, leprosy cases spread across more than 140 countries, with 22 countries accounting for 95% of global leprosy. These countries such as India, Brazil, Indonesia, Democratic Republic of Congo, Ethiopia, Nepal, Bangladesh and others have a high detection rate [3].

Bacillus has a high infectivity and low pathogenicity, that is, it infects many people, but only few become ill [1]. Leprosy is influenced by host genetic and mycobacterial factors, and environmental factors such as nutritional status and rate of exposure to bacillus. The immune response is of fundamental importance for the body's defense against exposure to the bacillus, but in some individuals, leprosy can lead to changes in the immune response and to the development of distinct clinical forms. Among those who fall ill, the degree of immunity varies by determining the clinical form and course of the disease [4].

The immune response to the *M. leprae* is a task of the T lymphocytes responsible for adaptive immunity. CD4+ T lymphocytes can be divided into two subpopulations, which exert different functions in the defense of the organism mainly against intracellular bacterial infections, such as leprosy. These lymphocytes have the ability to induce the cellular or humoral immune response that is related to the types of secreted cytokines and the development of Th1 or Th2 responses [5, 6].

The predominance of cellular or humoral immune response may influence the evolution of the leprosy and the clinical characteristics observed in the tuberculoid (TT) and lepromatous (LL) clinical forms. The patients with the TT form have a strong cellular immune response, with a predominance of Th1 cells, activation of macrophages and Th1 cytokines secretion, such as interleukin (IL)-2, IL-6, IL-12, IL-15, IL-18, tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ), limiting the disease to few localized lesions of the skin and peripheral nerves. Patients with the LL form present a humoral response and lack of cellular response, with a predominance of CD8+ suppressor T cells and Th2 standard cytokines, such as IL-4, IL-5, IL-10 and IL-13, which inhibit the activation of macrophages. Here there is a proliferation of bacillus and presence of many lesions in the skin and peripheral nerves [5–7].

The disease can be classified into three forms: (i) Madrid (1953) classification, based on clinical and bacteriological criteria [8]; (ii) Classification of Ridley and Jopling (1966) that emphasizes clinical, bacteriological, immunological and histological aspects [9] and (iii) World Health Organization (WHO) (1982) operational classification with therapeutic purpose, based on the bacilloscopic index, which is related to the clinical forms [10]. In 1988, this operational classification was updated and clinical criteria were also established, considering paucibacillary (PB) patients such as those with less than five cutaneous lesions and/or one affected nerve trunk and multibacillary (MB) such as those with more than six lesions and/or more than one affected nerve trunk. It is still considered MB when the bacilloscopy is positive, regardless the number of lesions [11]. The classifications adopted for clinical forms of leprosy such as Madrid, Ridley and Jopling and WHO are summarized and listed in **Table 1**.

WHO	Paucibacillary (PB)		Multibacillary (MB)	
MADRID	Indetermined (I)	Tuberculoid (T)	Dimorph (D)	Virchowian (V)
Ridley and Jopling		TT	BT BB BL	LL

TT: tuberculoid-tuberculoid, BT: borderline tuberculoid, although presenting characteristics of the paucibacillar form, it has been operationally classified as multibacillary, BB: borderline borderline, BL: borderline lepromatous, LL: lepromatous-lepromatous.

Table 1. Correlation between the classifications of Madrid [8], Ridley and Jopling [9] and WHO [10, 11] adopted for leprosy.

At present, it is known that there are several factors influencing the control and appearance of the disease, such as immune response, time of exposure to bacillus, virulence of the pathogen, environmental factors, genetic variation of the bacillus and, mainly, the immunogenetic variability of the host leading to susceptibility or resistance to leprosy *per se* [12–17], clinical forms [18–20] of the disease and leprosy reactions [21, 22] (**Figure 1**).

The selection of candidate genes in disease pathogenesis is usually based on two criteria: functional genes with a critical role in the pathogenesis of the disease and the location in the genomic region that may be involved in disease control; and yet a combination of the both.

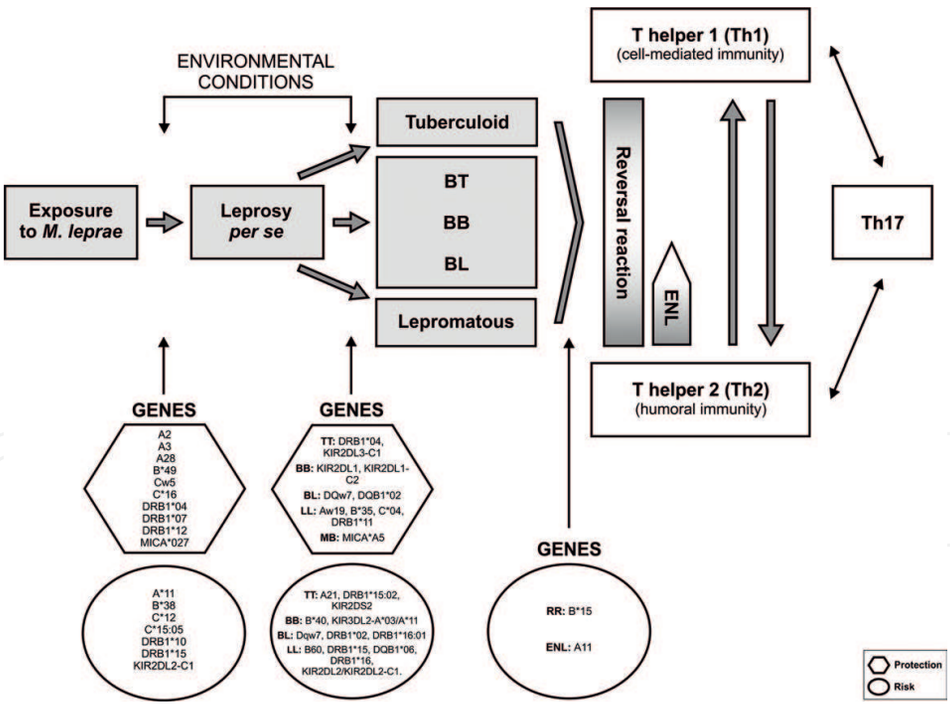

Figure 1. Schematic representation of the clinical spectrum of leprosy suggesting the participation of different genes (*HLA*, *MICA* and *KIR*) in the control of the pathogenesis of the disease. Susceptibility or resistance to leprosy *per se*, clinical forms and leprosy reactions were showed. After exposure, most individuals are resistant to leprosy. Susceptible individuals may present the infection *per se* or develop one of the clinical forms and reactional types of leprosy, which are dependent on the host's immune response pattern. MB: multibacillary, BB: borderline borderline, BL: borderline lepromatous, BT: borderline tuberculoid, LL: lepromatous leprosy, TT: tuberculoid leprosy; *per se*: leprosy independent of specific clinical manifestation. RR: type 1 or reversal reaction. ENL: type 2 reaction or erythema nodosum leprosum.

These genes are generally those that participate in the immune response in leprosy, such as cytokine genes, *HLA* (human leukocyte antigen) genes, *MICA* (major histocompatibility complex class I chain-related protein A) and *KIR* (killer cell immunoglobulin-like genes receptors), among others.

The two types of studies with molecular genetic markers are those of binding and association. The binding studies are related to the genetic mapping that allows the tracking of chromosomal regions linked to the disease. Gene-susceptibility/disease resistance studies are based on the comparison of the allelic frequencies of a genetic marker in populations (affected and unaffected individuals) [23].

Recently, a new approach to identify genes involved in human diseases is being carried out; it is the so-called genome-wide association study (GWAS). This is an association study of the entire genome in which many single nucleotide polymorphisms (SNPs) are tested in healthy controls and patients, allowing the analysis of hundreds or thousands of these polymorphisms at the same time. Genetic markers are considered to be associated with disease phenotypes when there is a significant difference in the frequencies observed between these two groups [24]. These works with genetic markers are performed aiming to contribute to the early diagnosis, prognosis, understanding of pathophysiology and improvement in the treatment of the disease.

Thus, the proposal of this chapter is to evidence the participation of some innate immune response genes, specifically, *HLA*, *MIC* and *KIR* genes, on overall leprosy and on evolution to the various clinic forms of disease.

2. Major histocompatibility complex

2.1. Introduction

The major histocompatibility complex (MHC) is composed of several genes, some of which are capable of encoding molecules that will display antigenic peptides on the cell surface for recognition by T cells. Other genes encode heat shock proteins, some cytokines and complement factors and approximately 40% of them have some function in the immune system [25, 26].

