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The role of IL-17A in axial spondyloarthritis and psoriatic arthritis: recent advances and controversies

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ABSTRACT

Although the pathogenic mechanisms underlying axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) are not fully elucidated, several lines of evidence suggest that immune responses mediated by interleukin 17A (IL-17A) play a pivotal role in both diseases. This is best highlighted by the significant clinical efficacy shown with inhibitors of IL-17A in treating axSpA and PsA. Nevertheless, a number of knowledge gaps exist regarding the role of IL-17A in the pathophysiology of spondyloarthritis in man, including its cellular origin, its precise role in discrete disease processes such as enthesitis, bone erosion, and bone formation, and the reasons for the discrepant responses to IL-17A inhibition observed in certain other spondyloarthritis manifestations. In this review, we focus on the latest data from studies investigating the role of IL-17A in ankylosing spondylitis (AS) and PsA that build on existing and emerging scientific knowledge in the field. Key remaining research questions are also highlighted to guide future research.

INTRODUCTION

The spondyloarthritis (SpA) comprise related but phenotypically distinct inflammatory diseases including psoriatic arthritis (PsA), non-radiographic axial spondyloarthritis (nr-axSpA) and radiographic axSpA (ankylosing spondylitis (AS)), arthritis associated with inflammatory bowel disease (IBD), reactive arthritis, juvenile idiopathic arthritis and acute anterior uveitis.^{1–3} The SpA diseases share common immunological and inflammatory components and present with overlapping clinical phenotypes.^{4–7} Indeed, multiple genetic polymorphisms within the interleukin (IL)-23/17 axis have been implicated across SpA.^{8–11} Intriguingly, despite the clinical and genetic similarities, these disorders are showing emergent and unexpected heterogeneity with respect to IL-23/17 axis therapeutic manipulation, a topic addressed later in this article.

IL-17A, a member of the IL-17 superfamily of cytokines, is known to play an important role in SpA manifestations related to the skin, joints and entheses, as reflected by the suppression of disease activity seen with IL-17A inhibitors in psoriasis, PsA and AS.^{12–19} However, in other settings where IL-17 family members have been found at sites of disease, such as gut inflammation and uveitis, IL-17A inhibition is not beneficial.^{20–22} These discrepant responses illustrate the need for clearer understanding of the aetiology of these inflammatory diseases, particularly the role of the IL-17 family in the context of the tissue(s) affected. IL-17 research has accelerated rapidly, with nearly 10 000 articles published on this topic in the last 5 years alone. In

this article we highlight the latest breakthroughs that expand understanding of the role of IL-17A in both homeostasis and in disease in axSpA and PsA.

IL-17A PRODUCTION AND SIGNALLING

The IL-17 superfamily consists of six ligands (IL-17A to IL-17F), which can bind to five receptor subtypes (IL-17RA to IL-17RE). The basic biology of most of the IL-17 superfamily has been reviewed extensively elsewhere.^{23 24} IL-17A, the prototypical ligand, is by far the best characterised member of the IL-17 family and can exist as a homodimer or in a heterodimer with IL-17F and signals through an obligate dimeric IL-17RA and IL-17RC receptor complex.²⁴ On binding to a receptor, IL-17A upregulates inflammatory gene expression either by inducing de novo gene transcription or by stabilising mRNA of pro-inflammatory cytokines and chemokines.²⁴

WELL-DEFINED ROLE OF IL-17A IN HOST DEFENCE

In healthy individuals, IL-17A, as well as other members of the IL-17 family, functions in host defence against a range of bacterial and fungal pathogens at epithelial and mucosal barriers in the skin, colon and airways.^{25–27} Although the exact interplay between the various IL-17 family members is poorly understood, epithelial cell-derived (especially IL-17C) and haematopoietic cell-derived IL-17s (IL-17A and F) may have complementary functions in response to pathogens, with the former predominantly enhancing barrier function and the latter propagating the inflammatory response.²⁸ The IL-23/17 axis co-ordinates barrier function in the skin and the gut, both of which are sites of either physical or chemical stress and are also sites of complex microbial interactions. What might the common denominator be between the IL-23/17 axis and inflammation at the sterile skeletal locations afflicted by SpA-associated pathology? We agree with the assertion that the IL-23/17 axis might be adapted to facilitate homeostasis at these highly mechanically stressed enthesal sites that are prone to microinjury.²⁹

An array of genetic defects in the IL-17 pathway, identified through human translational immunology, collectively point towards a role in anti-fungal immunity (table 1). Chronic mucocutaneous candidiasis (CMC) is a hallmark of individuals with genetic defects affecting IL-17 immunity, manifesting as recurrent or persistent infections of the skin, nails and mucosae with *Candida albicans*, with or without other clinical signs.³⁰ As can be

