Immunopathogenesis of Ankylosing Spondylitis: An Updated Review

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Abstract- Ankylosing spondylitis (AS) is a chronic immune-mediated inflammatory arthritis of unknown etiology, which belongs to a group of conditions known as spondyloarthopathies that comprises psoriatic arthritis, reactive arthritis, and enteropathic arthritis. AS causes pathologic new-bone formation in the axial skeleton, and leads to chronic pain, axial fusion, deformity, disability and skeletal fracture. Several genetic and environmental factors are known to be associated with AS. Notwithstanding the fact that a multitude of genes, such as human leukocyte antigen B27 (HLA-B27), endoplasmic reticulum-associated aminopeptidase 1 (ERAP1), and interleukin-23 receptor (IL-23R) have been previously speculated to be associated with individuals’ susceptibility to AS, no consensus about their precise role in the etiopathogenesis of AS has been reached. In the present study, we summarize the current literature on the immunogenetics of AS and contemporize the research advancement that has been made over the past decade.

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Introduction

Ankylosing spondylitis (AS) is a subclass of spondyloarthritides (SpAs) that affects the axial skeleton and leads to disability and axial fusion in many patients. Apart from affecting the complete axial skeleton, AS can also involve peripheral joints. Conditions classified as SpA include reactive arthritis, psoriatic arthritis, arthritis related to inflammatory bowel disease (IBD) and undifferentiated SpA. Their clinical manifestations include inflammatory back pain, enthesitis, peripheral oligoarthritis, anterior uveitis, psoriasis, and (IBD) (1-3).

The etiopathogenesis of AS is not fully understood, but genetic and environmental factors play important roles. Human leukocyte antigen B27 (HLA-B27) is a genetic factor directly involved in the pathogenesis of AS, but seems to contribute only about 16% of the total genetic risk of this disease. Non-B27 genes also appear to be involved in the etiology of the disease. AS initially presents during the third decade of life with a prevalence of between 0.1% and 1.4% globally (4). Men are twice as likely to be affected than women (5). Structural changes such as bamboo spine are more common in male patients than in females.

Juvenile-onset AS (JoAS) is a form of the disease that occurs in individuals of about 16 years of age and presents more commonly as peripheral joint manifestations (6). It is usually associated with clinical manifestations that include inflammatory back pain (7) which is dull and diffuse rather than localized, as well as syndesmophytes, which cause spinal stiffness and loss of spinal mobility (8). Other signs of disease are peripheral arthritis, enthesitis (9), ankylosis of affected joints (10), anterior uveitis (11), psoriasis (12), IBD (13), osteoporosis (14), and an increased rate of fracture (14).

Diagnosis of AS is usually based on the modified New York criteria which combine clinical features such as limitation of lumbar spine motion, persistent lower-back pain, limited chest expansion, and radiographic evidence of sacroiliitis (15). Sacroiliitis is the earliest manifestation of AS, but peripheral joints and extra-articular structures may also be affected (16). Immune cell infiltration into subchondral tissues is a remarkable
sign of this disease that causes irregular erosion and sclerosis of the affected joints and gradual replacement of normal tissue by fibrocartilage that then becomes ossified (17). When these lesions occur in the spine, cartilaginous structures of sacroiliac joints and intervertebral discs undergo irreversible change and are replaced by bone; ultimately, the vertebrae become fused. The bamboo spine is a long bony vertebral that can be seen in advanced stages of the disease.

Pathogenesis

The etiopathogenesis of AS and other spondyloarthritides is not fully understood, but genetic and environmental factors play important roles. Several AS-susceptibility genes exist, including HLA-B27 and other genes recently identified in genome-wide association studies (GWASs), but none are directly involved in ankylosis (Table 1). Environmental triggers such as gram-negative bacteria are also considered to be important in the initiation and progression of the disease.

Genetic factors

HLA-B27

HLA-B27 is a susceptibility factor for spondyloarthropathy, especially for AS. The precise pathogenic role of HLA-B27 is elusive, but it has unusual features, including a misfolding tendency (18, 19) and a predilection for heavy chain homodimer formation during cell surface recycling (20-22) that activates endoplasmic reticulum (ER) stress signaling pathways. The unfolded protein response promotes cytokine production (IL-23, IFN, IL-1) and activation of the IL-23/IL-17 axis (23). In most populations, the prevalence of AS is proportional to the frequency of HLA-B27 and studies indicate that 80% to 95% of AS patients are HLA-B27 positive. HLA-B27 is more common in northern Europeans and is rare in Africans.

