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Review

Detection of novel diagnostic antibodies in ankylosing spondylitis: An overview

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ABSTRACT

Ankylosing spondylitis (AS) is a debilitating, chronic, rheumatic disease characterized by inflammation and new bone formation resulting in fusion of the spine and sacroiliac joints. Since early treatment is impeded by a delayed diagnosis, it is highly important to find new biomarkers that improve early diagnosis and may also contribute to a better assessment of disease activity, prognosis and therapy response in AS. Because of the absence of rheumatoid factor, AS was long assumed to have a seronegative character and antibodies are thus not considered a hallmark of the disease. However, emerging evidence suggests plasma cells and autoantibodies to be involved in the disease course. In this review, the role of B cells and antibodies in AS is discussed. Furthermore, an overview is provided of antibodies identified in AS up till now, and their diagnostic potential. Many of these antibody responses were based on small study populations and further validation is lacking. Moreover, most were identified by a hypothesis-driven approach and thus limited to antibodies against targets that are already known to be involved in AS pathogenesis. Hence, we propose an unbiased approach to identify novel diagnostic antibodies. The already successfully applied techniques cDNA phage display and serological antigen selection will be used to identify antibodies against both known and new antigen targets in AS plasma. These newly identified antibodies will enhance early diagnosis of AS and provide more insight into the underlying disease pathology, resulting in a more effective treatment strategy and eventually an improved disease outcome.

Contents

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1. Introduction

Spondyloarthropathy consists of a group of inflammatory rheumatic diseases characterized by overlapping clinical signs and symptoms [1]. Based on the predominant occurrence of clinical symptoms, a more peripheral or axial involvement can be distinguished in SpA [2]. Axial SpA (axSpA) mainly affects the vertebral column and sacroiliac (SI) joints, and can be further subdivided by radiographic imaging in non-radiographic axSpA or in a radiographic subtype, which is also known as ankylosing spondylitis (AS) or Bechterew's disease [3]. AS is not only characterized by major inflammation of the spine and SI joints, but also by variable inflammatory involvement of peripheral joints and extra-articular tissues, including the skin, bowel or tendons [4]. Approximately 0.2–1.2% of the Western European population is suffering from AS, of which men appear to be most frequently affected [5]. Although first clinical symptoms occur between the ages of 20 and 40, diagnosis is delayed for 8–10 years in most patients [6]. This delay occurs since AS is diagnosed based on the presence of clinical symptoms and the use of the modified New York (mNY) classification criteria [7]. The mNY criteria appear to be inadequate for diagnosing early patients as they involve structural changes in the spine and SI joints, which are not detectable in early disease [8]. Inclusion of magnetic resonance imaging (MRI) to the new Assessment in SpondyloArthritis international Society (ASAS) criteria resulted in the detection of axial inflammation before structural changes evolve on conventional radiographic imaging [9,3,10]. Although MRI is able to detect inflammation in an early stage of disease, this imaging technique is only performed to confirm the rheumatologists' suspicion of AS diagnosis as it is expensive, relatively time-consuming and not everywhere available [11]. In addition, the ASAS classification criteria were not intended for diagnosing AS, but rather for the uniform classification of axSpA patients in smaller subgroups [8]. Since patients often display a wide variety of clinical features [4] and a good laboratory test is still lacking, a straightforward diagnosis of AS is impeded.

But why is it so important to diagnose AS as early as possible? Since regular intake of nonsteroidal anti-inflammatory drugs (NSAIDs) was not only shown to be effective in treating AS symptoms, but also reduced radiographic progression [12], an early diagnosis is essential in order to expedite treatment and reduce the burden of disease. A breakthrough was the discovery of the involvement of tumor necrosis factor (TNF)-α in disease pathology, leading to the development of therapeutic antibodies targeting this cytokine. In accordance to the updated ASAS recommendations in 2010, SpA patients who meet the ASAS classification criteria were allowed to be treated with these anti-TNF agents if first-line treatment with two NSAIDs for at least four weeks was not effective in reducing disease activity [13]. Highest efficacy in preventing irreversible destructive effects and ankylosis is achieved when these biologicals are provided at an early disease stage [14–16]. At an early stage, the disease is mainly characterized by inflammation, which progresses gradually over time into bone destruction and abnormal bone formation, resulting in stiffening and eventually total fusion of the spine and SI joints [17]. As disease activity increases over time, AS patients experience spinal and extra-articular manifestations that are associated with a more impaired functionality, resulting in an increased work disability [18,19]. Nonetheless, work withdrawal not only results in large economic and psychosocial consequences for the patient, it also has major socio-economic impact on the entire population. Surveys of Boonen et al. revealed that work disability and the associated decrease in productivity due to AS, involves high costs [20,21]. Earlier treatment is therefore more effective in reducing disease burden of AS patients and disease-related costs. This further emphasizes the urging need for biomarkers which allow early diagnosis of AS. In this review, a brief overview is provided of antibodies described in AS and their potential as biomarker. These putative biomarkers were mainly identified via hypothesis-driven approaches, limiting the identification of antibodies to known protein targets and key players in AS pathology. Therefore, an alternative unbiased strategy is proposed by which novel antibody biomarkers directed to known and novel targets in disease pathology can be identified in order to ameliorate future AS diagnosis and improve the assessment of disease activity, prognosis and treatment response.

