Pathogenesis of Axial Spondyloarthritis — Sources and Current State of Knowledge

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KEYWORDS

• pathogenesis • disease model • axial spondyloarthritis • ankylosing spondylitis

KEY POINTS

- Models of disease pathogenesis are informed by multiple lines of investigation. Animal studies are just one of many sources of knowledge.
- The development of axial SpA involves the interplay of genetic and environmental factors likely including mechanical stress and intestinal dysbiosis.
- The lack of access to diseased human tissue has hampered progress in understanding the pathogenesis of axial SpA.
- Randomized controlled trials with biologics are explorations of disease pathogenesis. Combining therapeutic drug trials with mechanistic studies would be desirable.

INTRODUCTION

Scientific breakthroughs, such as the discovery of rheumatoid factor in the 1940s and the development of techniques for histocompatibility testing in the 1960s, culminated in the development of the spondyloarthritis (SpA) concept as a family of rheumatic diseases, distinct from rheumatoid arthritis (RA), with overlapping clinical features and genetic risk factors.[1,2] The demonstration, by magnetic resonance imaging (MRI), of inflammatory lesions in the sacroiliac (SI) joints and spine of patients with axial symptoms of SpA who lacked radiographic features of ankylosing spondylitis (AS),[3,4] helped further refine the SpA concept by introducing axial SpA as a new entity.[5] Axial SpA includes patients with AS (also referred to as radiographic axial SpA) and patients with axial symptoms previously categorized as undifferentiated SpA (now nonradiographic axial SpA). AS was described more than 100 years before

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Rheum Dis Clin N Am 46 (2020) 193–206
https://doi.org/10.1016/j.rdc.2020.01.016
rheumatic.theclinics.com

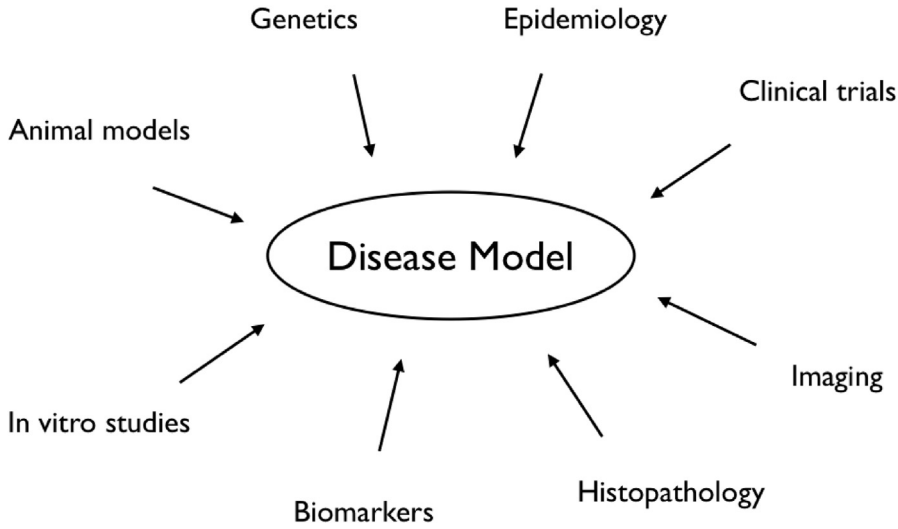

Fig. 1. Sources of knowledge informing the current (and future) understanding of axial SpA pathogenesis.

the development of the axial SpA concept and most clinical studies in axial SpA have been performed in AS. It is likely (although not proved) that the early events leading to axial inflammation are the same in all patients with axial SpA and that additional factors, environmental or genetic, drive progression to AS in a subset of patients. Ideas about pathogenesis, like disease concepts, evolve over time under the influence of new discoveries and changing scientific paradigms. This review examines the sources of knowledge that inform axial SpA pathogenesis (**Fig.1**), highlighting some of the current limitations and ending with a basic working model of axial SpA pathogenesis (**Fig. 2**).

