Review

Interactions of the innate and adaptive arms of the immune system in the pathogenesis of spondyloarthritis

M.L. Stoll

Matthew L. Stoll, MD, PhD

Department of Pediatrics, UT Southwestern Medical Center, Dallas, USA.

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Please address correspondence and reprint requests to: Matthew L. Stoll, MD, PhD UT Southwestern Medical Center, Department of Pediatrics, 5323 Harry Hines Boulevard, Dallas, TX 75390-9063, USA. E-mail: matthew.stoll@utsouthwestern.edu

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ABSTRACT

The immune system can be divided into the innate and adaptive arms. Historically, most of the research into the pathogenesis of spondyloarthritis (SpA) and other types of chronic arthritis focused on the adaptive immune system. Recently, the pendulum has shifted, and much current work in SpA focuses on innate immunity. Herein, I summarise evidence demonstrating that both the innate and the adaptive arms of the immune system are involved in the pathogenesis of SpA, propose a mechanism in which both arms interact to maintain chronic arthritis, and discuss potential research directions.

Introduction and historical perspective

Broadly speaking, the immune system can be divided into the innate immune system, which performs immediate recognition of pathogens and triggers a rapid immune response; and the adaptive immune system, capable of antigen specific responses and long term memory (1). Under current nomenclature, inflammatory diseases caused by aberrant adaptive immune elements are referred to as autoimmune, while those mediated by the innate immune system are considered autoinflammatory (2). Interest in the potential ability of the adaptive immune system to cause autoimmunity dates back over 100 years, to Paul Ehrlich's coining of the term "horror autotoxicus," referring to potential results of the formation of autoantibodies (3). Burnet's clonal selection theory also cemented the concept of disease caused by aberrant immune regulation (4). In contrast, research in the innate immune system began relatively recently, following the discovery of microbial pattern-recognition molecues, such as the toll-like receptors (TLRs), and their downstream pathways (5-7).

Spondyloarthritis (SpA) encompasses a group of disorders characterised by asymmetric inflammatory arthritis, spondylitis, enthesitis, and extra-articular complications involving the skin, eyes, and intestines; the different subtypes appear to share important clinical, genetic, and pathologic features (8, 9). Since the discovery of innate immunity, there has been an explosion of articles discussing the role of the innate immune system in inflammatory diseases, including SpA (10, 11). Several recent reviews have concluded that SpA may be largely governed by innate immunological abnormalities, with minimal role for adaptive events (12-14).

Despite the recent plethora of evidence focusing on the innate immunity in SpA, however, I believe that it is premature to sound the death bells for the adaptive immune system in SpA. Herein, I will summarise the evidence for both and propose a mechanism which may allow for both arms of the immune system to interact in promoting disease.

Evidence for involvement of the innate immune system

For many years, the strong association of human leukocyte antigen (HLA)-B27 with SpA, particularly ankylosing spondylitis (AS), led to the hypothesis that disease may be mediated by CD8+ T-cells responding to peptides presented by the HLA-B27 molecule (15-18). Recently, investigators have proposed alternative mechanisms whereby HLA-B27 may help mediate SpA. Specifically, it has been suggested that the HLA-B27 molecule may be prone to misfolding within the endoplasmic reticulum (ER) of the cell, leading to ER stress and the unfolded protein response (UPR) (19). Early data in support of this theory included studies demonstrating inefficient folding and sub-

sequent cytosolic degradation of B27 heavy chains, but not of B27 chains mutated to include part of the HLA-A2 sequence (20). Misfolding and the UPR have also been observed in the HLA-B27 transgenic rat models of AS (21). Further evidence that the disease in this model, as well as the HLA-B27 transgenic mouse model of AS, is likely to be independent of HLA-B27's traditional role in antigen presentation is indicated by the development of disease in transgenic rats lacking CD8+ cells (22) or transgenic mice lacking β2-microglobulin (23). Among humans, there are at least at least 30 HLA-B27 subtypes, some of which (*e.g.* B*2705) are strongly associated with AS, while others (*e.g.* B*2706 and B*2709) are less so (24, 25). In one study, subtypes strongly associated with AS folded less efficiently than did subtypes not considered to be associated with AS; however, this association was incomplete, as the AS-associated B*2707 allele folded as efficiently as did B*2706 and B*2709 (26). Moreover, the underlying assumption that HLA-B*2709 is protective against AS has been questioned (24).

