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IL-17A and IL-17F in tissue homeostasis, inflammation and regeneration

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IL-17 signalling regulates both protective and harmful immune responses; therefore, its complete inhibition can have adverse effects. Detailed consideration and fine-tuning of IL-17-inhibition strategies is needed to selectively regulate disease outcomes.

Rheumatic diseases often entail musculoskeletal, skin and neuropathological components that synthesize the cardinal signs of inflammation (redness, swelling, heat, pain and loss of function). Effective therapy is therefore considered the inhibition of all the active domains of the disease while restoring the loss of function by tissue repair after injury. The pleiotropic ability of cytokines such as IL-17A and IL-17F to regulate inflammatory processes and tissue repair is being unveiled at a fast pace and is of immense therapeutic importance.

The role of IL-17A in inflammation has been widely demonstrated in several mouse models in which mice deficient in IL-17A and/or IL-17F are protected against many autoimmune diseases. Similarly, mice that overexpress IL-17A show severe epidermal hyperplasia and psoriasis-like pathology concurrently with joint inflammation and an increase in osteoclastogenesis, exacerbating bone erosion and loss of joint function[1]. Thus, IL-17A modulates hallmark pathological features associated with a spectrum of rheumatic disorders. Recently, clinical trials of a monoclonal antibody that inhibits both IL-17A and IL-17F (bimekizumab) showed great efficacy across several active domains of psoriatic arthritis, confirming that IL-17A and IL-17F signalling is crucial in multiple pathways and systems in active disease[2].

IL-17A and IL-17F can exist as homodimers or IL-17A–IL-17F heterodimers and can signal through IL-17RA, IL-17RC and IL-17RD receptors (Fig. 1). IL-17A and IL-17F are mainly produced by αβ T (T helper 17, T_H17) and γδ T (γδT17) cells; however, an increasing number of innate immune cell types have been associated with their expression in various activation states, including innate lymphoid cells, activated monocytes and neutrophils. The activation and differentiation of cells that produce IL-17A, IL-17F and/or IL-17A–IL-17F are differentially regulated by other cytokines expressed in the microenvironment of each tissue. Thus, different populations of IL-17A- and IL-17F-producing cells might be present in the skin, joint or other tissues where they affect the clinical manifestations and course of the disease. Although T_H17 cells co-produce both IL-17A and IL-17F, in some tissue microenvironments IL-17A and IL-17F are produced by different cell types. Moreover, single-cell RNA sequencing demonstrated that even under optimal T_H17 cell differentiation conditions in vitro, more T cells produce IL-17F than IL-17A, but that the vast majority of pathogenic T_H17 cells produce both cytokines together[3]. Therefore, the first important consideration is that different subtypes of IL-17A, IL-17F or IL-17A–IL-17F double-producing cells are present at different tissues and hence IL-17 inhibition outcomes will vary.

Similarly, the expression of IL-17 receptors is also differentially regulated in different tissues. IL-17RD, which was previously considered an orphan receptor, is highly expressed in skin relative to other tissues. IL-17RD forms a heterodimer with IL-17RA that directly binds IL-17A but not IL-17F or the IL-17A–IL-17F heterodimer[4]. IL-17A-mediated gene expression is defective in *Il17rd*-deficient keratinocytes; however, IL-17F and/or IL-17A–IL-17F expression remain unaffected. Furthermore, *Il17rd* deficiency in non-haemopoietic cells attenuates imiquimod-induced psoriasis-like skin inflammation. Therefore, a second consideration for IL-17 inhibition strategies is that in addition to the complexities of IL-17A and IL-17F expression in various cells and microenvironments, the effects of these cytokines are also modulated at the receptor level. The differential regulation of IL-17 expression and IL-17RD signalling in the skin versus the joints could account for the discrepancy in the efficacy of IL-17A inhibition between individuals with psoriasis and those with psoriatic arthritis.

A third consideration is that IL-17 signalling is not strictly pathogenic but has beneficial roles in mediating tissue homeostasis, and contributes to regeneration after tissue injury including bone fracture and muscle damage. In homeostasis, T_H17 cells are present in vast numbers at mucosal surfaces, where IL-17 has been shown to have a crucial role in limiting microbial invasion and promoting barrier functions. Although IL-17A clearly contributes to bone destruction by increasing RANK expression in osteoclast precursors, IL-17A can also promote bone formation. Indeed, bone repair is impaired in IL-17A-deficient mice owing to a defect in osteoblastic bone formation, and IL-17A stimulation accelerates bone formation by enhancing osteoblast proliferation and differentiation[5]. Together with IL-22, another hallmark T_H17 cytokine, IL-17 has been shown to promote epithelial growth and thereby heal injured mucosal barriers. Other studies have shown that IL-17A also promotes muscle regeneration after acute injury[6]. This muscle regeneration process involves the accumulation of IL-17A-producing γδ T cells at the wound site, which orchestrates the early inflammatory events of the process, and specifically the recruitment of neutrophils that foster the proliferation of muscle stem and progenitor cells to accomplish regeneration[6]. Oligoclonal expansion of γδ T cells that favour myelopoiesis and neutrophil recruitment has also been described in infection and inflammatory arthritis, demonstrating similar patterns between inflammatory and regenerative events[7,8]. The exact molecular triggers that dictate when these cells become pathogenic or regenerative remains to be determined.

