Review

Progress in spondylarthritis

Immunopathogenesis of spondyloarthritis: which cells drive disease?

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Abstract

Spondyloarthritides, or SpA, form a cluster of chronic inflammatory diseases with the axial skeleton as the most typical disease localisation, although extra-articular manifestations such as intestinal inflammation may frequently occur during the course of the disease. This review summarises recent progress in our understanding of the immunopathogenesis of SpA with special emphasis on the cellular constituents considered to be responsible for the initiation and/or perpetuation of inflammation. There are several arguments favouring a role for haematopoietic cells in the pathophysiology of spondyloarthritis, including HLA-B27-associated dendritic cell disturbances, HLA-B27 misfolding properties and T helper 17 cells. In addition, recent studies have pointed toward a pivotal role for stromal cells. A major challenge, however, remains to determine how recently identified genetic associations such as interleukin-23 receptor polymorphisms may influence cellular targets in spondyloarthritis.

Introduction

Spondyloarthritides, or SpA, are a group of chronic inflammatory diseases that affect about 0.5% of the Western population. The most typical disease localisation is the axial skeleton, more specifically the spine and sacroiliac joints. Additionally, enthesitis or peripheral arthritis of the large joints of the lower limbs frequently occurs. Extra-articular manifestations are also a common feature in SpA. They include anterior uveitis, psoriasis and inflammatory bowel disease (IBD).

SpA refers to a cluster of disorders that were formerly considered separate disease entities. It comprises ankylosing spondylitis (AS), reactive arthritis (ReA), IBD-associated arthritis and some forms of psoriatic arthritis (PsA). This grouping was based on three important considerations: (a) the different disease phenotypes could consecutively manifest in the same patient, (b) overlaps that make it impossible to distinguish between the different disorders are often seen, and (c) different disorders can affect different members of the same family. Apart from the presence of shared environmental factors, this familial aggregation can be explained for the most part by an important hereditary component in the pathogenesis of the disease. First-degree relatives of SpA patients are 40 times more likely than the general population to develop SpA [1,2].

Features of inflammation in spondyloarthritides

For many years, an intimate relationship between mucosal and joint inflammation has been established (reviewed in [3]). Pioneering studies by Mielants and Veys [4] demonstrated that about 60% of SpA patients displayed microscopic signs of inflammation in the colon and/or ileum which were unrelated to clinical gastrointestinal symptoms. This illustrates that SpA is a disorder in which many different types of organs may be involved. Extensive studies have been undertaken to characterise the nature of the inflammatory infiltrates in synovial tissue, entheses as well as extra-articular tissues such as colon and/or ileum. Bone marrow inflammation may also occur during the course of SpA and is even considered by some investigators to be one of the principal and initial events [5]. This inflammation can be focal or diffuse. It can be located in both sacral and iliac bones and consists of an accumulation of mononuclear cells. These cells were reported to contain plenty of T lymphocytes that can be $CD4^+$ as well as $CD8^+$ [6-9].

ARE = AU-rich element; AS = ankylosing spondylitis; DC = dendritic cell; ER = endoplasmic reticulum; HLA-B27 DC = HLA-B27 transgenic dendritic cell; Huβ2m = human beta 2 microglobulin; IBD = inflammatory bowel disease; Ig = immunoglobulin; IL = interleukin; IL-23R = interleukin-23 receptor; ILT = immunoglobulin-like transcript; KIR = killer cell immunoglobulin receptor; LILR = leukocyte immunoglobulin-like receptor; MHC = major histocompatibility complex; NK = natural killer; PsA = psoriatic arthritis; RA = rheumatoid arthritis; ReA = reactive arthritis; SpA = spondyloarthritides; Th17 = T helper 17; TNF = tumour necrosis factor; TNFRI = tumour necrosis factor receptor 1; UPR = unfolded protein response.

