REVIEW ARTICLE

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Reframing Immune-Mediated Inflammatory Diseases through Signature Cytokine Hubs

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Immune-mediated inflammatory diseases (IMIDs) are a heterogeneous group of diseases characterized by chronic inflammation and organ damage. IMIDs were traditionally classified on the basis of the predominant organ involvement. Improving the pathogenic characterization of IMIDs, however, should allow for a refined mechanistic understanding of these diseases and should make it possible to develop a molecular-based classification. The transition from organ-based to molecular-based classification was initiated by insights into associated genetic mutations and polymorphisms of key immune pathways and the development of monoclonal antibodies that target signature cytokine hubs in IMIDs. As compared with an organ-based classification, molecular classification better addresses pathophysiological commonalities across IMIDs that affect different organs but also accounts for substantial mechanistic differences among IMIDs that affect the same organ (Fig. 1).

Inflammation of the Inner Surfaces of the Body

IMIDs affecting the inner surfaces of the body, such as the gut (inflammatory bowel disease [IBD]: Crohn's disease[1] and ulcerative colitis[2]) and the joints (inflammatory arthritis: rheumatoid arthritis,[3] psoriatic arthritis,[4] and axial spondyloarthritis[5]), affect about 3% of the general population. Their overall prevalence has increased over the past several decades.[6] Both inflammatory arthritis and IBD are characterized by remarkable chronicity, often affecting people at a young age and persisting throughout adulthood, with substantial disease progression and attendant damage and loss of function of affected organs. The skin, as the outer barrier of the body, and inner barriers, such as the gut and the joints, appear to be particularly prone to IMIDs, since they are required to maintain tissue homeostasis at sites exposed to microbial, chemical, and mechanical challenges. A high-level load in pathogen-associated molecular patterns (PAMPs) could continuously trigger immune activation.[7,8] Accordingly, these barriers are equipped with sophisticated regulatory systems that control, suppress, and resolve inflammation through antiinflammatory cytokines, lipid mediators, and immune regulatory cells.[9,10] Furthermore, arthritis and IBD are associated with IMIDs of the skin (e.g., psoriasis[11]); this association supports a strongly interdisciplinary approach toward explaining the molecular pathogenesis of IMIDs.

Shared and Individual Features of Joint and Gut Inflammation

Inflammatory arthritis and IBD share several features. First, their pathogenesis is based on a combination of genetic susceptibility loci (major histocompatibility

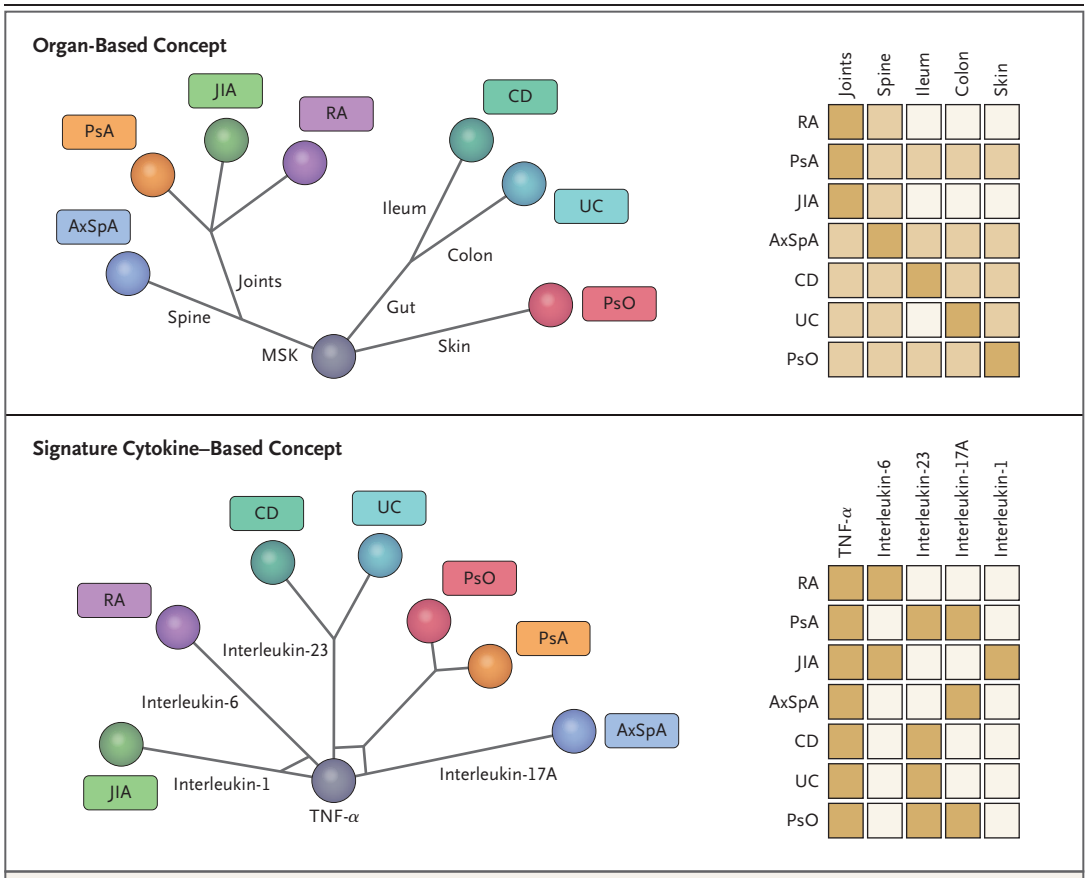

Figure 1. Organ-Based and Signature Cytokine–Based Concepts of Immune-Mediated Inflammatory Diseases (IMIDs) of the Joints and Gut.

The top panel shows IMIDs of the joints and gut on the basis of the affected organs. The chart at the right shows the extent of organ involvement, with the darkest squares indicating that the organ is usually involved, the medium-color squares indicating that the organ is sometimes involved, and the lightest squares indicating that the organ is involved rarely or not at all. The bottom panel shows IMIDs of the joints and gut on the basis of the signature cytokine. The chart at the right shows the response to cytokine inhibition, with dark squares indicating a response and light squares indicating little or no response. AxSpA denotes axial spondyloarthritis, CD Crohn's disease, JIA juvenile idiopathic arthritis, MSK musculoskeletal disease, PsA psoriatic arthritis, PsO psoriasis, RA rheumatoid arthritis, TNF-α tumor necrosis factor α, and UC ulcerative colitis.

complex [MHC] genes and non-MHC genes) and environmental triggers (smoking, mechanical stress, or microbiome changes). Second, the clinical onset of the two disorders is based in sustained exuberant immune responses that infiltrate target tissues with activated immune cells. Third, both disorders have a chronic clinical course characterized by sequential disease flares alternating with silent phases and a low potential for spontaneous resolution. Fourth, the systemic inflammatory character of these disorders can lead to complications, such as an increased risk of inflammatory eye disorders (e.g., uveitis or scleritis) or skin lesions (e.g., psoriasis, erythema nodosum, or pyoderma), cardiovascular disease, and premature osteoporosis. Finally, both disorders can have a substantial effect on the central nervous system by altering pain perception and imprinting sickness behavior associated with fatigue and depressive symptoms.[12]

Despite these similarities, individual IMIDs are remarkably heterogeneous at multiple levels and have differences in genetic features, immune pathogenesis, and treatment responses (Table 1). Organ-specific definitions fail to usefully separate IMIDs affecting the joints from those affecting the gut. We contend that a molecular approach to IMIDs is required, particularly as the range of immune-targeted therapeutics rapidly expands.