Table 1 Diseases characterised by mutations and deficiencies in the IL-23/IL-17 pathway

| Disease | Genes/proteins involved | Common infections | Effect on IL-23/IL-17 signalling | References |
|----------------------|-------------------------|--|---|---------------------|
| MSMD | IL-12Rβ1 | Mycobacterium tuberculosis, salmonella, candida albicans | Impaired IFN-γ-mediated immunity Decreased IL-17A-producing T cells Impaired IL-12 signalling | 176 181 183–187 189 |
| | IL-12β | Mycobacterium tuberculosis, salmonella | | |
| | IFN-γR1 | Mycobacterium tuberculosis, salmonella, candida albicans | | |
| | STAT1 | Mycobacterium, candida albicans | | |
| | IL-12/23 p40 | Mycobacterium tuberculosis, salmonella | | |
| Salmonella infection | IL-23R | Salmonella | Th17 depletion, reduced production of IL-17A | 188 190 |
| | IL-12/23p40 | | | |
| | IL-12Rβ1 | | | |
| CMCD | STAT1 | Candida albicans, mycobacterium | Reduced production of IL-17A, IL-17F, IL-22 | 182 183 191 193 202 |
| | CARD9 | Candida albicans | No response to IL-17A; reduced response to IL-17F; IL-17E response maintained | |
| | IL-17RA | Candida albicans Staphylococcus | Impaired neutrophil function | |
| | IL-17RC | Candida albicans | | |
| | IL-17F | Candida albicans | | |
| | ACT1 | Candida albicans Staphylococcus | | |
| APECED | AIRE | Candida albicans | Increased autoantibodies to IL-17A, IL-17F, and IL-22 | 194 197 |
| HIES | STAT3 | Candida albicans, staphylococcus, aspergillus | Increased serum IgE Eosinophilia | 49 198 201 203 |
| | DOCK8 | Candida albicans, staphylococcus, aspergillus | Impaired development of Th17 cells Reduced IL-17A production | |
| | TYK2 | Staphylococcus, mycobacterium, salmonella | | |

The genes and proteins involved and the resultant effects on IL-17 signalling that lead to increased susceptibility to certain infections are listed.^{49 176–201} IL-12 and IL-23 share cytokine and receptor subunits and the association with mycobacterial disease is thought to represent an effect on dysregulated IFN gamma production in the IL-12 pathway. Therefore IL-17 blockers or IL-23 p19 subunit blockers are not expected to have a link with mendelian susceptibility to mycobacterial disease.

AIRE, autoimmune regulator; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; CARD9, caspase recruitment domain-containing protein 9; CMCD, chronic mucocutaneous candidiasis disease; DOCK8, dedicator of cytokinesis 8; HIES, hyper IgE syndrome; IFN, interferon; IFN-γR1, interferon gamma receptor 1; IL-12Rβ1, interleukin 12 receptor β1; MSMD, Mendelian susceptibility to mycobacterial disease; STAT, signal transducer and activator of transcription; TYK2, tyrosine kinase 2; Th-17, T helper 17 cell.

seen from [table 1](#), these syndromes result from genetic defects affecting several immune processes, with the commonality being that the defects involve more than one cytokine or immune function. The genetic defects that are often shared between the IL-12 and the IL-23 pathway that are upstream of the IL-17 pathway are not linked to fungal infection but may be linked to mycobacterial infections consequent to impaired interferon gamma signalling.³¹

Preclinical and ex vivo studies also implicate IL-17A in immunity against a range of other pathogens including bacteria such as *Escherichia coli*, fungi such as *Cryptococcus neoformans*, parasites such as *Trypanosoma cruzi*, and viruses such as influenza (reviewed in Matsuzaki and Umemura).²⁸ Although as with all drugs that modulate immune response there is the potential for an increased infection risk with IL-17A inhibitors, clinical data show no risk from specific pathogens, with the exception of candidiasis.^{18 19 32–35} Reassuringly, no association between mycobacterial disease and blockade of IL-17A biological activity has been observed in man.³⁴

ROLE OF IL-17A IN SPA

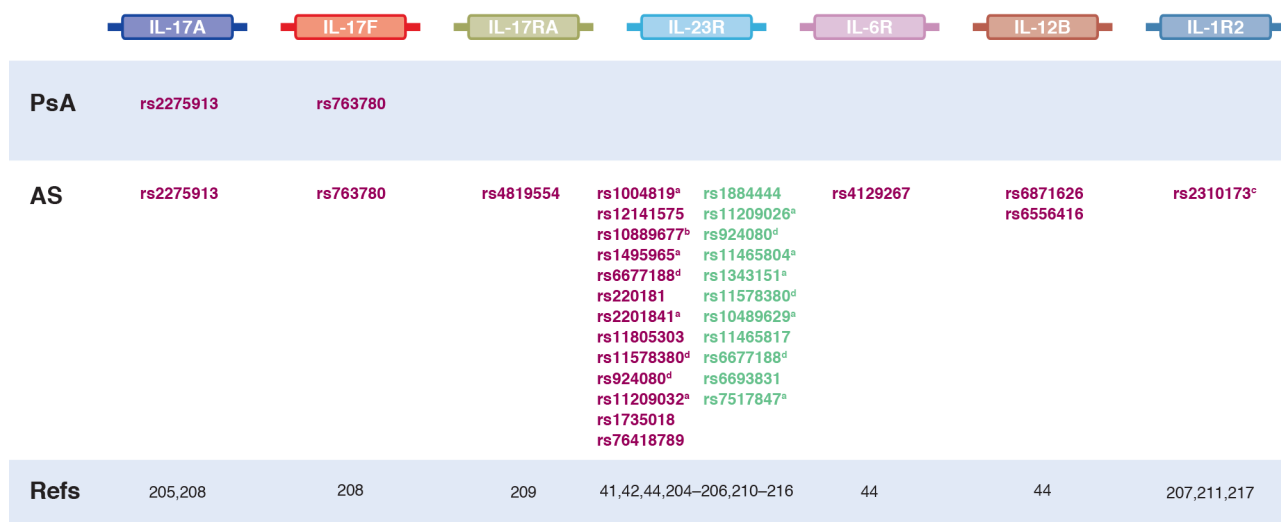
Although IL-17A cytokine expression has been detected in a multitude of autoimmune and autoinflammatory diseases, a key role in psoriasis, PsA and axSpA is evident.