In relation to antigen presentation on the cell surface, the antigenic peptides originate from several sources, such as intracellular bacteria and viruses, products of cellular metabolism or proteins and lipids own or foreign to the organism [26].

In humans, a MHC sub region, called human leukocyte antigen (HLA), is located on the short arm of chromosome 6 and gives rise to HLA class I and II molecules. The HLA is polymorphic and each locus has many alleles contributing to human diversity as well as meeting the need for presentation of a wide range of antigens. The set of *HLA* alleles present on each chromosome is called haplotype, so all heterozygous individuals have two codominant *HLA* haplotypes [25, 27].

Understanding the mechanism of the presentation of antigens is of great importance for immunology, since it is able to explain events such as transplant rejection, autoimmune diseases, tumor immunity and response to infection, such as leprosy [28].

2.2. Structural characteristics

Each HLA molecule consists of a peptide-binding cleft, immunoglobulin (Ig)-like domains and transmembrane and cytoplasmic domains. Class I HLA has the α-chain encoded by MHC genes and the β2-microglobulin chain encoded by a non-MHC region. Class II HLA has both the α- and β-chain encoded in the MHC (**Figure 2**). The cleavage site is the site where the peptides are established during their presentation to the T lymphocytes. In addition, cleft are the polymorphic residues, that the amino acids responsible for differentiating the HLA from each other, as well as making the presentations more antigenic specific. The Ig domains are non-polymorphic and are responsible for binding between HLA and T cell: class I HLA molecules bind to CD8+ T cells and HLA class II molecules bind to the helper T cells CD4+ T cells [29, 30].

2.3. Nomenclature

The convention for the use of a four-digit code to name *HLA* alleles and distinguish them from the nomenclature given to coded proteins was introduced by the Nomenclature Report 1987. Currently, an allele name can be composed of four, six or eight digits, depending on its sequence. The first two digits describe the allele family. The third and fourth digits refer to the way in which DNA sequences were discovered.

Alleles that are different in the initial four digits have differences in nucleotide substitutions, which alter in protein coding. The fifth and sixth digits are used to distinguish alleles that differ by the synonymous substitutions of nucleotides in the coded sequence. The seventh and eighth digits are used when the alleles differ by sequence polymorphisms in introns or in 5′ and 3′ untranslated regions.

Each HLA allele name has a unique number, corresponding to up to four sets of digits, separated by a colon. The first two sets of digits are assigned to all alleles and the other two only for longer names and when needed (**Figure 3**) [31].

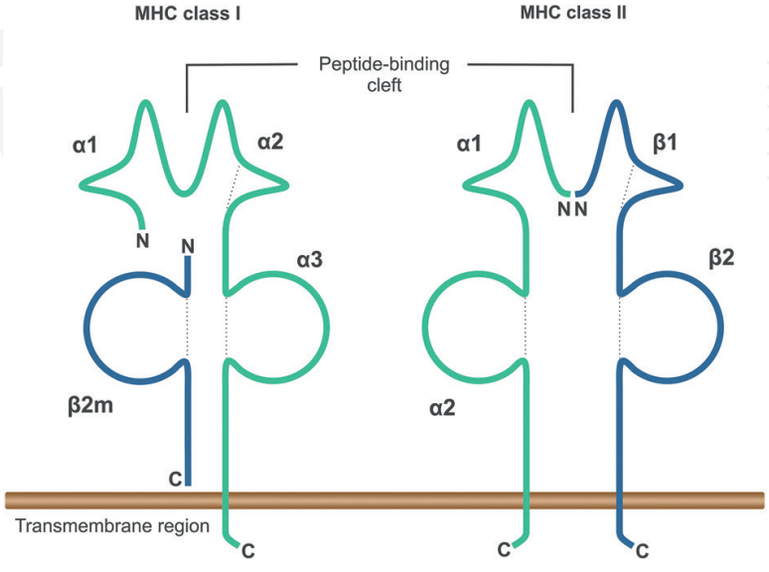

Figure 2. Structure of the class I and II MHC molecules.

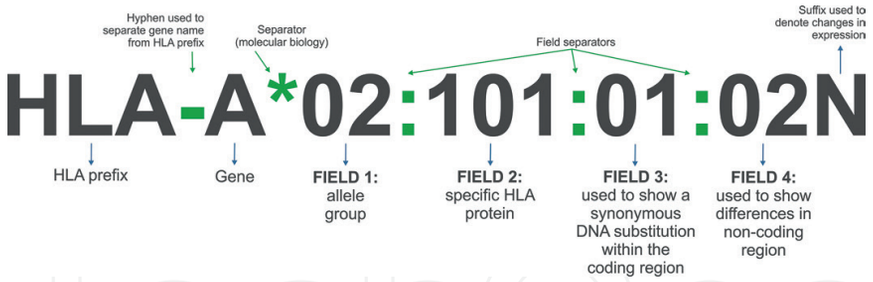

Figure 3. Schematic example of the meanings for each code in the HLA nomenclature [31].

2.4. HLA classical

2.4.1. HLA class I

There are three classical *loci* belonging to MHC class I: *HLA-A*, *HLA-B* and *HLA-C*. They encode molecules that have the same name as their respective genes. HLA class I molecules are expressed in all nucleated cells and platelets, as these molecules present the antigenic peptides for CD8+ T lymphocytes, which kill infected cells or with tumor antigens. The *HLA-E*, *HLA-F* and *HLA-G loci* also belong to *HLA* class I, but are considered non-classical (**Figure 3**) [32]. They are expressed at low levels when compared to classical *HLA* class I as well as do not have as many polymorphisms, and their functions in the immune system are limited [29, 30].

2.4.2. HLA class II

HLA class II molecules are expressed in dendritic cells, B lymphocytes, macrophages and other cell types, and present the antigenic peptides to the virulent CD4+ helper T lymphocytes, which recognize the antigens in the secondary lymphoid organs. Differentiated CD4+ helper T cells activate other cells, together with B lymphocytes, so that the extracellular microorganisms are eliminated. The three *HLA* class II *loci* are called *HLA-DP*, *HLA-DQ* and *HLA-DR*. The two chains of each molecule of class II are encoded by two different MHC genes. Thus, the extracellular parts of α and β chains are subdivided into two segments, A1 and A2, or B1 and B2, both of which are polymorphic chains, that is, each of the DP, DQ and DR *loci* contain separate genes designated as A or B, which encode α and β chains, respectively, in each copy of chromosome 6. Each individual has one HLA-DRA (DRA1), one to three DRB (DRB1 and DRB3, 4 and/or 5), one DQA (DQA1), one DQB (DQB1), one DPA (DPA1) and one DPB (DPB1) [25, 29, 30].

2.5. *MICA* and *MICB* genes

The human MHC class I chain-related genes (*MICA* and *MICB*) are located in the *HLA* class I region in chromosome 6, but are not part of the classical *HLA* (**Figure 4**). These genes show about 30% of homology to HLA class I, but the transcribed molecules do not present antigenic peptides on the cell surface. These genes are mainly transcribed into fibroblasts and epithelial cells. The MIC molecules bind to NKG2 receptors, activating NK cells and also modulate the function of CD8+ T cells. Studies have related associations of polymorphisms in *MICA* and *MICB* genes with several diseases (ankylosing spondylitis, psoriasis, dengue and tuberculosis) [32–36], one of them being leprosy, which will be discussed in a next topic in this chapter.

