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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

Table 1
Genetic loci associated with AS.

Gene	Locus	SNP	Putative Function	Reference
IL-23R	1p31	rs11209026	Cell activation/differentiation	[11]
		rs12141575	Cell activation/differentiation	
IL-6R	1q21	rs4129267	Th17 cell differentiation, other immunological effects	[19]
IL-1R2-R1	2q11	rs4851529	IL-1 response	[20]
		rs2192752	IL-1 response	
PTGER4	5p13	rs12186979	Induction of IL-23 expression, driving activation/differentiation of IL-23R-expressing cells; bone anabolism	[6]
IL-7R	5p13	rs11742270	Lymphocyte differentiation	[20]
ERAP1	5q15	rs30187	Peptide trimming prior to HLA class I presentation	[11]
ERAP2	5q15	rs2910686	Peptide trimming prior to HLA class I presentation	[20]
IL-12β	5q33	rs6871626	Activation/differentiation of IL-23R- expressing cells	[21]
		rs6556416	Activation/differentiation of IL-23R- expressing cells	
HLA-A*0201	6p21.3	rs2975033	Peptide presentation to T cells	[20]
HLA-B	6p21.3	rs116488202	Peptide presentation to T cells; peptide misfolding leading to endoplasmic reticulum stress reaction; homodimer formation leads to NK cell activation	[22–24]
HLA-DRβ1*0103	6p21.3	rs17885388	Peptide presentation to T cells	[20]
HLA-DPβ1	6p21.3	rs1126513	Peptide presentation to T cells	[20]
CARD9	9q34	rs1128905	Th17 cell activation after β-glucan exposure	[6]
IL-27	16p11	rs75301646	Balance between Th17/Th1 cell differentiation	[20]
		rs35448675	Balance between Th17/Th1 cell differentiation	
TBX21	17q21	rs11657479	ILCs differentiation	[6]
TYK2	19p13	rs35164067	Signaling from cytokine receptors, including IL-23R	[20]

IL-23R, interleukin 23 receptor; ILC, innate lymphoid cell; SNP, single-nucleotide polymorphism; TCR, T-cell receptor; Th1, T helper type 1; Th17, T helper type 17.

reports of Anti-CD74 antibodies (directed against the class 2-associated invariant-chain peptide, CLIP) in 85% of axial spondyloarthritis compared whit 8% of the control group [43]. Nevertheless, these data require approval in bigger studies.

5.2. HLA-B27 misfolding/unfolded protein response pathway theory

This theory states that HLA-B27 may be misfolding due to impairment of intracellular disulfide bonds formation in the endoplasmic reticulum (ER) environment, probably due to the incorrect formation of intermolecular covalent bonds in the quaternary structure. With this feature, the HLA-B27 can have a “toxic effect” on the cell and induce cellular stress responses [44,45]. These responses are known as UPR and ER overload response (EOR) [46]. These cellular responses can undermine the normal conditions of the cell and lead to the production of inflammatory cytokines such as IL-1 [44], IL-23 [47], and INF-β [48] involved in the pathogenesis of ankylosing spondylitis and activate the IL-23/IL-17 immune pathway. UPR pathway restores homeostasis of ER to misfolding proteins while the EOR tries to revive normal ER function during protein accumulation. Interestingly, unlike humans rats present marked spondyloarthritis features in HLA-B27 transgenic. It has been demonstrated that aberrant folding and unfolding of HLA-B27 and UPR pathway activation can be responsible for an elevated IL-23 expression by myeloid cells and activation of Th17 cells that express KIR3DL2, respectively [47,49,50]. However, the molecular mechanism remains to be clarified. Recently, in support of this hypothesis, Rezaiemanesh et al. showed an up-expression of UPR pathway genes (CHOP, BiP, and XBP1) and IL-23 in M-CSF-derived macrophages from AS patients compared to healthy controls [51]. Recently, it has been suggested that autophagy pathway, processes responsible for the degrading and recycling of cellular organs, instead of UPR pathway regulate the gut production of IL-23 in AS disease [52].