Table 1. Clinical and Pathological Features of Immune-Mediated Inflammatory Diseases and Approved Treatments.*

Variable	Rheumatoid Arthritis	Crohn's Disease	Ulcerative Colitis	Axial Spondyloarthritis	Psoriatic Arthritis
Genetic characteristics	MHC class II (DR4) PTPN22, CTLA4	MHC class II (DRB1) Interleukin-23R, NOD2	MHC class II (DRB1) Interleukin-23R, interleukin-10R	MHC class I (B27) Interleukin-23R, ERAP1	MHC class I (C06) Interleukin-23R, A20
Drivers	Autoimmunity	Microbial dysbiosis and barrier dysfunction	Microbial dysbiosis and barrier dysfunction	Mechanical stress	Mechanical stress and metabolism
Key pathological process	Synovitis	Granuloma formation	Cryptitis and goblet-cell loss	Axial enthesitis	Enthesitis and synovitis
Cellular immune response	B cells, Tph or Tfh cells, macrophages, fibroblasts	Th1/Th17 cells, dendritic cells, macrophages	Th2/Th9/Th17 cells, neutrophils	Th17 cells, T γ/δ cells, ILC3, neutrophils	Th17 cells, T γ/δ cells, ILC3, neutrophils, fibroblasts
Key associated disease	Interstitial lung disease	Erythema nodosum	Primary sclerosing cholangitis	Anterior uveitis	Psoriasis
NSAID responsiveness	Absent	Absent	Absent	High	Moderate
Glucocorticoid responsiveness	High	High	High	Absent	Moderate
Conventional anchor drug	Methotrexate	Azathioprine	Cyclosporine	Sulfasalazine†	Methotrexate
Approved TNF-α inhibitors	Adalimumab, certolizumab, etanercept, golimumab, infliximab	Adalimumab, certolizumab (U.S.), infliximab	Adalimumab, certolizumab (U.S.), golimumab, infliximab	Adalimumab, certolizumab, etanercept, golimumab, infliximab	Adalimumab, certolizumab, etanercept, golimumab, infliximab
Approved cytokine signature drugs (targets)	Tocilizumab (interleukin-6R), sarilumab (interleukin-6R)	Ustekinumab (interleukin-12/23)	Ustekinumab (interleukin-12/23)	Secukinumab (interleukin-17A), ixekizumab (interleukin-17A)	Secukinumab (interleukin-17A), ixekizumab (interleukin-17A), ustekinumab (interleukin-12/23), guselkumab (p19, interleukin-23)
Other approved targeted therapies	Abatacept, rituximab	Vedolizumab	Vedolizumab	None	Apremilast, abatacept
Approved JAK inhibitors	Tofacitinib, baricitinib, upadacitinib, filgotinib (E.U.)	None	Tofacitinib	Upadacitinib (E.U.)	Tofacitinib, upadacitinib (E.U.)

* A20 protein is also known as tumor necrosis factor α (TNF-α)–induced protein 3. CTLA-4 denotes cytotoxic T-lymphocyte–associated protein 4, ERAP1 endoplasmic reticulum aminopeptidase 1, E.U. European Union, ILC3 innate lymphoid cells type 3, interleukin-10R interleukin 10 receptor, interleukin-23R interleukin-23 receptor, JAK Janus kinase, MHC major histocompatibility complex, NOD2 nucleotide-binding oligomerization domain–containing protein 2, NSAID nonsteroidal antiinflammatory drug, PTPN22 protein tyrosine phosphatase nonreceptor type 22, Tfh follicular helper T cell, Th helper T cell, Tph peripheral helper T cell, and U.S. United States.

† Sulfasalazine is recommended only for the treatment of peripheral spondyloarthritis.

DRUG-RESPONSE PATTERNS IN ARTHRITIS AND IBD

Responses to conventional drug therapy differ across IMIDs. Probably the best example is nonsteroidal antiinflammatory drugs, which work in axial spondyloarthritis and psoriatic arthritis but are less effective in rheumatoid arthritis; in Crohn's disease and ulcerative colitis, they can have adverse effects due to impairment of epithelial barrier function. Furthermore, conventional immune modulatory agents show predilections for efficacy in individual IMIDs, with methotrexate used in rheumatoid arthritis, sulfasalazine in psoriatic arthritis and spondyloarthritis (though mostly in peripheral, not axial, disease), azathioprine in IBD, and cyclosporine in ulcerative colitis (Table 1). Nonetheless, it has been notoriously difficult to link these drugs to single cytokine expression patterns, since their mode of action is based on inhibiting several different inflammatory pathways and is not truly pathogenesis-driven in inception. Furthermore, the subgroup of patients who have an excellent response to conventional drugs is limited, which suggests that master control pathways in individual diseases are not targeted.

TNF-α AS A COMMON DOWNSTREAM EFFECTOR PATHWAY

Tumor necrosis factor α (TNF-α) was the first key cytokine targeted in the treatment of inflammatory arthritis and IBD.[13] Inhibition of TNF-α proved remarkably efficacious in rheumatoid arthritis; this led to a reconceptualization of the pathogenesis of IMIDs, which showed that a complex inflammatory process can depend largely on a single master regulatory cytokine. TNF-α inhibition has demonstrable efficacy in all major forms of arthritis (rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis), as well as in the two main forms of IBD. Unfortunately, TNF-α inhibition is more the exception than the rule in its breadth of efficacy. However, not all IMIDs depend on TNF-α: giant-cell arteritis does not respond to TNF-α inhibition, and multiple sclerosis may even worsen with TNF-α inhibitors.

TNF-α probably represents a common effector pathway that acts downstream in the inflammatory process (Fig. 2). Functionally, TNF-α is an important activator and product of macrophages that stimulates cytokine production in immune cells and activates fibroblasts, with subsequent tissue remodeling.[14] TNF-α is also a product of neutrophils and activated T cells, which are enriched in the inflamed synovial membrane and entheseal structures (insertion sites of tendons and ligaments) in arthritis and in the intestinal wall in IBD. Furthermore, TNF-α is a potent stimulator of osteoclasts, accounting for the widely observed osteoporosis in IMIDs, as well as the formation of bone erosions in rheumatoid and psoriatic arthritis.