EPIDEMIOLOGY

Axial SpA is a disease that typically begins in young adulthood and is equally common in men and women. In contrast, AS is more common in men, with a male:female ratio of 2 to 3:1 by current estimates.[6] This suggests that male sex controls the progression from inflammation to structural damage rather than susceptibility to axial inflammation. On the other hand, women with axial SpA tend to have higher disease activity and are less responsive to treatment with tumor necrosis factor (TNF) inhibitors.[7] The mechanistic understanding of these sexual dimorphisms is still in its infancy.[8] Relatively little is also known about environmental risk factors for the development of axial SpA, which may reflect the fact that genetic factors play a much greater role. A study from 2008 analyzed the occupational history of 397 patients with long-standing AS[9] and found an association between jobs requiring dynamic flexibility (repeated stretching, bending, twisting, or reaching) and functional impairment as measured by Bath Ankylosing Spondylitis Functional Index (BASFI). Moreover, certain types of workplace exposures, including whole-body vibration, were associated with worse radiographic disease. In light of the current interest in the role of mechanical stress in axial SpA, this study carries substantial weight, but confirmation in independent studies is required. Whether similar

associations exist between workplace exposure and susceptibility to axial inflammation has not been studied. Smoking predominantly affects the progression from inflammation to structural damage.[10,11]

GENETICS

Twin studies in AS have demonstrated concordance rates in monozygotic twins greater than 50%, which is substantially higher than in other rheumatic diseases and suggests that genetic factors are the major determinant of disease risk in AS.[12] The association between HLA-B27 and AS was first described in 1973.[13,14] It is likely the strongest genetic association of any complex polygenic autoimmune/inflammatory disease with *P* values less than 10^{-100}.[15] Several hypothesis have been proposed but the precise mechanism underlying this association remains unknown.[16] Genome-wide association studies (GWAS) performed over the past 10–15 years in AS have identified multiple disease-associated loci outside of the major histocompatibility complex. In addition to genes involved in peptide processing and interleukin (IL)-23 receptor signaling, several disease-associated polymorphisms were found in genes relevant to lymphocyte biology, including RUNX3, TBX21, EOMES, ZMIZ1, IL7, IL7R, and BACH2. Currently, more than 100 risk loci for AS have been identified, which together explain 27.8% of the heritability of AS, with HLA-B27 contributing 20.4%.[17] Thus, much remains to be learned, including the identification of the actual risk variants in many of the identified risk loci.

The HLA-B27 association holds true for the broader category of axial SpA, although it is slightly lower than in AS.[18] GWAS studies have not been performed in (nonradiographic) axial SpA. One study applied a genetic risk score developed for AS to a cohort of patients with axial SpA and found a lower discriminatory capacity compared with AS.[19] The authors reasoned that this might indicate differences in the genetic make-up between the studied cohorts. Whether this truly reflects differences in genetic risk factors between nonradiographic axial SpA and AS remains to be shown. Heterogeneity of patient populations captured by the axial SpA criteria is a major problem for genetic studies.

IMAGING

MRI has revolutionized the axial SpA field by providing means to detect inflammation before skeletal changes become evident on radiographs.[3,4] Unfortunately, imaging studies have largely focused on diagnosis, and relatively few studies have utilized imaging to study disease pathogenesis.

Two types of lesions are frequently seen with MRI in patients with axial SpA—bone marrow edema (BME) and fat lesions. BME is considered to be the equivalent of inflammation whereas fat lesions are thought to represent a later lesion. Both types of lesions occur in the pelvic bone marrow adjacent to the SI joints as well as at the edges of vertebral bodies and in the posterior spinal elements. Observational studies have provided evidence that inflammatory vertebral corner lesions may either disappear or progress to become fat lesions, which are associated with an increased risk for subsequent syndesmophyte formation.[20,21] Fat lesions have also been observed as intermediary lesions in the SI joints filling in erosions (backfill) prior to progression to bony ankylosis.[22] Unfortunately (from the scientists' perspective), MRI entered the axial SpA world at about the same time as TNF inhibitors. Many patients in the aforementioned observational studies were thus treated with a TNF inhibitor and a comprehensive MRI account of the natural (untreated) history of sacroiliitis and vertebral corner inflammation in axial SpA is lacking.

