JOURNAL OF INTERFERON & CYTOKINE RESEARCH
Volume 31, Number 12, 2011
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DOI: 10.1089/jir.2011.0094

# A Cytokine-Centric View of the Pathogenesis and Treatment of Autoimmune Arthritis

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Cytokines are immune mediators that play an important role in the pathogenesis of rheumatoid arthritis (RA), an autoimmune disease that targets the synovial joints. The cytokine environment in the peripheral lymphoid tissues and the target organ (the joint) has a strong influence on the outcome of the initial events that trigger autoimmune inflammation. In susceptible individuals, these events drive inflammation and tissue damage in the joints. However, in resistant individuals, the inflammatory events are controlled effectively with minimal or no overt signs of arthritis. Animal models of human RA have permitted comprehensive investigations into the role of cytokines in the initiation, progression, and recovery phases of autoimmune arthritis. The discovery of interleukin-17 (IL-17) and its association with inflammation and autoimmune pathology has reshaped our viewpoint regarding the pathogenesis of arthritis, which previously was based on a simplistic T helper 1 (Th1)-Th2 paradigm. This review discusses the role of the newer cytokines, particularly those associated with the IL-17/IL-23 axis in arthritis. Also presented herein is the emerging information on IL-32, IL-33, and IL-35. Ongoing studies examining the role of the newer cytokines in the disease process would improve understanding of RA as well as the development of novel cytokine inhibitors that might be more efficacious than the currently available options.

Rheumatoid arthritis (RA) is a chronic autoimmune disease that represents a typical T-cell–mediated disease (Harris 1990; Lipsky 2005). This systemic disease is characterized by inflammatory cell infiltration of the synovium, synovial hyperplasia, angiogenesis, and cartilage and bone erosion (Harris 1990; Scott and others 2003; Lipsky 2005). Cytokines released by the T cells and other joint-infiltrating cells associated with the disease have many immunologic functions ( McInnes and Schett 2007; Kunz and Ibrahim 2009) and are categorized as predominantly proinflammatory or anti-inflammatory (Abbas and others 1996; Romagnani 1997; Bingham 2002; Brennan and McInnes 2008) (Fig. 1). Tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and interferon-γ (IFN-γ) have been extensively examined for their role in the disease process in arthritis (Bessis and Boissier 2001; Bingham 2002; Dinarello 2002; Smolen and Maini 2006; Brennan and McInnes 2008; Nurmohamed 2009; Feldmann and Maini 2010; Dinarello 2011). In this review, we discuss the role of other cytokines, particularly the newer cytokines, in arthritis (Table 1). Most of the information presented here is based on studies in experimental models of RA. Two of these models that are commonly used for such studies are described below.

Adjuvant arthritis (AA) is a well-studied animal model for RA (Pearson 1956; Taurog and others 1988; Moudgil and others 1997). AA can be induced in a susceptible rat strain (e.g., Lewis [RT.1[l]]) by subcutaneous injection of heat-killed *Mycobacterium tuberculosis* H37Ra in oil (complete Freund's adjuvant (CFA]) at the base of the tail (Kim and others 2006). After an incubation period of about 10 days, the immunized rats develop arthritic inflammation that generally affects the hind paws more than the fore paws. The disease reaches its peak around 18 days after injection and then regresses spontaneously. The characteristic features of the disease are joint inflammation, cellular infiltration of the synovial tissue, pannus formation, and cartilage and bone destruction (Pearson 1956; Taurog and others 1988; Moudgil and others 1997). The pathogenesis of AA involves immune response to the mycobacterial heat-shock protein 65, which is a component of *Mycobacterium tuberculosis* H37Ra present in CFA (Moudgil and others 1997; Kim and others 2006). The Wistar Kyoto and Fisher F344 rats are relatively resistant to AA and serve as excellent controls for the arthritis-susceptible Lewis rat (Kim and others 2006; Kim and Moudgil 2009; Moudgil and others 2001).

Collagen-induced arthritis (CIA) is another widely used rodent model of RA (Trentham 1982; Wooley 1988; Brahn 1991). For the induction of CIA, type II collagen (CII) is injected into a susceptible rodent strain (e.g., DBA/1 mice) in CFA intradermally at the base of the tail, followed by a booster injection of CII in incomplete Freund's adjuvant

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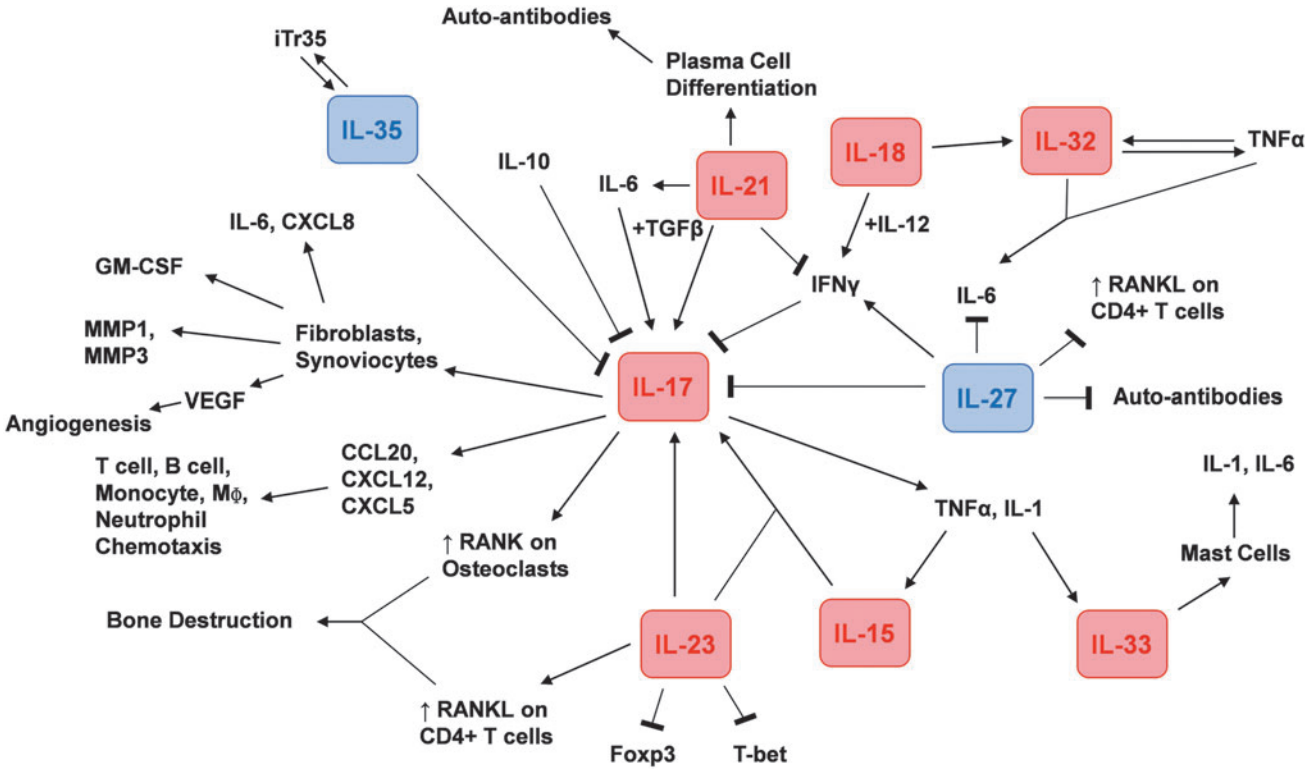