5.3. HLA-B27 heavy chain homodimers/free heavy chains theory

Either the major role of HLA-B27 in Ankylosing spondylitis is the presentation of autoantigen to $CD8^+$ T-cells − which is suggestive of autoimmune disease − or is activating the innate immune responses secondary to bacterial or mechanical stress in keeping with autoinflammatory disorder remains to be clarified [53]. It seems that the unusual biochemical properties of HLA-B27 molecules provide a better explanation for their link with spondyloarthritides. Specifically, HLA-B27 molecules demonstrate an elevated tendency to misfolding and to form unusual disulfide-linked heavy chain homodimers via the cysteine residue at position 67 [54]. Liye Chen et al. investigated specific residues variations in the HLA-B heavy chain, most of the association with AS could be elucidated by variations affecting amino acid position 97, which locates at the bottom of the peptide-binding groove, in the C terminal pocket. Asn (N) at position 97 confers the highest risk of AS through increased HLA-B27 free heavy chains (FHCs) expression [55]. Several forms of HLA-B27 free heavy chains (FHCs) are expressed as monomer and dimer at the surface of peripheral blood mononuclear cells (PBMCs) and leukocytes following the endosomal recycling phenomenon [56]. Homodimers and FHCs are bound to immune receptors in T cells and natural killer cells (NKs). These receptors include KIR3DL1, KIR3DL2, and LILIRB2 [57]. In fact, the biological function of the HLA-B27 FHCs is because of its high binding affinity compared to the classical HLA-B27 binding to these receptors [58]. Both these KIR and LILR receptors play important roles in immune hemostasis, including increasing T cell survival, differentiating macrophages and DCs, and inducing Treg cells [59]. The KIR3DL2/HLA-B27 FHC reaction can have pro-inflammatory effects in both NK cells and T cells and is associated with increased Th17 phenotype in AS disease [36] (Fig. 1).

5.4. The IL-23/IL-17 pathway theory

For over 10 years, the predominant pattern of AS pathogenesis has been concentrated to prove the importance of the Th1 pathway and TNF-α. The efficacy of anti-TNF agents for axial disease provided strong proof for this model when no different treatments were effective for this manifestation. The discovery of IL-23 and other members of the IL-17 pathway, however, revealed additional mechanisms and targets. Information on the involvement of IL-23/Th17 immune axis in spondyloarthritides is derived from narrow clinical investigations [60]. It has been described that polymorphisms in the receptor for IL-23 are related with ankylosing spondylitis; thus, IL-23 and its receptor potentially play a key role in the susceptibility to disease and the immunopathogenic of AS [19]. Serum concentrations of IL-23 and IL-17 have been found to be at high levels in patients with AS [61]. Moreover, studies reported that macrophages AS patients produce more levels of IL-23 in reaction to lipopolysaccharide (LPS) [62]. The existence of $IL-17^+$ cells has also been reported in AS facet joints [63]. In addition to