The same caveat applies to recent studies that used serial computed tomography (CT) imaging to visualize and quantify syndesmophyte growth in AS.[23,24] These studies have shown that the distribution of syndesmophytes around the perimeter of the vertebral body is not random and that they occur most frequently at the posterolateral aspect of the vertebral body.[25] A more recent study demonstrated that anterior syndesmophytes in the thoracolumbar spine were smaller and less frequent in close proximity to the aorta.[26] Together these data provide circumstantial evidence that mechanical factors, intrinsic or extrinsic to the spine, may influence syndesmophyte formation.

Molecular imaging is an umbrella term for imaging modalities that permit insight into function.[27] Several studies have demonstrated the utility of PET-CT, PET-MRI or SPECT to identify inflammatory or bone forming lesions using ^{18}F-Fluorodeoxyglucose or ^{18}F-Sodium Fluoride tracers or ^{99m}Tc (Technetium)–labeled antibodies.[28–33] Radiation exposure associated with these approaches is likely a major reason that they have not used been more widely.

MRI studies in axial SpA typically rely on the standard sequences used in routine clinical practice. Newer MRI approaches, including 7T imaging or zero echo time MRI,[34] have not been applied in the axial SpA field yet and may offer higher spatial resolutions or insight into tissue properties that currently cannot be visualized.

CLINICAL TRIALS

While TNF inhibitors showed broad efficacy across many rheumatic diseases, including all diseases in the SpA family, subsequent studies of other inhibitors yielded more diverse results. IL-17A inhibitors (secukinumab and ixekizumab) showed clinical efficacy similar to TNF inhibitors in patient with active AS and nonradiographic axial SpA, including patients with AS who previously failed or were intolerant of TNF inhibitors.[35–38] In contrast, IL-6 antagonists (tocilizumab and sarilumab) failed to demonstrate efficacy in clinical trials in AS.[39,40] Perhaps even more surprising was finding that the IL-23p19 inhibitor rizankizumab and the IL-12/23p40 inhibitor ustekinumab did not meet their primary endpoints in clinical trials in AS and axial SpA, respectively.[41,42] Multiple lines of evidence point toward a role for the IL-23/IL-17A pathway in axial SpA, including the efficacy of IL-17A inhibition in axial SpA, in vitro data documenting the reliance of IL-17A producing lymphocytes on IL-23 stimulation, association of AS with multiple genetic polymorphisms in the IL-23 signaling pathway, and data from animal models.[43] Why then did IL-23 inhibition not work in axial SpA? Both rizankizumab and ustekinumab have demonstrated efficacy in other diseases of the SpA spectrum, including psoriasis and Crohn disease (rizankizumab) and psoriasis, psoriatic arthritis, Crohn disease, and ulcerative colitis (ustekinumab), making pharmacokinetic problems less likely. The fact that both a p19 and a p40 inhibitor showed negative trial results effectively rules out hypotheses invoking IL-23–related cytokines, such as IL-12 and IL-39 (a heterodimer of IL-23p19 and EBI3).[44] The most likely explanation might be that IL-23 plays a role during the initiation of axial inflammation but is dispensable at later time points, when factors other than IL-23 may drive the expression of IL-17A.[45]

As documented by these results, randomized controlled trials of biologics (typically monoclonal antibodies with high specificity) do not just test therapeutic efficacy, they also interrogate disease pathogenesis. Unfortunately, most clinical trials in axial SpA focus on clinical disease activity scores, serum C-reactive protein and standard

MRI of the SI joints as outcome measures and rarely collect additional mechanistic information. A lost opportunity.