At present, nearly 135 different HLA-B27 subtypes have been identified (http://hla.alleles.org/alleles/class1.html). Several studies indicate that AS occurs with the following subtypes: B*2702 (24), *2703 (25), *2704 (26), *2705 (24), *2706 (27), *2707 (28), *2708 (28), *2714 (29), *2715 (29), and *2719 (30). Of these subtypes, HLA-B*2702-5, *2707, and *2708 have been postulated to increase AS risk. Subtypes B*2706 in Southeast Asia, and B*2709 in Sardinia are not associated with AS (31, 32) but, AS cases have been reported to carry these two subtypes (32,33).

GWASs have found a single nucleotide polymorphism (SNP) in the major histocompatibility complex (MHC) gene region (rs4349859) that has been shown to strongly tag HLA-B27 and can identify HLA-B27 in persons of European descent with a sensitivity of 98% and a specificity of 99%. It is argued that the need for HLA-B27 genotyping might be replaced by detection of this SNP (34). This SNP also shows the strongest association with AS. Another SNP (rs13202464) has shown higher sensitivity (98.7%), but lower specificity (98.0%) for HLA-B27 (34). In East Asian populations, rs13202464 has been reported to have high sensitivity and specificity for AS (35).

Population studies indicate that only 2% of HLA-B27-positive individuals develop AS, implying that other factors contribute to disease development. In addition to HLA-B27, associations have been identified between AS and the following loci: IL23R, ERAP1, ERAP2, LNPEP, NPEPPS, CARD9, ANTXR2, IL12B, IL1-1Ra, RUNX3, KIF21B, PTGER4, TKBKP1, TNFRSF1A, IL6R, FCGR2A, UBE2E3, GPR35, BACH2, ZMIZ1, NKX2-3, SH2B3, GPR65, IL27, NOS2, TYK2, ICOSLG, chromosomes 2p15 and 21q22 (34, 36-39), and 2 loci in the Han Chinese population (HAPLN1-EDIL3 and ANO6) (35).

Aminopeptidase genes

Endoplasmic reticulum-associated aminopeptidase 1 (ERAP1), which is also known as puromycin-insensitive leucine-specific aminopeptidase, and aminopeptidase regulator of TNFR shedding 1 (ARTS-1), is a polyfunctional zinc metallopeptidase involved in the final processing, stability, and immunological properties of peptides that bind to MHC class I (MHC-I) (40, 41). It also regulates blood pressure, angiogenesis, as well as macrophage activation (42-44). Shedding of cytokines’ receptors is another ERAP1 function that has been previously postulated to have significant role in AS pathogenesis. This hypothesis had been supported by three investigations, which reported involvement of ERAP1 in shedding of tumor necrosis factor receptor (TNFR)1, IL-6R, and IL-1R2 (45-47). However, as the aforesaid findings have not been replicated by other groups, there is no evidence that ERAP1 may be involved in AS pathogenesis through this mechanism. For instance, Haroon et al., observed no differences in the serum levels of IL-6R, TNFR1, and IL-1R2 among AS patients, following ERAP1 polymorphism (48). The results of another study conducted by Evans et al., which detected no altered levels of soluble TNFR and IL-6R in cell culture supernatants of ERAP1-/- or wildtype mouse spleen cells, were consistent with the findings of the formerly mentioned investigation (34).
ERAP1 presents normally in many tissues and is strongly induced after stimulation by interferon (IFN) and tumor necrosis factor-alpha (TNF-α) (49). GWASs have shown that ERAP1 is a susceptibility factor for AS (26% of AS risk) and other MHC-I associated diseases, such as Behcet’s disease and psoriasis (37).