A fourth consideration is the importance of IL-17-producing innate immune cells, which have been largely overshadowed by T_H17 and γδT17 cells. Although the exact role of these IL-17-expressing innate immune cells is still under investigation, IL-17 released from

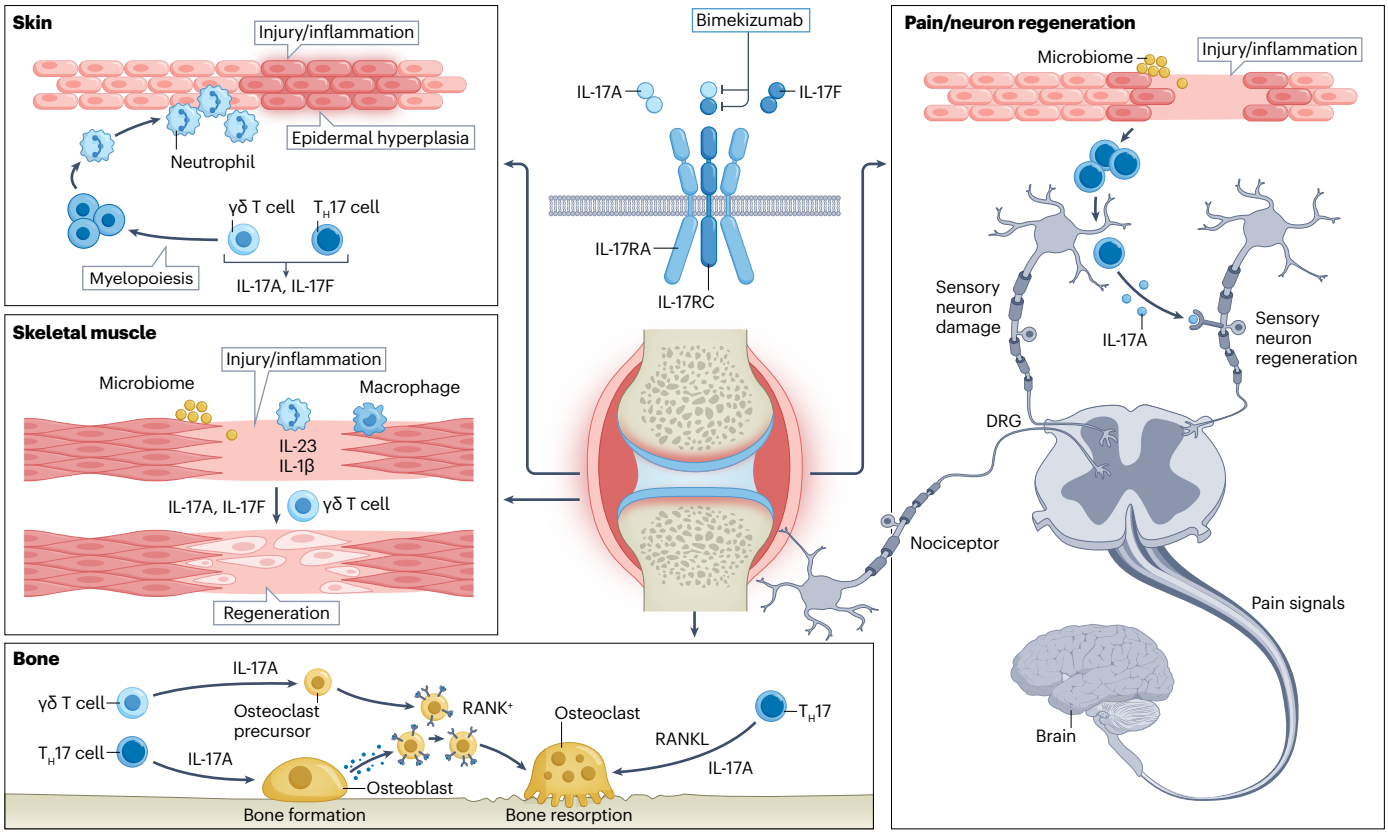

Fig. 1 | IL-17 signalling in joint inflammation and regeneration. IL-17A and IL-17F homodimers and heterodimers activate IL-17R downstream signalling through IL-17RA and IL-17RC receptor complexes. The differential expression of specific IL-17 receptors in each tissue, such as IL-17RD in the skin, dictates the tissue-specific potency of IL-17A and IL-17F. The effects of IL-17 signalling are also regulated by the presence of other inflammatory mediators, formulated by the unique tissue-specific resident cells and presence of commensal bacteria in homeostatic or inflammatory conditions. These inflammatory changes regulate tissue-destruction and also regulate tissue regeneration after injury.

macrophages is crucial in evoking mechanical pain via the activation of TRPV1-nociceptors leading to hyperalgesia in inflammatory arthritis[9]. Although IL-17-expressing macrophages are involved in the pain pathway, another report demonstrated that IL-17-expressing T cells promote neuronal axon growth and local nerve regeneration after injury. Injury induces the expression of IL-17RA in the dorsal root ganglion sensory neurons, which accept signals from IL-17A released by commensal-specific T_H17 cells. This IL-17A–IL-17RA-dependent signalling promotes the regeneration of peripheral sensory neurons[10]. These findings not only provide key insights into the cause of hyperalgesia in inflammatory arthritis but also indicate the need for further research to fully determine the proper strategy for blocking pathogenic IL-17A signalling while avoiding the inhibition of the homeostatic and/or regenerative capacity of IL-17.

The use of anti-IL-17 to treat inflammatory bowel disease exemplifies this phenomenon, as anti-IL-17 did not help inhibit tissue inflammation but made the disease worse. Clearly, the interplay between effectors and transducers that regulate the pleiotropic effects of IL-17A and IL-17F in tissue homeostasis and inflammation needs to be carefully examined to exploit the beneficial effects of IL-17 but inhibit its pro-inflammatory effects.

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Competing interests

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