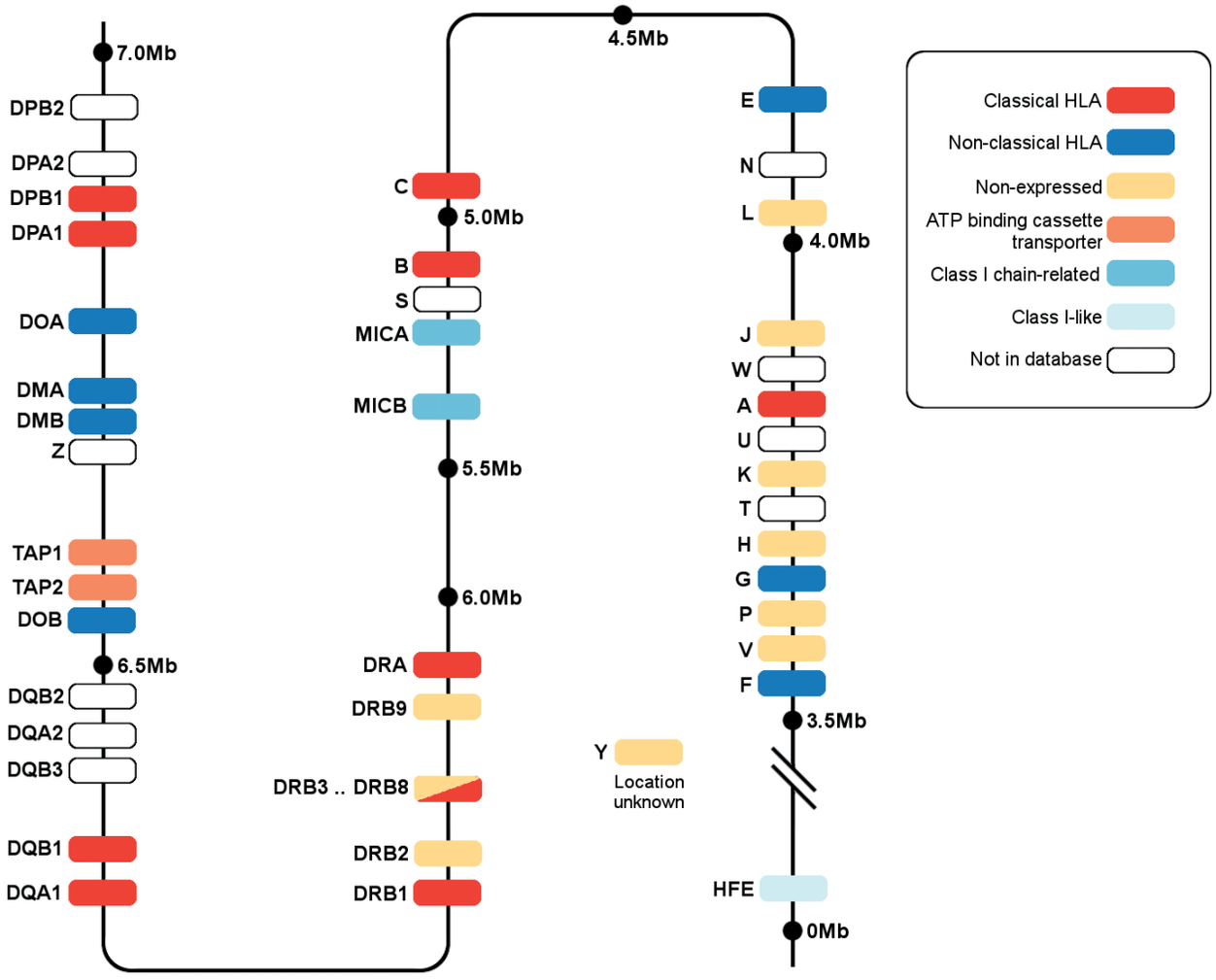

Figure 4. Schematic map of the human *MHC* gene [32].

2.6. HLA polymorphism

The immune system has the complex task of responding to different types of pathogens that come in contact with the human organism. Adaptation that ensures antigen protection and increased immune system efficiency can occur through life-long genetic recombination, such as antibody formation, or the different HLA molecules in the population. HLA molecules are responsible for presenting a fraction of the antigenic peptide (epitope) for T cells; however, the choice to determine which epitope will be presented according to the *HLA* genes and their alleles in each individual. Thus, the regions responsible for the antigenic presentation in the HLA molecules present high polymorphism rates. This means that with the advancement of diagnostic methodologies, the discovery of allelic variations of HLA has increased exponentially (**Figure 5**) [27, 29].

The evolutionary success in the amplification of the HLA repertoire may explain why it is difficult to associate a specific HLA phenotype with the susceptibility or protection against a particular disease, since the change of a single amino acid in the sequence of the HLA molecule can affect the adaptive immune response of the individual [32]. Despite this difficulty, studies have shown associations among several HLA and autoimmune and infectious diseases [27, 29].

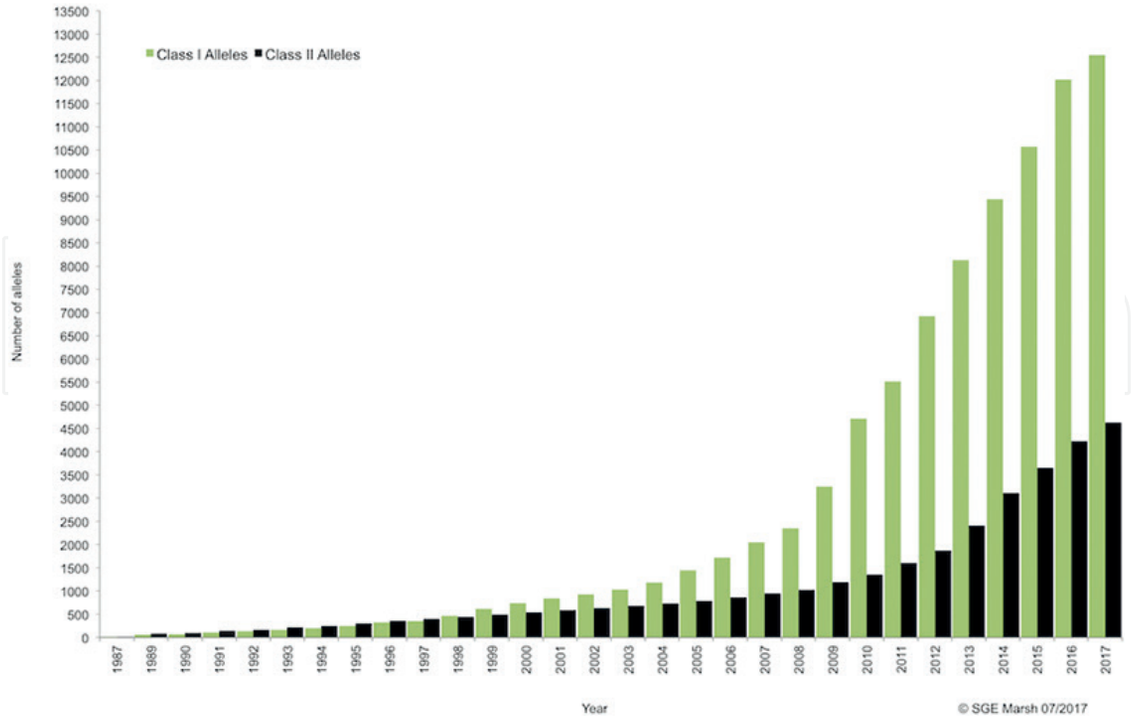

Figure 5. Advances in the findings of allelic variations in *HLA* class I and II *loci* over the past 30 years. Class I *HLA* alleles are represented in green and class II *HLA* alleles in black [32].

2.7. Influence of HLA on leprosy

The role of HLA molecules in leprosy is to present epitopes of the bacillus to T lymphocytes. However, polymorphisms in *HLA* genes or incorrect presentation of the antigenic peptide may interfere or contribute to the success of the response of the host against the pathogen. In view of this, several studies have indicated genes associated with susceptibility or protection against leprosy in different populations (**Tables 2** and **3**).

Allele, haplotype	Population	Population size	Phenotype	Association
*A*02:06*	Southern Indian	32 leprosy patients and 67 healthy individuals	Leprosy *per se*	Susceptibility [37]
*A*02:06*	Mumbai/Indian	103 leprosy patients and 101 healthy individuals	Leprosy *per se*	Susceptibility [14]
*A*11*	Brazilian	225 leprosy patients and 450 healthy individuals	Leprosy *per se*	Susceptibility [38]
*A*11:02*	Southern Indian	32 leprosy patients and 67 healthy individuals	Leprosy *per se*	Susceptibility [37]
*A*11:02*	Mumbai/Indian	103 leprosy patients and 101 healthy individuals	Leprosy *per se*	Susceptibility [14]
*B*15*	Brazilian	202 leprosy patients and 478 healthy individuals	RR	Susceptibility [22]
*B*18:01*	Mumbai/Indian	103 leprosy patients and 101 healthy individuals	Leprosy *per se*	Susceptibility [14]