The Welcome Trust Case Control Consortium and Australo-Anglo-American Spondylitis Consortium (WTCCC-TASC) identified 5 non-synonymous SNPs associated with increased risk of the disease (36). In these SNPs (rs2287987, rs30187, rs10050860, rs17482078, and rs27044), the minor allele frequency at positions rs30187 and rs27044 are significantly greater in AS cases than in controls and confer greater susceptibility to AS (36). Other studies have confirmed the aforesaid associations with AS and have also

### Table 1. Multiple loci identified to increase individuals’ susceptibility to ankylosing spondylitis as reported by previous studies

<table>
<thead>
<tr>
<th>Chromosomal location</th>
<th>Gene</th>
<th>SNP</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>6p21</td>
<td>HLA-B27</td>
<td>rs4349859, rs13202464, rs116488202, rs27044, rs17482078, rs30187</td>
<td>(34)</td>
</tr>
<tr>
<td>5q15</td>
<td>ERAP1</td>
<td>rs10050860, rs27037, rs2287987, rs27434, rs2549782, rs2248374, rs290686, rs11200026, rs10489629, rs1004819, rs11465804</td>
<td>(37), (38)</td>
</tr>
<tr>
<td>1p31</td>
<td>IL-23R</td>
<td>rs1343151, rs12141575, rs10889677, rs11200032, rs1495965, rs2856836</td>
<td>(37), (38)</td>
</tr>
<tr>
<td>2q14</td>
<td>IL1A</td>
<td>rs17261, rs1894399</td>
<td>(76)</td>
</tr>
<tr>
<td>2q11</td>
<td>IL1R2</td>
<td>rs2310173</td>
<td>(37)</td>
</tr>
<tr>
<td>2q14</td>
<td>IL-1Ra</td>
<td>IL1RN*2</td>
<td>(39)</td>
</tr>
<tr>
<td>9q34</td>
<td>CARD9</td>
<td>rs4077515, rs1128905, rs10781500, rs1128905</td>
<td>(34), (38), (84)</td>
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<tr>
<td>22q13</td>
<td>CYP2D6</td>
<td>CYP2D6*4</td>
<td>rs6759298, rs10865331, rs4672495</td>
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<tr>
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<td>-</td>
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<td>KIF21B</td>
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<td>rs6600247, rs11249215, rs6556416, rs6871626</td>
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<td>(34)</td>
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<tr>
<td>12p13</td>
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<td>rs1860545, rs7954567, rs4389526, rs4333130</td>
<td>(34), (38)</td>
</tr>
<tr>
<td>4q21</td>
<td>ANTXR2</td>
<td>rs10440635</td>
<td>(34)</td>
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<td>5p13</td>
<td>PTGER4</td>
<td>rs8070463</td>
<td>(34)</td>
</tr>
<tr>
<td>17q21</td>
<td>TBKBP1</td>
<td>rs39200954</td>
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identified new associations between other SNPs in the ERAP1 gene and disease susceptibility (34,50,51). The association of ERAP1 with AS occurs only among HLA-B27-positive individuals (34). Central to this consideration is the involvement of the enzyme in the trimming and eventual processing of MHC-I-bound peptides. The investigations revealing epistasis of ERAP1 and MHC-I genes in AS and other MHC-I associated diseases as well as the significant effects of ERAP1 polymorphism on the HLA-B27 peptidome, through affecting the expression level of various peptides, altering the balance between epitope production and devastation, and regulating HLA-B27 immunogenicity via the effect of the aforementioned interaction on epitope presentation in both the quantitative and qualitative ways, suggest that the functional interaction between ERAP1 and MHC-I, which is mainly mediated by MHC-I ligands, acts as a major actor in the pathogenesis of MHC-I associated diseases (52).

ERAP2 and LNPEP are other members of the endoplasmic reticulum aminopeptidase family that have sequence homology with ERAP1 and both are encoded on chromosome 5q15 immediately centromeric to the ERAP1 locus. These two loci have recently been described as a possible risk factor for the development of AS in the large International Genetics of AS Consortium immunochip study (38). Several SNPs on the ERAP2 gene have been associated with diseases such as IBD, psoriasis, and acute anterior uveitis (53-55). Among them, rs2549782, rs2248374, and rs2910686 are also associated with AS (38,56,57).

