The interleukin-23/interleukin-17 axis and the role of Treg/Th17 cells in rheumatoid arthritis and joint destruction

S AlFadhli*

Abstract

Introduction

Rheumatoid arthritis is caused by a complex mechanism involving synoviocytes, osteoclasts and immune cells that are interconnected via cytokines and other signalling molecules. Effective medical treatment for joint destruction in rheumatoid arthritis is lacking because the molecular mechanisms leading to joint destruction are incompletely understood. However, it is known that cytokine-mediated immunity and perturbations in the balance of effector cells at the disease site play a crucial role in rheumatoid arthritis pathogenesis. Cellular and cytokine inhibitors have been used for treatment purposes. Increasing evidence has revealed the importance of IL-17, an activated T cell-derived inflammatory cytokine, and IL-23 in the pathogenesis of rheumatoid arthritis. The role of IL-17 has been of particular interest, as IL-17 affects the differentiation and activation of pathogenic osteoclasts. Cellularly, the key features of rheumatoid arthritis include disturbance of the Th17/Treg balance and plasticity, deregulated Th17 responses and the reduction or absences of Treg cells. Recent developments in the area of CD4+ T-cell differentiation, together with experimental and preclinical findings on inhibitors of the IL-17 pathway and the use of Treg cell-based therapy, indicate that CD4+ effector cells, TH17 and Treg, could be effective targets for restoring immune tolerance. In this critical review, we summarise the progress in our understanding of the role of IL-23, IL-17 and CD4+ T-cell differentiation into specialised effectors, focusing on Th17 and Treg cells, in the pathogenesis of rheumatoid arthritis.

Conclusion

Pathogenesis of rheumatoid arthritis is slow and complex. Cytokines and cell-mediated immunity are involved in irreversible bone and cartilage destruction. Cytokine levels and the Treg/Th17 balance might be relevant for the diversity of clinical manifestations in rheumatoid arthritis patients and might be critical for the development of improved treatment methods.

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease. In RA, inflammation usually affects multiple peripheral joints, but other tissues and organs are also involved. RA can affect any joint that has a synovial-fluid-filled joint cavity lined by a synovial membrane and regions in which cartilage overlies the bone. Komatsu et al. suggested that the clinical progression of RA involves three phases in the progression from an immune response to bone destruction. These are summarised as follows:

- Initiation phase: An antigen(s) triggers immune responses, and symptoms are not yet observed in the joints.
- Inflammatory phase: This phase begins when inflammatory symptoms, such as swelling, are recognised in the joints and continue until structural damage occurs.
- Bone and cartilage destruction phase: In this phase, structural damage is observed in the bone and cartilage. Disease progression occurs slowly between initiation and the observation of clinical symptoms.

Although the precise mechanisms of RA pathogenesis are still unclear, it is generally well recognised that numerous inflammatory cells, such as T cells, B cells, fibroblast-like synoviocytes, macrophages, monocytes, dendritic cells (DCs) and plasma cells, and the extensive production of pro-inflammatory mediators by these cells, are involved in chronic joint inflammation, as well as progressive cartilage destruction and osteoclast-mediated bone destruction. In simple words, RA is caused by a complex mechanism involving osteoclasts, synoviocytes and immune cells, which communicate via cytokines and other signalling molecules. Herein, we describe the involvement of certain cytokines and cells that play a major role in RA pathogenesis, particularly in osteoelasticity (Figure 1). Several pro-inflammatory cytokines, including tumour necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6 and interferon (IFN)-γ, and the newly recognised cytokines IL-23 and IL-17, have been extensively examined for their role in the disease process in arthritis in terms of their expression, functional activity in synovial tissues and their use as prognostic factors. Some of these cytokines are now targeted in the standard treatment of RA patients, and others, such as IL-23, are being tested as targets.
**Critical review**

IL-23, which is a pro-inflammatory, heterodimeric cytokine, is expressed primarily by macrophages and DCs. Its receptor (IL-23R) is found on memory T cells, natural killer T cells, macrophages, DCs and naïve T cells, upon activation by tumour growth factor (TGF)-β and IL-6.