The broad antiinflammatory effect of TNF-α inhibition is mainly based on its effect on myeloid-cell activation, which is common in many forms of IMIDs. Nevertheless, there are important differences in TNF-α responsiveness between arthritis and IBD. The dimeric fusion protein etanercept, which mainly targets soluble TNF-α, is clinically effective in arthritis rather than in IBD, whereas antibodies blocking soluble and membrane-bound TNF-α (infliximab, adalimumab, certolizumab, and golimumab) are effective in both diseases.[15] In fact, membrane-bound TNF-α on macrophages may act as a potent trigger for T-cell cytokine production and T-cell survival in IBD.[16] Thus, although TNF-α is a major cytokine hub in IMIDs, specific signaling pathways differ among disease entities, with important clinical implications.

SIGNATURE CYTOKINE HUBS

INTERLEUKIN-6 IN RHEUMATOID ARTHRITIS

In rheumatoid arthritis, interleukin-6 is a critical cytokine node. Currently, rheumatoid arthritis is the only IMID that shows combined TNF-α and interleukin-6 dependency (Fig. 1). Interleukin-6 receptor inhibition (with tocilizumab and sarilumab), although effective in rheumatoid arthritis,[17] is ineffective in axial spondyloarthritis[18] and psoriatic arthritis. Psoriatic skin disease is occasionally exacerbated on interleukin-6 inhibition. In IBD, interleukin-6 inhibition has yielded limited benefits but also adverse effects such as abscess formation and perforations, probably by inhibiting intestinal barrier function.[19] Interleukin-6 was originally described as a B-cell factor that stimulated immunoglobulin production. Accordingly, the rationale for its use in rheumatoid arthritis was initially based on inhibiting T-cell–mediated B-cell activation, which is important

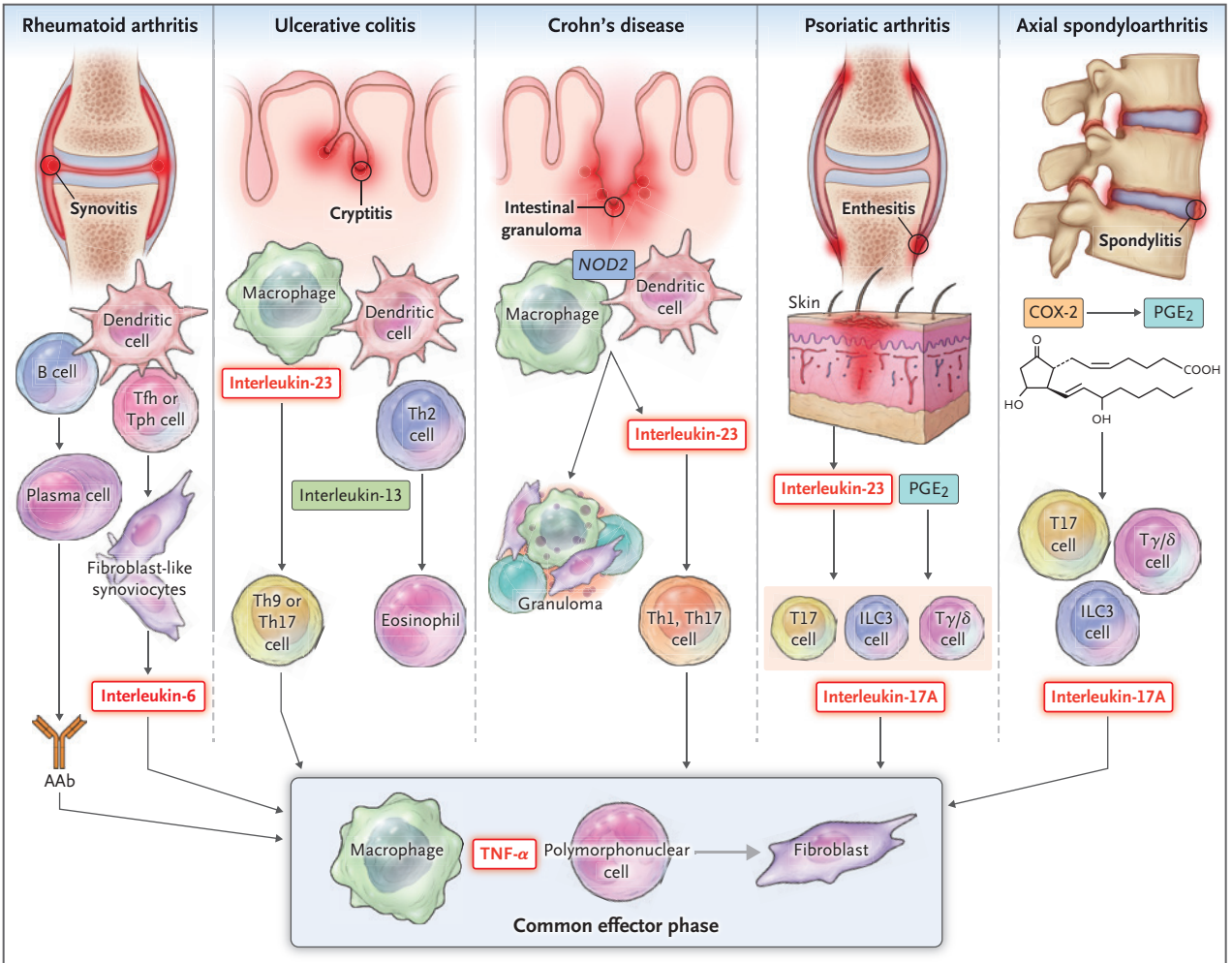

Figure 2. Signature Cytokines and Their Functions in the Inflammatory Process of Arthritis and Colitis.

The pathognomonic feature of rheumatoid arthritis is synovitis. The disease develops on the basis of a breach of immune tolerance involving dendritic cells, follicular or peripheral helper T (Tfh or Tph) cells, and B cells in the lymph nodes and the synovial membrane. This process leads to plasma-cell differentiation and autoantibody (AAb) production, as well as activation of fibroblast-like synoviocytes with interleukin-6 release. Ulcerative colitis is characterized by cryptitis. Dendritic cells and macrophages in the intestinal wall produce increased amounts of interleukin-23, which activates helper T (Th) cell types 17 (Th17) and 9 (Th9). In addition, Th2 cells are enriched in ulcerative colitis and induce eosinophils through interleukin-13. Crohn's disease is characterized by intestinal granuloma formation. In association with nucleotide-binding oligomerization domain–containing protein 2 (*NOD2*) mutations, dendritic cells and macrophages produce increased amounts of interleukin-23 in the ileal and colonic wall, aided by activation of Th1 cells and Th17 cells. Psoriatic arthritis is characterized by enthesitis and is closely associated with skin psoriasis as a source of interleukin-23. In addition, proinflammatory lipids such as prostaglandin E_2 (PGE_2) are produced in the context of mechanoinflammation in the entheses. Interleukin-23 and PGE_2 induce interleukin-17A production by T17 cells (consisting of both CD4+Th17 and CD8+Tc17 [cytotoxic T17] cells), innate lymphoid cells type 3 (ILC3), and T γ/δ cells. Axial spondyloarthritis is characterized by spondylitis. It depends on sustained production of proinflammatory lipids (e.g., PGE_2) by cyclooxygenase 2 (COX-2), which stimulates interleukin-17A production by T17 cells, ILC3, and T γ/δ cells independently from interleukin-23. A shared effector phase in all five immune-mediated inflammatory diseases is the activation of bone marrow–derived macrophages, polymorphonuclear neutrophils, and fibroblasts at sites of inflammation associated with the production of increased amounts of tumor necrosis factor α (TNF-α). The red boxed text indicates the signature cytokines for the diseases.

