The transition of acute to chronic bowel inflammation in spondyloarthritis

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Abstract | That gut and joint inflammation are linked in spondyloarthritis (SpA) has been recognized for almost three decades. Intriguingly, microscopic gut inflammation, which occurs frequently in patients with SpA, is an important risk factor for clinically overt Crohn's disease and ankylosing spondylitis. This Review describes current insights into the underlying mechanisms that lead to chronic gut inflammation in patients with SpA. We propose that the development of chronic bowel inflammation in these individuals occurs through a transition phase, in which inflammation evolves from an acute into a chronic state. Our transition model implies that different cell types are involved at different stages during disease progression, with stromal cells having an important role in chronicity. In addition, deficient regulatory feedback mechanisms or genetically determined alterations in antigen presentation, endoplasmic reticulum stress, autophagy or cytokine signaling might also favor a transition from self-limiting acute inflammation to chronic inflammation. We anticipate that this transition phase might be an important window for therapeutic intervention.

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Introduction

The subtypes of spondyloarthritis (SpA) share certain clinical features, including peripheral arthritis (principally of the lower limb joints), enthesitis and inflammation of the axial skeleton. The estimated prevalence of SpA in white populations is approximately 0.5–2%, and is slightly higher in men than in women.[2]

Subtypes of SpA include ankylosing spondylitis (AS), reactive arthritis, arthritis in patients with inflammatory bowel disease (IBD) and some forms of psoriatic arthritis.[1,2] Patients with SpA can be broadly classified according to whether their disease predominantly involves axial or peripheral manifestations (axial SpA versus peripheral SpA; the classification and diagnosis of patients with SpA is reviewed elsewhere in this Focus issue).[3]

Several extra-articular manifestations—acute anterior uveitis (AAU), skin lesions such as psoriasis and erythema nodosum, and inflammatory gut mucosa lesions that can evolve into IBD—are associated with SpA and indirectly related to the locomotor disease. All of these factors can lead to important comorbidities that can influence the efficacy of therapeutic approaches.[4] An intriguing example of such an effect is the finding that IBD does not respond to treatment with the soluble TNF receptor etanercept.[5]

The prominent link between IBD and AS has been known for many years: 6.5% of patients with AS develop IBD, and, conversely, AS frequently develops in patients who are primarily diagnosed with IBD (with a prevalence of up to 10%).[6] Moreover, >60% of patients with AS in a study published in 1995 showed microscopic signs of gut inflammation without any major sign of gastrointestinal discomfort.[7] Experience at our own center suggests a similar prevalence of underlying gut involvement in patients with axial and peripheral SpA (L. Van Praet, *et al.* unpublished data).

The role of gut inflammation in the pathogenesis of SpA has been extensively studied. Marked progress has been made in our understanding of the genetics, clinical features and immunopathogenesis of SpA and IBD, although the exact mechanisms by which mucosal inflammation might lead to disease have not yet been ascertained.

The aim of this Review is to highlight changing concepts in extra-articular SpA manifestations, with an emphasis on mucosal inflammation.

Microscopic gut inflammation

The high frequency of microscopic gut inflammation in patients with different subtypes of SpA discovered by Mielants *et al.*[7] has been corroborated by several other investigators.[8–10] Indeed, microscopic gut inflammation was observed in 60% of patients with AS, 90% of patients with enterogenic reactive arthritis, 20% of patients with urogenital reactive arthritis, 65% of patients with undifferentiated SpA, 16% of those with the pauciarticular and axial forms of psoriatic arthritis, and in 80% of patients with late-onset pauciarticular juvenile chronic arthritis or juvenile SpA.[11–13] Gut inflammation in patients with SpA can have the same histological characteristics as acute inflammation (in which neutrophils predominate, resembling acute bacterial enterocolitis) or chronic inflammation (which

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is characterized by a mixed inflammatory infiltrate and structural remodelling of the intestinal mucosa, resembling Crohn's disease).[14] Most patients with normal histology or acute intestinal lesions have transient arthritis, whereas the majority of those with chronic intestinal lesions have persistent joint inflammation. A tight relationship between gut and joint inflammation has been revealed in prospective follow-up studies of patients with SpA: clinical remission of joint inflammation was associated with resolution of gut inflammation, whereas the presence of gut inflammation was associated with persistent joint inflammation.[15,16]