IL-23 belongs to the IL-12 cytokine family and is composed of two subunits, p19 and p40; the p40 subunit is shared with IL-12. Both IL-12 and IL-23 are involved in the expansion of activated IL-17-producing helper T (Th17) cells (Figure 1). Th17 cells play a key role in RA pathogenesis and produce IL-17A, IL-17F, IL-6, IL-22, TNF-α and granulocyte-macrophage colony-stimulating factor (GM-CSF). IL-12 and IL-23 are expected to play separate roles at different stages of the inflammatory response. IL-12 promotes the initiation of the inflammatory response by inducing the development of Th1 cells, which produce IFN-γ, whereas IL-23 regulates late-stage inflammatory processes and is involved in the expansion of Th17 cells. Recent evidence suggests that IL-23, rather than IL-12, is the crucial factor in the pathogenesis of various immune-mediated disorders. IL-23 expression is important in the inflammatory response not only in RA but also in psoriasis and inflammatory bowel disease. IL-23 is found in the synovial membrane of RA patients, in the skin of psoriasis patients and in the bowel wall of patients with chronic inflammatory bowel disease. Inflammatory macrophages express IL-23R and are activated by IL-23 to produce IL-1, TNF-α and IL-23 itself, which is known as the autocrine loop of IL-23 in macrophages. Moreover, an association of IL-23 and IL-23R polymorphisms, with susceptibility to RA, has been reported. Therefore, IL-23 and its receptor are promising treatment targets for such inflammatory diseases. Ustekinumab, which

---

**Figure 1:** Schematic representation of the effects of TH17, Th1 and Th2 cells producing cytokines on osteoclast formation and function. Role of Th17 cells on bone resorption induced during inflammation of the joint through enhanced osteoclast function. Th17 cells are produced by differentiation of naïve T cells in the presence of TGF-β, IL-6 and IL-1β. IL-23 induces proliferation of TH17 cells. Th17 cells produce IL-17, which induces osteoclast function, and supporting cells such as synovial fibroblasts and osteoblasts, and make them express RANKL. Th17 cells also contribute directly to bone loss by producing RANKL. IL-17 also strongly induces the secretion of TNF-α and IL-1 by synovial macrophages (Φ) and induces osteoclast formation. It also shows the inhibitory effect of Th1 and Th2 cells on osteoclast differentiation through the release of IFN-γ and IL-4, respectively. Treg cells are an immunosuppressive CD4+Th cell subset differentiated from naïve T cells with the help of TGF-β1.

DCs, dendritic cells; GM-CSF, granulocyte-monocyte colony-stimulating factor; IFN-γ, interferon-γ; IL, interleukin; MMPs, matrix metalloproteinases; RANK, receptor activator for NF-kB; RANKL, receptor activator for NF-kB ligand; TGF-β, tumour growth factor beta; Th17, interleukin-17-producing helper T cells; TNF-α, tumour necrosis factor alpha; Treg, T regulatory cells.
inhibits IL-12 and IL-23 by blocking p40, has been shown to be effective at treating cutaneous psoriasis and psoriatic arthritis as well as Crohn’s disease. Treatments that specifically target IL-23 (antibodies specific for p19) are being developed. This critical review discusses the IL-23/IL-17 axis and the role of T regulatory cells (Treg)/Th17 cells in RA and joint destruction.

**Discussion**

**Role of the IL-23p19/IL-17 axis in RA**

IL-23p19 and IL-17 correspond to a new axis that drives immune activation and chronic inflammation through the differentiation and activation of Th17 cells. Both IL-17 and IL-23 were found to be present in the synovial fluid, synovial tissue and serum of patients with RA, whereas they were absent in healthy joints and other types of arthritis such as osteoarthritis. The significant role of IL-17 in RA is highlighted by the current success of clinical trials with neutralizing antibodies specific for IL-17. Blocking IL-17 during the reactivation of antigen-induced arthritis diminishes joint swelling, joint inflammation and bone erosion. This cytokine has diverse immune functions, including activation of synovial fibroblasts to produce IL-6, IL-8 and vascular growth factors, chemotraction of neutrophils, stimulation of the expression of the receptor activator of NF-kB ligand (RANKL) (a factor that is crucial for osteoclastogenesis) and mediation of direct pro-osteoclastogenic effects. In addition, IL-23 plays an important role in RA in animal models. IL-23 gene-targeted mice do not develop clinical signs of arthritis and are resistant to the development of joint and bone pathology. In addition, this resistance correlates with an absence of IL-17-producing CD4+ T cells. Other than regulating the expansion of Th17 cells, IL-23 induces IL-17 production by Th17 cells and TNF-α, IL-6, IL-22, GM-CSF and other novel factors associated with the induction of autoimmune inflammation. The serum and synovial fluid levels of IL-23 are correlated positively with the concentration of IL-17, in addition to that of other cytokines such as TNF-α and IL-1β, indicating that IL-23 is closely linked to the production of other pro-inflammatory and anti-inflammatory cytokines in the course of RA. These findings highlight the importance of the IL-23p19/IL-17 axis as an essential inflammatory mediator in the destructive phases of autoimmune arthritis.