**FIG. 1.** The cytokine milieu in the lymphoid tissues and the joints in autoimmune arthritis is rather complex. Cytokines play an important role in altering immune cell function and other effector responses in arthritis, acting in a pathogenic, proinflammatory (red) or a protective, anti-inflammatory (blue) fashion. In addition, different cytokines display such characteristics as pleiotropy (one cytokine having multiple effects on various cell types), redundancy (the same or overlapping actions of different cytokines), and duality of action (revealing both pro- and anti-inflammatory activities under different set of conditions), which compound the analysis and interpretation of their role in the disease process. CCL, chemokine (C-C motif) ligand; CXCL, chemokine (C-X-C motif) ligand; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; MMP, matrix metalloproteinase; RANKL, receptor activator of nuclear factor κB ligand; TGF, transforming growth factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

usually given 1 week after initial immunization. The CII-challenged animals develop arthritis 3–5 weeks after immunization. The induction and progression of arthritis in this model depend on anti-CII antibodies and CII-specific T-cell response (Trentham 1982; Wooley 1988; Ridge and others 1988; Brahn 1991). The antibodies fix complement and drive the immune response.

## IL-15

Interleukin-15 is a type I cytokine that contains the typical four-α-helical structure and has structural homology with IL-2. It binds to a heterotrimeric IL-15 receptor that contains IL-2Rβ (CD122), IL-15Rα, and the common γ chain (CD132; γc) (Giri and others 1994). The complete IL-15R is expressed on the surface of several different cell types, including fibroblasts, monocytes, dendritic cells (DCs), natural killer (NK) cells, B cells, and T cells. Interleukin-15 promotes T- and B-cell survival and activates monocytes, mast cells, and neutrophils (McInnes and Gracie 2004). The ability of IL-2Rβ (IL-15Rβ) and γc complex to interact with IL-15Rα bound by IL-15 on a neighboring cell allows cross-talk between cells: for example, between monocytes/macrophages and T cells (Dubois and others 2002). This mechanism of IL-15 remaining bound to IL-15Rα may be associated with a prolonged IL-15 signal, which in the context of T cells is important for their survival (Dubois and others 2002). The IL-15R complex signals through Janus kinase (JAK)1, JAK3, signal transducer, and activator of transcription (STAT)3, and STAT5 via IL-15Rβ and γc, and also can signal through TNF receptor–associated factor 2 (TRAF2) leading to activation of nuclear factor κ-light-chain-enhancer of activated B cells (NF-kB) (Johnston and others 1995; Carroll and others 2008).

Interleukin-15 is a proinflammatory cytokine. In patients with RA, IL-15 is expressed in the synovial tissue, and the serum levels of IL-15 correlate with disease severity (Gonzalez-Alvaro and others 2003). Furthermore, the levels of IL-15 in the synovial fluid correlate with that of IL-17 (Ziolkowska and others 2000). Interleukin-15 has been found to be released by fibroblast-like synoviocytes and synovial tissue-resident macrophages. *Ex vivo* experiments have shown that the treatment of these cells with TNF-α or IL-1β stimulates the production of IL-15 (Harada and others 1999). Interleukin-15 has been shown to stimulate the production of IL-17 in human synovial fluid mononuclear cells. In mice with CIA, IL-15 expands the population of IL-17–secreting CD4+ T helper cells (Th17) and exacerbates the disease (Ziolkowska and others 2000; Yoshihara and others 2007). In addition, IL-15 has been shown to synergize with IL-23 to increase IL-17 production. This may be caused by the increased expression of IL-23R on T cells in the presence of IL-15 (Yoshihara and others 2007). This IL-15 to IL-17 cytokine pathway appears to

