

# Crossing the boundaries: IL-23 and its role in linking inflammation of the skin, gut and joints

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## Abstract

Several lines of evidence point towards the central role of IL-23 as a crucial inflammatory mediator in the pathogenesis of SpA—a group of inflammatory arthritic diseases whose symptoms span the skin, gastrointestinal tract and joints. While therapeutic blockade of IL-23 proved successful in the treatment of IBD, psoriatic skin disease and peripheral SpA, it failed in patients suffering from SpA with predominantly axial involvement. Here we review state-of-the-art discoveries on IL-23 signalling pathways across target tissues involved in SpA. We discuss the discrepancies in resident IL-23-responding cells and their downstream activities across skin, gut and joint that shape the unique immunological landscape of SpA.

**Key words:** interleukin 23, spondyloarthritis, psoriasis, inflammatory bowel disease

### Rheumatology key messages

- The unique composition of tissue-resident and infiltrating immune cells responding to IL-23 across different tissues can account for the divergent physiological effects induced by IL-23 signalling.
- Animal studies underline the importance of innate and innate-like immune cells in the early events of IL-23-driven pathology, while findings from patients suggest complex, multidirectional interplay of innate and adaptive pathways in spondyloarthritis.
- The kinetics of IL-23 signalling should be addressed to unravel the roles of specific cell populations at different stages of the disease.

## The multifaceted nature of SpA

SpA is a group of inflammatory rheumatic arthritides of remarkable clinical heterogeneity. Distinct disease phenotypes are reflected by not only the predominant involvement of axial or peripheral joints, but also the spectrum of other affected organs, spanning from entheses, through skin, nails and gastrointestinal tract to the eye [1]. The search for a common culprit, linking the diverse SpA manifestations, first led to the identification of *HLA-B27* as a shared genetic risk factor, followed by the discovery of the IL 23/17 (IL-23/IL-17) axis in immune-mediated inflammatory diseases. Novel

therapeutic strategies targeting the key cytokines of the IL-23/IL-17 pathway were developed and employed across the disease spectrum [2]. The clinical trial programs, however, yielded some unexpected surprises that shed new light on the immunobiology of IL-23 signalling in distinct tissues and the pathogenesis of SpA, and urged in-depth research focusing on cellular sources of type 17 cytokines (also known as type 3 immunity of the Th17 response) [3] and upstream pathways leading to IL-17 induction, including their dependency on IL-23 and link with the host-microbiota interaction. While the IL-23/IL-17 blockade was anticipated to effectively tackle all domains of the disease, clinical trials revealed substantial differences in efficacy between disease subsets. These differences are illustrated by the striking lack of response to therapeutic blockade of IL-23 in axial vs peripheral disease and the fact that IL-17 inhibition proved to be efficacious in skin, joint, entheses and spine, while failed or even exacerbated overt IBD.

Regardless of the disease phenotype, we found a high frequency of microscopic gut inflammation in all subsets of SpA, suggesting that the loss of barrier

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integrity is a common denominator across the entire disease spectrum [4]. Microscopic gut inflammation represents an important risk factor for evolution into full-blown IBD [5]. It has also been linked to SpA disease activity, including the degree of bone marrow oedema in SI joints and structural outcomes [6]. Breach of natural barriers is also exemplified by PsA, a prototypic form of peripheral SpA that usually develops subsequently to skin manifestations [7].

The aforementioned therapeutic discrepancies suggest that distinct mechanisms of immune surveillance could mediate the homeostasis of the varied tissues affected by SpA. This assumption is plausible in view of their divergent functions: while skin and mucosal barriers represent an interface between the external world and the internal immune environment, the primary function of joint tissues is to enable movement. Therefore, it is critically important to demarcate the IL-23/IL-17 pathway in the skin, gut, synovium and entheses of both axial and peripheral joints, including overlapping concepts and differences, and this is the subject of the current review.

### IL-23, an IL-12 cytokine family member and its receptor

IL-23 was identified as a member of the IL-12 cytokine family [8]. The IL-12 family cytokines are characteristically composed of an  $\alpha$  and a  $\beta$  chain, these chains being uniquely paired across the family members [9]. IL-23 is comprised of the p40 and p19 subunits (IL-23 subunit  $\alpha$ ), which are shared with IL-12, and a theoretical family member, IL-39, respectively [10]. IL-23 secretion has been reported by all antigen-presenting cells, as well as neutrophils and respiratory and gastrointestinal epithelial and secretory cells [11–14]. The mechanisms of IL-23 secretion regulation, point towards its tight link with host defence and physiological role in barrier tissues homeostasis. Fig. 1 is a schematic representation of IL-23 and IL-12 receptors.

