J Rheum Dis 2023;30(4):220-233
https://doi.org/10.4078/jrd.2023.0041
pISSN: 2093-940X, eISSN: 2233-4718

Review Article

Updates on ankylosing spondylitis: pathogenesis and therapeutic agents

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Ankylosing spondylitis (AS) is an autoinflammatory disease that manifests with the unique feature of enthesitis. Gut microbiota, HLA-B*27, and biomechanical stress mutually influence and interact resulting in setting off a flame of inflammation. In the HLA-B*27 positive group, dysbiosis in the gut environment disrupts the barrier to exogenous bacteria or viruses. Additionally, biomechanical stress induces inflammation through enthesial resident or gut-origin immune cells. On this basis, innate and adaptive immunity can propagate inflammation and lead to chronic disease. Finally, bone homeostasis is regulated by cytokines, by which the inflamed region is substituted into new bone. Agents that block cytokines are constantly being developed to provide diverse therapeutic options for preventing the progression of inflammation. In addition, some antibodies have been shown to distinguish disease selectively, which support the involvement of autoimmune immunity in AS. In this review, we critically analyze the complexity and uniqueness of the pathogenesis with updates on the findings of immunity and provide new information about biologics and biomarkers.

Keywords: Biological products, Hereditary autoinflammatory diseases, Gastrointestinal microbiome, Enthesopathy, Adaptive immunity

INTRODUCTION

Ankylosing spondylitis (AS) is a radiographic axial spondyloarthritis (axSpA), mainly involving the spine and sacroiliac joint, and characterized by inflammation leading to ankylosis. AS is a chronic inflammatory disease with a critical gene, HLA-B*27, associated with environmental factors such as infections or injury due to high mechanical stress [1-3]. AS also manifests with peripheral involvement including enthesitis, dactylitis, arthritis, and extra-articular symptoms such as uveitis, psoriasis, and inflammatory bowel disease (IBD). Enthesitis, inflammation of the tendons and ligaments attached to bone, is a distinctive feature that plays a central role in the pathophysiology of AS [4]. Osteogenesis occurs at enthesial sites, and there is evidence that fatty degeneration in combination with inflammation could contribute to new bone formation in patients with AS [5-7].

Unlike other rheumatic diseases, AS is generally perceived as an autoinflammatory disease that is induced by the innate immune system. However, it remains unclear whether autoantibodies or autoantigen-specific T cells are involved in AS pathogenesis. Thus, AS has been regarded as a more autoinflammatory disease than autoimmune diseases such as other rheumatic diseases. Studies on the pathogenesis of AS are still underway, and evolving proteogenomics brings adaptive immunity to the surface. Currently, AS is suggested as an assembly of autoinflammation and autoimmunity, with growing evidence of autoimmune responses in patients with AS [2].

In this review, we have discussed the new mechanisms of

Received July 27, 2023; **Revised** August 7, 2023; **Accepted** August 8, 2023, **Published online** September 6, 2023

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pathogenesis, newly detected antibodies, and additionally verified immune reactions.

TRIGGER OF INFLAMMATION

Gut microbiome

Microbiota is a general term for a community of microorganisms themselves [8-10]. The human gastrointestinal tract contains 100 trillion microorganisms, most of which colonize bacteria with viruses, fungi, and protozoa. The microbiome is a collective genome of microorganisms in a particular environment and considered one of the body organs. This microbial organ mutually affects the host and influences the host immune system through metabolites. There are two concepts regarding the interaction mechanism between HLA-B*27 and the gut microbiota. First, HLA-B*27 exhibits molecular mimicry of some bacterial antigen components, which could increase the number of cells producing interferon (IFN)-γ [11]. Another theory is that the misfolding of HLA-B*27 in endoplasmic reticulum (ER) could cause ER stress, inducing an unfolded protein response or autophagy [12]. Microorganisms could be pathogenic in patients with AS, because molecular mimicry causes autoimmunity and immunological cross-reactivity [13,14]. Among the bacteria, *Klebsiella pneumoniae* in human feces was associated with AS and stronger in patients with active AS. In addition, there was an overlap of homologous peptides in HLA-B*27.1. Moreover, *K. pneumoniae* nitrogenase reductase was revealed to have six consecutive amino acids [11]. AS and rheumatoid arthritis (RA) have distinct gut microbiome features. However, it is unclear whether these differences are the cause or result of HLA alleles. Asquith et al. [15] examined intestinal tissues and stools in patients with AS and RA and found that the microbial composition was associated with HLA alleles. This supports the hypothesis that HLA-B*27 could affect the gut microbiota. Microbiota in patients with AS was found to be reduced in diversity, whereas taxonomic diversity in the mucosal-associated microbiota was increased [16-19]. In a recent study, healthy controls with HLA-B*27 showed reduced microbiota, similar to patients with SpA [20]. This study used DNA shotgun sequencing of the microbiome in human stool, which is superior to metagenomic analysis. It verified that the disease activity in patients with AS was associated with a lesser extent of dysbiosis, whereas *Ruminococcus gnavus*, *Erysipelatoclostridium ramosum*, *Clostridium symbiosum,* and *Clostridium bolteae* were enriched in those with severe disease. Inflammasome activation has been evaluated in peripheral blood monocytes and the gut of AS rodent models [21]. Although there is no evident cause of inflammasome activation, microorganisms could induce immune genetic factors.