Allele, haplotype	Population	Population size	Phenotype	Association
*B*18:01*	Southern Indian	32 leprosy patients and 67 healthy individuals	Leprosy *per se*	Susceptibility [37]
*B*35*	Brazilian	225 leprosy patients and 450 healthy individuals	LL	Protection [38]
*B*38*	Brazilian	225 leprosy patients and 450 healthy individuals	Leprosy *per se*	Susceptibility [38]
*B*51:10*	Southern Indian	32 leprosy patients and 67 healthy individuals	Leprosy *per se*	Susceptibility [37]
*B*51:10*	Mumbai/Indian	103 leprosy patients and 101 healthy individuals	MB	Susceptibility [14]
*C*04*	Brazilian	225 leprosy patients and 450 healthy individuals	LL	Protection [38]
*C*04:07*	Southern Indian	32 leprosy patients and 67 healthy individuals	Leprosy *per se*	Susceptibility [37]
*C*04:07*	Mumbai/Indian	103 leprosy patients and 101 healthy individuals	MB	Susceptibility [14]
*C*04:11*	Mumbai/Indian	103 leprosy patients and 101 healthy individuals	MB	Protection [14]
*C*04:11*	Southern Indian	32 leprosy patients and 67 healthy individuals	Leprosy *per se*	Protection [37]
*C*05*	Brazilian	202 leprosy patients and 478 healthy individuals	B	Protection [22]
*C*07*	Brazilian	225 leprosy patients and 450 healthy individuals	Leprosy *per se*	Susceptibility [38]
*C*07:03*	Southern Indian	32 leprosy patients and 67 healthy individuals	Leprosy *per se*	Susceptibility [37]
*C*07:03*	Mumbai/Indian	103 leprosy patients and 101 healthy individuals	MB	Susceptibility [14]
*C*12*	Brazilian	225 leprosy patients and 450 healthy individuals	Leprosy *per se*	Susceptibility [38]
*C*16*	Brazilian	225 leprosy patients and 450 healthy individuals	Leprosy *per se*	Protection [38]
*C*15:05*	Indian	364 leprosy patients and 371 healthy individuals	Leprosy *per se*	Susceptibility [15]
*C*15:05*	Vietnamese	198 families	Leprosy *per se*	Susceptibility [15]
*C*15:05*	Vietnamese	292 families	Leprosy *per se*	Susceptibility [15]
*A*11-B*40*	Mumbai/Indian	103 leprosy patients and 101 healthy individuals	ML	Susceptibility [14]

MB: multibacillary, PB: paucibacillary; B: borderline leprosy, BB: borderline borderline, BL: borderline lepromatous, BT: borderline tuberculoide, LL: lepromatous leprosy; TT: tuberculoid leprosy, *per se*: Leprosy independent of specific clinical manifestations, ENL: type 2 reactions or erythema nodosum leprosum, RR: Type I or reversal reaction.

Table 2. Associations between ***HLA*** class I and leprosy.

Allele, haplotype	Population	Population size	Phenotype	Association
*DQA1*01:02*	Indian	93 leprosy patients and 47 healthy individuals	LL	Susceptibility [39]
*DQA1*01:03*	Indian	93 leprosy patients and 47 healthy individuals	LL	Susceptibility [39]
*DQA1*02:01*	Indian	93 leprosy patients and 47 healthy individuals	LL	Susceptibility [39]
*DQA1*03*	Japanese	93 leprosy patients and 114 healthy individuals	Leprosy *per se*	Protection [40]
*DQB1*02*	Brazilian	202 leprosy patients and 478 healthy individuals	B	Protection [22]
*DQB1*02:01*	Brazilian	76 families (1166 individuals)	TT	Protection [41]
*DQB1*02:01*	Brazilian	76 families (1166 individuals)	Leprosy *per se*	Protection [41]
*DQB1*02:01*	Argentinean	89 leprosy patients and 112 healthy individuals	LL	Protection [42]
*DQB1*02:02*	Argentinean	89 leprosy patients and 112 healthy individuals	LL	Protection [42]
*DQB1*02:03*	Argentinean	89 leprosy patients and 112 healthy individuals	LL	Protection [42]
*DQB1*04:01*	Japanese	93 leprosy patients and 114 healthy individuals	Leprosy *per se*	Protection [40]
*DQB1*05:01*	Brazilian	76 families (1166 individuals)	TT	Susceptibility [41]
*DQB1*05:01*	Brazilian	76 families (1166 individuals)	Leprosy *per se*	Susceptibility [41]
*DQB1*05:03*	Indian	93 leprosy patients and 47 healthy individuals	TT	Protection [39]
*DQB1*06:01*	Indian	93 leprosy patients and 47 healthy individuals	TT	Susceptibility [39]
*DQB1*06:01*	Indian	93 leprosy patients and 47 healthy individuals	LL	Susceptibility [39]
*DRB1*02*	Japanese	79 leprosy patients and 50 healthy individuals	BL/LL	Susceptibility [43]
*DRB1*04*	Brazilian	578 leprosy patients and 691 healthy individuals	Leprosy *per se*	Protection [44]
*DRB1*04*	Euro-Brazilian	578 leprosy patients and 691 healthy individuals	Leprosy *per se*	Protection [44]
*DRB1*04*	Vietnam	194 single-case families	Leprosy *per se*	Protection [44]
*DRB1*04*	Argentinean	89 leprosy patients and 112 healthy individuals	TT	Protection [42]
*DRB1*04:05*	Japanese	93 leprosy patients and 114 healthy individuals	Leprosy *per se*	Protection [40]
*DRB1*04:05*	Taiwanese	65 leprosy patients and 190 healthy individuals	MB	Protection [45]
*DRB1*07*	Brazilian	76 families (1166 individuals)	Leprosy *per se*	Protection [41]
*DRB1*07*	Euro-Brazilian	578 leprosy patients and 691 healthy individuals	Leprosy *per se*	Protection [44]

Allele, haplotype	Population	Population size	Phenotype	Association
*DRB1*07*	Brazilian	578 leprosy patients and 691 healthy individuals	Leprosy *per se*	Protection [44]
*DRB1*07*	Brazilian	202 leprosy patients and 478 healthy individuals	B	Protection [22]
*DRB1*07:01*	Indian	93 leprosy patients and 47 healthy individuals	LL	Susceptibility [39]
*DRB1*08*	Brazilian	169 leprosy patients and 217 healthy individuals	LL	Susceptibility [46]
*DRB1*08:08*	Argentinean	71 leprosy patients and 81 healthy individuals	Leprosy *per se*	Protection [47]
*DRB1*09*	Southern Indian	230 leprosy-affected sib-pair	TT	Protection [48]
*DRB1*09*	Chinese	305 leprosy patients and 527 healthy individuals	Leprosy *per se*	Protection [49]
*DRB1*10*	Brazilian	578 leprosy patients and 691 healthy individuals	Leprosy *per se*	Susceptibility [44]
*DRB1*10*	Afro-Brazilian	578 leprosy patients and 691 healthy individuals	Leprosy *per se*	Susceptibility [44]
*DRB1*10*	Vietnam	194 single-case families	Leprosy *per se*	Susceptibility [44]
*DRB1*11*	Brazilian	70 leprosy patients and 77 healthy individuals	LL	Protection [50]
*DRB1*11:03*	Argentinean	71 leprosy patients and 81 healthy individuals	Leprosy *per se*	Protection [47]
*DRB1*12*	Brazilian	578 leprosy patients and 691 healthy individuals	Leprosy *per se*	Protection [44]
*DRB1*12*	Japanese	79 leprosy patients and 50 healthy individuals	Leprosy *per se*	Protection [43]
*DRB1*14*	Brazilian	85 leprosy patients and 85 healthy individuals	TT	Susceptibility [20]
*DRB1*14:01*	Argentinean	71 leprosy patients and 81 healthy individuals	Leprosy *per se*	Susceptibility [47]
*DRB1*14:06*	Argentinean	71 leprosy patients and 81 healthy individuals	Leprosy *per se*	Susceptibility [47]
*DRB1*15*	Afro-Brazilian	578 leprosy patients and 691 healthy individuals	Leprosy *per se*	Susceptibility [44]
*DRB1*15*	Brazilian	578 leprosy patients and 691 healthy individuals	Leprosy *per se*	Susceptibility [44]
*DRB1*15*	Chinese	305 leprosy patients and 527 healthy individuals	Leprosy *per se*	Susceptibility [49]
*DRB1*15*	Indian	93 leprosy patients and 47 healthy individuals	TT	Susceptibility [39]
*DRB1*15*	Indian	93 leprosy patients and 47 healthy individuals	LL	Susceptibility [39]
*DRB1*15*	Indian	54 leprosy patients and 44 healthy individuals	TT	Susceptibility [51]

