

Clinical-state-of-the-art

Pathophysiology of ankylosing spondylitis: What's new?

Thao Pham*

Service de Rhumatologie, CHU Conception, 147, Boulevard Baille, 13005 Marseille, France

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Abstract

Ankylosing spondylitis is a chronic inflammatory joint disease that predominantly affects the sacroiliac joints and spine. Its pathophysiology remains one of the most vexing enigmas of rheumatology. However, new insights have been provided by the recent identification of susceptibility genes other than HLA-B27; evidence of a pivotal role for several proinflammatory cytokines including interleukins 23 and 17; and the recognition that inflammation and structural progression proceed separately from each other.

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1. Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory joint disease that chiefly affects the sacroiliac joints and the spine. The pathophysiology of AS remains largely unknown. Its association with HLA-B27 was first established in the early 1970s, and AS is one of the best examples of diseases linked to genetic markers. The role of HLA-B27 remains incompletely understood [1]. However, advances made in many fields over the last few years have shed some light on the pathophysiology of AS. The objective of this article is to describe recent data, such as the identification of susceptibility genes other than HLA-B27, the demonstration that proinflammatory cytokines other than TNF are involved in AS, and the dissociation between inflammation and structural progression.

2. Ankylosing spondylitis is a polygenic disease

2.1. HLA-B27 is a major marker but not the sole marker, for ankylosing spondylitis

A huge body of evidence establishes that AS is associated with HLA-B27. This association has been found in many

populations and ethnic groups, on multiple haplotypes [2]. Some of the HLA-B27 subtypes are not associated with AS, suggesting that subtype polymorphism may modulate the disease [3]. The results of animal studies support these epidemiological findings. Rats transgenic for HLA-B27 and human beta2-microglobulin develop a disease that shares many similarities with human AS. In this model, the disease phenotype can be modulated by manipulating HLA-B27, its peptide repertoire, or its folding [4]. However, although over 90% of patients with AS express HLA-B27, AS develops in less than 5% of HLA-B27-positive individuals, suggesting a role for susceptibility genes outside the major histocompatibility complex (MHC) [5–8]. Twin studies support this possibility: concordance rates are higher in monozygotic twins than in dizygotic twins, indicating a role for genetic factors. Concordance rates for AS are 23% in dizygotic and 63% in monozygotic twins positive for HLA-B27. Similarly, the inherited nature of the disease phenotype (age at onset, activity, and severity) may be only partly dependent on HLA-B27 [9]. In sum, these data suggest that AS may depend on multiple genes [10].

2.2. The four best candidate genes for a role in ankylosing spondylitis

2.2.1. HLA-B27

The leading candidate is HLA-B27, whose strong link with AS long hindered the detection of other associations in

* Tel.: +33 4 91 38 34 62; fax: +33 4 91 38 38 87.

E-mail address: thao.pham@ap-hm.fr

familial databases. The latest meta-analysis of linkage studies showed that the most robust and strongest link occurred with the MHC region on the short arm of chromosome 6 [11]. However, links have been found with other regions, most notably on 16q and 10q.

HLA-B27 may contribute about 20–50% of the total genetic risk of AS [10]. New techniques, most notably genome screening, have enabled the identification of susceptibility genes located outside the MHC region [12]. Although many genes outside the MHC region have been investigated, only three likely candidates have been identified: the interleukin-1 (IL-1) gene cluster, ARTS1, and the IL-23 receptor gene (IL-23R) [13].

2.2.2. The IL-1 cluster

The IL-1 cluster contains nine genes on chromosome 2, including the genes for IL-1 α , IL-1 β , and the IL-1 receptor antagonist (IL-1RN). An association between AS and allelic polymorphisms of the IL-1RN gene was suggested. However, five recent studies found no evidence supporting a role for IL-1RN. In contrast, studies support a role for IL-1 α and IL-1 β in North America and the United Kingdom, and perhaps in South Korea [14–17]. Although the association linking IL-1 to AS is strong, the magnitude of the genetic risk related to each variant is small, with an attributable risk estimated at 4–6%. IL-1 α is a proinflammatory cytokine produced chiefly by activated macrophages. IL-1 overexpression in mice causes severe chronic proliferative arthritis. The role for IL-1 has not been evaluated in animal models of AS and remains unclear in humans [18]. In two therapeutic trials, the IL-1 inhibitor anakinra was effective, suggesting a role for IL-1 in AS. However, the effect was small compared to that of TNF antagonists [19–21]. Extracellular inhibitors seem to have little influence on the effects of IL-1 α . Researchers are therefore focusing on the intracellular activity of IL-1 and on its proinflammatory effects.

