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SPONDYLOARTHRITIS (MA KHAN, SECTION EDITOR)

Revisiting MHC Genes in Spondyloarthritis

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Abstract Spondyloarthritis (SpA) refers to a variety of inflammatory rheumatic disorders with strong heritability. Shared genetic predisposition, as shown by familial aggregation, is largely attributable to the major histocompatibility complex (MHC) locus, which was estimated to account for approximately half of the whole disease heritability. The first predisposing allele identified more than 40 years ago is HLA-B27, which is a major gene predisposing to all forms of SpA. However, despite intensive research, its pathogenesis remains uncertain. Other MHC alleles belonging to the class I and class II regions have been identified to exert additional effect. Candidate-gene approaches and genome-wide studies have recently allowed identification of several new loci residing outside of the MHC region that are involved in the predisposition to SpA. Interestingly, some of those new genes, such as ERAP1, ERAP2, and NPEPPS, code for aminopeptidases that are involved in MHC class I presentation and were shown to interact with HLA-B27.

Keywords HLA, HLA-B27 · HLA-E · HLA-DR · HLA-DP · MHC · Spondyloarthritis · Ankylosing spondylitis · Psoriatic arthritis · Peptide · Peptidome · ERAP · MICA · Natural killer cell · Transgenic rat · Dendritic cell · Antigen-presenting cell

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Introduction

Spondyloarthritis (SpA) is one of the most frequent groups of inflammatory rheumatic disorders. It refers to conditions which were originally considered as separate entities. These "seronegative spondylarthritides" comprise ankylosing spondylitis (AS), a subset of psoriatic arthritis, arthritis associated with idiopathic inflammatory bowel diseases (AIBD), reactive arthritis, and undifferentiated SpA. Overlapping clinical manifestations between members of the group and their tendency to aggregate with each other in families suggested a possible commonality of causal factors and underlied their grouping. Association of all SpA subtypes with the major histocompatibility complex (MHC) antigen HLA-B27, discovered more than 40 year ago, convincingly reinforced such assumption [1]. This fostered the development of several internationally validated classification criteria systems which recapitulate major clinical characteristics of the group. The most recent one, which was developed by the Assessment of SpA international Society, distinguishes axial from peripheral SpA, according to the distribution pattern of joint manifestations [2]. Using those

criteria, the prevalence of SpA in adult population of western countries was recently estimated to 0.4–0.7 % [3•, 4].

Genetic Predisposition

Family Studies

Other cases of SpA among relatives of patients are much more frequent than expected by chance [5]. Such familial aggregation was described a long time ago and can be taken as evidence that genetic factors predispose to the development of this disorder. Interestingly, with the notable exception of AIBD, different SpA subtypes appear to be distributed at random within families [6]. Furthermore, all articular and extraarticular manifestations making the spectrum of SpA tend to segregate together in those families [7]. All of this suggested that the various SpA subtypes co-existing in multiple cases families could be considered as phenotypic variations of the same disease, sharing a common genetic background [5, 8•].

Genetic Epidemiology

The major goals of genetic epidemiology are to estimate the degree of heritability of a given disorder and also to infer some model of its inheritance. A classical way to approach those questions is to ascertain the magnitude of recurrence of a trait among different categories of relatives. Based on the rate of concordance among twin-pairs, it was estimated that genetic factors overall may contribute to as much as 90 % of the whole predisposition to SpA [9]. The most important part of the genetic risk is due to the MHC, and more precisely to the HLA-B27 allele, which is present in 75 % of the Caucasian SpA patients versus 7.2 % of the population and increases the disease risk 39-fold, as compared with HLA-B27-negative subjects [3•]. A single copy of this allele is sufficient to confer disease risk, albeit it has been shown that HLA-B27 homozygosity would further increase it [10, 11••]. Nevertheless, inheritance of HLA-B27 is neither mandatory nor sufficient for SpA to develop. It has been estimated that only a minority representing 3 to 6 % of the HLA-B27-positive individuals would ever develop SpA [3•, 12]. Noteworthy, HLA-B27-negative cases tend to be structurally less severe with older disease onset and a lower frequency of uveitis [13, 14]. Thus, the predisposition to SpA is complex, polygenic, implicating several loci interacting with each other [15]. The risk of SpA in first-degree relatives of patients is 40-fold greater than in the general population [16]. This ratio, the λ_1 value is remarkably elevated, consistent with a highly inheritable disorder. A λ_{MHC} of 6.25, accounting for the genetic weight of the MHC region, was deduced from linkage analysis [17]. The $\lambda_{non\text{-}HLA}$, which corresponds approximately to the part of inheritability due to non-MHC loci, was estimated to 6.5, very similar to that of the entire HLA locus [9, 16]. Thus, it is assumed that MHC and non-MHC genes, interacting multiplicatively, account each for roughly half of the genetic predisposition to SpA.