TISSUE SPECIMENS

The importance and value of studying immune responses in the diseased tissue has been demonstrated in RA.[46,47] SpA research has been lagging behind because spine biopsies are considered unacceptable and too invasive for research purposes. Autopsies were an important source of biological specimens for research in the past, including in AS,[48] but are infrequently performed today. Moreover, except for rare circumstances,[49] autopsy specimens provide tissue only from late-stage disease, which is of limited value for understanding the critical early events in axial SpA pathogenesis. The same is true for specimens obtained during corrective spine surgery,[50,51] which occasionally is performed in patients with long-standing AS. Several studies have reported results from CT-guided needle biopsies of the SI joints.[52–55] These studies have demonstrated the presence of inflammation in the SI joints as well as evidence for cartilage erosion, pannus formation, and osteoproliferation. The value of this approach is limited, however, because the obtained specimens are small and the targeting of specific structures in the SI joints is challenging.[55]

An alternative more easily accessible biopsy target might be the pelvic BME lesions seen on MRI in patients with active axial SpA. BME is a radiological term that describes lesions in bone with low-intermediate signal on T1 and high signal on T2-weighted MRI sequences. On short tau inversion recovery (STIR) or similar sequences that suppress the high T2 signal of fat, BME lesions are hyperintense compared with regular BM. Since the original description in 1988,[56] BME has been observed in multiple conditions, including RA, SpA, trauma, degenerative disk disease, osteoarthritis, and primary BME syndrome.[57] Although the usage of the BME term across multiple conditions suggests shared pathology, histopathologic studies have demonstrated variable findings. A single study of surgical facet joint specimens from patients with long-standing AS described the "accumulation of eosinophilic fluid in the bone marrow interstitium" consistent with edema.[58] Studies performed in other diseases, however, do not support the idea that BME represents the accumulation of interstitial fluid as the name suggests. In osteoarthritis, BME seems to correlate with tissue fibrosis and necrosis[59,60] whereas studies in RA revealed the presence of inflammatory cell infiltrates in regions with BME on MRI.[61,62] The histopathologic equivalent of subchondral BME lesions in axial SpA or similar lesions in healthy individuals[63–65] is unclear. With regard to MRI fat lesions at vertebral corners, a recent histology study in advanced AS demonstrated that these lesions were indeed characterized by the accumulation of adipocytes[51].

BLOOD BIOMARKERS

Peripheral blood is easily accessible and can be sampled repeatedly with minor risk for morbidity.[66] Multiple cytokines and other soluble markers have been studied in AS. In order to understand these measurements in their relationship to the disease process in the axial skeleton, it would be important to assess disease status and activity at the time of blood sampling using appropriate imaging techniques (for instance whole body MRI) rather than rely on patient reported disease activity measures or serum C-reactive protein. To date such studies are lacking.[67] Many research groups have analyzed immune cells from patients with AS comparing them to healthy controls or patients with other rheumatic diseases. Numerical or functional abnormalities have

been found in patients with AS in multiple lymphocyte subsets, including $CD4^+$ T cells, $CD8^+$ T cells, $\gamma\delta$ T cells, invariant natural killer (NK) T cells, NK cells, and mucosal-associated invariant T (MAIT) cells.[8,68–74] An expansion of IL-17A–producing cells has been a common finding in the more recent studies. This is consistent with the success of IL-17A inhibitors in AS clinical trials and supports a critical role for the IL-23/IL-17A axis in AS pathogenesis. However, the identity of the expanded IL-17A producing lymphocyte populations varied between studies. It is unclear whether this is due to differences in experimental design (each study only analyzed a limited spectrum of cell types) or patient selection. It is feasible that subsets of AS patients exist with abnormalities in distinct lymphocyte populations that reflect differences in disease pathogenesis. Alternatively, different cell types may play a role at different time points during the evolution of the disease.