Allele, haplotype	Population	Population size	Phenotype	Association
*DRB1*15:01*	North Indian	113 leprosy patients and 111 healthy individuals	BL/LL	Susceptibility [52]
*DRB1*15:01*	Indian	93 leprosy patients and 47 healthy individuals	LL	Susceptibility [39]
*DRB1*15:02*	Southern Indian	230 leprosy-affected sib-pair	TT	Susceptibility [48]
*DRB1*15:02*	Indian	93 leprosy patients and 47 healthy individuals	TT	Susceptibility [39]
*DRB1*15:02*	Indian	85 leprosy patients and 104 healthy individuals	TT	Susceptibility [53]
*DRB1*15:02*	Asian Indian	27 leprosy patients and 19 healthy individuals	TT	Susceptibility [54]
*DRB1*16*	Brazilian	85 leprosy patients and 85 healthy individuals	LL	Susceptibility [20]
*DRB1*16:01*	Brazilian	169 leprosy patients and 217 healthy individuals	BL	Susceptibility [46]
*DRB5*01:01*	Indian	93 leprosy patients and 47 healthy individuals	LL	Susceptibility [39]
*DRB1*15:01-DRB5*01:01-DQA1*01:02-DQB1*05:02*	Indian	85 leprosy patients and 104 healthy individuals	TT	Protection [53]

MB: multibacillary, PB: paucibacillary; B: borderline leprosy, BB: borderline borderline, BL: borderline lepromatous, BT: borderline tuberculoide, LL: lepromatous leprosy; TT: tuberculoid leprosy, *per se*: Leprosy independent of specific clinical manifestations, ENL: type 2 reactions or erythema nodosum leprosum, RR: type 1 or reversal reaction.

Table 3. Associations between ***HLA*** class II and leprosy.

3. *MIC* genes

The findings of new immune response genes are occurring in order to clarify their possible participation in the occurrence or severity of a disease. Among them, we can highlight *MIC* (MHC class I chain-related genes) that were discovered during a search for new coding sequences, located near the *HLA-B* gene [55].

MIC constitutes a second lineage of non-classical *MHC* class I genes and correspond to the *MICA*, *MICB*, *MICC*, *MICD*, *MICE*, *MICF* and *MICG loci* (**Figure 6**). *MICA* genes are located on the short arm of chromosome 6 (6p21.3), about 46.5 kb from HLA-B toward the centromere. Only *MICA* and *MICB* are expressed in proteins that belong to the immunoglobulin superfamily (IgSF) [56–58].

Like classical HLA genes, *MICA* also shows a high polymorphism in humans, whereas *MICB* appears to be less polymorphic, although it has been little explored. Since the discovery and characterization of NKG2D as its corresponding receptor in NK cells and in subsets of T cells, these genes have received increasing attention in the context of organs and stem cell

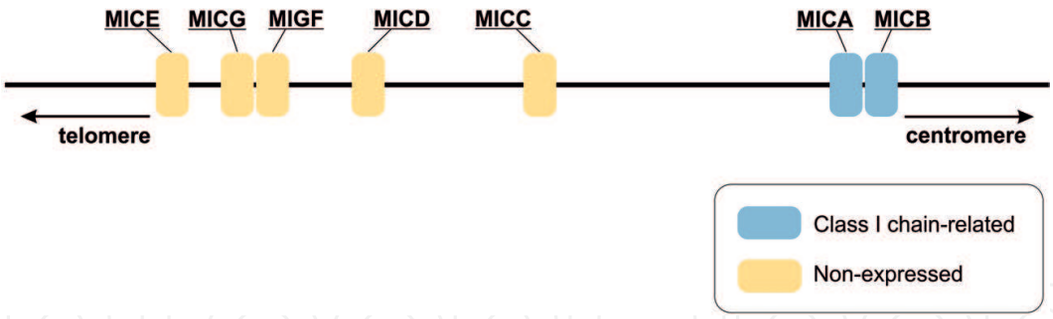

Figure 6. Genes and pseudogenes of the *MIC* family on region class I of the human MHC. Functional genes are represented in blue and the pseudogenes in yellow.

transplantation. *MICA* and *MICB* encode glycoproteins, which are stress induced and can be recognized by receptors such as NKG2D (C-type lectin-like activating immunoreceptor). They are capable of inducing immune responses involving Tγδ cells and NK cells, independently of the processing of conventional class I MHC antigens [57, 59, 60].

3.1. Structure of the MIC molecule

MICA molecules are codominantly expressed and are polypeptides of 383–389 amino acids with a size of 43 kDa in length [56, 57] and the MICB molecules are also polypeptides with a similarity of 83% amino acids with MICA. The structure of the MICA molecule is similar to HLA class I antigens, with three extracellular domains (α1, α2 and α3), a transmembrane domain and a cytoplasmic tail. MICA molecules have an extremely flexible rod connected to the platform formed by the α1/α2 domains and the α3 domain. Four α-helices are arranged under eight pleated β-strands forming a reduced slit that it would not be possible to attach a peptide composed of more than three or four amino acid residues (**Figure 7**) [61].

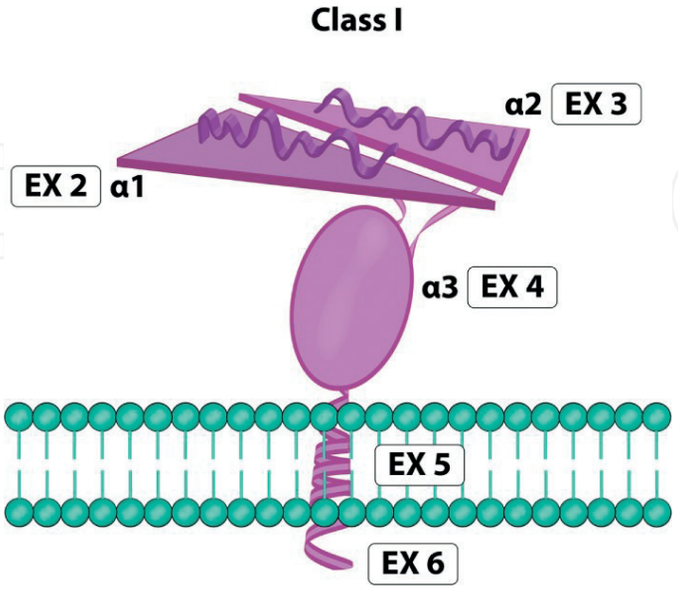

Figure 7. The structure of the *MICA*. Exon 2 encodes a leader peptide, exons 2–4 encode three extracellular domains, exon 5 a transmembrane domain and exon 6 a cytoplasmic tail [61].

In exon 5, there is a short tandem repeat sequence (STR) at position 304 consisting of GCT nucleotide breaks, which encode the amino acid alanine in the transmembrane region (TM). STR is absent in *MICB*. Based on the number of GCT, the alleles are named as A4, A5, A5.1, A6, A7, A8, A9 and A10. A5.1 differs from A5 by the insertion of a guanine nucleotide in the GCT (GGCT) [62], leading to a change in the reading matrix causing a terminus premature codon within the exon that encodes the transmembrane domain [33, 63, 64]. Thus, A5.1 is a 35–40 kDa truncated glycoprotein that eventually reaches the cell surface, but not at its physiological site. This is another characteristic of the *MICA* polymorphism: several alleles have identical extracellular domains but differ in the TM region. The identification of the polymorphism in the TM region is essential to avoid ambiguities [65].

The expression of the *MICA* gene was recognized in gastrointestinal and thymic epithelial cells in isolated endothelial cells, fibroblasts and keratinocytes. MICA molecules are ligands of the NKG2D receptors and Tγδ cell receptors (TCRγδ). The recognition of the MICA molecules by Tγδ Vδ1 cells through the interaction with the α1 and α2 domains was confirmed later in another study [66].

Tγδ cells constitute a small population of T cells expressing antigenic receptor proteins that resemble those of CD4+ and CD8+ T cells, but are not identical. Tγδ cells recognize many different types of antigens, including some proteins and lipids, as well as small phosphorylated molecules and alkyl amines. These antigens are not presented by MHC molecules [25]. It is not known whether there is a need for a particular cell type or distinct antigen presentation system for the presentation of antigens to these cells. MICA molecules are also recognized by their NKG2D receptors present on the surfaces of NK cells, associated with DAP10 molecule. This NKG2D-MICA complex activates phosphorylation of the tyrosine residues of the DAP10 molecule, triggering a cascade of cell signaling that enhances the cytotoxicity of NK cells. This complex also enhances the production of IFN-γ by NK cells, participating as a co-stimulator factor in the immune response against *Mycobacterium* [67].