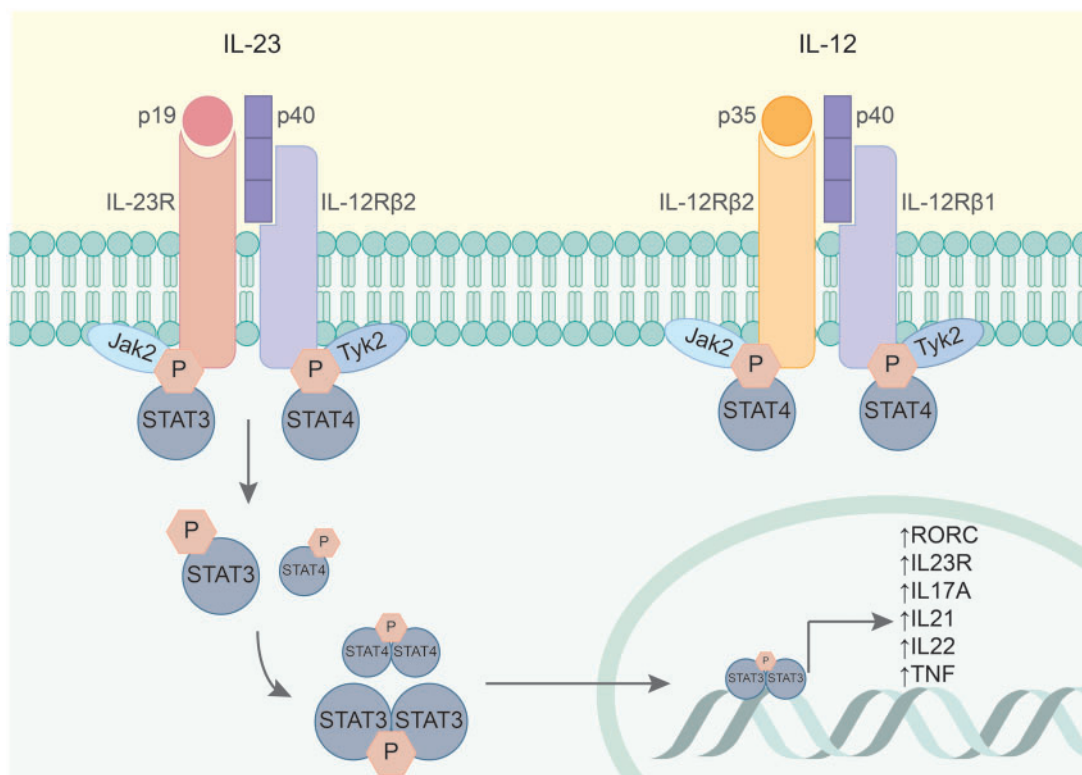
IL-23 signalling induces the expression of a unique set of inflammatory genes, engaging type 17 immune responses [15]. This includes the retinoic acid receptor-related orphan receptor- $\gamma$ t (ROR $\gamma$ t, encoded by the *Rorc* gene) – a master-regulator of type 17 helper T (Th17) cells [16]. The interaction between IL-23 and ROR $\gamma$ t appeared to be bidirectional, as ROR $\gamma$ t transcriptional activity is required for the expression of the IL-23 receptor. The IL-23 receptor complex is found on subsets of memory T cells, NKT cells,  $\gamma\delta$  T cells and innate lymphoid cells (ILCs), but not naive T cells [16–20]. This finding was initially quite puzzling, given the ascribed role of IL-23 in inducing the distinct type 17 immune phenotype in helper T cells [21]. Consequent studies demonstrated that simultaneous priming with TGF- $\beta$ , IL-6 and IL-1 activates ROR $\gamma$ t, and induces IL-23 receptor expression, enabling further IL-23 signalling [22, 23]. The subsequent IL-23 signal is critical for maturation and stabilization of

the proinflammatory Th17 phenotype [21]. Because Th17 cells are crucial for host defence against certain infections such as extracellular microbes and fungi [19, 24], the significance of IL-23 signalling in shaping Th17 effector functions has also been examined in models of both infectious and inflammatory disease. Intriguingly, IL-23 is indispensable for the development of some full-blown immune-mediated inflammation models, but IL-23 blockade did not abolish antimicrobial responses [20, 25]. These observations suggest that Th17 cells activated through different pathways exert distinct functions. These IL-23-independent and IL-23-dependent pathways promote mucosal defence and tissue integrity or reinforce chronic inflammation and even promote autoimmunity, respectively [26].

