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Interleukin-23 in perspective

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Rheumatology key messages

- IL-23 acts locally in tissues by activating IL-23R^{+} cells.
- IL-23 is a coordinating cytokine in psoriasis, psoriatic arthritis and inflammatory bowel disease.

IL-23 history

IL-23 was discovered 20 years ago in an *in silico* bioinformatics search for novel members of the IL-6 cytokine family [1]. This immune modulator is a heterodimeric cytokine comprising a p19 subunit linked to a p40 subunit shared with IL-12. Importantly, the same common p40 subunit links to a unique p35 subunit to form IL-12. Because of the shared p40 subunit, much of the pathobiology attributed to IL-12 (1989–2002) was in fact driven by two distinct cytokines, IL-12 and IL-23. The discovery of IL-23 prompted re-examination of immune pathways regulating inflammatory diseases. At that time it was thought that the classical Th1 cell-induced IFN-γ response is required for induction and maintenance of autoimmune inflammation. Historically Th1 cells were thought to promote autoimmunity, principally through studies using p40-deficient mice and p40 neutralizing antibodies. However, there were inconsistencies. As previously reviewed, mice lacking critical components of the Th1–IFN-γ pathway (e.g. IFN-γ$^{-/-}$, IFN-γR$^{-/-}$, IL-12Rβ2$^{-/-}$ and IL-12p35$^{-/-}$ mice) are highly susceptible to autoimmune inflammation [2]. When we set out to re-examine the relative contribution of IL-12 *vs* IL-23, using IL-23-deficient p19$^{-/-}$ mice, p35$^{-/-}$ (IL-12 deficient) and p40$^{-/-}$ (IL-12 and IL-23 deficient) mice, IL-23 was shown to be the critical player in autoimmune inflammation [3]. It was remarkable that the disease-resistant IL-23p19$^{-/-}$ mice developed normal autoantigen-specific Th1 responses, while being severely impaired in the development of IL-17-producing T cells. In contrast, the disease-susceptible p35$^{-/-}$ mice (lacking IL-12) displayed impaired Th1 responses, with greater frequency of IL-17-producing pathogenic Th17 cells.

We recognized in 2004 that IL-23 promoting IL-17 production is linked to multiple human autoimmune disorders [4], including multiple sclerosis [5] and psoriasis [6], suggesting a role for the Th17 pathway in human diseases. IL-17-producing T cells were found in the synovium of Lyme arthritis patients [7], pointing to involvement of IL-17 in infection-induced immunopathology. The IL-17A receptor (IL-17RA), which binds both IL-17A and IL-17F, is commonly expressed in a broad range of cell types, including endothelial cells, skin epithelial cells and gut enterocytes [8]. Activation of IL-17A and/or IL-17F in these cells promotes the expression of IL-1, IL-6, IL-8 and TNF, which perpetuates chronic inflammatory responses. These early studies set the stage for the development of IL-17 and IL-23 inhibitors (IL-17i and IL-23i) approved to treat autoimmune disorders. Today, three IL-17i and four IL-23i agents are approved to treat patients with moderate–severe psoriasis: ustekinumab (anti-IL-12/23p40), secukinumab and ixekizumab (anti-IL-17A), brodalumab (anti-IL-17RA) and tidrakizumab, risankizumab and guselkumab (anti-IL-23p19). Currently guselkumab, ixekizumab and secukinumab are also approved to treat patients with active PsA.

IL-23 and anatomical pathology

Although initial studies investigating IL-23 biology focussed on antigen-mediated T cell responses, it became apparent that the cytokine plays an important role within a cluster of seronegative diseases for which the role of specific antigens is less clear. Of great interest,

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SUPPLEMENT

these diseases reveal a very strong relationship between IL-23 biology and specific anatomical features. IL-23 not only plays a prominent role at externally facing barrier surfaces, particularly the skin [9] and gut [10], but it also drives inflammation at internal sterile sites such as the joints [11]. While the skin and gut barrier is characterized by the presence of an extensive microbiome, a fundamental feature of the joints is the presence of high biomechanical stress. IL-23-responsive cells appear to specifically localize to these barrier surfaces and structures that transmit biomechanical force. These tissue-resident cells are present even in the healthy state and may have roles in regulating barrier function and tissue repair and maintenance.