Data from several ileocolonoscopic studies indicate that chronic gut inflammation, found in approximately 30% of patients with SpA, can be considered as an early stage of Crohn's disease.[16] Chronic gut lesions are associated with a family history of AS and Crohn's disease, with markers of inflammation (elevated C-reactive protein levels and erythrocyte sedimentation rate), reduced axial mobility, the presence of sacroiliitis, destructive joint lesions, a diagnosis of AS, and *HLA-Bw*62* positivity.[17] Most importantly, chronic inflammatory lesions were found to be a risk factor for Crohn's disease; indeed, 20% of patients with chronic lesions developed clinically overt IBD over a 5-year period.[15] Multiple factors are thought to contribute to the development of chronic gut inflammation (Figure 1).

Key points

- Microscopic gut inflammation occurs in approximately two-thirds of patients with spondyloarthritis
- Chronic inflammatory lesions are an important risk factor for the development of Crohn's disease and ankylosing spondylitis, therefore indicating a potential link between gut and joint inflammation
- The transition of acute inflammatory lesions into chronic inflammatory lesions is influenced by deficient feedback of regulatory T cells
- Mesenchymal cell types are important effector cells in the chronic phase of disease

Risk factors for developing IBD in AS

Substantial hereditability applies in SpA. Genetic variants that confer susceptibility to AS, PsA and IBD—and their implications for pathology—are discussed more thoroughly elsewhere in this Focus issue.[18] In this section we discuss the shared genetic backgrounds of Crohn's disease, IBD, psoriasis and SpA. In addition, we discuss the interplay between genetic and environmental factors that contribute to the development of acute and chronic gut inflammation. Factors that influence progression from acute intestinal inflammation to chronic pathology can be summarized in a transition model (Figure 1). Details of the genetic, molecular and cellular participants in this process are provided throughout this Review and in Figure 2.

Genetic factors

AS has a large genetic component and, similarly, the potential contribution of susceptibility genes for IBD has become increasingly studied. Remarkably, the genetic susceptibility for these diseases seems to overlap.[19] This overlap was uncovered using an Iceland genealogy database, in which an elevated crossrisk ratio was identified between IBD and AS.[19] First-degree relatives of patients with AS had a threefold greater risk of IBD than unrelated controls matched for age and sex. Similarly, first degree relatives of patients with IBD had a higher risk of developing AS than unrelated controls.[19] Although the genes and mechanisms that underlie this association have not yet been fully elucidated, marked progress has been made using genome-wide association studies (GWAS).[20] Indeed, GWAS have identified a set of IBD-associated genes that link the condition to previously unappreciated pathological pathways.[21,22] Genetic defects associated with IBD typically affect genes responsible for the regulation of innate immune defense against intestinal bacteria (such as *NOD2* and *ATG16L1*), modulation of the adaptive immune response (such as *IL23R* and *IL10*) or epithelial cell integrity and repair (such as *PTPRS*).[21,22]

Several common genetic predispositions between SpA and IBD have been identified, of which the association with *IL23R* polymorphisms is most prominent.[23] IL-23R promotes the differentiation (and subsequent survival) of naive CD4$^+$ T helper (T_H) cells into type 17 T_H (T_H17) cells. The Arg381Gln polymorphism in IL-23R, which is a protective factor for AS, seems to reduce the risk of developing Crohn's disease and psoriasis.[23,24]

ERAP1 has also been associated with AS, Crohn's disease and psoriasis.[20,25,26] The product of *ERAP1* is involved in peptide trimming in the context of MHC peptide processing and presentation[27] and is also reported to be involved in the cleavage of cytokine precursors.[28] Either of these functions might explain the association of *ERAP1* with AS and SpA.[29] Polymorphisms of *ERAP1*, however, only affect the risk of AS in *HLA-B27*$^+$ individuals.[30] These findings therefore provide strong evidence that *HLA-B27* operates in AS through a mechanism involving aberrant processing of antigenic peptides.