Genetics

Although a detailed examination of the genetic basis of SpA is outside the scope of this article (reviewed in detail in Taams *et al* and Brown *et al*),^{11 36} the strongest association with genetic susceptibility to axSpA and PsA lies within the MHC class I region and in particular the HLA-B27 region.^{8–10} Multiple immunological functions can be altered by these genetic associations, including several relevant to IL-17A signalling through activation of CD8+T cells and CD4+T cells.^{11 37–40} Several single nucleotide polymorphisms in genes directly involved in IL-17 signalling have also been linked to AS and PsA ([figure 1](#)), including variants in the IL-12 p40 subunit, the IL-23 p19 subunit, the IL-23 receptor, IL-17A and IL-17RA.^{41–48} Additional susceptibility variants have been identified in genes encoding IL-17-related signalling molecules including TYK2, TRAF3IP2 and STAT3.^{43 44 47 49–53}

IL-17A production

There has been significant interest in identifying the sources of IL-17A in SpA and a number of innate and adaptive immune system cell types have been implicated (reviewed in Taams *et al*) ([figure 2](#)).¹¹ Increased levels of type 3 innate lymphoid cells (ILC3) have been identified in blood and synovia of patients



■ Risk ■ Protective

Figure 1 Single nucleotide polymorphisms identified in the IL-17 signalling pathway that have been linked to axial spondyloarthritis and psoriatic arthritis. ^aSignificant association shown in European but not Asian populations²⁰⁴; ^bNo risk associated with this SNP shown in certain studies^{204–206}; ^cNo risk associated with this SNP shown in certain studies²⁰⁷; ^dSNP can be associated with risk or protection depending on the specific mutation. AS, ankylosing spondylitis; IL-1R2, interleukin 1 receptor; IL-6R, interleukin 6 receptor; IL17R, interleukin receptors; PsA, psoriatic arthritis; SNP, single nucleotide polymorphism.

with SpA, and these levels correlate with PsA disease activity.^{54,55} Recently, resident populations of both ILC3 and $\gamma\delta$ T cells have been identified at the human enthesis for the first time where they may produce the IL-17A that drives enthesitis, a key early pathological lesion in SpA.^{56–59} Recent studies have also reported

increased numbers of IL-17+invariant natural killer T (iNKT) cells and $\gamma\delta$ T cells in SpA patient peripheral blood.⁶⁰ Indeed, these ROR γ t+innate like T cells, and not conventional T cells, represented about half of all IL-17 producing blood circulating T cells and were further skewed towards IL-17 expressing subsets