Table 1. Role of the Newer Cytokines in the Pathogenesis of Autoimmune Arthritis

| *Cytokine* | *Cell source* | *Receptors* | *Cells affected* | *Pathways influenced* | *Reference* |
|---|---|---|---|---|---|
| IL-15 | Fibroblast-like synoviocytes, macrophages | IL-15Rα, IL-15Rβ, common γ-chain (γC) | T cells, NK cells, B cells, monocytes, macrophages, neutrophils, mast cells, dendritic cells, fibroblasts | Induces IL-17 production | Giri and others 1994; Dubois and others 2000; Ziolkowska and others 2000 Yoshihara and others 2007 |
| IL-17 | Th17, γδ T cells, CD8+ T cells, NKT cells | IL-17RA, IL-17RB, IL-17RC, IL-17RD, IL-17RE | T cells, NK cells, B cells, monocytes, macrophages,, neutrophils, mast cells, dendritic cells, fibroblasts | Induces angiogenesis, proinflammatory cytokine production, cell infiltration, innate immune response, and RANK expression on osteoclasts | Albanesi and others 2000 Bush and others 2001 Toy and others 2006 Rong and others 2009 Shahrara and others 2009 Pickens and others 2010 Sawa and others 2011 |
| IL-18 | Macrophages, dendritic cells, fibroblasts, chondrocytes | IL-18Rα IL-18Rβ | T cells, NK cells, macrophages, chondrocytes | Facilitates IFN-γ production, monocyte recruitment into the synovium, and angiogenesis | Gracie and others 1999 Yamamura and others 2001 Ruth and others 2010 |
| IL-21 | T cells | IL-21R, common γ-chain (γC) | B cells, T cells, NKT cells, NK cells | Induces Th17 differentiation and plasma cell differentiation, inhibits IFN-γ | Habib and others 2002 Korn and others 2007 Nurieva and others 2007 Ettinger and others 2008 Yang and others 2008 |
| IL-23 | Dendritic cells, monocytes, macrophages | IL-12Rβ1, IL-23R | T cells | Helps maintain Th17 cells, induces RANKL on CD4+ T cells | Parham and others 2002 Murphy and others 2003 Yago and others 2007 Lemos and others 2009 |
| IL-27 | Dendritic cells, monocytes, epithelial cells | WSX1, gp130 | T cells | Stimulates IFN-γ production, blocks IL-6, inhibits IL-17, downregulates RANKL | Pflanz and others 2004 Awasthi and others 2007 Niedbala and others 2008 Rajaiah and others 2010 Kamiya and others 2011 |
| IL-32 | NK cells, T cells, epithelial cells, monocytes, fibroblasts | PR3 | Monocytes, macrophages, epithelial cells | Stimulates the production of TNF-α, IL-1β, IL-18 | Dinarello and Kim 2006 Joosten and others 2006 Novick and others 2006 Shoda and others 2006 Heinhuis and others 2011 |
| IL-33 | Fibroblasts | T1/ST2 | Mast cells | Activates mast cell release of proinflammatory cytokines | Leung and others 2004 Schmitz and others 2005 Xu and others 2008 Palmer and others 2009 |
| IL-35 | T regulatory cells, $iT_R35$ | IL-12Rβ2, gp130 | T cells | Suppresses Th17 differentiation, induces IL-35+ Foxp3- T cells | Devergne and others 1997 Collison and others 2007 Niedbala and others 2007 Collison and others 2010 |

Foxp3, Forkhead box 3; IFN, interferon; IL, interleukin; $iT_R35$, inducible T regulatory cell 35; NK, natural killer; NKT, natural killer T; PRT3, proteinase 3; RANK, receptor activator of nuclear factor κ B (RANK); RANKL, RANK ligand; Th, T helper cell; WSX, tryptophan-serine-X.

be a positive feedback mechanism as IL-17 stimulates the production of TNF-α and IL-1 by neutrophils, which in turn can increase IL-15 production (Edwards and Hallett 1997). The increase in IL-17 production by IL-15 has been shown to be significantly reduced *in vitro* after the treatment of human peripheral blood mononuclear cells with the immunosuppressive drug cyclosporine A (Ziolkowska and others 2000).

In the CIA model, IL-15–transgenic mice exhibited enhanced severity of arthritis, whereas IL-15–deficient mice showed slight reduction in disease severity (Yoshihara and others 2007). In another study in CIA, treatment of mice with soluble IL-15Rα (Ruchatz and others 1998) or mutant IL-15-Fc protein (Ferrari-Lacraz and others 2004) protected them against arthritis. Anti–IL-15 monoclonal antibodies are being examined for their anti-arthritic activity. Baslund and colleagues conducted a phase I/II clinical trial of a human IgG1 anti–IL-15 monoclonal antibody, HuMax IL-15. This antibody could neutralize various biological effects of IL-15 in synovial tissue *in vitro*, and it caused significant improvement in disease activity at 12 weeks after treatment initiation (Baslund and others 2005).

## IL-17

Interleukin-17 has been implicated in the pathogenesis of a wide range of diseases, including RA. Interleukin-17 is best defined as a product of CD4+ Th17 cells, but it also can be produced by CD8+ T cells, γδ T cells, NKT cells, and the recently described lymphoid tissue inducer cells (Albanesi and others 2000; Sawa and others 2011). The differentiation of Th17 cells can be induced by a combination of transforming growth factor (TGF)-β and IL-6 (Bettelli and others 2006; Veldhoen and others 2006) or by TGF-β and IL-21 (Korn and others 2007; Nurieva and others 2007), whereas their maintenance requires IL-23 (Bettelli and others 2006; Veldhoen and others 2006). Activated Th17 cells produce IL-17 along with other cytokines, such as IL-22. Interleukin-17 exists as a family of cytokines with six major isoforms, IL-17A through F; IL-17A was the first discovered and is the most widely studied. This cytokine signals through the IL-17 receptor (IL-17R), a heteromeric receptor of which there are at least five isoforms that preferentially bind specific isoforms of IL-17 (Toy and others 2006; Rong and others 2009). Of the six isoforms, IL-17A and IL-17F are implicated in autoimmune diseases and are found to be increased in the arthritic joint. Interleukin-17A is commonly referred to simply as IL-17, whereas the other isoforms are specifically named when studied. We use this nomenclature for the remainder of this article.

Interleukin-17 is a proinflammatory cytokine. It is detectable during the preclinical phase of AA, and its levels are actively upregulated during the acute as well as the chronic phase of the disease (Bush and others 2001; Stolina and others 2009a). An acute rise in intra-articular levels of IL-17 after onset of symptoms of arthritis indicates that this cytokine may be involved in the progression rather than the induction of the disease (Bush and others 2001; Stolina and others 2009a). In AA, neutralization of IL-17 by treatment with soluble IL-17R is found to reduce the severity of the disease (Bush and others 2002). Additionally, treatment with several anti-arthritic agents, including natural plant products, has been shown to ameliorate AA, along with a significant decrease in systemic and local IL-17, which supports the pathogenic role of this cytokine in arthritis (Kim and others 2008a; Kim and others 2008b; Satpute and others 2009; Meyer and others 2010; Venkatesha and others 2011; Wang and others 2011; Yu and others 2011). Levels of IL-17 follow similar trends during the course of the disease in human RA (Moran and others 2009) and rat AA (Moran and others 2009; Stolina and others 2009a). Reduction in the level of IL-17 *in vivo* has become a benchmark for assessing the control of arthritic disease.