**Th17/RANKL is the bridge between the immune and skeletal systems and leads to bone destruction in RA**

Bone destruction in RA is mainly attributable to the abnormal activation of osteoclasts. Osteoclasts are multinucleated cells of the monocyte/macrophage lineage that degrade bone matrix and dynamically remodel the skeleton. The generation of osteoclasts is physiologically supported by mesenchymal cells such as osteoblasts, which provide essential signals for differentiation of the osteoclast lineage: macrophage colony-stimulating factor, RANKL and costimulatory signals for RANKL. Osteoprotegerin (OPG) is a soluble decoy receptor for RANKL that blocks the pro-osteoclastogenic activity of RANKL. In inflammatory arthritis, the RANK/RANKL pathway is activated, resulting in deregulated bone remodelling. In patients with RA, the synovial tissues exhibit an increased ratio of RANK:OPG mRNA expression, indicating that pro-osteoclastogenic conditions dominate the microenvironment of RA-affected joints. There is accumulating evidence that bone destruction in RA is driven by the Th17-cell-mediated induction of RANKL expression in synovial cells, which together with inflammatory cytokine production, stimulates the differentiation and activation of osteoclasts and therefore bone resorption. IL-17 has been shown to increase the spontaneous production of matrix metalloproteinases by synoviocytes and activate chondrocytes to inhibit matrix synthesis and induce cartilage matrix degradation. In mice, intra-articular injection of IL-17 into the knee joint results in joint inflammation and damage. In addition, it is well documented that blocking IL-17/IL-17R signalling is effective at controlling local and systemic inflammatory manifestations, lowering the level of RANKL and blocking cartilage and bone destruction. These findings indicate that Th17 and RANKL bridge the skeletal and immune systems and have led to a new research field called osteoimmunology. This interdisciplinary field is important for the treatment of diseases associated with the bone and immune systems.

**Perturbations in the balance between Treg and Th17 cells lead to osteoclastogenesis and bone destruction**

Th17 cells and CD4+CD25+Foxp3+ Treg cells are novel CD4+Th cell subsets that are distinct from Th1 and Th2 cells. Treg cells are an immunosuppressive CD4+Th cell subset that contribute in maintaining peripheral self-tolerance and preventing the development of various inflammatory diseases through direct contact with effector immune cells and the secretion of anti-inflammatory cytokines, such as IL-10 and TGF-β1. It has been proposed that Treg cells are generated in the thymus, presumably by a moderately high-affinity interaction between developing autoreactive T-cell receptor-bearing T cells and self-antigens presented in the thymus. Once generated, Treg cells are seeded into the peripheral immune compartment, where they regulate the activation and effector functions of auto-reactive T cells throughout the life of an individual. Foxp3 is a transcription factor that is specifically expressed in CD4+CD25+ Treg cells. Its expression is crucial for the anergic phenotype of these cells in vitro and for their suppressor function. TGF-β1 is a critical differentiation factor for...
the generation of Tregs. It has been revealed that the effector function of Th cells (i.e., Th1, Th2 and Th17 cells) is regulated by Tregs. However, the Th17 subset of Th cells is pro-inflammatory; it plays vital roles in host defense and has been shown to be involved in the pathogenesis of autoimmune and inflammatory diseases primarily by secreting IL-17A and other cytokines, such as IL-21 and IL-22. It is therefore clear that Th17 and Treg cells have a functional antagonism, in which Tregs act as immunosuppressive cells and Th17 cells are involved in inducing autoimmunity. There is also an opposition in their generation. Both Th17 and Treg cells are induced from uncommitted CD4+ T cells by different cytokine-driven signalling pathways. The IL-6/STAT3 pathway is crucial for differentiation into Th17 cells and completely inhibits the TGF-β–induced generation of Foxp3+ Tregs. The deletion of STAT3 in CD4+ T cells impairs differentiation into Th17 cells and production of IL-17A and limits the development of experimental autoimmune encephalomyelitis. By contrast, the IL-2/STAT5 pathway is essential for the maintenance of homeostasis and for the competitive fitness of Treg cells, and it suppresses differentiation into Th17 cells. Treg cells and Th17 effectors arise in a mutually exclusive fashion, depending on whether they are activated in the presence of TGF-β or TGF-β plus IL-6. In a healthy individual or in the absence of any inflammatory trigger, TGF-β produced in the immune system will suppress the generation of Th17 effector cells and induce Foxp3+ Treg cells and thereby maintain self-tolerance. However, during infection or inflammation, IL-6 produced by the activated innate immune system suppresses the generation of TGF-β–induced Treg cells and induces a pro-inflammatory T-cell response predominated by Th17 cells. Although IL-6 plays a critical role in the development of the Th17 response and in the inhibition of Treg functions, it is also thought that additional control steps must exist during this process and that other cytokines might participate in differentiation into Th17 cells.

