Animal Models of Ankylosing Spondylitis

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Introduction

Ankylosing spondylitis (AS) and related spondyloarthropathies (SpA; referred to, for convenience, as AS) are among the most common inflammatory rheumatic diseases. In the US and Northern Europe, these disorders have an estimated prevalence of at least 0.1% to 0.2%, but may be significantly higher [1]. In developing countries, it has been recognized that AS tends to have an earlier age of onset, and a greater propensity for disability compared with patients in North America and Western Europe. Disease onset occurs most commonly in late adolescence and early adulthood, and nearly 80% of affected people are symptomatic by age 30. In addition to the strong genetic predisposition, partly because of human leukocyte antigen (HLA)-B27, the characteristic clinical features of AS include inflammatory back pain usually caused by sacroiliitis and enthesitis in well-defined locations. Although AS typically involves the axial skeleton, the peripheral joints, such as shoulders and hips, and extra-articular structures are also affected. This pathology may include more generalized enthesitis, anterior uveitis, aortitis, aortic valve insufficiency, upper lobe pulmonary fibrosis, and immunoglobulin A (IgA) nephropathy.

The etiology and the pathogenesis of AS is poorly understood, and it is derived mainly from studies at autopsy [2] and biopsies of sacroiliac (SI) joints and sites of enthesitis [3,4]. Because the pathology is difficult to access, particularly involving the spine, animal models have special value, and provide opportunities for investigative studies. An ideal animal model of spondylitis should enable a better understanding of the genetic association of HLA-B27 with AS, the molecular organization of the spine and SI joints, entheses, which are susceptible to inflammatory attack in AS, and the molecular and biochemical mechanisms involved in the pathology of AS. Herewith, the authors will review three animal models for AS. Each model has its advantages and disadvantages. The pathology of AS will be examined first, so that readers may better appreciate and consider the models at their disposal.

The Pathology of Ankylosing Spondylitis

Relatively little is known about the cellular and molecular mechanisms involved in the initiation and progression of AS. A number of features of the disease suggest that immunity to self or non-self may be important. These include an inflammatory histopathology, elevated serum levels of IgA and acute phase protein, a close association
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with HLA-B27, and extra-articular manifestations. However, no specific self-antigen or exogenous agent, which has been universally accepted as a causative agent, that triggers the onset of AS has been recognized in human studies.

Human leukocyte antigen-B27 association
Human leukocyte antigen-B27 is a major histocompatibility complex class I (MHCCI) molecule, and its normal function is to present intracellularly generated antigenic peptides to CD8+ T cells. In most populations, over 90% of patients with AS carry the HLA-B27 genes. The association between AS and HLA-B27 is one of the strongest HLA-disease associations [5]. Recently, an HLA-B27-restricted CD8 response to a synthetic self-peptide (residues 400-408 of vasoactive intestinal peptide receptor 1) has been observed in patients with AS, but not in healthy control individuals [6]. However, at least two of the 12 known HLA-B27 subtypes are not, or are only very weakly, associated with AS. Moreover, there is debate concerning the association of the B27 subtypes with their peptide-binding specificity [7]. Evidence for a direct role of HLA-B27 in autoimmunity is provided by the observation that HLA-B27 transgenic rats spontaneously develop arthritis with evidence for a spondylitis [8•,9]. Nonetheless, the molecular mechanism(s) whereby a susceptible B27 allele may lead to AS remains a mystery.

Spondylitis and the structure of the lumbar spine
In recent decades, molecular biology has greatly advanced the study of the skeleton, but there are few data that reveal the molecular compositions of the skeletal structures involved in AS. The joints of the spine are devoid of synovium. Their structure is shown in Figure 1. The cartilage-like nucleus of the intervertebral disc is laterally bound by the annulus, which in turn, is bound by spinal ligaments; both structures are inserted into bone. These junctions are called entheses. They are very specialized structures. Combined with the ligaments, they contain type I collagen in a matrix that is rich in the proteoglycan versican (Fig. 1). The binding of versican to hyaluronan is stabilized by link protein in each case. Versican, like aggrecan, binds to hyaluronan via a globular (G) 1 domain. Not surprisingly, the structures of the G1 domains of versican and aggrecan are similar (Fig. 2), and share regions of common sequence in the G1 domain and potential antibody or T cell recognition sites (epitopes). The macromolecular aggregates that are formed from these molecules provide a hydrated environment, because of the water-binding capacity of the chondroitin sulfate chains of versican. In the human annulus, type I and II collagens are present [10], along with versican [11] and smaller concentrations of the proteoglycan aggrecan [10]. Aggrecan and type II collagen are the major components of hyaline cartilages [12•]. They are present in high concentrations in the nucleus [10]. The intervertebral disc abuts the hyaline cartilages of the end plates of the intervertebral joint that cover the ends of the vertebrae bounding the joint (Fig. 1).

In contrast, SI joints are more like a diarthrodial joint, but differ in that movement is very restricted, and a hyaline cartilage covering the ilium articulates with the fibrous cartilage of the sacrum. These joints also have ligament insertions that control articulation, and these ligaments also contain the proteoglycan versican. Whereas versican is present in the hyaline articular cartilage of the SI joint, as well as in the fibrous component, rodent studies reveal that it is absent from the hyaline cartilages of diarthrodial joint, such as the knee and end plates, and is also absent from the nucleus (Shuiliang et al., Unpublished data).

The entheses share composition and structure with ligaments and hyaline cartilages. Versican and aggrecan are present, as are link protein and types II and I collagens [13]. In AS, early inflammatory mononuclear cell lesions involving macrophages, but not T cells, are commonly seen at entheses [14]. Chondroid metaplasia may develop and calcify, which contributes to ankylosis and bony fusion of vertebrae. In a subset of about 25% of patients, an erosive polyarthritis is seen.