Inhibition of IL-17 response in antigen-induced arthritis (AIA) and CIA results in reduced inflammation and bone destruction (Koenders and others 2005; Sarkar and others 2009). However, in one study in CIA, no significant increase in systemic IL-17 was observed in arthritic rats compared with the controls (Stolina and others 2009b). In the staphylococcal cell wall–induced arthritis model, IL-17 was found to be increased locally but not systemically (Henningsson and others 2010). In the proteoglycan-induced arthritis model, disease induction was originally reported to be IL-17 independent (Doodes and others 2008; Henningsson and others 2010), but subsequently it was shown that IL-17 was necessary for disease induction in IFN-γ–deficient mice, suggesting hierarchical pathogenic roles of IFN-γ and IL-17 (Doodes and others 2010). In the K/BxN antibody-mediated model of arthritis, Th17 cells are shown to provide IL-17–dependent T-cell help to antibody-producing B-cell populations, thereby promoting autoantibody production and worsening of the disease (Jacobs and others 2009). However, the exact role of IL-17 in this model has yet to be fully defined.

There are several proposed mechanisms by which IL-17 mediates the pathogenic events in the course of arthritis:

(1) By upregulating the production of proinflammatory cytokines. Interleukin-17 is shown to stimulate fibroblast-like synoviocytes and other local cells in the joints to produce proinflammatory cytokines, IL-6 and IL-8, as well as matrix-degrading enzymes, matrix metalloproteinase 1 and 3 (Agarwal and others 2008; Kehlen and others 2003). In addition, IL-17 upregulates the receptor activator of NFκB (RANK) on osteoclast precursors causing increased sensitivity to RANK ligand (RANKL) signaling leading to increased bone destruction (Adamopoulos and others 2010).
(2) By facilitating cellular infiltration into the synovium. Signaling through IL-17RA and IL-17RC, IL-17 is directly chemotactic for monocytes, causing them to migrate into the local tissue (Shahrara and others 2009). Interleukin-17 also stimulates the production of chemokines, such as chemokine (C-C motif) ligand 20, chemokine (C-X-C motif) ligand (CXCL) 12, and CXCL5 that attract T cells, B cells, monocytes, macrophages, neutrophils, and other cells that infiltrate the synovium during arthritis (Ruddy and others 2004; Hirota and others 2007; Kim and others 2007c; Kawashiri and others 2009).
(3) By enhancing innate immune response. Interleukin-17 stimulates synovial fibroblasts to secrete granulocyte-macrophage colony-stimulating factor, which aids in the recruitment and survival of neutrophils in the arthritic synovial fluid and pannus (Parsonage and others 2008). In the K/BxN arthritis model, activation of the complement cascade is involved in the pathogenesis of arthritis (Tsuboi and others 2010). Furthermore,

IL-17 upregulates the expression of the complement system components in fibroblasts, which may exacerbate tissue destruction (Katz and others 2000; Tsuboi and others 2010).

(4) Through the induction of angiogenesis. Interleukin-17 is able to increase vascularity by directly promoting blood vessel growth, by stimulating synovial fibroblasts to secrete vascular endothelial growth factor, and by activating endothelial cells, which then migrate into the synovium by chemotaxis, resulting in neovascularization (Honorati and others 2006; Ryu and others 2006; Pickens and others 2010; Plum and others 2009). Accordingly, antiangiogenic treatment is shown to decrease arthritic disease as well as levels of IL-17 (Lainer-Carr and Brahn 2007; Plum and others 2009; Szekanecz and Koch 2009; Rajaiah and others 2011; Yang and others 2011).

Interleukin-17 response can be modulated by multiple cytokines. Interferon-γ is shown to inhibit the expression of IL-17 and aid in the recovery from acute arthritis (Chu and others 2007; Kim and others 2008a; Sarkar and others 2009; Doodes and others 2010; Rajaiah and others 2011). Similarly, IFN-γ–deficient mice develop exacerbated arthritis owing to upregulation of the IL-17–mediated mechanisms (Irmler and others 2007) demonstrating the suppressive effect of IFN-γ on IL-17 response. In the AA model, treatment of arthritic rats with IFN-γ caused increased expression of IL-27, which in turn downregulated IL-17 and suppressed AA (Rajaiah and others 2011). Similarly, in the absence of IFN-γ, neutralization of IL-4 led to increased arthritis without an increase in IL-17 levels, showing that IL-4 regulates arthritis in an IL-17–independent manner (Sarkar and others 2009). Interleukin-10 is an inhibitor of Th17 differentiation and maintenance, and upon upregulation of IL-10, IL-17 expression is suppressed and arthritic inflammation is decreased (Heo and others 2010). Conversely, IL-6 and IL-21 production skews the T-cell population toward Th17, which leads to increased IL-17 response and aggravation of arthritis (Chen and others 2010; Niu and others 2010). Similarly, exogenous IL-15 induces IL-17 production in synovial cells, indicating an indirect role of IL-15 in the pathogenesis of arthritis (Halvorsen and others 2011). A combination treatment of infliximab, an anti–TNF-α antibody, and methotrexate, an antimetabolite, is shown to significantly reduce disease along with decrease in the frequency of Th17 cells and the levels of IL-17 in RA patients without significant adverse effects (Shen and others 2010). The above-mentioned Th17/IL-17–influencing factors represent therapeutically relevant regulators of IL-17.

Clinical trials aimed at inhibiting IL-17 response show that such an agent holds promise as an efficacious treatment for arthritis. Treatment of RA patients with a humanized anti–IL-17 antibody (LY2439821) given intravenously is shown to improve the signs and symptoms of the disease (Genovese and others 2010). In another study in RA, treatment with AIN457 (anti-IL-17) induced clinically relevant responses, although of variable magnitude (Hueber and others 2010).