IN VITRO STUDIES

In vitro studies represent a reductionist approach to study the "behavior" of certain cells types under defined conditions. Recent studies demonstrated that tissue-derived osteoblast precursors from AS patients more readily differentiated into osteoblasts in vitro than cells from controls; this was linked to increased JAK2/STAT3 and alkaline phosphatase activity in AS cells. [75–77] These are difficult studies to perform as one major drawback of experiments with primary cells is the difficulty obtaining these cells from patients and controls at the right time and from the right location. Experiments with cells isolated from patients cannot distinguish between primary abnormalities driving disease from secondary effects occurring as the result of disease. An alternative strategy is thus the introduction of genetic modifications in cell lines using clustered regularly interspaced short palindromic repeats (CRISPR)/Cas to study the impact of genetic variants under controlled conditions.

ANIMAL MODELS

The human HLA-B27 transgenic rat (of which several versions exist) has been a particularly influential animal model of SpA.[78] The fact that expressing a human risk gene in a different species resulted in disease was a major argument at that time that HLA-B27 itself and not a closely linked gene mediates the disease.[79] Findings in the human HLA-B27 transgenic rat model that influenced the thinking about SpA pathogenesis include (1) dependence of the disease on lymphocytes but not CD8+ T cells[80,81], (2) evidence for a critical role of intestinal microbiota[82], and (3) demonstration that an HLA-B27-induced unfolded protein response could trigger inflammation[83,84]. Arguably, the demonstration that CD8+ T cells were dispensable for disease development in HLA-B27 transgenic rats had a major impact on the field by focusing research activities on lymphocytes other than CD8+ T cells.

While mice transgenic for human HLA-B27 do not develop arthritis[85] several other models with SpA-like features exist including SKG mice, TNF transgenics, mice with proteoglycan-induced arthritis and IL-23 minicircle-induced arthritis.[78] Studies using these models have provided critical insight into disease mechanisms but have important limitations. For instance, mice are quadrupeds with a tail. The weight of an adult mouse is about 1/3000 of a human but its body structures are built with cells that are the same size as human cells. Even with the most sophisticated techniques to "humanize" mice, a murine vertebral body or Achilles enthesis models the biology of the equivalent human structures only to a certain extent. Recent studies demonstrating the impact of mechanical strain on the development of arthritis in mice thus need to be interpreted with caution with regard to their external validity for human disease.[86–88]

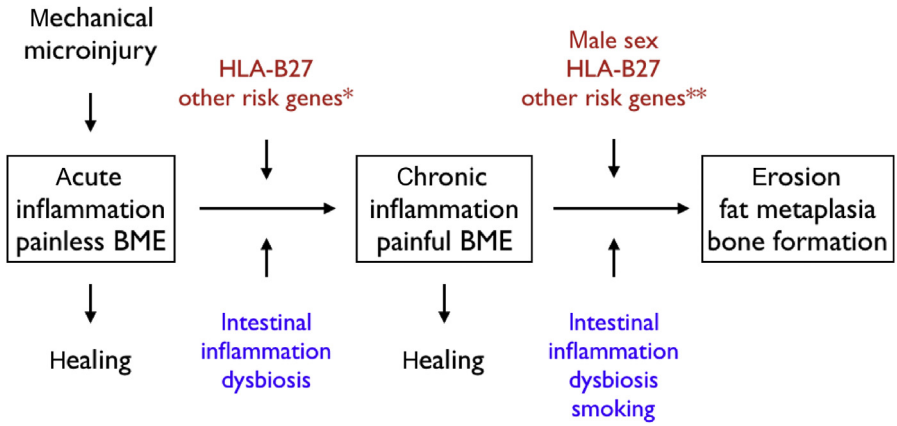

Fig. 2. A working model of axial SpA pathogenesis. Nonmodifiable risk factors (genes and sex) are in red; modifiable risk factors (intestinal inflammation, dysbiosis, and smoking) are in blue. Genetic risk factors controlling the development of chronic inflammation (*asterisk*) may be different from those controlling progression to structural damage (*double asterisk*).

