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Immunomodulatory role of T helper cells in rheumatoid arthritis

A COMPREHENSIVE RESEARCH REVIEW

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Rheumatoid arthritis (RA) is an autoimmune disease that involves T and B cells and their reciprocal immune interactions with proinflammatory cytokines. T cells, an essential part of the immune system, play an important role in RA. T helper 1 (Th1) cells induce interferon-γ (IFN-γ), tumour necrosis factor-α (TNF-α), and interleukin (IL)-2, which are proinflammatory cytokines, leading to cartilage destruction and bone erosion. Th2 cells primarily secrete IL-4, IL-5, and IL-13, which exert anti-inflammatory and anti-osteoclastogenic effects in inflammatory arthritis models. IL-22 secreted by Th17 cells promotes the proliferation of synovial fibroblasts through induction of the chemokine C-C chemokine ligand 2 (CCL2). T follicular helper (Tfh) cells produce IL-21, which is key for B cell stimulation by the C-X-C chemokine receptor 5 (CXCR5) and coexpression with programmed cell death-1 (PD-1) and/or inducible T cell costimulator (ICOS). PD-1 inhibits T cell proliferation and cytokine production. In addition, there are many immunomodulatory agents that promote or inhibit the immunomodulatory role of T helper cells in RA to alleviate disease progression. These findings help to elucidate the aetiology and treatment of RA and point us toward the next steps.

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Keywords: Rheumatoid arthritis, T helper cells, Immunomodulatory

Article focus

- This article reviews the immune function and mechanism of T helper (Th) cells in rheumatoid arthritis (RA).

Key messages

- Various Th cells are involved in the pathogenesis of RA.
- Some Th cells promote inflammation, while others suppress it.
- Research into the role of Th cells in RA could lead to new drugs.

Strengths and limitations

- This paper reviews the role of Th cells in the pathogenesis of RA and provides new ideas for the treatment of RA.
- As all the studies included are in English, the literature in this review may not be sufficiently comprehensive.

Introduction

Rheumatoid arthritis (RA) is a common autoimmune disease characterized by synovial inflammation and hyperplasia, autoantibody production, cartilage and bone destruction, and systemic features, including cardiovascular, pulmonary, psychological, and skeletal disorders.[1] Although the aetiology of RA is unknown, T and B cells and their reciprocal immune interactions with proinflammatory cytokines are thought to be involved in the pathophysiology of RA.[2,3] For example, in pathologically inflamed non-lymphoid tissues, peripheral T helper (Th) cells promote B cell responses and antibody production.[4]

CD4+ Th cells are an essential and complex component of the immune system that proliferate and spread to activate other types of immune cells to produce direct immune responses.[5] Cytokines are central mediators

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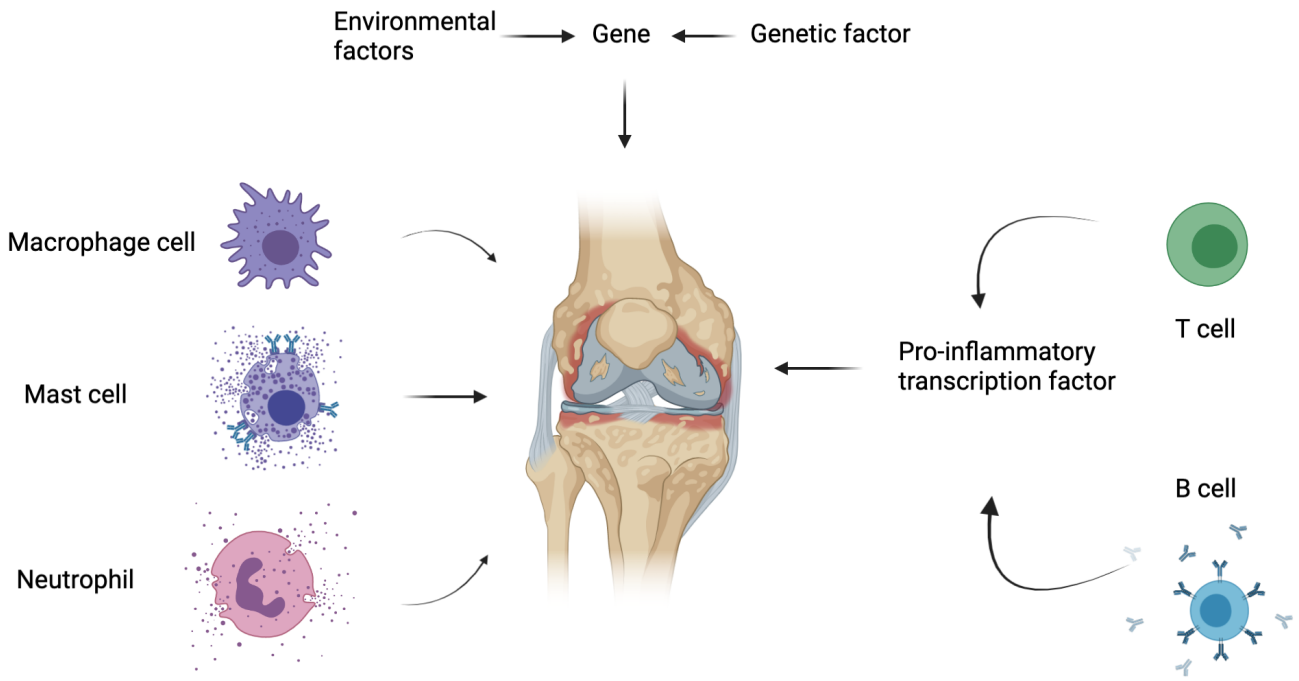

Fig. 1

The immune cells involved in the regulation of rheumatoid arthritis (RA). The development of RA involves the interaction of genotype and environmental triggers. Both environmental and genetic factors cause alterations in gene expression, thereby causing the development of RA. Effector T cells, together with B cells and other innate effector cells, form a complex network that promotes the production of pro-inflammatory cytokines, which trigger the activation of resident fibroblast-like synovial cells and lead to cartilage and bone damage. Neutrophils and mast cells, along with macrophages, play an important role in the development of synovitis.

of the immune response, and CD4+ Th cells are specialized cytokine-producing cells. Through the production of effector cytokines, Th cells play a key role in the adaptive immune response to infection.[6]

Th cells are clearly involved in the pathophysiological process of RA, and their involvement has been the focus of discussion, with the immune regulation of Th cells in RA having been extensively studied. Because understanding the immune regulation of Th cells in the pathogenesis of RA is important for exploring the pathophysiological process of RA and developing therapies for long-term remission in terms of clinical relevance and basic theory, the purpose of this review article is to discuss how Th cells are immunomodulated during the pathogenesis and treatment of RA.

RA pathogenesis

RA involves a complex interplay between genotype and environmental triggers. For example, studies on twins suggest a genetic component of RA, with a 15% to 30% chance of concurrent RA in identical twins and 5% in dizygotic twins. In addition, genome-wide analysis has shown that immunomodulatory factors underlie the disease (Figure 1).[7]

One of the features of RA is persistent synovitis, which is caused by a continuous influx of immune cells into the joints.[8,9] Synovitis occurs when leucocytes infiltrate the synovial cavity. Endothelial cell activation in synovial microvessels promotes cell migration, which increases the expression of adhesion molecules, including integrins, selectins, and members of the immunoglobulin superfamily, as well as chemokines.[1] Therefore, neoangiogenesis induced by local hypoxic conditions and cytokines, as well as inadequate lymphangiogenesis that limits cellular exit, are characteristic of early synovitis.[10,11] These microenvironmental changes, combined with deep synovial structural reorganization and local fibroblast activation, allow the formation of synovial inflammatory tissue in RA. In this context, effector T cells, together with B cells and other innate effector cells, form a complex network that promotes the production of proinflammatory cytokines, which trigger the activation of resident fibroblast-like synovial cells and lead to cartilage and bone damage.[12] Marzaioli et al[13] found that the frequency of synovial CD4+ $CD8^{dim}$ T cells correlates with RA disease activity. Natural immune cells, such as neutrophils and mast cells, contribute to the development of synovitis, as do macrophages.[14-16] In addition to the classic M1 and M2 macrophages, there are also tumour-associated macrophages, CD169+ macrophages, and T cell receptor+ (TCR+) macrophages.[17] The recently described MER proto-oncogene tyrosine kinase+ (MerTK+) and MerTK-tissue-resident memory (TRM) subsets have also been demonstrated to have different effects on synovial

fibroblast repair and inflammatory response.[17] In addition, synovial tissue macrophages are involved in the immune regulation of RA pathogenesis.[18] Several cytokines are also involved in the development of RA, such as interleukin (IL)-4 and IL-13, which activate Th cells, IL-5, which induces proliferation of eosinophils, IL-33, which mediates polarization of macrophages, IL-10 production by regulatory B cells, IL-27, which mediates inhibition of lymphoid follicle formation, and other cytokine-mediated processes involved in the regulation of inflammation in RA.[19] In RA, the leucocyte-derived cytokine TNF interacts with IL-17A to activate fibroblasts as a major source of the signature cytokine IL-6.[20]

Loss of normal synovial protection alters the protein-binding characteristics of the cartilage surface, promoting adhesion and invasion by fibroblast-like synoviocytes (FLSs), and the proliferation of FLSs is the main cause of invasive pannus formation in RA pathogenesis.[21,22] FLSs synthesize matrix metalloproteinases (MMPs), particularly MMP-1, -3, -8, -13, -14, and -16, promoting breakdown of the type II collagen network, a process that alters glycosaminoglycan content and water retention, directly leading to biomechanical dysfunction.[23] A recent study found that overexpressed microRNA (miR)-486 accelerates the reduction of aggregative proteoglycan by upregulating the expression of A disintegrin and metalloproteinase with thrombospondin motifs-4 (ADAMTS4) and MMP-13, resulting in more decomposition of chondrocytes.[24] Transforming growth factor-β2 (TGF-β2) not only promotes cartilage repair by promoting collagen and fibronectin synthesis and downregulating protease synthesis, but also inhibits lymphocyte entry into arthritic joints of RA.[25] In addition, articular cartilage itself has limited regenerative potential. Chondrocytes physiologically regulate matrix formation. Under the influence of synovial cytokines, especially IL-1 and IL-17A, and reactive nitrogen intermediates, chondrocytes undergo apoptosis. These processes eventually lead to the destruction of surface cartilage and the manifestation of joint space narrowing. Zhang et al[26] found that tert-butylhydroquinone can promote chondrocyte differentiation by inhibiting chondrocyte apoptosis and inhibiting apoptosis inflammation. Bone erosion prolongs and exacerbates synovial inflammation.[27,28] Synovial cytokines promote osteoclast differentiation and invasion of the periosteum near the articular cartilage. Destruction of cortical bone allows synovial access to the bone marrow, which leads to bone marrow inflammation and gradual arthroplasty of bone marrow fat by T cell and B cell aggregates.[29]

T helper cells are involved in the immunomodulatory process of RA

T helper cell profile. Naive CD4 T cells differentiate into distinct Th subpopulations upon activation, producing spectrum-specific cytokines.[6,30] By producing a unique set of cytokines, effector Th subpopulations play a key role in coordinating the immune response to various challenges and are involved in the pathogenesis of many inflammatory diseases, including autoimmunity, allergies, and asthma (Figure 2).[31]