Th17 cells, however, are not the only cells responding to IL-23 signalling by a potent production of type 17 cytokines. IL-23 receptor-bearing populations of innate-like T cells: gamma delta ( $\gamma\delta$ ), NKT and mucosal-associated invariant T (MAIT) cells, as well as innate-lymphoid cells (ILCs). These cells are typically enriched in the mucosal sites and have been identified in the skin and joint tissues [27–29]. This is an important discovery as innate production of proinflammatory cytokines is rapid and precedes the adaptive IL-17 response. Indeed, innate-like T cells are often referred to as the first line of defence against pathogens, bridging the innate and adaptive arms of immunity. These innate-like cells have been found to be enriched in inflamed tissues of SpA patients, with distinct subpopulations and phenotypes described across affected organs. Moreover, we and others have demonstrated that major production of IL-17 in SpA can be ascribed to innate-like cells [30]. Studies on animal disease models, including pathologies from the SpA spectrum, underpin the plausible crucial role of innate-like T cells in the development of immune-mediated inflammatory diseases [31], while not disregarding the importance of adaptive, proinflammatory cell populations [32].

The IL-23/IL-17 signalling pathway in innate-like T cells bears similarities to what has been found in conventional T cells. Accordingly, IL-17 production occurs both dependent on and independently from IL-23 signalling (via direct activation of innate immunity receptors by microbial stimuli and endogenous mediators as well as T cell receptor activation) [33–35]. In addition to stimulating IL-17 production, IL-23 triggers further differentiation of  $\gamma\delta$ -T cells into a  $\gamma\delta$ 17 proinflammatory phenotype [36], promotes the expansion of  $\gamma\delta$ -T and MAIT cells and induces their migratory properties [37, 38]. As in case of Th17 cells, the effector functions of IL-23-responding NKT and  $\gamma\delta$ -T cells are dependent on ROR $\gamma$ t expression [34, 39–41]. The plasticity of unconventional type 17 T cells has been suggested to even exceed this of Th17 cells, raising hope for possible therapeutic application [42]. Other cells representing the innate immune system, namely ILCs type 3 (ILC3s) and epithelial cells, also respond to IL-23 [43]. These cells have mostly been studied in the context of intestinal tissues and will be discussed below.

**Fig. 1** IL-23 and IL-12 share the molecular subunit p40 and its receptor IL-12 $\beta$ 1, but their signalling cascades proved to exert distinct effects in health and disease



The IL-23 receptor complex is made of the IL-12R $\beta$ 1 and the IL-23R transmembrane proteins, with high-affinity binding capacities for the p40 and the p19 cytokine subunits, respectively [21]. Recent studies have shown that cytokine binding occurs in a highly coordinated manner, with the IL-23: IL-23R binary complex as an obligate mechanistic step for the recruitment of the IL-12R $\beta$ 1 subunit [22]. The complex has no intrinsic enzymatic activity and is coupled to two Janus-associated kinase (JAK) family members, namely Jak2 and Tyk2. Upon IL-23 binding, receptor complex oligomerization occurs, followed by the phosphorylation and activation cascade of downstream signalling molecules: Jak2, Tyk2 and signal transducer and activator of transcription (STAT) proteins. STAT proteins further undergo dimerization and nuclear translocation, where they bind to the promoter regions of certain immune mediators and transcription factors. IL-23 binding to its receptor preferentially activates STAT3, whereas IL-12 results in predominant STAT4 activation, the STAT proteins engaging different target genes [23]. STAT3 activity upregulates the expression of type 17 immunity signature genes, such as RORC, IL23R, IL17A and IL22.

