The Major Histocompatibility Complex and Reactive Arthritis

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Overview

The major histocompatibility complex (MHC) is one of the most intensely studied regions in the human genome. Spanning four megabases on the short arm of chromosome 6 (6p21.3), it contains the most polymorphic genes in the human genome (Table 33.1), which are involved in many critical aspects of the innate immune response, including transplantation and defense against infection, and in most immune-mediated and autoimmune diseases. In this era where genome-wide association studies have extensively dissected the genetic basics of many of the rheumatic diseases, in most instances, most of the genetic variance is attributable to the MHC.

In the 45 years that have passed since the first description of the association of HLA-B27 with reactive arthritis [1], intense investigation has ensued studying the roles of this remarkable molecule and other MHC genes and susceptibility to spondyloarthritis (SpA) (summarized in references [2–6]). First of all, although at least a third of the genetic variance in SpA susceptibility has been attributed to HLA-B27 and other genes of the MHC and HLA-B27 has been shown to play a variety of roles in pathogenesis, how HLA-B27 actually causes ReA is still unknown, although current evidence suggests it may influence disease susceptibility by different mechanisms.

This chapter will present an overview of the MHC and its organization and explore how HLA-B27 and other genes of the MHC may influence susceptibility and outcome in reactive arthritis.

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Organization of the Major Histocompatibility Complex (MHC)

The 4-Mb human MHC (also known as the HLA complex) encodes over 220 genes, many of which are involved in the immune response, graft rejection, and disease susceptibility. Most prominent of these include HLA class I and II molecules, which initiate the cell-mediated immune response by displaying antigenic oligopeptides to the αβ-T-cell receptor. This interaction is critical in combating microbiological invasions, controlling malignant cell proliferation, and governing transplant success [7] (Fig. 33.1).

MHC Class I Region (Fig. 33.2)

The MHC contains not only the "classical" HLA class I genes (HLA-A, HLA-B, and HLA-C), whose products present peptides to CD8-positive T-cells and natural killer (NK) cells, but also a several "nonclassical" class I genes (MICA, MICB, HLA-E, HLA-F, and HLA-G), pseudogenes (HLA-H, HLA-K, HLA-J, HLA-N), and class I gene fragments (HLA-L, HLA-P, HLA-S, HLA-T, and HLA-W). These additional class I genes vary between species, and their functions are unknown, although it is likely that they have a role in contributing to the sequence diversity of other class I genes. Also contained in the MHC class I region are genes involved in other immunologic functions (immune early response (IER) and ATP-binding cassette subfamily F member 1 (ABCF1) genes).

"Classical" MHC Class Ia Genes

The HLA class I genes are involved in antigen presentation. HLA-A, HLA-B, and HLA-C in humans are highly diverse, whereas other class I genes are of much more limited diversity. They are the most polymorphic in the human genome (Table 33.1), reflecting their primary role in interfacing with an ever-changing environment, and serve especially in antiviral and other infectious immunity and immune tolerances

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Table 33.1 Polymorphism of MHC genes, March 2019

Gene	Alleles	Proteins	Null genes
A	4846	3286	255
B	5881	4088	190
C	4654	3070	185
E	27	8	1
F	38	6	0
G	61	19	3
H	12	0	0
J	9	0	0
K	6	0	0
L	5	0	0
N	5	0	0
P	5	0	0
S	7	0	0
T	8	0	0
U	5	0	0
V	3	0	0
W	11	0	0
Y	3	0	0
DRA	7	2	0
DRB	2841	2043	99
DQA1	114	46	4
DQB1	1498	1007	46
DPA1	85	32	0
DPA2	5	2	0
DPB1	1312	868	64
DPB2	6	3	0
DMA	7	4	0
DMB	13	7	0
DOA	12	3	1
DOB	13	5	0

Data from Robinson et al. [139, 140]. Available at https://www.ebi.ac.uk/ipd/imgt/hla/stats.html

(such as is encountered in transplantation and cancer). This diversity is reflected not only in the polymorphism of proteins expressed at the cell surface (the result of nonsynonymous substitutions, which is a nucleotide mutation that alters the amino acid sequence of a protein) but also synonymous substitutions which do not alter amino acid sequences but result in an increased number of alleles compared to proteins.

"Nonclassical" MHC Class Ib Genes

In comparison to the classical HLA class Ia molecules, HLA-E, HLA-F, and HLA-G genes and proteins show very limited polymorphism, and their expression is limited to particular cells and tissues [8, 9] (Fig. 33.2). Although the protein products of these genes bind a limited, but still diverse, set of peptides, their primary role is probably in modulating immune functions through direct interaction with several receptors on diverse subsets of immune cells [8, 9]. The tolerogenic properties of HLA class Ib molecules, and especially the immunosuppressive role of the HLA-G protein, were initially discovered in relation to feto-maternal tolerance and proved important in relation to a successful pregnancy.

HLA-E has the rather unique property of presenting leader sequences from other MHC class I molecules and is recognized by the innate immune receptor CD94/NKG2A expressed predominantly on natural killer (NK) cells and a small subset of T-cells from peripheral blood. Surface expression of HLA-E can protect target cells from lysis by CD94/NKG2A+ NK cell clones.

HLA-F is considered to be the progenitor of modern human MHC class I HLA genes [10]. Unlike class Ia molecules, HLA-F has an intracytoplasmic domain. It is expressed mainly in lymphoid tissue and T- and B-cells, with a lower expression in the spleen and the skin. There is increased expression of HLA-F genes during the last trimester of pregnancy, unlike HLA-G, which is expressed during the totality of pregnancy. At this point, it is not clear whether HLA-F associates with β2-microglobulin or binds peptides. In fact, current evidence suggests that HLA-F exists as an open conformer without β2-microglobulin or peptide that acts as a ligand for NK cell receptors such as KIR3DS1 [11].

HLA-G is primarily expressed on fetal-derived placental cells, although its expression has been shown in other milieus. The tolerogenic properties of HLA class Ib molecules, and especially the immunosuppressive role of the HLA-G protein, were initially discovered in relation to feto-maternal tolerance and proved important in relation to a successful pregnancy. The primary function of HLA-G is that of an immune checkpoint molecule, inhibiting the activity of several cells of the immune system. Membrane-bound or soluble HLA-G strongly binds its inhibitory receptors on NK cells, T-cells, B-cells, monocytes, and dendritic cells and serves an inhibitory function. HLA-G function may therefore be beneficial because when expressed by a fetus or a tissue transplant, it protects them from rejection or deleterious when expressed by a tumor. HLA-G expression can be stress induced and plays important roles in cancer [12], parasitic diseases [13], and transplant immunology [14].

MHC Class I HLA Pseudogenes and Gene Fragments

Since 1992, the existence of multiple other HLA class I genes has been known [15], including the pseudogenes designated HLA-H, HLA-J, HLA-K, and HLA-N (Fig. 33.2). However, sequencing studies have demonstrated the presence of deleterious mutations in these genes which prevent them from being active in antigen presentation or even expressed at the protein level. Evolutionary relationships as assessed by construction of trees suggest the four modern loci, HLA-A, HLA-G, HLA-H, and HLA-J, were formed by successive duplications from a common ancestral gene [11, 15]. In this scheme, one intermediate locus gave rise to HLA-A and HLA-H and the other to HLA-G

