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Review

An update on biomarkers in axial spondyloarthritis

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ABSTRACT

Axial spondyloarthritis is a chronic inflammatory disease with the onset at a young age, and, if undiagnosed and untreated, it may result in permanent damage and lifelong disability. Rates of early diagnosis have improved, due in particular to the addition of magnetic resonance imaging into the diagnostic armamentaria; however, it is costly, not widely available, and requires experienced readers to interpret the findings. In addition to clinical measures and imaging techniques, biomarkers that will be described in this review may represent useful tools for diagnosis, monitoring disease activity and outcomes as well as therapeutic responses. Currently, HLA-B27 remains the best genetic biomarker for making a diagnosis, while CRP currently appears to be the best circulating measure for assessing disease activity, predicting structural progression and therapeutic response. Interestingly, key molecules in the pathogenesis of the disease and essential therapeutic targets, such as tumour necrosis factor (TNF)α, interleukin (IL)-17 and IL-23, show only limited association with disease characteristics or disease progression. Some genetic biomarkers and particularly anti-CD74 antibodies, may become a promising tool for the early diagnosis of axSpA. Further biomarkers, such as matrix metalloproteinases (MMP)-3, calprotectin (S100A8/9), vascular endothelial growth factor (VEGF), C-terminal telopeptide of type II collagen (CTX-II) or dickkopf-1 (DKK-1), are not sufficient to reflect disease activity, but may predict spinal structural progression. In addition, recent data have shown that monitoring calprotectin might represent a valuable biomarker of therapeutic response. However, all of these results need to be confirmed in large cohort studies prior to use in daily clinical practice.

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1. Introduction

Axial spondyloarthritis (axSpA) is a group of heterogeneous inflammatory rheumatic diseases predominantly affecting the axial skeleton, which is associated with chronic back pain due to sacroiliac joint and spinal inflammation [1]. Diverse clinical manifestations are common in axSpA and include enthesitis, peripheral arthritis (mostly affecting the large joints of the lower extremities) and characteristic extra-articular manifestations, such as uveitis, psoriasis or inflammatory bowel diseases.

The Assessment of SpondyloArthritis international Society (ASAS) has recently developed new set of classification criteria for axSpA that were initially intended for clinical research purposes [2]. These criteria cover the whole spectrum of axial involvement ranging from patients with non-radiographic axSpA (nr-axSpA) to the well-known group of patients who already fulfil the modified New York classification criteria for ankylosing spondylitis (AS) [3]. Because magnetic resonance imaging (MRI) is now a common practice in many countries for evaluating patients suspected of having axSpA, MRI-detected active sacroiliitis has become an important tool for the recognition and early diagnosis of axSpA [4].

However, the diagnosis of the early phases of axSpA still represents a clinical challenge in daily practice because chronic back pain is a common symptom and MRI inflammatory abnormalities can also be detected in healthy individuals. Furthermore, HLA-B27 can be often positive with no associated clinical presentation. Assessment and monitoring of disease activity is mostly limited to patient reported outcomes that do not necessarily correlate with MRI-detected inflammation [5] and to measuring the CRP, which is less sensitive in axSpA [6], and can also be used in assessing progression of structural damage [7], particularly of the spine, and response to therapy [8]. In the context of pathogenic mechanisms (Fig. 1, Table 1), we summarize here the genetic components, biomarkers of inflammation and tissue remodelling, cytokines and other immune mediators, including parameters of angiogenesis and autoantibodies that may improve the diagnosis, prognosis and treatment outcomes in axSpA.

2. Genetic components

HLA-B27 is a class I surface antigen that plays a major role in protective immunity. It is encoded by the B locus of the major histocompatibility complex (MHC) and presents peptide antigens to the T-cells. Whether the major role of HLA-B27 in axSpA is the auto-antigen presentation to CD8 + T-cells suggestive of autoimmune disease, or whether its main function is triggering the innate immune responses secondary to bacterial or mechanical stress in keeping with autoinflammatory disease remains to be elucidated [1]. Irrespective of its pathophysiological function, HLA-B27 is strongly associated with axSpA and represents a core laboratory test for the diagnosis of axSpA. No clear associations between HLA-B27 and sacroiliac or spinal radiographic progression over two years were found in patients with early axSpA [7], however, more severe radiographic progression may be observed in HLA-B27 positive AS patients in long-term [9].