## IL-18

Interleukin-18 is an 18-kDa member of the IL-1 cytokine superfamily and is derived from an inactive pro–IL-18 precursor following cleavage by IL-1–converting enzyme. It is produced primarily by activated macrophages. Other sources of IL-18 include DCs, synovial fibroblasts, and articular chondrocytes (Ruth and others 2010). Interleukin-18 acts on a variety of IL-18R–expressing cells (e.g., macrophages, T cells, NK cells, and chondrocytes) (Ruth and others 2010). Interleukin-18 receptor (IL-18R) consists of the ligand-binding IL-18Rα and the signal-transducing IL-18Rβ (Kato and others 2003; Yamamoto and others 2004). IL-18–binding protein (IL-18BP) is a secreted receptor-like molecule that can neutralize the activity of IL-18. Interleukin-18 has been shown to synergize with IL-12 to help Th1 cells produce IFN-γ (Yamamura and others 2001). Interleukin-12–polarized resting Th1 cells produce increased amounts of IFN-γ with the help of IL-18, but IL-18 itself cannot polarize naïve T cells into Th1 cells (Robinson and others 1997). Interleukin-18 facilitates monocytic recruitment into the synovium as well as angiogenesis, both of which contribute to the disease process in arthritis (Amin and others 2010; Ruth and others 2010).

Interleukin-18 has been shown to be increased in the serum, synovial fluid, and synovium of RA patients, and it enhances the production of TNF-α and IFN-γ (Gracie and others 1999). In the CIA model, injection of IL-18 increases disease severity, indicating that it plays a role in disease pathogenesis (Gracie and others 1999). Treatment of mice with IL-18BP or anti–IL-18 antibodies reduces the severity of CIA (Plater-Zyberk and others 2001; Banda and others 2003; Smeets and others 2003). Furthermore, IL-18–deficient mice develop less severe disease as tested in the CIA model (Wei and others 2001) and the zymosan-induced arthritis model (Ruth and others 2010). For an in-depth review on the effects of IL-18 on autoimmune arthritis, please refer to the article titled "Interleukin-18: A Mediator of Inflammation and Angiogenesis in Rheumatoid Arthritis' by Volin and Koch (2011) in volume I of the special issue of *JICR*, "Cytokines and Autoimmunity" (pp. 745–751).

## IL-21

Interleukin-21 is a class I cytokine that contains the typical four-α-helical secondary structure associated with this family of cytokines. This cytokine has structural homology with IL-2 and IL-15. The IL-21 receptor (IL-21R) has the conserved tryptophan-serine-X-tryptophan-serine–containing sequence motif in its extracellular cytokine-binding domain, which is found in many other class I cytokine receptor family members (Parrish-Novak and others 2002). In the presence of IL-21, the IL-21R heterodimerizes with γc, allowing signal transduction primarily through JAK3 and STAT5 (Habib and others 2002; Parrish-Novak and others 2002). Interleukin-21 is produced by activated CD4+ T cells and NKT cells and influences the activity of T cells, B cells, and NK cells (Parrish-Novak and others 2002; Ettinger and others 2008). In regard to the T cells (in the mouse), Th1, Th2, and Th17 can produce IL-21 (Leonard and Spolski 2005; Korn and others 2007; Ettinger and others 2008). Also, the T follicular helper cells in the B-cell follicles of the lymph nodes also produce IL-21 (Chtanova and others 2004).

Interleukin-21 facilitates the induction of Th17 cells, resulting in increased IL-17 production (Niu and others 2010; Wurster and others 2002). In conjunction with TGF-β, IL-21 is capable of inducing Th17 differentiation of naïve T cells, indicating an alternative pathway to that requiring TGF-β and IL-6 (Yang and others 2008b). Mice lacking IL-21 or IL-21R

have an reduced number of Th17 but an increased number of CD4+ forkhead box P3 (Foxp3)+ regulatory T cells (Treg) (Nurieva and others 2007). In the case of B cells, IL-21 has been shown to induce the activation and differentiation of B cells, as well as the terminal differentiation of plasma cells (Ettinger and others 2008). Thereby, IL-21 can promote autoimmunity via its effects on autoantibody production.

Through its role in Th17 induction and IL-17 production, IL-21 leads to increased joint inflammation and synovial cellular infiltration (Niu and others 2010). Treatment with IL-21RFc chimeric protein of mice having CIA and rats having AA resulted in significantly reduced disease severity (Young and others 2007). In mice with CIA, the level of IL-6 was reduced, but that of IFN-γ was increased. The latter finding is supported by results of other studies in CIA showing an arthritis-protective effect of IFN-γ (Vermeire and others 1997; Guedez and others 2001). Also, studies in the AA model have revealed the disease-protective effect of IFN-γ (Kim and others 2008a). In addition, IL-21 has been shown to inhibit Th1 differentiation (Wurster and others 2002). This finding indirectly supports the observed increase in IFN-γ production in mice treated with agents that neutralize IL-21 activity.

Increased level of IL-21 has been reported in RA sera, and the concentration of IL-21 in serum and synovial fluid was higher in RA than osteoarthritis (Niu and others 2010). Furthermore, studies in RA patients have revealed high percentage of IL-21R+ inflammatory cells (e.g., macrophages and fibroblasts) in synovial fluid and blood (Jungel and others 2004).

As IL-21 signals via JAKs, inhibitors of the JAK pathway are of therapeutic interest. A study testing a JAK2/JAK3 inhibitor (CP-690,550) in the rat AA model showed reduction in arthritis (paw edema) and plasma levels of IL-6 and IL-17 (Meyer and others 2010). Currently, clinical trials using different JAK inhibitors (e.g., pan-JAK inhibitor, JAK3 inhibitor, JAK1 inhibitor) in RA patients are underway.