A set of Crohn's disease susceptibility genes were identified in a large cohort of patients with AS.[31] A new susceptibility locus was found within the intergenic region at chr1q32, near the gene *KIF21B*, which encodes a protein of the kinesin motor family that is involved in transport along axonal and dendritic microtubules. Associations were also found with *STAT3*, implicated in IL-23R signal transduction, and with the p40 subunit shared between IL-12 and IL-23. Owing to the role of these components in the T_H17 pathway, these findings lend further credence to the potential role of T_H17 cells in the pathogenesis of AS and Crohn's disease. The functional implications of these links to the T_H17 pathway, however, remain unclear as although IL-17 blockade was beneficial in patients with AS,[32] the results in those with Crohn's disease[33] are unclear. The most promising clinical results when targeting the T_H17 pathway have been obtained with ustekinumab (a human monoclonal antibody that targets the p40 subunit common to IL-12 and IL-23) and induced marked clinical improvements

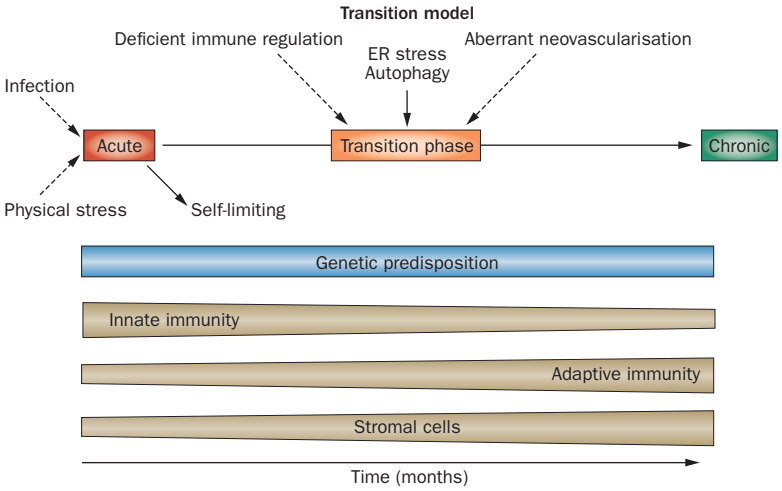

Figure 1 | Transition of gut inflammation from acute to chronic in spondyloarthritis. Acute inflammatory episodes that affect the gut or joints can be triggered in an individual by a variety of factors (such as certain bacterial infections or biomechanical stress), and typically resolve with time. However, genetic factors that affect multiple cellular processes—including immune system regulation, endoplasmic reticulum stress and autophagy—mean that in some individuals these acute insults cannot be resolved. Lack of resolution of acute inflammation can lead into transition to a chronic phase. We anticipate that adaptive immunity and stromal cells have a more prominent role as the disease progresses, as the innate immune response decreases.

in patients with psoriasis, psoriatic arthritis and Crohn's disease.[34–36] Developments in therapies for SpA are discussed elsewhere in this focus issue.[37]

The association of AS with *STAT3* was confirmed in a study of a Han Chinese population which also found evidence that a haplotype within the *JAK2* locus is related to AS. Interestingly, the Arg381Gln polymorphism in IL-23R was not found in this population.[38] Two other loci that have shown significant associations with both AS and IBD are *CARD9*,[39,40] a gene involved in host defense, and the 21q22 chromosomal region.[41]

One important, yet largely neglected, aspect of the shared genetic backgrounds we have discussed is whether the high frequency of microscopic bowel inflammation in patients with AS could have affected the extent of the reported overlap between AS and IBD. This effect could be particularly relevant in patients with chronic inflammation. Indeed, the results of a study that investigated the prevalence of polymorphisms in *NOD2* (a susceptibility gene for Crohn's disease) in an SpA cohort illustrate this pitfall.[42] *NOD2* polymorphisms were found to be highly prevalent in patients with SpA who had chronic gut inflammation; indeed, substantially more so than in the control population, and at a level similar to that in patients with Crohn's disease.[42] By contrast, the prevalence of *NOD2* variants was unaltered in patients with SpA in whom gut inflammation was either lacking or present in acute lesion form.

How novel gene polymorphisms that are apparently shared between IBD and SpA relate to microscopic gut inflammation requires, therefore, further investigation. Furthermore, no prospective studies that have investigated the genetic risk factors for the transition of microscopic chronic gut lesions into overt IBD are currently available. Such a model, were one to be characterized, could prove to be useful in identifying early treatment strategies.