Therefore, MICA is a stress-induced MHC class I molecule that binds to NKG2D receptors, primarily NK cells, stimulating NK cells, T CD8+ cells and some Tγδ cells [68]. Previous studies have suggested that HLA-B *loci* alleles were associated with some diseases caused by pathogens and, as there is strong linkage disequilibrium between the two genes due to the proximity of *MICA*, this could indirectly contribute to this response.

3.2. Association of *MICA* and *MICB* genes with leprosy

Some infectious and noninfectious diseases such Behçet's disease, ankylosing spondylitis, Reiter's syndrome, Kawasaki disease, psoriasis vulgaris and Chagas disease have been associated to *MICA* genes. These studies suggest that allelic variants of *MICA* may be directly related to NKG2D receptor binding of Tγδ and NK cells affecting the effects of cells activation [35, 69–74].

In the first study of association between the *MICA* gene and leprosy, the *MICA**A5 allele was found associated with protection against MB form in Chinese patients [19]. In India, the *MICA*5A5.1, MICB*CA16* and *MICB*CA19* alleles were associated with susceptibility to leprosy *per se* and *MICB*CA21* allele with protection [48]. Recently, in a study in Brazil, the *MICA*010* and *MICA*027* alleles were associated with protection against the MB form and *MICA*027* was associated with protection to leprosy *per se* [16].

4. Killer cell immunoglobulin-like receptors (KIRs)

4.1. Natural killer cells

Natural killer (NK) cells make up about 10–15% of the lymphocytes in human peripheral blood, with an important participation on the innate immune response. In addition, they are sources of type I cytokines, IFN-γ, as well as TNF-α, granulocyte macrophage colony-stimulating factor (GM-CSF) and other cytokines and chemokines [75]. In their original lineage, repertoire of receptors and effector functions, the NK cells appear to be a transitional cell type, which would be a bridge between the innate and adaptive immune system. The name is derived from two aspects: (*i*) NK cells are able to mediate their effector function (lysis of target cells) spontaneously in the absence of prior sensitization and are then called "killer" and "natural" and (*ii*) another aspect is that they perform their function with a very limited repertoire of receptors encoded in progenitor lines that do not undergo somatic recombination. The absence of previous sensitization and the absence of gene rearrangement for the formation of receptors for target cells indicate that NK cells are part of the innate immune system [76]. The major surface markers associated with NK cells are CD16 and CD56, while the T cell receptor (TCR) is absent [77].

The function of NK cells is to remove abnormal cells from the host, as infected cells or tumor cells, by exocytosis of lytic proteins (perforin/granzyme pathway) and by FasL or TRAIL (factor-apoptosis inducing linker of tumor necrosis) expression. Chemokines secreted by NK cells, such as IFN-γ and TNF-α, can mediate cytotoxic effects, activate dendritic and T cells, and influence the individual's immune response [78].

NK cells perform their task using two sets of receptors: activators and inhibitors present on their surface that interact with binding molecules on the surface of the target cell. The balance of these interactions determines whether or not the NK cell will be activated [9]. The major activation receptors expressed on NK cells include FcγRIIIA (CD16), DNAM-1 (CD226), NKG2C (KLRC2: killer cell lectin-like C2 receptor), NKG2E (KLRC3: killer cell lectin-like C3 receptor), NKG2D (KLRK1: killer cell lectin-like receptor K1), KIR-activating forms (KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5 and KIR3DS1), natural cytotoxicity receptors (NCRs) called NKp30 (natural cytotoxicity triggering receptor 3), NKp46 (NCR1: natural cytotoxicity triggering receptor 1), NKp65 (KLRF2: killer cell lectin-like F2 receptor) and NKp80 (KLRF1: killer cell lectin-like F1 receptor). The inhibitory receptors are KIR2DL1, KIR2DL2, KIR2DL3, KIR2DL5, KIR3DL1, KIR3DL2, KIR3DL3, NKG2A (KLRC1: killer cell lectin-like C1 receptor), LILRB1 (leukocyte immunoglobulin-like B1 receptor), KLRG1 (NKR2B4: natural killer cell receptor 2B4), NKp44 (NCR2: natural cytotoxicity triggering receptor 2) and KIR2DL4 (NKR2B4: natural killer cell receptor 2B4) [75].

4.2. KIR molecules

KIRs are members of a group of regulatory molecules found on the surface of NK cells and T cell subpopulations. They were first identified for their ability to confer some specificity in cytolysis mediated by NK cells [79, 80]. This specificity occurs through the interaction of isotypes of KIR with HLA class I molecules, protecting unaltered cells from the destruction caused by NK cells. Different types of KIRs can be expressed on the surface of NK cells,

which may be activators or inhibitors [79], with a combinatorial selection of receptors to be expressed by the cell.

Thus, in an individual, NK cells can randomly express a different set of activating and inhibitory receptors, and not all NK cells in an individual have the same receptors. This differential expression between NK cells and certain KIR/HLA interactions may contribute to heterogeneity in NK cell activation levels, observed both among different individuals and among distinct NK cell subpopulations of the same individual [81].

NK cells become responsible for tolerance when their inhibitory KIRs identify class I HLA surface molecules as self-antigens, and trigger inhibitory signaling through the tyrosine kinase phosphorylation of intracytoplasmic inhibition motifs based on tyrosine immunosorbent (ITIM) [82]. Even with the presence of activating receptors, the inhibitory signal is translated into tolerance, absence of cytotoxicity and cytokine production by NK cells when the target cell is normal. When the cell is infected with a virus or transformed into a tumor cell, this tolerance environment is altered, especially by the low or no expression of HLA class I molecules, which is known as part of the escape mechanism of tumor cells to the adaptive immunity [83].

NK cells are activated to produce cytotoxicity and cytokines, precisely due to the escape mechanism of altered ITIM cells; but alternatively there are positively charged transmembrane residues, which facilitate the physical association with DAP12 accessory proteins, releasing the activating signal via immunoreceptor tyrosine-based activation motifs (ITAM) [75].

4.3. *KIR* genes

The *KIR* genes are located on chromosome 19 (19q13.4) in a 1 Mb gene complex called the leukocyte receptor complex (LRC) which is shown in **Figure 8**. There are several gene families in the LRC region, among them leukocyte Ig-like receptors (LILRs); Ig-like transcripts (ILTs); killer cell Ig-like receptors (KIRs); platelet collagen receptor glycoprotein VI (GPVI); Fc IgA receptors, FcGammaR; natural cytotoxicity triggering receptor 1 (NRC1); leukocyte-associated Ig-like receptors (LAIRs); sialic acid-binding immunoglobulin-like lectins (SIGLECs); members of the CD66 family, such as the carcinoembryonic antigen (CEA) genes and the genes encoding the transmembrane adapter molecules DAP10 and DAP12 [84, 85].

The *KIR* gene family has 15 genes (*KIR2DL1, KIR2DL3, KIR2DL4, KIR2DL5A, KIR2DL5B, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2D5, KIR3DL1, KIR3DL2, KIR3DL3* and *KIR3DS1*) and 2 pseudogenes (*KIR2DP1* and *KIR3DP1*). They are divided into two functional groups: inhibitors that prevent lysis of the target cell and the activators that cause lysis of the target cell. The inhibitory group has eight genes that are *KIR2DL1, KIR2DL2, KIR2DL3, KIR2DL5A, KIR2DL5B, KIR3DL1, KIR3DL2* and *KIR3DL3;* the activator group has genes such as *KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5* and *KIR3DS1*; while *KIR2DL4* may be an activator or inhibitor. Between them, there are four *KIR* genes that are called structural (framework) genes, since they are present in almost all individuals: *KIR3DL3, KIR3DP1, KIR2DL4* and *KIR3DL2* [85, 86].

4.4. Structure and nomenclature of KIR

The naming of *KIR* genes is responsibility of the HUGO Genome Nomenclature Committee (HGNC) [87]. The designation of the *KIR* gene system considers the structure of the KIR protein.