Association of SpA with MHC Genes

The MHC Complex

The MHC contains the highest density of genes in the human genome. It spans 3.6 megabases on the short arm of chromosme 6 (from 6p22.1 to 6p21.3) and contains 240 genes. It is subdivided into three regions. The class I region, the most telomeric, contains the classical HLA class I genes: HLA-A, HLA-C, and HLA-B (as ordered from telomere to centromere) and related genes, such as MHC class I chain-related gene (MIC)A and MICB; the class II region is the most centromeric and contains HLA class II genes coding for HLA-DR, HLA-DQ, HLA-DP, HLA-DM, and HLA-DO antigens (from telomere to centromere). The region lying between class I and II genes is designated as MHC class III. It contains several genes important for immunobiology but distinct from the HLA genes, such as for instance the TNFSF1, 2, and 3, coding for lymphotoxin α (also known as TNFβ), TNFα, and lymphotoxin β, respectively.

In addition to its high density of genes, the MHC is characterized by an extreme degree of polymorphism of several of the genes that it contains, most notably the classical HLA genes, and also by the high degree of linkage disequilibrium (LD) that exists between them (meaning that particular alleles at separate loci tend to pair with each other more frequently than expected by chance). Thus, it may turn to be extremely difficult to dissect out which causal polymorphism(s) truly account for a given association.

Association of SpA with HLA-B27

The association between HLA-B27 and SpA is one of the most significant between an HLA molecule and any disease. It was described at a time where only few HLA alleles were distinguished, based on serological reactions [18].

Association Differences Between HLA-B27 Subtypes

More than 40 years later, it appears that as many as 135 distinct HLA-B27 subtypes (designated HLA-B*27:01 to-B*27:135) coded by many more allelic variations of the genetic sequence have been identified. They differ from each other by one or more mutations, generally affecting the polymorphic part of the molecule, i.e., its peptide binding groove. These alleles belong to some 3,760 distinct alleles described at

the HLA-B locus, coding for 2,789 proteins (update available at http://www.ebi.ac.uk/ipd/imgt/hla/stats.html).

Association with SpA has been well established for the most frequent subtypes, i.e., HLA-B*27:05, the ancestral allele from which other subtypes have derived, HLA-B*27:02, HLA-B*27:04, and HLA-B*27:07, which are distributed in the Mediterranean area and Asia [19]. Noteworthy, HLA-B*27:04 may carry a higher risk for SpA predisposition than HLA-B*27:05, in areas where both subtypes coexist, such as in China or India [20, 21]. Association with HLA-B*27:03 remained doubtful for some time, because this rare subtype was initially described on the west coast of Africa, in Gambia where SpA by itself is relatively scarce [22]. Finally, it was occasionally reported as associated with SpA in Africans and other populations such as the North American African, Tunisian, or Chinese [23, 24]. Albeit relatively rare, HLA-B*27:08 and HLA-B*27:15 appear also as associated with SpA [20, 25].

Two other HLA-B*27 subtypes, HLA-B*27:06 and -B*27:09, are of particular interest, since they were reported as non-associated with SpA. The first one, B*27:06 is rather frequent among several populations of Southeast Asia, where it coexists with B*27:04 [19]. In this area, it was identified in 3.9 % of the B27+control population overall versus 0.4 % in the B27+SpA cases ($p<10^{-4}$) [26•, 27]. As concerns HLA-B*27:09, it is a rare allele that was nevertheless identified in 20 % of the B27+population in central Sardinia and at a much lower rate in continental Italy (3.3 % of the B27 carriers in the latter place) [19]. Strikingly, it was not found in any of more than 200 SpA patients in those areas in the initial reports [28]. However, it was later identified in at least 10 SpA patients overall, including 2 in Tunisia where it was not found in the healthy population, questioning the reality of its « non-association »[29–31]. As an alternative explanation for the absence of HLA-B*27:09+SpA case in Sardinia, the place where it was convincingly shown as non-associated, it was further established that this allele was borne on a particular extended MHC haplotype in that island [32]. Thus, it is possible that other alleles of nearby gene(s) that are in LD with HLA-B*27:09 could afford protection from SpA development [19].

