Spreading spondyloarthritis: are ILCs cytokine shuttles from base camp gut?

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A series of discoveries has transformed concepts of spondyloarthritis and proinflammatory cytokine interleukin-23 (IL-23) has taken centre stage. The IL-23 frenzy kicked off with the identification of single nucleotide polymorphisms in the IL-23 receptor (IL-23R) gene that are associated with ankylosing spondylitis (AS)1 and also with related disorders such as psoriasis, psoriatic arthritis and Crohn’s disease. The most striking and direct evidence comes from an in vivo IL-23 overexpression study in mice that phenocopies the human disease and its Janus-faced characteristics: joint inflammation and structural damage presenting as new bone formation.2 Patient studies reported increased serum levels of IL-23 in AS3-5 and the presence of IL-23-positive cells was shown in facet joints of patients with AS.6 Direct clinical evidence comes from a prospective, open-label clinical trial with ustekinumab, an antibody binding to the shared p40 subunit of IL-23 and IL-127 and successful clinical trials targeting IL-17, one of the downstream cytokines associated with IL-23 signalling.8 Key to the hypothesis and evidence proposed in the mouse model is the presence of an IL-23 receptor-positive T-cell population in the enthesis of mice. As enthesitis is one of the main characteristics of AS and was proposed as the primary lesion,9 it is hard to ignore the potential key role of such cells. However, until now, these IL-23 receptor-positive cells have not yet been demonstrated in human samples.

Ciccia et al10 report on the presence of a population of IL-23R-positive innate lymphoid cells (ILCs) in the gut, peripheral blood, synovial fluid and bone marrow of patients with AS. Numbers of such cells are increased as compared with different controls and their surface characteristics show similarities with the mouse cells identified earlier. However, these ILCs are a rare cell type whose significance in human disease is as yet uncertain. In two previous studies Ciccia et al11,12 showed increased IL-23 expression in the gut of patients with AS as compared with healthy controls. In AS synovium and peripheral blood cells, however, no differences in expression of IL-23 were found.13-14

They characterised these cells as Ly6C+IL-22+Ly6C−NKp44+Tbet+RORc−ILC3s in gut samples of patients with AS.15-21 Although this observation is not consistent,22-24 IL-17-producing cells were also found in the subchondral bone marrow cells of affected facet joints of patients with AS.6 Interestingly, the majority of these IL-17-positive cells were rather innate immune cells (CD11b+ neutrophils and MPO+ cells of the myeloid lineage) than CD4+ T cells.6 Obviously, the most convincing proof of principle that IL-17 plays a key role in spondyloarthritis is found in the clinical trials evaluating the effect of secukinumab, a monoclonal anti-IL-17A antibody that rapidly reduced clinical and biological signs of active AS.8

IL-22 has also earned its place in the spotlight as it has been associated with enthesitis/arthritis development in mice and with upregulation of genes potentially involved in the new bone formation process (such as Wnts and bone morphogenetic proteins).2 However, the role for IL-22 in AS and related disorders seems to be tissue dependent—as demonstrated in a study by Benham et al23 using the SKG mouse model. In this mouse model curdinal injection in SKG mice leads to IL-23-dependent axial and peripheral arthritis and ileitis. When IL-22 was neutralised by an IL-22 antibody, the mice developed a reduced severity of enthesitis but an exacerbation of ileitis.23 This finding highlights that the effects of interleukins in the pathogenesis of AS are not always straightforward but can vary from tissue to tissue and be influenced by tissue-dependent environmental factors. It is important to note that the current
attention towards IL-23, IL-17 and IL-22 to some extent neglects the critical role of tumour necrosis factor (TNF) in this type of diseases. A TNF overexpression model mimics many features of the disease and TNF inhibition is currently the mainstream approach with high and sustained efficacy in SpA. Bringing together the different proinflammatory cytokines in one paradigm is therefore an interesting challenge.

Detailed histological analysis of the gut biopsies drives the authors to propose the hypothesis that IL-23 receptor-positive ILC3s differentiate in the gut and then migrate to extraintestinal sites where they produce IL-17 and IL-22. This hypothesis was formulated in part on the abundant expression of α4β7 integrin on ILC3s, a β7 integrin with marked gut tropism, even though earlier work demonstrated its presence on synovial T cells in SpA synovium. Although this hypothesis touches the limits of careful observation in human samples without additional mechanistic experiments, the concept is certainly worth considering. Moreover, earlier this year Mackley et al provided the first in vivo evidence of ILC3 traffic starting from the gut in mice. The concept is also in line with old and new insights into the role of gut inflammation in spondyloarthritis. Five per cent to 10% of patients with AS suffer from clinically apparent inflammatory bowel disease (IBD) and even a much larger proportion of AS patients suffer from subclinical gut inflammation as already suggested in 1985.

In a recent study by Van Praet et al 46.2% of patients with AS showed microscopic gut inflammation of which 16.9% was acute and 29.2% was chronic inflammation. Patients with AS with chronic gut inflammation also have a higher degree of bone marrow oedema, as seen on MRI, further supporting a link between mucosal inflammation and progressive disease in AS. The gut is a barrier tissue continuously faced with the challenge of maintaining the symbiotic gut microbiome while avoiding local and systemic disease development by pathogenic microorganisms. New technologies can assess the gut microbiome in a systematic way. Different efforts are underway to link the microbiome with gut inflammation and joint disease in SpA and the results are eagerly awaited.

ILC3s are required for human immunity against extracellular bacteria and also play a role in chronic inflammation due to its proinflammatory characteristics. Keeping in mind that intestinal bacteria could play a role in the pathogenesis of AS, as described above, and that AS is a chronic inflammatory disease, the hypothesis that ILC3s are directly involved in the pathogenesis of AS sounds plausible. Of course, further research is necessary to, first, confirm the data and, second, further explore this hypothesis. If the hypothesis about the migration of IL-23 sensitised gut-resident ILC3s is correct, one of the key residual questions, for example, is how HLA-B27, the strongest risk factor for AS, fits in this story. Since HLA-B27 is a major histocompatibility complex class I molecule it will present endogenous antigens/peptides originating from the cytoplasm on the cell surface. These antigens/peptides include self-peptides and can derive from viruses and bacteria. This peptide presentation could then possibly be the link to the gut microbiome. As the HLA-B27 gene is not linked to IBD, another possibility is that HLA-B27 does not play a role in disease induction in the gut, but only plays a role in inflammation at the joint level. Another question is how to explain joint inflammation in patients with AS without currently detectable gut inflammation. Notwithstanding the many additional questions, the paradigm proposed by Ciccia et al focusing on ILC3 cells as cytokine shuttle travelling from gut to blood, synovium and bone marrow in AS is an interesting new approach to the unraveling of spondyloarthritis’ pathogenesis.

**REFERENCES**


Received 8 June 2015
Revised 3 July 2015
Accepted 5 July 2015
Published Online First 21 July 2015

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