Original Research

IMMUNOLOGICAL SIGNATURES AND BIOMARKERS FOR ANKYLOSING SPONDYLITIS: FROM PATHOGENESIS TO PRECISION MEDICINE

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ABSTRACT
Ankylosing spondylitis (AS) is a chronic inflammatory autoimmune disorder that primarily affects the axial skeleton, leading to sacroiliitis, progressive spinal stiffness, structural damage, and long-term disability. Although human leukocyte antigen B27 (HLA-B27) remains the strongest genetic risk factor associated with AS, recent advances have identified a broader spectrum of immunological biomarkers, including cytokines, acute-phase reactants, autoantibodies, immune-cell signatures, and genetic and epigenetic determinants. These biomarkers contribute to early diagnosis, assessment of disease activity, prediction of radiographic progression, and monitoring of therapeutic response. This review summarizes the current understanding of immunological biomarkers in AS, with emphasis on their mechanistic relevance, diagnostic value, and emerging role in precision medicine.

Keywords: Ankylosing Spondylitis, Immunological Biomarkers, HLA-B27, Cytokines, TNF-Alpha, IL-17/IL-23 Axis, Precision Medicine.

INTRODUCTION
AS belongs to the immune-mediated, progressive, chronic type of diseases belonging to the group of axial spondyloarthritis. The main target organs of AS include the bones of the axial skeleton and the joints of the sacroiliac region. Still, it is not impossible that other parts of the body, such as the skin, eyes, and gastrointestinal tract, and the joints outside the spine will be affected by this disease. Some characteristics of AS include chronic inflammation of the entheses. Entheses refers to the area where the ligaments and tendons attach. Chronic inflammation can lead to pathological new bone development, syndesmophyte development, fusion of the spine, bone remodeling, and eventually ankylosis. All of these can significantly affect posture and mobility. Typically, AS affects people who are young adults, ranging from the age of twenty to forty. Therefore, AS often affects individuals at the peak of their physical and intellectual abilities. Consequently, AS can have socio-economic consequences due to chronic pain, fatigue, functional impairment, reduced work capacity, and low quality of life [1].

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The etiopathogenesis of ankylosing spondylitis (AS) is extremely complicated and involves many interacting components, such as genetic predisposition, environmental factors, microbial agents, biomechanical stress, and dysregulation of innate and adaptive immunity. Among all genetic risk factors currently recognized, the strongest one by far is represented by HLA-B27 allelic polymorphism. While the vast majority of AS patients have a positive test result for HLA-B27, it should be pointed out that only a few people carrying the HLA-B27 allele actually develop AS, suggesting that other genetic and immunological variables are also very important to disease onset and progression. The identification of some non-HLA loci through genome-wide association analysis includes ERAP1, ERAP2, IL23R, TYK2, RUNX3, and IL7R. These genetic variants play a role in antigen presentation, cytokine action, T-cell development, and inflammatory response regulation [2].

At the present moment, a lot of scientific evidence exists concerning the role of IL-23/IL-17 immune cascade activation in the aetiology of AS. The rise of pro-inflammatory cytokines TNF-α, IL-17, IL-23, IL-6, and IL-22 causes chronic inflammation, disturbances in the osteoimmune system, and problems with bone remodeling in AS. In addition, the importance of innate immunity cells, such as macrophages, dendritic cells, neutrophils, and innate lymphoid cells, in the course of the disease should be emphasized. At the same time, today the hypothesis about gut dysbiosis and its significance

as a factor of the disease through the gut-joint axis is gaining popularity in the scientific community [3].

In recent years, there have been significant attempts in science to identify new immunological markers of AS in order to detect and diagnose the disease. This wide range of markers can include various elements, both molecules and cells, such as genetic, acute-phase proteins, cytokines, chemokines, autoantibodies, neutrophil-derived mediators, markers of bone metabolism, oxidative stress markers, microRNA, extracellular vesicles, and, more recently, ferroptosis markers. The classical biomarkers of inflammation, CRP and ESR, are still used extensively in clinical practice despite their low sensitivity and specificity because a considerable number of individuals with ongoing disease may show normal findings. The requirement is in finding more sensitive and specific biomarkers of disease, which would be capable of reflecting inflammation status, radiographic progression, and therapeutic effectiveness [4].

Recent advances in the field of molecular immunology and omics science have contributed to the identification of new biomarkers related to the disease and its complications. Micro RNAs were demonstrated to play a role in regulating inflammatory pathways, bone differentiation and inflammatory processes, while the ferroptosis pathway is being increasingly considered due to the involvement of oxidative stress and lipid peroxidation in chronic inflammatory injury and aberrant bone formation in AS. Bone turnover markers, DKK-1, sclerostin, osteoprotegerin, and RANKL, were analyzed for their predictive value regarding the disease progression and ankylosis.

Beyond their role in diagnostic purposes, the importance of these novel immunological biomarkers is further seen in several other aspects of patient care. These include better patient stratification, identification of those prone to rapid radiographic progression, prediction of patient responses to biological therapies, such as anti-TNFs and IL-17 inhibitors, among others. Biomarker-based techniques used during the era of precision medicine can greatly enhance the prospects of early intervention, treatment, and better patient outcomes for AS patients [5].