Regarding other HLA-B27 subtypes, several of them have been identified in SpA patients and are presumably associated with this disease, given their rarity in the control populations. This concerns B*27:01, B*27:10, B*27:12, B*27:13, B*27:14, B*27:17, B*27:19, B*27:24, B*27:27, and B*27:49, but the epidemiological evidence for their association has remained weak, given the small number of reported positive cases [10, 23, 24, 33, 34].

Interpretation of HLA-B27 Subtypes Association Differences

One major interest of determining the level of association of different HLA-B27 subtypes with SpA is to help unravel the molecular basis for such association, a question that has not yet been fully elucidated. Hence, HLA-B27 differs from other HLA-B alleles by a few residues clustered in the two alpha 1 and alpha 2 N-terminal domains of the molecule, forming the peptide binding groove. Thus, from the early identification of HLA class I structure, it appeared that few residues were unique to the very first HLA-B27 subtypes identified: His-9, Glu-45, Cys-67, Lys-70, Ala-71, and Asn-97 [35] (Table 1). However, residue 97 could probably be considered as not so critical, since it is mutated for a Ser in the disease-associated B*27:07 subtype (Table 1). Interestingly, all the other unique disease-specific residues cluster around the B-pocket of the peptide binding groove that accommodates the second anchor residue of the antigenic peptide. Moreover, this unique constellation of residues constrains the binding motif of the presented peptide, so that it uniformly contains an Arg at position 2, but for a few exceptions where it can be replaced by a Gln [36, 37]. This observation led to the first of the current theories on the role of HLA-B27 in disease predisposition: the « arthritogenic » peptide hypothesis. This theory speculates that the pathogenicity of HLA-B27 should arise from its unique capacity to accommodate and to present a particular repertoire of peptide(s) to pathogenic CD8+ T cells [19]. There are however several problems with such theory. One of the main issues is the failure to identify a set of peptide(s) distinctly presented by disease-associated HLA-B27 subtypes [37, 38]. Another contradiction came from the formal demonstration that CD8+ T cells seem not to be required for disease to develop in the HLA-B27 transgenic rat model of SpA [39–41].

Association with Other MHC Alleles

Trying to identify other MHC alleles associated with SpA besides HLA-B27 has been a tremendous challenge because of the overwhelming influence of HLA-B27 itself. One of the hurdles to be overcome for that purpose comes from the tight LD that spreads across the MHC region. Such goal is however very relevant, given that LD extends around HLA-B27 itself over nearly 400 kb (our personal unpublished data) and that other allelic variants situated in the close vicinity of the HLA-B gene could contribute to its pathogenicity, and also to differential associations between subtypes.

Association with Other MHC Class I Alleles

The most consistent has been an association of SpA with HLA-B*40:01, serologically defined as HLA-B60. Such association was reproducibly described in B27+ positive Caucasian patients, as a co-factor multiplying HLA-B27 effect by 3.6- to 4.7-fold [42•, 43]. This allele, as well as B*40:02 (B61), was otherwise found as associated with HLA-B27-negative SpA in the Taiwanese [44]. The mechanism underlying such epistatic association is currently unknown, given

Table 1 Alignment of polymorphic residues between the principal HLA-B27 and HLA-B14 subtypes with established SpA-association status and those of HLA-B*07:05