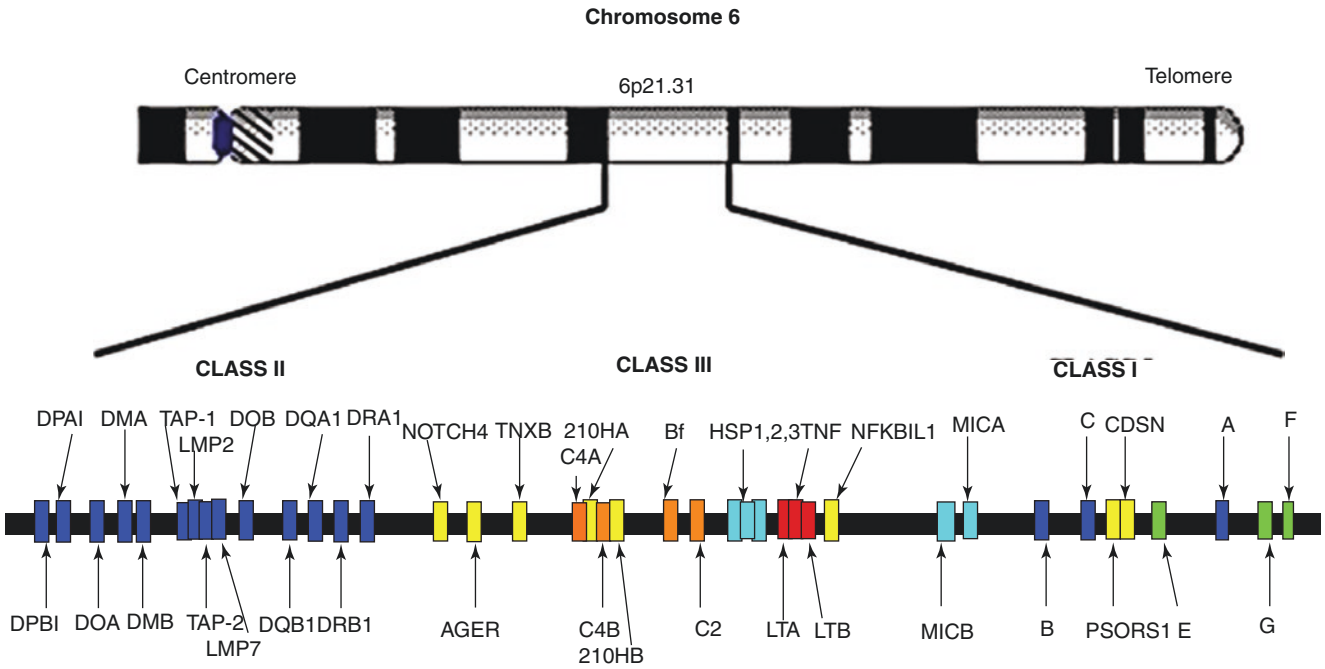

Fig. 33.1 Schematic of the MHC. The 3.6 Mb MHC contains over 220 genes and is divided into three classes. The location of genes involved in antigen processing or presentation is shown in blue, and "nonclassical" HLA genes (HLA-E, -F and -G) are shown in green. Early components of the complement cascade (C4, C2, properdin factor B) are shown in orange. Genes involved in stress responses (HSP1, HSP2, and HSP3; MICA and MICB) are shown in turquoise. The tumor necrosis factor group of genes (LTA, TNF, and LTB) is shown in red. Other genes, such as NOTCH 4, AGER, TNXB, 21-OH-A and 21-OH-B, PSORS1, and CDSN, are shown in yellow. (From Reveille [141]. Reprinted with permission from Springer Nature)

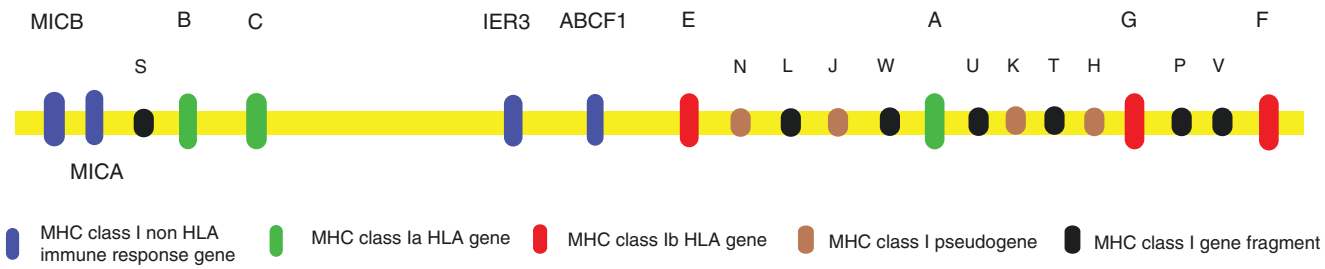

Fig. 33.2 HLA and other immune response genes in the MHC class I region

and HLA-J. Beyond these genes are MHC class I gene fragments designated HLA-L, HLA-P, HLA-S, HLA-T, HLA-U, HLA-V, HLA-W, HLA-Y, and, in the MHC class II region, HLA-Z [16–19].

Non-HLA Immune Response Genes in the Class I MHC Region

MICA and MICB

The major histocompatibility complex class I polypeptide-related sequence A and B genes (MICA and MICB) encode a membrane-bound protein acting as a ligand to stimulate an activating receptor, NKG2D, expressed on the surface of essentially all human natural killer (NK), γδ-T-, and CD8(+) αβ-T-cells [20] and highly expressed in intestinal epithelium. Upon binding to MICA, NKG2D activates cytolytic responses of NK and γδ-T-cells against infected and tumor cells expressing MICA. Therefore, membrane-bound MICA acts as a signal during the early immune response against infection (especially viral) or spontaneously arising tumors. On the other hand, the proteolytic cleavage of MICA proteins from expressing cells, termed as MICA shedding, produces soluble MICA that may control the immune process by downmodulating NKG2D expression and facilitate expansion of an immunosuppressive CD4+ T-cell subset. In addition, MICA can be excreted in exosomes which can also downregulate NKG2D activity [21]. It was reported that *MICA∗008* generated protein was preferentially released from cells in exosomal form [21]. Therefore, the balance between membrane-bound MICA

and soluble MICA/exosomal MICA may control the outcome of immune function via NKG2D regulation. At current, there are 107 recognized MICA alleles coding for 82 proteins and 47 MICB alleles coding for 30 proteins.

The Immune Early Response Gene

Located between HLA-C and HLA-E, the immune early response (IER) gene product functions in the protection of cells from Fas- or tumor necrosis factor-alpha-induced apoptosis [22]. Partially degraded and unspliced transcripts are found after virus infection in vitro, but these transcripts are not found in vivo and do not generate a valid protein.

ATP-Binding Cassette Subfamily F Member 1 (ABCF1)

ABCF1 is an E2 ubiquitin-conjugating enzyme that regulates macrophage function from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype by promoting TLR4 endocytosis and activation of TRIF-dependent signaling [23]. ABC transporter family protein that has been shown to regulate innate immune response is a risk gene for autoimmune pancreatitis and rheumatoid arthritis. Unlike other members of ABC transporter family, ABCF1 lacks transmembrane domains and is thought to function in translation initiation through an interaction with eukaryotic translation initiation factor 2 (eIF2).

MHC Class II Region (Fig. 33.3)

HLA-DR Subregion

The MHC class II HLA-DR molecule is a heterodimer consisting of an alpha (DRA) and a beta chain (DRB), both anchored in the membrane. It plays a central role in the immune system by presenting peptides derived from extracellular proteins. HLA-DR molecules are expressed in antigen-presenting cells (APC: B-lymphocytes, dendritic cells, macrophages). Within the DR molecule, the beta chain contains all the polymorphisms specifying the peptide-binding specificities. Over alleles, 2444 HLA-DRB1 alleles have been described encoding over 1741 different DRB1 chain allotypes. HLA-DRB1 is present in all individuals and is expressed five times higher than other DRB genes that produce beta chains (DRB3, DRB4, and DRB5) [24]. Different alleles of DRB1 are linked with either none or one of the genes DRB3 (found only on *HLA-DRB1∗03-*, *DRB1∗11-*, *DRB1∗12-*, *DRB1∗13-*, and *DRB1∗14*-bearing haplotypes) (Fig. 33.4), DRB4 (found only on *DRB1∗04-*, *DRB1∗07-*, and *DRB1∗09*-bearing haplotypes), and DRB5 (found only on *HLA-DRB1∗15-* and *DRB1∗16*-bearing haplotypes). *HLA-DRB1∗08* haplotypes are unique as they appear to have resulted from a gene contraction/deletion event. There are four related pseudogenes (DRB2, DRB6, DRB7, DRB8, and DRB9) whose presence varies on different DRB1 haplotypes (Fig. 33.4). HLA-DRB1 is the most polymorphic locus in the MHC class II region and has been implicated in a variety of autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, systemic sclerosis, type I diabetes mellitus, autoimmune thyroid disease, and multiple sclerosis), infectious diseases (leprosy), and other diseases (narcolepsy) [25].

The HLA-DQ Subregion

HLA-DQ belongs to the HLA class II beta chain paralogs. Like HLA-DR, HLA-DQ is a heterodimer consisting of an alpha (DQA) and a beta chain (DQB), both anchored in the membrane. Like HLA-DR, it plays a central role in the immune system by presenting peptides derived from extracellular proteins to the same system of antigen-presenting cells and has the same genetic organization, with greater polymorphism in the DQB chain. Located centromeric to HLA-DQA1 and HLA-DQB1, the DQA2, DQB2, and DQB3 loci represent gene duplication events, although whether they actually express cell surface proteins is unclear [26].