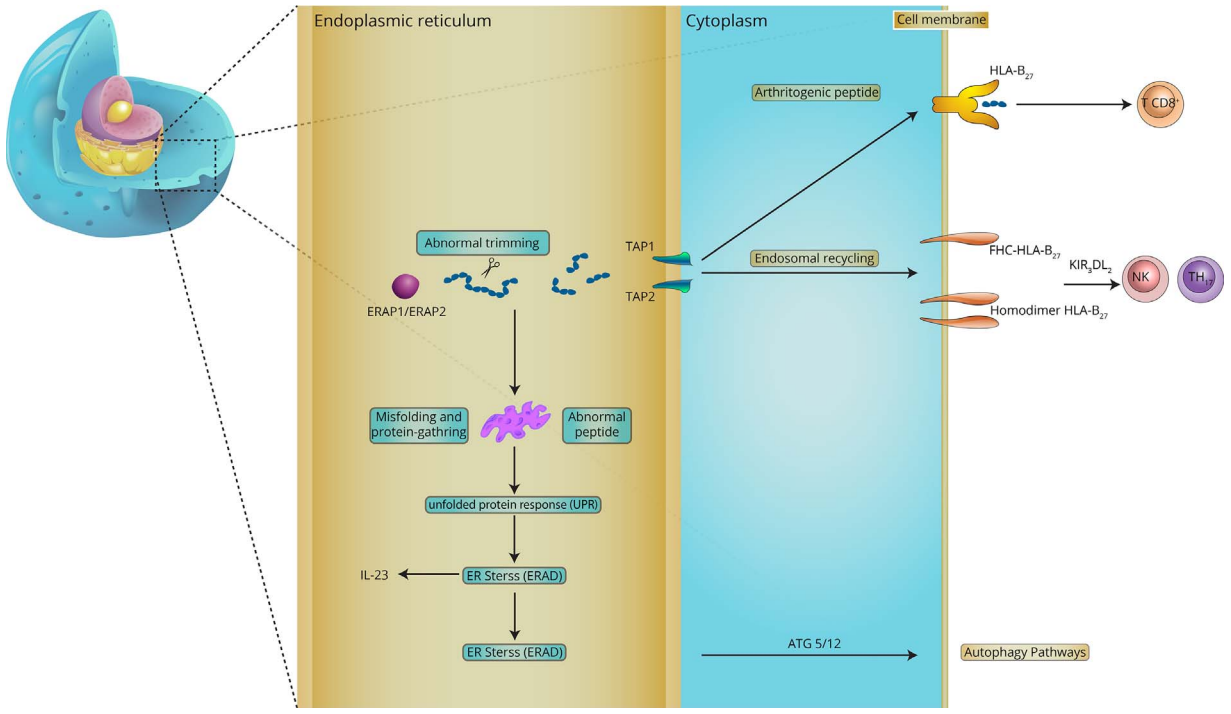

Fig. 1. Hypotheses of how HLA-B27 and ERAP ½ could cause disease in ankylosing spondylitis. HLA-B-27 presents arthritogenic peptide to CD8 + T cells contribute to the induction of disease, peptides enter the endoplasmic reticulum (ER) and additionally are trimmed by endoplasmic reticulum aminopeptidase 1 (ERAP1), and ERAP2, abnormal peptide complexes can form due to altered ERAP1 or ERAP2 trimming, cause unusual free heavy chains (FHC) and homodimers HLA-B27 via endosomal recycling on cell membrane. Subsequently can lead to activation of natural killer (NK) cells and Th17 cells via killer cell immunoglobulin-like receptors (KIRs) especially with KIR3DL2. Unstable peptide-HLA-B27 complexes can gather in the ER, activate the unfolded protein response (UPR), ER stress, ER-associated protein degradation (ERAD) and autophagy pathways.

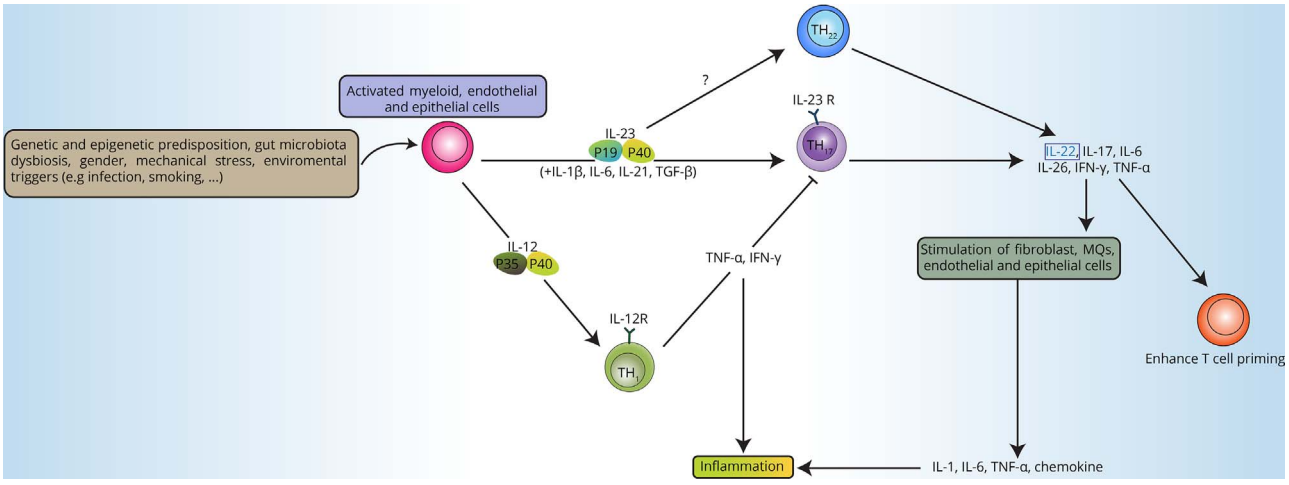

Fig. 2. The IL-23/17 pathway in immunopathophysiology of ankylosing spondylitis. The interaction genetic and epigenetic factors, especially Th17 and Th22 cells, with several types of stress (including mechanical stress, gut microbiota stress, and environmental triggers) leads to the production of proinflammatory cytokines (i.e., IL-17, IL-22, TNF-α, and IL-23).

AS, high levels of IL-17 have been reported in the synovial fluid of patients with undifferentiated SpA and reactive arthritis [64]. Although preclinical studies suggested this axis to be involved in both rheumatoid arthritis and spondyloarthritis, human translational reports and clinical trials exhibited that IL-23 and IL-17 are major cytokines in only axial spondyloarthritis and psoriatic arthritis [65] (Fig. 2).