for the generation of autoantibodies. However, interleukin-6 inhibition does not significantly lower autoantibody levels in rheumatoid arthritis, nor does it preferentially work in the subgroup of rheumatoid arthritis with autoantibodies, as observed for B-cell depletion (with

rituximab) or costimulation blockade (with abatacept), suggesting another mode of action.[20] Recent evidence from single-cell sequencing studies of synovial tissue in rheumatoid arthritis indicates that a major product of resident synovial fibroblasts is interleukin-6, which in addition to chemokines, orchestrates the influx of immune cells into the joint.[21] Hence, interleukin-6 receptor inhibition may have regulatory effects on the resident tissue, as well as block the function of infiltrating leukocytes (Fig. 2).

Interleukin-6 receptor inhibition does not necessarily have higher therapeutic efficacy than TNF-α inhibition in rheumatoid arthritis; however, its therapeutic specificity for rheumatoid arthritis is higher. Furthermore, interleukin-6 receptor inhibition does not require cotreatment with methotrexate to reach maximum efficacy.[22] Also, Janus kinase (JAK) inhibitors, such as baricitinib, upadacitinib, tofacitinib, and filgotinib, which at least partially act by inhibiting interleukin-6 receptor signaling, do not require methotrexate.[23] Accordingly, monotherapy with anti–interleukin-6 receptor antibody or JAK inhibitors achieves significantly better therapeutic responses than treatment with methotrexate in previously untreated patients with rheumatoid arthritis, whereas such differences are not found with TNF-α monotherapy.[24,25] Finally, interleukin-6 influences tissue responses and bone metabolism. Hence, blockade of interleukin-6 receptor, as well as blockade of JAKs, corrects suppressed bone formation in rheumatoid arthritis and induces partial repair of damaged joints, which supports the role of interleukin-6 as a signature cytokine hub in rheumatoid arthritis.[26]

Interleukin-1 in Systemic Juvenile Idiopathic Arthritis

Interleukin-1 inhibition has been approved for the treatment of rheumatoid arthritis but not psoriatic and axial spondyloarthritis or IBD. Its potency in controlling inflammation in rheumatoid arthritis, however, is at best low to moderate. Nonetheless, a small subgroup of patients have rheumatoid arthritis that may indeed be predominantly driven by interleukin-1 activation, and these patients have a good response to interleukin-1 inhibition. These findings[27] (which were subsequently noted also with interleukin-17A inhibition[28]) suggest that the clinical term "rheumatoid arthritis" encompasses a mixture of molecular conditions (pathotypes). Hence, specific cytokine targeting, like molecular tissue characterization, may unravel certain pathotypes or even disease mimics (e.g., gout mimicking rheumatoid arthritis) that have a common pathway.[29] Although interleukin-1 is of limited importance in rheumatoid arthritis, it constitutes a signature cytokine that drives destructive arthritis in diseases associated with genetic activation of the inflammasome, such as the Muckle–Wells syndrome (a genetically determined autoinflammatory disease that is caused by a mutation in *CIAS1*/*NLRP3* and increased activity of the protein cryopyrin, with fever and arthritis), or with danger signal–mediated activation of the inflammasome, such as gout.[30] Furthermore, interleukin-1 inhibition (by the monoclonal antibody canakinumab or the soluble receptor antagonist anakinra), like interleukin-6 inhibition, is highly effective in the treatment of systemic juvenile idiopathic arthritis and adult-onset Still's disease[31,32] (Fig. 1). Both diseases are characterized by genetically controlled hyperresponsiveness of macrophages to alarmins such as S100A8 and S100A9, leading to deregulated production of interleukin-1β, interleukin-6, and interleukin-18.

Interleukin-23 in Crohn's Disease and Ulcerative Colitis

Therapy of IBD involves molecular targets regulating immune-cell trafficking and cytokine function. Blocking $\alpha_4\beta_7$ integrin–MAdCAM (mucosal addressin cell adhesion molecule) interaction with the neutralizing antibody vedolizumab is clinically effective in both Crohn's disease and ulcerative colitis, highlighting the importance of T-cell migration to the intestinal wall.[33,34] With respect to cytokines, interleukin-23 constitutes the second cytokine hub, next to TNF-α, in both Crohn's disease and ulcerative colitis (Fig. 1). Both diseases respond to treatment with the interleukin-12 and interleukin-23 inhibitor ustekinumab, which targets p40, the common subunit of interleukin-12 and interleukin-23.[35,36] As with psoriasis, selective inhibition of interleukin-23 by targeting its specific p19 subunit (e.g., with risankizumab or guselkumab) appears to be effective in clinical studies,[37] highlighting interleukin-23 as the cytokine that orchestrates the development of IBD. This notion is supported by

biopsy studies that show substantial down-regulation of genes related to the interleukin-23–interleukin-17A axis in the ileum and colon in patients with IBD who were treated with p19-targeting antibodies.[38]

Moreover, Crohn's disease and ulcerative colitis share a genetic association with interleukin-23 receptor alleles.[39] Interleukin-23 is primarily produced by dendritic cells and macrophages, which are abundant in the inflamed intestinal wall. The cytokine promotes differentiation and activation of classical type 17 helper T (Th17) cells, T γ/δ cells, and innate lymphoid cells type 3 (ILC3). The pathogenicity of interleukin-23 in IBD was initially linked to interleukin-17A production.[40] However, this concept has been challenged by the negative outcome of interleukin-17A and interleukin-17A receptor targeting in Crohn's disease.[41] Preclinical studies suggest that the pathogenic effect of interleukin-23 in the gut is based on the activation of T cells that bear markers for both type 1 helper T (Th1) and Th17 cells (Fig. 2).[40] At the same time, interleukin-23 inhibits the differentiation of Foxp3-positive regulatory T cells and interleukin-10–producing T cells, thereby creating an imbalance between proinflammatory and antiinflammatory T cells in the intestinal wall. TNF-α inhibition in Crohn's disease can lead to an interleukin-23–mediated escape mechanism of inflammation, with up-regulation of mucosal interleukin-23 and interleukin-23 receptor expression and an increase in apoptosis-resistant interleukin-23 receptor–positive T cells, highlighting the cross-connection between TNF-α and interleukin-23 in IBD.[42]