Th cells are classified according to their cytokine profile. Th1 and Th2 cells preferentially produce interferon γ (IFN-γ) and IL-4, respectively.[32] Th1's major cytokine products include IFN-γ, tumour necrosis factor-α (TNF-α), and IL-2, which are primarily used for host defence against intracellular pathogens and are responsible for the development of some forms of organ-specific autoimmunity.[33] Th2 cells produce IL-4, IL-5, IL-9, IL-10, IL-13, and dual-regulatory proteins.[34,35] Another type of immunosuppressive T cell that expresses CD25 are regulatory T cells (Tregs).[36] In addition to CD25, Tregs also express cytotoxic T-lymphocyte antigen 4 (CTLA-4) and glucocorticoid-induced tumour necrosis factor receptor-related protein (GITR). A third major CD4 Th effector cell population, Th17, was subsequently identified to produce IL-17,[37] and the signature cytokines of Th17 cells include IL-17A, IL-17F, and IL-22. Th17 cell differentiation is promoted by IL-1β, IL-6, IL-21, IL-23, and TGF-β. In addition, Th17 cells express high levels of interleukin-23 receptor (IL-23R).[38] Another prominent subpopulation of Th cells are T follicular helper (Tfh) cells, which promote humoral immunity within the germinal centre (GC).[39] Th9 cells develop from primary T cells in the presence of TGF-β and IL-4.[40] Th9 cells produce not only IL-9, but also other cytokines such as IL-10, IL-17, IL-21, and IL-22.[40] Th22 cells, first described by Trifari et al,[41] are identified by secretion of various cytokines such as IL-13, TNF-α, and IL-22. It has been found that the differentiation of Th22 is mainly mediated by the transcription factor aromatic hydrocarbon receptor (AHR).[41,42] Th22 cells can secrete IL-22, IL-13, IL-26, and TNF-α, but not IL-17, IFN-γ, or IL-4 (Figure 2).[42]

Th1 cells are involved in the immunomodulatory mechanism of RA. The involvement of Th1 cells in immune regulation in the pathogenesis of RA has been the focus of research since Th1 cells were first identified. Several cytokines produced during the initial presentation of antigens to naive T cells regulate the development of Th1 and Th2 cells, with IL-12 and IFN-γ causing a shift to a Th1 response and IL-4 directing the progression to Th2 cells.[43,44] The chronic immune response in RA may be driven by activated Th1 cells coupled with insufficient Th2 cell differentiation to downregulate inflammation.[44] The imbalance between Th1 and Th2 cells is thought to be pathogenic.[45] Th1 cells promote the development of a proinflammatory microenvironment in the synovium by inducing the secretion of proinflammatory cytokines, including IFN-γ, TNF-α, and IL-2, ultimately leading to cartilage destruction and bone erosion.[46] One study reported that IFN-γ secretion by Th1 cells in the peripheral blood of early untreated RA patients was significantly lower than that of healthy controls.[47] IL-18 induces IFN-γ production in Th1 cells and natural killer cells.[48] Janus kinase 3 (JAK3)-deficient T cells are unable to produce IFN-γ, whereas IL-2-activated signal transducer and activator of

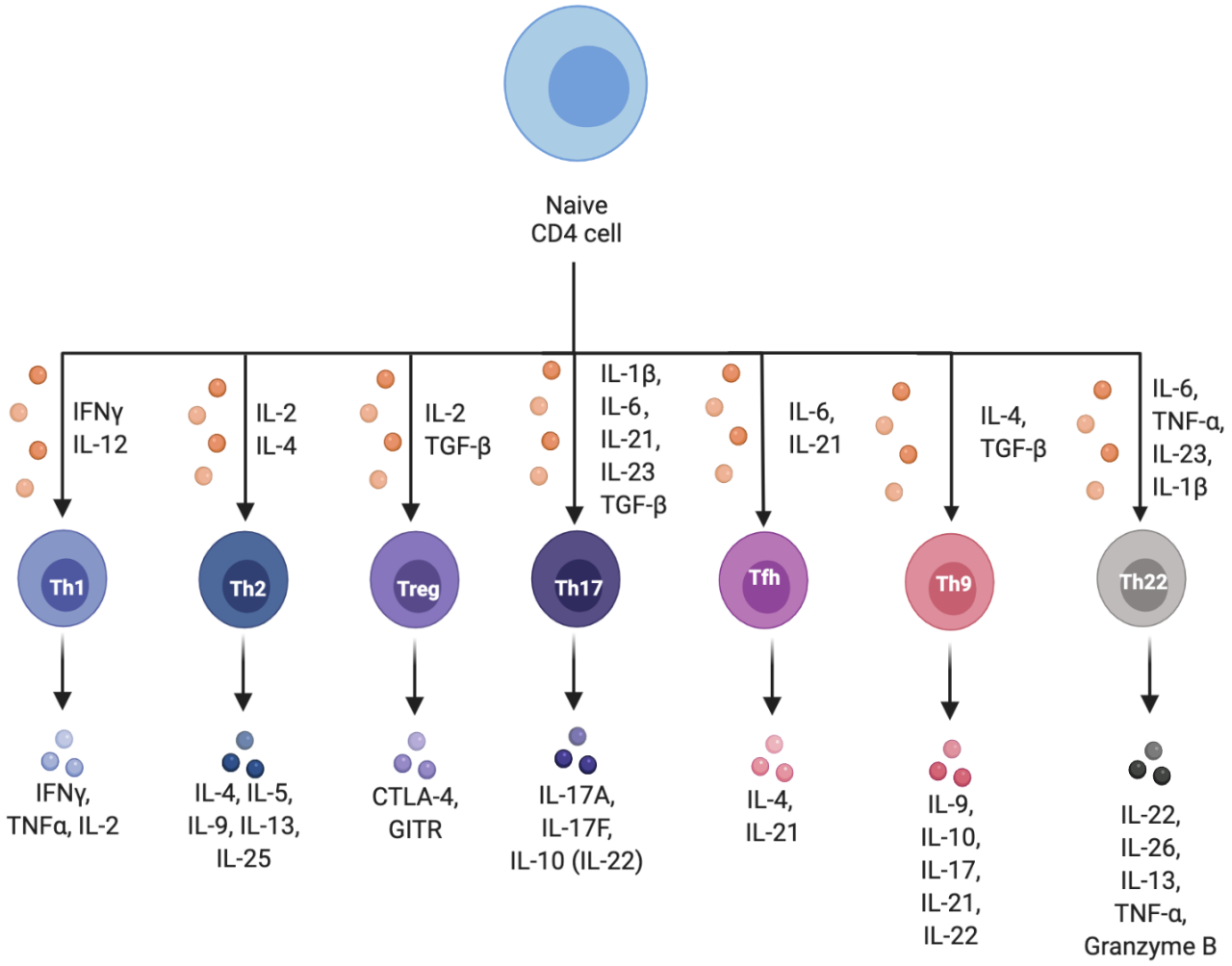

Fig. 2

The differentiation of the naïve CD4+ T cell. Naïve CD4 T cells differentiate into distinct T helper subpopulations upon activation, producing spectrum-specific cytokines. Depending on their cytokine profile, different types of Th cells exist. Th1 major cytokine products are interferon-γ (IFN-γ), tumour necrosis factor-α (TNF-α), and interleukin (IL)-2. Th2 cells produce IL-5, IL-9, IL-10, IL-13, IL-25, and dual-regulatory proteins. Another type of immunosuppressive T cells that can express CD25 are called regulatory T cells (Tregs); in addition to CD25, Treg cells also express cytotoxic T-lymphocyte antigen 4 (CTLA-4) and glucocorticoid-induced tumour necrosis factor receptor-related protein (GITR). A third major CD4 Th effector cell population, Th17, was subsequently identified to produce IL-17, and the signature cytokines of Th17 cells include IL-17A, IL-17F, and IL-22. Th17 cell differentiation is promoted by IL-1β, IL-6, IL-21, IL-23, and transforming growth factor-β (TGF-β). Another prominent subpopulation of Th cells are the T follicular helper (Tfh) cells, which promote humoral immunity within the germinal centre (GC). Th9 cells are derived from primary T cells and contain TGF-β and IL-4. TH9 cells produce not only IL-9, but also other cytokines such as IL-10, IL-17, IL-21, and IL-22. The differentiation of Th22 is mainly mediated by the transcription factor aromatic hydrocarbon receptor (AHR). Th22 cells can secrete IL-22, IL-13, IL-26, and TNF-α.

transcription 5 (STAT5) is required for IFN-γ secretion.[49] Many studies have confirmed that IL-2 regulates the differentiation, development, and expression of both Tregs and Th17 cells.[50-53] Moreover, the reduced number of Tregs in patients with autoimmune diseases is significantly and negatively correlated with disease activity, suggesting that Treg reduction-mediated immune tolerance disruption may be an important factor in the pathogenesis of RA.[54] Studies have shown that the number of Tfh cells in the peripheral blood of RA patients is significantly higher than that of healthy controls,[55,56] and the presence of Tfh cells in RA synovial tissue is tightly correlated with the severity of synovial pathology,[57] suggesting the involvement of Tfh cells in the progression of RA. A recent study suggests that Th1 cells generate the novel C-X-C motif chemokine ligand 9 (CXCL9)/10-producing T-bet+ effector B cells that could be an ideal pathogenic B cell target for RA therapy.[58] It has been shown that deletion of B-cell lymphoma (Bcl)-6 prevents CD4+ T cells from differentiating into Tfh cells, suggesting that the master transcription factor Bcl-6 is required for Tfh cell development.[59] Given the expression characteristics of Bcl-6, the use of IL-2 effectively inhibits the differentiation of Tfh cells.[60,61] This is because IL-2 preferentially activates STAT5 and inhibits STAT3, leading to reduced binding to the Bcl-6 gene.[62] On the other hand, IL-2 promotes the