Many other IL-23/IL-17 immune axis-related genes such as IL-1R1, IL-2R, IL-6R, IL-12B, IL-27, STAT3, TYK2, CARD9, and RUNX3 have also been involved in AS [66], suggesting the potential significance of IL-17/IL-23 axis in the ankylosing spondylitis. The combination of epigenetic and genetic fine mapping of causal variants related to autoimmune diseases further uncovered the relatedness of AS, psoriasis and inflammatory bowel diseases; all three disorders demonstrated a Th17 cell-specific epigenetic hallmark for the known variants [67]. Studies on animals also exhibit that IL-23-driven inflammation can lead to bone regeneration in AS. The findings from the proteoglycan-induced spondylitis (PGISp) mouse model of AS further suggests that bone regeneration and inflammation extend consecutively and not in a parallel direction. Inflammation leads to intervertebral disk destruction and provides a precondition for axial disease progression [68]. Findings of this study [68] further suggest that inflammation causes expanded osteoproliferation, which consequently leads to modified bone phenotypes in AS. Additional support for the significance of IL-17 in spondylitis is provided by the prophylactic administration of anti-IL-17 antibodies, which obstruct the development of ankylosis in male SKG1 mice [69]. In addition to spondyloarthritides, in other autoimmune diseases, for example in the study of Babaloo et al. [70,71] showed an increase in serum levels and the expression of IL-17A and IL-17F mRNA

in peripheral blood mononuclear cells (PBMCs) of patients with multiple sclerosis compared to the controls. Taken together, these studies indicate that the IL-23/IL-17 immune axis is centrally involved in the immunopathogenesis of ankylosing spondylitis and that targeting this axis may be an effective approach in this group of disorders. Studies have demonstrated inflammation of the entheses (enthesitis) to be IL-23-dependent [72–74]. In mice, up-expression of IL-23 *in vivo* stimulated the development of the characteristics of human AS, including enthesitis and bone regeneration [72]. Description of the IL-23 responsive cells show a subset of RORγt^+CD3$^+$IL-23R$^+$CD4$^-$CD8$^-$ resident T cells that produced IL-22 and IL-17 expose to IL-23 [72]. Furthermore, spondylitis and arthritis were mediated by T-cells and were dependent on IL-23 [73]; moreover, enthesitis which are likewise especially dependent on IL-17 and IL-22 [74,75]. Systemic up-expression of IL-23 in an animal model induced an enthesitis, which is similar to the one seen in spondyloarthritis, confirming the idea that IL-23 might play a pathogenic role for inflammation of the gut [72]. In the context of AS, it is of special interest that these cells (RORγt^+CD3$^+$IL-23R$^+$CD4$^-$CD8$^-$ resident T cells) produce IL-17 to activate osteoclasts but could also secrete IL-22 upon exposure to IL-23, which can activate osteoproliferation. IL-17 suppresses bone regeneration, though the precise effect of IL-17 on bone regeneration still needs to be elucidated [76]. Investigation of samples from AS patients revealed that the abundant of Th17 [77,78], Th22 [77] and γ/δ T cells [79] increase in the peripheral blood and there were high levels of IL-17 [61,80,81] and IL-23 [9,61,82] in the serum and synovium. It has been additionally revealed that the KIR3DL2$^+$ Th17 cells, which are responsive to HLA-B27 free heavy chain (FHC), are expanded in the peripheral blood of AS patients [36]. The majority of these previous reports on Th17 cells in AS concentrated on patients with established disease, whereas pathogenic events in the early phase of AS were not underlined [83]. Additional studies are important to resolve these contradictory results. It is well proved that in patients with AS, men are more likely than women to have radiographic changes in the sacroiliac joints and increased CRP, but the two sexes experience similar levels of pain and functional damage. The basic biology responsible for these differences is undefined. These data suggest different agents of disease in male and female AS patients and may account for the more severe bone phenotypes, which are often observed in males. Interestingly, in this case, the sex bias in terms of IL-17 axis-related gene hallmarks were shown to be independent of sex hormone levels [84]. Additional studies are required, however, to better understand the basic biology responsible for the sexual dimorphism in the Th17 signature in AS. Data from previous studies on human beings [63,85] also suggested that in AS, apart from Th17 cells, innate immune cells can serve as a key source of IL-17 particularly in target tissues. The recognition that innate lymphoid cells (ILCs) stimulate inflammation in a range of disorders is now apparent. With respect to AS, emerging evidence suggests that ILC3 cells that respond to IL-23 also serve as key sources of IL-17, IL-22, and other related cytokines. Besides, it is suggested that this population is expanded in the joints of patients with psoriatic arthritis but not those with reactive arthritis [86,87]. In AS patients, IL-17 and IL-22-secreting NKp44+ ILC3 cells were expanded in the intestinal, synovial fluid, bone marrow and peripheral blood [88]. It is worth mentioning that ILC3 cells present in synovial fluid, bone marrow and peripheral blood of AS patients expressed the $\alpha 3\beta 7$ integrin, suggesting that these cells are presumptively developed in the intestinal. The ILC3 cells secrete distinct cytokines in the individual tissue compartments, although IL-22 production augmented in most specimens, while only a small percentage of cells in peripheral blood expressed IL-17 alone or in combination with IL-22 [89,90]. These studies confirm the potential significance of ILCs-lymphoid axis in disease pathogenesis and raise the possibility that they may be used for therapeutic purposes.