Environmental factors

In addition to genetic susceptibility, much attention has also been given to the role of environmental factors in triggering the onset of rheumatic disease. Given the prototypical link between certain bacterial infections and the onset of reactive arthritis, several studies have aimed to assess the role of intestinal flora in disease progression, as well as the resulting changes in mucosal response. One such study found that the response of patients with SpA to intestinal microbes is evidenced by the presence of IBD-associated circulating antibodies that target a subset of commensal microbial antigens, including anti-*Saccharomyces cerevisiae* antibodies (ASCA), anti-*Escherichia coli* outer membrane porin C (anti-OmpC) antibodies and perinuclear antineutrophil cytoplasmic antibodies (pANCA).[43,44] The presence of these antibodies demonstrates a loss of tolerance to commensal intestinal microorganisms. In a small pilot study, 55% of patients with AS (but without manifest IBD) showed at least one of these IBD-associated antibodies; indeed, pANCA, ASCA (IgA and/or IgG), and anti-OmpC antibodies were found in 21%, 30%, and 19% of patients, respectively. As pANCA was more frequently present in patients with AS and concurrent ulcerative colitis than in those with AS alone, it seems to be an indicator for ulcerative colitis in patients with AS.[45] In another pilot study, the median anti-I2 response (associated with anti-Pseudomonal activity) was significantly higher in patients with AS than in controls.[47] The exact role of these antimicrobial IBD-associated antibodies in SpA demands further research, as does the link with other antibodies that have been putatively associated with IBD (for example, anti-flagellin antibodies such as anti-CBir1), and the link with microscopic gut inflammation.

Of interest, changes in mucosal responses from inflammatory cells, most notably neutrophils, have also been linked to bowel inflammation in the context of SpA. Hence, fecal markers of neutrophil influx into the mucosa are promising indicators of intestinal inflammation. Indeed, calprotectin (a complex formed of the calcium-binding proteins S100A8 and S100A9) has been used as a fecal marker of IBD for more than 10 years,[46] and shows a substantial correlation with IBD activity. Similarly, significantly increased fecal concentrations of calprotectin were found in patients with AS (compared with healthy controls)[48,49] which were comparable to the concentrations found in patients with Crohn's disease. Further research is again necessary to investigate the correlation of these findings with microscopic gut inflammation in patients with SpA.

Intestinal microbiome in inflammation

The composition of the intestinal flora is generally referred to as the microbiome (Box 1). The most apparent connection between the microbiome and SpA is the appreciation that certain bacterial species, of genera