aa	9	**45**	59	63	**67**	69	70	71	74	77	80	81	82	83	97	113	114	116	131	152	156	163
B*2705	His	**Glu**	Tyr	Glu	**Cys**	Ala	Lys	Ala	Asp	Asp	Thr	Leu	Leu	Arg	Asn	Tyr	His	Asp	Ser	Val	Leu	Glu
B*2703	–	–	His	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
B*2701	–	–	–	–	–	–	–	–	Tyr	Asn	–	Ala	–	–	–	–	–	–	–	–	–	–
B*2702	–	–	–	–	–	–	–	–	–	Asn	Ile	Ala	–	–	–	–	–	–	–	–	–	–
B*2708	–	–	–	–	–	–	–	–	–	Ser	Asn	–	Arg	Gly	–	–	–	–	–	–	–	–
*B*2709*	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	*His*	–	–	–	–
B*2707	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Ser	His	Asn	Tyr	Arg	–	–	–
B*2704	–	–	–	–	–	–	–	–	–	Ser	–	–	–	–	–	–	–	–	–	Glu	–	–
*B*2706*	–	–	–	–	–	–	–	–	–	Ser	–	–	–	–	–	–	*Asp*	Tyr	–	Glu	–	–
B*1403	Tyr	–	–	Asn	–	Thr	Asn	Thr	–	Ser	Asn	–	Arg	Gly	Trp	Tyr	Asn	Phe	Ser	Val	Arg	Thr
*B*1402*	Tyr	–	–	Asn	–	Thr	Asn	Thr	–	Ser	Asn	–	Arg	Gly	Trp	Tyr	Asn	Phe	Ser	Val	–	Thr
*B*0702*	Tyr	–	–	Asn	*Tyr*	–	Gln	–	–	Ser	Asn	–	Arg	Gly	Ser	His	*Asp*	Tyr	Arg	Glu	Arg	–

HLA-B*07:02 is shown as a non-associated reference allele. Amino acid (aa) position numbering starts from the alpha 1 N-terminal domain. The residues common to all SpA-associated subtypes appear in bold. Non-associated subtypes and their distinctive residues italicized

that those alleles do not share the disease-associated HLA-B27 motif.

Another striking association has been described in several sub-Saharan African populations (Togo, Zambia, and Burkina Faso) with HLA-B*14:03 [45]. In those areas where both SpA and HLA-B27 are rare, the very rare HLA-B*14:03 allele was detected in 8 of 25 (32 %) SpA patients but in none of 204 healthy controls ($P=1.2\times10^{-8}$). Most interestingly, HLA-B*14:03 contains two of the key residues specific for all HLA-B27 subtypes, i.e., Glu-45 and Cys-67. Despite that resemblance, it shares very little of its peptide-binding characteristics with HLA-B*27:05 [46] (Table 1). With regard to the possibility that those similarities could account for disease-association, it is puzzling that B*14:02, which is much more frequent than B*14:03 and not associated with SpA, is identical to it except for a Leu-156 that it shares with HLA-B27, instead of an Arg-156 in B*14:03 (Table 1). It is interesting to underline that this single mutation between both B*14 alleles tremendously impacts their peptide-binding repertoire [46].

Regarding other class I genes, HLA-A*02:01 appears as weakly but definitely associated with SpA, independently of HLA-B27 [11••].

Association with MICA Alleles

Besides HLA genes, there is strong evidence for an association of MICA alleles with SpA. It is the closest known gene near HLA-B, which lies only 50 kb telomeric to it. This gene is also polymorphic, with as many as 100 known alleles coding for 79 distinct proteins, and in strong LD with HLA-B, making it difficult to separate its effect from that of HLA-B alleles [47]. A recent study sequenced MICA in two large ethnically separate cohorts, one North American Caucasian (1,070 patients and 1,003 controls) and the other Han Chinese (473 patients and 536 controls) to assess possible association of this gene with SpA. Two MICA alleles were found as positively associated with SpA: MICA*007:01 in both cohorts and MICA*019 in the Chinese one. Most importantly, those associations were found both in B27-positive and B27-negative carriers, and appear thus as independent of HLA-B27 [48••]. MICA is normally expressed on the cell membrane of epithelial cells in response to stress stimuli, such as gut infectious agents. It activates immune cells response through binding to the natural killer (NK) receptor NKG2D that is expressed on the surface of NK cells, intestinal γδ T cells, and αβ CD8+ T cells. One allele of MICA results in a truncated soluble form that is rather immunosuppressive [49]. Interestingly, this allele corresponds to MICA*008 which was decreased in both the American and Chinese populations. Moreover, since this allele is in LD with the HLA-B*27:06 subtype [47], it might at least in part contribute to the lack of association of this subtype with SpA. Thus, the differential association of B27 subtypes with SpA should be revisited in view of other haplotypic influences, including MICA polymorphisms.