In the synovium of patients with AS, the abundant of c-Kit$^+$ mast cells increased compared with that of rheumatoid arthritis (RA). Analyses of bone biopsy samples of the sacroiliac joints from patients with ankylosing spondylitis indicated staining for IL-17. However, it appears that this local IL-17 production is by cells of the innate immune system rather than by adaptive immune system [63]. Some of these cells have been described as c-Kit$^+$ mast cells in tissue smear samples from the synovium [85]. Mast cells, which were the primary IL-17$^+$ cell population in the AS synovium, expressed significantly more IL-17 than their analog ones in the RA synovium [85]. Important to notice, clinically effective anti-TNF therapy did not regulate the mast cell/IL-17 immune pathway in AS [85]. Curiously, clinically effective anti-TNF therapy did not regulate the mast cell/IL-17 immune pathway in AS [85]. These data suggest that innate immune response might be of greater relevance to AS immunopathogenesis than the Th17-mediated adaptive immune response, raising the question that whether inflammation in AS is basically more auto-inflammatory than autoimmunity (MHC-I-Opathy Hypothesis) [63,91–93].

6. MHC-I-opathy hypothesis

According to the idea of “MHC-I-Opathy”, emerging immunogenetic and immunopathogenic data suggest immunological diseases continuum involving both innate and adaptive immunity in HLA-B27 related disorders as well as in Behçet disease, ankylosing spondylitis, and psoriasis − all disorders which are known to the boundary between auto-inflammatory and autoimmunity. This unifying hypothesis elucidated that there are a newly-termed group of disorders that is defined by (1) a genetically HLA-I related class (2), tissue-specific triggers such as mechanical stress (injury and microdamage) and localized activation of innate immune response at sites of barrier disturbed, and (3) activation of innate lymphoid cells axis stress surveillance through Th17 immune responses [94].

7. Gut microbiota theory

The human digestive tract is not a perfect barrier. It is comprised of a single layer of intestinal epithelial cells (IECs) that creates a physical and biochemical barrier against commensal and pathogenic microorganisms and separates the intestinal lumen from the lamina propria [95]. Intestinal epithelial cells produce soluble agents that are important to gut homeostasis. Examples of such agents are anti-microbial peptides and mucins (e.g., lysozymes, lipocalins, defensins, and cathelicidins) and C-type lectins (e.g., RegIIIγ). A group of the RegIII family of gut C-type lectins is antibacterial proteins that play a key role in preserving microbiota-host homeostasis in the mammalian intestinal [96–98]. Secretion of these molecules into luminal crypts is thought to suppress microbial invasion into the crypt microenvironment and restrict microbiota-epithelial cell contact [97,99]. In the human gut, there are trillions of bacteria that organize the complex homeostatic ecosystem and play the pivotal role in intestinal health including the development of the immune system, intestinal epithelial barrier, and food digestion [100]. The human gut microbiome of AS patients are obviously dissimilar from that of healthy controls [101]. The healthy human gut is controlled by the presence of four families of bacteria: Bacteroidetes (most abundant), Actinobacteria, Proteobacteria, and Formicates [102]. The word “Microbiota” refers to the population of symbiotic and pathogenic bacteria at a special anatomical position in the human body, and “Microbiome” mentions to the collective genes encoded by all bacteria of that special position. In current years, with the development of microbiome research, alterations in the composition of gut microbiota have been correlated with a diversity of autoimmune disorders, and several roles linking these together have been supposed such as immune response activation, change of intestinal permeability, and molecular mimicry [103,104].

7.1. Increased gut permeability

Perseverance of intestinal and microbiota homeostasis is

progressively recognized to be critical in maintaining and promoting the general health [105]. The effective crosstalk between intestinal epithelial cells, microbiota and the immune system is significant to gut homeostasis, but it is also suggested to play a role in disease pathogenesis [106]. In AS disease, tight junctions between intestinal epithelial cells are dysregulated, leading to increased permeability between intestinal epithelial cells termed a leaky gut [107,108]. Gut leaky of the intestinal epithelial cells can lead to damage the intestinal mucosal immunity as well as increasing entrance of gut microbiota, proinflammatory cytokines, and chronic inflammatory phenotype of AS [109]. Studies performed on AS patients and their first-degree relatives and in animal models showed that they also increase gut permeability, suggesting that they may allow a greater expose systemically to gut microbes [110,111]. Lipopolysaccharide (LPS) will cause a dangerous systemic inflammatory response if entrancing the circulation system. Some primitive proof has proposed that high serum levels of intestinal fatty acid-binding protein, LPS, LPS-binding protein, and zonulin can be present in AS, which is importantly related with impairment of the gut permeability and the gut vascular barrier [112,113].