Interleukin-23 Receptor

The human interleukin-23 receptor (IL-23R) gene is located on chromosome 1p31 and encodes a protein that in combination with the IL-12Rβ1 subunit makes a complete receptor for IL-23. IL-23 is a covalently-linked heterodimeric pro-inflammatory cytokine that comprises a unique p19 subunit and the p40 subunit of IL-12 (58). IL-23 is mainly produced by activated antigen-presenting cells and binds to its receptor on CD4+ T-cells. It stimulates the generation and stabilization of Th17 cells that can induce autoimmune tissue inflammation, as shown in experimental autoimmune encephalomyelitis and collagen-induced arthritis (59,60).

The importance of IL-23 in the development of numerous autoimmune diseases has now been well-established. Human Th17 cells produce the cytokines IL-17A, IL-17F and express the IL-23 receptor (IL-23R) (61). Several studies have documented dysregulation of the IL-23/IL-17 immune axis in the peripheral blood and affected tissues of patients with AS (62-64). IL-17 exerts potent pro-inflammatory and joint-destructive activity by stimulating macrophages to produce IL-1 and TNF-α that induce secretion of IL-6 and IL-8 in synovial fibroblasts and up-regulation of the receptor activator of NF-κB ligand (RANKL) that positively regulates osteoclast activity and osteoclastogenesis (Figure 1) (65-67). In patients with AS, this inflammatory process in the axial skeleton and increased osteoblast activity leads to excessive bone apposition that can result in joint fusion (68).

In a recent GWAS, several genetic polymorphisms in the IL23R have been identified to be associated with AS (36). The strongest association was seen for the rs11209032 (odds ratio (OR)= 1.3, 95% confidence interval (CI)=1.2–1.4, P=7.5×10⁻⁷) (36). Several studies have confirmed this association (69,70), however, two investigations, performed in Iranian and Han Chinese populations, have not revealed any significant association between the aforesaid gene variant and AS susceptibility (71,72), which could be partly due to smaller study populations in these two latter studies, or the genetic diversity among different ethnic groups, a phenomenon which warrants further investigations in different ethnicities so as to delineate the precise association between IL-23R SNPs and AS susceptibility. IL-23R genetic variants have been determined to be associated with other chronic inflammatory conditions such as Crohn’s disease, ulcerative colitis, and psoriasis (73,74).

Interleukin-1 gene cluster

The IL-1 family includes two agonists (IL-1α and IL-1β), two receptors (biologically active IL-1R1 and inert IL-1R2), and a specific receptor antagonist (IL-1Ra). IL-1Ra binds to IL-1 receptors and inhibits IL-1α and IL-1β activity and modulates a variety of interleukin 1-related immune and inflammatory responses. These balance between IL-1 and IL-1Ra in local tissues appears to have an important role in the susceptibility to and severity of many diseases (75).

The IL-1 gene family is located on chromosome 2q14. Several SNPs within the IL-1α gene have been reported to increase AS susceptibility, including rs2856836, rs17561, and rs1894399 (76). The IL-1Ra gene is another member of this family with a variable number tandem repeat (VNTR) in intron 2 that causes up to five variants, depending on the number of repeats of the 86-base pair (bp) fragment. The four-repeat (IL-
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IL1RN*1) and two-repeat (IL-1RN*2) alleles are the most common forms with a combined frequency of greater than 95%. Several studies have shown that allele 2 (IL1RN*2) could be associated with increased risk of chronic inflammatory and autoimmune diseases (77,78).

The association between IL1RN*2 and AS was first determined in a study on patients in Scotland (16% in patients with AS vs. 8% in healthy controls; OR=2.3; 95% CI= 1.2–4.4; P=0.01) (39) and was subsequently confirmed in Dutch Caucasians (OR=1.60; 95% CI=1.20–2.80; P=0.031) (79) and Indians (26.3% in patients with AS vs. 16.2% in healthy controls; P=0.015) (80).

Figure 1. Schematics of IL-23/IL-17 immune axis involved in the pathogenesis of ankylosing spondylitis

Caspase recruitment domain-containing protein 9

Caspase recruitment domain-containing protein 9 (CARD9) is a signaling protein that is highly expressed in macrophages and dendritic cells. Its signaling mediates both the mammalian innate immune responses against pathogens and the induction of the adaptive immunity, including activation of Th1 or Th17 cells (81, 82). CARD9 is located on chromosome 9q34. Several polymorphisms in this gene have been reported to be associated with inflammatory conditions such as IBD (83). CARD9 variant rs4077515 has recently been associated with AS (OR=1.2; 95% CI=1.1-1.4; P=0.0004) (84). The association between CARD9 gene variants and individuals’ vulnerability to AS may be due to its central role in the innate immune system and responses to both intracellular and extracellular bacterial/fungal elements (which are plausible environmental triggers for the development of AS) through pattern recognition receptors, such as NOD2, widely known as a pattern recognition receptor for intracellular bacteria. SNPs in the NOD2 gene are strongly correlated with Crohn’s disease as well (85).

