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The role of gut microbiota and IL-23/IL-17 pathway in ankylosing spondylitis immunopathogenesis: New insights and updates

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ABSTRACT

Ankylosing spondylitis (AS) is a type of arthritis that is referred to a group of chronic immune-mediated inflammatory diseases termed as seronegative spondyloarthropathies or spondyloarthritides. It typically affects the joints of the spinal and axial skeleton and exhibits common clinical features and genetic factors such as human leukocyte antigen class I allele HLA-B27, the Endoplasmic Reticulum Aminopeptidase 1 (ERAP1), and environmental factors such as microbial triggers. Although the precise etiopathogenic mechanisms that implicate the pathogenesis of AS have still remained to be clarified, the IL-23/IL-17 immune axis has been detected as an important factor in the immunopathogenesis of AS. Moreover, therapeutic options targeting this signaling pathway have been demonstrated to be effective in various other inflammatory diseases that share similar genetic etiology and pathogenetic pathways. In mammalian intestinal, there are trillions of commensal microbes that create the intricate symbiotic relationship with host well-known as the microbiota and play the major role in human health and disease. Several publications have appeared in recent years documenting the pivotal role of the gut microbiota and the IL-23/IL-17 pathway in the pathogenesis of spondyloarthritides. In this review, several points are discussed and summarized including recent advances on the role of the IL-17/IL-23 immune pathway in the pathogenesis of AS, HLA-B27, and ERAP 1 and 2 mediated pathogenesis, AS-related microbiota compositions, and new potential therapies for AS.

1. Introduction

Ankylosing spondylitis (AS) belongs to a typical group of arthritides called seronegative spondyloarthritides (SpAs) due to the lack of rheumatoid factor, which is an autoantibody commonly seen in rheumatoid arthritis. Some disorders in this group include reactive arthritis (ReA), psoriatic arthritis (PsA), arthritis associated with inflammatory bowel disease (SpA-IBD), and undifferentiated spondyloarthritides (uSpA) [1]. AS targets fundamentally the spine and sacroiliac joints and is characterized pathophysiologically by entheseal inflammation, dactylitis (inflammation of the fingers), and uveitis (inflammation of the uvea). Disease progression in AS is described by excessive bone regeneration (ankylosis) and syndesmophyte formation that slowly bridges the gap between joints, and ultimately fuses joints and causes stiffness, pain, significant morbidity, and expanded mortality [2]. The prevalence of AS, depending on the population studied and the geographical area usually ranges from 0.1% to 1.40% [3]. The ratio of male to female in this disease approximately is 2–3:1. The delay between the onset of symptoms and the definitive diagnosis is between 8 and 10 years due to the gradual progression of the AS disease [4]. Since the 1970s till now, although rapid advancement in many research fields has provided acquisition of an important insight of the functional and biochemical features of HLA-B27, its precise role in AS disease is unidentified and there are presently at least four theories that attempt to elucidate it [5]. The Endoplasmic Reticulum Aminopeptidase 1 (ERAP1) has the second genetic association with the attributable risk (30%) after HLA-B27 with attributable risk (50%) with ankylosing spondylitis only in patients with HLA-B27 positivity. The ERAP1 is a protease that trims peptides to optimal sizes for antigen presentation [6]. The disruptions in ERAP1 function cause changes in the expression

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of the classical forms of HLA-B27 and non-classical free heavy chains (FHC) forms of HLA-B27 in antigen presenting cells [7]. Compared to genetic factors, the role of external triggers on disease development has been far less investigated in AS disease. The most recent theory based on HLA molecules is HLA-B27 that helps form the gut microbiome and place HLA-B27 changes on gut microbiota as a mediator in disease susceptibility. Therefore, AS may be a microbiome-driven disorder [8]. Technological advancements in bioinformatics and novel sequencing techniques will help the description of the gut flora and probably provide data on the early phase of AS pathogenesis. In this connection, alterations in gut flora or intestinal dysbiosis can be considered a new therapeutic option for AS. Spondyloarthritides respond significantly to biological agents targeting TNF-α and do not appear to be effective in all patients. Furthermore, recent data, including therapeutic experiments in AS patients, has powerfully implicated a pivotal role for the IL-23/IL-17 pathway in the immunopathogenesis of spondyloarthritis [9,10]. This review also discusses recent advances in the immunologic pathway in the pathogenesis of AS, HLA-B27 and the aminopeptidase mediated pathogenesis, AS-related microbiota, and new potential therapies for AS.

2. Genetics: the first hints of IL-23/IL-17 relevance in AS

The first definitive evidence that IL-23 or IL-17 may be associated with the immunopathogenesis of AS, specifically, was documented through a genetic investigation reported in 2007 that identified a relationship with a single nucleotide polymorphism (SNP) in IL-23-Receptor [11]. This finding was fascinating, as IL-23R had recently been involved in both Crohn's disease and psoriasis, circumstances bearing a clinical overlap with AS. Further, the protective SNP at rs11209026 results in a non-synonymous amino acid alteration (R381Q) that significantly diminishes IL-23R function [12]. IL-23R variant rs11209026 (Arg381Gln) offers protection against AS by indicating diminished STAT3 phosphorylation [13], which eventually prompts an exclusive deficiency in the production of IL-17 [12]. Strangely, this relationship was not regenerated in Han Chinese, who are non-polymorphic at this SNP [14]. Be that as it may, high throughput sequencing later distinguished other disease-related IL-23R polymorphisms in this populace [9,15]. AS has the best heritability of the immune-mediated inflammatory disorder (IMID) approximated from reports on twins as higher than 90% [16]. Genome-wide association studies (GWAS) have discovered a few genes related to ankylosing spondylitis. In one expansive study [17], 20–44% of the genetic susceptibility was due to major histocompatibility complex (MHC) variants (for the most part HLA-B27, and additionally, HLA-B40, HLA-B51, HLA-B7, HLA-A2, and HLA-DPβ1), and well over 100 non-MHC variants. The remaining of genetic susceptibility remained to be identified. Besides, more recently, research has demonstrated that extra environmental triggers (such as microbiomes, infections and medication and toxin-exposure) play a pivotal role in AS immunopathogenesis [18] (Table 1).