The responses to cytokine targeting in Crohn's disease and ulcerative colitis contradict the concept of a strict interleukin-23–interleukin-17A inflammation axis, since interleukin-23 inhibition is beneficial in these disorders, whereas interleukin-17A inhibition may exacerbate intestinal inflammation.[41] This difference in treatment response shows that cytokine networks and functions are tissue-dependent and can vary substantially across specific organs. For instance, the intestinal epithelial layer is impaired and leaky in IBD but is hyperproliferative and thickened in psoriasis.[7,11] Interleukin-17A may promote epithelial integrity and antimicrobial defense in both the gut and the skin. But although interleukin-17A inhibition is beneficial in the skin, since it impairs disease-intrinsic hyperproliferation, it further impairs an already damaged barrier function in the gut. Indeed, preclinical studies show that interleukin-23 inhibition ameliorates intestinal inflammation, whereas interleukin-17A inhibition worsens it.[43] Exacerbation of experimental colitis by interleukin-17A inhibition was associated with impaired intestinal barrier function. Interleukin-17A maintains the expression of claudins, which control epithelial barrier function; the expression of the polymeric immunoglobulin receptor, which shuttles secretory IgA into the intestinal lumen; and the expression of antimicrobial peptides by epithelial cells.[44] Interleukin-23 is not essential for interleukin-17A–mediated maintenance of intestinal barrier function, which could explain why interleukin-23 inhibition does not automatically impair the homeostatic functions of interleukin-17A in the gut.[45]

Although interleukin-23 represents a cytokine hub for both Crohn's disease and ulcerative colitis, no differential use of cytokine blockers between the two IBDs has been identified. This is remarkable, since Crohn's disease and ulcerative colitis constitute substantially different pathological disorders. Crohn's disease is characterized by a transmural inflammation associated with granuloma formation, whereas ulcerative colitis is characterized by a more superficial inflammation with neutrophil-based cryptitis.[1,2] Also, the genetic features of Crohn's disease and ulcerative colitis are partially different: Crohn's disease is linked with variants of nucleotide-binding oligomerization domain–containing protein 2 (*NOD2*), a ligand for bacterial peptidoglycans, whereas ulcerative colitis is linked to variants of interleukin-10 receptor (*IL10RA*). Finally, in ulcerative colitis but not in Crohn's disease, CD4+ Th2 and type 9 helper T (Th9) lymphocytes, innate lymphoid cells type 2 (ILC2), and eosinophils are preferentially enriched in the colon wall.[1,46] This finding supports the concept that blocking interleukin-13 may be beneficial in ulcerative colitis. However, blocking interleukin-13 with tralokinumab or anrukinzumab has not proved efficacious in ulcerative colitis.[47,48]

INTERLEUKIN-17A IN AXIAL SPONDYLOARTHRITIS

Although axial spondyloarthritis shares the interleukin-23 receptor genetic link with IBD, cyto-

kine dependency differs between the two disorders. Interleukin-17A constitutes a major cytokine hub in axial spondyloarthritis,[49] whereas interleukin-23 appears to have no major role[50] (Fig. 1). Again, this is an example of how tissue factors influence the response to individual cytokine blockers in diseases that share a genetic background and even have similar clinical manifestations. About 5% of patients with axial spondyloarthritis have concomitant clinical IBD,[51] and 3% of patients with IBD have concomitant axial spondyloarthritis, with axial spondyloarthritis developing more frequently than ulcerative colitis in patients with Crohn's disease.[52]

Inhibition of interleukin-17A (with secukinumab or ixekizumab) has remarkable efficacy in axial spondyloarthritis, with amelioration of signs and symptoms, as well as regression of inflammatory spinal lesions.[49] Several interleukin-17A–producing cell types, including T17 cells (consisting of both CD4+Th17 and CD8+ cytotoxic T17 [Tc17] cells), T γ/δ cells, and ILC3, are present at entheseal sites in the vertebral bodies, even in steady-state conditions.[53] Furthermore, interleukin-17A has been shown to orchestrate inflammatory responses in human tendons.[54] Thus, tendons and their insertions (entheses) appear to represent the tissue that mounts specifically robust interleukin-17A responses in the absence of interleukin-23. Mechanistically, enhanced interleukin-17A production at entheseal sites is most likely related to an exaggerated mechanical stress response[55] and sustained production of prostaglandin E_2 through cyclooxygenase 2 (COX-2) activation. COX-2 rapidly mounts inflammatory responses, such as vasodilatation and neutrophil attraction to tissues, leading to spondylitis. COX-2 activation is also a robust signal for Th17-cell activation,[56] thus providing an alternative tissue-specific enhancement of interleukin-17A production, which does not necessarily require interleukin-23 (Fig. 2).

Although mechanically induced stress responses are physiologic and self-limited, they are enhanced and prolonged in axial spondyloarthritis. The reason for this phenomenon is not clear; however, genetic factors, impaired intestinal barrier function, or both, which are observed in axial spondyloarthritis, may play a role. Notably, interleukin-17A, like prostaglandin E_2, is an important pain mediator, which is expressed in the dorsal root ganglia. It is therefore not surprising that pain is the predominant clinical manifestation of axial spondyloarthritis.[57] Chronic entheseal inflammation in axial spondyloarthritis also leads to excessive local bone responses, which are associated with osteoblast differentiation initiated by prostaglandin E_2, interleukin-17A, and interleukin-22,[58,59] followed by activation of downstream bone morphogenic proteins and Wnt proteins as effector molecules of bone formation.[60,61] This process generates bony spurs at vertebral bodies and sacroiliac joints, eventually leading to bony fusions (ankylosis). It is commonly thought that early and effective intervention in the inflammatory process of spondylitis (resembling axial enthesitis) also inhibits the exaggerated bone response and ankylosis in axial spondyloarthritis.

COMBINED INTERLEUKIN-17A AND INTERLEUKIN-23 IN PSORIATIC ARTHRITIS

Approximately 30% of patients with psoriasis have psoriatic arthritis,[4] which affects the peripheral joints and entheseal structures and occasionally also the spine and resembles some features of axial spondyloarthritis. Psoriatic arthritis differs fundamentally from rheumatoid arthritis in three respects: psoriatic arthritis has a genetic link with the interleukin-23 receptor and MHC class I (e.g., C06) alleles; essentially lacks the autoimmune background of rheumatoid arthritis and has no signs of autoantibody formation or B-cell dependency; and displays a different clinical phenotype, which includes asymmetric arthritis (mostly oligoarthritis), inflammation of entheseal structures, and the subsequent formation of bony spurs and ankylosis.