The plasticity between the Th17 cell subsets is worth mentioning here. It was thought for many years that all CD4+ T cells (Th1, Th2, Th17 and Treg cells) are terminally differentiated lineages with a stable phenotype. However, recent evidence suggests that these cells display plasticity, as observed by the ability to change their pattern of expression of both cytokines and master regulator transcription factors in response to external stimuli, suggesting that apparently fully committed Th cells have a plasticity feature.

The role of Treg cells in RA has been reported in both patients and animal models, where the Treg subset represents approximately 5–10% of the CD4+ T cell population. Increasing evidence suggests that Treg cell function is impaired in chronic inflammatory diseases such as RA. Interestingly, many studies have shown that Tregs directly suppress differentiation into osteoclasts in vitro, and Treg depletion has been shown to aggravate various experimental autoimmune diseases, including collagen-induced arthritis. The underlying mechanism is not fully understood; however, pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β, and IL-21, which are present within the synovial environment, can reduce the suppressive function of Treg cells in vitro. Therefore, the potential for Treg cells to modulate ongoing inflammation in RA remains unclear.

A study by Ehrenstein et al. raises an important question. Is it only a reduction in the number of Treg cells that initiates RA, or is it a qualitative defect in Treg cells that induces the aggressiveness of RA? Ehrenstein et al. have presented evidence suggesting that Treg cells derived from patients with active RA are defective in the ability to suppress cytokine production and to convey a suppressive phenotype to CD4+ effector T cells. They demonstrated that the clinical response to anti-TNF-α therapy, but not conventional therapies, in RA patients, was correlated with an increased number of peripheral blood Treg cells. One possibility is that the presence of TNF-α and other pro-inflammatory cytokines may hinder the ability of Treg cells to prevent autoimmune disease.

**Conclusion**

In this critical review, we have summarised the progress in our understanding of the role of the cytokines IL-23 and IL-17 and the differentiation of CD4+ T cells into specialised effectors, focusing on Th17 and Treg cells, in the pathogenesis of RA. We conclude that the pathogenesis of RA is slow but complex and that both cytokines and cell-mediated immunity are involved in a complex process that eventually results in irreversible bone and cartilage destruction. Cytokine levels and the Treg/Th17 balance might be relevant to the diversity of clinical manifestations in RA patients and might be critical for the development of improved clinical management and therapeutic options.

Here are some further pointers:

- Targeting the IL-23/Th17 axis for drug therapy appears to be a realistic approach to alternative treatments of chronic inflammatory diseases.
- IL-23 induces osteoclastogenesis in humans via the induction of IL-17 expression.
- RANKL, expressed on T cells, osteoblasts and synovial fibroblast, induces osteoclastogenesis.
Th17 and RANKL bridge the skeletal and immune systems and have led to a new research field called osteoimmunology.

IFN-γ has been reported to inhibit osteoclastogenesis.

CD4+CD25+Foxp3+ Treg cells and CD3+CD4+IL-17-producing Th17 cells are two subsets of CD4+ T cells.

The Treg/Th17 balance is regarded as a key factor in immune homeostasis, and an imbalance in this ratio is associated with disease activity in several autoimmune diseases.

Disturbances in the number and/or function of Treg cells are a feature of autoimmunity.

Abbreviations list

DC, dendritic cells; GM-CSF, granulocyte-monocyte colony-stimulating factor; IFN, interferon; IL, interleukin; OPG, osteoprotegerin; RA, rheumatoid arthritis; RANKL, receptor activator for NF-κB ligand; TGF, tumour growth factor; Th17, interleukin-17-producing help T cells; TGF, tumour necrosis factor; Treg, T regulatory cells.

References


17. Petitt AR, Walsh NC, Manning C, Goldring SR, Gravallese EM. RANKL protein is expressed at the pannus–bone interface at sites of articular bone erosion in rheumatoid arthritis. Rheumatology. 2006 Sep;45(9):1068–76.


26. Licensor OA Publishing London 2013. Creative Commons Attribution License (CC-BY)


Licensee OA Publishing London 2013. Creative Commons Attribution Licence (CC-BY)