This review paper aims to evaluate the key immunological biomarkers linked to AS, which include genetic markers, inflammatory markers, cellular markers, molecular markers, and ferroptosis-related markers, among others, along with their relevance, applications, and role in the development of precision medicine for the diagnosis and management of AS.

HLA-B27 and Genetic Markers

HLA-B27

HLA-B27 is the most important and extensively researched genetic marker linked to Ankylosing Spondylitis. The discovery of the genetic marker HLA-B27 occurred nearly five decades ago; however, the genetic marker is still very useful in research regarding the genetic and immunological aspects of AS. About 80-95 percent of people suffering from AS carry the HLA-B27 marker; nevertheless, there are differences in the occurrence rate of AS among different racial and geographical groups. Conversely, only a few of those who carry the HLA-B27 genetic marker in the general population are known to suffer from Ankylosing Spondylitis, implying that although HLA-B27 is a crucial factor in the development of AS, it alone does not cause the disease. HLA-B27 has a higher prevalence among Northern Europeans, an average prevalence among Asians, and a lower prevalence among several African populations.

HLA-B27 is a member of the MHC class I molecule and is involved in the presentation of intracellular peptides to CD8+ T lymphocytes. Many pathogenetic mechanisms were put forward to explain HLA-B27 involvement in AS. Among the first was the hypothesis on the involvement of arthritogenic peptides. According to this hypothesis, HLA-B27 presents autoantigens or microorganisms' peptides that activate T-cells using molecular mimicry. There is some similarity between certain bacterial antigens obtained from organisms like Klebsiella, Salmonella, Shigella, and Yersinia and self-antigens; hence, there is a chance for the development of chronic autoimmune activity in a genetically predisposed patient [6].

The second significant pathogenic factor concerns the ability of HLA-B27 heavy chains to undergo misfolding in the endoplasmic reticulum (ER). Misfolded molecules accumulate in the ER and evoke ER stress, which results in the activation of the unfolded protein response (UPR). Activation of UPR causes an increased production of pro-inflammatory cytokines, including IL-23, TNF-α, and IL-17, thus supporting chronic inflammation. The experiments show that HLA-B27 misfolding facilitates the activation of innate immunity pathways and increases inflammatory reaction in macrophages and dendritic cells [7].

Besides misfolding, HLA-B27 heavy chains can also undergo aberrant homo-dimerization at the cellular surface and interact with innate immune receptors such as killer immunoglobulin-like receptor 3DL2 (KIR3DL2), which is expressed by NK cells and Th17 lymphocytes. The interaction between the homo-dimerized HLA-B27 proteins and the KIR3DL2 receptor results in the selection and survival of immune cells that are capable of producing IL-17. Consequently, the IL-23/IL-17 signaling pathway assumes more importance in AS pathogenesis. It has been observed that the number of Th17 lymphocytes positive for KIR3DL2 receptors is higher in AS patients [8].

It is important to mention here that all variants of the HLA-B27 gene are not equally responsible for developing ankylosing spondylitis. So far, there are more than 200 known HLA-B27 gene variants, but only some of them cause AS. Among these high-risk HLA-B27 variants are HLA-B27:05, HLA-B27:04, and HLA-B27:02. The low-risk HLA-B27 variants include HLA-B27:06 and HLA-B27:09 [9]. The reason for these differences may be attributed to the differential ability of peptides to bind, misfold, and stimulate immune cell stimulation among various HLA-B27 gene variants.

Moreover, HLA-B27 also predicts earlier onset, familial clustering, a higher chance of uveitis, and faster progression on X-rays. The role of HLA-B27 testing in AS is very significant from a clinical point of view for diagnosing and classifying the disease, especially in cases where there is inflammatory back pain and axial symptoms at early stages. Nevertheless, due to the presence of HLA-B27 even in healthy people, the test should always be correlated with clinical and imaging findings.

Non-HLA Genetic Markers

Although the role of HLA-B27 is important regarding genetic predisposition to AS, it represents only a minor genetic risk factor in AS. The development of GWAS and next-generation sequencing techniques has shown that AS is a complex polygenic disorder and involves several non-HLA genes as susceptibility genes [10].

One of the most confirmed non-HLA susceptibility genes in AS is endoplasmic reticulum aminopeptidase 1 (ERAP1). ERAP1 is a gene encoding a protein that acts as a protease, trimming antigens before loading them on MHC-I proteins (HLA-B27). Mutations of the ERAP1 gene can affect the length and structure of antigens. As a consequence, antigen presentation is altered; arthritogenic peptide generation is increased. Moreover, ERAP1 mutations can contribute to the misfolding of HLA-B27 proteins and cause increased endoplasmic reticulum stress, thereby provoking inflammation. Notably, mutations of the ERAP1 gene are particularly pathological in patients with HLA-B27 positivity. Another protein that resembles ERAP1 in structure and function and plays an important role in susceptibility to AS is the aminopeptidase ERAP2. ERAP2 mutations can affect peptide selection and processing as well as immune reactions through modification of their pathways. Both ERAP1 and ERAP2 demonstrate the key role of aberrant antigen processing in AS aetiology [11].