Mechanical stress is a disease precipitator for both psoriatic arthritis and axial spondyloarthritis, but like psoriatic skin disease, psoriatic arthritis is also strongly associated with metabolic disorders such as obesity and diabetes.[62] Furthermore, psoriatic arthritis responds to interleukin-17A and interleukin-23 inhibition,[63,64] whereas rheumatoid arthritis does not[65,66] (Fig. 1). It appears that the cytokine hubs are similar in psoriatic skin disease and psoriatic joint disease, indicating that the two disorders have the same pathophysiological features and are part of an overarching psoriatic disease. Excessive T-cell activation, neutrophil influx, and resident tissue

responses to mechanical stress are shared by psoriatic skin and joint disease. Stress response patterns similar to psoriatic plaques, but involving bone instead of epithelial proliferations, have been observed in the joints of patients with psoriatic arthritis (termed "deep Koebner's phenomenon").[67] Although interleukin-17A and interleukin-23 provide more robust control of the skin disease than TNF-α, such a "hierarchy" is not observed in arthritis, in which TNF-α inhibition is not inferior to interleukin-17A inhibition or interleukin-23 inhibition; however, for interleukin-23 inhibition, no data from formal head-to-head comparisons are available.[68,69]

The role of interleukin-17A, and probably interleukin-17F, in entheseal inflammation resembles that described for axial spondyloarthritis, suggesting that the interleukin-17 family forms a signature cytokine hub that mediates mechanoinflammation. Mechanoinflammation can be dependent on or independent of interleukin-23 and appears to be more dependent on interleukin-23 in psoriatic arthritis than in axial spondyloarthritis. The source of interleukin-23 in psoriatic arthritis may not necessarily be the joint but rather distant sites, such as clinically or subclinically inflamed skin or the gut (Fig. 2). Hence, interleukin-23 may act more systemically in psoriatic arthritis, whereas interleukin-17A behaves more like a local effector cytokine. Accordingly, systemic interleukin-23 overexpression in mice leads to site-directed inflammatory disease in skin and entheses.[59] Furthermore, circulating interleukin-23–dependent cells (e.g., ILC3) have been identified in active psoriatic arthritis, potentially conveying the effects of interleukin-23 from the skin to the joints. In addition, gut-derived mucosal-associated invariant T (MAIT) cells are enriched in the joints of patients with psoriatic arthritis, providing evidence for a gut–joint axis. Interleukin-23 may thus be the prerequisite for a proinflammatory environment in entheseal sites in patients with psoriasis. Treatment with ustekinumab targets interleukin-12 and interleukin-23 and reduces entheseal inflammation in very early and established psoriatic arthritis, providing further support for this concept.[70,71]

SINGLE- VERSUS MULTIPLE-CYTOKINE INHIBITION IN IMIDS

Although currently single cytokines are inhibited, identification of codependent cytokine hubs, as outlined above, would support multiple-cytokine inhibitory strategies to augment therapeutic responses. The treatment response to single-cytokine inhibition in arthritis and IBD is not as strong as the response in psoriasis; interleukin-23 or interleukin-17A inhibition virtually abrogates the disease in the majority of patients with psoriasis.[68] Furthermore, the identification of specific signature cytokines enlarged our therapeutic armamentarium but did not necessarily lead to outcomes that were substantially better than those associated with TNF-α inhibition. Although it is possible that ceiling effects in the instruments used to measure therapeutic efficacy limit the identification of stronger therapeutic responses, the presence of more than one cytokine hub may be an appealing explanation for limited clinical responses. On the basis of this concept, multiple-cytokine targeting — for instance, with the use of bispecific antibodies — may be an attractive strategy, but clinical data are thus far disappointing.[72]

More pertinently, JAK inhibitors, which block the signaling of several cytokines, are effective in a wide range of IMIDs, including arthritis and colitis.[73] Though the efficacy of JAK inhibitors in individual IMIDs is not necessarily higher than the efficacy of signature cytokine inhibitors, JAK inhibitors are effective in a wider range of IMIDs, reflecting the range observed for TNF-α inhibitors. Several but not all cytokine hubs that were discussed above signal through JAKs, including JAK1/2 (e.g., interleukin-6) and tyrosine kinase 2 (e.g., interleukin-6 and interleukin-23), which explains their efficacy across IMIDs. However, JAK inhibitors are also effective in axial spondyloarthritis, which involves TNF-α and interleukin-17A, cytokines that do not require JAK signaling. This initially surprising finding may be explained by the importance of other cytokines that are sensitive to JAK inhibition that have not yet been recognized as playing a role in axial spondyloarthritis. An example may be granulocyte–macrophage colony-stimulating factor, which could explain the efficacy of

a pan-JAK inhibitor though not of a JAK1-specific inhibitor.[74] Also, interleukin-7, which signals through JAK1 and JAK3, appears to have a role in axial spondyloarthritis, since it induces interleukin-17A expression in MAIT cells.[75] Alternatively, the effects of blocking a series of subordinate cytokines without targeting the main driving nodes may be similar to the effects of targeting one driving node. For instance, JAK1 inhibition affects several proinflammatory mediators, including interleukin-6, interleukin-22, granulocyte colony-stimulating factor, interferon-γ, and type I interferons, which are expressed in arthritis and colitis but each of which alone may not play a fundamental part in driving the disease process.

CONCLUSIONS

Therapeutic targeting of individual cytokines illuminated the pathophysiology of IMIDs that affect the joints and the gut. These findings challenge the long-standing concept of an organ-based disease classification and should pave the way for a mechanism-based understanding of IMIDs. Furthermore, data on responses to anticytokine therapy have propagated new, not yet fully characterized concepts, such as defined tissue determinants, which are pivotal in shaping the local function of cytokines and thereby determine their position in specific disease-associated cytokine networks. Moreover, cytokine profiles may change over time or during anticytokine therapy, highlighting the notion that cytokine profiles represent dynamic targets in the course of IMIDs. Detailed analysis of cytokine hubs by means of modern molecular technologies may be essential for improving clinical responses and identifying molecular pathotypes within a clinically defined disease. Hence, an interleukin-23–driven Crohn's disease pathotype may be more similar to an interleukin-23–driven psoriatic arthritis pathotype than to a distinct pathotype in Crohn's disease.