Besides HLA-B27, additional genetic factors suggest involvement of the innate immune system in SpA. Multiple linkage studies have identified polymorphisms in or near tumour necrosis factor (TNF)α (27-29), Interleukin (IL-1) (30-36) and TLRs (37) that are associated with increased risk of SpA. Recently, the first genomewide association study (GWAS) for AS was published (38). This study of over 2000 patients with AS and 5000 controls, validated with a replication set of 898 patients and over 1500 controls, identified several significantly associated genes, including the IL-23 Receptor (IL-23R) and an endoplasmic reticulum aminopeptidase (ERAP1), in addition to the anticipated linkage to the Major Histocompatibility complex. As reviewed by Brown (2010) (39), potential but non-definitive genes identified by the GWAS are also suggestive of innate immune involvement, including the Interleukin-1 Receptor 2, TNF (ligand) superfamily 15 (TNFSF15), and the TNF Receptor type-1 associated death doman (TRADD). The latter two had also been linked to SpA in separate studies (40, 41).

Since IL-23 is produced by T-cells (42), its linkage with AS may suggest evidence of adaptive immune involvement. However, IL-23 appears to have important innate functions. As reviewed by Abraham and Cho, IL-23 is present on multiple innate immune cells, such as dendritic cells and macrophages, whereupon expression can directly result in tissue damage (43); it is also produced as a result of activation of the UPR (44). It appears to play a role in inflammatory bowel disease (IBD), as it is highly expressed in the lamina propria and can promote expression of multiple inflammatory cytokines (45). IL-23 is required for murine colitis and is also over-expressed in the terminal ileum of patients with AS (46, 47).

Besides IL-23, there is additional evidence that the innate immune system may be up-regulated in SpA. For example, Chou *et al.* (2007) demonstrated increased TNF-α and IL-1 production from peripheral blood mononuclear cells of AS patients compared to their first-degree relatives (48). Similarly, Candia *et al.* (2007) reported increased TLR2 expression among antigen-presenting cells of psoriatic arthritis (PsA) patients, compared to healthy controls (49). Additionally, a population of macrophages characterised by CD163 expression is present in the synovium of SpA patients, with their numbers correlating with markers of disease activity and decreasing following therapy with TNF-α antagonists (50, 51).

Finally, responses to treatments targeting the innate immune pathway support the importance of innate immunity in SpAs. The effectiveness of TNF-α inhibiton in SpA has been demonstrated in multiple randomised studies (52-56). There are no randomised trials of IL-1 inhibition in SpA; open-label trials have shown mixed results (57, 58). A recent case report showed a dramatic response to IL-6 blockade in a patient with reactive arthritis (ReA) (59).

Evidence for involvement of the adaptive immune system

Although the UPR discussed above is one theory potentially explaining the association between HLA-B27 and SpA, this issue is not yet settled, as there are several lines of evidence indicating that HLA-B27s traditional role in antigen presentation may yet account for its disease association, and several recent reviews likewise discuss adaptive dysregulation in SpA (9, 60-62). Scofield *et al.* (1995) identified synthetic peptides derived from enteric bacteria that have sequence homology to HLA-B27 and were bound by the molecule itself, potentially suggesting self-presentation by HLA-B27 (63). AS patients, as compared to B27+ healthy control subjects, were more likely to have antibodies in their serum directed against portions of these peptides (64). Recent studies have demonstrated that cell lines transfected with the HLA-B27 molecule present similar cross-reactive peptides (65), and that this presentation of cross-reactive peptides may be absent in HLA-B27 alleles that are not associated with AS (66). Most recently, Ben Dror and colleagues purified 1,268 peptides from a B27+ cell line, of which 569 were verified to be tightly bound to B27 (67). 28 of the peptides were considered to be arthritogenic candidates, as they were derived from cartilage or bone (n=26) or from the B27 molecule itself (n=2). In addition, several peptides, some of which were among those derived from cartilage or bone, were homologous to enteric bacteria. The authors concluded that the peptides identified in their study may help recruit T-cells directly responsible for the disease. In an accompanying editorial, Lopez de Castro argued that while peptide sequences similar to those of bacteria may be found by chance and are thus not necessarily indicative of involvement of the associated bacteria in the disease, they do support the possibility that cross-reactive immunity may play a role in the development of B27-associated diseases (68).