The next susceptibility factor for AS is the IL23R gene coding for the interleukin-23 receptor. Mutations of this gene provide evidence for the essential role of the IL-23/IL-17 pathway in AS pathology. IL-23 induces differentiation and expansion of Th17 cells responsible for producing IL-17 and IL-22, along with other inflammatory molecules associated with inflammation and bone remodelling. Changes in the IL23R pathway can result in increased inflammation in patients with AS. The effectiveness of treatment with IL-17 inhibitors provides additional proof of its significance.

Other genes involved in AS susceptibility include RUNX3, CARD9, TNFSF15, PTGER4, TYK2, IL7R, and KIR3DL2. RUNX3 affects CD8+ T-cell differentiation, while CARD9 acts as part of innate immunity and participates in fungal recognition. TNFSF15 mediates cytokine-induced inflammation, whereas PTGER4 plays a role in prostaglandin signalling. However, the biological functions of the cytokine receptors and lymphocyte activation rely on both TYK2 and IL7R genes. Their interaction could possibly affect inflammatory cascades, cell differentiation and even interactions between host and pathogens [12].

In addition, recent studies have been carried out to investigate the functions of epigenetics and noncoding RNA in AS susceptibility. DNA methylation alteration, histone modification and microRNA dysregulation could induce immune-related gene expression changes, which would contribute to the immune system response and inflammation. Without any change in the DNA sequences of those genes, dysregulation of the immune-related genes could result in the dysregulation of cytokine production, bone formation and immune cell activation. For instance, microRNAs, including miR-146a, miR-155, and miR-21, are found to be involved in the regulation of these aspects.

Nevertheless, genetic susceptibilities themselves cannot contribute to the disease manifestation. Genetic susceptibilities, along with environmental and lifestyle factors, would trigger inflammation, hence causing AS. Among all the possible causative agents, gut dysbiosis is considered one of the important causes for AS pathogenesis. The dysbiotic gut could impair mucosal immunity and even increase intestinal permeability and trigger inflammation via the gut-joint axis. Additional possible causative agents could be microbial exposure, infections, smoking, and biomechanical factors [13].

Genetics and the environment ultimately cause the dysregulation of immune system activation, resulting in inflammation and abnormal bone formation, which characterise AS. Information regarding the genetics responsible for AS is important since this information could be used to predict and diagnose patients who are at risk of developing AS and provide information for biomarkers and biologics. Precision medicine in the near future should make it possible for treatment strategies to become increasingly personalised.

Cytokines and Immune Signalling Pathways

Proinflammatory Cytokines

Cytokine imbalance can be considered one of the key mechanisms of pathogenesis, since it helps connect genetic predisposition, immune response, chronic inflammation, bone metabolism, and damage. Cytokines are signaling agents that help mediate interactions between innate and adaptive immunity systems and processes of inflammation and immunity associated with the spine bones and entheses. The secretion of cytokines leads to the development of pathological processes, which are responsible for the destruction of tissues and the development of syndesmophytes, resulting in ankylosis.

One of the key pro-inflammatory agents involved in AS pathogenesis can be considered TNF-α, one of the most studied cytokines. It is synthesized by activated macrophages, monocytes, dendritic cells, T lymphocytes, and synovial fibroblasts. High concentrations of TNF-α correlate with an active clinical course of AS, inflammation of vertebrae, pain, and vertebral abnormalities [14].

This may be evidenced by the success of biologics targeting the inhibition of TNF-α, namely, infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol. However, some patients do not obtain adequate results of treatment with biologics, thus implying the presence of another inflammatory pathway involved in the development of the disease.

In addition, some recent research revealed the importance of the IL-23/IL-17 pathway, which is the main immune response pathway involved in AS development. This pathway involves the involvement of IL-23, which is mainly produced by dendritic cells and macrophages, which activates the proliferation and survival of Th17 cells and IL-17-producing cells, such as γδ T cells, MAIT cells, and innate lymphoid cells. Continuous IL-23 production results in chronic inflammation in the enthesis of patients predisposed genetically [15].

IL-17A possesses pronounced pro-inflammatory characteristics and promotes neutrophil migration and TNF-α, IL-6, and matrix metalloproteinase secretion. IL-17A plays an important role in osteoclastogenesis and pathological bone modeling through activation of RANKL. Chronic inflammation caused by IL-17A results in the development of syndesmophytes.

Moreover, participation of the IL-23/IL-17 pathway in the pathogenesis of AS may be evidenced by the success of biologics targeting inhibition of IL-17, namely, secukinumab and ixekizumab.

Besides TNF-α and IL-17, other cytokines are involved in the inflammatory pathway for AS. IL-6 plays a part in the acute-phase reaction, B-cell maturation, and systemic inflammation. Increased levels of IL-6 are associated with increased levels of CRP and active disease [16]. Moreover, the inflammatory pathway may be stimulated further by IL-1β as a result of the formation of the inflammasome. In addition, IFN-γ, predominantly secreted by Th1 cells and natural killer cells, participates in the disorder of inflammatory and immune responses.