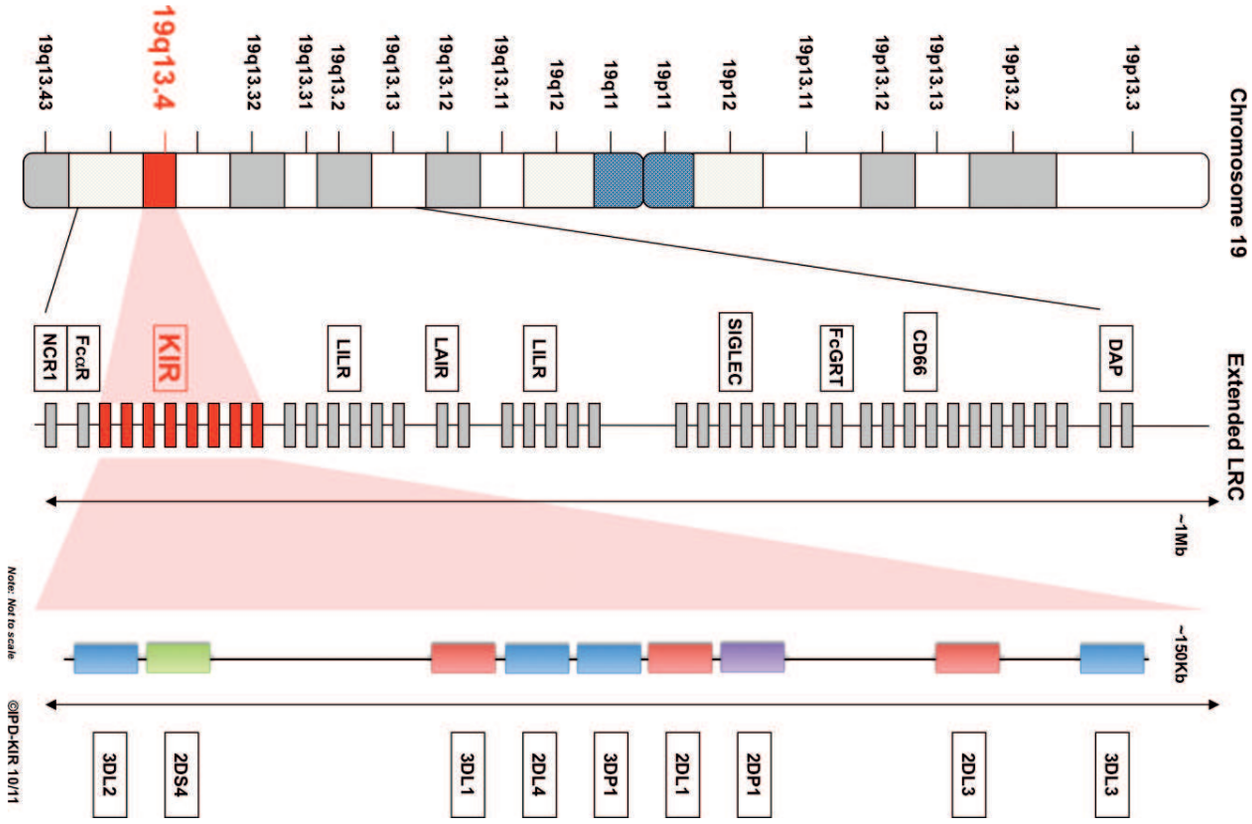

Figure 8. Diagram showing the cluster genes of the extended leukocyte receptor complex located (LRC) on chromosome 19 with highlight to *KIR* A haplotype at position 19q13.4 (in red). Among the molecules encoded by the extended LRC set of genes are the DAP adaptor proteins, CD66 antigens, SIGLEC, FcGRT, LILR, LAIR, FcAlphaR and NCR1 receptors. Within the *KIR* A haplotype are the framework genes (blue boxes), pseudogenes (purple box), inhibitory *KIR* (red boxes) and activating *KIR* genes (green box). *KIR2DL4* can be an inhibitory or an activating gene and *KIR3DP1* is also considered as framework gene [86].

They are classified based on two characteristics: number of extracellular Ig domains (2D or 3D) and characteristics of the cytoplasmic tail of the KIR protein, being S for short tail and L for long tail [88]. KIR3D is formed by the domains D0, D1 and D2, while KIR2DL1, KIR2DL2, KIR2DL3 and all KIR2DS have the D1 and D2 (Type I) domains; and KIR2DL4 and KIR2DL5 have the domains D0 and D2 (Type II) [89]. The long cytoplasmic tail (L) is associated with ITIM motifs that release a signal of inhibition to the cell. This signal of inhibition is due to the phosphorylation of a tyrosine residue that promotes the recruitment of (SHP-1 and SHP-2), which promote the dephosphorylation of protein substrates of tyrosine kinases related to the activation of NK cells. On the other hand, short tail (S) activation receptors have ITAM motifs in their transmembrane domain that associate with the adapter molecule DAP-12. The interaction of these receptors with their ligands results in the recruitment of SyK and ZAP-70 tyrosine kinases by ITAMs, resulting in the reorganization of the cytoskeleton to release granules and also in the transcription of cytokine and chemokine genes [90]. The structural characteristics of KIR that define their nomenclature are represented in **Figure 9**.

The *KIR* pseudogenes are identified by the letter "P" just after the digit corresponding to the domain type, as in the pseudogenes: *KIR2DP* and *KIR3DP*.

KIR genes follow a basic organization structure with 4–9 exons. Exons 1 and 2 encode the protein leader sequence; exons 3, 4 and 5 encode extracellular domains (D0, D1 and D2, respectively);

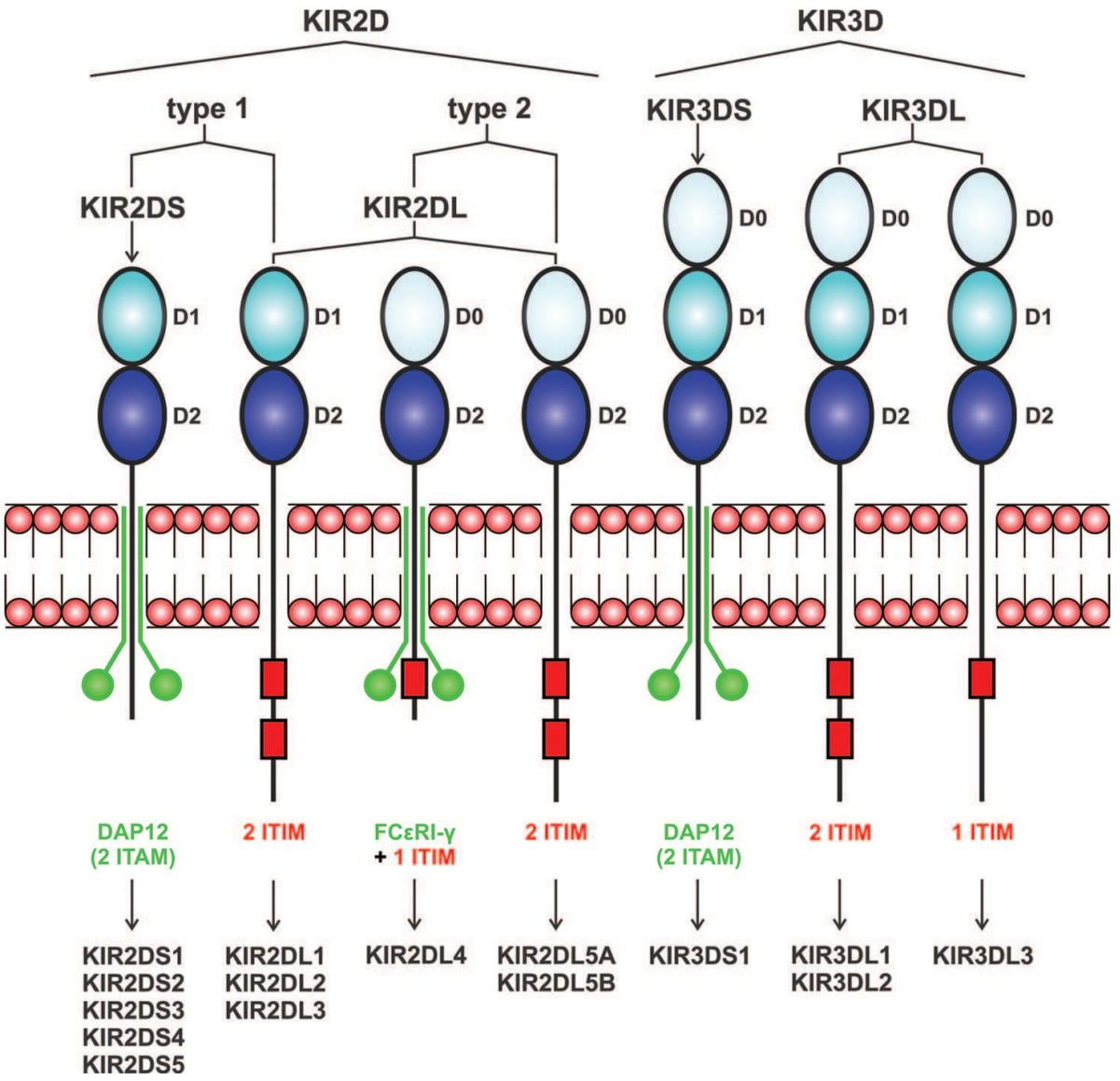

Figure 9. Domain structure of the KIR molecules. The structural characteristics of two and three Ig-like domain KIR proteins are shown. The association of activating KIR to adaptor molecules is shown in green, whereas the ITIM of inhibitory KIR are shown as red boxes. KIR2DL4 contains signature sequences of both activating and inhibitory receptors [86].

exon 6 encodes the tail, which lies between the extracellular domain and the membrane; exon 7, the transmembrane portion; and exons 8 and 9 encode the cytoplasmic tail [91].