The HLA-DP Subregion

The DP subregion of the HLA class II region contains genes encoding the alpha and beta chains of a heterodimeric, cell surface glycoprotein that presents antigens to CD4+ (helper) T-lymphocytes [26]. HLA-DPA1 is much less polymorphic; indeed, the HLA-DPB1 gene is the third most polymorphic gene in the MHC class II region, with 1312 alleles giving rise to 868 different allotypic beta chains. HLA-DPB1 alleles have been implicated in chronic berylliosis [27], as well as in the topoisomerase I response in systemic sclerosis, juvenile

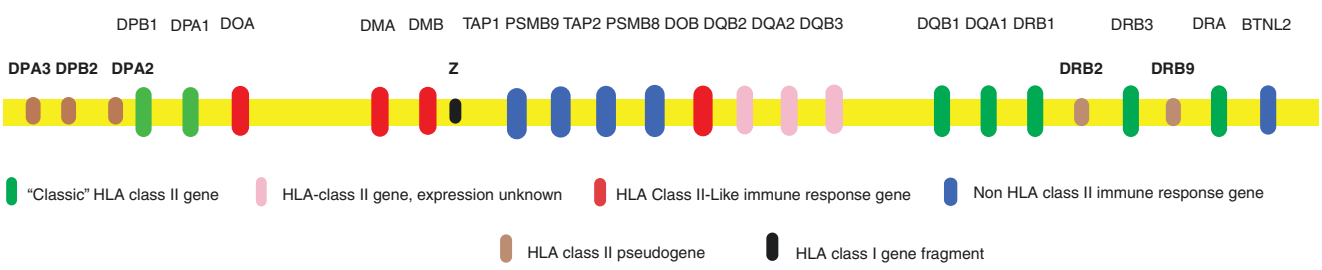

Fig. 33.3 HLA and other immune response genes in the MHC class II region

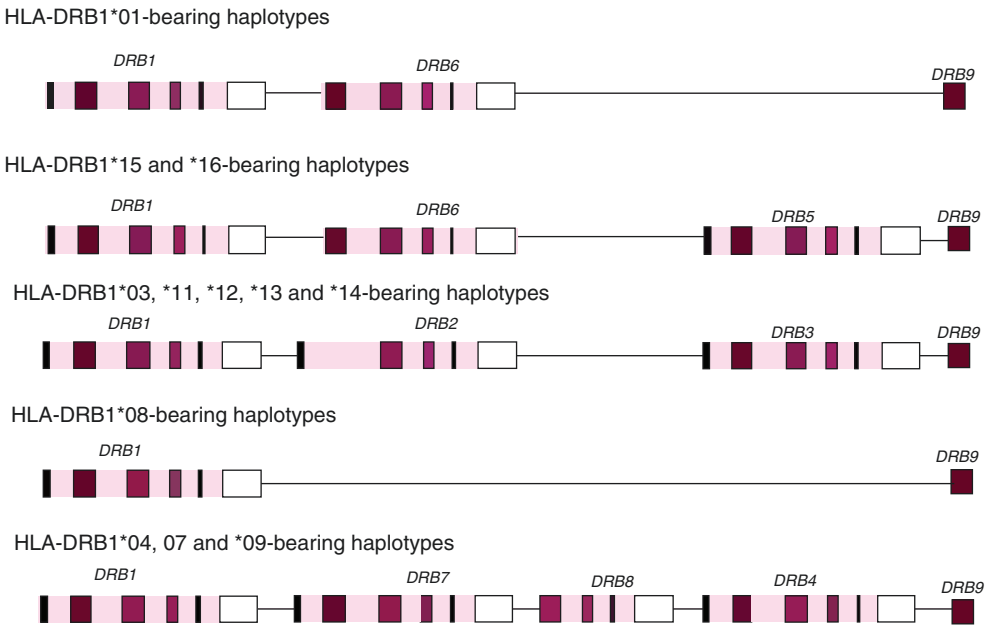

Fig. 33.4 The organization of genes and pseudogenes in the HLA-DR subregion differs by DRB1 haplotype

idiopathic arthritis, and spondyloarthritis. Also found here are pseudogenes HLA-DPA2, HLA-DPA3, and HLA-DPB2 (Fig. 33.3).

Non-HLA Immune Response Genes in the MHC Class II Region

Butyrophilin-Like Protein, Major Histocompatibility Complex Class II Associated (BTNL2)

BTNL2 encodes a major histocompatibility complex class II-associated, type I transmembrane protein which belongs to the butyrophilin-like B7 family of immunoregulators [28]. It is thought to be involved in immune surveillance, serving as a negative T-cell regulator by decreasing T-cell proliferation and cytokine release. The encoded protein contains an N-terminal signal peptide, two pairs of immunoglobulin (Ig)-like domains separated by a heptad peptide sequence, and a C-terminal transmembrane domain. Naturally occurring mutations in this gene are associated with sarcoidosis, rheumatoid arthritis, ulcerative colitis, inflammatory bowel disease, myositis, type I diabetes, systemic lupus erythematosus, acute coronary syndrome, and prostate cancer.

HLA-DM

HLA-DM is a non-polymorphic MHC class II-like molecule that does not bind peptides, but is necessary for the efficient displacement of CLIP from the MHC groove and its exchange for exogenous peptides. HLA-DM senses and interacts with the empty P1 pocket of HLA-DR heterodimers and induces conformational changes that disrupt bonds between the peptide and the binding groove, leading to dissociation of the bound peptide [29]. Removal of the bound peptide generates a receptive conformation that can readily scan suitable stretches of partially folded antigens or large antigenic fragments. This process continues until an optimal peptide is selected from the denatured protein antigen for further trimming and presentation to specific T-cells. Hence, in addition to the removal of CLIP, HLA-DM helps in the selection of immunodominant epitopes.

HLA-DOA and HLA-DOB

HLA-DO is a nonclassical MHC class II-like molecule which is an α/β-heterodimer encoded by the DOA and DOB genes that does not bind peptide [30]. The current understanding about HLA-DO can be distilled into two working hypotheses. In one model, HLA-DO forms a tight complex with HLA-DM in order to prevent HLA-DM from removing the invariant chain peptide CLIP; and in the other, HLA-DO differentially affects the presentation of structurally diverse peptides and acts as a second chaperone together with HLA-DM to fine-tune MHC class II repertoire selection.

Transporter Associated with Antigen Processing (TAP)

Peptides presented to CD8 cytotoxic T-cells (CTLs) by MHC class I proteins are generated by constant turnover of proteins by proteasomes in the cytosol. The peptides generated by the proteasomes are transported into the endoplasmic reticulum (ER) by TAP genes [31]. The TAP heterodimer is composed of TAP1 (ABCB2) and TAP2 (ABCB3), members of the ATP-binding cassette (ABC) family. In the ER, TAP and other proteins of the MHC class I peptide-loading complex (PLC) promote folding of MHC I molecules and ensure proper loading of peptides into the MHC class I

peptide-binding groove. Upon stable peptide loading, the peptide-MHC class I complex is translocated to the cell surface, where it displays the peptides to CD8+ CTLs.

Low-Molecular-Weight Proteasome Genes (PSMB8 and PSMB9)

The immunoproteasome, a distinct class of proteasome found predominantly in monocytes and lymphocytes, shapes the antigenic repertoire presented on major histocompatibility complex (MHC) class I molecules. PSMB8 (previously known as LMP7) and PSMB9 (formerly known as LMP2) function to amplify specific endopeptidase activities of the proteasome. An essential function of a modified proteasome, the immunoproteasome, is the processing of class I MHC peptides [32].