Gut dysbiosis increases the incidence of AS by draining lymph nodes from the gastrointestinal tract near the pelvic area where the sacroiliac joint is located. RNA-seq assists in identifying gut-origin trafficking molecules to verify the effect of the gut on arthritis. It was found in the synovial fluid from patients with AS that potential pathogenic CD8+T cell subsets had gut-associated trafficking molecules, CD103+β7+CD29+CD49a+, and distinct transcriptional profiles, unlike other joint-derived CD8+T cells with cytotoxic and regulatory transcriptomic effects [22]. CD103+β7+ binds to human intestinal microvascular endothelia cells [23] and CD49+CD29+, or VLA-1, is found on 48% of gut-resident CD8+T cells [24].

The link between the gut microbiome and joint inflammation can be explained by the metabolites produced by the gut microbiome. Metabolites from the gut microbiome containing short-chain fatty acids, tryptophan metabolites, amino acids, trimethylamine, and B vitamins have been found to modulate disease by balancing gut barriers, T cell regulation, and cytokines [10]. Compared to the indole produced by tryptophanase, which is exclusive to bacteria, indole-3-acetate and indole-3-acetaldehyde are increased in axSpA, irrespective of bowel inflammation [25].

Potential pathogens other than the gut microbiota affect the occurrence of AS. Unlike previous studies, the incidence of AS increased 6 years after Candida infection [26]. Human papilloma virus (HPV) infection had 1.348 times greater risk of AS compared with the non-HPV cohort and has the potential to trigger systemic lupus erythematosus [27,28]. Compared with other autoimmune diseases among human immunodeficiency virus (HIV)-positive population, AS showed the strongest association with HIV with adjusted hazard ratio 1.82 (1.03~3.21) [29].

The gut microbiota has received attention with increasing evidence of a connection between the gut environment and AS. Technological developments have enabled the verification of the personal gut microbiome. Specific flora can be used for diagnosis and treatment tailored to individuals, such as dietary supplements.

HLA-B*27

HLA-B*27 is the most critical genetic component in patients with AS. There is clear evidence that the pathogenic properties of HLA-B*27 depend on the subtype. Only subtle changes in the variation of a single amino acid in the HLA-B*27 molecule could induce a different tendency in the dimerization assembly [30]. In addition, pathogenic types such as HLA-B*27:05 showed prolonged binding to ERp57 and immunoglobulin protein compared with HLA-B*27:06, which is less associated with AS. A recent study has confirmed an association between the major histocompatibility complex (MHC) and amino acids in East Asians. HLA-C*15 showed the strongest risk association with AS, followed by HLA-B*40, under controlled HLA-B*27 in East Asians [31]. At the amino acid level, histidine at position 114 in HLA-B in uncontrolled analysis and lysine at position 70, followed by asparagine at position 97 in controlled HLA-B*27, showed the strongest association with AS. In a large cohort, there was a positive association between HLA-A*29,B*38,B*49, B*52,DRB1*11,andDPB1*03:01, and negative associations with-HLA-B*07, B*57, DRB1*15:01, DQB1*02:01, and DQB1*06:02 in HLA-B*27 negative AS [32].