Among chemokines, CXCL8 (IL-8), CCL20, and MCP-1 act as factors that intensify inflammation because of the attraction of immune cells to the inflamed entheses and synovium. Neutrophils release reactive oxygen species, leading to oxidative stress.

Inflammation influences bone metabolism in patients with AS. It is due to disturbances in the balance between the activity of osteoblasts and osteoclasts resulting from the constant exposure to inflammatory cytokines. TNF-α and IL-17 stimulate osteoclasts to mature because of increased RANKL secretion. In addition, ankylosis and syndesmophytes arise in the inflammation resulting from BMPs and Wnt pathways [17].

Moreover, there are new studies that emphasize the connection between the gut-joint axis and AS. Gut dysbiosis and mucosal immune response might cause an increased release of IL-23 in the intestinal milieu, resulting in a systemic increase in Th17 cell responses and attracting inflammatory cells to axial joints and entheses. The findings are further confirmation of the fact that AS is a systemic immune-mediated condition based on complicated interactions between mucosal immune response, cytokine signaling, and skeletal inflammation.

Emerging Cytokine Biomarkers

Apart from traditional inflammatory cytokines, modern research has discovered certain other cytokines and molecules associated with the immune system, which could potentially become novel biomarkers for diagnosing AS in the future. Among them is IL-40 – one of the cytokines that has recently started attracting the attention of researchers. This is a relatively new cytokine involved in B-cell activation, inflammatory responses, and autoimmunity. According to preliminary studies, serum concentration of IL-40 might be higher in patients with active AS. Still, the exact biological role and application of IL-40 as a biomarker remain unknown, and more research is needed [18].

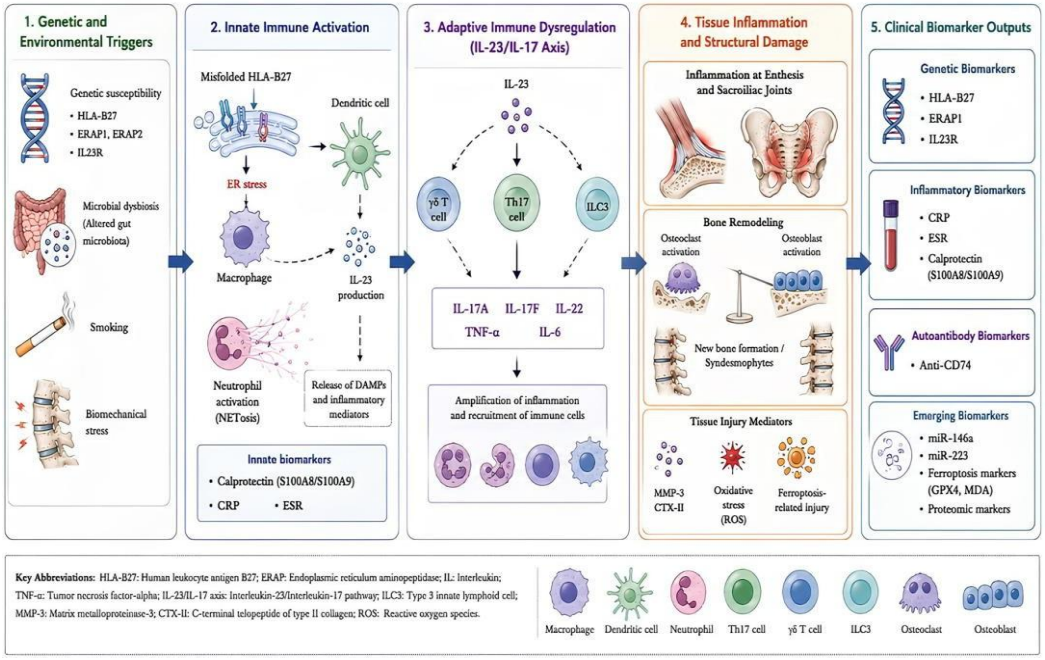
Other cytokines that are being studied include IL-31, IL-33, IL-37, and GM-CSF. Cytokines might be pro-inflammatory in nature, while others regulate immunity and function as anti-inflammatory cytokines. This alteration of the cytokine gene expression profiles may help classify the phenotypes, predict treatment responsiveness, and differentiate patients with radiographic and non-radiographic axial SpA.

Advances in technology have helped in the identification of cytokine profiles characteristic of this disease due to innovations in the field of

cytokine multiplex assays, as well as transcriptomics and proteomics. Combinations of cytokines are more effective as diagnostic and prognostic tools compared to individual biomarkers. In addition, biomarker studies will certainly add great value when considered in combination with genetics and imaging in personalized medicine for AS [19].

Given the increasing knowledge about immune pathways and signalling, the role of cytokines in AS will continue to remain significant in both the aetiology and the creation of biologics.

Figure 1. Immunopathogenesis of Ankylosing Spondylitis and Key Immunological Biomarkers.