Another key concept concerns the communication pathways between organs in IMIDs, such as the interaction of the joint and the gut; the concept also concerns the link to other surfaces of the body, such as the skin — a link that may be explained by circulation of soluble mediators and deregulated trafficking of immune effector cells. This concept may allow targeting of IMIDs through shared disease pathways. These new insights will further reframe our understanding of disease-associated signature cytokine hubs and offer new avenues for targeted intervention.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Baumgart DC, Sandborn WJ. Crohn's disease. Lancet 2012;380:1590-605.
2. Danese S, Fiocchi C. Ulcerative colitis. N Engl J Med 2011;365:1713-25.
3. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med 2011;365:2205-19.
4. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. N Engl J Med 2017;376:957-70.
5. Taurog JD, Chhabra A, Colbert RA. Ankylosing spondylitis and axial spondyloarthritis. N Engl J Med 2016;374:2563-74.
6. Bach J-F. The effect of infections on susceptibility to autoimmune and allergic diseases. N Engl J Med 2002;347:911-20.
7. Kiesslich R, Duckworth CA, Moussata D, et al. Local barrier dysfunction identified by confocal laser endomicroscopy predicts relapse in inflammatory bowel disease. Gut 2012;61:1146-53.
8. Culemann S, Grüneboom A, Nicolás-Ávila JÁ, et al. Locally renewing resident synovial macrophages provide a protective barrier for the joint. Nature 2019;572:670-5.
9. Serhan CN, Levy BD. Resolvins in inflammation: emergence of the pro-resolving superfamily of mediators. J Clin Invest 2018;128:2657-69.
10. Alivernini S, MacDonald L, Elmesmari A, et al. Distinct synovial tissue macrophage subsets regulate inflammation and remission in rheumatoid arthritis. Nat Med 2020;26:1295-306.
11. Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med 2009;361:496-509.
12. Hess A, Roesch J, Saake M, et al. Functional brain imaging reveals rapid blockade of abdominal pain response upon anti-TNF therapy in Crohn's disease. Gastroenterology 2015;149:864-6.
13. Elliott MJ, Maini RN, Feldmann M, et al. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. Lancet 1994;344:1105-10.
14. Beutler B, Greenwald D, Hulmes JD, et al. Identity of tumour necrosis factor and the macrophage-secreted factor cachectin. Nature 1985;316:552-4.
15. Sandborn WJ, Hanauer SB, Katz S, et al. Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. Gastroenterology 2001;121:1088-94.
16. Atreya R, Zimmer M, Bartsch B, et al. Antibodies against tumor necrosis factor (TNF) induce T-cell apoptosis in patients with inflammatory bowel diseases via TNF receptor 2 and intestinal CD14$^+$ macrophages. Gastroenterology 2011;141:2026-38.
17. Gabay C, Emery P, van Vollenhoven R, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet 2013;381:1541-50.
18. Sieper J, Porter-Brown B, Thompson L, Harari O, Dougados M. Assessment of short-term symptomatic efficacy of tocilizumab in ankylosing spondylitis: results

of randomised, placebo-controlled trials. Ann Rheum Dis 2014;73:95-100.
19. Danese S, Vermeire S, Hellstern P, et al. Randomised trial and open-label extension study of an anti-interleukin-6 antibody in Crohn's disease (ANDANTE I and II). Gut 2019;68:40-8.
20. Wunderlich C, Oliviera I, Figueiredo CP, Rech J, Schett G. Effects of DMARDs on citrullinated peptide autoantibody levels in RA patients — a longitudinal analysis. Semin Arthritis Rheum 2017;46:709-14.
21. Croft AP, Campos J, Jansen K, et al. Distinct fibroblast subsets drive inflammation and damage in arthritis. Nature 2019;570:246-51.
22. Teitsma XM, Marijnissen AK, Bijlsma JW, Lafeber FPJ, Jacobs JWG. Tocilizumab as monotherapy or combination therapy for treating active rheumatoid arthritis: a meta-analysis of efficacy and safety reported in randomized controlled trials. Arthritis Res Ther 2016;18:211.
23. Fleischmann R, Wollenhaupt J, Takiya L, et al. Safety and maintenance of response for tofacitinib monotherapy and combination therapy in rheumatoid arthritis: an analysis of pooled data from open-label long-term extension studies. RMD Open 2017;3(2):e000491.
24. Bijlsma JWJ, Welsing PMJ, Woodworth TG, et al. Early rheumatoid arthritis treated with tocilizumab, methotrexate, or their combination (U-Act-Early): a multicentre, randomised, double-blind, double-dummy, strategy trial. Lancet 2016;388:343-55.
25. Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004;363:675-81.
26. Adam S, Simon N, Steffen U, et al. JAK inhibition increases bone mass in steady-state conditions and ameliorates pathological bone loss by stimulating osteoblast function. Sci Transl Med 2020;12(530):eaay4447.
27. Cohen S, Hurd E, Cush J, et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002;46:614-24.
28. Patel DD, Lee DM, Kolbinger F, Antoni C. Effect of IL-17A blockade with secukinumab in autoimmune diseases. Ann Rheum Dis 2013;72:Suppl 2:ii116-ii123.
29. Humby F, Lewis M, Ramamoorthi N, et al. Synovial cellular and molecular signatures stratify clinical response to csDMARD therapy and predict radiographic progression in early rheumatoid arthritis patients. Ann Rheum Dis 2019;78:761-72.
30. Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, et al. Use of canakinumab in the cryopyrin-associated periodic syndrome. N Engl J Med 2009;360:2416-25.
31. De Benedetti F, Brunner HI, Ruperto N, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med 2012;367:2385-95.
32. Ruperto N, Brunner HI, Quartier P, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. N Engl J Med 2012;367:2396-406.
33. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 2013;369:711-21.
34. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2013;369:699-710.
35. Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2019;381:1201-14.
36. Sandborn WJ, Gasink C, Gao L-L, et al. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. N Engl J Med 2012;367:1519-28.
37. Feagan BG, Sandborn WJ, D'Haens G, et al. Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study. Lancet 2017;389:1699-709.
38. Visvanathan S, Baum P, Salas A, et al. Selective IL-23 inhibition by risankizumab modulates the molecular profile in the colon and ileum of patients with active Crohn's disease: results from a randomised phase II biopsy sub-study. J Crohns Colitis 2018;12:1170-9.
39. Duerr RH, Taylor KD, Brant SR, et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. Science 2006;314:1461-3.
40. Ahern PP, Schiering C, Buonocore S, et al. Interleukin-23 drives intestinal inflammation through direct activity on T cells. Immunity 2010;33:279-88.
41. Hueber W, Sands BE, Lewitzky S, et al. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. Gut 2012;61:1693-700.
42. Schmitt H, Billmeier U, Dieterich W, et al. Expansion of IL-23 receptor bearing TNFR2+ T cells is associated with molecular resistance to anti-TNF therapy in Crohn's disease. Gut 2019;68:814-28.
43. Maxwell JR, Zhang Y, Brown WA, et al. Differential roles for interleukin-23 and interleukin-17 in intestinal immunoregulation. Immunity 2015;43:739-50.
44. Kinugasa T, Sakaguchi T, Gu X, Reinecker HC. Claudins regulate the intestinal barrier in response to immune mediators. Gastroenterology 2000;118:1001-11.
45. Lee JS, Tato CM, Joyce-Shaikh B, et al. Interleukin-23-independent IL-17 production regulates intestinal epithelial permeability. Immunity 2015;43:727-38.
46. Neurath MF. Targeting immune cell circuits and trafficking in inflammatory bowel disease. Nat Immunol 2019;20:970-9.
47. Danese S, Rudziński J, Brandt W, et al. Tralokinumab for moderate-to-severe UC: a randomised, double-blind, placebo-controlled, phase IIa study. Gut 2015;64:243-9.
48. Reinisch W, Panés J, Khurana S, et al. Anrukinzumab, an anti-interleukin 13 monoclonal antibody, in active UC: efficacy and safety from a phase IIa randomised multicentre study. Gut 2015;64:894-900.
49. Baeten D, Sieper J, Braun J, et al. Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. N Engl J Med 2015;373:2534-48.
50. Deodhar A, Gensler LS, Sieper J, et al. Three multicenter, randomized, double-blind, placebo-controlled studies evaluating the efficacy and safety of ustekinumab in axial spondyloarthritis. Arthritis Rheumatol 2019;71:258-70.
51. Varkas G, Vastesaeger N, Cypers H, et al. Association of inflammatory bowel disease and acute anterior uveitis, but not psoriasis, with disease duration in patients with axial spondyloarthritis: results from two Belgian nationwide axial spondyloarthritis cohorts. Arthritis Rheumatol 2018;70:1588-96.
52. Karreman MC, Luime JJ, Hazes JMW, Weel AEAM. The prevalence and incidence of axial and peripheral spondyloarthritis in inflammatory bowel disease: a systematic review and meta-analysis. J Crohns Colitis 2017;11:631-42.
53. Watad A, Rowe H, Russell T, et al. Normal human enthesis harbours conventional CD4+ and CD8+ T cells with regulatory features and inducible IL-17A and TNF expression. Ann Rheum Dis 2020;79:1044-54.
54. Millar NL, Akbar M, Campbell AL, et al. IL-17A mediates inflammatory and tissue remodelling events in early human tendinopathy. Sci Rep 2016;6:27149.
55. Cambré I, Gaublomme D, Burssens A, et al. Mechanical strain determines the site-specific localization of inflammation and tissue damage in arthritis. Nat Commun 2018;9:4613.
56. Chizzolini C, Chicheportiche R, Alvarez M, et al. Prostaglandin E2 synergistically with interleukin-23 favors human Th17 expansion. Blood 2008;112:3696-703.
57. Richter F, Natura G, Ebbinghaus M,