Although approximately 90% of patients with AS carry HLA-B*27, positivity for HLA-B*27 is not directly related to the manifestation of the disease, indicating that genes other than MHC are necessary for developing AS [33]. Endoplasmic reticulum aminopeptidases (ERAP)-1 and ERAP-2 are important for trimming peptides present in MHC class I molecules in the ER [34,35]. Aberrant function of ERAP-1 and ERAP-2 leads to increased ER stress and autophagy activation [36]. ERAP-1 highly interacts with HLA-B*27 [37] and HLA-B*40 [38] in patients with AS, and ERAP-2 is significantly associated with AS in patients who are either HLA-B*27 positive or HLA-B*27 negative [39]. The percentage of ERAP-1/ERAP-2 heterodimers was found to be 10%~30%, which means that ERAP-1 needs ERAP-2 for trimming longer amino acids, while the majority of ERAP1 and ERAP2 exist in the monomeric form [40]. Phenotypes of ERAP-1/ERAP-2 are diverse and act in distinct ways [41]. High-activity ERAP-1 is related to increased nanomers more than longer ligands compared with low-activity ERAP-2, while cells expressing ERAP-2 and ERAP-2 positivity in low-activity ERAP-1 were associated with lower amounts of peptides compared with ERAP-2 negativity in high-activity ERAP-1. RNA-seq validated the ERAP-1 and ERAP-2 polymorphisms are associated with gene expression, which influences protein expression levels. In addition, disease-associated isoforms of ERAP-1, ENST00000443439, and ENST00000296754 are regulated by genetic splice-interfering variant [42]. Thus, the function of ERAP-1 and ERAP-2 is influenced by their alleles and play pivotal roles in AS pathogenesis.

Biomechanical stress

Inflammation is a discriminating feature of AS onset [4]. The enthesis is the area of tendons or ligaments attached to bones, and its role is to maintain stability and transduce mechanical forces [43]. Similar to human gait in the orthograde posture, sustained mechanical stress is imposed on the lumbar spine and lower extremities, which are susceptible to microdamage. Tenocytes are mainly composed of entheseal cells that transform into round chondroid cells near the bone and regulate mechanotransduction pathways to cope with biological stress [44]. When the enthesis is under mechanical stress, transforming growth factor-β (TGFβ) is induced and high concentration of TGFβ leads to tenocyte cell death [45]. Cell deaths generate toll-like receptor-danger-associated molecular patterns (DAMPs) and IL-1β activated by inflammasomes [46,47]. High-mobility group protein B1 acting as a DAMP was detected in inflamed tendon leading to production of IL-1β, IL-6, IL-33, CCL2, and CXCL12. IL-1β is a proinflammatory cytokine that initiates the molecular cascade and propagate inflammation by inhibiting tenogenic potential of in tendon progenitor cells [48,49]. Recent studies have revealed the existence of cytokine-producing cells in the entheseal zone of human tissues. In normal human enthesis and perientheseal bone, resident CD14+ myeloid cells are main producer of IL-23, IL-1β, tumor necrosis factor (TNF), and CCL20 in entheses [50]. In addition, γδT cells are found in human enthesis and perientheseal bone and produce IL-17A independently to IL-23 [51]. IL-23 is suggested to initiate AS because a rat experiment demonstrated that an IL-23 blocker completely inhibited the evolution of spondylitis and arthritis [52]. The population of resident endothelial cells may connect microdamage to the propagation of inflammation in patients with AS. Although the origin of immune cells is still debated, enthesial cells are suggested to be conductors that recruit cells from the inflamed gut or skin, resulting in the propagation of inflammation.

PROGRESSION OF INFLAMMATION

IL-23/IL-17 axis

The proinflammatory cytokines IL-23 and IL-17 play key roles in host defense and function as barriers to mucosal surfaces [53,54]. Evidence of the association and dysregulation of the IL-23/IL-17 pathway with AS pathogenesis has been identified. Serum levels of IL-23 and IL-17 were significantly elevated in the peripheral blood of patients with AS, strongly associated with AS [55,56]. IL-23 is a cytokine consisting of subunits p19 and p40 produced by antigen-presenting cells, which induces IL-17 production by Th17 cells [57,58]. In addition to entheseal dwelling cells, which produce IL-23, resident Paneth cells are a crucial source of IL-23 because IL-23 expression is upregulated in the terminal ileum in patients with AS [59]. IL-23 could play a key role in the initiation of reactive arthritis, as early inhibition of IL-23p19 blocked arthritis in SKG mice infected with *Chlamydia muridarum*, but not in the late stage [60]. Since macrophages carry *C. muridarum* to the joint, depletion of macrophages reduced the dissemination of bacteria and development of arthritis, and inhibition of TNF at infection or the beginning of arthritis decreased joint inflammation, suggesting that macrophages from SKG mice could induce TNF production for constant inflammation of joints.