The search for haplotype differences that might explain the lack of association of B*27:09 with SpA in Sardinia was carried before, as compared with B*27:05, given that both alleles belong to distinct conserved haplotypes in this Italian island [32, 50]. MICA was not extensively genotyped in that study, and no significant difference was found between patients and controls for that gene. Interestingly, however, the B*27:05+ patients had a distinct distribution of HLA-E polymorphisms, as compared with all B27+controls (either B*27:05+ or B*27 09+), a finding that was further replicated [51]. HLA-E is a non-classical HLA gene situated 1 Mb telomeric to HLA-B,

between HLA-A and C, and whose product binds signal peptides derived from classical class I HLA-molecules, such as HLA-B27. It is implicated in immune response as a ligand for the NKG2C activating and NKG2A inhibitory receptors on NK cells. The HLA-E variant associated with SpA in Sardinia was shown to bind poorly the B27 signal peptide, which might impair its immunoregulatory function [51].

Association with MHC Class II Alleles

Several MHC class II alleles have also been implicated in AS susceptibility. Few published studies have conclusively shown an implication of the HLA-DR locus, except for a French family-based study that evidenced a predisposing role for HLA-DR4. Such an association was recently replicated in a North American case–control study [52, 53].

Besides, a region located around the HLA-DPA1 and HLA-DPB1 loci was identified as weakly but significantly associated with AS in a large case–control study carried in the Spanish population (601 patients and 542 controls, all HLA-B27+). A positive association was found with the DPA1*01:03, DPA1*02:01, and DPB1*13:01 alleles [54]. The association with DPA1*01:03 was further replicated in the Portuguese population, reinforcing its validity [55•]. The HLA-DPA1 and -DPB1 gene products form a heterodimer which is implicated in the presentation of acquired extracellular antigens, such as microbial, to CD4+ T lymphocytes.

Association of SpA with Non-MHC Genes

During the recent years, several studies have successfully mapped and/or identified non-MHC genetic polymorphisms conferring increased susceptibility to SpA. Interestingly, the involvement of some of those genes appears to be dependent of an interaction with the HLA-B27 allele. Such observations are expected to shed light on the still mysterious role of HLA-B27 in SpA susceptibility.

Aminopeptidases

Several genome-wide case–control association studies have been carried in AS, leading to identification of numerous single-nucleotide polymorphisms associated with AS, belonging to 26 non-MHC genetic loci [11••, 56–58]. Interestingly, some of those genes, i.e., ERAP1, ERAP2, LNPEP, and NPEP PS code for aminopeptidases that are involved in antigen-processing pathway for MHC class I molecules. The association with ERAP1, which applies to the whole group of SpA, appears to be restricted to HLA-B27+ carriers, indicating an epistatic interaction between both susceptibility loci [58, 59]. The consequences of ERAP1 coding variants associated with SpA concur to increase the function of the enzyme, either through modification by the coding variants [60] or by upregulation of the transcript levels [61] or by both.

Killer Immunoglobulin-Like Receptor (KIR) Genes

The cluster of 15 KIR genes on chromosome 19 is of particular interest, regarding predisposition to SpA for several reasons. First, there is suggestive linkage between this region and SpA [62]. Moreover, KIR genes products are ligands of MHC class I molecules that are expressed on NK cells and subsets of T cells, and provide either activating or inhibitory signal. Finally, those genes are extensively polymorphic, combine in distinct haplotypes, and code for molecules that display variable affinity for different MHC class I alleles, resulting in NK and/or T cell activation/inhibition fine tuning [63]. Thus, it is necessary to consider the complexity of KIR genes polymorphisms in combination with HLA class I alleles to gain insight into the putative contribution of those genes. It is particularly interesting to note that several studies were consistent in showing an increased frequency of the carriage of activating KIR2DS1 and KIR3DS1 genes in SpA [64].

Functional Role of the MHC in SpA Predisposition

There is no doubt that the principle genetic factor predisposing to SpA is HLA-B27 itself. However, the mechanism of such association remains as yet unproven, and several distinct theories have been proposed to explain it, which we will briefly review, in light of recent advances in that field.

The Canonical Arthritogenic Peptide Hypothesis

As already discussed before, there is no clear evidence that particular antigenic peptide(s) presented by HLA-B27 could be the target of a pathogenic CD8+T cell-mediated response in SpA. Studies of peptidome binding variations between HLA-B27 subtypes failed generally to identify a simple rule that could explain distinct association levels [38]. Two recent studies compared the B27-bound peptidome isolated from C1R lymphoblastoid cell line, whether transfected with HLA-B27 subtypes considered as SpA-associated (B*27:02, B*27:03, B*27:04, B*27:05, B*27:07, B*27:08) or non-associated, i.e., B*27:06 and B*27:09 for those studies [37, 65]. Peptides isolated from the former group of subtypes tended to be longer and heavier than those bound to the latter [65]. Also, there were differences in the nature of the C-terminal position of the bound peptides, which was preferentially occupied by bulky aromatic and basic residues in the disease-associated subtypes, in contrast to small and aliphatic residues in the non-associated ones [37, 65]. Of several hundreds of peptides examined in one of those studies, 26 were found exclusively bound to all the four disease-associated subtypes [65].