The possibility that B27 may mediate disease through its traditional role of antigen presentation may be consistent with the finding mentioned above from the GWAS in AS showing linkage of ERAP1 with AS (38), data that confirmed several prior studies conducted in different populations (69-71). The

ERAP1 gene is involved in MHC Class I peptide processing, and its disruption in mice leads to impaired CD8 responses (72). Importantly, it has also been argued that ERAP-1 polymorphisms may be associated with AS by increasing shedding of the TNF receptor (73), although it is not clear whether this theory would account for the polymorphisms being located at the catalytic site of the aminopeptidase activity (39). In addition, ERAP2 polymorphisms may also be associated with AS, despite that ERAP2 is not involved in receptor shedding; furthermore, there is no association between ERAP1 polymorphisms and levels of soluble receptors (74, 75). However, the question regarding the mechanism of ERAP1 polymorphisms in AS remains open.

There is animal data to suggest a role for adaptive immunity in AS. Mikecz *et al*. (1987) induced polyarthritis and spondylitis in Balb/c mice with repeated immunisation with the human cartilage proteoglycan aggrecan, particularly the G1 domain (76, 77). Immunisation with the related molecule versican, which was found to be localised to the enthesis, sacroiliac joints, and intervertebral disc annulus, resulted in spondylitis in the absence of peripheral arthritis (78). Evidence of B-cell and T-cell immunity to the inciting antigens has also been demonstrated in these mice (78, 79). Although the relevance of this model to human disease is unknown, patients with AS may likewise have elevated T-cell responses to these proteoglycans (80, 81).

Histological data has provided evidence of adaptive immunological events in the synovium and cartilage of arthritis patients. Specifically, synovial biopsies of patients with ReA and AS contain B-cell rich follicles, with some reports additionally showing aggregates of T-cells and B-cells arranged into structures similar in appearance to germinal centers (82-85). Although the mere presence of lymphocytes could reflect recruitment secondary to pre-existing inflammatory processes, findings of T-cell/B-cell interactions and germinal center-like aggregates in inflamed synovium arguably suggest that the lymphocytes may be playing a more fundamental role in the etiopathogenesis of the disease. In addition, biopsies of femoral heads of AS patients revealed subchondral lymphoid infiltrates only in areas with cartilage; this was in contrast to RA patients, in whom subchondral inflammation was not affected by the presence of cartilage (86). These findings suggest that T-cell and possibly also B-cell immunological events may drive the inflammation at the bone-cartilage interface, as recently stated by Appel (87).

Studies of B-cell hypermutations have also provided evidence for adaptive immune activation within the synovium of inflamed joints. A proliferating B-cell will undergo random mutations, some of which will lead to changes in the linear amino acid sequence, while others will be silent; it has been argued that high ratios of mutations leading to amino acid changes (R) to silent mutations (S) (R:S ratios) are consistent with an antigen-driven process, enabling the study of such mutations within the synovium (88, 89). Voswinkel *et al*. found multiple immunoglobulin genes with R:S ratios greater than three in a germinal center obtained from the synovium of a patient with AS, findings suggestive of an antigen-driven process (84). On the other hand, AS has been described in two patients lacking B-cells (90).

A number of investigators have sought evidence of T-cell oligoclonality in the synovium of patients with SpA. A method to evaluate for oligoclonality consists of spectratyping, which involves performing PCR on cDNA obtained from each of the Vβ family members. In the absence of oligoclonality, each Vβ family member would be expected to demonstrate a Gaussian curve in their respective size spectra, while deviations from a Gaussian distribution are suggestive of oligoclonal expansions (91). An additional method to evaluate for oligoclonality involves quantitating the amount of RNA product across the different Vβ families, potentially identifying evidence of preferential use of one or more families (92). Using these techniques, several investigators have identified evidence of expanded oligoclonal T-cell populations in patients with AS and other adult and paediatric SpA (93-99). As further evidence of an antigen-driven process related to the synovium, some of these studies specifically reported that the clonal populations were present only in the synovium, not in the peripheral blood (93, 95, 97).