## IL-23

Interleukin-23 is an IL-12 superfamily heterodimeric cytokine that contains an α-chain subunit, p19, and a β-chain subunit, p40 (Oppmann and others 2000). Interleukin-23 binds to a heterodimeric receptor consisting of IL-23 receptor (IL-23R) and IL-12Rβ1. The p19 subunit of IL-23 binds to IL-23R, whereas the p40 subunit of IL-23, which is shared by IL-12, binds to IL12Rβ1 (Parham and others 2002). This ligand-receptor interaction activates the signaling pathway involving JAK2, tyrosine kinase 2 (Tyk2), and STATs (STAT 1, 3, 4, and 5) (Parham and others 2002). Antigen-presenting cells such as activated DCs, monocytes, and macrophages produce IL-23 (Andersson and others 2004; Paradowska-Gorycka and others 2010). Interleukin-23 contributes to chronic inflammation through multiple effector pathways. It is required for the amplification and stabilization of Th17 cells. In addition, IL-23 can induce secretion of IL-17 by non-T cells, and activate subsets of above-mentioned antigen-presenting cells leading to the production of other proinflammatory cytokines, such as TNF-α and IL-1β. Interleukin-17 in turn may induce IL-23 (e.g., in synovial fibroblasts), suggesting a feed-forward loop that might contribute to the progression of synovial inflammation in arthritis (Kim and others 2007a). Expectedly, mice transgenic for p19 display systemic inflammation (Wiekowski and others 2001).

Mice deficient in IL-23p19 are resistant to arthritis (CIA) (Murphy and others 2003). This resistance is associated with reduction in both anti-CII antibodies and IL-17 response. The significance of IL-23 in arthritis pathogenesis is further corroborated by the finding that the treatment of arthritic animals with anti–IL-23 antibody can attenuate the disease severity (Yago and others 2007). Moreover, IL-23 injected intra-articularly into mice causes neutrophil influx locally in part via increasing prostaglandin E2, which enhances IL-17 production by reducing the inhibitory IFN-γ (Lemos and others 2009). Studies in mice deficient in IL-1 receptor antagonist (IL-1Ra), which spontaneously develop arthritis (Cho and others 2006; Yago and others 2007; Ju and others 2008), have shown that IL-23 mediates tissue damage in the joints in part via stimulating the expression of RANKL on the surface of CD4+ T cells by signaling through STAT3.

Increased levels of IL-23 are found in the blood and synovial fluid of patients with RA, and the levels of IL-23 correlate with those of the proinflammatory cytokines IL-17, TNF-α, and IL-1β (Kim and others 2007b; Kageyama and others 2009). Moreover, IL-23 promotes osteoclastogenesis presumably via increasing the production of IL-17 relative to IFN-γ in a dose-dependent manner and thereby altering the balance in favor of IL-17 (Yago and others 2007).

Recent clinical studies associated with IL-23 inhibition in arthritis include the use of STA 5326 mesylate (apilimod mesylate), an orally administered inhibitor of IL-12/IL-23 in RA (Synta Pharmaceuticals Corp.), and Ustekinumab, an anti-IL-12/-23 p40 antibody in psoriatic arthritis (Gottlieb and others 2009).

## IL-27

Interleukin-27 is an IL-12 superfamily cytokine that plays a role in the immune effector responses in autoimmune diseases, including arthritis. Interleukin-27 is a heterodimeric protein composed of p28, an IL-12p35–related protein, and Epstein-Barr virus–induced gene 3 (EBI3), an IL-12p40–related protein (Pflanz and others 2002). Interleukin-27 is secreted by macrophages, DCs, and epithelial cells. It binds to the receptor complex of tryptophan-serine-tryptophan-1 (i.e., T-cell cytokine receptor) (IL-27Rα) and gp130, a signaling chain. IL-27R is expressed on a variety of cell types, including naïve CD4+ T cells, NK cells, activated B cells, mast cells, and monocytes (Pflanz and others 2004). Interleukin-27–IL-27R interaction results in activation of JAK/STAT signaling cascades (Pflanz and others 2002; Villarino and Hunter 2004; Stumhofer and others 2007).

The role of IL-27 as a pro- versus an anti-inflammatory cytokine has not yet been fully resolved (Villarino and Hunter 2004; Cao and others 2008). In early studies, IL-27 was shown to induce the differentiation of Th1 cells (Villarino and Hunter 2004; Owaki and others 2005). However, several subsequent studies have highlighted the anti-inflammatory role of IL-27 involving inhibition of Th1, Th2, and Th17 responses (Villarino and Hunter 2004; Batten and others 2006). In addition, IL-27 has been shown to induce the production of IL-10 by Th1 and Th2 cells (Stumhofer and others 2007), and to promote the generation of IL-10–producing Foxp3- regulatory T cells (Awasthi and others 2007).

In CIA, treatment of mice with IL-27 reduced the severity of arthritis, as well as the levels of IL-6, IL-17, and anti-CII antibodies (Niedbala and others 2008). In another recent

study on CIA, it was shown that injection of IL-27 (as an adenoviral IL-27 construct) intra-articularly attenuated arthritis (Pickens and others 2011). Besides reduction in clinical and histologic features of the disease, there was reduction of bone damage, proinflammatory cytokine production, and monocytic cellular influx into the joints. Another mechanism of IL-27–mediated protection against arthritis involves the inhibition of osteoclastogenesis (Kotake and others 2001; Furukawa and others 2009; Kamiya and others 2011). In the case of AA, IL-27 has been shown to be an important regulator of IL-17 expression leading to reduced severity of arthritis (Rajaiah and others 2011). Arthritic Lewis rats had little IL-27 response during the incubation phase of AA but showed much higher IL-27 response during the recovery phase of the disease (Rajaiah and others 2011). Further, injection of IL-27 into Lewis rats either during the incubation phase or during the onset of AA protected against subsequent disease, in part by inhibiting the IL-17 response.

Contrary to the above-mentioned protective role of IL-27 in arthritis, an earlier study in AA revealed the proinflammatory activity of IL-27 (Goldberg and others 2004). In that study, immunization of rats with IL-27 (as a DNA construct), which led to the production of neutralizing anti–IL-27 antibodies, was found to ameliorate arthritis. The proinflammatory role of IL-27 was also shown in the proteoglycan-induced arthritis model (Cao and others 2008). Mice deficient in IL-27R were protected from arthritis development. Unraveling the precise reasons underlying the conflicting role of IL-27 in arthritis pathogenesis would require further investigations (Fearon 2011).