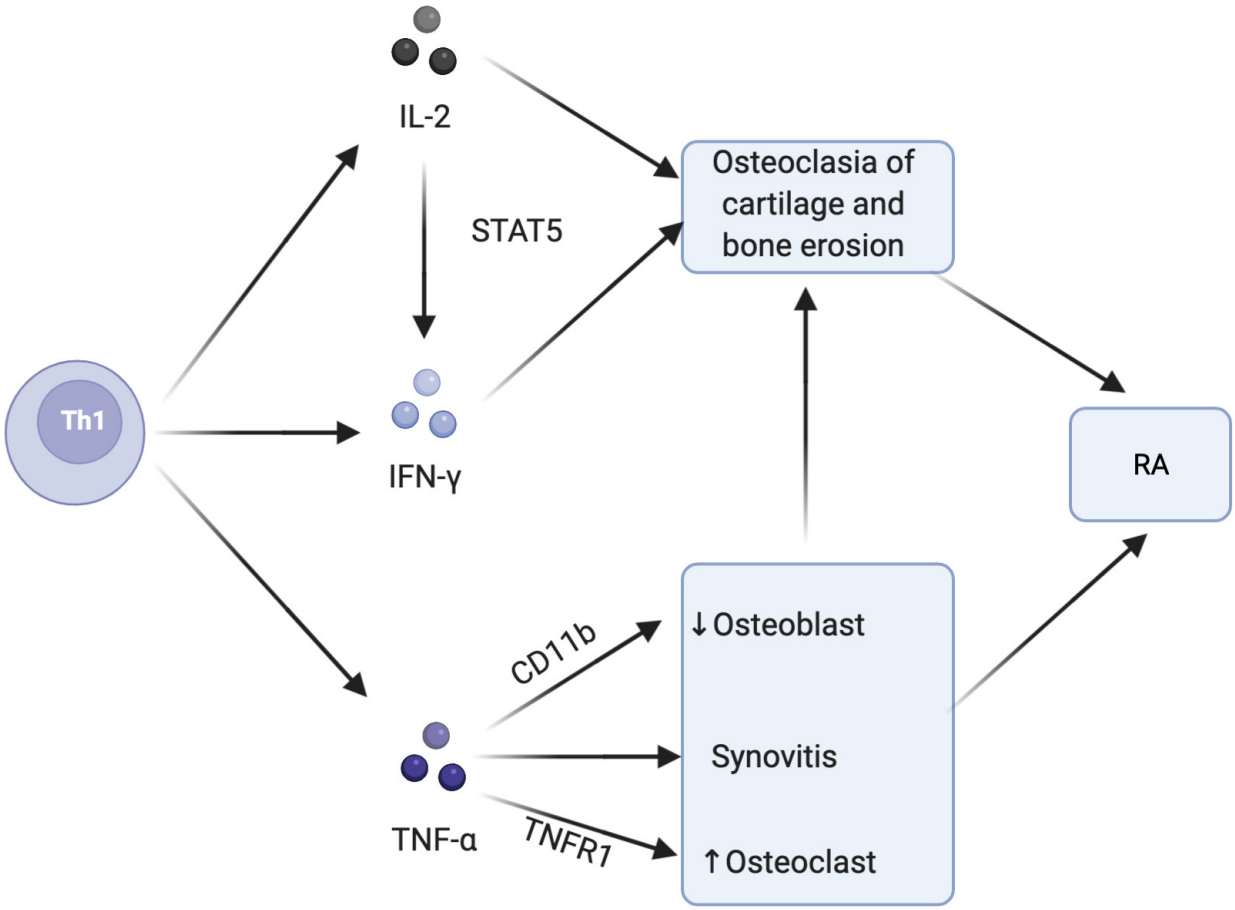

Fig. 3

Involvement of T helper 1 (Th1) cells in the immune regulation of rheumatoid arthritis (RA). Th1 cells secrete cytokines such as interleukin (IL)-2, interferon-γ (IFN-γ), and tumour necrosis factor-α (TNF-α), which participate in immune regulation in the pathogenesis of RA. IL-2 activates signal transducer and activator of transcription 5 (STAT5) to promote the secretion of IFN-γ, and the joint action of IL-2 and IFN-γ causes cartilage destruction and bone erosion. TNF-α can interact with IL-2 and IFN-γ to cause synovitis. In addition, TNF-α can combine with DC11b to inhibit osteoblast differentiation, and it can also combine with tumour necrosis factor receptor 1 (TNFR1) on osteoclast precursor to promote osteoclast formation. These pathological reactions are involved in the pathogenesis of RA.

expression of Blimp-1, which reduces the expression of Bcl-6.[61] In inflamed joints, both Th1 and B cells produce TNF-α, leading to chronic inflammation, and synovial Th1 cells directly contribute to synovitis by producing TNF-α.[63] In addition, TNF-α stimulates RA pathogenesis by promoting dendritic cell differentiation, leading to autoantigen presentation to T cells in the synovium of RA patients.[64] The high levels of TNF-α detected in RA patients can directly lead to osteoclastogenesis by binding to tumour necrosis factor receptor 1 (TNFR1) on osteoclast precursors and indirectly through receptor activator of nuclear factor-kappaB ligand (RANKL) production.[65] TNF-α further affects bone resorption by mobilizing the osteoclast precursor CD11b in the bone marrow and by inhibiting osteoblast differentiation and function to reduce bone formation.[66] However, T cells indirectly affect TNF-α levels primarily through the production of cytokines that stimulate other cells to produce TNF-α.[12] In addition, the interaction of T cells with neighbouring macrophages and synovial fibroblasts activates these cells and induces the production of TNF-α.[67] Recent studies have shown that TNF-α may promote osteoclast bone resorption.[68] These findings indicate that Th1 cells and their effector cytokines play a major role in the immune regulation of RA (Figure 3).

Immunomodulatory role of Th2 cells in RA. Under the guidance of the cytokine IL-4, naive Th cells differentiate into Th2 cells, which primarily secrete IL-4, IL-5, and IL-13. The anti-inflammatory factor IL-4 secreted by Th2 cells inhibits the secretion of proinflammatory factors, such as IL-1, TNF-a, IL-8, IL-6, and IL-12.[69-71] IL-4 also exerts an inhibitory effect on bone resorption by affecting the activity and survival of osteoclasts.[72] Physiologically, IL-4 and IL-13 share the same receptors, and both are capable of activating the STAT6 signalling pathway.[73] IL-4 and IL-13 are upregulated in the synovial fluid of early RA but not in established RA, suggesting that these cytokines are part of an early regulatory response that is

lost as patients progress to fully established disease.[74] Functionally, IL-4 and IL-13 are potent anti-arthritic cytokines that also inhibit cartilage damage and osteoclastogenesis,[75,76] and therefore display anti-inflammatory and anti-osteoclastogenic properties in models of inflammatory arthritis.[77] In a mouse model of arthritis, strong activation of the STAT6 signalling pathway was observed in IL-4- and IL-13-induced haematopoietic cells, followed by a shift in macrophage polarization towards an anti-inflammatory 'M2-like' phenotype, which is responsible for the suppression of arthritis.[78] In addition, IL-4 and IL-13 have direct anti-inflammatory effects in the synovium of RA, where they reduce the production of IL-1β and TNF through synovial macrophages, as well as their expression of CD16 and CD64.[79,80] IL-4 and IL-13 are important components of Th2 cell-mediated immunity.[81] The activation of the IL-4 and IL-13 pathways in RA is therefore an attractive option because it shifts the effector cell population to an immunomodulatory phenotype. IL-5 differentiates and mobilizes eosinophils from the bone marrow.[82] In patients with RA, blood concentrations of IL-5 and eosinophil chemokines are higher during early self-limiting disease and lower in established disease.[74] Two mechanisms can explain the potential anti-inflammatory role of eosinophils in RA. First, eosinophils support macrophage differentiation into the immunomodulatory M2 phenotype through the release of IL-4 and IL-13.[83] Second, eosinophils produce anti-inflammatory lipids, such as D1 protectin, a pro-catabolic lipid mediator with anti-inflammatory and tissue protective functions in a mouse model of arthritis.[84] IL-10 plays an independent regulatory role in RA. In RA synovial cultures, the addition of exogenous IL-10 leads to a decrease in TNF-α and IL-1β in RA synovial cultures.[85] Th2 cells and cytokines clearly play a suppressive role in the immune progression of RA (Figure 4).

Immunomodulation of Tregs during the course of RA. Tregs suppress various Th cell-mediated proinflammatory immune responses by releasing anti-inflammatory cytokines.[86] The transcription factor FOXP3+ plays a crucial role in Treg development.[87] In terms of the Treg phenotype, although Tregs were initially identified as CD25-high T cells, recent studies have shown that CD25 expression on the cell surface is not mandatory to confer regulatory properties. Indeed, the transcription factor FOXP3 is by far the most specific Treg marker and ensures suppressive activity independent of CD25 coexpression.[88,89] Most studies observed a reduced percentage of circulating Treg cells in RA compared to healthy individuals,[90-92] while some studies have reported an increase in the percentage of Treg cells compared to controls.[93,94] This seems somewhat contradictory, but some studies have suggested that the higher percentage of Treg cells may reflect contamination of activated cells.[94] Treg cells inhibit the autoimmune response. When the number and/or function of these cells is abnormal, the associated antigens cause an immune cascade of amplification, leading to a rapid increase in the levels of various cytokines such as IL-2 in the body, which activates macrophages.[95] CTLA-4 is likely to be involved in multiple mechanisms that give Tregs inhibitory properties. One proposed mechanism involves a direct interaction with CD80/CD86 expressed on activated Tregs.[96,97] In addition, it has been suggested that in RA Tregs, the regulation of T cell receptor signalling by CTLA-4 is impaired and associated with delayed re-recruitment of CTLA-4 to the immune synapse.[98] GITR is constitutively expressed in Tregs and is essential for the development and activity of Tregs.[99,100] Binding of GITR to effector T cells generates positive costimulatory signals and promotes T cell activation and proliferation, while activation of Tregs by GITR abolishes their suppressive function.[101,102] In addition, macrophages act as proinflammatory agents in a GITR-dependent manner in the development of autoimmune diseases.[103] In general, the pathogenesis of RA is very complex, and the dysfunction of Tregs is one of the potential mechanisms of self-tolerance breakdown leading to the progression of RA.[95]

Th17 cells are involved in the immune regulation of RA. Differentiation factors (TGF-β+, IL-6, and IL-21), growth, and stabilization factors (IL-23) and transcription factors (STAT3, retinoic acid-related orphan receptor-γt (RORγt), and retinoic acid-related orphan receptor-α (RORα)) involved in Th17 cell development have been identified.[104] Th17 cells secrete IL-17A, IL-17F, IL-10 (also known as IL-22), and IL21. Th17 cells and Th17-related cytokines play an important role in the pathogenesis of RA, and levels of Th17 cells in peripheral blood are associated with disease activity in RA.[105] IL-17A induces secretion of the proinflammatory cytokines TNF-α, IL-1b, IL-6, and IL-8 by macrophages, fibroblasts, chondrocytes, stromal cells, and other synovial joint cells.[106,107] Despite their proinflammatory effects, IL-17A and IL-17F alone are not potent inflammatory cytokines. In fact, their potent inflammatory effects are primarily related to their ability to recruit immune cells and their synergistic effects with other proinflammatory cytokines, such as TNF, IL-1β, IFN-γ, GM-CSF, and IL-22.[108] In addition, IL-17A has synergistic effects with IL-1 and TNF-α in upregulating nitric oxide (NO) and prostaglandin E2 (PGE2) production, leading to bone erosion.[109] Thus, IL-17 not only enhances inflammation but also stimulates osteoclast differentiation, leading to subsequent bone and cartilage damage.[110] IL-25 reduces RA by suppressing the Th17 immune response.[111] IL-23 receptors are essential for terminal differentiation of Th17 cells in vivo and for the pathogenic properties of the Th17 population.[112-114] However, it has been found that IL-23 does not depend on the inflammatory mechanism of TNF in the pathogenesis of RA.[115] IL-21 secreted by Th17 cells in RA synovium is closely associated with RA.[116] Furthermore, IL-21 induces T cell activation and promotes the secretion of proinflammatory cytokines in RA by suppressing FOXP3+ expression,[117] thereby promoting the differentiation and proliferation of Th17 cells.[118] IL-22 belongs to the IL-10 family, and IL-22 secreted by Th17 cells has been shown to promote the proliferation of synovial fibroblasts through induction of the chemokine CCL2.[119]