IL-17 is a signature cytokine secreted by Th17 cells [61]. Up-regulation of the IL-23 receptor with high expression of E receptor type 4 (EP4), a prostaglandin E2 receptor, promotes Th17 cell recruitment. Overexpression of EP4 in Th17cells is unique compared with RA or psoriatic arthritis (PsA) [62]. However, Th17 cells secreting IL-17 and contribution of IL-23 remain controversial [63]. IL-23 inhibition has less effect on AS. Thus, IL-23 independent production of IL-17 is thought to be an important pathway in the pathogenesis of AS [64]. In addition, there are several other cells producing IL-17: γδT cells [65], mucosal-associated invariant (MAIT) cells [66,67], type 3 innate lymphoid cells (ILC3) [68], CD4+ T cells [69], CD8+ T cells [70], CD3-CD56+ natural killer (NK) cells [71], and mast cells [72]. Cuthbert et al. [51] examined γδT cells and found that Vδ1 subset of γδT cells could produce IL-17 independent to IL-23 while Vδ2 subset expresses IL-23/IL-17 axis cytokine signaling. In this analysis, γδT cells were substantial source of IL-17A with IL-22 or TNF-α in addition to Th17cells. IL-17A production from MAIT cells was significantly higher than that of CD4+T cell, γδT cells, and CD8+T cells while expression of IL-17A by neutrophils could not reach the detection limit [73]. Upon induction with a combination of IL-7, IL-18, and anti-CD3/anti-CD28 antibodies, MAIT cells produced IL-17A, which was strongly independent of IL-23. Retinoid-related orphan receptor gamma (RORγt)-expressing γT cells produce IL-17 [74]. Oral RORγt inhibitor (PF-06747711) suppressing type-17 signaling pathway was shown to be effective in clinical manifestations such as bone loss, bone erosions, dermatitis, colitis, and weight loss in IL-23 overexpression mice [75].

In inflammation, IL-17 promotes neutrophilic inflammation by elevating expression of proinflammatory molecules such as TNF, IL-1α, IL-1β, IL-6, and IL-8. IL-17 also promotes neutrophil survival by producing granulocyte-colony stimulating factor (G-CSF) and granulocyte macrophage-CSF from IL-17-activated endothelial cells within microvessel wall [76,77]. In collaboration with TNF-α, IL-17A showed synergistic increase in neutrophil recruitment and endothelial activation [78]. IL-17 also induces inflammation by targeting fibroblasts and macrophages. In bone metabolism, IL-17 promotes osteoclast differentiation from its osteoclast precursor by direct stimulation of osteoclast and elevated expression of macrophage-colony stimulating factor (M-CSF) and receptor activator of nuclear factors κB ligand (RANKL) for osteoclast survival and differentiation [79]. Osteogenic differentiation and proliferation of mesenchymal stem cells (MSCs) are enhanced by IL-17 [80]. Thus, IL-17 is a crucial cytokine in AS progression.

T cell

Evidence of pathogenesis is largely associated with autoinflammation, depending on the genetic background. Although there is limited support for adaptive immunity in AS pathogenesis, evidence of adaptive immunity has accumulated in harmony with innate immunity.

The T-cell receptor (TCR) recognizes the peptides of antigens presented by MHC molecules, and this immune response mediates adaptive immunity. Complementary determining region 3 (CDR3) is responsible for antigen recognition [81]. CDR3a and CDR3b loops give a diversity of TCRβ as it is encoded with variable (V), diversity (D), and joining (J) genes. Based on this mechanism, immunosequencing of TCRβ diversity with peripheral blood mononuclear cells was performed in patients with AS with HLA-B27+ compared with healthy controls with HLA-B27+ [82]. AS has a higher diversity of TCR repertoire in CD4+ and CD8+ T cell populations, with a global reduction in periph-

eral T cell clonal expansion. In functional aspect, production of IFN-γ or TNF is reduced in CD4+ or CD8+ T cells, implicating disruption of TCR signaling cascade. In addition, expansion of the viral (Epstein-Barr virus and cytomegalovirus)-specific CD8 clonotype and public CD8 clonotype in AS with HLA-B27+ was detected, suggesting insufficient pathogen control due to an imbalanced regulatory mechanism [83]. TCR Rep-seq and CDR3 motif analyses showed that CD4+ and CD8+ T cells share the same CDR3 amino acid sequence, which could be explained by antigen stimulation [84]. During high disease activity in patients with AS, the diversity of terminally differentiated effector cells decreases and is inversely correlated with the disease activity. Thus, it could be deduced that disease progression could be accompanied by autoantigens.

There is a new clue for the recruitment of cytotoxic CD8+T cells to the joints as production of granzyme A, granzyme B, and granulysin was increased, while a decrease in perforin 1 production was incompatible with serum with reduced CD8+T cells in the blood. However, elevated cytotoxic T cells in synovial fluid implicate that these cells are important for joint inflammation in patients with AS [85].