The MHC Class III Region (Fig. 33.5)

Advanced Glycation End Product-Specific Receptor (AGER or RAGE)

This is a member of the immunoglobulin superfamily. It is a multiligand cell surface receptor. AGER principally binds AGEs (produced through glycation of proteins or lipids after sugar exposure), a polypeptide linked with neuronal growth (high-mobility group protein 1 (HMGB1) or amphoterin), and members from the S100 family (S100A8, S100A9, S100A11, S100A12, and S100B) [33]. AGER activation after ligand binding increases receptor expression and activation of pro-inflammatory and procoagulatory pathways, leading, for example, to vascular dysfunction. Several phosphoproteins (NFκB, Akt, p38, and MAP kinases) and adaptors (MyD88, TIRAP, Dock7, and DIAPH-1) are involved in AGER-associated intracellular pathways. AGER is involved in inflammatory and immune responses and causes an unfavorable pro-inflammatory state implicated in multiple pathways and inflammatory diseases, rheumatic or autoimmune diseases, as well as infectious diseases, diabetes, metabolic syndrome and its complications, obesity, insulin resistance, hypertension, atherosclerosis, neurological diseases such as Alzheimer's disease, cardiovascular diseases, pulmonary diseases such as chronic obstructive pulmonary disease (COPD), and cancer [33].

FK506-Binding Protein-Like (FKBPL)

FKBPL, a member of the immunophilin protein family, is a potent secreted antiangiogenic protein targeting the CD44 pathway [34] with a ubiquitous expression in the skin. It functions in immunoregulation and basic cellular processes involving protein folding and trafficking. The encoded protein plays an important role in angiogenesis and appears to have some involvement in the control of the cell cycle.

The Early Components of the Complement Cascade

Complement components 2 (C2) and 4 (C4) represent early steps in the classical complement activation cascade and factor B (Bf) in the "properdin" pathway. C2 and factor B represent gene duplication events, and C2 shows 39% identity with the functionally analogous complement factor B [35]. The copy number of C4 genes in a diploid human genome (i.e., the gene dosage) predominantly varies from two to six in the white population [36, 37]. Each of these genes encodes a C4A or C4B protein. C4 is a constituent of the four-gene module termed the "RCCX," which takes its designation from RP1 (see STK19; 604977), C4, CYP21, and tenascin-XB (TNXB), a glycoprotein of the extracellular matrix predominantly located in the outer reticular lamina of the basement membrane associated with Ehlers-Danlos type I and vesicoureteral reflux 8 syndrome. The C4B isotype of C4 displays three- to fourfold greater hemolytic activity than does the C4A isotype.

Heat Shock 70 Proteins HSP70A, HSP70B, and HSP70L

These duplicated intronless genes encode a 70 kDa heat shock protein which is a member of the heat shock protein 70 family. In conjunction with other heat shock proteins, this protein stabilizes existing proteins against aggregation and mediates the folding of newly translated proteins in the cytosol and in organelles. It is also involved in the ubiquitin-proteasome pathway through interaction with the AU-rich element RNA-binding protein 1 [38].

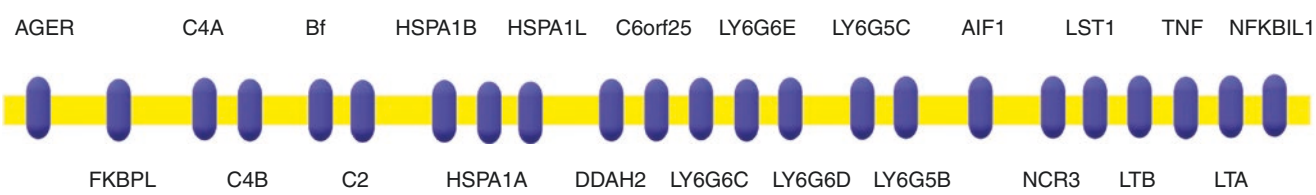

Fig. 33.5 Immune response genes in the MHC class III region

Dimethylarginine Dimethylaminohydrolase 2 (DDAH2)

This gene encodes a dimethylarginine dimethylaminohydrolase. The encoded enzyme functions in nitric oxide generation by regulating the cellular concentrations of methylarginines, which in turn inhibit nitric oxide synthase activity. The protein may be localized to the mitochondria. DDAH2 has been implicated in preeclampsia, sepsis, and renal, pulmonary, and cardiovascular diseases [39].

Megakaryocyte and Platelet Inhibitory Receptor G6b (MPIG6B or C6orf25)

This gene is a member of the immunoglobulin (Ig) superfamily and is located in the major histocompatibility complex (MHC) class III region. The protein encoded by this gene is a glycosylated, plasma membrane-bound cell surface receptor, but soluble isoforms encoded by some transcript variants have been found in the endoplasmic reticulum and Golgi before being secreted [40].

Lymphocyte Antigen 6 (LY6) Family Members LY6G5B, LY6G5C, LY6G6D, and LY6G6E [41]

The LY6 genes are located in the MHC class III region. Members of the LY6 superfamily typically contain 70–80 amino acids, including 8–10 cysteines. Most LY6 proteins are attached to the cell surface by a glycosylphosphatidylinositol (GPI) anchor that is directly involved in signal transduction. These represent 18% of the human Ly6 protein family and 50% of the secreted ones [41].

Allograft Inflammatory Factor-1 (AIF-1) [42]

This is a 17 kDa cytoplasmic, calcium-binding, inflammation-responsive scaffold protein that is mainly expressed in immunocytes. AIF-1 influences the immune system at several key points and thus modulates inflammatory diseases. AIF-1 boosts the expression of inflammatory mediators such as cytokines, chemokines, and inducible nitric oxide synthase (iNOS) and promotes inflammatory cell proliferation and migration [42].

Natural Cytotoxicity Triggering Receptor 3 (NCR3) [43]

NCRs have classically been defined as activating receptors that trigger cytotoxicity and cytokine responses by NK cells upon engaging with ligands on tumor cells. The encoded protein interacts with CD3-zeta (CD247), a T-cell receptor [43]. A single-nucleotide polymorphism in the 5′ untranslated region of this gene has been associated with mild malaria susceptibility.

Leukocyte-Specific Transcript 1(LST1) [44]

The protein encoded by this gene is a membrane protein that can inhibit the proliferation of lymphocytes [44]. Expression of this gene is enhanced by lipopolysaccharide, interferon-gamma, and bacteria. Recent data suggest that LST1 acts as a transmembrane adaptor protein with inhibitory signal transduction and as a membrane scaffold facilitating the formation of tunneling nanotubes.

Lymphotoxin-Alpha and Lymphotoxin-Beta (LTA and LTB) [45]

LTA and LTB encode proteins that are members of the tumor necrosis factor family. LTA is highly inducible and secreted and forms heterotrimers with LTB which anchor LTA to the cell surface. This protein also mediates a large variety of inflammatory, immunostimulatory, and antiviral responses, is involved in the formation of secondary lymphoid organs during development, and plays a role in apoptosis [45]. Genetic variations in this gene are associated with susceptibility to leprosy, myocardial infarction, non-Hodgkin's lymphoma, and psoriatic arthritis (PsA). The predominant form of the LTA/LTB complex on the lymphocyte surface is the LTA1/LTB2 complex, which is the primary ligand for the lymphotoxin-beta receptor.

Tumor Necrosis Factor (TNF)

This gene encodes a multifunctional pro-inflammatory cytokine that belongs to the tumor necrosis factor (TNF) superfamily [46]. This cytokine is mainly secreted by macrophages. It can bind to and thus functions through its receptors TNFRSF1A/TNFR1 and TNFRSF1B/TNFBR. This cytokine is involved in the regulation of a wide spectrum of biological processes including cell proliferation, differentiation, apoptosis, lipid metabolism, and coagulation. This cytokine has been implicated in a variety of diseases, including immune-mediated and autoimmune diseases, insulin resistance, and cancer.

NFκB Inhibitor-Like 1 (NFκBIL1) [47]

This gene encodes a divergent member of the I-kappa-B family of proteins. NFκBIL1 is important in the regulation of the NFκB pathway and has been implicated in the pathogenesis of rheumatoid arthritis, inflammatory myopathy, psoriasis, ulcerative colitis (association with the severe type), and systemic lupus erythematosus.

MHC Genes and Spondyloarthritis

HLA-B27

Over 45 years have passed since the original description of the association of HLA-B27 with reactive arthritis [1]. Even to this day, the association of HLA-B27 and spondyloarthritis remains one of the best examples of a disease association with a hereditary marker. In fact, the prevalence

of spondyloarthritis in general and reactive arthritis in particular corresponds to the population frequency of HLA-B27, with the highest frequencies in populations with high prevalence of HLA-B27 and the lowest in populations where HLA-B27 is rare (see in the following).