Cytochrome P450, family 2, subfamily D, polypeptide 6

The cytochrome P450, family 2, subfamily D, polypeptide 6 (CYP2D6) gene is located on chromosome 22q13 with over 100 documented alleles (http://www.cypalleles.ki.se/cyp2d6.htm). The gene encodes an enzyme that metabolizes 20% to 25% of clinically-used drugs (86). Different variants of the enzyme, including ultra-rapid metabolizers (UMs), extensive metabolizers (EMs), intermediate metabolizers (IMs), and poor metabolizers (PMs), have distinctive metabolic activities. There is considerable variability in the allele distribution among different ethnic groups, resulting in variable percentages of PMs, IMs, EMs, and UMs in a given population (87). Several studies have suggested an association between homozygosity for CYP2D6 null alleles, particularly CYP2D6*4, and susceptibility to AS (88,89). Homozygous null alleles of CYP2D6 encode nonfunctional enzymes responsible for the PM phenotype. It has been hypothesized that poor metabolism of xenobiotics (i.e. metals, drugs, industrial and natural chemicals), known to exert pro-inflammatory effects on T cells, which are in turn critical cells in the etiopathogenesis of B-27 related disorders, might explain the associations between CYP2D6 SNPs and AS pathogenesis (90,91).

2p15

A GWAS in 2010 identified a strong association (P=1.9×10^{−19}) between rs10865331 located on a gene desert on chromosome 2p15 and AS susceptibility (37). Several other studies have confirmed this association (34,92,93). SNP rs10865331 (2p15), maps to intergenic
genomic region. No genes are known to be codified at this locus. As rs10865331 SNP is not contained within the linkage disequilibrium (LD) blocks of its adjacent genes (HapMap #27, NCBI B36 assembly), it seems improbable that this SNP is in correlation with AS due to LD with a causal variant in a conterminous gene. The nearest protein-coding genes to rs10865331 are COMMD1 (copper metabolism domain containing 1), coding a protein known to preclude nuclear factor-kB activation, and B3GNT2 (UDP-GlcNAc: betaGal beta-1,3-N-acetylglucosaminyltransferase 1), encoding for a type II transmembrane protein, which is involved in poly-N-acetyllactosamine chains synthesis. Sánchez et al., have recently hypothesized the aforementioned intergenic region as a part of a long-range transcriptional regulatory factor involved in the modulation of its upstream genes, including COMMD1 and B3GNT2 genes, or, rather, as a proximal promoter component for hitherto unidentified protein-coding genes (94). These hypothesize were derived from an investigation, which revealed rs10865331 to be situated in putative transcription factor binding site (TFBS) for the transcription factor Tal1beta-E47S, only when the G allele is present. In the presence of susceptibility A allele, the binding of Tal1beta-E47S to this domain has been anticipated to be disrupted (94).

**Kinesin family member 21B**

The kinesin family member 21B (KIF21B) gene is located on chromosome 1q32 and encodes a protein that belongs to a family of plus end-directed kinesin motor proteins which help in transporting organelles, protein complexes, and mRNAs to specific destinations along microtubules (OMIM 608322). The major role of this gene in the development of autoimmune conditions may be explained by the involvement of KIF21B in the structural rearrangement of the cytoskeleton imperative for the generation of the immunological synapse, which could result in exerting important role in the induction of immune cells (95). It has been shown that this gene is associated with multiple sclerosis (96) and IBD (97,98). In recent years, GWASs have indicated a new susceptible SNP site, rs2297909, in KIF21B gene related to AS (34). Other studies have confirmed this association (99).