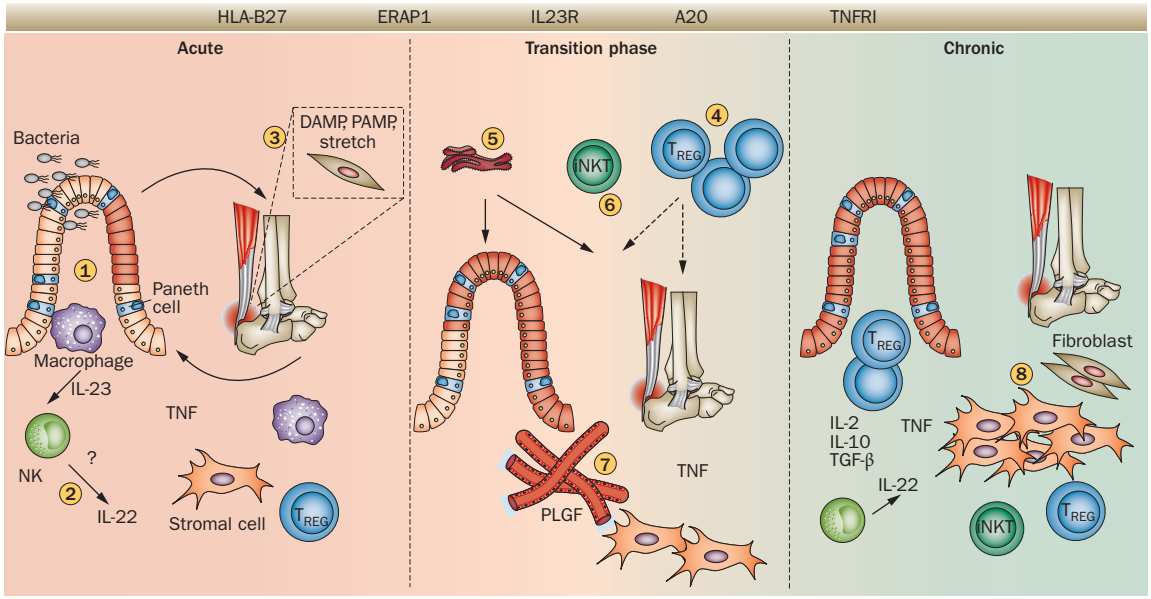

Figure 2 | A unifying concept linking gut and joint inflammation in SpA: transition model. In the acute phase of inflammation, bacterial infections can cause acute intestinal inflammation. Certain bacteria may survive intracellularly in macrophages (1) that can traffic to the joint and cause a reactive arthritis in a genetically predisposed host. Proinflammatory cytokines such as TNF and IL-23 are produced locally, with Paneth cells being the most important producers of IL-23 in the intestine. This expression can activate innate immune cells (NK) to produce IL-22 that may help control inflammation at mucosal sites (2). Otherwise, damage and pathogen associated molecular pattern molecules (DAMPs and PAMPs) and cellular stretch might promote initiation of joint inflammation (3). In the transition phase, acute intestinal and articular inflammation can be sustained due to defective immune regulation by T_{REG} cells (4), or by ER stress (5), whereas iNKT cells act as regulators to control inflammation (6). Proangiogenic factors such as PlGF can lead to aberrant neovascularisation (7). These events may lead to chronicity, further enhanced or maintained by repetitive cellular stress (8). In this stage, stromal cells become more important, as targets for pro-inflammatory cytokines. Abbreviations: DAMP, danger-associated molecular pattern; ER, endoplasmic reticulum; iNKT, invariant natural killer T cell; NK, natural killer cell; PAMP, pathogen-associated molecular pattern; PlGF, placental growth factor; T_{REG}, T-regulatory cell.

such as *Chlamydia*, *Salmonella*, *Shigella*, *Yersinia* and *Campylobacter*, can trigger reactive arthritis.

Microscopic gut inflammation in patients with AS is now considered to be an early stage of Crohn's disease. In Crohn's disease, an imbalanced interaction between the host and the commensal enteric bacteria is evident, resulting in a general dysbiosis.[50] In healthy individuals, immunological tolerance to the gut microbiome is maintained, whereas in those with IBD these homeostatic mechanisms are disrupted. Also, the composition of the intestinal flora in patients with IBD is altered when compared with healthy individuals, resulting in a general loss of diversity,[51] a depletion in Firmicutes and Bacteroidetes, and a relative increase in enterobacteriaceae, although their absolute numbers were unaltered.[52] The enteric flora is assumed to have a causative role in IBD, although the contributing species remain unidentified (partly owing to the enormous complexity of the microbiome).[53–55]

The intestinal flora influences the immune response. Proof of this concept was revealed by mice that are raised germfree; these mice fail to develop a normal immune system and exhibit reduced intestinal lymphoid tissue.[56,57] Furthermore, *HLA-B27* transgenic rats that are raised in a germfree environment do not develop arthritis or colitis, whereas the reintroduction of intestinal flora leads to the development of colitis within weeks.[58] In 2011, Rosenbaum and colleagues proposed the hypothesis that *HLA-B27* positivity predisposes individuals to the development of AS by influencing the composition of the body's endogenous flora; their manuscript summarizes circumstantial evidence that *HLA-B27* can direct the endogenous flora and alter the body's immune response to infectious agents.[59] *HLA-B27* encodes an antigen-presenting molecule that might present an arthritogenic peptide and induce an immune response.[60] Furthermore, *HLA-B27* regulates positive and negative selection of T cells in the thymus, and can form dimers that are recognized by natural killer cells, which might also promote inflammation and contribute to AS pathogenesis.[61]