The Evolution of HLA-B27

There are to date 187 different alleles of HLA-B27 (https://www.ebi.ac.uk/cgi-bin/ipd/imgt/hla/allele.cgi) that result in different proteins being produced, including two subtypes (*HLA-B∗27:59*, *HLA-B∗27:64*) whose gene was truncated and did not result in an expressed protein product. Another, *HLA-B∗27:22*, was found to be a sequencing error and is not counted as an allele of HLA-B∗27. Of these, by far the most common is *HLA-B∗27:05*, which has a worldwide distribution and is likely the initial HLA-B∗27 allele, evolving before *Homo sapiens* left Africa (Fig. 33.6). The major subtypes of HLA-B27 include *HLA-B∗27:02*, found in Europe around the Mediterranean Sea; *HLA-B∗27:04*, a common subtype in eastern Asia; *HLA-B∗27:06*, which likely evolved from *HLA-B∗27:04* and is most frequently found in Southeast Asia; and *HLA-B∗27:07*, found in central and near western Asia. *HLA-B∗27:03* is unique to western Africa and *HLA-B∗27:09* to Sardinia and Italy. The other HLA-B27 subtypes are rare and evolved from the major subtypes of HLA-B27 (Fig. 33.7). Most subtypes are derived from either the ubiquitous parent allele *HLA-B∗27:05* or B27 subtypes common in the same geographic region. These geographic regional differences are not as easy to explain in certain situations, for example, why certain HLA-B27 subtypes that appear to be derived from more common "parent" subtypes have been located in ethnic groups far distant, such as *HLA-B∗27:20*, described in individuals in Japan and Korea that appears to be related to *HLA-B∗27:07*, found in western and southern Asia, or *HLA-B∗27:40*, *HLA-B∗27:42*, and *HLA-B∗27:44*, found in China and Taiwan, which appear derived from *HLA-B∗27:08*, found in the United Kingdom, is not clear. Whether this represents a prehistoric migration, or more recent gene admixture, perhaps an independent mutation, is not clear. Still, the most common subtypes associated with spondyloarthritis worldwide are *HLA-B∗27:05* overall; *HLA-B∗27:02* in Europe, North and South America, North Africa, western Asia, and the Middle East; and *HLA-B∗27:04* in eastern and southern Asia.

HLA-B27 and Infection

HLA-B27-restricted cytotoxic T-lymphocyte (CTL) responses to viruses are often tightly focused, resulting in immunodominant responses to small numbers of epitopes. In HIV infection, viral mutation leading to loss of CTL recognition is consistently associated with disease progression, providing strong evidence for a key role of CTL in viral control [48–50]. Among the other genetic factors studied regarding HIV-1 outcome, the major histocompatibility complex (MHC) has been most extensively studied in case-control studies (reviewed in [48, 49]), including those associated with