**Runt-related transcription factor 3**

Runt-related transcription factor 3 (RUNX3) is one of three mammalian runt-domain transcription factors encoded by the RUNX3 gene on chromosome 1p36 (OMIM 600210). RUNX3 encodes an important transcription factor involved in CD8 lymphocyte differentiation (100). Several studies have implicated RUNX3 in immune-related diseases such as ulcerative colitis (101), celiac disease (102), Crohn's disease (103), and psoriasis (54). The association between the SNP in this gene and AS has recently been discovered (38). The rs6600247 was shown to be strongly associated with AS ($P=2.6\times10^{-5}$), in the aforementioned study. Whether this gene influence risk of AS directly through affecting CD8+ T cell differentiation is vague and remains to be elucidated.

**Interleukin 12B**

The interleukin 12B (IL12B) gene is located on chromosome 5q33 and encodes the IL12 p40 subunit (IL12B). IL12B heterodimerizes with the IL12 p35 subunit to form IL12 and with the IL23 p19 subunit to form IL23 (OMIM 161561). These two cytokines work in concert to regulate cellular immune response. Several studies have implicated IL12B in a wide variety of autoimmune disorders, including psoriasis (104), Crohn’s disease (105), ulcerative colitis (106), and Takayasu arteritis (107). It has recently been confirmed that rs6556416 ($P=1.9\times10^{-8}$) and rs6871626 ($P=3.1\times10^{-8}$) in the IL12B gene are associated with AS (34,38). Other studies have confirmed this association and suggest a possible role in disease activity (BASDAI, BASFI) (108). SNP rs6871626, located within a small LD block of 40kb in the 5’-flank of IL-12B gene, may contribute towards the immunopathogenesis of AS through interference with mRNA stability or protein translation by interacting with microRNAs (109).

**Environmental factors**

It is not yet fully understood how interactions between genes and environmental factors can cause autoimmune diseases such as ankylosing spondylitis. AS has been shown to coexist with gut inflammation and commonly occurs with IBD in families (110). Approximately, 5% to 10% of patients with AS develop clinically diagnosed IBD, and 70% develop subclinical gut inflammation (111,112). Although the role for the intestinal microbiome has been recommended in the pathogenicity of AS for a while, except for reactive arthritis, a distinct form of spondyloarthropathy (SpA) with self-limiting arthropathy which follows either gastrointestinal infection with Salmonella, Yersinia, Campylobacter or Shigella, or urogenital infection with Chlamydia, no definitive link has been hitherto established (113). A multitude of earlier investigations has indicated increased intestinal permeability in
The pathogenesis of AS is multifactorial, and it is probably based on interactions between several factors including individuals’ genetic susceptibility, and environmental agents such as bacterial flora. Genetic factors have long been concerned in AS, with HLA-B27 as the main susceptibility gene, which exists in 80%-95% of patients with AS. Genome-wide association studies have revolutionized the genetic study of AS in recent years and offers further potential for genetic discoveries in AS. The aforesaid studies, resulted in highlighting non-MHC genes found to be associated with AS pathogenesis, among which, ERAP1 and IL23R have shown significant associations with AS. Additional genes, including CYP2D6, IL1 gene complex, IL12B, RUNX3, KIF21B, CARD9, and gene desert at 2p15, are also implicated in AS proneness. The epistasis of ERAP1 and MHC-I genes in AS and other MHC-I-associated disorders have been a topic of intensive research to date. Conceding the fact that ERAP1 mainly affects MHC-I-associated disorders through its influence on the MHC-bound peptidome, other mechanisms, such as influencing the molecular stability and pathogenetic features of the MHC molecule, altering the vascular properties during inflammation process via its role in both angiogenesis and blood pressure regulation, and inducing macrophage activation, could be also kept in mind as other probable ways through which ERAP1 may take part in the AS pathogenesis.

There is obviously inextricable relationship between environmental factors and AS development. These environmental agents, including either pathogenic bacteria causing gut inflammation, or the aberrant expression of normal gut flora, could be influenced by the host genetic background. However, it is still unclear how interactions between host genes and microbes can predispose patients to the development of AS.

In the current review, the present knowledge on the immunogenetics of AS has been summarized. Improved knowledge of the genetic background together with predisposing environmental factors in patients with AS will probably provide important insights into the pathogenesis of AS. In order to delineate the precise role of the aforementioned gene variants in the development of AS, continuous research is required.

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