Paneth cells (intestinal secretory cells located at the bottom of the bowel crypts) have an important role in host defense against microorganisms. These cells have the ability to secrete anti-microbial products including lysosyme, human α-defensin (HD)-5 and HD-6. Interestingly, defensin levels are reduced in Crohn's disease.[62,63] By contrast, ileal biopsy samples from patients with AS and chronic inflammation or recent-onset Crohn's disease display a marked upregulation of antimicrobial peptides by Paneth cells, compared with samples from healthy individuals.[64] Patients with AS also show marked overexpression of IL-23, and Paneth cells are the major source of IL-23 both in physiological and in pathological

Box 1 | The intestinal microbiome

The composition of the intestinal flora, generally called the microbiome, is highly variable between individuals but is relatively stable over time. Numerous functions of the human body, such as digestion, production of vitamins and short-chain fatty acids, and defense against pathogenic organisms, are enriched by the microbiome. From this point of view, the human body together with its microbiome can be referred to as a superorganism. The genetic composition of the gut microbiome, its metagenome, varies between individuals and can be analyzed in fecal samples. Analysis of such samples from people of different nationalities has identified three distinct metagenomic clusters, called enterotypes. These enterotypes do not correlate significantly with the host's gender or nationality, but certain marker genes might enable classification of groups of people who would, for instance, respond differently to dietary variation or drug intake.[92]

conditions.[65] These observations suggest that dysfunction of Paneth cells occurs during the early stages of intestinal inflammation, and might have an important role in the development of AS.[64]

Regulation of gut and joint inflammation

Several studies have highlighted a variety of adaptive immune responses—including those mediated by regulatory T (T_{REG}) cells and natural killer T (NKT) cells—that work to counteract inflammation.[66,67] These adaptive immune responses, however, do not seem to be sufficient to combat inflammation in patients with SpA.

Regulatory T cells

$FOXP3^+CD4^+$ T_{REG} cells have emerged as the most important regulatory immune cell subset. These cells suppress the proliferation and cytokine production of effector T cells, mainly through direct cell–cell interactions.[67,68] In Crohn's disease, expansion of T_{REG} cell subsets occurs in mucosal lymphoid tissues, whereas in peripheral blood numbers of these cells are reduced when compared with healthy individuals.[70,71] Thus, active IBD is associated with a contraction of the peripheral blood T_{REG} cell pool, and an only moderate expansion of these cells in intestinal lesions, which indicates that compensatory mechanisms to prevent chronic inflammation are not successfully achieved in patients with IBD. Biopsy samples taken from the terminal ileum of patients with AS and chronic intestinal inflammation revealed high expression of *IL2*, *IL10*, genes encoding TGF-β, *FOXP3*, and *STAT5*, suggesting the presence and activity of T_{REG} cells.[72] A significantly greater frequency of $CD4^+CD25^{high}$ T_{REG} cells was detected in lamina propria mononuclear cells from ileal biopsy samples and in peripheral blood in patients with AS than in healthy individuals; interestingly, these cells were IL-10 producers.[72] Despite the clear IL-23 signature in the gut of patients with AS, T_H17 cell polarization is not observed, which could be due to T_{REG}-mediated suppression.[65] In the presence of IL-10 inhibition, substantial T_H17 cell expansion in isolated lamina propia mononuclear cell populations from patients with AS was reported.[72] Therapy with anti-TNF antibodies (infliximab or adalimumab) enhanced the number and suppressive function of $FOXP3^+$ T_{REG} cells in the peripheral blood of patients with IBD.[73] Moreover, a strong clinical response of patients with Crohn's disease to infliximab was associated with a marked increase in peripheral blood T_{REG} cells and TGF-β levels when compared with patients who did not respond to this treatment.[74]

Little is known about the frequency of T_{REG} cells and their function in SpA. In general, $FOXP3^+$ T_{REG} cells accumulate within inflamed joints during relapses, when compared with levels in peripheral blood, which suggests an active recruitment of these cells to the affected joint.[75,76] Appel and colleagues[76] reported a higher frequency of $FOXP3^+$ T_{REG} cells in patients with axial and peripheral SpA compared with those with definite AS and RA, which, according to the authors, might contribute to the spontaneous resolution of peripheral SpA as compared with the more persistent joint inflammation in RA.[76]