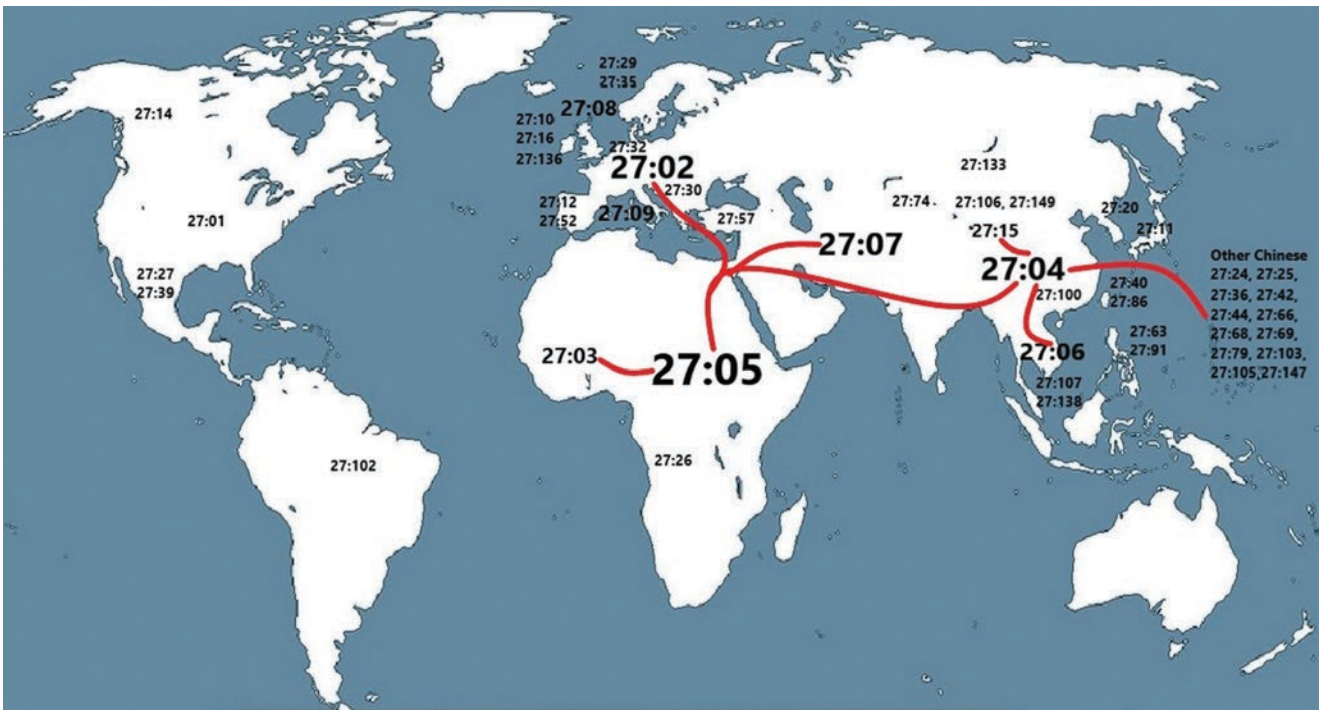

Fig. 33.6 HLA-B27 subtype origins

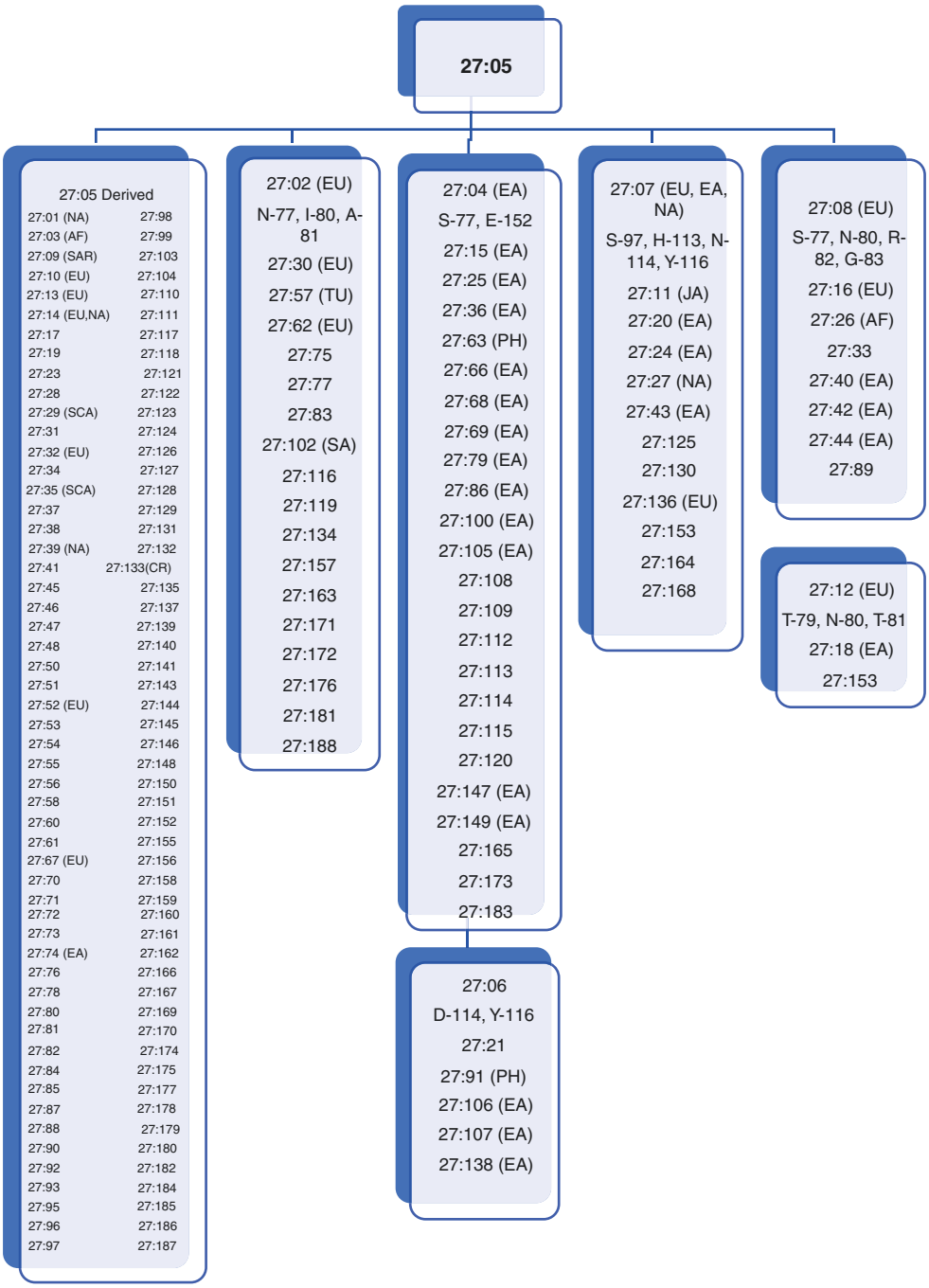

Fig. 33.7 HLA-B27 subtype derivations

slowed disease progression (the HLA-Bw4 family of alleles, most notably *HLA-B∗57*, *HLA-B∗27*, *HLA-B∗51*, *HLA-B∗58:01*, *HLA-B∗13*, *HLA-B∗81:01*, as well as *HLA-DRB1∗13* and possibly *HLA-DRB1∗01*), as well as those associated with accelerated disease progression (HLA class I homozygosity, certain *HLA-B∗35* alleles such as *HLA-B∗35:02* and *HLA-B∗35:03* but not *HLA-B∗35:01*, as well as *HLA-B∗38:02*, *HLA-B∗40:01*, *HLA-B∗50:01*, *HLA-B∗55:01*, and *HLA-DRB1∗15:03*). These associations relate to polymorphisms in the amino acids forming the peptide-binding groove of the HLA molecule involved in direct interaction with the peptide bound. HLA-B∗57 has been shown to have broad reactivity across multiple conserved gag epitopes and reduced fitness of HIV-1-1 escape mutation variants [6]. On the other hand, HLA-B27 presents a conserved immunodominant gag epitope that requires a complex pattern of mutation for escape. Other protective alleles are associated with strong CTL response to gag epitopes or, in the case of *HLA-B∗81:01*, lower replication capacity of escape variants. HLA-B27 also confers immunity in hepatitis C infection, promoting a spontaneous CD8+ T-cell-mediated viral clearance of HCV [50]. It is also of note that the prevalence of HLA-B27 is lowest in

regions of the world where the prevalence of malaria, an intracellular parasite, is highest, leading to speculation that it may confer a survival disadvantage in the face of malaria infection [51].

HLA-B27 and Spondyloarthritis

HLA-B27 has been associated with reactive arthritis worldwide; and in fact SpA and reactive arthritis are highest in frequency in populations where the frequency of HLA-B27 is highest, such as in Eskimos [52, 53] and Native Americans in the second wave (NaDene) of migration, such as the Haida and Navajos [54, 55], and lowest in the Middle East [56–58] and Africa [59, 60]. As far as HLA-B27 subtypes are concerned, *HLA-B∗27:05* and *HLA-B∗27:02* are seen in whites, Eskimos, and Latin Americans [53, 61] and *HLA-B∗27:04* in eastern Asians. On the other hand, certain HLA-B27 subtypes are non-disease associated, specifically *HLA-B∗27:06* (most commonly encountered in Southeast Asia) and HLA-*B∗27:09*, found in Sardinia (primarily). The molecular basis of this lack of disease association is unclear. HLA-B∗27:06 and HLA-B∗27:09 importantly share a tyrosine residue at position 116, not found in the "common" SpA-associated subtypes (*HLA-B∗27:05*, *HLA-B∗27:02*, and *HLA-B∗27:04*). However, this amino acid association is also seen with *HLA-B∗27:07*, which is SpA associated. HLA-B27 positivity has been associated with chronicity of symptoms [62]. In one interesting study [63], patients with positive fecal culture for *Salmonella*, *Campylobacter*, *Yersinia*, *Shigella*, and *E. coli* were addressed by questionnaires inquiring about gastrointestinal symptoms and the occurrence of joint pain in a previously healthy joint within 4 weeks after onset of infection. A significant association between joint pain beginning within 4 weeks of infection and HLA-B27 was found for *Salmonella*, *Shigella*, and *Yersinia*, not, however, for *Campylobacter* and *E. coli*; and a significant association between HLA-B27 and severity of joint pain was observed.

The Role of HLA-B27 in ReA Pathogenesis

The exact mechanism underlying the effect of HLA-B27 on disease susceptibility still has not been determined. To detail all the investigations of HLA and causation of SpA is outside the scope of this chapter and is covered in part in other chapters in this book as well as in recent reviews [2–5]. Five different theories for the role of HLA-B27 in influencing susceptibility to spondyloarthritis have been proposed:

Presentation of an Arthritogenic Peptide

As an MHC class I protein, the "classical" function of HLA-B27 is to present endogenous (i.e., viral, bacterial, tumor, self) peptides that have been degraded intracellularly in proteasomes to the αβ-T-cell antigen receptor on cytotoxic (CD8-positive) T-lymphocytes. However, in addition to their classical antigen-presenting role, HLA class I proteins (and the peptides presented therein) are recognized by members of the killer immunoglobulin receptor (KIR) family on natural killer cells. The HLA-B27 heavy chain is transcribed off of ribosomes in macrophages and retained in the endoplasmic reticulum (ER) by the molecular chaperones calnexin, calreticulin, and oxidoreductase ERp57, the latter a protein disulfide isomerase that reduces and oxidizes disulfide bonds. Then, it is folded into its tertiary structure and bound to β2-microglobulin, after which calnexin releases the complex and the dimer is associated with calreticulin, which in turn chaperones the formation of the peptide loading onto the complex of heavy chain, β2-microglobulin, and antigenic peptide, via the TAP proteins and tapasin. The antigenic peptide has been trimmed to optimal length by endoplasmic reticulum-associated aminopeptidases 1 and 2 (ERAP-1 and ERAP-2). Then, the trimolecular peptide complex (HLA-B27 heavy chain, β2-microglobulin, and peptide) travels to the cell surface, where the antigenic peptide is presented either to the αβ-T-cell receptor on CD8-positive T-lymphocytes or to the killer immunoglobulin receptor (KIR) on natural killer (NK) cells. Analysis of the peptides bound by HLA-B27 reveals a strong preference for peptides of 9–11 amino acids in length, which comprise 93% of the peptides examined, with only 2% of peptides being shorter than 9 residues [3]. There is also a preference for peptides that have an *arginine* at position 2, a consequence of "B pocket" specificity.

The *arthritogenic peptide* hypothesis suggests that ReA or other spondyloarthritides result from the ability of HLA-B27 to bind a unique set of antigenic peptides, either bacterial or self-derived. Disease which results from an HLA-B27-restricted cytotoxic T-cell response to this (these) peptide(s) is found only in joints and other affected tissues. Such a peptide could be bound and presented by all disease-associated HLA-B27 subtypes but not by other HLA class I molecules. After initial enthusiasm about molecular mimicry from *Klebsiella* peptides [64] could not be confirmed, identification of HLA-B27-restricted peptides from the *Chlamydia trachomatis* proteome [65–67], as well as from molecular mimicry between endogenous B27 peptides and this and other environmental antigens [66–73], raised this as a potential disease-causing mechanism. An autoantibody cross-reacting with altered self, such as a covalently modified form of HLA-B27, could play a role in initiating or perpetuating disease. Alternatively, $CD8^+$ CTLs that normally recognize foreign peptides presented by HLA-B27 during an infection might cross-react with arthritogenic self-peptides displayed by HLA-B27. Such autoreactive antibodies or CTLs could then mediate chronic inflammation. Peptide binding analyses of disease-associated and non-associated HLA-B27 subtypes produced contradictory results [74–78]. Detailed structural studies comparing *HLA-B∗27:05* and *HLA-B∗27:09* revealed that *HLA-B∗27:05* can display at least one self-peptide in two