Moreover, peptides bound to disease-associated subtypes were shown as the most resistant to ERAP1 enzymatic digestion, in comparison to those bound to the non-associated ones [65]. The influence of ERAP1 alleles was also investigated with regard to HLA-B27-bound peptidome. Interestingly, ERAP1 alleles that confer enhanced disease susceptibility result in an increased frequency of ERAP1-resistant residues, as a logical result of heightened enzymatic activity leading to a greater destruction of the most ERAP1-sensitive peptides [65]. Altogether, those results indicate that a motif of peptides preferentially bound to SpA-associated B27 alleles may indeed exist and that ERAP1 alleles favoring disease predisposition may enhance the preferential binding of such peptides, while favoring the destruction of others [66]. However, the second study failed to identify disease-associated subtype-specific peptide, albeit it showed quantitative binding differences of several peptides between associated and non-associated subtypes [37].

Hypotheses Implicating HLA-B27 Dysfunction

The lack of formal demonstration of the existence of an « arthritogenic » peptide stimulated, several years ago, the formulation of alternative hypotheses to explain HLA-B27 involvement in SpA [19]. The most popular of them speculate on particular biochemical behaviors of the HLA-B27 molecules.

Hence, a first intriguing observation was that the HLA-B27 heavy chain tends to form homodimers during in vitro refolding assay, in part due to its unpaired Cys-67 [67] (Fig. 1). It was further shown that such dimers were expressed at the cell surface in SpA patients and behave as unusual ligands for NK receptors, such as KIR3DL2, expressed on NK cells and CD4+ T cells. Moreover, interaction between B27 homodimers and KIR3DL2 stimulated CD4+ T cells to proliferate and to produce IL-17. HLA-B27 homodimers were also expressed on leukocytes from