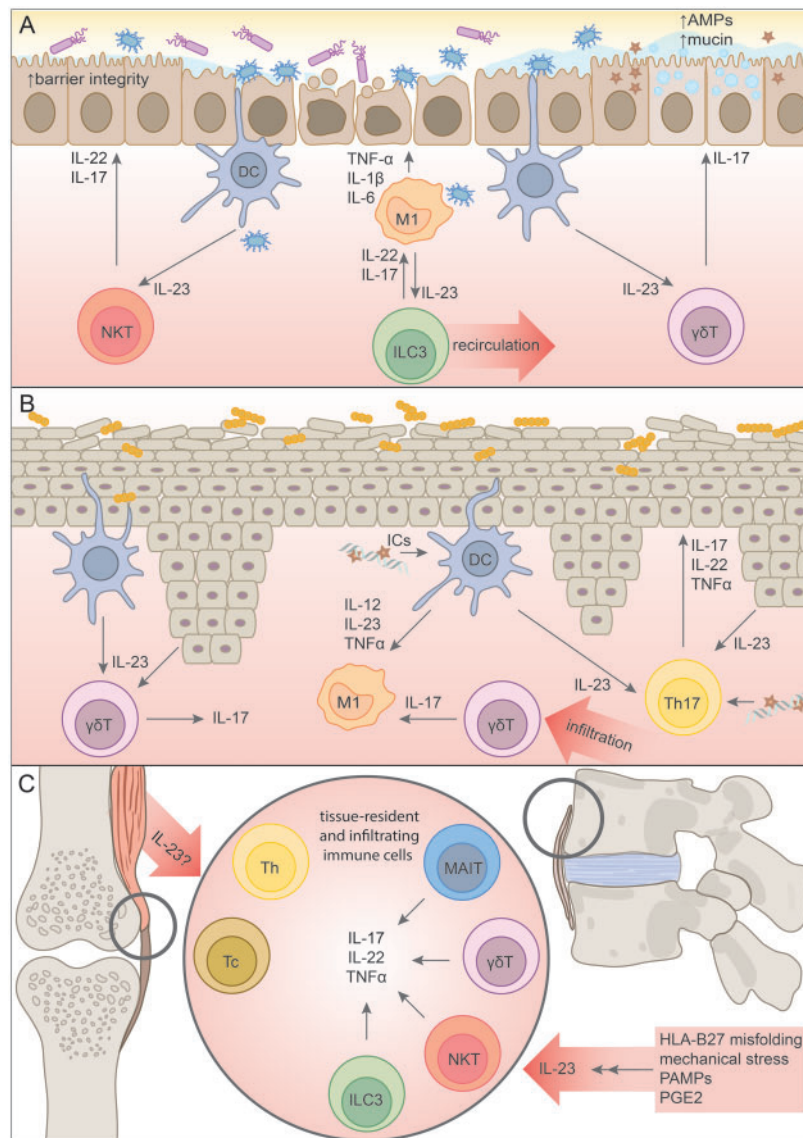
An interesting feature of the IL-23 signalling cascade is the positive-feedback loop induced in many cell types. The transcription factors activated by the IL-23 receptor complex binding (STAT3, ROR $\gamma$ t, Blimp1) enhance the receptor expression, therefore amplifying its own signalling [9, 44, 45]. Moreover, IL-23 binding has been shown to promote IL-23 receptor endocytosis and recycling in macrophages, which also promotes the signalling cascade [46]. Macrophages themselves are a major source of IL-23 in tissues, and interestingly IL-23 levels correlate with enhanced phagocytosis capacities and a proinflammatory phenotype of macrophages [47, 48]. These findings are particularly interesting in the disease context, since genome-wide association studies identified several polymorphisms in genes encoding IL-23 subunits, their receptors and downstream signalling molecules as associated with increased susceptibility to, or reversely, as variants protective from SpA spectrum pathologies: psoriasis, IBD and

arthritis [49]. Mechanistically, it has been shown that the SpA pathology-protective IL23R R381Q variant interferes with IL-23 receptor recycling mechanisms [2, 50]. IL-23 overexpression represents a disease model mimicking many features of SpA pathology, pointing to its crucial role in SpA pathology [42]. At the same time, differential effects of IL-23 signalling across cell types suggests that its ultimate effect depends on the local tissue context. Fig. 2 illustrates IL-23 signalling pathways in the tissues affected by SpA.

### Microbial contribution to type 17 immunity in SpA

In view of the IL-23/IL-17 pathway involvement in the host-microbiome crosstalk, defining the role of microbes in the development of SpA became a crucial goal of

**Fig. 2** Schematic representation of IL-23 signalling across tissues affected by SpA, with a focus on aberrant innate immunity signalling



**A**—IL-23 signalling in the intestinal mucosa: intestinal dysbiosis is associated with chronic activation of DCs, which abundantly produce IL-23 and activate resident and infiltrating immune cells, including ILC3s,  $\gamma\delta$ T and NKT cells. IL-17 and IL-22 produced by these cells seem to have a favourable effect on intestinal barrier integrity, but are countered by vast amounts of proinflammatory TNF $\alpha$ , IL-1 and IL-6.

**B**—Psoriatic skin is characterized by elevated levels of IL-23 produced by a plethora of cells, including keratinocytes, an overgrowth of pathogenic bacteria and expansion of proinflammatory macrophages and  $\gamma\delta$ T cells, both resident and tissue-infiltrating. The significance of defective innate immune mechanisms in psoriasis are underlined by the production of antibodies against AMPs and formation of ICs stimulating local antigen-presenting cells. Th17 cells are also highly present in psoriatic skin.

**C**—Entheses are the soft tissue where ligament, tendon and joint capsules attach to bone. Enthesitis is a pathognomonic symptom of SpA, thought to be dependent on an aberrant IL-23/IL-17 immune axis. Resident populations of innate-like immune cells responding to IL-23 have been identified in healthy entheses, and it has been suggested that they play a critical role in the development of the disease. Adaptive Th and Tc cells producing IL-17 have been identified in SF of PsA patients, but mechanisms for the development of these cell populations are currently unknown.