Finally, another line of evidence of involvement for adaptive immunity in AS is the reproducible findings of elevated IgA levels. Numerous studies have reported that patients with SpA have elevated total IgA levels compared to healthy controls (100-102). Several studies have also demonstrated correlations in AS patients between IgA levels and disease severity, including decreases in the IgA level following therapy (102-106). Other investigators have identified specific antigens against which elevated IgA levels have been found. With the exception of collagen (107), these are mostly enteric-associated antigens, such as Klebsiella (108-110), celiac proteins (111), and inflammatory bowel disease (IBD)-associated antigens (112-114). Not all studies have showed consistent findings, however (115).

Towards a unifying construct in SpA

I have summarised above evidence for involvement of both innate and adaptive immunological mechanisms in SpA. These possibilities are not mutually exclusive, as it is possible that each arm could play a separate role. Specifically, the data may suggest that arthritis results from an antigen-driven process, but chronic activation of the innate immune system is also required. That is, I am hypothesizing that for arthritis to be perpetuated, there needs not only to be an antigen-driven process, but also a chronic inflammatory stimulus.

The first question is: what is this chronic inflammatory stimulus? One possibility is trauma. Research by Dennis McGonagle and colleagues has elucidated the relationship between the synovial-entheseal complex and SpA (116). The entheses are sites of repeated biomechanical stress, resulting in foci of micro-trauma. These small injuries cause the release of fragments of fibronectin, hyaluron, and other molecules from damaged connective tissue, all of which

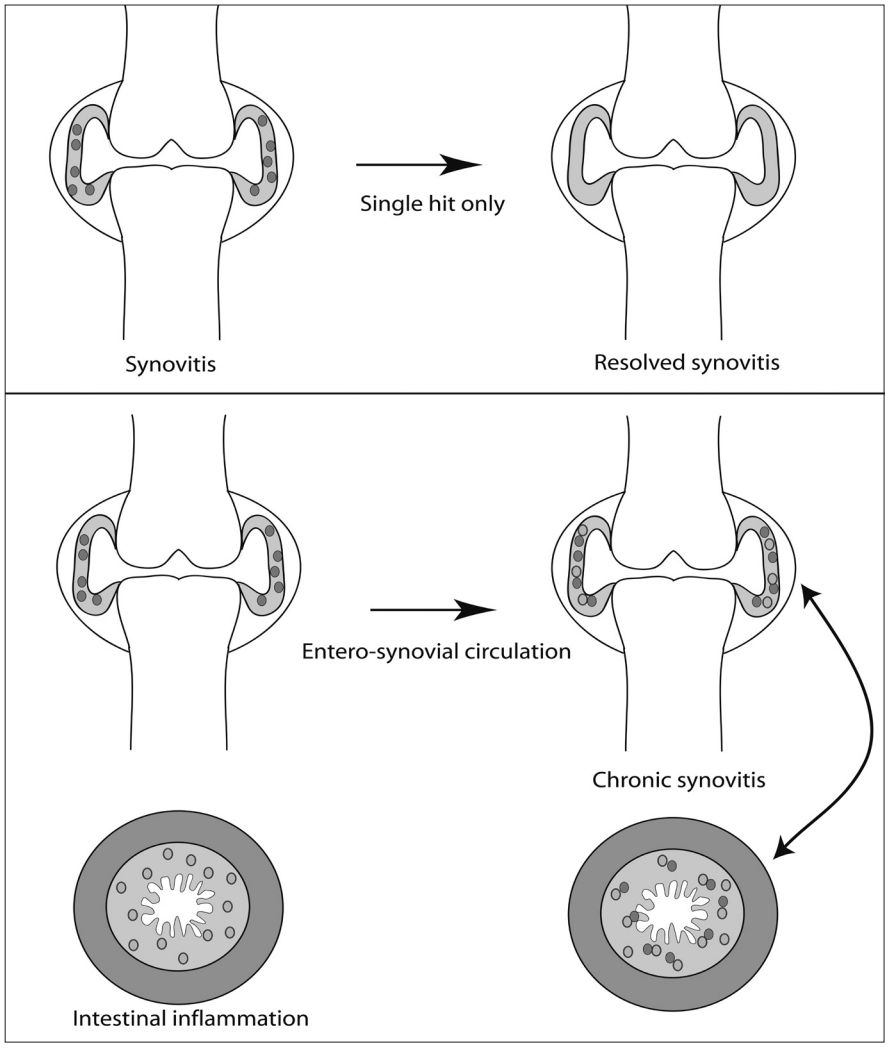

Fig. 1. Interaction between intestinal and synovial inflammation in the pathogenesis of SpA.
Legend: Intestinal inflammation (associated with IL-23R and TNFSF15) and synovial inflammation (associated with HLA-B27 and ERAP1) develop separately. However, circulation of immunological cells from the intestines to the synovium permits the synovitis to become chronic. Thus, SpA requires intestinal inflammation and is therefore associated with similar genetic markers as IBD. However, SpA also requires specific adaptive immunological events targeting the synovium, as reflected by the association with HLA-B27 and the ERAP1 polymorphism.