In the overlaying synovium and enthesis, the predominant cells are macrophages that often carry the scavenger receptor CD163 at the cell surface [10,11]. Intriguingly, in the gut, signs of acute inflammation, characterised by infiltration of polymorphonuclear cells, as well as of chronic inflammation, characterised by a mixed macrophage-lymphocyte infiltrate, can be found, and accordingly, subgroups of gut inflammation related to SpA have been described [4,12]. The macrophages in the gut are also frequently $CD163^+$ [13]. Remarkably, even in the absence of histological signs of active inflammation, the frequency of dendritic cells (DCs) and T cells was still found to be increased in ileal mucosa of SpA patients [14]. In all of the tissues involved in the SpA phenotype, an extensive neovascularisation is present [15]. A striking feature of SpA is that the joint involvement combines features of bone destruction versus bone remodelling, which distinguishes it from other inflammatory rheumatic disorders, notably rheumatoid arthritis (RA) [16]. In the remaining part of this review, we will summarise recent progress in our understanding of the immunopathogenesis of SpA, with special emphasis on the cellular constituents considered to be responsible for the initiation and/or perpetuation of inflammation in SpA.

The crucial role for mesenchymal cells in tumour necrosis factor-dependent inflammation

The strongest experimental evidence aimed at defining cellular targets for inflammation in SpA was found in the $TNF^{\Delta ARE}$ mouse model, characterised by a 69-base pair deletion of the tumour necrosis factor (TNF) AU-rich elements (AREs) from the mouse genome. This leads to increased steady-state TNF mRNA levels in both haematopoietic and stromal tissues as well as a diminished translational silencing of the TNF message. The animals spontaneously develop an inflammatory disease characterised by Crohn-like ileitis, sacroiliitis, enthesitis and peripheral arthritis, making this model very attractive for studying SpA [17]. Several mechanistic studies were undertaken to determine the cellular source providing pathogenic TNF loads as well as the cellular targets of pathogenic TNF.

Although gut and joint inflammation coexist in this model, it appeared that some striking differences do exist in the regulation of Crohn-like ileitis as opposed to peripheral arthritis. Hence, in the absence of mature B and T cells, peripheral arthritis still occurred whereas the intestinal phenotype was almost completely prevented [17], suggesting that intestinal inflammation in this model depends on adaptive immune responses. An additional study revealed that a redundancy in the cellular source of TNF-driving Crohn-like ileitis exists and that both myeloid cells or T lymphocytes are sufficient to provide pathogenic TNF loads [18].

To address which cell types respond to chronic TNF overexposure, bone marrow engraftment experiments were carried out to assess the role of TNF receptor I (TNFRI) in the development of arthritis and IBD in these mice. Transfer of $TNF^{\Delta ARE}$ $TNFRI^{-/-}$ bone marrow into wild-type irradiated recipients resulted in an IBD and arthritis phenotype similar to that of $TNF^{\Delta ARE}$-reconstituted wild-type mice. By contrast, when $TNF^{\Delta ARE}$ bone marrow was transferred to $TNFRI^{-/-}$ recipients, no signs of joint inflammation were found, although gut inflammation was present. This suggests that radiation-resistant, tissue stroma-residing cells are required TNF targets for the induction of arthritis. However, for the development of IBD, radiation-sensitive, bone marrow-derived cells are equally important and sufficient targets for pathogenic TNF. These findings clearly indicate the existence of independent, yet redundant, cellular pathways operating downstream of TNF in the pathogenesis of IBD [18,19].

Furthermore, activation of mesenchymal cell types from gut and joint appeared prior to the onset of clinically overt disease. A formal proof for the importance of stromal cells was shown recently by Armaka and colleagues [19] using Cre/loxP-mediated TNFRI expression in mesenchymal cells. In the presence of chronic TNF overexposure, signalling through TNFRI in synovial fibroblasts and intestinal myofibroblasts appears to be sufficient to develop combined gut and joint pathologies, a hallmark of SpA. However, it remains to be determined why stromal cells are preferentially activated at certain localisations (for example, enthesis, sacroiliac joints) in SpA rather than at other sites.

Contribution to inflammation of haematopoietic cells

Influence of HLA-B27-associated pathological events

The most important genetic contribution to SpA comes from the HLA-B27 gene, which accounts for approximately 30% of the hereditability [1,2]. In the HLA-B27/human beta 2 microglobulin (Huβ2m) transgenic rat model, only genetically predisposed strains (Lewis or Fisher rats) with a high copy number of the transgene develop an inflammatory syndrome consisting of spondylitis, sacroiliitis, peripheral arthritis, enterocolitis and psoriasiform skin lesions [20-22]. Hence, this model can be used to study SpA. The HLA-B27 subtype integrated in the transgene locus is the HLA-B*2705 subtype, which is the common ancestor of the closely related HLA class I allotypes and which has been positively associated with AS in multiple population studies [23]. Bone marrow engraftment experiments within this model showed that disease arises as a consequence of a high level of expression of the transgenes in cells of haematopoietic origin [24].