Natural killer T cells

Another subset of T cells with regulatory properties are NKT cells that express an invariant T-cell receptor—so called invariant NKT (iNKT) cells. In a mouse model of spondyloarthritis (the $TNF\Delta^{ARE}$ mouse, which is characterized by dysfunctional TNF mRNA stability) iNKT cells can dampen both intestinal and articular inflammation through enhanced crosstalk with inflammatory dendritic cells,[77] providing a natural feedback mechanism that also implicates IL-10. Interestingly, inflammatory dendritic cells occurring under chronic exposure of TNF were found to markedly upregulate the non-classical MHC molecule CD1d, which presents glycolipids to iNKT cells and induces production of immunoregulating cytokines.[77] Furthermore, iNKT cell activation occurring under these conditions does not require exogenous administration of glycolipid antigens but rather reflects an enhanced presentation of endogenous ligands. Importantly, a similar marked increase in CD1d levels in human patients with SpA was apparent,[77] but the functional role of human iNKT cells needs to be further addressed. Given the role of iNKT cells as sensors of microbial infection by recognition of microbially derived ligands,[69] it is tempting to speculate that at least part of the altered iNKT cell response is secondary to alterations in the intestinal microbiome.

Driving microscopic bowel inflammation

Whether SpA is a disease of innate versus adaptive immunity is still unclear. In patients with SpA, the major cell subsets that infiltrate the synovium are B cells, T cells and macrophages;[78] these cells have altered functional behavior and a decreased ratio of type 1 T_H (T_H1) cells to type 2 T_H (T_H2) cells.[79,80] Furthermore, a particular subset of macrophages that express the scavenger receptor CD163, which is also increased in noninflamed intestinal mucosa of SpA patients, is selectively increased in SpA synovia.[81] Whereas SpA was considered a T-cell driven condition for a certain period of time, with involvement of both T_H1 and T_H2 cells, the contribution of the IL-23–IL-17 axis to SpA (and other inflammatory conditions) has now been appreciated.[82,83] Moreover,

the fact that IL-23 receptor polymorphisms seem to confer protection against AS supports this hypothesis.[84] The IL-23–IL-17 axis is strongly activated in the colon of *HLA-B27* transgenic rats (an animal model of SpA), concurrent with intestinal inflammation.[85] In addition, HLA-B27 misfolding and the subsequent unfolded protein response strongly increases the production of IL-23.[85]

In addition to a role in joint inflammation, IL-23 also seems to be involved in microscopic gut inflammation in patients with AS. Ciccia and colleagues[65] reported that IL-23 (as well as TGF-β) was markedly upregulated at the mRNA and protein levels in the terminal ileum in patients with AS in comparison with healthy controls. However, this finding was not associated with a clear T_H17 polarisation, as upregulation of IL-17 and IL-17-inducing cytokines (that is, IL-6 and IL-1β) was not detected.

Although T cells were originally considered to be the primary source of IL-17 cytokines, innate immune cells might also have a major role in IL-17 production. Indeed, Appel and colleagues[86] reported that innate immune cells (rather than canonical T cells) express IL-17 in patients with axial SpA.[86] Histological analysis of zygoapophyseal joints of patients with established AS revealed that $CD15^+$ neutrophils and myeloperoxidase-positive myeloid cells, but not classical T cells, are the major cellular sources of IL-17 in the inflamed bone marrow.[86]

As the stroma undergoes numerous alterations in SpA, mesenchymal cells could be considered alternative players in its immunopathogenesis. In a mouse model of TNF-driven SpA-like disease (the $TNF\Delta^{ARE}$ mouse) stromal cells (intestinal myofibroblasts and synovial fibroblasts) were sufficient targets for chronic TNF to cause both articular and intestinal inflammation.[87] In addition, intestinal epithelial cells were sufficient to cause Crohn-like ileitis in the mice through endogenous TNF production. Therefore, in this model, epithelial-derived TNF can trigger the activation of intestinal myofibroblasts within the deeper layers of the bowel wall.[87] However, in $TNF\Delta^{ARE}$ mice in which *TNFRI* expression is limited to intestinal epithelial cells ($VillinCreTNFRI^{flxneo}$ x $TNF\Delta^{ARE}$ mice), deregulated TNF expression was not sufficient to cause chronic inflammation.[88] Further research is required to unravel the precise effector pathways by which stromal cells can induce bowel inflammation and arthritic disease.