High levels of IL-27 are detected in the synovial membrane and synovial fluid macrophages of RA patients with active disease compared with controls (Niedbala and others 2008; Shahrara and others 2008). Recent results showing IL-27–induced expression of proinflammatory cytokines, chemokines, and matrix-degrading enzymes in fibroblast-like synoviocytes from RA patients suggest the likely involvement of IL-27 in the disease process (Wong and others 2010). Considering the above-mentioned anti-inflammatory role of IL-27 in animal models (Niedbala and others 2008; Pickens and others 2011; Rajaiah and others 2011), it remains to be determined whether the level of IL-27 is not high enough to suppress active RA or that IL-27 is produced relatively late in the disease course to limit Th17 differentiation. On the contrary, in view of the proinflammatory role of IL-27 in animal models (; Goldberg and others 2004; Cao and others 2008), it remains to be determined whether this cytokine plays a similar role in RA as well.

## IL-32

Interleukin-32 was first discovered as an IL-18–induced transcript expressed by activated NK cells and T cells, and was originally named NK4 for its cell of origin. Subsequently, it was found that epithelial cells are the major source of this cytokine (Dinarello and Kim 2006; Joosten and others 2006) and that IL-32 also can be produced by monocytes (Dahl and others 1992; Kim and others 2005; Dinarello and Kim 2006; Joosten and others 2006; Shoda and others 2006). At the tissue level, IL-32 is expressed by lymphoid tissues (e.g., thymus, spleen, and intestine) (Shoda and others 2006). There are four splice variants of this proinflammatory cytokine: IL-32 $\alpha$, $\beta$, $\gamma$, and $\delta$. Production of IL-32, which can be stimulated by treatment with IL-18, induces inflammation by signaling through the typical NFκB and p38 MAP kinase pathways (Joosten and others 2006; Kim and others 2005). Association between proteinase 3 (PR3) and IL-32$\alpha$, the most common IL-32 isoform, has allowed PR3 to be identified as a potential cytokine receptor. PR3 can influence intracellular processes, and this effect is not linked with its proteolytic activity (Novick and others 2006).

Upon IL-32 treatment, monocytes and macrophages produce TNF-$\alpha$, while various epithelial cell types produce the proinflammatory cytokines IL-1$\beta$, IL-18, and IFN-$\gamma$ (Kim and others 2005; Joosten and others 2006; Shoda and others 2006). Studies using synovial fibroblasts from RA patients and other cell types (e.g., CD4 T cells and DCs) suggest the existence of a reciprocal induction between TNF-$\alpha$ and IL-32, creating a TNF-$\alpha$–IL-32–TNF-$\alpha$ positive feedback loop that might contribute to chronic RA by these two cytokines collaborating to sustain increased production of IL-1$\beta$, IL-6, and CXCL8 (Heinhuis and others 2011). In addition, synovial fibroblasts can be activated by toll-like receptor agonists to synthesize and release IL-32, which in turn increases the expression of TNF-$\alpha$ and IL-1$\beta$. Thus, IL-32 links the innate and adaptive immune responses in RA (Alsaleh and others 2010). Furthermore, anti–TNF-$\alpha$ therapy reduces the amount of IL-32 expressed by fibroblasts and some other synovium-infiltrating cells in RA patients (Heinhuis and others 2011).

It has been shown that IL-32 gene expression is higher in patients with RA than in patients with osteoarthritis (Cagnard and others 2005). Interleukin-32 messenger RNA expression in lymphocytes infiltrating the synovium of arthritis joints has also been reported (Shoda and others 2006). Furthermore, the synovial tissue of RA patients was found to express high amounts of IL-32, and the levels correlated with the severity of the disease as well as with the expression of other proinflammatory cytokines (e.g., IL-18, TNF-$\alpha$, IL-1$\beta$) (Joosten and others 2006; Shoda and others 2006).

In mice overexpressing human IL-32$\beta$ (BM-hIL32), the severity of collagen antibody-induced arthritis was enhanced compared to the mock controls (Shoda and others 2006). Furthermore, the adoptive transfer of CD4+ T cells expressing hIL-32$\beta$ caused aggravation of CIA induced by immunization with CII (Shoda and others 2006). Interestingly, these effects of IL-32 were significantly reduced following TNF-$\alpha$ blockade, again emphasizing the interplay between IL-32 and TNF-$\alpha$ in mediating the immune pathology in arthritis. Intra-articular injection of IL-32$\gamma$ in naïve mice caused joint swelling, migration of inflammatory cells into the joints, and cartilage damage (Dinarello and Kim 2006; Joosten and others 2006). These effects (excluding cartilage damage) were markedly reduced in TNF-$\alpha$–deficient mice, supporting the TNF-$\alpha$–dependent effects of IL-32.

## IL-33

Interleukin-33 is an IL-1 family cytokine that, similar to IL-1, is produced in a pro-form, which, once cleaved, becomes the mature cytokine. Interleukin-33 is produced primarily by epithelial cells and endothelial cells (Moussion and others 2008; Xu and others 2008; Saidi and others 2011). Interleukin-33 binds to its receptor consisting of the orphan receptor ST2 (IL-33R$\alpha$ chain) and IL-1 receptor accessory protein (IL-1RAcP) (Leung and others 2004; Xu and others 2008; Alves-Filho and others 2010; Saidi and others 2011). Although ST2

is a member of IL-1R family, it does not bind IL-1α, IL-1β, or IL-1 receptor antagonist (IL-1Ra). ST2 is expressed by Th2 cells, mast cells, basophils, eosinophils, and DCs, but not by Th1 cells ( Leung and others 2004; Xu and others 2008; Alves-Filho and others 2010; Saidi and others 2011). Accordingly, IL-33 plays an important role in Th2 effector responses. Interleukin-33 is a chemoattractant for Th2 cells and facilitates the production of Th2 cytokines (Rossler and others 1995; Gachter and others 1996; Saidi and others 2011). Furthermore, a differentially spliced form of ST2, soluble ST2 (sST2), can be produced by fibroblasts. This sST2 acts as a decoy receptor of IL-33 and is a natural inhibitor of IL-33 (Rossler and others 1995; Saidi and others 2011). The membrane-bound T1/ST2 signals through NF-κB and MAP kinase pathways, ERK, p38, and JNK (Schmitz and others 2005). Interleukin-33 has been characterized as both a pro- and anti-inflammatory cytokine depending on the inflammation model (Miller and others 2008; Xu and others 2008).