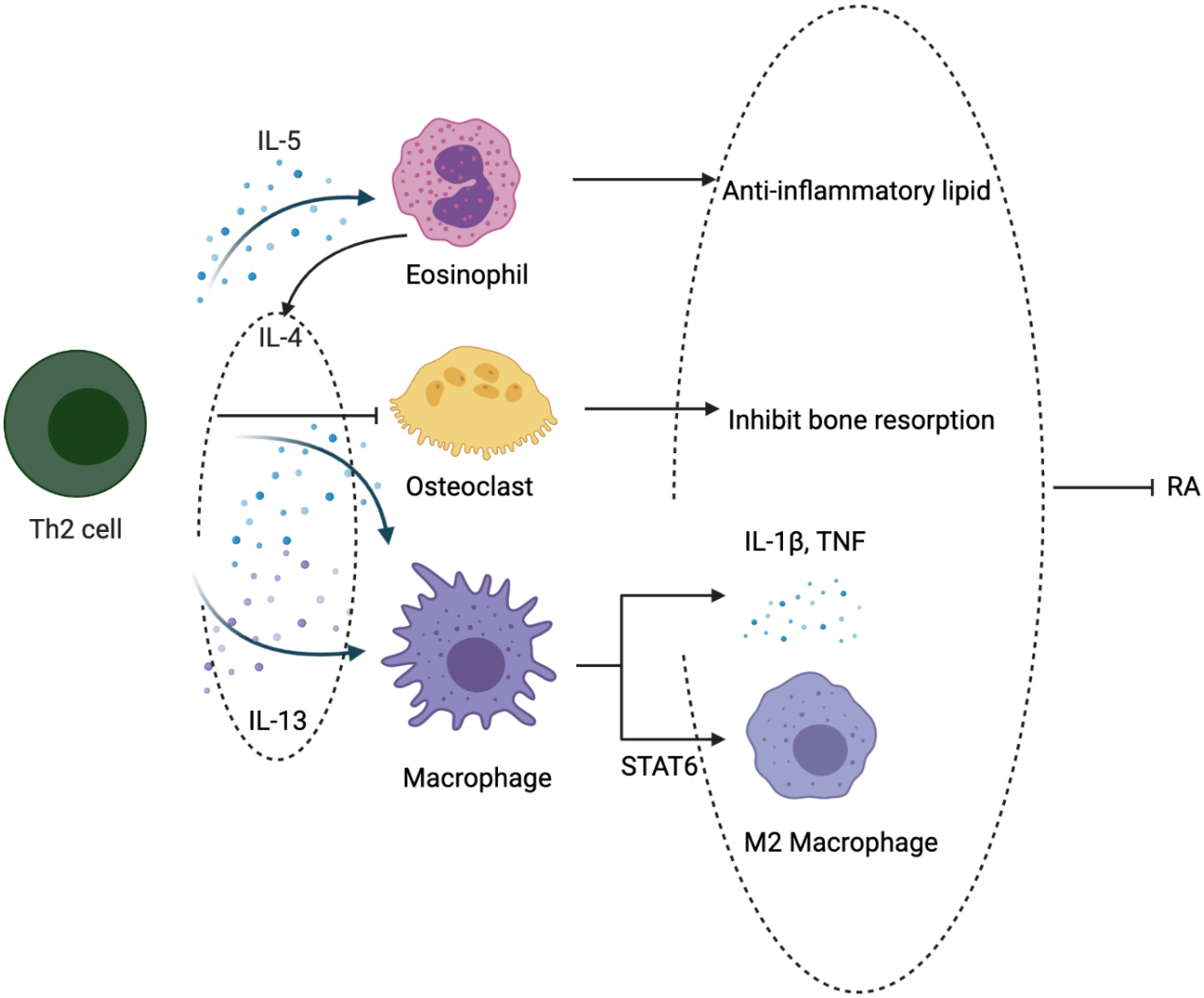

Fig. 4

Involvement of T helper 2 (Th2) cells in the immune regulation of rheumatoid arthritis (RA). Interleukin (IL)-5 is able to differentiate and mobilize eosinophils from the bone marrow. IL-4 also shows an inhibitory effect on bone resorption by affecting the activity and survival of osteoclasts. Furthermore, IL-4 and IL-13 share the same receptors, and both are capable of activating the signal transduction and activator of transcription 6 (STAT6) signalling pathway. Strong activation of the STAT6 signalling pathway was found in IL-4- and IL-13-induced haematopoietic cells, inducing a shift in macrophage polarization toward an anti-inflammatory 'M2-like' phenotype, which is responsible for the suppression of arthritis. In addition, IL-4 and IL-13 have direct anti-inflammatory effects in the synovium of RA, where they reduce the production of IL-1β and tumour necrosis factor (TNF) by synovial macrophages, as well as their expression of CD16 and CD64.

In the same study, IL-22 was found to promote osteoclastogenesis, an effect that may be associated with a reduction in severe arthritis in IL-22-deficient mice. However, another study has shown that IL-22 reduces the severity of collagen-induced arthritis (CIA) through a mechanism associated with elevated IL-10 levels.[120] These findings suggest that IL-22 exerts a dual function in inflammatory arthritis, i.e. protective or pathogenic, depending on the stage of disease progression. Thus, Th17 cells and the cytokines they secrete play a very important role in the immune regulation of RA (Figure 5).

Although RA is typically considered a disease mediated by type 1 Th cells, increasing attention has been focused on Th17 cells and their production of IL-17A, IL-17F, IL-21, IL-22, and TNF-α.[121] Tregs detected in the tissues of patients with RA appear to have limited function.[122] This imbalance between Th17 and Tregs may also be caused by localized TNF-α, as it blocks the activity of Tregs.[123] Another pathogenic pathway includes antigen-nonspecific T cell contact-mediated activation of macrophages and fibroblasts, acting through interactions between cluster of differentiation 40 (CD40) and CD40 ligands (CD40L), CD200 and CD200L, and intracellular adhesion molecule 1 and leucocyte function-associated antigen 1.[124] Ye et al[125] recently found that casein kinase II is an important regulator of the Th1 and Th17 cell axes and can aggravate the development of RA.[125]

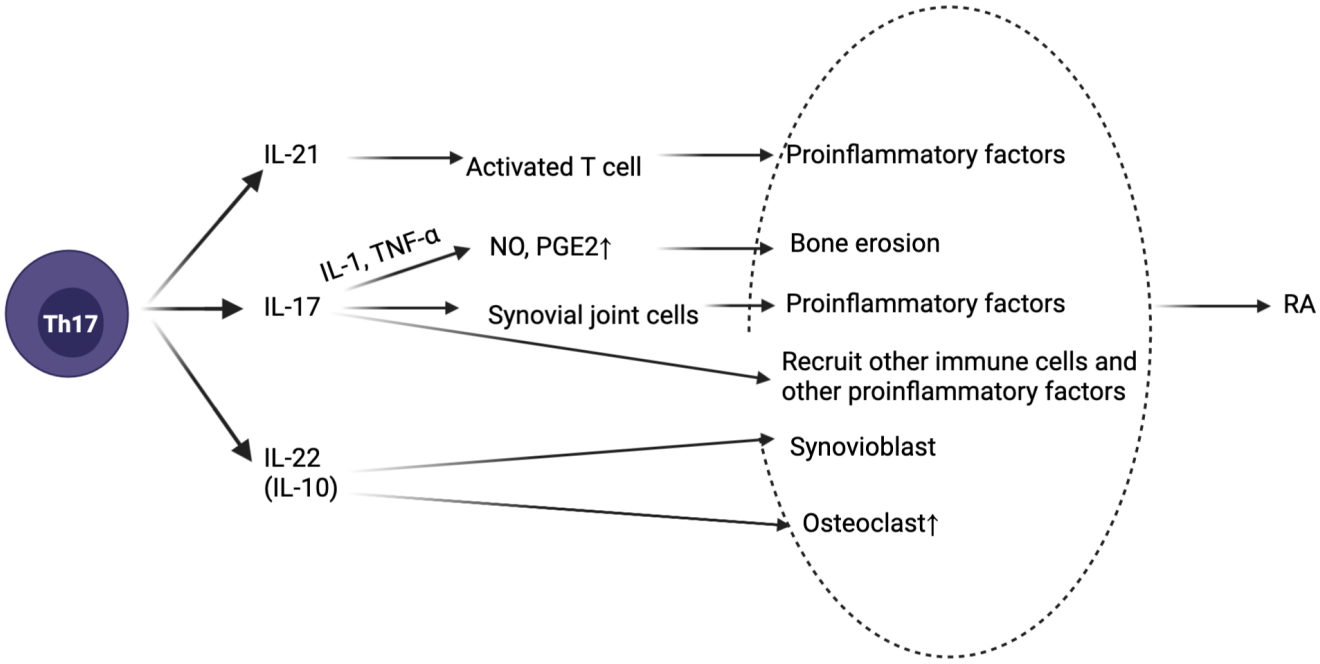

Fig. 5

Involvement of T helper 17 (Th17) cells in the immune regulation of rheumatoid arthritis (RA). Interleukin (IL)-21 induces T cell activation and promotes secretion of pro-inflammatory cytokines in RA. IL-17A has synergistic effects with IL-1 and tumour necrosis factor-α (TNF-α) in upregulating nitric oxide (NO) and prostaglandin E2 (PGE2) production, leading to bone erosion. IL-22 was found to promote osteoclastogenesis, however another study has shown that IL-22 reduces the severity of collagen-induced arthritis by a mechanism associated with elevated IL-10 levels.[120]

Tfh cells are involved in the immune regulation of RA. Tfh cells play a critical role in the formation of lymphatic follicle-generating centres (GCs),[126,127] which are important for inducing B cell proliferation and differentiation, leading to the production of high-affinity antibodies. Increasing evidence suggests an important role for Tfh cells in the pathogenesis of RA.[128,129] For example, in the regulation of humoral immunity Tfh cells can play the opposite role: Tfh cells promote the proliferation and differentiation of B cells and produce high-affinity antibodies, such as anti-cyclic citrullinated peptide (CCP), to mediate cartilage and bone destruction in RA patients.[130-132] Tfh cells secrete IL-21 and express various immunomodulatory molecules, such as T cell inducible costimulator (ICOS), CD40L, signal transduction lymphocyte activator adaptor protein (SAP), and programmed cell death protein-1 (PD-1).[133] Bcl-6 is a transcription factor that is required for Tfh cell differentiation, while IL-21 or IL-6 induces the expression of Bcl-6.[59] Tfh cells produce IL-21, which is essential for B cell stimulation by the expression of C-X-C chemokine receptor 5 (CXCR5) and coexpression with PD-1 and/or ICOS.[134,135] In CIA models, CXCR5 is thought to be important for the induction of inflammatory autoimmune arthritis because CXCR5-deficient mice and mice with selective deletion of CXCR5 on T cells are resistant to CIA.[136]

RA is characterized by chronic and sustained T cell activation in the joints, leading to joint destruction and disability. One study identified increased PD-1 expression in human RA synovial tissue and RA synovial fluid, and PD-1 inhibited T cell proliferation and cytokine production. Therefore, the PD-1/programmed death-ligand 1 (PD-L1) pathway is thought to be a protective factor in RA.[137] In addition, negative costimulation of the PD-L1/PD-1 pathway is important for maintaining peripheral tolerance by inhibiting T cell activation.[138,139] IL-21 affects local T cell activation and proliferation but also promotes aggressive migration, invasion, and metalloproteinase secretion by FLSs.[140,141] Neutralization of IL-21 and IL-15 inhibits their proinflammatory cytokine production in RA synovial cell culture.[142] In addition, high levels of serum soluble protein were detected in patients with RA.[143] One study found that the CD40/CD40L interaction is critical for T cell help in B cell activation and humoral response.[2] Tfh cells may also produce IL-4, which is important for the conversion of immunoglobulin classes in B cells.[144]

Th9 cells are involved in the pathogenesis of RA. Studies have shown that IL-9, the main expression product of Th9 cells, is significantly increased in the serum of RA patients.[145] High levels of IL-9 were also detected in the sera of first-degree relatives of patients with RA or asymptomatic RA-associated autoimmunity.[146,147] IL-9 has been reported to be significantly overexpressed in synovial tissue in RA patients and is associated with the degree of tissue inflammation, and the expression of IL-9 and IL-9R has been shown to be directly related to the degree of inflammatory infiltration and lymphoid tissue in RA

patients.[148] Citrullinated arthritogenic aggrecan peptide has been recognized as a biomarker of RA and identified in the peripheral blood of RA patients.[149] It is considered to be candidate autoantigen of RA and plays a role in the buffer of synovial joints.[149,150] In RA patients, citrullinated arthritogenic aggrecan peptide led to notable expansion of Th9 cells, and these results suggest an association between the presence of autoreactive Th9 cells and the occurrence of synovitis and citrullination processes.[148]

Th22 cells are involved in the pathogenesis of RA. The levels of Th22 cells, Th17 cells, and IL-22 in RA patients were significantly higher than those in healthy controls, and the number of Th22 cells was positively correlated with the level of IL-22.[151] Recent studies have found that Th22 cells promote osteoclast differentiation by producing IL-22 and play an important role in bone destruction in RA patients.[152,153] In addition, IL-22 induces osteoclast formation through the p38 mitogen-activated protein kinase (MAPK)/nuclear factor-κB (NF-κB) and JAK2/STAT3 signalling pathways in synovial fibroblasts.[152] High levels of IL-22 in synovial tissue induce the proliferation of synovial fibroblasts and the production of chemokines to enhance the inflammatory response of synovial tissue.[119] In addition, Th22 cells migrate to synovial tissue, which may be associated with high expression of C-C chemokine ligand 28 (CCL28) in RA patients.[152] The present study supports the hypothesis that Th22/IL-22 plays a pathogenic role in the pathogenesis of RA, although this mechanism requires further investigation.[153] Blocking IL-22 could be a new and effective treatment for this disease.