A specific subset of natural killer cells, NK22 cells have been assigned a role in intestinal inflammation.[89,90] NK22 cells are located in the mucosa-associated lymphoid tissue and secrete IL-22 following acute exposure to IL-23. These cells provide an innate source of IL-22 that might help control inflammation and provide protection at mucosal sites.[91] Interestingly, the IL-22 receptor is exclusively expressed on mesenchymal cells. The ligand–receptor distribution enables immune cells to regulate responses of tissue-resident stromal cells. This pathway seems to be crucial at barrier surfaces. Whether it is also operational in the inflamed joint has yet to be elucidated.

Transition model of chronic joint disease

At present the factors that favor chronicity of disease in SpA remain unclear. Characterizing such factors is crucially important, as better understanding of the mechanisms that promote sustenance of inflammation might have therapeutic implications. In the context of mucosal inflammation in SpA, we propose that chronic gut inflammation (a risk factor for chronicity of gut and joint disease in SpA) proceeds through an initial acute inflammatory event (Figure 2). Acute inflammatory episodes can be induced in any individual by a variety of factors including certain bacterial infections or biomechanical stress— involving a number of microbial or endogenous danger signals at the molecular level. Acute inflammatory episodes are likely to be mediated by cells primarily of the innate immune system, such as macrophages and neutrophils, and typically resolve with time in the majority of individuals. However, susceptible individuals who are under the influence of a variety of genetic factors that affect antigen processing, endoplasmic reticulum stress, autophagy or cytokine signaling, are unable to appropriately resolve these acute inflammatory insults. Acute inflammation can then transition into a more chronic phase. Here, cells of the adaptive immune system are also involved, and, although natural regulatory feedback mechanisms are engaged, they are unable to resolve the inflammation. In the absence of regulation by T_{REG} cells or NKT cells, gut and joint disease are markedly aggravated. Interestingly, the transition phase is also characterised by a particular proangiogenic profile with upregulation of placental growth factor (PlGF).[93] PlGF has a redundant role in vascular development and maintenance but has a major regulating function in pathological angiogenesis, such as during tumor development and inflammation. Moreover, PlGF directly links angiogenesis and inflammation by promoting the recruitment and activation of proangiogenic monocytes and macrophages. The chronic phase is characterized by the emergence of a strong stromal response leading to a more autonomous and self perpetuating nature of inflammation. New emerging cell types such as NK22 cells might contribute to either the angiogenic and/or the self-perpetuating phases of inflammation, as they might provide important crosstalk between lymphoid and stromal cells. Genetic polymorphisms might also influence each of these pathways. We anticipate that future therapeutic strategies will need to target the transition phase to prevent the occurrence of chronic SpA. Indeed, on the basis of the underlying mechanisms of the acute, transition and chronic phases, we speculate that profoundly different strategies will be demanded to approach the chronic as opposed to the transition or acute phases of the disease.

Conclusions

Marked progress has been made in understanding the link between gut and joint inflammation in SpA with the discovery of new cellular players such as mesenchymal cell types and NK22 cells. The integration of data on genetic susceptibility to SpA with the effect

of particular gene variants on the function of the mucosal immune system remains, however, largely to be conducted. Similarly, as new technological approaches have emerged, sophisticated strategies to unmask the intestinal microbiome at an individual patient level have now become feasible. These approaches will generate highly interesting data on the underlying mechanistic basis of the transition phase that leads to chronicity of inflammation in SpA. Clearly, exciting times are coming.

Review criteria

A search for original articles published between 1985 and 2012 was performed in MEDLINE and PubMed. The search terms used were "spondyloarthritis", "gut inflammation", "inflammatory bowel disease" and "microbiome", alone and in combination. All articles identified were English-language, full-text papers. We also searched the reference lists of identified articles for further relevant papers.

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Author contributions

L. Van Praet and P. Jacques contributed equally to researching data for the article, discussing the content of the article and writing the article. F. Van den Bosch and D. Elewaut substantially contributed to discussions of the article content, wrote the article and reviewed and edited the manuscript before submission. D. Elewaut also researched some of the data for the article.