different conformations that can be distinguished by $CD8^+$ CTL, while the same self-peptide appeared in only one conformation when crystallized with *HLA-B∗27:09* [74]. This suggested that altered display of a self-peptide ("dual-peptide conformations") might generate autoreactivity [74]. These studies were extended to *HLA-B∗27:04* and *HLA-B∗27:06* (the latter not associated with SpA) crystallized with the same peptide. Contrary to the results with *HLA-B∗27:05* and *HLA-B∗27:09*, the disease-associated *HLA-B∗27:04* subtype displayed only a single peptide conformation, whereas the non-associated *HLA-B∗27:06* subtype exhibited two conformations [75]. In the latter study, the disease-associated subtypes (*HLA-B∗27:04* and *HLA-B∗27:05*) showed significant heavy-chain conformational flexibility, whereas the non-associated subtypes (*HLA-B∗27:06* and *HLA-B∗27:09*) did not show flexibility. A recent analysis of the peptidomes of the eight most common HLA-B27 subtypes found significant overlap in the spectrum of peptides bound suggesting quantitative rather than qualitative differences in peptide repertoires might underlie differential disease association [78]. This led to the identification of 26 peptides presented in lower abundance by *HLA-B∗27:06* and *HLA-B∗27:09* than disease-associated subtypes. This is an interesting observation and provides a tractable list of putative arthritogenic peptides that can be used to search for autoreactive $CD8^+$ T-cells in patients with ankylosing spondylitis [74–78]. The strongest evidence against this theory is that a specific "arthritogenic peptide" has yet to be demonstrated either in ReA or other types of SpA.

Misfolding and ER Stress

Another tendency the HLA-B27 heavy chains have is to misfold in the ER [79–82]. HLA-B27 misfolding within the endoplasmic reticulum, and the accumulation of misfolded B27 heavy chains, results in a process known as ER-associated degradation (ERAD) that degrades misfolded HLA-B27 heavy chains, similar to what occurs with HLA class I heavy chains produced in the absence of β_2-microglobulin or TAP (where misfolding in the ER is more likely to occur). Misfolding activates XBP1 splicing and leads to the upregulation or activation of pro-inflammatory unfolded protein response (UPR) transcription factors (e.g., XBP1s, ATF4, and ATF6α) and downstream target genes including BiP and CHOP (reviewed in [3]). It also exhibits prolonged interactions with misfolded proteins, preventing premature exit from the ER. However, correction of the HLA-B27 folding defect and the UPR in B27 transgenic rats did not affect the presence or severity of the peripheral or axial arthritis, although beneficial effect on the colitis was seen [83].The UPR intersects with innate immune signaling pathways to synergistically upregulate IFN-β and IL-23 and to promote expression of other cytokines in response to toll-like receptor (TLR) agonists.

Another mechanism to eliminate misfolded peptides is by autophagy, a process where cells move unwanted material into vesicles for transport to lysosomes where degradation occurs. Self-association is a unique property of the HLA-B27 molecule. A recent study blocking autophagy flux with bafilomycin resulted in the accumulation of misfolded HLA-B27 dimers and oligomers as well as monomers, which was comparable with the results of blocking endoplasmic reticulum-associated degradation (ERAD) with the proteasome inhibitor bortezomib. HLA-B7 monomers also accumulated after blocking each degradation pathway. Activation of autophagy with rapamycin rapidly eliminated ~50% of misfolded HLA-B27, while folded HLA-B27 or HLA-B7 monomeric heavy chains were minimally affected [84]. This also suggested that manipulation of the autophagy pathway should be further investigated as a potential therapeutic target in spondyloarthritis.

These properties (homodimer formation and misfolding of HLA-B27 heavy chain in the endoplasmic reticulum [ER]) may trigger ER stress signaling pathways in host cell, which in turn may modulate cell signaling in favor of ReA-triggering bacteria [85]. Intracellular impairment of peptide processing or loading into HLA-B27 by viruses or intracellular bacteria can cause a selective impairment of the immune response.

Homodimer Formation

Self-association is a unique property of the HLA-B27 molecule. HLA-B27 heavy chains can form homodimers in vitro that are dependent on disulfide binding through their *cysteine*-67 residues in the extracellular α1 domain [79, 86, 87]. Heavy-chain self-association can either occur through misfolding in the endoplasmic reticulum or self-association of free heavy chains at the cell surface. A unique property of HLA-B27 is that free heavy chains of HLA-B27 can reach the cell surface in the absence of β2-microglobulin and maintain their peptide-binding groove in vitro. Alternative recognition of different forms of HLA-B27 by leukocyte receptors could influence the function of cells from both innate and adaptive immune systems and may indicate a role for various leukocyte populations in SpA [85–87]. Alternatively, HLA-B27 homodimers migrate to the cell surface where they either become antigenic themselves or present peptide to receptors on other inflammatory cells, especially when the cell's antigen-presenting function is impaired.

Alteration of intracellular invasion/killing of arthritogenic organisms may contribute to the cellular basis for ReA, but the molecular basis of the bactericidal pathways in synoviocytes has not been fully resolved. HLA-B27-positive U937 cells kill *Salmonella* less efficiently than controls and show upregulated production of interleukin-10 and, to a lesser extent, tumor necrosis factor (TNF)-alpha [85, 88]. In fact, HLA-B27-associated modulation of cytokine response

profiles may have importance in the pathogenesis of ReA and has been shown to modulate intracellular growth of *Salmonella* mutants and production of cytokines in infected monocytic U937 cells [85, 88–90]. Certain SPI-2 genes in wild-type bacteria suppress *Salmonella* intracellular growth and production of cytokines in infected HLA-B27-transfected cells [91]. HLA-B27-associated modulation of *Salmonella* SPI-2 genes and cytokine production causes intracellular bacterial persistence and may be important in the persistent infection of the bacteria and the pathogenesis of reactive arthritis. HLA-B27-dependent modulation of *Salmonella* gene expression has been shown also to result in not only persistence but also increased *Salmonella* replication in HLA-B27-positive cells [85, 92, 93]. All of this suggests that limiting intracellular growth might be a strategy for persistence of bacteria in host cells, keeping a balance between pathogenic growth and pathogenesis.

Presentation to CD4-Positive T-Cells

HLA-B27 itself and peptides derived therefrom also can act as autoantigens, where either the trimolecular complex presents processed peptide to the αβ-T-cell receptor on CD4-positive T-lymphocytes or free HLA-B27 heavy chains or HLA-B27 homodimers themselves are recognized as antigenic by the T-cell receptor thence or processed antigenic fragments of HLA-B27 are presented to the T-cell receptor of CD4-positive T-lymphocytes, either itself or via presentation by HLA class II (DR, DQ, and DP) heterodimers [94]. In previous years, amino acid homology between HLA-B27 and microbes triggering reactive arthritis supported the concept of *molecular mimicry*, such as has been described for an outer membrane protein YadA of *Yersinia enterocolitica* that shares a linear tetrapeptide with HLA-B27, a cationic outer membrane protein OmpH of *Salmonella typhimurium*, a hexapeptide of *Klebsiella pneumoniae* nitrogenase, and a pentapeptide shared by a *Shigella flexneri* protein and HLA-B27 [72]. However, this has not been widely confirmed.

Interaction with the Microbiome

Subclinical intestinal inflammation occurs in a significant number of patients affected by SpA and is correlated with the severity of spine inflammation [95]. The gut microbiome has recently been shown to influence several HLA-linked diseases. However, the role of HLA-B27 in shaping the gut microbiome has not been previously investigated. One study identified differences in the cecal microbiota of Lewis rats transgenic for HLA-B27 and human β2-microglobulin (hβ2m), and 16S RNA sequencing revealed significant differences between transgenic animals and wild-type animals by principal coordinates analysis. Further analysis of the data set revealed an increase in *Prevotella* bacterial species and a decrease in *Rikenellaceae* relative abundance in the transgenic animals compared to the wild-type animals [96]. Another study of 16S ribosomal RNA gene sequencing from terminal ileum biopsy specimens obtained from patients with recent-onset tumor necrosis factor antagonist-naive AS and from healthy controls showed that the terminal ileum microbial communities in patients with AS differ significantly from those in healthy controls which showed a higher abundance of five families of bacteria, *Lachnospiraceae*, *Ruminococcaceae*, *Rikenellaceae*, *Porphyromonadaceae*, and *Bacteroidaceae*, and a decrease in *Veillonellaceae* and *Prevotellaceae* [97]. These findings were confirmed in another study of 16S ribosomal fecal RNA sequencing, where a significantly increased abundance of *Ruminococcus gnavus* in SpA was seen, as compared with both patients with RA and healthy controls. Of note, significant difference in microbiota composition was also detected between HLA-B27$^+$ and HLA-B27$^-$ healthy control siblings, indicating that the genetic background may influence the microbiota composition [98]. These data all strongly suggest that HLA-B27 (and likely other HLA alleles) may influence the composition of the gut microbiome. In fact, it has been proposed that spondyloarthritis-associated subclinical gut inflammation may be considered the occult engine of the disease [99]. In the gut, the complex interactions between the microbiome and the host immune system, especially HLA-B27, may lead to the alteration of intestinal barriers and to the aberrant activation of innate immune cells. The role of the microbiome per se and gut-related factors in reactive arthritis pathogenesis is discussed in more detail in another chapter in this textbook.