Although HLA-B27 is positive more often in established disease—AS (80–90%), it is less commonly present in early phases of the disease in nr-axSpA patients (73–75%) [7,10]. Although the test has a good sensitivity, it has a low specificity as the prevalence of HLA-B27 in healthy subjects varies across regions ranging between 4 to 25% in western to northern European countries [11] and only 1.3–6% of the HLA-B27 positive population develops AS [1,12]. This is suggestive of contribution of additional genes to susceptibility to axSpA [13].

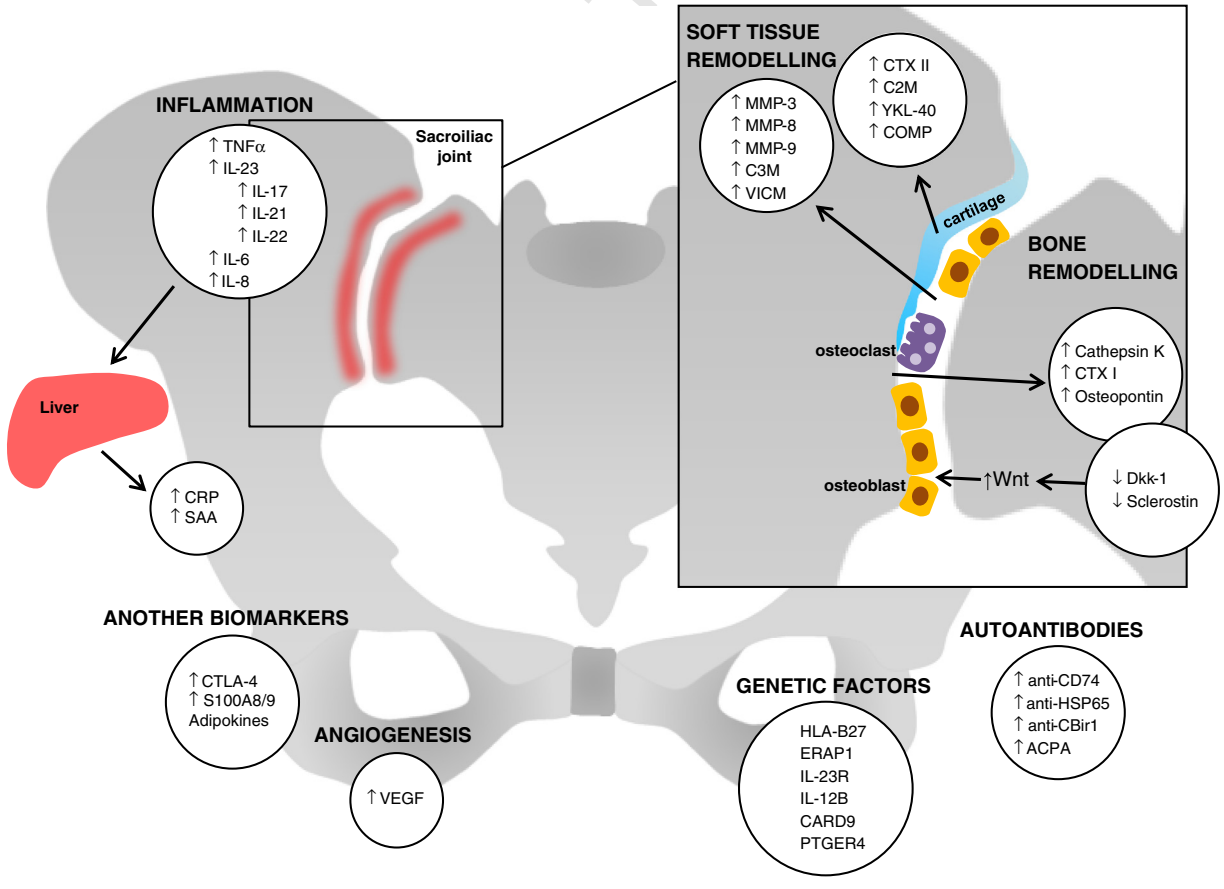

Fig. 1. Biomarkers of axial spondyloarthritis according to pathogenic mechanisms.

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