et al. Interleukin-17 sensitizes joint nociceptors to mechanical stimuli and contributes to arthritic pain through neuronal interleukin-17 receptors in rodents. Arthritis Rheum 2012;64:4125-34.
58. Zhang X, Schwarz EM, Young DA, Puzas JE, Rosier RN, O'Keefe RJ. Cyclooxygenase-2 regulates mesenchymal cell differentiation into the osteoblast lineage and is critically involved in bone repair. J Clin Invest 2002;109:1405-15.
59. Sherlock JP, Joyce-Shaikh B, Turner SP, et al. IL-23 induces spondyloarthropathy by acting on ROR-γt+ CD3+CD4-CD8- entheseal resident T cells. Nat Med 2012; 18:1069-76.
60. Diarra D, Stolina M, Polzer K, et al. Dickkopf-1 is a master regulator of joint remodeling. Nat Med 2007;13:156-63.
61. Lories RJU, Derese I, Luyten FP. Modulation of bone morphogenetic protein signaling inhibits the onset and progression of ankylosing enthesitis. J Clin Invest 2005;115:1571-9.
62. Scher JU, Ogdie A, Merola JF, Ritchlin C. Preventing psoriatic arthritis: focusing on patients with psoriasis at increased risk of transition. Nat Rev Rheumatol 2019;15:153-66.
63. Mease PJ, McInnes IB, Kirkham B, et al. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. N Engl J Med 2015;373:1329-39.
64. Deodhar A, Helliwell PS, Boehncke W-H, et al. Guselkumab in patients with active psoriatic arthritis who were biologic-naive or had previously received TNFα inhibitor treatment (DISCOVER-1): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet 2020;395:1115-25.
65. Genovese MC, Durez P, Richards HB, et al. Efficacy and safety of secukinumab in patients with rheumatoid arthritis: a phase II, dose-finding, double-blind, randomised, placebo controlled study. Ann Rheum Dis 2013;72:863-9.
66. Smolen JS, Agarwal SK, Ilivanova E, et al. A randomised phase II study evaluating the efficacy and safety of subcutaneously administered ustekinumab and guselkumab in patients with active rheumatoid arthritis despite treatment with methotrexate. Ann Rheum Dis 2017;76: 831-9.
67. Simon D, Tascilar K, Kleyer A, et al. Structural entheseal lesions in patients with psoriasis are associated with an increased risk of progression to psoriatic arthritis. Arthritis Rheumatol 2020 February 26 (Epub ahead of print).
68. Reich K, Armstrong AW, Langley RG, et al. Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomised controlled trial. Lancet 2019; 394:831-9.
69. McInnes IB, Behrens F, Mease PJ, et al. Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial. Lancet 2020;395:1496-505.
70. Araujo EG, Englbrecht M, Hoepken S, et al. Effects of ustekinumab versus tumor necrosis factor inhibition on enthesitis: results from the Enthesial Clearance in Psoriatic Arthritis (ECLIPSA) study. Semin Arthritis Rheum 2019;48:632-7.
71. Savage L, Goodfield M, Horton L, et al. Regression of peripheral subclinical enthesopathy in therapy-naive patients treated with ustekinumab for moderate-to-severe chronic plaque psoriasis: a fifty-two-week, prospective, open-label feasibility study. Arthritis Rheumatol 2019;71: 626-31.
72. Mease PJ, Genovese MC, Weinblatt ME, et al. Phase II study of ABT-122, a tumor necrosis factor- and interleukin-17A-targeted dual variable domain immunoglobulin, in patients with psoriatic arthritis with an inadequate response to methotrexate. Arthritis Rheumatol 2018;70:1778-89.
73. Schwartz DM, Kanno Y, Villarino A, Ward M, Gadina M, O'Shea JJ. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. Nat Rev Drug Discov 2017;16:843-62.
74. Regan-Komito D, Swann JW, Demetriou P, et al. GM-CSF drives dysregulated hematopoietic stem cell activity and pathogenic extramedullary myelopoiesis in experimental spondyloarthritis. Nat Commun 2020;11:155.
75. Gracey E, Qaiyum Z, Almaghlouth I, et al. IL-7 primes IL-17 in mucosal-associated invariant T (MAIT) cells, which contribute to the Th17-axis in ankylosing spondylitis. Ann Rheum Dis 2016;75: 2124-32.