Other HLA-B Genes

HLA-B60 is a serologically defined specificity that correlates at the DNA level with *HLA-B∗40:01*. Several studies have documented a small role for HLA-B60 (B∗40) in susceptibility to SpA [100–107]. One large study of whites, Han Chinese, and blacks was able to confirm the association of *HLA-B∗40:01* with AS in three ethnic groups [105] (Table 33.2).

Table 33.2 MHC genes positively and negatively associated with AS in three ethnic groups

	Whites		Han Chinese		Blacks	
	$N = 1948$		$N = 446$		$N = 67$	
HLA-B	OR	*P*-value	OR	*P*-value	OR	*P*-value
B∗27:05	36.5	$<10^{-375}$	9.2	$<1 \times 10^{-8}$	41.3	$<1 \times 10^{-8}$
B∗27:02	10.9	1×10^{-15}	n.a.	n.a.	n.a.	n.a.
B∗27:04	n.a.	n.a.	22.6	$<1 \times 10^{-8}$	n.a.	n.a.
B∗07:02	0.35	$<1 \times 10^{-8}$	0.06	6×10^{-4}	0.46	0.05
B∗15:00	0.43	$<1 \times 10^{-8}$	0.40	1×10^{-4}	n.a.	n.a.
B∗35:00	0.46	$<1 \times 10^{-8}$	0.03	0.001	0.24	0.02
B∗40:01	1.41	0.008	1.41	0.008	7.5	0.03

Studies of HLA-B alleles in Latin American patients with SpA, including patients with AS, reactive arthritis, and undifferentiated SpA, found associations with HLA-B∗15 [108–110]. This has also been observed in Tunisian patients with undifferentiated SpA. In Africans with SpA, HLA-B27 was less commonly seen; instead, associations with *HLA-B∗14:03* have been reported (a HLA-B∗14 subtype we did not observe in 67 African-American patients with AS and in French SpA families) [60, 111]. The Immunochip study, which imputed HLA alleles, also implicated *HLA-A∗02:01* in susceptibility to this disease independently of HLA-B27 [106].There is substantial evidence that non-B27 major histocompatibility complex (MHC) genes are associated with spondyloarthritis (SpA).

MICA Genes

Given that balance between membrane-bound MICA and soluble MICA/exosomal MICA may control the outcome of immune function via NKG2D regulation and its high expression in gut epithelium, it is tempting to postulate a role of MICA in SpA pathogenesis. One large study of white and Han Chinese AS patients found a highly significant association of two pro-inflammatory alleles of MICA, namely, *MICA∗007* and *MICA∗019*, with AS [112]. However, given the known linkage disequilibrium of these two alleles with *HLA-B∗27:05* and *HLA-B∗27:04*, respectively, a subsequent imputation analysis could confirm this [113]. A more recent study of MICA and natural killer group 2D receptor (NKG2D) polymorphisms in 162 patients with spondyloarthritis and 124 healthy controls found associations of MICA and NKC3 polymorphisms (related to a low NK cell cytotoxic activity) with spondyloarthritis [114]. Thus, a role for MIC genes in SpA pathogenesis is indeed suggested, but more work needs to be done to establish this with surety.

MHC Class II Genes

Earlier data suggested AS and spondyloarthritis in whites to be associated with HLA-DR1, specifically the *HLA-DRB1∗01:01* allele [115–118]. Another HLA-DR1 allele, namely, *HLA-DRB1∗01:03*, was implicated in AS susceptibility by imputation, as well as with enteropathic arthritis in another study. However, more recent studies have suggested this to be explained by an extended HLA-B27 haplotype, thereby reflecting linkage disequilibrium with *HLA-B∗27:05* and not a primary disease association. In fact, in one large study of white HLA-B27-negative patients with AS, no association was seen [105]. No such association has been demonstrated in nonwhites. *HLA-DPB1∗03:01* has been implicated in AS susceptibility in studies of whites by direct HLA typing [105, 119, 120], as well as in studies showing an association of SNPs around the HLA-DPB1 locus recently established by imputation [106, 119].

Studies of Other MHC Genes and AS Susceptibility

Older, small-scale studies have also suggested associations of ReA and SpA with TAP genes [121, 122], low-molecular-weight proteasome (LMP or PSMB) genes in the MHC class II region [123], and anti-TNF genes in the MHC class III region [124, 125]. However, these have not been confirmed in larger cohorts which studied by gene chip analyses and likely reflect linkage disequilibrium with HLA-B or other disease-associated MHC genes.

Psoriatic Arthritis

The association of HLA-B27 with psoriatic spondylitis and peripheral arthritis in whites soon followed that of ankylosing spondylitis in the early 1970s, soon to be followed by the finding of splits of HLA-B16, namely, HLA-B38 initially and eventually HLA-B37 [126–128]. Some other early HLA associations with psoriatic arthritis (PsA), such as with splits of the broad HLA specificity HLA-B17 (namely, HLA-B57 and HLA-B58) and HLA-Cw6 (now known as *HLA-C∗06:02*), eventually were found to be linked to susceptibility to psoriasis per se than PsA [129, 130]. More recent studies utilized large numbers of patients, and gene chip technologies have implicated *HLA-C∗12:03* and HLA-B alleles with amino acid substitutions at position 45 in PsA susceptibility. Some initial studies implicated MICA genes, located next to HLA-B; however, more recent studies have shown that this reflects linkage disequilibrium with HLA-B [131].

A role for genes of the MHC class II subregion has also been described, such as with *HLA-DRB1∗07:01*, though this has not been widely confirmed [132, 133]. Fewer studies exist in nonwhites with psoriasis and PsA. The best reproduced association has been of *HLA-C∗06:02* and *HLA-B∗57* with psoriasis per se [132–134]. Of note was also the implication of HLA-DPB1 and HLA-BTNL2 genes. PsA in Chinese has primarily been linked to *HLA-B∗27* and *HLA-C∗12:01* [135].

In the setting of HIV-1 infection, where the clinical distinction between reactive arthritis and PsA becomes more difficult, HLA-B27 has emerged as a significant risk factor for the development of inflammatory joint involvement [136].

MHC haplotypes have also been implicated in the clinical presentation of PsA. *HLA-B∗27:05* haplotypes have been positively associated with enthesitis, dactylitis, and symmetric sacroiliitis, whereas the *HLA-B∗08:01-C∗07:01* haplotype has been positively associated with joint fusion and deformities, asymmetrical sacroiliitis, and dactylitis.

HLA-C∗06:02 was negatively associated with asymmetrical sacroiliitis. The highest risk of severe PsA was with *HLA-B∗27:05-C∗02*, *HLA-B∗08:01-C∗07:01*, and *HLA-B∗37:01-C∗06:02* haplotypes, but not with the *HLA-B∗27:05-C∗01* or *HLA-B∗57:01-C∗06:02* haplotype [137]. In contrast, *HLA-B∗44*-bearing haplotypes were associated with presence of milder disease. In another very large study, *HLA-C∗06:02* was protective of PsA compared to psoriasis without arthritis, instead predicting younger age at psoriasis onset; in fact, no association of PsA was seen with HLA-C∗06:02 [138].

Conclusions

In reactive arthritis, as in many of the other rheumatic diseases, the MHC is a "prime mover" in pathogenesis, led by the overwhelming influence of HLA-B27. The MHC influences a variety of immune responses, which are now the targets of novel therapies. HLA-B27 in particular plays a variety of potential roles in pathogenesis, likely joined by other MHC factors. Understanding the complexity of this remarkable cassette of genes and their interaction with each other, with non-MHC influences, and with environmental factors is necessary to understand the pathogenesis of reactive arthritis.

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