may directly activate synovial macrophages via TLRs and other pattern-recognition molecules. Activation of these molecules results in the up-regulation of approximately 600 stress-related genes (117, 118). Because of the anatomical connections between the enthesis and the synovium, as well as the marked vascularity of the latter, inflammation in the enthesis spills over into the synovium, causing local arthritis (119).

The innate stimulus need not be localised to the joint, and it appears likely that in many cases, an additional stimulus may be present elsewhere (Fig. 1). The most evident example of this is the association between gut inflammation and SpA; approximately 20–25% of patients with IBD have peripheral arthritis (120, 121) and conversely, nearly two-thirds of adult SpA patients have sub-clinical gut inflammation detected by colonoscopy, with similar results reported in a small paediatric study (122, 123). This sub-clinical gut inflammation has not typically been found in patients with other forms of arthritis, even among patients similarly treated with non-steroidal anti-inflammatory drugs (123, 124). Further clinical evidence suggesting a link between the gut and the joints comes from longitudinal studies demonstrating that the presence of gut inflammation at baseline predicts persistence of the arthritis at follow-up evaluations 1–9 years later (122, 125). There is also a strong genetic link; several genes identified by GWAS studies in IBD, particularly the Interleukin-23 receptor (IL-23R) and TNFSF15, have also been linked to AS (38, 126, 127).

SpA encompasses several different entities, including AS, ReA, IBD-associated arthritis, undifferentiated SpA, and psoriatic arthritis (PsA) in adults (8); as well as the enthesitis-related arthritis subtype of juvenile idiopathic arthritis in children (128). As summarised above, sub-clinical gut inflammation has been demonstrated in patients with AS, undifferentiated SpA, ReA, and juvenile SpA (122, 123, 129), and patients with IBD-associated arthritis by definition have both IBD and arthritis, typically SpA (130). PsA has long been recognised to be highly heterogeneous, with a subset resembling SpA (131). Gut inflammation has likewise been detected in the subset resembling SpA (132); given the heterogeneity of PsA, it is likely that other mechanisms may be involved in the other subtypes. However, the presence of gut inflammation in the majority of patients with most subtypes of SpA underscores its importance in the pathogenesis of SpA (133).

The cause of this auto-inflammatory stimulus is of course elusive. However, data is emerging demonstrating shared impairments in responses to gut flora in both IBD and AS. Specifically, although the foecal flora in patients with AS and rheumatoid arthritis (RA) appears to be similar (134), AS patients are unable to mount appropriate immunological responses to foecal flora, as evidenced by decreased IL-10 production by peripheral blood mononuclear cells exposed to bacteroides species (135). Likewise, multiple studies have shown that patients with IBD have either decreased proliferative responses or decreased TLR-2 mediated signaling to foecal flora, particularly among those with NOD2 mutations (136-138). NOD2 is an intracellular pattern recognition molecule, mutations in which have been shown to be associated with a substantially increased risk of Crohn's Disease (139-141). It has been hypothesized that the decreased responsiveness

to flora permits bacterial overgrowth, focal injury, and inflammation (136, 137, 142). Since IL-23 and TNFSF15 both appear to be involved in the response to mucosal flora, polymorphisms in this gene may account for alterations in the handling of this flora that permit a chronic inflammatory state within the intestines of both IBD and SpA patients (46, 143, 144). In contrast, HLA-B27 and ERAP1 polymorphisms are unique to AS (38).

The second question is: what are the adaptive immunological targets in SpA? In some cases, the adaptive immunological events may be triggered by enteric infections. Mononuclear cells infected with Salmonella can travel to lymphoid tissue and induce a T-cell response (145) and also have increased affinity for synovial endothelial cells (146). Perhaps consequentially, bacterial antigens or genetic material has been identified in the joints of patients with ReA and other types of SpA (147-149). This may trigger humoural immunity, as patients with ReA and other types of SpA generate IgA and IgG antibodies against Salmonella and other enteric organisms (150-152).