Immunomodulation of T helper cells in RA therapy

Induction of immunomodulatory and inflammatory resolution pathways is a valuable alternative approach for addressing inflammation in RA. Disease flares frequently occur when patients with RA reduce their use of antirheumatic therapies, and restoration of immunomodulatory pathways that are dysfunctional in established disease may be particularly important for preventing disease flares.[154] Although this approach does not necessarily reduce disease more than targeting proinflammatory mediators, the importance of this intervention may lie in its ability to restore immune homeostasis and make long-term remission possible. As with proinflammatory pathways, individual anti-inflammatory mediators may play differential roles in distinct forms of inflammatory arthritis. For example, at present, topatinib, which is aimed at inhibiting JAK1 and JAK3, has proved to be effective in the treatment of RA.[155] IL-27 may have a more substantial anti-inflammatory effect in RA than in spondyloarthritis because it controls adaptive immune responses, such as lymphoid follicle formation, whereas the cluster of cytokines associated with the Th2 cell response (IL-4, IL-13, and IL-5) may have a role in spondyloarthritis by shifting the balance of Th17 cell- and innate lymphoid cell (ILC)3-driven responses to Th2 cell- and ILC2-driven responses, which play a protective role in spondyloarthritis.[78] In this context, it is important that immunomodulatory cytokines act synergistically with each other. This synergy may provide an opportunity to enhance any effect by targeting more than one of these mediators at a time. In particular, IL-4, IL-13, and IL-5 act synergistically to convey the anti-inflammatory effects of a cellular network composed of ILC2, Th2 cells, eosinophils, and M2 macrophages.[78]

The spectrum of anti-inflammatory cytokines present in RA patients indicates a regulatory function of the type 2 immune response in RA. Cytokines such as IL-4, IL-5, IL-9, IL-13, and IL-33 are involved in triggering diseases such as asthma and atopic dermatitis in susceptible individuals; however, this type of immune response is not only proinflammatory but also exerts a strong intrinsic regulatory effect. Alternatively, helminth infections can activate immunomodulatory type 2 immune responses through the release of immunomodulatory peptides. For example, helminth-derived products (e.g. excretory-secretory protein 62 (ES-62)) and synthetic ES-62 small molecule analogues are highly effective in suppressing experimental arthritis.[156-159] The protective effects of these peptides are mediated by stimulating a type 2 immune response that results in downregulation of Th17 cells, upregulation of IL-10-stimulated B cells, and termination of joint inflammation. Selection of other anti-inflammatory pathways may result from direct regulation of macrophage function and polarization. The anti-inflammatory effects of various immune cell lines, including Tregs and M2 macrophages, are mediated through the release of IL-10; however, IL-10 supplementation alone does not appear to be sufficient to compensate for the effects of proinflammatory cytokines produced by macrophages and other immune cells.[160] Thus, reprogramming macrophages from a proinflammatory M1 phenotype to a regulatory M2 phenotype is critical to ensure adequate, long-term local production of anti-inflammatory effector cytokines in tissues.[161]

There are many theoretical bases for drug therapies targeting regulatory Th cells and the cytokines they produce, such as those targeting MMPs to prevent tissue destruction in RA. Th17 cells are known to induce the production of MMPs, such as MMP-1 and MMP-3, in RA patients, in addition to secreting proinflammatory cytokines.[162] MMP causes cartilage destruction and leads to disease progression. Th17 cells also downregulate the production of tissue inhibitors of matrix metalloproteinases (TIMPs), such as TIMP-1.[163] Therefore, therapies targeting regulation of the MMP/TIMP ratio may be a useful strategy for reducing the severity of RA. Since then, clinical studies have shown that anti-IL-17 can effectively treat RA without increasing the risk of any or serious adverse events.[164] In addition, therapeutic strategies targeting cytokines and regulating the levels of Th cell subsets currently hold great promise, such as exogenous IL-2 to regulate the balance among Th1, Th17, and Treg cells in RA patients by promoting the

development of Treg cells. Therefore, recombinant IL-2 in combination with various biological agents may be an innovative therapy for RA. In addition, IL-18 is known to play a crucial role in the development of Th1 cells, and IL-18 deficiency reduces the incidence and severity of RA.[165] IL-15 has osteolytic properties and induces TNF-α production.[12] Therefore, IL-15- and IL-18-blocking antibodies can also be used to treat RA. Inhibition of Th17 cell-mediated responses by IL-25 has been observed in mouse models and human experiments, suggesting an anti-inflammatory role for IL-25 in RA.[111] Therefore, treatment targeting IL-25 production may also be a potential approach for improving RA. Exogenous IL-27 is known to modulate IL-17-mediated inflammatory responses in RA.[166] In addition, IFN-γ also leads to IL-27 upregulation in rat synovial-like fibroblasts, suggesting that IFN-c and IL-27 interact to regulate the inflammatory microenvironment to prevent disease progression.[166] Thus, IL-27 may also be a potential therapeutic target for RA treatment. However, the effect of targeting IL-27 may depend on the stage of disease progression. Currently, the modular cumulative scoring approach is also being used to find drug targets for RA.[167] Therefore, given the regulatory role of various Th cells and cytokines in RA, development of the abovementioned innovative therapeutic strategies will help to overcome the limitations of existing RA treatment regimens.

In conclusion, the pathogenesis of RA involves multifaceted immune regulation, and Th cell subsets such as Th1, Th2, Treg, Th17, and Tfh cells and their secreted cytokines are involved in immune regulation during the course of RA, playing a role in promoting inflammation or immune protection. In addition, there are many immunomodulatory agents that promote or inhibit the immunomodulatory role of Th cells in RA to alleviate the progression of RA. These results will help us to explore the aetiology and treatment of RA in subsequent research.

References

1. **McInnes IB**, **Schett G**. The pathogenesis of rheumatoid arthritis. *N Engl J Med*. 2011;365(23):2205–2219.
2. **Smolen JS**, **Steiner G**. Therapeutic strategies for rheumatoid arthritis. *Nat Rev Drug Discov*. 2003;2(6):473–488.
3. **Smolen JS**, **Aletaha D**, **Koeller M**, **Weisman MH**, **Emery P**. New therapies for treatment of rheumatoid arthritis. *Lancet*. 2007;370(9602):1861–1874.
4. **Rao DA**, **Gurish MF**, **Marshall JL**, **et al**. Pathologically expanded peripheral T helper cell subset drives B cells in rheumatoid arthritis. *Nature*. 2017;542(7639):110–114.
5. **Saravia J**, **Chapman NM**, **Chi H**. Helper T cell differentiation. *Cell Mol Immunol*. 2019;16(7):634–643.
6. **Zhu J**, **Yamane H**, **Paul WE**. Differentiation of effector CD4 T cell populations (*). *Annu Rev Immunol*. 2010;28:445–489.
7. **Wellcome Trust Case Control Consortium**. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature*. 2007;447(7145):661–678.
8. **Ji M**, **Ryu HJ**, **Hong JH**. Signalling and putative therapeutic molecules on the regulation of synoviocyte signalling in rheumatoid arthritis. *Bone Joint Res*. 2021;10(4):285–297.
9. **Schett G**, **Elewaut D**, **McInnes IB**, **Dayer J-M**, **Neurath MF**. How cytokine networks fuel inflammation: Toward a cytokine-based disease taxonomy. *Nat Med*. 2013;19(7):822–824.
10. **Szekanecz Z**, **Pakozdi A**, **Szentpetery A**, **Besenyei T**, **Koch AE**. Chemokines and angiogenesis in rheumatoid arthritis. *Front Biosci (Elite Ed)*. 2009;1(1):44–51.
11. **Polzer K**, **Baeten D**, **Soleiman A**, **et al**. Tumour necrosis factor blockade increases lymphangiogenesis in murine and human arthritic joints. *Ann Rheum Dis*. 2008;67(11):1610–1616.
12. **McInnes IB**, **Schett G**. Cytokines in the pathogenesis of rheumatoid arthritis. *Nat Rev Immunol*. 2007;7(6):429–442.
13. **Marzaioli V**, **Canavan M**, **Floudas A**, **et al**. CD209/CD14$^+$ dendritic cells characterization in rheumatoid and psoriatic arthritis patients: activation, synovial infiltration, and therapeutic targeting. *Front Immunol*. 2021;12:722349.
14. **Cascão R**, **Rosário HS**, **Souto-Carneiro MM**, **Fonseca JE**. Neutrophils in rheumatoid arthritis: More than simple final effectors. *Autoimmun Rev*. 2010;9(8):531–535.
15. **Hueber AJ**, **Asquith DL**, **Miller AM**, **et al**. Mast cells express IL-17A in rheumatoid arthritis synovium. *J Immunol*. 2010;184(7):3336–3340.
16. **Haringman JJ**, **Gerlag DM**, **Zwinderman AH**, **et al**. Synovial tissue macrophages: a sensitive biomarker for response to treatment in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2005;64(6):834–838.
17. **Boutet M-A**, **Courties G**, **Nerviani A**, **et al**. Novel insights into macrophage diversity in rheumatoid arthritis synovium. *Autoimmun Rev*. 2021;20(3):102758.
18. **Kurowska-Stolarska M**, **Alivernini S**. Synovial tissue macrophages: friend or foe? *RMD Open*. 2017;3(2):e000527.
19. **Chen Z**, **Bozec A**, **Ramming A**, **Schett G**. Anti-inflammatory and immune-regulatory cytokines in rheumatoid arthritis. *Nat Rev Rheumatol*. 2019;15(1):9–17.
20. **Slowikowski K**, **Nguyen HN**, **Noss EH**, **et al**. CUX1 and IκBζ (NFKBIZ) mediate the synergistic inflammatory response to TNF and IL-17A in stromal fibroblasts. *Proc Natl Acad Sci U S A*. 2020;117(10):5532–5541.
21. **Rhee DK**, **Marcelino J**, **Baker M**, **et al**. The secreted glycoprotein lubricin protects cartilage surfaces and inhibits synovial cell overgrowth. *J Clin Invest*. 2005;115(3):622–631.
22. **Lou A**, **Wang L**, **Lai W**, **et al**. Advanced oxidation protein products induce inflammatory responses and invasive behaviour in fibroblast-like synoviocytes via the RAGE-NF-κB pathway. *Bone Joint Res*. 2021;10(4):259–268.
23. **Sabeh F**, **Fox D**, **Weiss SJ**. Membrane-type I matrix metalloproteinase-dependent regulation of rheumatoid arthritis synoviocyte function. *J Immunol*. 2010;184(11):6396–6406.
24. **Yang J**, **Zhou Y**, **Liang X**, **Jing B**, **Zhao Z**. MicroRNA-486 promotes a more catabolic phenotype in chondrocyte-like cells by targeting SIRT6: possible involvement in cartilage degradation in osteoarthritis. *Bone Joint Res*. 2021;10(7):459–466.
25. **Duan M**, **Wang Q**, **Liu Y**, **Xie J**. The role of TGF-*β2* in cartilage development and diseases. *Bone Joint Res*. 2021;10(8):474–487.
26. **Zhang H**, **Li J**, **Xiang X**, **et al**. Tert-butylhydroquinone attenuates osteoarthritis by protecting chondrocytes and inhibiting macrophage polarization. *Bone Joint Res*. 2021;10(11):704–713.
27. **Visser H**, **le Cessie S**, **Vos K**, **Breedveld FC**, **Hazes JMW**. How to diagnose rheumatoid arthritis early: a prediction model for persistent (erosive) arthritis. *Arthritis Rheum*. 2002;46(2):357–365.
28. **van der Heijde DM**. Joint erosions and patients with early rheumatoid arthritis. *Br J Rheumatol*. 1995;34 Suppl 2:74–78.
29. **Jimenez-Boj E**, **Redlich K**, **Türk B**, **et al**. Interaction between synovial inflammatory tissue and bone marrow in rheumatoid arthritis. *J Immunol*. 2005;175(4):2579–2588.
30. **Zhu J**, **Paul WE**. CD4 T cells: fates, functions, and faults. *Blood*. 2008;112(5):1557–1569.
31. **Zhu J**. T helper cell differentiation, heterogeneity, and plasticity. *Cold Spring Harb Perspect Biol*. 2018;10(10):a030338.
32. **Mosmann TR**, **Coffman RL**. TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties. *Annu Rev Immunol*. 1989;7:145–173.
33. **Paul WE**, **Seder RA**. Lymphocyte responses and cytokines. *Cell*. 1994;76(2):241–251.
34. **Le Gros G**, **Ben-Sasson SZ**, **Seder R**, **Finkelman FD**, **Paul WE**. Generation of interleukin 4 (IL-4)-producing cells in vivo and in vitro: IL-2 and IL-4 are required for in vitro generation of IL-4-producing cells. *J Exp Med*. 1990;172(3):921–929.
35. **Swain SL**, **Weinberg AD**, **English M**, **Huston G**. IL-4 directs the development of th2-like helper effectors. *J Immunol*. 1990;145(11):3796–3806.
36. **Sakaguchi S**, **Sakaguchi N**, **Asano M**, **Itoh M**, **Toda M**. Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. *J Immunol*. 1995;155(3):1151–1164.
37. **Park H**, **Li Z**, **Yang XO**, **et al**. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. *Nat Immunol*. 2005;6(11):1133–1141.