Natural killer cell

NK cells are involved in the inflammatory process from initiation to remission. NK cells in autoimmune diseases play an important role in bridging innate and adaptive immunity [86]. There are altered subsets of AS. There was a significant reduction in CD3-CD56+NK cells in the peripheral blood mononuclear cells in patients with AS compared with those in the control group (4.95% versus 10.53%, $p<0.001$) [87]. Among NK subsets, the $CD56^{dim}$NK cells were diminished which has killing capacity while $CD56^{bright}$NK cells regulating lymphocytes were increased. In addition, cytotoxicity-related molecules, such as granzymes and GZMB+NK cells, were significantly reduced. In a previous study, expression of A20 which has anti-nuclear factor-κB effect was dramatically reduced in $CD56^{bright}$NK cells in patients, whereas expression of A20 in $CD56^{dim}$subset had no difference compared with healthy control group [88]. Biologics in rheumatic diseases affect NK cell activity. TNF inhibitors (TNFi) showed good response rates in CD8+NK cell subsets [89]. However, treatment with secukinumab showed no change in NK cells in patients with AS [90]. An altered NK cell population could be a cell-based parameter for the selection of therapeutic agents.

BONE FORMATION AFTER INFLAMMATION

Factors contributing to new bone formation have been recognized and may help identify new therapeutic targets. However, seizing the progression of new bone formation using current medications remains challenging. Inflammation of the sacroiliac joints and the spine leads to new bone formation and abnormalities that restrict spinal mobility. Resolution of inflammation is replaced by fat metaplasia, which was associated with ankylosis on T1-weighted magnetic resonance imaging (MRI) [91]. The fatty signal on MRI corresponds to adipocytes, which was found in 90.5% of patients with AS [92]. Vertebral corner inflammation and fat deposition are strongly associated with new bone formation on MRI [6]. However, 40% to 66% of new bone could develop without the detection of MRI inflammation or fat degeneration. A study showed that the subchondral bone plate was invaded by fibrous tissue originating from the bone marrow, resulting in thinning and degeneration of the cartilage and subchondral bone, while the trabecular bone was unaffected in patients with AS [93]. This fibrous tissue could play a critical role in bone remodeling. The same study group found that granulation tissue in the subchondral bone marrow could carry capabilities of bone formation, as osteoblasts are found in the lining of granulation tissue near the cartilage in the facet joints [94].

IL-22 is directly induced by IL-23 from Th17 cells, DCs, Th22 cells, γδT cells, and ILC3s and is associated with AS [95,96]. IL-22 in combination with IFN-γ and TNF promotes MSCs to activate bone formation via maintenance, proliferation and migration of MSCs and this process consequently results in new bone formation [7]. In vitro, MSCs treated with IL-22 produced more calcium than did the untreated MSCs. IL-22 produced by entheseal resident cells activates signal transducer and activator of transcription 3 (STAT3)-dependent osteoblast-mediated bone remodeling [96]. Thus, IL-22 plays a key role in new bone formation in patients with AS, as it affects the enthesis.

The IL-23/IL-17 pathway is influenced by the Janus kinase (JAK)/STAT pathway, and STAT3 mediates intracellular signaling in osteoblasts and osteoclast [97-99]. In a mouse model, a STAT3 inhibitor suppressed new bone formation comparable to that of an IL-17A blocker [100]. Osteogenesis is reduced in the spinal enthesis cells. Thus, STAT3 inhibitors are promising agents for targeting new bone formation and inflammation. Resident MSCs in the normal spinal enthesis promotes osteo-

genesis induced by IL-17A and TNF [101].

TNF is the important target in patients with AS and RA even though the immunological role of TNF is not fully elucidated. Unlike erosive arthritis in patients with RA, AS has distinctive features of new bone formation and TNF mechanism. The Relationship between osteoproliferation and TNF is still not fully understood. In AS synovial fluid, transmembrane TNF (tmTNF) was increased, while soluble TNF (sTNF) was decreased compared with RA synovial fluid, with decreased activity of A disintegrin and metalloproteinase or TNF-α converting enzyme [102]. Mice overexpressing tmTNF manifested spondylitis and peripheral arthritis with synovitis, enthesitis, and osteitis. In addition, TNF-receptor II could be essential for osteoproliferation in tmTNF signaling as tmTNF and sTNF have different affinity for subsets of TNF-receptors. Alkaline phosphatase and collagen type I expression in fibroblasts from tmTNF transgenic mice were significantly increased, and excessive mineralization was observed in the presence of IL-17A. Thus, tmTNF contributes to new bone formation in patients with AS and to the clinical features of the SpA family.