7.2. IL-23/Th17 axis

A current study [114], additionally, revealed that AS patients exhibit altered dendritic cells, macrophages, and T-cell populations, further indicating the role of IL-23 in gut inflammation. In another study, IL-17 and IL-22 secreting by ILC3 cells were present in greater number in the gut of AS patients compared with that of the healthy controls [88]. ILC subsets are specialist effector cells involved in the modulation of innate immune system and inflammation via the production of especial chemokines and cytokines. These ILC3 cells appeared to chiefly increase in the more inflamed gut of the AS patients, and TNF-blocker agents were shown to be effective in decreasing their frequency in the gut [90]. Accordingly, the results show that the existence of a gut-bone pathway in AS whereby ILC3 may be the key effector secreting IL-17, IL-22, and possibly other inflammatory cytokines. IL17, IL-22, and IL-23 have been suggested to be involved in the gut-bone axis of inflammation. A growing body of recent literature revealed the strong association between gut inflammation and spondylitis [18,115] that involves HLA-B27 alleles and the IL-17/IL-23 immune axis as central pathogenic factors. Studies on the HLA-B27-transgenic rats show that intestinal inflammation in these rats simultaneously occurs with an increased expression of IL-17 and IL-23 in the colonic tissues and similarly in mice, wherein segmented filamentous bacteria (SFB) increase the expansion of pro-inflammatory Th1 and Th17 cells in the small intestine [47,116]. It remains indistinct whether changes in innate mucosal defenses lead to alterations in intestinal resident microbial flora or whether early changes in the microbiome create gut host responses. Current studies, additionally, show an altered gut microbiota in the HLA-B27-transgenic rats compared with wild-type rats [117]. About 5–10% of patients with AS were clinically diagnosed with inflammatory bowel disease (IBD) in more than 70% of patients with AS indicate subclinical intestinal inflammation [118]. Salzman et al. argued that α-defensins modulate mucosal T-cells response by regulating the commensal composition, but not the total numbers of bacteria in the gut microbiota. By examining the gut microbiota of mice carrying the human α-defensin gene, they demonstrated important α-defensin-dependent alterations in the commensal composition that lead to fewer IL-17 producing lamina propria T lymphocytes [119]. The mechanism by which the microbiota affects IL-17-producing lymphocytes activation is still being identified. In Ivanov's study, it was shown that serum amyloid A, produced in the terminal ileum can cause Th17 differentiation of CD4+ T lymphocytes. It has also been shown that the development of Th17 lymphocytes in the intestine is stimulated by microbiota-induced IL-1β production [120]. Colonizing with Clostridial species has been shown to stimulate intestinal TGF-β production and, in turn, increase IL-10$^+$ Treg cells activation. Clostridial colonization of neonatal mice reduced the severity of colitis by using oxazolone and decreased serum IgE levels in adulthood [121]. So, it is likely that alterations in gut microflora or invasion of the gut by pathogenic bacteria affect the balance of IL-17 and IL-23 producing cells, affecting susceptibility to local and systemic immune-mediated diseases. Overall, these findings suggest that the disruption in the IL-23/IL-17 axis activation is a major characteristic in AS patients and targeting the IL-23/IL-17 pathway could probably be a therapeutic option for AS patients.