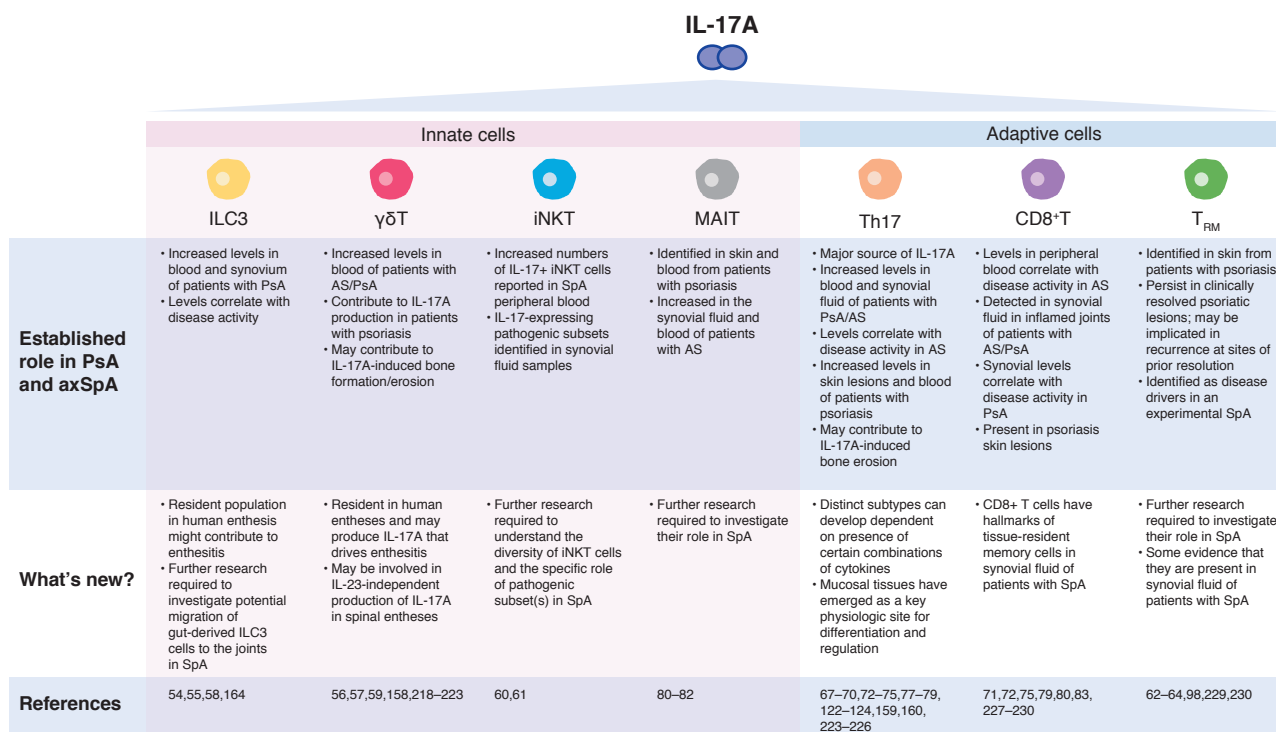


Figure 2 Key sources of IL-17A in spondyloarthritis. AS, ankylosing spondylitis; ILC3, type 3 innate lymphoid cell; iNKT, innate natural killer T cell; MAIT, mucosal-associated invariant T cell; PsA, psoriatic arthritis; SpA, spondyloarthritis; Th17, T helper 17 cell; T_{RM}, resident memory T cell.

in synovial fluid samples, as determined by both advanced cytometric methodologies and intracellular cytokine IL-17 staining.⁶⁰ In vivo evidence for enrichment of pathogenic subsets in the joints was recently shown in mannan-induced arthritis in SKG mice, an IL-23/17 axis dependent disease.⁶¹

Tissue-resident memory T cells (T_{RM}) represent approximately 50%–70% of the pool of resident T cells in healthy skin, and can produce a variety of cytokines, including IL-17A.^{62–64} In patients with psoriasis, IL-17-producing CD8+ T_{RM} cells have been identified in non-involved skin and may be involved in recurrence of psoriasis at sites of prior resolution.^{62–64} Efforts are ongoing to investigate the role of T_{RM} cells in tissues affected by SpA. A study in patients with PsA has shown the presence of IL-17 expressing CD4+ (CD8+) T cells in the synovium.⁶⁵ However, no studies have been reported in axial disease to date.

Adaptive immune cells are key drivers of chronicity in SpA and as such, are also a major source of IL-17A. The presence of T helper 17 (Th17) cells in SpA is relatively well established.⁶⁶ Increased levels of both Th17 cells and IL-17A are found in skin lesions and the blood of patients with psoriasis as well as the blood and synovial fluid of patients with AS and PsA.^{67–75} IL-17A initiates several feedback-loop mechanisms in SpA leading to increased expansion of Th17 cells and thereby further production of IL-17A.⁷⁶ Evidence suggests that there are distinct subtypes of Th17 cells whose differentiation is dependent on specific combinations of cytokines.⁷⁷ Furthermore, there is likely to be considerable plasticity between Th17 cells and FOXP3+ regulatory T cells.⁷⁸ Identification of the subtype(s) of Th17 cells and their regulation and relevance to axSpA and PsA is an important topic of ongoing research.

Although not found in rheumatoid arthritis synovial fluid, IL-17A-producing conventional CD8+T cells are present in synovial fluid of inflamed joints in patients with AS and PsA where their levels correlate with disease activity.^{71 72 79} IL-17-producing mucosal-associated invariant T (MAIT) cells have been identified in skin and blood from patients with psoriasis⁸⁰ and are also increased in the synovial fluid and blood of patients with AS, where they produce IL-17A in an IL-7-dependent fashion.^{81 82}

It has been suggested that neutrophils contribute to the amplification of the inflammatory response in SpA by producing further IL-17A and although IL-17A-positive neutrophils have been reported in psoriatic skin, the synovium of patients with PsA, and in AS facet joints,^{83–88} the emerging consensus is that neutrophils do not produce IL-17A mRNA or protein, even after strong stimulation with various cytokine combinations.⁸⁹ Similarly, although IL-17A-positive mast cells have been found in synovial tissue from patients with SpA,⁹⁰ the concept is of exogenous IL-17A capture and release, as opposed to synthesis.⁹¹ A recent study indicated that levels of IL-17A were higher in joint-resident mast cells following IL-17A inhibition, which supports the concept of storage of this cytokine under normal tissue homeostasis and mast cell release during inflammation.⁹²

A key research question for the future will be identifying all IL-17A-producing populations, especially at the entheses in SpA. It is noteworthy that measurement of serum levels of IL-17A is likely to be of minimal relevance due to the local tissue responses seen in SpA via IL-17A-producing resident cells.

Enthesitis

Considerable recent developments have occurred in experimental enthesitis research where high mechanical stressing at entheses is associated with local immune system activation.^{59 93 94} Non-SpA-related enthesitis can result from repeated mechanical

strain in healthy individuals (eg, tennis elbow) and usually resolves spontaneously, whereas inflammation in SpA shows chronicity.⁵⁹ The underlying mechanisms behind this pathologically exaggerated immune response, which is driven by a combination of genetic factors and disturbed epithelial barrier function, are starting to be unravelled.^{59 95–97}

Enthesitis is triggered predominantly by an innate immune response. Prostaglandin E2 (PGE2) and IL-23 may be important early mediators, activating resident immune cells to produce IL-17A and other inflammatory cytokines. Indeed, peri-enthesal bone involvement and the often excellent responses observed with NSAIDs incriminate PGE2 in axial disease.⁵⁹ In mice, hepatic expression of IL-23 induces spondyloarthropathy by acting on ROR- γ t+CD3+CD4-CD8- enthesal resident T cells to produce inflammatory mediators including IL-17A.⁹⁸ γ/δ T cells have been shown to constitute the large majority of murine IL-17A producing cells, proliferating at the site of injury, and enhancing bone regeneration.^{99 100} However, although enthesitis appears to be a cardinal lesion in several IL-23/17 axis murine models of inflammatory arthritis,^{101–107} other models have indicated that disease can arise in a T-cell independent manner including that mediated by TNF production from enthesal myeloid and stromal cells.^{94 108–110}