Macrophage migration inhibitory factor (MIF) is a proinflammatory cytokine that binds to its high-affinity receptor, CD74, on antigen-presenting cells, and the serum level of MIF is increased in patients with AS [103,104]. MIF was not affected by TNFi, and radiographic progression was associated with serum MIF levels (p=0.031) [105]. MIF signaling activates Wnt/β-catenin pathway by triggering stabilization of β-catenin, a key regulator of osteoblast differentiation and maturation. Wnt signaling is blocked by dickkof-related protein 1 (DKK1) and sclerostin. DKK1 is negatively associated with the formation of osteophytes and spinal ligament ossification, and sclerostin levels are lowered in patients with AS [106-108]. RANKL is essential for osteoclast differentiation and maturation of monocytes and macrophages regulated by CD16+ monocytes. It was found that the levels of CD16+ monocytes and osteoclasts decreased, which was associated with lower RANKL/osteoprotegerin (OPG) ratios in patients with AS [109]. RANKL SNPs were also associated with syndesmophyte formation in patients with AS [110]. Osteoimmunology, which refers to bone homeostasis affected by cytokines and immune system signaling pathways, is important for new bone formation in patients with AS [111].

Therapeutic options

TNFi have been successfully used over the past two decades as the mainstay treatment of AS. TNFi, including etanercept, infliximab, adalimumab, and golimumab showed similar response rates of approximately 60% according to the Assessment in Ankylosing Spondylitis Response Criteria(ASAS) 20 and 40% according to ASAS 40 [112-115]. All TNFi treatments improve pain, function, stiffness, and global well-being [116]. Spinal and sacroiliac joint inflammation detected on MRI also improved in the TNFi group. In cases of uveitis and IBD, TNF-α monoclonal antibodies are recommended over other biologic drugs because they have a lower incidence of disease recurrence and exacerbation [117]. However, it has been reported that TNFi induced psoriasis and paradoxical arthritis in IBD by dysregulating type I IFN [118,119]. Although there are no evident therapeutic options for new bone formation, TNFi can inhibit spinal radiographic progression if used for more than 4 years [120]. Unfortunately, it was not possible to demonstrate the effect of TNFi initiation in the advanced stages [121].

IL-23 blockers showed a lack of efficacy in patents with AS, whereas these drugs were beneficial for psoriasis [122,123]. Ustekinumab is a human monoclonal antibody that binds to the p40 subunit of IL-12 and IL-23. Clinical trials of AS failed to demonstrate improvements in symptoms and were discontinued [124,125]. According to a rat experiment, an IL-23 blocker was capable of suppressing disease onset, with no effect on inflammation [60]. In addition, the production of IL-17A is not solely dependent on the IL-23/IL-17A axis. Thus, blocking IL-23 may not inhibit the inflammation which is provoked through IL-17. Unlike AS, IL-23 blockers showed good efficacy in peripheral synovitis and enthesitis in psoriasis, and there was an improvement in spinal domain pain in PsA [126,127]. Whether there is efficacy in peripheral arthritis in patients with AS and the initiation of axial manifestations in PsA is still questionable.

Secukinumab was the first recombinant human monoclonal antibody that directly blocked IL-17A from binding to the IL-17 receptor [128]. Secukinumab achieved approximately 40% ASAS 40 and lowered C-reactive protein (CRP), SIJ edema scores on MRI, and quality of life at week 16 [129]. Histopathological examination of synovial inflammation showed that CD15+ neutrophils and CD56+ macrophages decreased from baseline 12weeks after beginning of secukinumab 300 mg [130]. Ixekizumab showed effects on joint improvement comparable to those of adalimumab [131]. In an extended study on PsA, ixekizumab showed persistent efficacy, safety, and inhibition of radiographic progression [132]. In addition to skeletal

symptoms, IL-17A blockers showed improvement in the skin. However, there was a lack of efficacy in gut symptoms with aggravation or new-onset IBD [133]. In addition, secukinumab has an advantage in tuberculosis infections because there was no evidence of the incidence or reactivation of tuberculosis [134]. Brodalumab, an anti-IL-17 receptor A monoclonal antibody, showed ASAS 40/20 response rates of 43.8% and 67.5%, respectively, at week 16 in patients with active axSpA in a phase 3 trial [135]. In the extension trial, in which the placebo group switched to brodalumab at week 16, the placebo group did catch up with the brodalumab group in efficacy, with a sustained effect and clinical index. In addition, MRI showed an improvement in the Berlin Spine Score in both groups at week 68 [136]. Serious drug- and treatment-related adverse event included one case each of herpes zoster oticus, acute myocardial infarction, cellulitis, appendicitis, and diverticulitis. A study of monoclonal antibody neutralizing IL-17A and IL-17F, bimekizumab, showed that 46% of patients administered 160 mg and 320 mg every 4 weeks achieved ASAS 40 at week 12, and approximately 60% of patients responded at week 48 in phase IIb [137]. In the non-responder imputation analysis, the ratio of ASAS 40 and partial remission was 53.7% and 28.0%, respectively, with a gradual reduction in ASDAS at week 156 [138].