Role of antigen-presenting cells and modulation by HLA-B27

Recently, a hypothesis that implies aberrant formation of immunological synapses was proposed. Additional cell transfer experiments in this model suggested an indispensable and provocative role for HLA-B27, a major histocompatibility complex (MHC) class I molecule, in modulating $CD4^+$ T-cell activation [25].

In response to antigen recognition and following adhesion between DCs and T cells, T-cell receptor signalling in cooperation with costimulatory signals mediated by CD28 is critical for initiation and stabilisation of the immunological synapse [26]. By contrast, much less is known about the antigen-independent immunological synapse formation, in which a majority of naive $CD4^+$ T cells exhibit a Ca^{2+} response upon contact with DCs in the absence of nominal antigen. It can be expected that costimulatory molecules also play a prominent role in this process [27]. Because of the lack of a demonstrable role of MHC class I-restricted $CD8^+$ T cells, new hypotheses to explain the pathogenicity of HLA-B27 in this model are based on these non-antigen-specific mechanisms as opposed to the classic arthritogenic peptide-based hypotheses.

In those antigen-independent systems, HLA-B27 transgenic DCs (HLA-B27 DCs) showed a dramatically decreased capacity to stimulate T cells. This was not related to altered chemokine production by HLA-B27 DCs but resulted rather from the formation of fewer conjugates between HLA-B27 DCs and T cells. Blocking costimulatory molecules (CD86 on DCs or CD28, CD2 and CD4 on T cells) inhibited a greater proportion of the conjugates formed with control DCs than with HLA-B27 DCs, indicating that HLA-B27 DCs failed to use several T-cell costimulatory molecules involved in synapse formation.

This defective DC function is not secondary to chronic inflammation, because it was also found in premorbid disease-prone rats. In contrast, DC function was not significantly reduced in disease-resistant lines bearing a low copy number of the HLA-B27/Huβ2m transgene or a high copy number of the HLA-B7/Huβ2m transgene [27,28].

All together, these findings indicate that defective DC function is a feature particularly related to HLA-B27 and is dependent on the number of copies of the HLA-B27/Huβ2m transgene. Hacquard-Breban and colleagues [27,28] proposed that DC function may be a causal mechanism for SpA-like development in this transgenic rat model, perhaps by affecting the induction or maintenance of MHC class II-restricted regulatory T cells. Intriguingly, when DC-induced allogeneic T-cell proliferation was compared among different transgenic lines and crosses with distinct levels of susceptibility to SpA-like disease, stimulatory capacity was inversely correlated with disease susceptibility [29]. However, formal proof of this indispensable role of DC dysfunction in SpA pathogenesis still needs to be established in non-transgenic animal models or using adoptive transfer experiments. Evidently, it remains to be determined whether these effects of HLA-B27 on DC function can also be found in humans.

HLA-B27 misfolding and formation of homodimers

Another hypothesis regarding immunopathogenesis relates to the structural capacities of the HLA-B27 molecule, which consists of a trimer of heavy-chain, β2 microglobulin and short peptide. The heavy chain has the tendency to misfold, to accumulate in the endoplasmic reticulum (ER) and to form disulfide-linked homodimers, thereby inducing ER stress.

This accumulation may cause an unfolded protein response (UPR), which induces profound changes in the cellular metabolism, including inhibition of general translation but also transcriptional upregulation of molecular chaperone genes [30,31]. The contribution of HLA-B27 to spondyloarthritis through misfolding and formation of heavy-chain dimers was recently challenged in the transgenic rat model (as well as in human disease).