AMPs: antimicrobial proteins; M1: proinflammatory macrophages; DC: dendritic cells; NKT: NK T cells; ILC3: innate lymphoid cells type 3;  $\gamma\delta$ T:  $\gamma\delta$  T cells; Th17: type 17 helper T cells; Tc: cytotoxic T cells; MAIT: mucosal-associated invariant T cells; PAMPs: pathogen-associated molecular patterns; PGE2: prostaglandin E2.

many studies [51]. Profound intestinal and skin dysbiosis has been reported in patients with SpA, regardless of clinical manifestations, yet it is currently unclear whether this is the cause or consequence of inflammation [52–55]. Indirect microbial signalling has long been associated with different forms of joint pathology: from migratory arthralgia to overt arthritis. Under certain circumstances, particular microbial triggers may induce reactive arthritis, part of the SpA disease spectrum [56]. Studies in animal models further support the role of host microbiota in the development of arthritis, the HLA-B27 transgenic rats being the prototypical example [57]. The Western-type diet, strongly linked to a proinflammatory status and known to induce intestinal dysbiosis, has recently been demonstrated to facilitate and aggravate joint inflammation in a mouse model of SpA [58]. Furthermore, some bacterial strains, such as segmented filamentous bacteria, are notoriously known to boost type 17 responses in mice [59]. It is not yet known if specific bacteria associated with SpA, such as the *Dialister* genus [53], also preferentially trigger a type 17 immune response like segmented filamentous bacteria.

Moreover, accumulating evidence is challenging the assumption that joints are isolated from direct microbial influence. Microbial DNA and RNA have been detected in the SF of ReA [60, 61], PsA and RA patients [62], and even in the synovial tissue and cartilage of OA individuals [63]. How pathogens and microbial products translocate to the joints, and how this contributes to non-purulent arthritis remains unknown.

### IL-23 as gatekeeper of barrier integrity in the gut

The physiology of IL-23 signalling advocates for its orchestrating role in the maintenance of intestinal barrier homeostasis. Elevated levels of IL-23 have been found in the tissues of patients suffering from overt IBD, as well as in patients with subclinical gut inflammation, both pathologies falling within the SpA spectrum [14]. Intestinal inflammation is associated with enhanced gut barrier permeability and increased evasion of pathogen-associated molecular patterns into the host [64]. This leaky gut results in chronic activation of host defence mechanisms, leading to overproduction of IL-23, thought to play a key role in SpA pathogenesis. The chicken-and-egg conundrum of the IL-23 oversignalling and dysbiosis in SpA remains unresolved. While recently it has been proven that intestinal dysbiosis and consequent inflammation in an animal model of SpA is driven by IL-23 signalling [65], other groups point towards dysbiosis as the causative factor. Environmental factors such as diet were shown to have a predominant effect on the gut microbial community composition, and aggravate susceptibility to arthritis and psoriasis in an IL-23 overexpression-based model [58]. Elucidating the intricacies of the host–microbiome interplay in patients is the focus of multiple research groups [51].

Gut epithelial cells possess the IL-23 receptor complex but, unlike the immune cells localized in the intestine, they do not produce IL-17 nor IL-22. Selective blockade of IL-23 signalling in gut epithelial cells did not evoke spontaneous inflammation but led to increased susceptibility to inflammation induced by epithelial integrity loss [66]. This state was characterized by a decrease in IL-22-producing immune cells, impaired wound-healing mechanisms, and overgrowth of flagellated bacteria, pathogens implicated in IBD development [67, 68]. Exogenous administration of IL-23 restored IL-22 production and gut recovery [69]. IL-22 is known to promote intestinal barrier mechanisms by promoting epithelial cell proliferation and production of mucin and antimicrobial peptides [70], yet may also aggravate intestinal inflammation in some models [71]. IL-22 signalling in IBD is distorted, with elevated levels of the cytokine found in patients' blood and increase in IL-22-producing ILC3s, countered by a concurrent upregulation of the neutralizing IL-22-binding protein [72–74]. Interestingly, increased numbers of IL-22- and IL-17-producing ILC3s were found not only in the gut, but also in the peripheral blood and SF of SpA patients. These cells expressed homing integrin  $\alpha 4\beta 7$ , suggesting their recirculation from the gut to the inflamed tissues [75]. The increase in proinflammatory ILC3s in the gut was linked to the ability of IL-23-producing macrophages to promote intestinal inflammation [76, 77].

In contrast to successful therapeutic inhibition of IL-23 in animal models of IBD and in the clinic, the blockade of IL-17A (the most studied member of the IL-17 cytokine family, for simplicity referred to throughout the text as IL-17) demonstrates lack of efficacy and even exacerbation of IBD, despite its efficacy in several preclinical models [78–80]. Intriguingly, intestinal microbiota analyses pinpointed substantial differences in anti-IL-17A vs anti-TNF-treated patients, suggesting a putative link in host–microbial interaction [81]. In this context, IL-17 deficiency exacerbated chemical gut inflammation and promoted intestinal dysbiosis followed by Th17 cell expansion [82, 83]. While the development of intestinal Th17 cells has been linked to the presence of pathogenic microbes, expansion of IL-22-producing, IL-23-responding ILC3s was ascribed to endogenous signalling associated with bacterial colonization [84]. In acute intestinal injury, the production of protective IL-17 was attributed to resident  $\gamma\delta$ -T cells and found to be IL-23-independent [85].