3. Role of HLA-B27 in AS

After its discovery in the 1970s, the human leukocyte antigen class I (HLA-B27), was encoded by the B locus in the major histocompatibility complex (MHC). Although 80%-95% of patients with ankylosing spondylitis were HLA-B27 positive, only 5% of positive HLA-B27 people develop AS [23,25,26]. By now, over 140 subtypes of HLA-B27 have been characterized at the level of protein sequence (www.ebi.ac.uk/ipd/imgt/hla/), termed HLA-B*27:01 to HLA-B*27:140. Relationships with ankylosing spondylitis are strongly established for subtypes B*27:02 (Mediterranean), B*27:04 (Chinese), B*27:05 (Caucasian), and B*27:07 (South Asian and Middle Eastern) and may be potential risk factors. The subtypes B*27:06 and B*27:09 (Sardinian and Southeast Asia) are not associated or only weakly associated with AS. These subtypes differ from 1 to 7 amino acids in the mature protein [27,28]. Alterations in these substitutions can alter the intracellular and biochemical behaviors, the repertoire of bound peptides. Besides, the aberrant features of the HLA-B27 heavy chain are subjected to misfolding and dimerizing. Overall, these characteristic features are associated with susceptibility to AS disease [29,30]. Although major role of HLA-B27 in the immunopathogenesis of AS is not fully understood, several mechanisms have been hypothesized.

4. The roles of aminopeptidases in AS

ERAP 1 and 2 are ER-resident aminopeptidases that belong to the oxytocinase subfamily of M1 zinc metallopeptidases. In humans, ERAP1/2 genes, which are encoded on chromosome 5q15, share a 50% sequence homology. ERAP1 has the second highest genetic association with 30% of population attributable risk after HLA-B27 with AS disease [11]. The ERAP1 has been known by many other names including ARTS1 (aminopeptidase regulator of TNF-R1 shedding) and, in the mouse, ERAAP (ERA associated with antigen processing) [31]. The ERAP1 trim amino acid residues at the N-terminal to optimize their length for binding to MHC class I molecules [32]. In addition to this role, it is also involved in stimulating the proteolytic shedding of various cytokine receptors, including TNF-R1, IL-6Rα and type II IL-1 decoy receptor (IL-1RII), hence inhibiting intracellular cytokine signaling [33]. However, this function of ERAP1 was not proven in ERAP1 knockout mice and AS patients [34]. In addition to ERAP1/2, two other members of the aminopeptidases including NPEPPS (puromycin-sensitive aminopeptidase, PSA) and LNPEP (insulin-regulated aminopeptidase, IRAP or placental leucyl/cystinyl aminopeptidase, P-LAP) are associated with AS disease [35]. Evans et al. pointed out that polymorphisms of ERAP1 influence the risk of development of ankylosing spondylitis in individuals with HLA-B27 positivity, hence indicating that the unusual processing of antigenic peptides is important in disease immunopathogenesis [6]. Recently, Liye Chen et al. exhibited that inhibition of ERAP1 reduced HLA-B27 free heavy chain expression by PBMCs and inhibited Th17 expansion seems to be a potential therapeutic approach for AS [36]. The ERAP1 association is limited to HLA-B27-positive AS while, ERAP2 are associated with HLA-B27-negative AS, showing that peptides presented by HLA-B27 might be of relevance [6]. ERAP1 polymorphisms may play a pivotal role in the theories involved in AS pathogenesis. Five SNPs have been identified in ERAP1, which include rs30187, rs27044, rs2287987, rs10050860, and rs174820 [37,38]. The role of ERAP1 variants on ER stress and HLA-B27 misfolding is not known. With this view, it is unclear whether ERAP1/2 change disease risk via the production of arthritogenic peptides, alteration of HLA-B27 free heavy chains, and homodimers and misfolding in ER. Therefore, theories for how ERAP1 involved in AS must align with the suggested roles for HLA-B27 in AS pathogenesis. The following theories exist to describe how HLA-B27 involved to AS.

5. Pathogenic theories of HLA-B27

5.1. Arthrogenic peptide theory

This theory proposed that peptides derived from arthritis-causing pathogens (Arthritogenic Peptide), specifically those presented by HLA-B27, induces T $CD8^+$ immune responses. In fact, this theory represents Molecular mimicry and Cross-reaction. Firm data to prove this "arthritogenic peptide" hypothesis has never been obtained, considering the fact that there is a clear proof that $CD8^+$ T cells do not prevent disease phenotype in the HLA-B27-transgenic rat model [39,40] and another reason is that no specific peptide targeted by $CD8^+$ T cells has been detected [41]. Recently, Purcell et al. investigated a great peptide repertoire from AS-related alleles and non-AS-related HLA-B27 alleles; however, they were unsuccessful in recognizing qualitative changes in their peptide repertoire [42]. This theory recently challenged with