The introduction of additional Huβ2m in a disease-prone line resulted in an increased prevalence and severity of arthritis with no effect on diarrhea since this developed in all rats independently of extra Huβ2m. In addition, the introduction of additional Huβ2m in a previously healthy HLA-B27/Huβ2m line (lower transgene copy numbers) induced an even more severe inflammatory syndrome: rats more frequently developed a more severe arthropathy, with more clinical and histopathological similarities to SpA (increased prevalence of axial disease) than in the original model. Moreover, in contrast to disease-prone lines, no evidence of gut inflammation was observed. However, in accordance with the original hypothesis, less HLA-B27 heavy-chain misfolding and dimer formation in combination with lower BiP (binding protein) mRNA (marker of UPR triggering) levels was seen in these rats compared with the same line when no additional Huβ2m was introduced [22]. However, care needs to be taken when interpreting these results. Folding properties and UPR triggering of stimulated splenocytes rather than macrophages were analysed in this study. Turner and colleagues [30] pointed out that the biological consequences of HLA-B27 misfolding may differ considerably depending on the cell type. On the one hand, appropriate stimulation of HLA-B27 transgenic macrophages resulted in HLA-B27 upregulation, accumulation of misfolded heavy chains and consequently upregulation of UPR target gene expression. On the other hand, stimulated HLA-B27 transgenic splenocytes revealed little activation of the UPR, which was consistent with minimal HLA-B27 upregulation. Thus, the degree to which additional Huβ2m may reduce the UPR caused by HLA-B27 upregulation has not been formally established yet. Furthermore, folding properties of HLA-B27 subtypes in humans showed incomplete correspondence to AS, indicated by the fact that one of the four AS-associated HLA-B27 subtypes folded with the same high efficiency as the non-disease-associated subtypes [32]. It is not yet clear whether misfolded molecules participate in AS pathogenesis.

HLA-B27 as cell surface ligand for immunomodulatory receptor families

Intriguingly, HLA-B27 in classical (trimer of heavy chain, β2 microglobulin and short peptide) as well as β2m-independent

forms may also act as cell surface ligands for immunomodulatory receptor families called the killer cell immunoglobulin (Ig) receptors (KIRs) and the leukocyte Ig-like receptors (LILRs)/Ig-like transcripts (ILTs). KIRs and ILTs modulate activation of other immune receptors [33,34]. Peripheral blood and synovial fluid leukocytes from patients with spondyloarthritis were shown to express cell surface HLA-B27 heavy-chain dimers [35]. In addition, DCs of an HLA-B27$^+$ individual displayed induction of dimer formation on appropriate stimulation [36]. These β2 microglobulin-independent homodimer forms bind a distinct pattern of the KIRs and LILRs compared with classical HLA-B27 complexes [34]. Moreover, KIR3DL2-expressing natural killer (NK) and CD4 T cells are expanded in the periphery and synovial fluid of patients with HLA-B27-associated arthritis [37]. Interestingly, KIR3DL2 ligation by HLA-B27 homodimers inhibited NK-cell and T-cell clone interferon-gamma production [33]. These differences in binding, expression and function of classical HLA complexes on the one hand and β2 microglobulin-independent forms on the other could be involved in the pathogenesis of SpA.

Is spondyloarthritides a T helper 17-mediated disease?

Recently, the role of haematopoietic interleukin-17 (IL-17)-producing T cells, the T helper 17 (Th17) cells, has been raised in a wide variety of autoimmune diseases. These cells typically express the IL-23 receptor (IL-23R) on their membrane (reviewed in [38]). In addition, recent studies in IBD [39], psoriasis [40] and most importantly AS [41-43] show an important genetic contribution for polymorphisms in the gene that codes for this IL-23R. Thus, the active polymorphisms in the IL-23R gene could indicate an important role for this pathogenic T-cell subset in the development and maintenance of AS. IL-23 by itself does not contribute to early Th17 differentiation. However, it favours the expansion and maintenance of this pathogenic T-cell subset [38,44]. This suggests that IL-17-producing T cells in SpA patients could abnormally expand under the influence of IL-23. Recently, it was also shown that the expression of CCR6 receptor, with CCL20 as its ligand, selectively identified healthy-control peripheral blood CD4$^+$ T cells producing IL-17 [45].

Intriguingly, Jandus and colleagues [46] found increased numbers of Th17 cells in the peripheral blood of PsA and AS patients compared with RA patients and healthy controls. These cells were more differentiated than their RA and healthy control counterparts. In addition, CCR6$^+$ cells were more efficient in the production of IL-17 as compared with their CCR6$^-$ counterparts. However, no significant differences were observed in the frequency of Th17 cells among the CCR6$^+$ population in healthy controls and arthritis patients.