Latest efforts in therapeutics development included the IL-17F family member [the cytokine family member with the highest homology (50%) to IL-17A]. Although an overlap in IL-17A and IL-17F signalling has been observed, with shared use of receptors resulting in the activation of the TNF $\alpha$  pathway, differences in physiology between the two cytokines are apparent [86]. IL17F is constitutively produced by intestinal cells (including activated monocytes, basophils and mast cells, which do not secrete IL-17A), and, unlike IL-17A, bind with greater affinity to the IL-17RC receptor

preferentially expressed on non-hematopoietic cells. A recent study showed that this constitutive production is increased in intestinal inflammation, and that IL-17F or IL-17A/IL-17F deficiency is protective against colitis symptoms [87]. However, in this experimental setting, neither the major source of IL-17F, nor the role of IL-23 signalling were defined. Nevertheless, this finding is of particular importance in the light of the advent of dual IL-17A/IL-17F inhibitors, which proved efficacious and safe in PsA and axial SpA patients [88–90]. The phase II study of the dual neutralization in ulcerative colitis, however, was terminated early due to an imbalance of adverse events with no clear evidence of benefits [91]. Initial molecular studies confirm that synchronized blockade of IL-17A and IL-17F holds the promise of increased efficacy in neutralizing inflammation and establishing new therapeutic targets [88, 92].

### IL-23 inducers and responders in the skin: gateway to psoriasis

IL-23 signalling also plays a pivotal role in maintaining barrier homeostasis in the skin, the second major interface between host and environment. IL-23 is upregulated in various skin pathologies, most notably psoriasis, exemplified by the remarkable clinical efficacy data. Interestingly, IL-23 serum levels have been shown to negatively correlate with the disease duration, suggesting the cytokine's role in early events leading to lesion formation [93]. The sources of IL-23 in the skin include keratinocytes, epidermal Langerhans cells, dermal dendritic cells, and macrophages, cells equipped to respond to microbial and endogenous inflammatory stimuli [94]. Dysbiosis of psoriatic skin microbiota has been suggested as central to chronic stimulation of innate immunity mechanisms and provoking increased IL-23 production [95, 96]. Defective host defence mechanisms in psoriasis are illustrated by the observation that an antimicrobial peptide, cathelicidin LL37, serves as an autoantigen in this disease, as well as PsA [97, 98]. These autoantigens have been shown to bind to DNA and RNA and form immunostimulatory complexes, which are consequently delivered to dendritic cell endosomal TLRs [99]. Activation of TLR8 in dendritic cells induces production of IL-12, TNF $\alpha$  and IL-23 [100].

IL-23 promotes Th17 cell differentiation via STAT3-dependent activation of ROR $\gamma$ t [101]. Th17 cells are expanded in the lesional psoriatic skin and secrete classical type 17 cytokines—IL-17, IL-22 and TNF  $\alpha$ —acting on keratinocytes and local immune cells in a vicious, positive-feedback loop [100]. Studies on animal models of psoriasis confirm the significance of the IL-23-dependent production of type 17 cytokines [102, 103]. Local administration of IL-23 to the skin (intra-dermal injection) has been validated as a psoriasis model, which mimics many aspects of human disease [104]. This model has been shown to be TLR dependent, and a comparison of skin transcriptomes between mice

subjected to intra-dermal IL-23 injection and human psoriasis patients showed a significant overlap in differentially expressed genes [105]. Moreover, IL-23 signalling has been shown to result in an infiltration with proinflammatory macrophages and CCR6-expressing  $\gamma\delta$ -T cells [106]. IL-23 produced by Langerhans cells in the Imiquimod-induced skin inflammation activates skin  $\gamma\delta$ -T cells to produce IL-17 [107], and induction of psoriasis in  $\gamma\delta$ -T cell-deficient mice was found to be significantly impaired [108]. It is important to note that the mouse  $\gamma\delta$ -T cell landscape is unique, including a resident epidermal population (dendritic epidermal T cells), disallowing for direct translation of these mechanisms into humans. At the same time, dermal  $\gamma\delta$ -T cells were expanded in human psoriatic skin and shown to readily respond to IL-23 by increased IL-17 production [108]. Infiltration of circulating  $\gamma\delta$ -T to psoriatic skin has also been indicated [109]. These findings suggest that  $\gamma\delta$ -T cells could be the major responders to IL-23 in the skin, although the contribution of other cell types, such as the macrophages and tissue resident memory T cells, has also been reported [110]. This includes identification of oligoclonal populations of IL-17-producing  $\alpha\beta$  T cells in active and resolved psoriatic lesions, outnumbering  $\gamma\delta$ -T cells [111]. Autoantigen recognition resulting in robust IL-17 production has also been reported [112], proving that the complex interplay of innate and adaptive, local and infiltrating cell populations remains to be unravelled.