38. **Mangan PR**, **Harrington LE**, **O'Quinn DB**, **et al**. Transforming growth factor-beta induces development of the T(H)17 lineage. *Nature*. 2006;441(7090):231–234.
39. **Kim CH**, **Lim HW**, **Kim JR**, **Rott L**, **Hillsamer P**, **Butcher EC**. Unique gene expression program of human germinal center T helper cells. *Blood*. 2004;104(7):1952–1960.
40. **Schmitt E**, **Klein M**, **Bopp T**. Th9 cells, new players in adaptive immunity. *Trends Immunol*. 2014;35(2):61–68.
41. **Trifari S**, **Kaplan CD**, **Tran EH**, **Crellin NK**, **Spits H**. Identification of a human helper T cell population that has abundant production of interleukin 22 and is distinct from T(H)-17, T(H)1 and T(H)2 cells. *Nat Immunol*. 2009;10(8):864–871.
42. **Hossein-Khannazer N**, **Zian Z**, **Bakkach J**, **et al**. Features and roles of T helper 22 cells in immunological diseases and malignancies. *Scand J Immunol*. 2021;93(5):e13030.
43. **Isomäki P**, **Luukkainen R**, **Lassila O**, **Toivanen P**, **Punnonen J**. Synovial fluid T cells from patients with rheumatoid arthritis are refractory to the T helper type 2 differentiation-inducing effects of interleukin-4. *Immunology*. 1999;96(3):358–364.
44. **van der Graaff WL**, **Prins AP**, **Niers TM**, **Dijkmans BA**, **van Lier RA**. Quantitation of interferon gamma- and interleukin-4-producing T cells in synovial fluid and peripheral blood of arthritis patients. *Rheumatology (Oxford)*. 1999;38(3):214–220.
45. **Berner B**, **Akça D**, **Jung T**, **Muller GA**, **Reuss-Borst MA**. Analysis of th1 and th2 cytokines expressing CD4+ and CD8+ T cells in rheumatoid arthritis by flow cytometry. *J Rheumatol*. 2000;27(5):1128–1135.
46. **Zwerina J**, **Hayer S**, **Tohidast-Akrad M**, **et al**. Single and combined inhibition of tumor necrosis factor, interleukin-1, and RANKL pathways in tumor necrosis factor-induced arthritis: effects on synovial inflammation, bone erosion, and cartilage destruction. *Arthritis Rheum*. 2004;50(1):277–290.
47. **Pandya JM**, **Lundell A-C**, **Hallström M**, **Andersson K**, **Nordström I**, **Rudin A**. Circulating T helper and T regulatory subsets in untreated early rheumatoid arthritis and healthy control subjects. *J Leukoc Biol*. 2016;100(4):823–833.
48. **Dinarello CA**. IL-18: A TH1-inducing, proinflammatory cytokine and new member of the IL-1 family. *J Allergy Clin Immunol*. 1999;103(1 Pt 1):11–24.
49. **Shi M**, **Lin TH**, **Appell KC**, **Berg LJ**. Janus-kinase-3-dependent signals induce chromatin remodeling at the Ifng locus during T helper 1 cell differentiation. *Immunity*. 2008;28(6):763–773.
50. **Abbas AK**, **Trotta E**, **R Simeonov D**, **Marson A**, **Bluestone JA**. Revisiting IL-2: Biology and therapeutic prospects. *Sci Immunol*. 2018;3(25):eaat1482.
51. **Boyman O**, **Sprent J**. The role of interleukin-2 during homeostasis and activation of the immune system. *Nat Rev Immunol*. 2012;12(3):180–190.
52. **Sadlack B**, **Merz H**, **Schorle H**, **Schimpl A**, **Feller AC**, **Horak I**. Ulcerative colitis-like disease in mice with a disrupted interleukin-2 gene. *Cell*. 1993;75(2):253–261.
53. **Laurence A**, **Tato CM**, **Davidson TS**, **et al**. Interleukin-2 signaling via STAT5 constrains T helper 17 cell generation. *Immunity*. 2007;26(3):371–381.
54. **Zhang S-X**, **Ma X-W**, **Li Y-F**, **et al**. The proportion of regulatory T cells in patients with systemic lupus erythematosus: a meta-analysis. *J Immunol Res*. 2018;2018:7103219.
55. **Sage PT**, **Ron-Harel N**, **Juneja VR**, **et al**. Suppression by T_{FR} cells leads to durable and selective inhibition of B cell effector function. *Nat Immunol*. 2016;17(12):1436–1446.
56. **Yu M**, **Cavero V**, **Lu Q**, **Li H**. Follicular helper T cells in rheumatoid arthritis. *Clin Rheumatol*. 2015;34(9):1489–1493.
57. **Chu Y**, **Wang F**, **Zhou M**, **Chen L**, **Lu Y**. A preliminary study on the characterization of follicular helper T (Tfh) cells in rheumatoid arthritis synovium. *Acta Histochem*. 2014;116(3):539–543.
58. **Nakayama T**, **Yoshimura M**, **Higashioka K**, **et al**. Type 1 helper T cells generate CXCL9/10-producing T-bet$^+$ effector B cells potentially involved in the pathogenesis of rheumatoid arthritis. *Cell Immunol*. 2021;360:104263.
59. **Nurieva RI**, **Chung Y**, **Martinez GJ**, **et al**. Bcl6 mediates the development of T follicular helper cells. *Science*. 2009;325(5943):1001–1005.
60. **Spolski R**, **Li P**, **Leonard WJ**. Biology and regulation of IL-2: from molecular mechanisms to human therapy. *Nat Rev Immunol*. 2018;18(10):648–659.
61. **Choi YS**, **Kageyama R**, **Eto D**, **et al**. ICOS receptor instructs T follicular helper cell versus effector cell differentiation via induction of the transcriptional repressor Bcl6. *Immunity*. 2011;34(6):932–946.
62. **Johnston RJ**, **Choi YS**, **Diamond JA**, **Yang JA**, **Crotty S**. STAT5 is a potent negative regulator of TFH cell differentiation. *J Exp Med*. 2012;209(2):243–250.
63. **Grivennikov SI**, **Tumanov AV**, **Liepinsh DJ**, **et al**. Distinct and nonredundant in vivo functions of TNF produced by t cells and macrophages/neutrophils: protective and deleterious effects. *Immunity*. 2005;22(1):93–104.
64. **Wehr P**, **Purvis H**, **Law S-C**, **Thomas R**. Dendritic cells, T cells and their interaction in rheumatoid arthritis. *Clin Exp Immunol*. 2019;196(1):12–27.
65. **Li P**, **Schwarz EM**, **O'Keefe RJ**, **Ma L**, **Boyce BF**, **Xing L**. RANK signaling is not required for TNFalpha-mediated increase in CD11(hi) osteoclast precursors but is essential for mature osteoclast formation in TNFalpha-mediated inflammatory arthritis. *J Bone Miner Res*. 2004;19(2):207–213.
66. **Gilbert L**, **He X**, **Farmer P**, **et al**. Inhibition of osteoblast differentiation by tumor necrosis factor-alpha. *Endocrinology*. 2000;141(11):3956–3964.
67. **McInnes IB**, **Leung BP**, **Sturrock RD**, **Field M**, **Liew FY**. Interleukin-15 mediates T cell-dependent regulation of tumor necrosis factor-alpha production in rheumatoid arthritis. *Nat Med*. 1997;3(2):189–195.
68. **Hameister R**, **Lohmann CH**, **Dheen ST**, **Singh G**, **Kaur C**. The effect of TNF-α on osteoblasts in metal wear-induced periprosthetic bone loss. *Bone Joint Res*. 2020;9(11):827–839.
69. **DeKruyff RH**, **Fang Y**, **Wolf SF**, **Umetsu DT**. IL-12 inhibits IL-4 synthesis in keyhole limpet hemocyanin-primed CD4+ T cells through an effect on antigen-presenting cells. *J Immunol*. 1995;154(6):2578–2587.
70. **te Velde AA**, **Huijbens RJ**, **Heije K**, **de Vries JE**, **Figdor CG**. Interleukin-4 (IL-4) inhibits secretion of IL-1 beta, tumor necrosis factor alpha, and IL-6 by human monocytes. *Blood*. 1990;76(7):1392–1397.
71. **Hart PH**, **Vitti GF**, **Burgess DR**, **Whitty GA**, **Piccoli DS**, **Hamilton JA**. Potential antiinflammatory effects of interleukin 4: suppression of human monocyte tumor necrosis factor alpha, interleukin 1, and prostaglandin E2. *Proc Natl Acad Sci U S A*. 1989;86(10):3803–3807.
72. **Miossec P**, **Chomarat P**, **Dechanet J**, **et al**. Interleukin-4 inhibits bone resorption through an effect on osteoclasts and proinflammatory cytokines in an ex vivo model of bone resorption in rheumatoid arthritis. *Arthritis Rheum*. 1994;37(12):1715–1722.
73. **Kaplan MH**, **Schindler U**, **Smiley ST**, **Grusby MJ**. Stat6 is required for mediating responses to IL-4 and for development of Th2 cells. *Immunity*. 1996;4(3):313–319.
74. **Raza K**, **Falciani F**, **Curnow SJ**, **et al**. Early rheumatoid arthritis is characterized by a distinct and transient synovial fluid cytokine profile of T cell and stromal cell origin. *Arthritis Res Ther*. 2005;7(4):R784-95.
75. **Bessis N**, **Chiocchia G**, **Kollias G**, **et al**. Modulation of proinflammatory cytokine production in tumour necrosis factor-alpha (TNF-alpha)-transgenic mice by treatment with cells engineered to secrete IL-4, IL-10 or IL-13. *Clin Exp Immunol*. 1998;111(2):391–396.
76. **Bessis N**, **Boissier MC**, **Ferrara P**, **Blankenstein T**, **Fradelizi D**, **Fournier C**. Attenuation of collagen-induced arthritis in mice by treatment with vector cells engineered to secrete interleukin-13. *Eur J Immunol*. 1996;26(10):2399–2403.
77. **Yamada A**, **Takami M**, **Kawawa T**, **et al**. Interleukin-4 inhibition of osteoclast differentiation is stronger than that of interleukin-13 and they are equivalent for induction of osteoprotegerin production from osteoblasts. *Immunology*. 2007;120(4):573–579.
78. **Chen Z**, **Andreev D**, **Oeser K**, **et al**. Th2 and eosinophil responses suppress inflammatory arthritis. *Nat Commun*. 2016;7:11596.
79. **Hart PH**, **Ahern MJ**, **Smith MD**, **Finlay-Jones JJ**. Regulatory effects of IL-13 on synovial fluid macrophages and blood monocytes from patients with inflammatory arthritis. *Clin Exp Immunol*. 1995;99(3):331–337.
80. **Isomäki P**, **Luukkainen R**, **Toivanen P**, **Punnonen J**. The presence of interleukin-13 in rheumatoid synovium and its antiinflammatory effects on synovial fluid macrophages from patients with rheumatoid arthritis. *Arthritis Rheum*. 1996;39(10):1693–1702.
81. **Iwaszko M**, **Biały S**, **Bogunia-Kubik K**. Significance of interleukin (IL)-4 and IL-13 in inflammatory arthritis. *Cells*. 2021;10(11):3000.
82. **Collins PD**, **Marleau S**, **Griffiths-Johnson DA**, **Jose PJ**, **Williams TJ**. Cooperation between interleukin-5 and the chemokine eotaxin to induce eosinophil accumulation in vivo. *J Exp Med*. 1995;182(4):1169–1174.
83. **Stolarski B**, **Kurowska-Stolarska M**, **Kewin P**, **Xu D**, **Liew FY**. IL-33 exacerbates eosinophil-mediated airway inflammation. *J Immunol*. 2010;185(6):3472–3480.
84. **Isobe Y**, **Kato T**, **Arita M**. Emerging roles of eosinophils and eosinophil-derived lipid mediators in the resolution of inflammation. *Front Immunol*. 2012;3:270.
85. **Katsikis PD**, **Chu CQ**, **Brennan FM**, **Maini RN**, **Feldmann M**. Immunoregulatory role of interleukin 10 in rheumatoid arthritis. *J Exp Med*. 1994;179(5):1517–1527.
86. **Sakaguchi S**, **Yamaguchi T**, **Nomura T**, **Ono M**. Regulatory T cells and immune tolerance. *Cell*. 2008;133(5):775–787.
87. **Piccirillo CA**, **d'Hennezel E**, **Sgouroudis E**, **Yurchenko E**. CD4+Foxp3+ regulatory T cells in the control of autoimmunity: in vivo veritas. *Curr Opin Immunol*. 2008;20(6):655–662.
88. **Shevach EM**, **Thornton AM**. tTregs, pTregs, and iTregs: similarities and differences. *Immunol Rev*. 2014;259(1):88–102.
89. **Yuan X**, **Cheng G**, **Malek TR**. The importance of regulatory T-cell heterogeneity in maintaining self-tolerance. *Immunol Rev*. 2014;259(1):103–114.