2. Pathogenesis of AS

Although the etiology of AS is not completely understood, current existing evidence points towards the involvement and interaction between genetic risk factors and environmental factors.

Genetic studies demonstrate the inheritance of AS to be more than 90%, in which a particular strong genetic link exists with major histocompatibility complex (MHC) class I allele human leukocyte antigen (HLA)-B27 [22]. In the Caucasian population, it was estimated that no more than 5% of HLA-B27-positive people develop AS, whereas approximately 90% of AS patients carry this allele [23]. Although the exact role of HLA-B27 in AS pathogenesis is incompletely understood, several hypotheses have emerged [24]. Firstly, the arthritogenic peptide hypothesis implies complex formation between HLA-B27 and β-2 microglobulin in order to present bacterial or arthritogenic peptides to CD8-positive T lymphocytes. Subsequently, these cytotoxic T lymphocytes can cross-react with self peptides due to molecular mimicry of bacteria and their peptides [25,26]. However, CD8-positive T lymphocytes are apparently not essential for AS onset [27,28]. Secondly, HLA-B27 has a unique property allowing two heavy chains to adhere to each other, resulting in an incorrectly folded HLA-B27 protein in the endoplasmic reticulum (ER) [29]. HLA-B27 homodimers migrate towards the cell surface [13], where they can be antigenic themselves or present peptides to T lymphocytes or natural killer cells, especially if normal antigen-presentation is disrupted [30–32]. Misfolded HLA-B27 can accumulate in the ER and induce an unfolded protein response [33], resulting in the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and eventually increased expression of pro-inflammatory cytokines, including interleukin (IL)-23 and TNF-α [34–36]. TNF-α is a highly interesting cytokine in AS pathology as it may provide a possible link between inflammation and disturbed bone homeostasis [37,38]. Additionally, misfolded HLA-B27 does not only induce an unfolded protein response, but also other autophagy-associated processes resulting from cytosolic aggregation [39–41]. Next to these different functionalities of HLA-B27, the expression level of HLA-B27 was suggested to be relevant for AS predisposition. HLA-B27-positive AS patients demonstrate a higher expression level of HLA-B27 on peripheral blood mononuclear cells compared with HLA-B27-positive healthy individuals [42]. Since HLA-B27 is estimated to be responsible for 40% of the genetic risk of AS [22,23], also a number of single nucleotide polymorphisms (SNPs) were identified using genome-wide association studies [43–46]. Other genes predisposing for AS are related to the IL-17/IL-23 pathway, NF-κB signaling, antigen presentation and T cell phenotype, including the IL-23 receptor (IL-23R), prostaglandin E receptor 4 (PTGER4), endoplasmic reticulum aminopeptidase 1 (ERAP1), Runt-related transcription factor 3 (RUNX3) or Scr homology 2 adaptor protein 3 (SH2B3) [47].

Within genetically predisposed individuals, two central processes arise: inflammation and new bone formation, in which gut inflammation and enthesitis have been proposed to be key players (Fig. 1). AS is not only associated with gut inflammation [48,49], the link between AS and Crohn's disease is dependent on HLA-B27 positivity [50]. Evidence suggest that HLA-B27 interferes with a proper host defense and cells' ability to resist bacteria [51,52], resulting in leakage of gut mucosa and interactions between bacteria and the immune system [53,54]. Although no particular micro-organism could be identified as a specific trigger for SpA [55], a pivotal role of bacteria – either endogenous or infectious – is further supported by the finding that HLA-B27 transgenic mice did not develop SpA-like disease in a germ-free environment [56]. Interestingly, synovial fibroblasts infected with arthritogenic