### Innate-like T cells as sensors of IL-23 signalling in joints

In contrast to the gastrointestinal membrane and skin (both interfaces of the vast host-microbiome interplay), joint tissues were long considered to be non-immune organs free from microbial stimuli. The emerging roles of tissue-resident immune cells in the joints is challenging this presumption, suggesting that the synovium could in fact constitute an important barrier [113]. Moreover, microbial metabolic products and nucleic acids were found in the circulation and in the joints of non-purulent arthritis patients [54, 62]. Potential translocation of intracellular pathogens targeting immune cells has been suggested, as exemplified by Whipple's disease, a multisystemic pathology with arthritis and features of spondylodiscitis [114]. Trafficking of intracellular microbes into the joints within lymphoid cells or monocytes has also been shown in ReA [115, 116]. Furthermore, in a mouse model of ReA, dissemination of intracellular bacteria (*Chlamydia*) was linked to IL-23-mediated joint pathology [116]. Upregulated levels of chemokines have been found on immune cells circulating in the peripheral blood of SpA patients, but whether this was due to intracellular pathogen invasion remains to be determined. Local triggers of IL-23 production, whose levels are upregulated in inflamed joints of SpA and RA patients, remain less evident than in other SpA-affected tissues. Immune cells circulating between the gut and

the joints were suggested as one possible source of IL-23 in SpA [75, 117]. Alternatively, the propensity of HLA-B27 heavy chain to misfold, followed by activation of innate immune responses and IL-23 production by myeloid cells was also suggested [118]. PGE<sub>2</sub>, which represents an endogenous inflammatory stimulus and a classical target of NSAIDs, also upregulates myeloid cell IL-23 production [119]. IL-23 and IL-17 have been shown to exert a profound effect on bone cells, resulting in systemic bone loss and enthesal bone formation. Mechanisms in which these cytokines induce SpA skeletal features have been reviewed in detail by Gravalles *et al.* [120].

The role of IL-23 in SpA was boosted by the discovery of resident immune cells responsive to IL-23 in the murine enthesis—the area of soft tissue where ligament, tendon and joint capsules attach to bone [27, 121]. Overexpression of IL-23 in susceptible mouse strains results in enthesitis, a hallmark of SpA [27]. Initiation of SpA inflammation in the joints, however, was shown to be independent of Th17 adaptive responses, but rather relying on unconventional innate-like T cells, later identified as enthesal  $\gamma\delta$ -T cells [27, 121]. They express high levels of the IL-23 receptor and can produce large quantities of IL-17 and IL-22 in an ROR $\gamma$ t-dependent manner [122]. An analogous  $\gamma\delta$ -T cell population has recently been isolated from non-inflamed human entheses [123]. IL-17-producing subpopulations of innate-like T cells, including  $\gamma\delta$ -T, NKT, MAIT cells and ILC3s were furthermore found to be expanded in the joints and circulation of SpA patients [28, 75, 122]. Recently, a population of resident spinal enthesal  $\gamma\delta$ -T-cells capable of IL-23-independent IL-17 production has also been described in healthy, non-inflamed spinal entheses, suggesting these cells may have important homeostatic roles [124].

The observation that innate-like T cells such as  $\gamma\delta$ -T cells are potent producers of IL-17 in human joints affected by the SpA pathology, coupled with their ability to do this in the presence or absence of IL-23, is of major interest in view of the differential response of axial vs peripheral disease to IL-23 blockade, whereas both respond equally well to anti-IL-17 [125]. MAIT cells in the blood of healthy subjects were shown to produce IL-17F, rather than IL-17A, upon IL-12 and IL-18 signalling [35]. In the blood and peripheral joints of SpA patients, MAIT cells have been shown to acquire an exaggerated type 17 phenotype in response to activation with IL-7 [28], a pathway also described in IL-17-producing  $\gamma\delta$ -T cells and in the development of ILCs [126, 127]. The upstream signals in the spine leading to IL-17 induction at present are still unclear and have been suggested to include other cytokines such as IL-39, although direct evidence for such pathways is currently lacking [128].