4.5. *KIR* haplotypes

The *KIR* genes in the LRC form haplotypes on the same chromosome passed in blocks from generation to generation. There are two groups of *KIR* haplotypes: A and B, differentiated mainly by the number of activator *KIR* genes [92].

The A haplotype has seven *KIR* genes, predominantly the genes that encode the inhibitor receptors, such as *KIR2DL1*, *KIR2DL3*, *KIR2DL4*, *KIR3DL1*, *KIR3DL2* and *KIR3DL3*, with only

one activator gene, *KIR2DS4*. The B haplotype has a greater diversity of genes: *KIR2DL5, KIR2DL2, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS5* and *KIR3DS1*, with the activation signals predominating. A and B haplotypes have the frameworks genes [86, 93].

The KIR Nomenclature Committee considered that the distinction between A and B haplotypes is useful in biological and clinical terms, and thus developed a consistent and logical set of criteria to distinguish them. Therefore, a haplotype can, for example, be called KH-001A or KH-022B [86]. The haplotypic diversity of *KIR* genes varies in different populations, suggesting that there may be variable effects of the receptors on several diseases, offering protection against one particular pathology or predisposition to the other.

4.6. KIR ligands

NK cells perform the recognition of foreign cells in the body through the interaction of KIRs on own cell surface with ligands on target cells surface: classical class I HLA-specific molecules (HLA-A, HLA-B and HLA-C) and non-classical (HLA-E and HLA-G) [94]. The activity of NK cells requires the interaction between a given class I HLA antigen expressed on the surface of the cells and a specific KIR, inhibitor or activator.

HLA-C molecules are the major ligands of KIR and can be distinguished in two groups of ligands (C1 and C2). All HLA-C carry a valine (V) at position 76 and a dimorphism in the position 80, which may be asparagine (N) or lysine (K). The alleles that have asparagine at position 80 are called C1 group (codifying by *C*01, C*03, C*07, C*08, C*12, C*13, C*14, C*16:01, C*16:03* and *C*16:04*) and are the ligands of KIR2DL2/KIR2DL3 and KIR2DS2. On the other hand, the molecules that possess lysine at position 80 (K80) belong to the C2 group (codifying by *C*02, C*04, C*05, C*06, C*15, C*16:02, C*17* and *C*18* genes) and bind to KIR2DL1 and KIR2DS1 [95].

Some HLA-B molecules express Bw4 epitopes that are also present in some HLA-A molecules encoded by HLA-A*09, HLA-A*23, HLA-A*24, HLA-A*24:03, HLA-A*25 and HLA-A*32. The KIR3DL1 and the KIR3DS1 interact with HLA-Bw4, which differs from Bw6 due to a polymorphism at position 77 and 80. Bw4 molecules may have multiple amino acids at the position 77, either asparagine or aspartic acid or serine, and a dimorphism at the position 80, which may be isoleucine or threonine. The allotypes containing Bw4 with Isoleucine (Bw4-80I) generally exhibit strong inhibition, while Bw4 alleles with Threonine (Bw4-80 T), such as those encoded by HLA-B*13, HLA-B*27, HLA-B*37:01 and HLA-B*44, appear to be better ligands for certain KIR3DL1 subtypes. Other KIRs have less defined specificities, such as KIR3DL2, which recognizes HLA-A variants (A3 and A11), KIR2DL4 recognizing HLA-G and KIR2DS4 recognizing C*04. The ligands for KIR2DL5, KIR2DS3, KIR2DS5, KIR3DS1 and KIR3DL3 have not been identified to date [95, 96].

Although KIR activators exhibit a ligand recognition structure very similar to inhibitory receptors, as in the 2DL1/2DS1-C2 group pair and the triad of 2DL2/2DL3/2DS2-C1 group, the binding affinity of the activating variants is strongly reduced in comparison to the inhibitory variants. Therefore, when there are binding of inhibitory and activating receptors at the same time, it is believed that the inhibitory signal prevails [96].

4.7. Influence of *KIR* genes and ligands on leprosy

It is known that the interaction of KIRs and their HLA ligands can result in activation or inhibition of NK cells and the occurrence of different immunological and clinical responses to various types of diseases, such as infectious diseases (AIDS, malaria, tuberculosis, Chagas disease, dengue fever and leprosy) [97–101], autoimmune and inflammatory diseases (psoriasis, rheumatoid vasculitis and Crohn's disease) [102–104] in different populations and ethnicities.

The pioneering studies of *KIR* genes in leprosy were carried out in Brazil. The first study was performed in the southern region of Brazil, where the *KIR2DL1* inhibitor gene with its C2 group ligand was shown to be protective for BB and its homozygous ligand (*KIR2DL1*-C2/C2) was associated with the clinical form TT. Another inhibitory gene and its ligands (*KIR3DL2*-A*03/A*11) were associated with susceptibility to borderline leprosy. The activating genes *KIR2DS2* and *KIR2DS3* were shown to be a risk factor for TT form, compared to the more widespread form LL. Thus, TT patients with both activating genes (*KIR2DS2* and *KIR2DS3*) may develop better activation of NK cells and a competent cellular immune response with a more localized manifestation of the disease. The inhibitory *KIR2DL3*-C1 and *KIR2DL3*-C1/C1 were associated to protection against TT form, when compared to the control group and other clinical forms [105].

The second study of *KIR* genes with leprosy was performed in a hyperendemic region of Brazil, and the *KIR2DL1* inhibitory gene was a protective factor for leprosy *per se* and its BB form. The frequency of the homozygous *KIR2DL2* gene in the presence of the C1 group (*KIR2DL2*/*KIR2DL2*-C1) was higher in leprosy patients *per se* and in clinical forms TT and LL, when compared to the control group. The *KIR2DL2*/*KIR2DL3* haplotype with its homozygous C1 ligand (C1/C1) was associated with protection for leprosy *per se* and TT and LL forms [17].

The inhibitory effect of *KIR2DL2*/*2DL2*-C1 may contribute to the development of leprosy, mainly to a worse prognosis in *M. leprae* infections. The activating *KIR2DS2* gene with its C1 ligand was a risk factor for leprosy *per se* and the clinical form TT. In this same study, it was observed that higher frequency of inhibitory genes may favor the susceptibility of the development of the disease [17]. Thus, this study confirmed the influence of *KIR* genes and their HLA ligands on the immunopathology of leprosy.

Activating and inhibitory *KIR* genes in the presence of their HLA ligands may have an impact on the development of leprosy and its clinical forms. The balance between these genes may interfere with the progression of the disease to a more localized (TT) or disseminated (LL), or to maintain an intermediate pattern between the two poles (BB), thus highlighting the role of NK cells and the production of cytokines.

5. Conclusions

This chapter outlined the contribution of the innate and adaptive immune genes to leprosy pathogenesis, highlighting the *HLA*, *KIR* and *MIC* polymorphism genes contribution for clinical forms and reactions of leprosy. Immune responses against the *M. leprae* vary considerably between populations, which can be partly attributed to the genetic variation of the immune response to ensure the survival of populations. HLA and non-HLA genes should act together

affecting the susceptibility to leprosy, resulting in different clinical manifestations or reactions. Hence, for a complete understanding of the genetic mechanisms of leprosy susceptibility, it will be necessary to join efforts to present a pattern of genes that would in fact be important to predict a clinical form or more severe reaction of the disease.

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