Acute-Phase Reactants and Innate Immunity

C-Reactive Protein (CRP)

Speaking about the assessment and treatment of AS patients, it should be said that the inflammatory biomarker that is widely applied is C-reactive protein. C-reactive protein is an inflammatory biomarker that is mainly produced in response to IL-6, TNF-α, and IL-1β in hepatocytes. Increased levels of CRP are associated with active inflammation and confirm the results of DAS score, sacroiliitis, spinal inflammation on MRI, and radiographic progression. In addition, increased CRP level is correlated with the development of syndesmophytes and radiographic progression. The employment of C-reactive protein as a biomarker to assess the efficacy of biological treatment using TNF and IL-17 inhibitors is a routine practice in modern medicine. Nevertheless, despite its significance, CRP is characterised by several shortcomings. For example, in many AS patients, CRP can be at a normal level, even if the disease is in its active phase, or at least a non-radiographic axial spondyloarthritis stage [20].

Erythrocyte Sedimentation Rate (ESR)

As an additional indicator of systemic inflammation in AS, erythrocyte sedimentation rate (ESR) can be taken into consideration. According to its definition, ESR is the speed at which red blood cells move down a column of plasma. ESR is an indirect measure of the degree of inflammation because of the increase in fibrinogen and acute-phase protein concentrations. High values of ESR are linked to inflammation activity, pain intensity, and systemic inflammatory load [21]. Nevertheless, ESR can be considered less sensitive and less specific than CRP. Results of ESR may depend on several factors, such as age, gender, anaemia, and others. At the same time, ESR can be used in combination with CRP and clinical examination to diagnose inflammation.

Calprotectin (S100A8/S100A9)

Calprotectin is a complex of S100A8 and S100A9 proteins synthesized mainly by activated neutrophils and monocytes. An elevated level of both serum calprotectin and faecal calprotectin was found in patients with AS activity, systemic inflammation, and MRI lesions. Particularly, an increased level of faecal calprotectin is important as a marker indicating subclinical intestinal inflammation and proving the concept of the gut-joint axis in the pathogenesis of AS [22].

Innate immunity plays an essential part in AS, particularly during the initial stages of the development of the disease. In contrast to other autoimmune diseases, when the dominant component of the body's immune system is adaptive immunity, in AS, there is a substantial activation of

innate immune cells such as macrophages, neutrophils, dendritic cells, and innate lymphocytes. Accordingly, the synthesis of inflammatory mediators occurs in innate immune cells, resulting in a long-term inflammatory reaction in the entheses and axial joints. The activity of neutrophils results in ROS and proteases release as well as NETs formation, contributing to the increase in the inflammatory response [23].

Additionally, some other markers of innate immunity have recently been found to be potential biomarkers of inflammation in AS. They include pentraxin-3, lipocalin-2, and soluble CD14. Increasing evidence points to innate immune pathway dysregulation as a factor causing constant inflammatory response in AS. For example, Toll-like receptor activation and inflammasome signalling can cause continuous cytokine synthesis, leading to AS progression. Consequently, innate immunity is responsible not only for initiating inflammation but also for maintaining it.

Autoantibodies and Adaptive Immune Biomarkers

Anti-CD74 Antibodies

Inflammatory arthritis is described through seronegativity of autoantibodies in ankylosing spondylitis. Such autoantibodies include RF and anti-CCP, which are commonly identified in various other autoimmune rheumatic disorders. In contrast to the condition of rheumatoid arthritis, where the existence of autoantibodies is one of the main clinical manifestations, AS has conventionally been thought of as relying on the cellular form of immunity rather than the humoral form. Recent discoveries of new autoantibodies have altered the perception of immune responses in AS and enabled biomarker discovery for the disease.

As a case in point, anti-CD74 autoantibodies may serve as one of the most significant adaptive immune biomarkers for AS. CD74 is otherwise known as the invariant chain and represents a transmembrane glycoprotein involved in antigen presentation through MHC-II. The molecule plays a vital part in antigen processing and presentation, immune cell activation, and adaptive immune response regulation. Several studies have reported a high prevalence of anti-CD74 autoantibodies, particularly IgA and IgG subclasses, in AS and early-onset axial spondyloarthritis. Anti-CD74 autoantibodies arise from immune responses against antigen-presenting CD74 cells at sites of inflammation [24].

The interest in anti-CD74 autoantibodies is also fueled by their potential for aiding in the early diagnosis of AS, especially in cases of non-radiographic AS or in subjects that have not yet met radiographic criteria for diagnosing the condition. High concentrations of anti-CD74 antibodies have been correlated with inflammatory back pain, active sacroiliitis, and enhanced inflammatory status. There is also some indication that anti-CD74 positivity is linked to radiographic progression and, thus, can serve as a prognostic marker. In addition, high IgA anti-CD74 antibodies are thought to be markers of mucosal and intestinal inflammation.