The role of the adaptive arm of the immune system in the production of proinflammatory mediators within the joint, IL-17 in particular, cannot be overlooked. Expansion of IL-17-producing Th and cytotoxic T (Tc) cells has been shown in the joints of patients suffering from RA and PsA

[129–131]. These cells were described to have a highly proinflammatory phenotype, associated with IL-23-driven maturation [132]. Innate immunity triggers ultimately affect adaptive immune responses. Although HLA-B27 has mostly been associated with autoinflammation, arthritis-developing, HLA-B27 transgenic rats display expansion of Th17 cells and dysbiosis [133]. A cutting-edge study investigating T cell receptor sequences of the Th and Tc populations in PsA blood and SF determined that the increase in cell numbers was the consequence of clonal expansion; moreover, it established that T cell receptor recognition was shared between patients [134]. This discovery is a significant counter-argument against the hypothesis that PsA pathogenesis is dependent on aberrant innate signalling. Innate and innate-like cells, however, also possess features of adaptive immunity players [134], and adaptive type 17 responses across cell subsets in SpA could account for perpetuation of inflammation.

## Concluding remarks

Even though therapeutic inhibition of the IL-23 signalling cascade is successfully exploited in the treatment of various inflammatory, immune-mediated diseases, its role in health and disease remains incompletely understood. Evidence in mouse and man demonstrates a range of IL-23-producing and -responding cells across tissues, enabling a fine-tuned, tissue-specific response. These findings provide a plausible explanation of the seemingly paradoxical effect of blocking of IL-23 and its downstream cytokine IL-17 in various pathologies from the SpA disease spectrum. They also provide a theoretical background to hypothesize that targeting the IL-23 signalling pathway in distinct cell populations could help control pathological processes in certain subsets of SpA patients without interfering with physiological, homeostatic mechanisms. However, it should be noted that discrepant findings from IL-23 overexpression-driven animal models of SpA have been reported, including differential organ involvement and pathology severity across genetic strains, suggesting multifactorial disease mechanisms [27, 102, 135].

Studies on the role of IL-23 have also reinforced the notion of host-microbiome interactions as modulators of both local and systemic immune responses. IL-23 has been shown to restore epithelial barrier integrity and promote defence mechanisms against pathogens. Interestingly, many of the cell types involved in host defence are also potent producers of proinflammatory cytokines in SpA pathology, suggesting contribution of skewed antimicrobial responses to the disease pathogenesis. Unambiguous conclusions, however, are momentarily still lacking. The observation that innate-like cells highly responsive to IL-23 are present at anatomical sites affected by SpA, including non-barrier tissues such as entheses, points towards their shared homeostatic role, but also possible utility as a therapeutic target. Production of immune mediators by cells representing the innate arm of the immune system outpaces

the adaptive responses, suggesting the identified innate-like cells could be the early effectors inciting inflammation in the SpA pathogenesis. This hypothesis is further encouraged by studies on animal models of the disease, in which experimental depletion of innate-like cell populations has been shown to be protective against the development of the pathology. Investigation of these steps in humans remains challenging. Elevated levels of IL-23 in patients with active, established disease could be attributed to the positive feedback loop in IL-23 signalling. It seems plausible that early-responding innate-like cells support differentiation and phenotype maturation of adaptive type 17 immune cells identified in the joints of patients with overt inflammatory arthritis. The emergence of autoantigens and oligoclonal Tc and Th populations in psoriasis and PsA underpins the importance of adaptive responses across tissues and acts in favour of an autoimmune rather than autoinflammatory nature of the disease [136].

Importantly, in both innate-like and adaptive immune cells the production of IL-17 can be induced independently of IL-23 signalling. This potential is of particular interest in the light of the confirmed homeostatic role of the IL-23-independent production of IL-17 in the gut, and the lack of therapeutic efficacy of IL-23 inhibition in axial SpA. The recent discovery of resident  $\gamma\delta$ -T cells capable of IL-23-independent IL-17 production in spinal entheses could be the first step into understanding of the latter. MAIT cells, ILC3s and NKT cells—subsets implicated in the pathogenesis of SpA—have also been shown to strengthen IL-17 proinflammatory signalling and contribute to the development of arthritis independently of IL-23 priming. Furthermore, inflammatory cytokine signalling cascades are interconnected, and parallel pathways converge for perpetuation of inflammation. Elucidating the kinetics of IL-23 signalling in the pathogenesis of SpA is therefore of critical importance.

Clinical trials and everyday practice with biologics have provided crucial real-world data on the intricacies of IL-23/IL-17 signalling in disease. As new therapeutic targets are being investigated, our understanding of common and divergent mechanisms across cell types and tissues is broadening. Therapeutic strategies targeting different steps in the IL-23 signalling cascade may unravel the discrepancies seen between SpA subtypes. These efforts are represented by the development of Jak and Tyk2 tyrosine kinase inhibitors and blockers of transcription factors, such as ROR $\gamma$ t [101, 103]. Blockade of ROR $\gamma$ t-inhibited IL-17 production while not affecting IL-22 [122], whereas Tyk2 blockade inhibited IL-22 production with a lesser effect on IL-17 [103]. Such highly selective therapeutic approaches could represent a new area for the development of precision medicine. Results of these ongoing studies will complement our knowledge on IL-23 signalling across the tissues affected by SpA.

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## Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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