7.3. Molecular mimicry

HLA-B27 itself may have cross-reactivity with Gram-negative bacteria. For example, Klebsiella pneumonia is a candidate bacterium involved in the development of AS, which is elevated in stools of patients with AS [122]. AS patients with a higher frequency of Klebsiella pneumoniae in intestinal had Crohn's-like lesions in the ileocecal regions [123]. HLA-B27 and Klebsiella pneumoniae have been found to show immunological cross-reactivity and molecular similarity with Klebsiella pneumoniae nitrogenase reductase, which may be an explanation for the elevated antibody seen in AS against both HLA-B27 peptide and Klebsiella pneumoniae [124]. However, no important immune response to Klebsiella pneumoniae was found in patients with AS [125]. Elsewhere, another enzyme, Klebsiella pullulanase, also showed molecular mimicry with HLA-B27 [126]. Moreover, the major genetic factors in AS, HLA-B27 might predispose AS by changing the gut microbiome. Of particular relevance, was that the finding of dysbiosis (i.e., a change in the microbial composition) in the intestinal microbiome of AS patients can be distinguished by increased higher frequency of five families of bacteria via 16S rRNA sequencing including Lachnospiraceae, Bacteroidaceae, Rikenellaceae, Ruminococcus, and Porphyromonadaceae and decreased frequency of two families of bacteria (i.e., Veillonellaceae and Prevotellaceae) in the terminal ileum of AS patients compared with healthy controls [127]. More recently, in the study of Berman et al. it was shown that the microbiota composition was significantly different between AS patients and healthy controls, showing a two to threefold increase in the frequency of Ruminococcus gnavus in AS group compared with healthy controls [128]. Overall, several groups of studies strongly imply gut flora as a possible trigger for onset and progression of AS. Thus, description of the intestinal resident microbial flora associated with AS and the precise mechanism for the functional role of gut microbiota in disease progression should be the focus of investigation in the future. The discovery of a special profile of gut microbiota in AS disease will aid uncover novel diagnostic markers and therapeutic targets. The strategies for targeting the gut microbiota are summarized in Table 2.

8. AS management and therapy

8.1. Interleukin-23 antagonists: Ustekinumab and Bi655066

Ustekinumab (a fully human monoclonal antibody against the p40 subunit of IL-12 and IL-23) has also proved to have therapeutic benefits in the treatment of AS. Ustekinumab administration was demonstrated to be highly efficient in diminishing active inflammation of the sacroiliac joints and the spine (diminutions of 41% and 31%, respectively) in therapy responders based on MRI assessment [143,144]. Also, a fully human IgG1 monoclonal antibody against the p19 subunit of IL-23 (i.e., BI655066) is under investigation in a 48-week phase III randomized, double-blind, placebo-controlled clinical trial in patients with AS (ClinicalTrials.gov ID – NCT02047110) [145] (Table 3).

8.2. Interleukin-17 antagonists: secukinumab, ixekizumab, and brodalumab

Since their discovery, Th17 cells have been suggested in ankylosing spondylitis. Blocking the Th17 pathway, either by suppressing IL-17 directly or through inhibiting Th17 cell differentiation, is now a field of

Table 2
The targeting strategy of the gut microbiota.

The targeting Strategy	Mechanism	Example's
Antibiotics usage	The reducing of microbial diversity, immunosuppression, translocation, metabolism, enzymatic degradation [129]	Sulfasalazine [130], Moxifloxacin [131], Vancomycin [132], Azathioprine [133]
Malnutrition	The reducing growth of the gut microbiota such as Bifidobacterium, Clostridium [134]	Low-starch diet [123]
Probiotics and Prebiotics	The immunomodulation of intestinal microbiota, strengthening of the epithelial barrier, inhibit colonization by pathogens, secretion of antimicrobial substances and neurotransmitters [135]	Lactobacillus casei [136], Lactobacillus rhamnosus GG [137], Lactobacillus bifidus [138]
Fecal Microbial Transplantation	The restoring a stable microbial community of the gut [139]	IBD, diabetes, allergic diseases and ulcerative colitis [140–142]

IBD: Inflammatory bowel disease.

comprehensive therapeutic development. Secukinumab is a fully human monoclonal antibody (mAb) that discriminatively binds and neutralizes IL-17A. In an earlier phase II randomized double-blinded placebo-controlled trial, secukinumab was efficient in controlling symptoms of AS patients [146]. Subsequent phase III trials provided further findings of its effectivity in AS patients [147]. In phase III trials, secukinumab was effective for patients with ankylosing spondylitis [147]. Besides, on the basis of the results of these trials, it has now been approved for ankylosing spondylitis in Europe, the USA, and other parts of the world. A dose of 300 mg secukinumab, which is more effective than 150 mg for the treatment of psoriasis, has not yet been investigated for ankylosing spondylitis. Although no head-to-head trial has been done so far, the exhibited efficacy of secukinumab appears to be close to the response rates seen in TNF-blocking trials undertaken in a similar patient group. Secukinumab was also effective in a subgroup of patients for whom TNF-blocking therapy failed or stopped for other reasons [148]. However, the place of IL-17 inhibitors in the therapy of axial spondyloarthritis remains to be defined as larger clinic experience grows. In addition, it is not known whether IL-17 inhibitors might decrease the progression of bone regeneration, as was considered on the basis of the results of one uncontrolled ankylosing spondylitis trial [149]. Ixekizumab is a humanized monoclonal antibody that neutralizes IL-17A and has shown a similar efficacy to date in psoriasis and AS. In addition to cytokine neutralization, IL-17 suppression can be performed by blocking the IL-17 receptor. Brodalumab as a human monoclonal antibody that binds to the IL-17A receptor is needed for forming the dimeric receptors necessary for IL-17A, IL-17F, IL-17A/F, IL-17C, and IL-17E (IL-25) signaling [150,151].