In humans, IL-17A-producing entheses-resident ILC3 and γ/δ T cells have recently been described.^{56–58} Resident myeloid cells that can locally produce IL-23 have also been described,¹¹¹ and their numbers in man may be linked to mechanical load.¹⁰⁸ IL-17A likely acts as an amplifier of enthesitis, inducing several other cytokines by resident mesenchymal cells.^{98 112 113} Prolonged enthesal inflammation leads to new bone formation and also, to a much lesser extent, bone erosion, and is subject to considerable research interest.⁵⁹

Bone damage

Preclinical and clinical data suggest that bone erosion and new bone formation in SpA may occur simultaneously at different anatomical sites,^{114–117} with IL-17A playing a complex role in these processes.

Bone erosion

Numerous preclinical studies have indicated that IL-17A promotes bone resorption in experimental arthritis.^{118–121} Recent efforts have focused on elucidating the mechanisms behind these effects and indicate that IL-17A stimulates receptor activator of nuclear factor- κ B ligand (RANKL) expression and inhibition of Wnt signalling, thereby inhibiting osteoblast activity (figure 3).^{122–128}

Clinical data in patients with PsA show a significant reduction in joint radiographic progression with IL-17A inhibitors versus placebo in the short-term and low long-term rates of radiographic progression.^{13 14 129} Furthermore, recent data from the PSARTROS study showed no progression of catabolic and anabolic bone changes in the joints of patients with PsA treated with secukinumab for 24 weeks.¹³⁰

New bone formation

The precise role of IL-17A in new bone formation in axial SpA and PsA is currently unknown, with contradictory experimental findings observed. Studies favouring a role in new bone formation include data from both animal models and human primary cells (summarised in figure 3). IL-17A has been reported to boost osteogenesis via enhancing osteoblast differentiation from local mesenchymal stem cell populations,^{100 131–133} and the subsequent

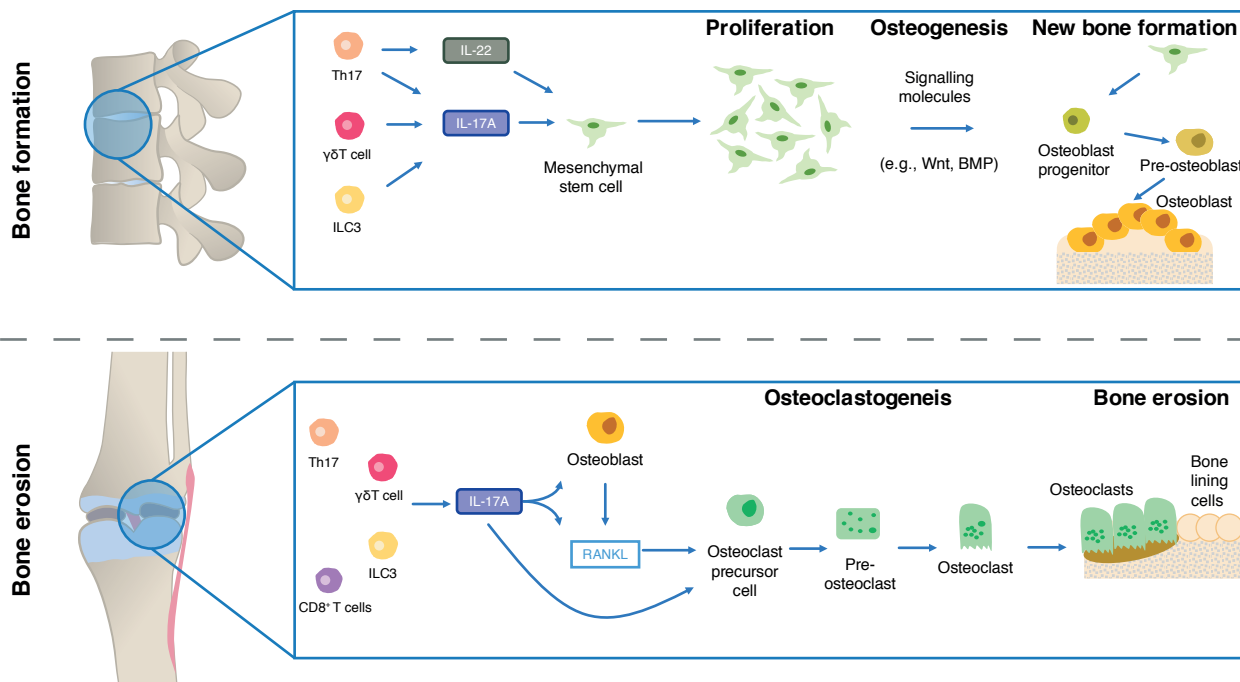


Figure 3 The role of IL-17A in bone erosion and bone formation in spondyloarthritis. Adapted from Schett *et al* and Gravallesse *et al* [59 223 231]. BMP, bone morphogenetic protein; ILC3, type 3 innate lymphoid cell; RANKL, receptor activator of nuclear factor kappa-B ligand; Th17, T helper 17 cell.