90. **Jiao Z**, **Wang W**, **Jia R**, **et al**. Accumulation of FoxP3-expressing CD4+CD25+ T cells with distinct chemokine receptors in synovial fluid of patients with active rheumatoid arthritis. *Scand J Rheumatol*. 2007;36(6):428–433.
91. **Sempere-Ortells JM**, **Pérez-García V**, **Marín-Alberca G**, **et al**. Quantification and phenotype of regulatory T cells in rheumatoid arthritis according to disease activity score-28. *Autoimmunity*. 2009;42(8):636–645.
92. **Kawashiri S-Y**, **Kawakami A**, **Okada A**, **et al**. CD4+CD25(high)CD127(low/-) Treg cell frequency from peripheral blood correlates with disease activity in patients with rheumatoid arthritis. *J Rheumatol*. 2011;38(12):2517–2521.
93. **van Amelsfort JMR**, **Jacobs KMG**, **Bijlsma JWJ**, **Lafeber F**, **Taams LS**. CD4(+)CD25(+) regulatory T cells in rheumatoid arthritis: differences in the presence, phenotype, and function between peripheral blood and synovial fluid. *Arthritis Rheum*. 2004;50(9):2775–2785.
94. **Han GM**, **O'Neil-Andersen NJ**, **Zurier RB**, **Lawrence DA**. CD4+CD25high T cell numbers are enriched in the peripheral blood of patients with rheumatoid arthritis. *Cell Immunol*. 2008;253(1–2):92–101.
95. **Jiang Q**, **Yang G**, **Liu Q**, **Wang S**, **Cui D**. Function and Role of Regulatory T Cells in Rheumatoid Arthritis. *Front Immunol*. 2021;12:626193.
96. **Manzotti CN**, **Tipping H**, **Perry LCA**, **et al**. Inhibition of human T cell proliferation by CTLA-4 utilizes CD80 and requires CD25+ regulatory T cells. *Eur J Immunol*. 2002;32(10):2888–2896.
97. **Paust S**, **Lu L**, **McCarty N**, **Cantor H**. Engagement of B7 on effector T cells by regulatory T cells prevents autoimmune disease. *Proc Natl Acad Sci U S A*. 2004;101(28):10398–10403.
98. **Flores-Borja F**, **Jury EC**, **Mauri C**, **Ehrenstein MR**. Defects in CTLA-4 are associated with abnormal regulatory T cell function in rheumatoid arthritis. *Proc Natl Acad Sci U S A*. 2008;105(49):19396–19401.
99. **McHugh RS**, **Whitters MJ**, **Piccirillo CA**, **et al**. CD4(+)CD25(+) immunoregulatory T cells: gene expression analysis reveals a functional role for the glucocorticoid-induced TNF receptor. *Immunity*. 2002;16(2):311–323.
100. **Mahmud SA**, **Manlove LS**, **Schmitz HM**, **et al**. Costimulation via the tumor-necrosis factor receptor superfamily couples TCR signal strength to the thymic differentiation of regulatory T cells. *Nat Immunol*. 2014;15(5):473–481.
101. **Tone M**, **Tone Y**, **Adams E**, **et al**. Mouse glucocorticoid-induced tumor necrosis factor receptor ligand is costimulatory for T cells. *Proc Natl Acad Sci U S A*. 2003;100(25):15059–15064.
102. **Shimizu J**, **Yamazaki S**, **Takahashi T**, **Ishida Y**, **Sakaguchi S**. Stimulation of CD25(+)CD4(+) regulatory T cells through GITR breaks immunological self-tolerance. *Nat Immunol*. 2002;3(2):135–142.
103. **Bae E**, **Kim W-J**, **Kang Y-M**, **et al**. Glucocorticoid-induced tumour necrosis factor receptor-related protein-mediated macrophage stimulation may induce cellular adhesion and cytokine expression in rheumatoid arthritis. *Clin Exp Immunol*. 2007;148(3):410–418.
104. **Korn T**, **Bettelli E**, **Oukka M**, **Kuchroo VK**. IL-17 and Th17 cells. *Annu Rev Immunol*. 2009;27:485–517.
105. **Kim J**, **Kang S**, **Kim J**, **Kwon G**, **Koo S**. Elevated levels of T helper 17 cells are associated with disease activity in patients with rheumatoid arthritis. *Ann Lab Med*. 2013;33(1):52–59.
106. **Fossiez F**, **Djossou O**, **Chomarat P**, **et al**. T cell interleukin-17 induces stromal cells to produce proinflammatory and hematopoietic cytokines. *J Exp Med*. 1996;183(6):2593–2603.
107. **Jovanovic DV**, **Di Battista JA**, **Martel-Pelletier J**, **et al**. IL-17 stimulates the production and expression of proinflammatory cytokines, IL-beta and TNF-alpha, by human macrophages. *J Immunol*. 1998;160(7):3513–3521.
108. **Onishi RM**, **Gaffen SL**. Interleukin-17 and its target genes: mechanisms of interleukin-17 function in disease. *Immunology*. 2010;129(3):311–321.
109. **LeGrand A**, **Fermor B**, **Fink C**, **et al**. Interleukin-1, tumor necrosis factor alpha, and interleukin-17 synergistically up-regulate nitric oxide and prostaglandin E2 production in explants of human osteoarthritic knee menisci. *Arthritis Rheum*. 2001;44(9):2078–2083.
110. **Moseley TA**, **Haudenschild DR**, **Rose L**, **Reddi AH**. Interleukin-17 family and IL-17 receptors. *Cytokine Growth Factor Rev*. 2003;14(2):155–174.
111. **Liu D**, **Cao T**, **Wang N**, **et al**. IL-25 attenuates rheumatoid arthritis through suppression of Th17 immune responses in an IL-13-dependent manner. *Sci Rep*. 2016;6:36002.
112. **McGeachy MJ**, **Chen Y**, **Tato CM**, **et al**. The interleukin 23 receptor is essential for the terminal differentiation of interleukin 17-producing effector T helper cells in vivo. *Nat Immunol*. 2009;10(3):314–324.
113. **Croxford AL**, **Mair F**, **Becher B**. IL-23: one cytokine in control of autoimmunity. *Eur J Immunol*. 2012;42(9):2263–2273.
114. **Cua DJ**, **Sherlock J**, **Chen Y**, **et al**. Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. *Nature*. 2003;421(6924):744–748.
115. **Millier MJ**, **Fanning NC**, **Frampton C**, **Stamp LK**, **Hessian PA**. Plasma interleukin-23 and circulating IL-17A+IFNγ+ ex-th17 cells predict opposing outcomes of anti-TNF therapy in rheumatoid arthritis. *Arthritis Res Ther*. 2022;24(1):57.
116. **Xing R**, **Yang L**, **Jin Y**, **et al**. Interleukin-21 induces proliferation and proinflammatory cytokine profile of fibroblast-like synoviocytes of patients with rheumatoid arthritis. *Scand J Immunol*. 2016;83(1):64–71.
117. **Li J**, **Shen W**, **Kong K**, **Liu Z**. Interleukin-21 induces T-cell activation and proinflammatory cytokine secretion in rheumatoid arthritis. *Scand J Immunol*. 2006;64(5):515–522.
118. **Niu X**, **He D**, **Zhang X**, **et al**. IL-21 regulates Th17 cells in rheumatoid arthritis. *Hum Immunol*. 2010;71(4):334–341.
119. **Ikeuchi H**, **Kuroiwa T**, **Hiramatsu N**, **et al**. Expression of interleukin-22 in rheumatoid arthritis: potential role as a proinflammatory cytokine. *Arthritis Rheum*. 2005;52(4):1037–1046.
120. **Sarkar S**, **Zhou X**, **Justa S**, **Bommireddy SR**. Interleukin-22 reduces the severity of collagen-induced arthritis in association with increased levels of interleukin-10. *Arthritis Rheum*. 2013;65(4):960–971.
121. **Genovese MC**, **Van den Bosch F**, **Roberson SA**, **et al**. LY2439821, A humanized anti-interleukin-17 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: A phase I randomized, double-blind, placebo-controlled, proof-of-concept study. *Arthritis Rheum*. 2010;62(4):929–939.
122. **Behrens F**, **Himsel A**, **Rehart S**, **et al**. Imbalance in distribution of functional autologous regulatory T cells in rheumatoid arthritis. *Ann Rheum Dis*. 2007;66(9):1151–1156.
123. **Nadkarni S**, **Mauri C**, **Ehrenstein MR**. Anti-TNF-alpha therapy induces a distinct regulatory T cell population in patients with rheumatoid arthritis via TGF-beta. *J Exp Med*. 2007;204(1):33–39.
124. **McInnes IB**, **Leung BP**, **Liew FY**. Cell-cell interactions in synovitis. Interactions between T lymphocytes and synovial cells. *Arthritis Res*. 2000;2(5):374–378.
125. **Ye H**, **Fu D**, **Fang X**, **et al**. Casein Kinase II exacerbates rheumatoid arthritis via promoting Th1 and Th17 cell inflammatory responses. *Expert Opin Ther Targets*. 2021;25(11):1017–1024.
126. **Chung Y**, **Tanaka S**, **Chu F**, **et al**. Follicular regulatory T cells expressing Foxp3 and Bcl-6 suppress germinal center reactions. *Nat Med*. 2011;17(8):983–988.
127. **Nurieva RI**, **Chung Y**, **Hwang D**, **et al**. Generation of T follicular helper cells is mediated by interleukin-21 but independent of T helper 1, 2, or 17 cell lineages. *Immunity*. 2008;29(1):138–149.
128. **Wang J**, **Shan Y**, **Jiang Z**, **et al**. High frequencies of activated B cells and T follicular helper cells are correlated with disease activity in patients with new-onset rheumatoid arthritis. *Clin Exp Immunol*. 2013;174(2):212–220.
129. **Zhang Y**, **Li Y**, **Lv T-T**, **Yin Z-J**, **Wang X-B**. Elevated circulating Th17 and follicular helper CD4(+) T cells in patients with rheumatoid arthritis. *APMIS*. 2015;123(8):659–666.
130. **Park H-J**, **Kim D-H**, **Lim S-H**, **et al**. Insights into the role of follicular helper T cells in autoimmunity. *Immune Netw*. 2014;14(1):21–29.
131. **Crotty S**. T follicular helper cell biology: a decade of discovery and diseases. *Immunity*. 2019;50(5):1132–1148.
132. **Linterman MA**, **Pierson W**, **Lee SK**, **et al**. Foxp3+ follicular regulatory T cells control the germinal center response. *Nat Med*. 2011;17(8):975–982.
133. **King C**, **Tangye SG**, **Mackay CR**. T follicular helper (TFH) cells in normal and dysregulated immune responses. *Annu Rev Immunol*. 2008;26:741–766.
134. **Bryant VL**, **Ma CS**, **Avery DT**, **et al**. Cytokine-mediated regulation of human B cell differentiation into Ig-secreting cells: predominant role of IL-21 produced by CXCR5+ T follicular helper cells. *J Immunol*. 2007;179(12):8180–8190.
135. **Breitfeld D**, **Ohl L**, **Kremmer E**, **et al**. Follicular B helper T cells express CXC chemokine receptor 5, localize to B cell follicles, and support immunoglobulin production. *J Exp Med*. 2000;192(11):1545–1552.
136. **Moschovakis GL**, **Bubke A**, **Friedrichsen M**, **Falk CS**, **Feederle R**, **Förster R**. T cell specific Cxcr5 deficiency prevents rheumatoid arthritis. *Sci Rep*. 2017;7(1):8933.
137. **Raptopoulou AP**, **Bertsias G**, **Makrygiannakis D**, **et al**. The programmed death 1/programmed death ligand 1 inhibitory pathway is up-regulated in rheumatoid synovium and regulates peripheral T cell responses in human and murine arthritis. *Arthritis Rheum*. 2010;62(7):1870–1880.
138. **Fife BT**, **Pauken KE**. The role of the PD-1 pathway in autoimmunity and peripheral tolerance. *Ann N Y Acad Sci*. 2011;1217:45–59.
139. **Dai S**, **Jia R**, **Zhang X**, **Fang Q**, **Huang L**. The PD-1/PD-Ls pathway and autoimmune diseases. *Cell Immunol*. 2014;290(1):72–79.
140. **Xing R**, **Jin Y**, **Sun L**, **et al**. Interleukin-21 induces migration and invasion of fibroblast-like synoviocytes from patients with rheumatoid arthritis. *Clin Exp Immunol*. 2016;184(2):147–158.