9. Conclusion

The pathogenesis of AS is the outcome of a combination of host genetic and environmental factors. Currently, four major theories exist to elucidate pathogenic mechanism of AS. However, the molecular mechanism of these hypotheses remains to be fully described. Cumulative evidence implicates the existence of IL-23/IL-17 pathway, NF-kβ pathway activation, and T cell phenotype in chronic immune-mediated inflammatory arthritis. Monoclonal antibodies and small molecules inhibitors targeting distinctive targets such as STAT3, RORγt, and ACT1 pathway predominate the recent clinical development of agents, which can successfully block IL-23 activity. Moreover, there are preliminary but promising results in blocking IL-17A activity.

Table 3
Targeting the IL-17/IL-23 axis.

Target	Therapeutic Agent	Type/Mechanism	Disease	Phase/Status	Reference
IL-17	Secukinumab (also known as AIN457)	mAb to IL-17	Psoriasis	Phase III	NCT01544595
			Rheumatoid arthritis	Phase III terminated	NCT01770379
			Ankylosing spondylitis	Phase III completed	NCT01358175
			Psoriatic arthritis	Phase III	NCT01892436
			Asthma	Phase II terminated	NCT01478360
			Multiple sclerosis	Phase II terminated	NCT01874340
			Type 1 diabetes	Phase II terminated	NCT02044848
			Crohn's disease	Phase II terminated	NCT01009281
	Ixekizumab (also known as LY2439821)	mAb to IL-17	Psoriasis	Phase III	NCT01597245
			Rheumatoid arthritis	Phase II completed	NCT00966875
	Brodalumab (also known as AMG 827)	mAb to IL-17R	Psoriasis	Phase III terminated	NCT01708590
			Psoriatic arthritis	Phase III completed	NCT02024646
			Asthma	Phase II terminated	NCT01902290
			Crohn's disease	Phase II terminated	NCT01150890
IL-23 (p19 subunit)	Guselkumab	mAb to IL-23	Psoriasis	Phase II completed	NCT01483599
			Rheumatoid arthritis	Phase II completed	NCT01645280
	Tildrakizumab	mAb to IL-23	Psoriasis	Phase III	NCT01729754
	BI 655066	mAb to IL-23	Ankylosing spondylitis	Phase II completed	NCT02047110
			Crohn's disease	Phase II completed	NCT02031276
			Psoriasis	Phase II completed	NCT02054481
IL-12 and IL-23 (p40 subunit)	Ustekinumab	mAb to IL-12 and IL-23	Psoriasis	Approved 2009	NA
			Crohn's disease	Phase III completed	NCT01369329
			Ankylosing spondylitis	Phase II completed	NCT01330901
			Rheumatoid arthritis	Phase II completed	NCT01645280
			Psoriatic arthritis	Phase III completed	NCT01009086
			Multiple sclerosis	Phase II completed	NCT00207727
			Graft-versus-host disease	Phase II	NCT01713400
			Atopic dermatitis	Phase II completed	NCT01945086

IL-17A, interleukin-17A; IL-17RA, IL-17 receptor A; mAb, monoclonal antibody; IL-23p19, p19 subunit of IL-23; NA, not applicable; TNF, tumor necrosis factor. *Clinical trial identifiers are provided for reference; please see the ClinicalTrials.gov website for further details. Data are accurate as of July 2017.

Comprehension of IL-23 and IL-17 may help control the disease progression of AS. Additional research is required to better describe the role of crucial aminopeptidases and gut inflammation in AS pathogenesis and to explain how, when and where cytokines such as IL-17, IL-22 and IL-23 influence the pathogenesis of AS. Molecular-based techniques such as metagenomics, metatranscriptomics, and metaproteomics profiling studies have provided more extensive and exact identity of the species composition of gut microbiota compared to traditional culture-based techniques. However, many challenges still exist for meaningful discovery in this field. Comprehending the pathways through which the gut microbiota affects the disease state can be most likely done via the immune responses and biomechanical stressors and may help the future progression of treatments. Altering the intestinal microbiota may form another option to regulate bowel immunology. Probiotics, prebiotics, low-starch diets, and fecal microbial transplantation can reconstruct deficient strains, thereby renewing the balance and diversity of the intestinal microbiota. A more profound understanding of the pathogenesis of this circumstance can pave the ground for progressing toward more effective therapies and developing novel therapeutic strategies to target the gut microbiota and the IL-23/IL-17 immune pathway.

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