activation of the osteoblasts via activation of the JAK2/STAT3 signalling pathway, which is associated with osteogenesis.¹³¹ IL-17A knockout models have been associated with impaired bone regeneration at both 14 and 21 days post a drill-hole fracture in the femur when compared with wild type mice.¹⁰⁰ Furthermore, in the mycobacterium tuberculosis-induced diseased HLA-B27 transgenic rat model of SpA, IL-17A blockade significantly suppressed pathological new bone formation.¹³⁴ In humans, IL-17A levels are elevated in the days following fracture, which in turn is associated with callus formation.¹³⁵

In contradistinction, cutaneous-restricted overexpression of IL-17A was associated with bone loss in murine models.¹³⁶ Moreover, rat calvarial defects show impaired healing when exposed to IL-17A, combined with significant impairments in osteogenesis in the isolated cells when exposed to IL-17A.¹³⁷ In vivo, IL-17A is associated with osteoclastogenic activation and systemic bone loss in rheumatoid arthritis.^{122 124} Thus, determining the role of IL-17A in new bone formation remains an important avenue of future research.

Pain

The immune system plays a critical role in modulating acute and chronic pain in both the peripheral and central nervous systems.^{138 139} Although pain in SpA is often assumed to be a surrogate marker for inflammation, evidence is emerging to suggest a more complex picture. In axSpA, pain does not always correlate with inflammation or radiographic measures of disease.¹⁴⁰ Furthermore, neuropathic pain as well as inflammatory pain has been observed in patients with AS and PsA.^{141 142}

IL-17A can modulate inflammatory pain by directly increasing nociceptor excitability and potentiating hyperalgesia through the induction of secondary factors.^{139 143–146} Both IL-17RA and IL-17RC are expressed in murine neuronal tissue where they contribute to inflammatory responses.^{147 148} Preclinical studies also suggests a role for IL-17A in neuropathic pain.^{149–152} Clinical data with inhibitors of IL-17A in AS and PsA show rapid and

significant pain reduction,^{153 154} but work to assess whether this represents a reduction in neuropathic as well as inflammatory pain is needed.

Gut inflammation in SpA

The role of IL-17A in IBD and its potential link to the pathogenesis of axSpA and PsA has been the subject of some controversy. Historically, preclinical data investigating the outcome of IL-17A inhibition in mouse IBD models have been inconsistent, with some studies showing disease protection and others showing exacerbation.^{155 156} Clinically, IL-17A inhibition was ineffective in moderate-to-severe Crohn's disease.²⁰ Long-term clinical trial and postmarketing safety data in psoriasis, PsA and AS indicate that the overall incidence of IBD is low, within the expected range in these disorders, and not exacerbated by secukinumab treatment.¹⁵⁷ This highlights one of the pitfalls of translating preclinical data to a clinical setting and has led researchers to reconsider the preclinical IBD models. Nevertheless, long-term data with IL-17A inhibitors in clinical practice are required to investigate this issue further.

The $\gamma\delta$ T cell was the principal source of gut-derived IL-17A in a mouse model of colitis, where IL-17A-dependent regulation of the tight junction protein occludin during epithelial injury was shown to maintain barrier integrity.¹⁵⁸ Mucosal tissues have also emerged as a key physiological site for the differentiation and regulation of Th17 cells.^{77 159 160} A role for ILC3 and innate-like T cells such as $\gamma\delta$ T cells and MAIT cells in IBD is also postulated based on their high representation at barrier sites.^{161–163} Putative links have also been suggested between gut inflammation, migration and accumulation of IL-17A-producing ILC3 cells in the joints of patients with AS.¹⁶⁴ A recent study also found that pathogenic bacteria can induce intestinal barrier defects and translocate to systemic organs, triggering autoimmune disease.¹⁶⁵

Uveitis

Like IBD, anterior uveitis in SpA shares common genetic risk factors and the involvement of certain pro-inflammatory

| | Secukinumab ^{12–16,20,21,168,232–235} | Ixekizumab ^{17–19,169,236,237} |
|-----------------------------------|--|---|
| Approved indications | Psoriasis, PsA, AS | Psoriasis, PsA |
| MoA | Fully-human anti-IL-17A antibody | Humanised anti-IL-17A antibody |
| PsA | | |
| Peripheral arthritis | ● | ● |
| Enthesitis | ● | ● |
| Dactylitis | ● | ● |
| Skin | ● | ● |
| Nail | ● | ● |
| Axial disease | ● | ⊘ |
| Structural progression | ● | ● |
| AS | | |
| Signs and symptoms | ● | ● |
| Disease activity | ● | ● |
| Function | ● | ● |
| Structural progression | ● | ● |
| Non-radiographic axial SpA | ● | ● |
| Psoriasis | ● | ● |
| Crohn's disease | ● | ⊘ |
| Uveitis^a | ⊘ | ⊘ |

● Effective ● Under investigation ● Not effective ⊘ Not assessed

Figure 4 Summary of clinical efficacy with IL-17A inhibitors in spondyloarthritis. ^aNo efficacy shown with secukinumab in non-infectious uveitis; not investigated in anterior uveitis, the form of the disease most common in patients with spondyloarthritis. AS, ankylosing spondylitis; PsA, psoriatic arthritis; SpA, spondyloarthritis.

cytokines. Clinical trials have demonstrated the efficacy of anti-TNF monoclonal antibody therapy in panuveitis or posterior uveitis but clinical trials with inhibitors of IL-17A have failed to meet their primary endpoints for these forms of the disease that are pathophysiologically distinct from anterior uveitis.²¹ Both IL-17A and IL-17F have been detected in anterior uveitis (reviewed in Weinstein and Pepple), but whether they play a critical role is unclear.¹⁶⁶ In secukinumab-treated AS patients there was no evidence suggesting uveitis flares in patients with previous anterior uveitis.¹⁶⁷ Further research is required to extend our understanding of the precise role of IL-17A in the pathogenesis of anterior uveitis.