Interleukin-33 has been shown to be expressed in the early phases of the disease in the joints of mice having CIA, and the ability of IL-32 to upregulate IL-1β and TNF-α indicates that IL-33 may aid in the progression of acute arthritis to a chronic disease (Leung and others 2004; Xu and others 2008). Furthermore, the inhibition of IL-33 receptor signaling with anti-ST2 antibodies (Palmer and others 2009) or soluble ST2-Fc fusion protein (Leung and others 2004) resulted in reduced CIA. The decrease in disease severity is associated with reduction in IFN-γ and IL-17 produced in the draining lymph nodes, and RANKL expression in the joints (Palmer and Gabay 2011). The results of the above studies are corroborated by that of another study showing that mice deficient in ST2 showed decreased severity of CIA (Xu and others 2008). Furthermore, the disease severity was significantly enhanced following injection of IL-33 into wild-type mice as well as in ST2-deficient mice that had been reconstituted with wild-type mast cells, but not in ST2-deficient mice (Xu and others 2008). In regard to IL-33 injection into mice, similar results were obtained in the anti–glucose-6 phosphate isomerase autoantibody-induced arthritis model (Xu and others 2010), as in the CIA model (Xu and others 2008). The role of mast cells in RA or its animal models is not completely understood, but it has been shown that IL-33-stimulated mast cells produce increased amounts of proinflammatory cytokines IL-1β, IL-6, and IL-17 (Xu and others 2008).

Interleukin-33 has been detected in the synovial tissue and cultured fibroblasts of RA patients (Xu and others 2008). Synovial fibroblasts have been shown to constitutively express low levels of IL-33 messenger RNA, but IL-33 expression increases rapidly following the addition of IL-1β and TNF-α (Schmitz and others 2005; Xu and others 2008; Palmer and others 2009). In RA patients receiving anti–TNF-α therapy, serum levels of IL-33 are found to be increased in responders but not in nonresponders (Matsuyama and others 2011). Thus, IL-33 serum levels correlated well with response to anti–TNF-α treatment.

## IL-35

Interleukin-35 is an IL-12 family member cytokine that is composed of the α subunit p35, which is commonly associated with IL-12, and the β subunit $EBI_3$, also found in IL-27 (Devergne and others 1997). $EBI_3$ is a homolog of p40; p40 associates with the p35 subunit to form IL-12 (Devergne and others 1997; Niedbala and others 2007). Among the CD4+ T cells, $EBI_3$ and p35 gene expression is detectable predominantly in CD4+ $Foxp3^+$ Treg cells compared to the effector CD4+ T cells, while only Treg cells constitutively secrete IL-35 protein as an $EBI_3$/p35 dimer (Collison and others 2007). Human and mouse naïve T cells treated with exogenous IL-35 differentiate into $Foxp3^-$ '$iT_R35$' cells that mediate suppressive function via IL-35, not IL-10 and TGF-β (Collison and others 2010). This subset of Treg neither expresses nor requires Foxp3 for their action. It has recently been shown that human Treg express IL-35 and require this cytokine for their optimal suppressive effect (Chaturvedi and others 2011).

The adoptively transferred $iT_R35$ can effectively suppress autoimmune diseases as tested in different experimental model systems. *In vivo*, IL-35 derived from natural Treg can induce the generation of $iT_R35$ from suppressed target T cells in mice. Interleukin-35 regulates T-cell activity, as evidenced by the suppression of T-cell proliferation following the addition of recombinant IL-35 *in vitro*. Furthermore, the suppressive capacity of Treg from $EBI_3$-/- and p35-/- mice is significantly reduced, and the percentage of Treg and the expression of Foxp3 are unaffected. However, these mice do not display any signs of overt autoimmunity or inflammation. This phenotype is presumably owing to reduced levels of proinflammatory cytokines (e.g., IL-27, IL-12) using the receptor subunits $EBI_3$ and p35 (Collison and others 2007). Splenic cells of $EBI_3$-deficient mice produce high levels of IL-17 and IL-22 and show increased expression of retinoic acid receptor–related orphan receptor-γt when restimulated *in vitro* with heat-killed *Listeria monocytogenes* (Yang and others 2008a). These findings reinforce a potential mechanism (e.g., suppression of Th17 response) that Tregs can use to control pathogenic T-cell responses in RA.

Interleukin-35 has yet to be examined in the AA model, but in the CIA model it has been shown to inhibit the progression of CIA (Niedbala and others 2007). This protective effect was associated with expansion of Treg, with reduction of IL-17 response but an increase in IFN-γ production. In another study using the CIA model, treatment of mice with IL-35 reduced disease severity, which was associated with stimulation of CD39+ CD4+ regulatory T cells; reduction in IL-17, IFN-γ, anti-CII antibodies; and an increase in IL-10 production (Kochetkova and others 2010).

## Conclusion

The progression and chronicity of acute inflammatory arthritis are associated with sustained production of inflammatory cytokines and deregulation of anti-inflammatory cytokines. Innovative research on the biology of cytokines associated with autoimmune inflammation has improved understanding of the disease-related mechanisms in RA. In the past decade, important advances have been made in defining the role of the newer cytokines in the induction (e.g., IL-17) and regulation (e.g., IL-27) of inflammatory arthritis (Fig. 1, Table 1). Future research into some of the newer cytokines might pose major challenges owing to the sharing of cytokine/receptor subunits among them, as with the IL-12 family of cytokines. Nevertheless, eventually the results of these investigations would allow the development of disease-specific therapeutic products that are expected to be more efficacious than the current treatment modalities.

## Acknowledgments

This work was supported by grants (R01AT004321; Moudgil, K.D.; and P01 AT002605: Berman, B.M.) from the National Center for Complementary and Alternative Medicine/National Institutes of Health, Bethesda, Maryland. We thank Dr. Berman for his encouragement and support and Hua Yu, Shivaprasad H. Venkatesha, Siddaraju M. Nanjundaiah, Ying-Hua Yang, and Rajesh Rajaiah (all from University of Maryland) for helpful discussions.

## Author Disclosure Statement

No competing financial interests exist.

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Received 9 September 2011/Accepted 9 September 2011