Although there are promising results, the diagnostic usefulness of anti-CD74 autoantibodies is inconsistent among various studies and populations. Different sensitivity and specificity rates have been reported in regard to the test type, AS duration, and ethnic differences. Anti-CD74 tests are still not part of any clinical routine or recommendations for AS diagnosis. Yet, anti-CD74 antibodies are still valuable research biomarkers [25].

Anti-beta2 Microglobulin and Anti-Keratin Antibodies

Moreover, other types of autoantibodies have also been studied in AS; however, their clinical importance is still questionable. Anti-beta2 microglobulin autoantibodies have been found in some AS patients, possibly representing immunologic disturbances in connection with MHC class I protein complexes, such as HLA-B27. Beta2 microglobulin forms part of MHC class I protein complexes and participates in the process of antigen presentation and interactions between immune cells. Immune reactions against beta2 microglobulin can be involved in continuous inflammation, but the data available are insufficient and contradictory.

In addition, anti-keratin autoantibodies have also been identified in specific populations of AS patients. Keratins form part of epithelial cell structures, and autoantibodies against keratin antigens may suggest tissue damage or changes in the immune system. Nevertheless, unlike anti-CCP antibodies in RA, anti-keratin autoantibodies have not been demonstrated to have any diagnostic value in AS [26].

Other potential adaptive immune biomarkers that are being investigated now include microbial antigen-specific antibodies, heat shock proteins, and extracellular matrix components. These studies suggest that there may be more of a role for humoral immunity in the pathology of AS than is currently known. However, most of the autoantibodies identified so far have certain limitations in terms of their accuracy, specificity, and reproducibility in diagnosis.

In summary, the study of autoantibodies and adaptive immune biomarkers in AS seems to be an emerging field that could yield valuable insights into the development of novel biomarkers for personalized medicine in AS [27].

Neutrophils and NETosis

Recently, the role of NETs and NETosis in the development of AS has become more relevant. Netosis refers to an alternative activation of

neutrophils, characterized by secretion of DNA-containing extracellular weblike structures consisting of histones, MPO, neutrophil elastase, and antibacterial peptides. Although the release of NETs serves as a protective mechanism from the host perspective, its excess or dysregulation may lead to chronic inflammation, tissue injury, and autoimmunity.

Elevated levels of markers associated with NETs, including cell-free DNA, nucleosomes, neutrophil elastase, and MPO-DNA complexes, were shown in AS patients in the active stage of the disease. Excessive production of NETs is characteristic not only for peripheral blood, but also for sites of inflammation in the sacroiliac joint or entheseum in AS patients [28].

There are several pathways involved in which NETs could be involved in progressing AS. First, the cytokine production induced by NETs could lead to IL-23 production from macrophages, dendritic cells, and epithelial cells. Thus, the pathway would contribute to the further activation of the inflammatory axis IL-23/IL-17. In addition to the mentioned mechanisms, NETs are the source of oxidative stress and endothelial dysfunction. Enzymes and pro-inflammatory proteins associated with NETs induce tissue damage and pathological bone remodeling. This causes the development of syndesmophytes and ankylosis [29].

According to the findings obtained, NETs could potentially become effective biomarkers for assessing inflammation in AS patients. It might be assumed that the targeting of NETosis pathways could represent a prospective treatment option for AS.

Biomarkers of Bone and Cartilage Turnover

The progression of AS structure is connected with a complicated interplay between inflammation, cartilage degradation, osteolysis, and pathological osteoblast growth. Opposite to other forms of inflammatory arthritis diseases, AS is distinguished by both destructive and osteoproliferative processes. Namely, AS is characterized by syndesmophyte formation and ankylosis due to the excessive osteogenic activity. For this reason, biochemical markers related to bone and cartilage metabolism become increasingly significant for predicting the progression and prognosis of AS.

Among the known biochemical indicators, CTxII is widely investigated for cartilage destruction evaluation. Type II collagen is a protein that makes up the main component of cartilages, the degradation of which leads to CTxII production. Increased serum and urinary concentrations of CTxII indicate cartilage damage, sacroiliitis, and structural progression of AS. On the other hand, procollagen type II C-propeptide (CPII) indicates collagen production and cartilage repair, and collagen type II cleavage product (C2C) – cartilage destruction. Therefore, the ratio of CPII/C2C might show the ratio between the cartilage production and its destruction [30].

The most valuable biomarker in AS has become MMP-3. This enzyme is released by synoviocytes, chondrocytes, and inflammatory cells. MMP-3 is responsible for tissue matrix remodeling and degradation. Elevated concentrations of this biomarker in the serum are correlated with active processes, MRI findings, and risk of X-ray progression. Therefore, elevated and stable concentrations of MMP-3 are indicators of active pathology and destruction in the tissues [31].

OPG, RANKL, sclerostin, and DKK-1 have been suggested as biomarkers to provide more information on the possible bone disorders that develop in patients with AS.

Emerging Molecular Biomarkers

microRNAs

The presence of small RNAs that specifically bind mRNAs and control translation processes is well established. Recent scientific publications have provided convincing evidence of the importance of miRNAs for the regulation of immune-inflammatory processes in AS. The disruption of miRNA functions causes the disruption of the expression of cytokines, changes in the development of T lymphocytes, the activation of osteoblasts, and inflammation. All of these mechanisms contribute to AS pathology.