Alternatively, the adaptive events may be unrelated to infectious agents and instead may be directed towards cartilaginous structures. This possibility is supported by the evidence discussed above of antibodies and T-cell reactivity to proteoglycans and collagen in patients with SpA (80, 81, 107). Even if antibodies prove to be an epiphenomenon, T-cell immunity may yet prove essential to the disease; indeed, this would be predicted based upon the very finding of a Major Histocompatibility Class I, rather than Class II, association with SpA.

To summarise, in addition to their joints, many patients with SpA appear to have a chronic inflammatory process in at least one other organ, particularly the gut or the enthesis. Gut inflammation may result from dysfunctional interactions between local immunologic cells and microbiologic flora, while enthesitis may reflect microtrauma. This inflammation appears to be mediated by the innate immune system. However, there is evidence suggesting that T-cell immunity or T-cell / B-cell interactions may be responsible for the arthritis in SpA. The shared innate involvement of the gut inflammation in IBD and most types of SpA may be reflected by the findings of similar IL-23R and TNFSF15 polymorphisms in the above conditions (38, 127, 153). In contrast, the specificity of the adaptive dysregulation in SpA may be reflected by ERAP1 polymorphisms and the HLA-B27 molecule, neither of which is associated with IBD.

Questions and research directions

This hypothesis suggests that the difference between, for example, IBD without SpA and IBD with SpA consists of specific adaptive immunological events targeting the synovial-entheseal complex. This possibility might be pursued with investigations evaluating for T-cell or humoural reactivity to cartilaginous structures such as proteoglycan and collagen in patients with IBD with or without arthritis, as well as in patients with SpA.

It is generally accepted that the cartilage-bone interface is the primary target in SpA, with synovitis occurring largely as a spillover effect (14). However, some of the data summarised above supports the possibility that the synovium may also be an immunological target. It may be the case that enthesitis and synovitis result from different processes, with the former primarily autoinflammatory and the latter with an autoimmune component. This possibility would be consistent with histological studies: as reviewed by Vandooren, mixed B-cell and T-cell infiltrates are typically detected in the synovium, while a study of entheseal histology revealed a predominant macrophage population (154). Paired entheseal/synovial biopsies could evaluate this question.

Another question is whether different mechanisms underlie peripheral versus axial arthritis. Flares of peripheral arthritis appear to be more tightly linked to IBD flares as compared to axial disease (120), and peripheral arthritis is more likely to be associated with subclinical gut inflammation as compared to spondylitis (155). In addition, peripheral and axial arthritis respond differently to conventional therapies (156), all of which suggests that the two may differ at the mechanistic level. There may be support for this possibility from imaging studies: while knee MRIs appear to demonstrate both entheseal changes as well as joint fluid (157), MRIs of sacroiliac joints are often negative for joint fluid, and its presence is not supportive of a diagnosis of sacroiliitis (158). These findings may warrant further exploration. Because of the obvious difficulties in accessing spinal tissue, no systematic anatomical comparisons have been performed. However, imaging studies may shed some light on differences between peripheral and axial arthritis.

Finally, if gut inflammation in SpA is providing an autoinflammatory stimulus that is driving some of the arthritis, then we as rheumatologists arguably need to be aware of the status of the intestines in SpA patients. Studies using colonoscopy have shown that SpA patients with sub-clinical inflammation were more likely to have active arthritis at follow-up visits (122, 125), underscoring the prognostic value of this information. It is not feasible to perform colonoscopy on asymptomatic SpA patients in clinical practice, so research should be directed towards non-invasive tests of intestinal inflammation, such as the foecal biomarkers calprotectin and lactoferrin (159-162).

Conclusion

Adaptive and innate immune components both appear to be important in SpA. In this review, I propose that the adaptive immune system targets the inflammation into the joints, while autoinflammatory stimuli in the intestines and the enthesis are also essential. Multiple questions remain undefined, including the fine specificity of the adaptive targets, the role of antibodies *versus* T-cell immunity, mechanistic differences between peripheral and axial SpA, and the potential role for monitoring gut inflammation in clinical practice in SpA patients.

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