TARGETING IL-17A IN SPA

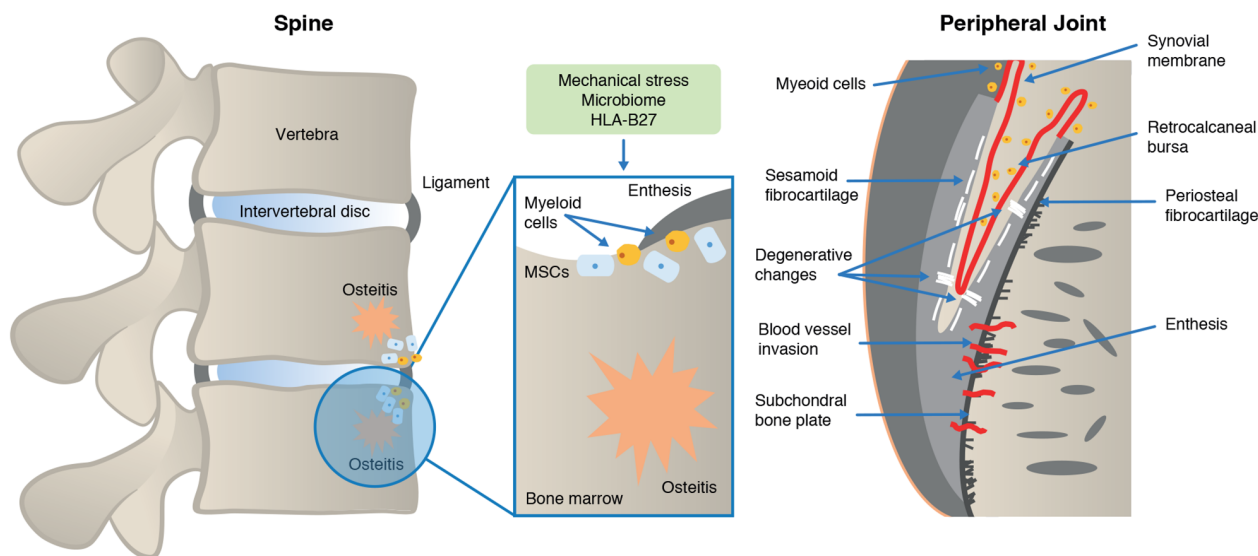
The key role played by IL-17A in the pathogenesis of AS and PsA is highlighted by the efficacy shown by inhibitors of IL-17A in clinical trials. Secukinumab, a fully human anti-IL-17A monoclonal antibody, is approved for the treatment of psoriasis, PsA and AS based on the results of several large randomised controlled trials.^{12–16 168} Ixekizumab, a humanised anti-IL-17A antibody, is approved for the treatment of psoriasis and PsA and has shown significant efficacy in two large phase III trials in AS.^{17–19 169 170} The efficacy of IL-17A inhibitors across all manifestations of disease in AS and PsA, including skin, nails, peripheral arthritis, axial disease, dactylitis and enthesitis, highlights the utility of drugs targeting this pathway (figure 4). Inhibitors of IL-17A have also been shown to have an overall favourable long-term safety profile in clinical trials,^{32 33 35} including low rates of serious infections, *Candida* infections

and malignancy, with no evidence of increased suicidality or IBD exacerbation above expected background levels.¹⁵⁷ Nevertheless, the long-term safety of IL-17A inhibitors will need to be monitored in a real-world setting.

WHAT IS THE BASIS FOR DIVERGENT IL-17A AND IL-23 RESPONSES IN AXIAL DISEASE?

IL-23 plays a key role in amplifying and maintaining IL-17A production in many cells, so it was expected that IL-23 inhibitor therapy would have similar results to IL-17A inhibition in axSpA. Interestingly, clinical studies with ustekinumab, an IL-12/23 inhibitor, in axial SpA were terminated due to lack of efficacy¹⁷¹ and the IL-23 p19 inhibitor risankizumab also failed to show efficacy in AS in a phase II proof of concept study.¹⁷² Conversely, the efficacy of IL-17A inhibition in AS suggests that IL-17A and not IL-23 is the major cytokine mediating disease pathogenesis in axSpA and in this context, IL-17A is likely to be produced in a largely IL-23-independent manner. Understanding the reasons for these divergent roles of IL-23 and IL-17A in the pathophysiology of axSpA is one of the hottest topics in current IL-17A research. Emerging evidence suggests there may be anatomical and immunological differences between axial and peripheral enthesitis and subsequent downstream disease manifestations (figure 5). For instance, there is generally more enthesal soft tissue inflammation or synovio-enthesal complex disease in peripheral enthesitis in PsA,¹⁷³ and more peri-enthesal osteitis in the spine in AS, with this bone proclivity being linked to carriage