Recently, several groups have investigated the levels of IL-17, IL-23 and CCL20 cytokines in serum and/or synovial fluid from SpA patients. Melis and colleagues [47] reported no significant differences in serum and synovial fluid levels of IL-17 in non-PsA SpA patients with peripheral arthritis versus controls, whereas Wendling and colleagues [48] showed elevated serum levels in an AS patient population and Singh and colleagues [49] showed elevated synovial fluid levels in a cohort of patients with ReA and undifferentiated spondyloarthritis. Importantly, it was shown that CCL20 is capable of attracting effector memory T cells, especially Th17 cells [50]. Of interest, we found that synovial fluid CCL20 levels were elevated greatly over the serum levels [47], suggesting a true chemotactic role for CCL20 in attracting this pathogenic T-cell subset to the SpA joint.

Interestingly, an apparent paradoxical relationship between TNF and the IL-23/IL-17 pathway appears to exist. In SpA patients, for example, serum levels of p40 IL-12/23 did not differ significantly from controls and these levels did not change after TNF blockade treatment in contrast to systemic parameters of inflammation [51]. These results were confirmed by Melis and colleagues [47] using a more specific p19 IL-23 assay. By contrast, in the TNF$^{\Delta ARE}$ mouse model of SpA, an increased frequency of Th17 cells was recently reported. Elevated levels of IL-17-producing CD4 T cells in the terminal ileum of these mice were observed compared with controls [52], although it is unclear whether the disease itself can be attenuated by IL-17 blockade. In addition, the putative relationship between TNF and IL-23 in this model has not been explored yet.

IL-23 seems to be involved in subclinical gut inflammation seen in AS patients as well. Ciccia and colleagues [53] reported that IL-23 was markedly upregulated at the mRNA and protein levels in the terminal ileum in comparison with healthy controls. However, this finding was not associated with a well-defined Th17 response since upregulation of IL-17 and the IL-17-inducing cytokines IL-6 and IL-1β was not seen.

Recently, the contribution of IL-17 was also assessed in proteoglycan-induced arthritis, an SpA model dependent upon immunisation with aggrecan. Although spondylitis – a hallmark of SpA – was not assessed, peripheral disease appeared to occur equally well in the presence or absence of IL-17 [54]. This indicates that peripheral SpA-associated arthritis is not IL-17-dependent in this model.

In summary, although some data point toward an involvement of haematopoietic Th17 cells in SpA pathogenesis, the current knowledge is too limited to draw firm conclusions. Clearly, more studies are required to evaluate the contribution of Th17 cells in SpA-associated inflammation. Particularly, the biological role of IL-23R polymorphisms on survival and expansion of Th17 cells is still an open question. In addition, the significance of CCL20 to this Th17 system or to the immunopathogenesis of SpA in general is not clear at present.

Conclusions and prospects for the future

Although the cause of SpA is unknown, it is generally accepted that SpA is a multifactorial disease in which a disturbed interplay occurs between the immune system and environmental factors on a predisposing genetic background. Several trails linking the diverse sites of inflammation in SpA have been followed during the past decades. They involve aberrant migration of intestinal lymphocytes or mononuclear cells, particularly macrophages, but neither of these hypotheses has been formally proven. Recent studies have shed new insight into the putative role of an old and intriguing player in SpA pathogenesis, HLA-B27, which displays aberrant folding properties and can form ER and cell surface homodimers. To date, however, it is not clear whether misfolded molecules participate in AS pathogenesis. Other research groups focus on the role of HLA-B27 in affecting DC function in an antigen-independent manner. However, formal proof that DCs are major drivers in SpA pathogenesis is currently lacking. The most convincing experimental breakthrough in defining responsible cellular targets in SpA pathogenesis points toward stromal cells. Hence, TNFRI expression on mesenchymal cells can phenocopy the entire disease spectrum from a TNF-driven model of SpA. Nonetheless, several important questions remain to be addressed. The role of novel identified associations such as the IL-23R – important for Th17 expansion and maintenance – will have to be explored, especially as many of the associated single-nucleotide polymorphisms were associated with a protection against disease.

In conclusion, there is ample evidence that bone marrow as well as stromal cells seem to be involved in SpA pathogenesis. However, the interaction of these cell types remains to be established, especially in human SpA. Furthermore, the potential combined action of HLA-B27 and IL-23R polymorphisms in the pathogenesis of SpA will require a coordinated approach with geneticists as well as immunologists. Hence, all of the identified predisposing genes largely affect adaptive immune responses. With the availability of the various mouse engineering tools that allow these questions to be addressed in a sophisticated manner, it is clear that exciting times for SpA research lie ahead.

Competing interests

The authors declare that they have no competing interests.

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