JAK inhibitors, tofacitinib and upadacitinib have been approved for AS by U.S. Food and Drug Administration. Upadacitinib, a selective JAK1 inhibitor, administered at 15 mg once daily was effective in AS refractory to a previous history of biologic disease-modifying antirheumatic drugs with ASAS 40 at 45% at week 14 in a phase 3 trial [139]. The incidence rate of serious infections was 2.4% consisting of 5 cases; 4 cases were coronavirus disease 2019-related infections and one case was uveitis. The zoster infection rate was 0.9%. Tofacitinib is a first-generation JAK inhibitor targeting JAK3, JAK1, and JAK2 [140]. Tofacitinib had response rate of 40.6% in the ASAS 40 at week 14 [141]. There were 2.3% non-serious herpes zoster cases and 0.8% serious infections. In the two studies on upadacitinib and tofacitinib, there were no major adverse cardiovascular events, thromboembolic events, malignancies, or deaths while there are still concerns about risks of major adverse cardiovascular events and cancer in RA.

Granulocyte-macrophage colony stimulating factor (GM-CSF) is a cytokine that could result in joint damage by inducing matrix metalloproteinases and osteoclasts and showed improved signs and symptoms of RA in a phase II trial [142,143]. Namilumab is a monoclonal antibody targeting GM-CSF, and a phase IIa study of namilumab with primary endpoint of ASAS 20 at week 12 is currently being assessed [144].

Biomarker

The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have a high possibility of utility, similar to the existing biomarkers erythrocyte sedimentation rate (ESR) and CRP [145]. The cutoff values were 3.669 for NLR and 242.466 for PLR, while the ESR was 22 mm/h and 1.980 mg/dL for CRP. Each parameter had a good predictive value for radiographic sacroiliitis, and NLR or PLR with existing inflammatory markers showed better outcomes for the effect of TNFi treatment. In addition, the lymphocyte-to-monocyte ratio, with a cutoff value of 4.26 showed a good predictor of radiologic progression in patients with AS (sensitivity, 94.9%; sensitivity, 97.4%; AUC, 0.975) [146].

Although HLA-B*27 has been widely used for the detection of AS, negative HLA-B*27 results can delay diagnosis and treatment initiation. Proteomic analysis could aid in identifying new targets for the early detection of the disease. In 2020, it was reported that eight AS-specific proteins were upregulated (>1.5-fold) in the synovial fluid of Korean patients with AS: HP, MMP1, MMP3, serum amyloid P-component, complement factor H-related protein 5 (CFHR5), mannose-binding lectin 2, complement component 9 (C9), and complement C4-A [147]. Among these, MMP3, C9, and CFHR5 have been identified as potential markers.

Autoantibodies are useful tools for distinguishing autoimmune diseases and verifying their disease activity. AS is considered an autoinflammatory disease; thus, it is difficult to classify patients with AS based on nonspecific chronic low back pain in the early disease phase. Novel antibodies and biomarkers have been explored for early detection of AS. Recently, antibodies against AS were identified. Three antibodies against axSpA peptides have been detected in the axSpA cohort at Hasselt University [148]. The three novel antibodies were tested in patients with axial SpA from the University Hospital Leuven (Bio) SPAR cohort. The other antibody is against CD74. The immunoglobulin (Ig) A anti-CD74 antibody is associated with radiographic changes in AS because CD74, an MHC class II invariant chain, leads to cell proliferation and TNFα production [149]. Anti-CD74 IgA showed potential diagnostic value, as the area under the ROC curve for the diagnosis of axSpA compared with