A. Anatomic differences between spinal and peripheral entheses



B. Differential cytokine effects in AS, PsA and PsO

| | AS | PsA | PsO |
|--------|----|-----|-----|
| IL-23 | - | + | ++ |
| IL-17A | ++ | ++ | ++ |
| TNF | + | + | + |

C. IL-17A production in spinal entheses

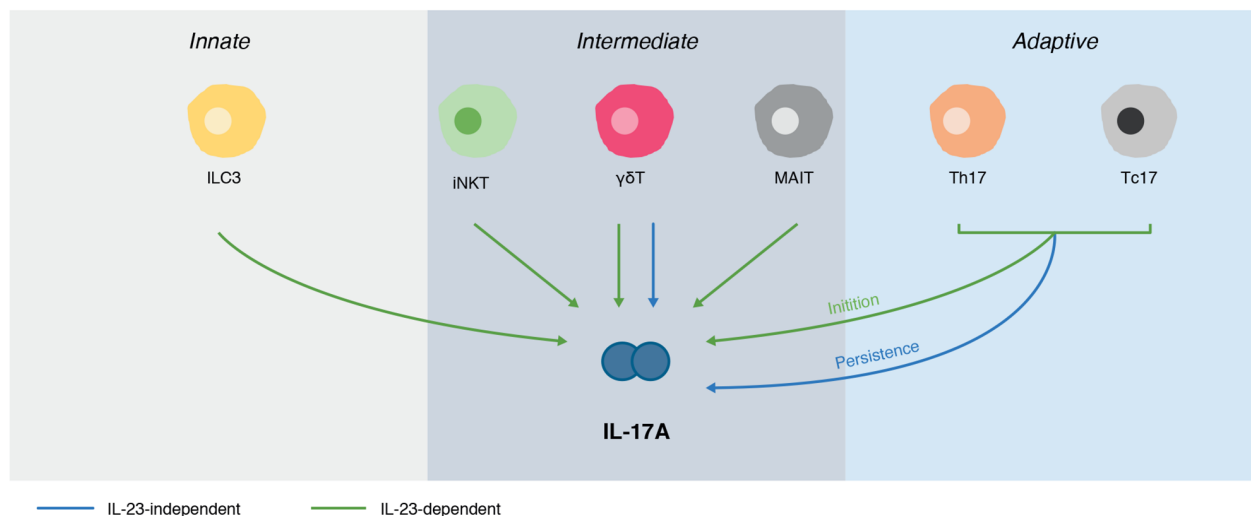


Figure 5 Emergent scheme to explain IL-23/–17 axis pathway divergence in PsA and AS. IL-23 pathway blockade is highly effective in psoriasis but not in AS, which is unexpected given the IL-23 SNPs and related gene SNPs associated with AS. Anatomical differences between entheses in the spine versus peripheral joints could play a role (A). The peripheral skeleton has numerous synovio-enthesal complexes,¹⁷³ which contain abundant myeloid cells, while these cells are rare in the spine. Spinal enthesitis is also associated with peri-enthesal bone disease and osteitis.^{59 173 238} The role of inflammatory cytokines, namely IL-23, IL-17A and TNF α , also differs across the spondyloarthritides (B).^{12 14–16 167 168 172 239–248} IL-17A can be produced by several different sources in spinal entheses (C).^{56–59 74 75 81 82 99 100 158 175 249} Emerging evidence supports the cellular basis for IL-17 production that is independent of IL-23.^{56 57 158 175} Animal models also show that IL-23 has a redundant role once adaptive immunity is primed.¹⁷⁵ Where ++, strong involvement; +, involvement; –, no involvement. AS, ankylosing spondylitis; $\gamma\delta$ T, gamma delta T cells; HLA-B27, human leucocyte antigen B27; IL-17A, interleukin 17A; IL-23, interleukin 23; ILC3, Type three innate lymphoid cells; iNKT, innate natural killer T cell; MAIT, mucosal associated invariant T cell; MSCs, mesenchymal stem cells; PsA, psoriatic arthritis; PsO, psoriasis; Tc17, CD8+T cells; Th17, T helper 17 cells; TNF, tumour necrosis factor α .

of the HLA-B27 gene for axial disease.¹⁷⁴ In terms of control of IL-17 production, IL-23 receptor positive and negative subpopulations of $\gamma\delta$ T cells have been identified in human spinous processes entheses, pointing to a role for IL-23-independent IL-17A production,⁵⁷ and entheses-resident myeloid cells are capable of IL-23 production locally.¹¹¹ Further research is required to investigate the drivers of this process in the future although data in mice indicate that the initiation, but not the persistence, of experimental SpA is dependent on IL-23.¹⁷⁵

CONCLUSION

The IL-17A inhibitors show efficacy in treating multiple facets of SpA, including psoriasis, enthesitis, synovitis, bone erosion, new bone formation and pain, which illustrates the importance of IL-17A in disease pathophysiology. Future research will investigate key remaining gaps, such as the role of human entheses-resident innate and adaptive T cells in SpA and our understanding of IL-23-independent IL-17A production. The ongoing assessment of IL-17A inhibitors in a real-world setting will also be important as these agents become more widely prescribed in clinical practice. Ongoing research efforts will attempt to answer these and other open questions and shed further light on the role of IL-17A in SpA in the hope of furthering our understanding and improving treatment of these diseases.

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