A MODEL OF AXIAL SPONDYLOARTHRITIS PATHOGENESIS

The idea of enthesitis as the central lesion in AS was originally proposed by John Ball in 1971[89]. It was later resurrected and popularized through the work of Dennis McGonagle and colleagues.[90,91] Entheses are attachment sites of ligaments or tendons to bone which are constantly exposed to mechanical stress. This is thought to result in microinjury, which may in genetically predisposed individuals and influenced by environmental factors lead to chronic inflammation. Supporting evidence for this concept comes from recent studies that demonstrated the reciprocal impact of mechanical off-loading or running on arthritis development in mice[86–88]. However, an enthesis-centric disease model cannot explain axial SpA entirely, as early SI joint inflammation is primarily characterized by BME in the subchondral pelvic bone whereas enthesitis is rare.[92] A basic working model of axial SpA pathogenesis is presented in (**Fig. 2**) that focuses on the SI joints and surrounding pelvic bone. Clearly, this model contains multiple gaps and can only be considered as a preliminary framework for future experimental studies.

- The identification of pelvic BME lesions in healthy subjects, in particular athletes, military recruits and post-partum women suggests that mechanical stress may result in micro-injury giving rise to BME lesions on MRI. These lesions are typically not painful.[63–65] The sensitivity of currently available imaging modalities is limited and abnormalities may not be detectable in all cases.[54]
- Such micro-injuries may heal spontaneously, or in a genetically predisposed individual and under the influence of environmental factors progress to chronic inflammation. At some point the lesions become painful. Interestingly, the mechanism of inflammatory back pain in axial SpA is one of the least understood phenomena in this disease.
- The evolution from (sub)acute microinjury to chronic inflammation may be controlled by HLA-B27. The precise role of HLA-B27 in SpA pathogenesis is not understood[16]. One potential mechanism involves the presentation of tissue-specific antigens and activation of HLA-B27-restricted antigen-specific CD8+ T cells.[93] Subclinical inflammation in the gut may participate in this

process via travel of activated lymphocytes from the intestine to the early bone marrow lesion in the pelvis or via long-distance effects of microbial products leaking from the intestine into the blood stream.

- Inflammation may spread from the subchondral bone marrow into the SI joint space, either by direct invasion or through vascular channels[94], leading to synovitis, pannus formation and cartilage destruction.[95]
- Reparative processes continue to be activated. However, the ability to restore tissue homeostasis is lost at some point and resolution of inflammation (if it occurs) is accompanied by permanent structural damage visible on radiographs. Healing may involve the formation of an intermediary tissue dominated by fat cells ultimately leading to new bone formation and fusion of the SI joints (or syndesmophyte formation in the spine).

SUMMARY

Research efforts to understand the pathogenesis of axial SpA should focus primarily on the human disease. Mouse and rat models are extremely valuable by permitting detailed mechanistic studies that cannot be performed in humans. However, diseases in rodents at best resemble human disease. Limited access to biopsy specimens from the spine, in particular from patients with nonradiographic axial SpA, is a major obstacle. Novel molecular imaging techniques may circumvent the need for invasive procedures. Clinical trials with highly specific monoclonal antibodies have shown value as explorations of disease pathogenesis, which could be increased further by tagging on more mechanistic studies (beyond measuring standard parameters of inflammation). Ideally, pathogenetic studies should be coordinated across the whole spectrum of SpA diseases. A comparative analysis of patients with axial SpA, psoriatic arthritis, psoriasis, inflammatory bowel disease, uveitis, or combinations thereof can be expected to be extremely insightful.

DISCLOSURE

Supported by research grants from the Arthritis National Research Foundation and the National Psoriasis Foundation.

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