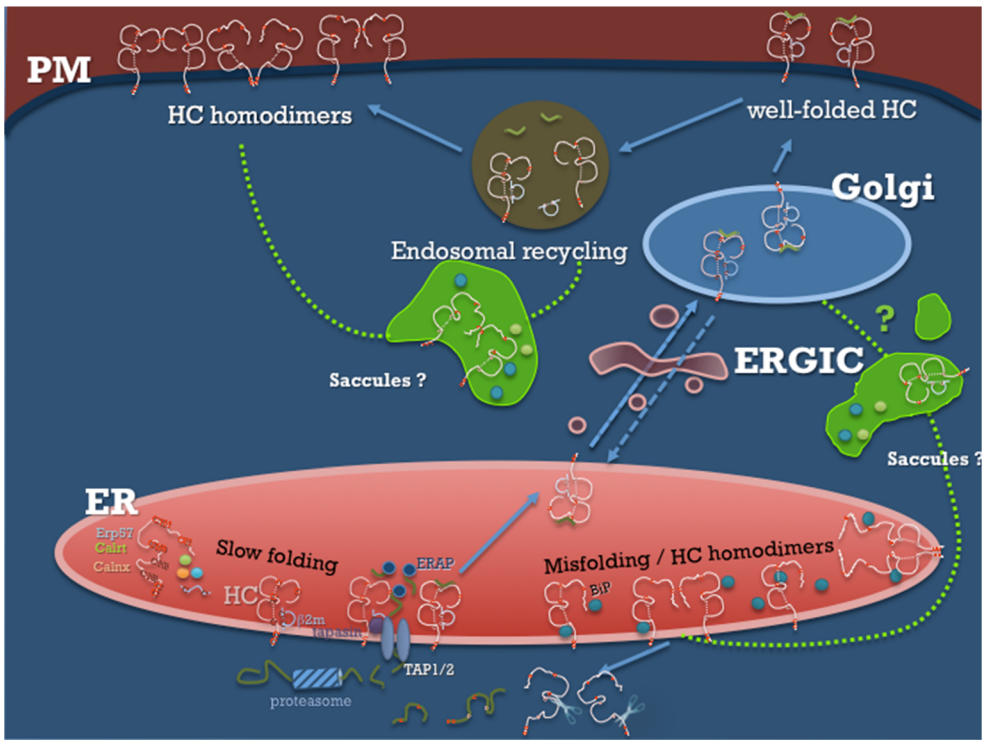

Fig. 1 Intra-cellular behaviors of HLA-B27 from its synthesis in the ER to its expression at the plasma membrane (PM). The nascent HLA-B heavy chain (HC) is assisted during folding by ER chaperones such as calnexin (Calnx) and calreticulin (Calrt) and protein disulfide isomerase such as Erp57. Folded HC is stabilized by binding to beta2-microglobulin (β2m) and antigenic peptides. The latter are provided by the degradation of intra-cytoplasmic proteins by the proteasome. The resulting peptides enter the ER through TAP1/2 heterodimeric transporter system and are further trimmed to optimal length by ERAP1/2 enzymes. Their binding to the folded HLA-B HC is assisted by tapasin. The mature HLA-B molecule normally exits from the ER, passes through the Golgi, and reaches the PM as an heterotrimeric complex (HC+β2m+peptide). It has been shown however that HLA-B27 HC has a tendency to misfold and to form homodimers in the ER. These complexes tend to bind to the chaperone BiP, triggering and unfolded protein response and activating an ER-associated degradation process, which leads to the retrotranslocation of HC to the cytoplasm for degradation. At high expression levels, SpA-associated HLA-B27 subtypes have a tendency to accumulate intracellularly, in a misfolded conformation, in large vesicles (i.e., saccules) together with BiP. These saccules contain calreticulin and may correspond to intermediate compartments between the ER and the Golgi (ERGIC) [81•]. Moreover, HLA-B27 molecules expressed at the cell surface are recycled by endocytis. During this endosomal recycling, they can form homodimers of HC, which are expressed at the PM, where they interact with KIR receptors. Intra-cellular saccules discussed above may alternatively be part of the endo-lysosome–autophagosome pathway

HLA-B27 transgenic rat. Antibodies developed to block specifically HLA-B27 dimers opened the perspective to interfere with, and more closely examine, the pathogenicity of these dimers [68].

Another theory came from the rather slow folding of the HLA-B27 molecule during its synthesis in the endoplasmic reticulum (ER), which may in some instance result in misfolding, the formation of heavy chain homodimers residing in the ER, and stimulate an unfolded protein response (UPR), with putative pro-inflammatory consequences [69] (Fig. 1). An UPR was well documented in HLA-B27 expressing macrophages from disease-prone transgenic rats, but such phenomenon has not yet been convincingly established in patients [70, 71] and its relevance for SpA remains inconclusive.

Several other consequences of HLA-B27 expression have been described in transfected cells, transgenic animals, or patients, which may also explain its pathogenicity. These include aberrant functions of antigen-presenting cells in B27 transgenic rats that have also been partly observed in cells from patients, including enhanced apoptosis [72, 73], defective T cell activation [74–77], altered cytoskeleton [73], reverse-interferon γ signature [78•], and a bias of T cells differentiation towards Th17 profile [79•, 80]. HLA-B27 subtypes were also shown to accumulate intra-cellularly in saccules that remain to be identified, in a way that correlates well with disease predisposition [81•] (Fig. 1). Moreover, HLA-B27 expression in monocytic cell line resulted in aberrant phosphorylation of STAT1, which may lead to activation of the cell [82]. In all cases, more investigation will be required to explain the underlying molecular mechanism of those observations and their putative pathogenic consequences for patients.

Conclusions

The MHC is critical for SpA predisposition. HLA-B27 itself is the central player. This allele has now been subdivided in a broad variety of subtypes with differential association patterns that turn to be helpful to dissect out the precise molecular implication of this allele. Whether binding of a specific « arthritogenic » peptide is critical for pathogenicity remains uncertain, whereas several aberrant biochemical behaviors of HLA-B27 could provide alternate explanations for its functional role. Genetic studies indicate that other genes than HLA-B combine with it to modulate disease predisposition. This is notably the case for MHC genes that code for ligands of the NKG2 family of NK receptors, i.e., HLA-E and MICA, and for a cluster of genes on chromosome 19 that code for another class of NK receptors, highlighting the putative importance of such receptors in SpA pathogenesis.

Compliance with Ethics Guidelines

Conflict of Interest Maxime Breban, Félicie Costantino, Claudine André, Gilles Chiocchia, and Henri-Jean Garchon declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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