2.2.3. Aminopeptidase regulator of TNFR1 shedding (ARTS1 or ERAP1)

One of the most exciting discoveries made in recent years is that the ARTS1 gene may contribute as much as 26% of the risk of developing AS [22]. ARTS1 is an endoplasmic reticulum aminopeptidase that has two known effects. One effect is cleavage of cytokine receptors (IL-1, IL-6, and TNF) from the cell surface [23–25]. Loss of function of ARTS1 variants may therefore induce proinflammatory effects. The second effect of ARTS1 is cleavage of the N-terminus of peptide precursors in the reticulum, which ensures that the final peptide length is appropriate for presentation by MHC class I HLA molecules [26,27]. ARTS1 knock-out mice are characterized by decreased expression of surface MHC class I molecules, significantly increased alteration of MHC class I surface markers, and decreased antigen stability with defective antigen presentation at the cell surface [28,29]. As mentioned earlier, the role for HLA-B27 in the pathophysiology of AS remains unclear. Among the many hypotheses put forward to date, one involves presentation of an arthritogenic peptide by HLA-B27. AS does not develop in mice transgenic for HLA-B27 and human β 2 microglobulin that are kept in a sterile environment.

Nevertheless, this hypothesis has not been fully proven. The role for ARTS1, which tailors peptides for presentation by the MHC, supports the involvement of a group of arthritogenic peptides. These peptides may share a similar shape, rather than an amino acid sequence. Further studies of this possibility are needed.

2.2.4. The interleukin-23 receptor (IL-23R)

Whereas ARTS1 may explain the association between HLA-B27 and AS, the IL-23R gene seems to link the spondyloarthropathies to chronic inflammatory bowel disease and psoriasis. A study reported in late 2006 established that Crohn's disease was associated with the IL-23R gene on chromosome 1p31, a finding that was confirmed in subsequent studies [30,31]. Shortly afterward, an association between IL-23R and psoriasis was demonstrated [32]. Several studies have shown that IL-23R is a major susceptibility gene for AS [22,33,34]. The key role for IL-23 in the pathophysiology of AS will be discussed later on.

In sum, the polygenic nature of AS is firmly established [35]. The identification of new susceptibility genes – IL-1, ARTS1, and IL-23R – has shed light on the pathophysiology of AS, most notably regarding the role for HLA-B27.

3. Is ankylosing spondylitis an autoinflammatory disease?

Hypotheses regarding the role for HLA-B27 fall into two main groups. One group ascribes a role to environmental factors, such as arthritogenic peptides and molecular mimicry involving the adaptive and innate immune systems. The other group involves the biochemical characteristics of the HLA-B27 molecule, whose abnormalities may affect cell function. Thus, misfolding of the HLA-B27 molecule or the formation of heavy-chain homodimers has been suggested [36]. The formation of homodimers that are unable to present antigens leads to the build-up of chaperonins such as BIP (immunoglobulin heavy-chain binding protein) and to a stress response related to the endoplasmic reticulum (the unfolded protein response), which in turn induce inflammatory factors such as IL-23.

Thus, HLA-B27 may modulate the inflammatory response to infectious agents, via misfolding with an unfolded protein response and/or via antigen recognition. Therefore, diseases associated with HLA-B27 may be autoinflammatory rather than autoimmune diseases [37], with the entheses being the target in AS.

4. The key role for the IL-23/IL-17 axis in ankylosing spondylitis

4.1. Cytokines IL-23 and IL-17

IL-23 is a recently identified heterodimeric cytokine that belongs to the IL-12 family. Of the two subunits, p19 and p40, the latter is shared with IL-12. Under the influence of IL-6 and TGF β , which induce the expression of IL-23R on Th17 cells, IL-23 maintains the orientation of naïve CD4 + T cells to Th17 cells that produce IL-17. IL-17 is a proinflammatory cytokine that induces the production of IL-1, IL-6, TNF, and

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