141. **Lu J**, **Wu J**, **Xia X**, **Peng H**, **Wang S**. Follicular helper T cells: potential therapeutic targets in rheumatoid arthritis. *Cell Mol Life Sci*. 2021;78(12):5095–5106.
142. **Andersson AK**, **Feldmann M**, **Brennan FM**. Neutralizing IL-21 and IL-15 inhibits pro-inflammatory cytokine production in rheumatoid arthritis. *Scand J Immunol*. 2008;68(1):103–111.
143. **Schlom J**, **Jochems C**, **Gulley JL**, **Huang J**. The role of soluble CD40L in immunosuppression. *Oncoimmunology*. 2013;2(1):e22546.
144. **Reinhardt RL**, **Liang HE**, **Locksley RM**. Cytokine-secreting follicular T cells shape the antibody repertoire. *Nat Immunol*. 2009;10(4):385–393.
145. **Dantas AT**, **Marques CDL**, **da Rocha Junior LF**, **et al**. Increased serum interleukin-9 levels in rheumatoid arthritis and systemic lupus erythematosus: pathogenic role or just an epiphenomenon? *Dis Markers*. 2015;2015:519638.
146. **Barra L**, **Summers K**, **Bell D**, **Cairns E**. Serum cytokine profile of unaffected first-degree relatives of patients with rheumatoid arthritis. *J Rheumatol*. 2014;41(2):280–285.
147. **Hughes-Austin JM**, **Deane KD**, **Derber LA**, **et al**. Multiple cytokines and chemokines are associated with rheumatoid arthritis-related autoimmunity in first-degree relatives without rheumatoid arthritis: Studies of the Aetiology of Rheumatoid Arthritis (SERA). *Ann Rheum Dis*. 2013;72(6):901–907.
148. **Ciccia F**, **Guggino G**, **Rizzo A**, **et al**. Potential involvement of IL-9 and Th9 cells in the pathogenesis of rheumatoid arthritis. *Rheumatology (Oxford)*. 2015;54(12):2264–2272.
149. **von Delwig A**, **Locke J**, **Robinson JH**, **Ng W-F**. Response of Th17 cells to a citrullinated arthritogenic aggrecan peptide in patients with rheumatoid arthritis. *Arthritis Rheum*. 2010;62(1):143–149.
150. **Glant TT**, **Radacs M**, **Nagyeri G**, **et al**. Proteoglycan-induced arthritis and recombinant human proteoglycan aggrecan G1 domain-induced arthritis in BALB/c mice resembling two subtypes of rheumatoid arthritis. *Arthritis Rheum*. 2011;63(5):1312–1321.
151. **Zhang L**, **Li J-M**, **Liu X-G**, **et al**. Elevated Th22 cells correlated with Th17 cells in patients with rheumatoid arthritis. *J Clin Immunol*. 2011;31(4):606–614.
152. **Miyazaki Y**, **Nakayamada S**, **Kubo S**, **et al**. Th22 cells promote osteoclast differentiation via production of IL-22 in rheumatoid arthritis. *Front Immunol*. 2018;9:2901.
153. **Jiang Q**, **Yang G**, **Xiao F**, **et al**. Role of Th22 cells in the pathogenesis of autoimmune diseases. *Front Immunol*. 2021;12:688066.
154. **Haschka J**, **Englbrecht M**, **Hueber AJ**, **et al**. Relapse rates in patients with rheumatoid arthritis in stable remission tapering or stopping antirheumatic therapy: interim results from the prospective randomised controlled RETRO study. *Ann Rheum Dis*. 2016;75(1):45–51.
155. **Kawalec P**, **Holko P**, **Moćko P**, **Pilc A**. Comparative effectiveness of abatacept, apremilast, secukinumab and ustekinumab treatment of psoriatic arthritis: a systematic review and network meta-analysis. *Rheumatol Int*. 2018;38(2):189–201.
156. **Pineda MA**, **McGrath MA**, **Smith PC**, **et al**. The parasitic helminth product ES-62 suppresses pathogenesis in collagen-induced arthritis by targeting the interleukin-17-producing cellular network at multiple sites. *Arthritis Rheum*. 2012;64(10):3168–3178.
157. **McInnes IB**, **Leung BP**, **Harnett M**, **Gracie JA**, **Liew FY**, **Harnett W**. A novel therapeutic approach targeting articular inflammation using the filarial nematode-derived phosphorylcholine-containing glycoprotein ES-62. *J Immunol*. 2003;171(4):2127–2133.
158. **Harnett MM**, **Kean DE**, **Boitelle A**, **et al**. The phosphorycholine moiety of the filarial nematode immunomodulator ES-62 is responsible for its anti-inflammatory action in arthritis. *Ann Rheum Dis*. 2008;67(4):518–523.
159. **Rodgers DT**, **Pineda MA**, **McGrath MA**, **Al-Riyami L**, **Harnett W**, **Harnett MM**. Protection against collagen-induced arthritis in mice afforded by the parasitic worm product, ES-62, is associated with restoration of the levels of interleukin-10-producing B cells and reduced plasma cell infiltration of the joints. *Immunology*. 2014;141(3):457–466.
160. **van Roon J**, **Wijngaarden S**, **Lafeber F**, **Damen C**, **van de Winkel J**, **Bijlsma JWJ**. Interleukin 10 treatment of patients with rheumatoid arthritis enhances fc gamma receptor expression on monocytes and responsiveness to immune complex stimulation. *J Rheumatol*. 2003;30(4):648–651.
161. **Martinez FO**, **Gordon S**. The M1 and M2 paradigm of macrophage activation: time for reassessment. *F1000Prime Rep*. 2014;6:13.
162. **Schminke B**, **Trautmann S**, **Mai B**, **Miosge N**, **Blaschke S**. Interleukin 17 inhibits progenitor cells in rheumatoid arthritis cartilage. *Eur J Immunol*. 2016;46(2):440–445.
163. **Moran EM**, **Mullan R**, **McCormick J**, **et al**. Human rheumatoid arthritis tissue production of IL-17A drives matrix and cartilage degradation: synergy with tumour necrosis factor-alpha, Oncostatin M and response to biologic therapies. *Arthritis Res Ther*. 2009;11(4):R113.
164. **Kunwar S**, **Dahal K**, **Sharma S**. Anti-IL-17 therapy in treatment of rheumatoid arthritis: a systematic literature review and meta-analysis of randomized controlled trials. *Rheumatol Int*. 2016;36(8):1065–1075.
165. **Joosten LA**, **van De Loo FA**, **Lubberts E**, **et al**. An IFN-gamma-independent proinflammatory role of IL-18 in murine streptococcal cell wall arthritis. *J Immunol*. 2000;165(11):6553–6558.
166. **Rajaiah R**, **Puttabyatappa M**, **Polumuri SK**, **Moudgil KD**. Interleukin-27 and interferon-gamma are involved in regulation of autoimmune arthritis. *J Biol Chem*. 2011;286(4):2817–2825.
167. **Li X**, **Yang Y**, **Sun G**, **et al**. Promising targets and drugs in rheumatoid arthritis: a module-based and cumulatively scoring approach. *Bone Joint Res*. 2020;9(8):501–514.

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