Experimental overactivity of the IL-23 pathway within these sites leads to hallmark pathological features of IBD, psoriasis and PsA in mice [9–11]. It is well known that in humans these diseases are closely linked; patients with one disease have an elevated risk of developing another. Further evidence that these conditions constitute a fundamental unity comes from the observation that in patients with one disease, subclinical disease is often present at another anatomical site. Thus patients with IBD or psoriasis are at increased risk of having subclinical enthesitis or sacroiliitis [12, 13]. Patients with enthesiopathic arthritis often have subclinical bowel inflammation, which is associated with elevated production of IL-23 in the gut [14]. Intestinal dysbiosis not only occurs in IBD, but also in PsA [15]. All of these conditions are associated with uveitis, and patients with apparently isolated uveitis not only have a tendency for subclinical bowel inflammation [16], but also extensive subclinical enthesitis [17]. Such unifying clinical observations are further supported by shared genetic components, many of which are in the IL-23 pathway and include IL-23R and Tyk2.

IL-23 can induce inflammation in the gut, skin and joints in a remarkably efficient manner. Indeed, IL-23 alone can directly, rapidly and reproducibly induce the hallmark clinical features of human psoriasis [9] and PsA in mice [11]. While mucosal immunology is much more complex and IL-23 is produced in the gut in the healthy state, recent work has shown that IL-23 expression in the gut in combination with other perturbations can induce relapsing–remitting gut inflammation [18].

IL-23R is constitutively expressed on natural killer (NK) cells, innate lymphoid cells, γ-δ T cells and mucosal-associated invariant T (MAIT) cells, all of which recognize structural elements via invariant T cell receptor or other recognition motifs. Engagement of IL-23R activates a range of Janus kinases (JAKs) and signal transducers and activators of transcription (STATs), including JAK2, tyrosine kinase 2 (TYK2) and STAT3, STAT4 and STAT5, with TYK2 and STAT3 being the dominate drivers of Th17 immune-pathway signature genes. The ability of IL-23 to act rapidly on barrier tissues is particularly interesting since the rapid responsiveness of these anatomical tissues is due to the presence of resident type 17 cells, which already express IL-23R. Isolated entheses from both mice [11] and humans [19] have small numbers of IL-23-responsive cells. The pattern of tissue localization of IL-23R thus determines the clinical anatomical structures that become inflamed when IL-23 biology is dysregulated. This is particularly marked in the joints, where the IL-23R$^+$ cells localize to tensile fibres at 'entheseal' insertions of tendons or ligaments to bone. Thus IL-23 expression induces enthesitis in mice along with multiple features of human enthesiopathic arthritis, such as periostitis and entheseal and periosteal new bone formation and bone erosion in the absence of an initial synovitis. Later, a 'secondary' synovitis develops, which is highly destructive and reminiscent of PsA mutilans [11]. This pattern of disease is strikingly different from RA in which a seropositive response drives a primary synovitis without a crucial role for IL-23.

IL-23 in the clinic

Today, clinical evaluation of IL-17 and IL-23 inhibitors has corroborated the initial thinking that the IL-23–Th17 pathway can promote many barrier and 'high-stress tissue'–associated immune diseases. Studies are showing clinical benefits for skin, joint and gastrointestinal tissue inflammation. Both the IL-17 class and IL-23 class of agents are effective for psoriasis, including secukinumab and ixekizumab (anti-IL-17A), brodalumab (anti-IL-17RA) and tidrakizumab, risankizumab and guselkumab (anti-IL-23p19). Currently secukinumab, izekizumab and guselkumab are also approved to treat PsA. Importantly, long-term clinical trial data have shown that ≥80% of patients maintained a durable response of ≥90% skin clearance and more than half of the patients maintained a durable response with complete skin clearance [20].

The anti-IL-12/23p40 agent ustekinumab is also approved to treat ulcerative colitis and Crohn's disease, and emerging data from phase 2 studies have indicated that the anti-IL-23p19 agents guselkumab, mirikizumab and risankizumab are effective and safe in patients with these conditions [21–23]. Pivotal registrational studies for all three IL-23is are ongoing in these indications.

The progression of immunological thought is at an inflection point. Molecular and cellular immunology combined with new ways of aggregating and utilizing large clinical data sets are transforming research ideas into new medicines for diseases thought intractable only a few years ago. One of the major challenges ahead is to test novel concepts targeting a broad range of rare disease indications of the skin, eye, central nervous system, blood vessels and endocrine glands. To block the entire Th17 pathway, a drug must target IL-23R$^+$ tissue resident cells (often behind the blood–tissue barrier) as well as migrating cell populations that engage IL-23 and become reprogrammed to promote inflammation. These same cells are the drivers of chronic injury responses, which are responsible for many autoimmune diseases. There remains much work to be done. Achieving even greater frequency of complete and durable clinical remission is the new goal in immunology trials. We eagerly

anticipate new treatment strategies that will change the lives of patients.

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Data availability statement

Data are provided in the article.

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