Deregulation of miRNA expression was demonstrated by many recent studies conducted among patients with AS. These miRNAs included, for example, miR-146a responsible for the regulation of the NF-κB signaling pathway and inflammatory cytokine expression. Increased miR-146a expression is connected with the severity of AS activity and elevated CRP and ESR levels. Furthermore, the mode of action of miR-223 seems to be associated with macrophages' activation and osteoclast differentiation, implying its role in inflammation and bone formation. Many different miRNAs were also identified, like miR-155, miR-21, and miR-29, responsible for immune system malfunctioning and pathological bone growth [32]. miRNAs are present in sera, plasma, and synovial fluids; thus, they make good non-invasive biomarkers for diagnosis of the disease, disease development tracking, and evaluation of the effectiveness of therapy.

Ferroptosis-Associated Biomarkers

It is possible to assume that ferroptosis is a newly discovered form of cell death caused by oxidative stress and lipid peroxidation due to iron accumulation. Based on some recent studies, it has been found that the occurrence of ferroptosis might play an important role in inflammatory processes, immune dysfunction, and the damage to various

organs seen in the case of AS. Due to metabolic disorders related to the imbalance between iron levels and oxidative stress, AS is associated with high inflammation and remodeling of the tissues in the spine.

There are a few genes linked to ferroptosis that show abnormal expressions among AS patients, including ACSL1, SLC40A1, XBP1, and GZMM. Some of the biological processes that are under the control of these genes involve lipid metabolism, iron balance, unfolded protein response, and cytotoxic immunity. Among potential markers of ferroptosis, there are ferritin, transferrin receptor, malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), glutathione, and SLC7A11. Elevated MDA and 4-HNE concentrations are related to lipid peroxidation, whereas low glutathione indicates problems with antioxidant defence [33].

Proteomic Biomarkers

The application of proteomic approaches made it possible to investigate the profile of protein expression in serum, plasma, and synovial fluid from AS patients. The research results identified some proteins differently expressed, which were implicated in inflammatory processes, complement activation, ECM breakdown, and immune system reactions.

It has been demonstrated that the higher level of complement component C9, complement factor H-related protein 5 (CFHR5), orosomucoid-1 (ORM1), and matrix metalloproteinase-3 (MMP-3) is observed among AS patients. To be more precise, MMP-3 correlates with the inflammatory process and radiologic disease progression among AS patients. On the contrary, the lower level of clusterin and vitamin D-binding protein was observed among AS patients.

The application of proteomic biomarkers could be considered advantageous to provide early diagnosis, prognosis, and personalized therapy [34].

Table 1. Major immunological biomarkers in ankylosing spondylitis: types, sources, functions, and clinical relevance.

Biomarker Category	Biomarker	Source / Specimen	Major Function / Association in AS	Clinical Relevance
Genetic Markers 	HLA-B27	Peripheral blond (DNA)	Strongest genetic association, influences antigen presentation, ES stress, and lonate immune activation	Risk assessment; not diagnostic alone
	ERAP1	Peripheral blond (DNA)	Peptide trimming, interects with HLA-B27, polymorprimns increase AR lisk	Risk prediction; disease susceptibility
	IL-23R	Peripheral blond (DNA)	Regulates IL-23/IL-17 pathrery, vastants influence susceptibility and severity	Risk prediction, therapestic target
	Other gener*	Peripheral blond (DNA)	TNFSF15, ERAP2, RUNX3, CARD9, KIR3DL2 modulate immune activation	Risk prediction, pathway insights
Cytokines and Chemokines 	TNF-α	Serum / Plasma	Contral pro-inflamolatory cytokine, drives inflammation and structural damage	Disease activity; predicts response to anti-TNF
	IL-17A/F	Serum / Plasma	Produced by Tb17 cells, promotes neutropiul recruitment and bone changes	Disease activity; target for therapy
	IL-23	Serum / Plasma	Macianins Th17 cells, upstream driver of IL-17	Disease activity; therapeutic target
	IL-6	Serum / Plasma	Induces acute phase response, corvelates with inflammation	Disease activity; prognosis
	IL-22	Serum / Plasma	Produced by Tb17/7h15 cells: linked to inflamess and oew bone formation	Disease activity; severity
	CCL2, CXCL10	Serum / Plasma	Cherookiase driving immune cell recruitment	Disease activity; potential biomarkers
Acute Phase Proteins 	CRP	Serum	Hegatic protein indused by IL-6, reffects systemic inflammation	Disease activity; monitoring
	EER	Whole bland	Noo-specific marker of infornmation	Disease activity; monitoring
	SAA	Serum	Sensitive acute phase reactant, corvelates with CRP and disease activity	Disease activity; early marker
Autoantibodies 	Anti-α-enolase	Serum	Autoantilualy against glycolytic enzyme; associated with disease activity	Disease activity; potential prognostic marker
	Anti-collagen II	Serum	Associated with cartilage damage and progression	Disease severity; prognosis
	Anti-Seratin 8/10	Serum	Linked with extre-erticular manifactations	Disease activity
Immune Cells and Subsets 	Th17 cells	Peripheral blond	Key effector cells producing IL-17	Disease activity; therapentic target
	γδ 7 cells	Peripheral blond	Expanded in AS, produce IL-THIFN-γ	Disease activity; severity
	Regulatory T cells (Tregs)	Peripheral blond	Dysfunctional/reduced in AS	Disease activity; prognosis
	Neutrophila (NETosis)	Peripheral blond	NETs promote inflommation and enthestils	Disease activity; potential target
Emerging Biomarkers 	miRNAs (miR-21, mill-155, mifi-146a)	Serum / Plasma	Regulate immune responses and cytokine networks	Disease activity; monitoring prognosis
	Perroptosic markers (GPS4, 166A)	Serum / Plasma	Linked to vxidative stress and cell death	Disease activity; novel therapeutic targets
	Metabolomics (Tryptophan pathway)	Serum / Plasma	Altered metabolites reflect immune activation	Disease activity; early detection
	microbiome signature	Stool	Dyshiosis associated with disease sisk and activity	Disease risk; therapeutic target