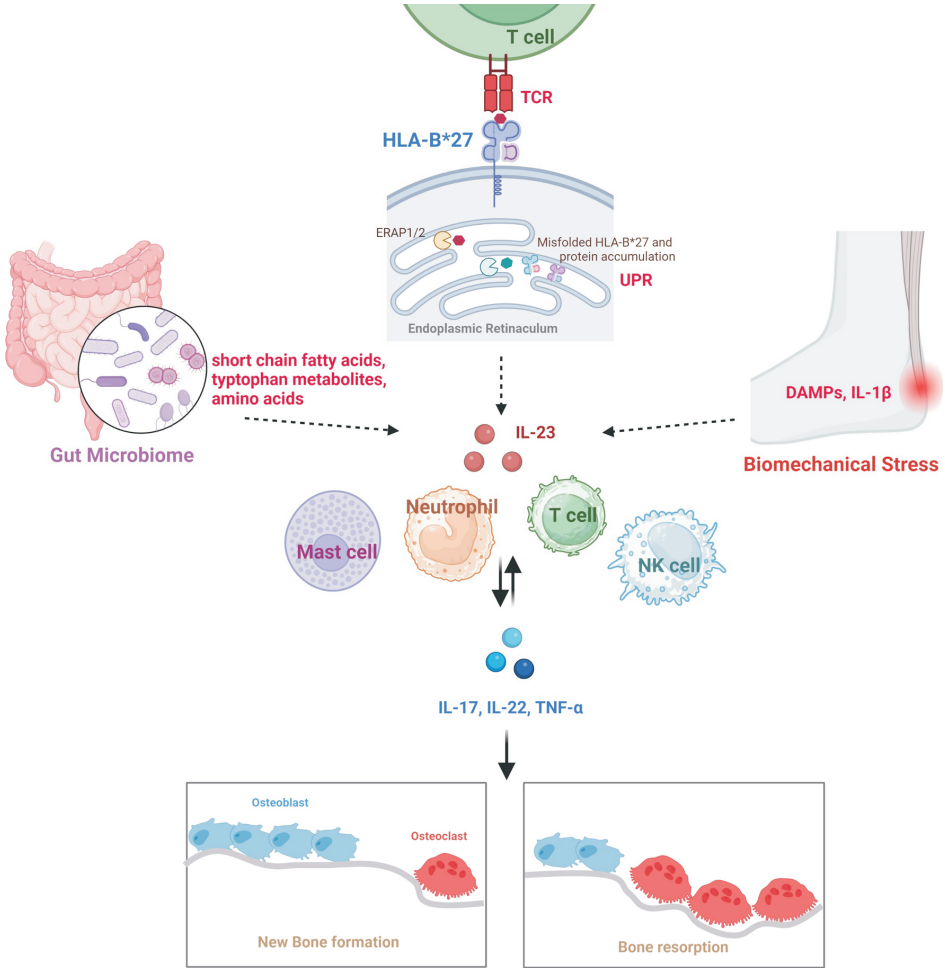

Figure 1. Pathogenesis of ankylosing spondylitis. Gut microbiome produces short-chain fatty acids, tryptophan metabolites, and amino acids. Also, Paneth cells are source of IL-23 in the terminal ileum. HLA-B*27 provides arthritogenic peptide to TCR, and misfolded HLA-B*27 and accumulated protein induce UPR resulting in production of IL-23. Mechanical stress in enthesis induce DAMPs and IL-1β. As a result, produced IL-23 plays a pivotal role in initiating ankylosing spondylitis. Immune cells are involved to progress the disease by inducing IL-17, IL-22, and TNF-α. Bone remodeling is activated, as a result, new bone formation and bone resorption are promoted through cytokines. TCR: T-cell receptor, UPR: unfolded protein response, DAMPs: danger-associated molecular pattern, IL: interleukin, TNF: tumor necrosis factor, NK: natural killer, ERAP: endoplasmic reticulum aminopeptidases.

fibromyalgia was 0.705, while there was no correlation with gut inflammation [150]. In addition, the anti-CD74 IgG antibody was associated with disease activity, whereas there was no difference between the ratios of early and late phases of the disease [151]. Thus, anti-CD74 antibodies may serve as good detectors with high specificity [152,153].

CONCLUSION

The latest evidence on the pathogenesis of AS provides new perceptions and clues into the unexplained mechanisms. AS is a complex network between the autoinflammatory and autoimmune systems (Figure 1). HLA-B*27 creates an environment susceptible to various stimuli such as infection and trauma. Consequently, the IL-23/IL-17 pathway is activated, and immune cells contribute to the perpetuation of joint inflammation. The cytokines generated by these mechanisms are involved in bone homeostasis, resulting in new bone formation, which is an authentic feature of AS. New therapeutic choices and diagnostic biomarkers are emerging against the background of new discoveries, and we look forward to personalized treatments for better outcomes.

FUNDING

None.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conceptualization: SHL. Data curation or/and Analysis: all authors. Writing - original draft: SHK. Writing - Review & Editing: all authors. All authors read and approved the final manuscript.

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