*Includes TNFSF15, ERAP2, RUNX3, CARD9, KIR3DL2, PTGER4, IL-1 family genes, and others.

Clinical Utility and Future Directions

Despite substantial advances in understanding of the molecular and immune bases of AS, relatively few biomarkers have been implemented into daily medical practice so far. Today, HLA-B27, CRP, and ESR testing remain the most common approach. Indeed, HLA-B27, CRP, and ESR are helpful in diagnosis of AS but lack certain flaws. In particular, while HLA-B27 is not completely specific since it is found in a lot of healthy people, CRP and ESR may also be within normal range in actively inflamed patients. Therefore, there arises a pressing need in highly specific biomarkers that would be able to evaluate disease severity, predict outcome, and determine therapy.

It seems likely that future achievements in the field will be linked with application of a multimarker approach using different types of biomarkers including genetic, genomic, transcriptomic, cytokine, proteomic, metabolic, and cellular ones. Using biomarker panels will make it possible to identify disease endotypes and detect the disease at the early stages, particularly in case of non-radiographic axial spondyloarthritis patients. Moreover, they will help in predicting radiographic progression, extra-articular manifestations, and treatment effectiveness [35].

New fast-growing technologies can accelerate the biomarker identification process. Specifically, single-cell RNA sequencing may contribute to the characterization of immune-cell populations and the identification of pathogenic cell populations in patients with AS. In addition, machine learning and artificial intelligence methods can be used to predict biomarker signatures and personal risk profiles by integrating the information acquired in clinical trials and molecular investigations. Deep immune phenotyping and multi-omics techniques can play an important role in understanding disease heterogeneity and therapy response.

At the moment, research efforts focus on developing new biomarkers involved in the IL-23/Th17 pathway, gut microbiome interactions, complement system activation, extracellular vesicles, and ferroptosis. The analysis of the cargo inside extracellular vesicles (including microRNA and inflammation proteins) may help identify highly sensitive immune activation and tissue remodeling biomarkers. Overall, all of these approaches may pave the way toward personalized therapies for patients with AS [36].

CONCLUSION

Ankylosing Spondylitis (AS) is an auto-inflammatory chronic disease whose pathogenesis is considered to be extremely complex and multi-component. It occurs due to interactions between genetic, environmental factors, the activation of innate immunity, the disruption of acquired immunity, oxidative stress, and pathological bone remodeling. From the perspective of the role of genetics in the development of this disease, it should be noted that HLA-B27 remains a major biomarker in the diagnosis of AS and the identification of patients at high risk of developing the disease. However, there is increasing evidence that additional mechanisms and factors are needed in addition to HLA-B27 for the development of AS.

Recent advances in molecular immunology and omics have resulted in many new candidate biomarkers of AS. These new biomarkers include a variety of molecules such as mediators of IL-17 and IL-23 signaling, calprotectin, MMPs, NET-derived products, anti-CD74 antibodies, microRNAs, extracellular vesicles, and molecules involved in ferroptosis.

However, despite the numerous advantages of such discoveries, there exist some issues that need to be considered before applying such innovations. For instance, it can be argued that many of the biomarkers identified by researchers have not been validated on diverse ethnic populations for a sufficiently long time before incorporating them into practical medicine. Moreover, the problems of standardization of the tests, reproducibility, and cost-effectiveness could be an obstacle to the creation of some biomarkers.

The future progress in this field is most likely to include a multi-marker approach, namely, taking into account the genetic, gene expression, protein, metabolite, and cellular profile of AS patients along with the use of bioinformatics technologies, including machine learning algorithms, to process the results obtained. As a result, it would become possible to offer personalized treatment based on diagnosis, disease prognosis, therapy selection, and monitoring the disease progression. To achieve this goal, interdisciplinary cooperation among immunologists, rheumatologists, molecular biologists, and bioinformaticians will prove indispensable.

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Author Contributions

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