The New and Evolving Science of IL-6 in Rheumatoid Arthritis

The Contributions of IL-6 to Disease Manifestations of RA

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Dear Colleagues,

This is a very exciting time in the field of rheumatoid arthritis (RA). The more we understand from basic and clinical research about the pathogenesis of RA, the more equipped we are to understand this disease. We now know that cytokines play many key roles in the inflammation that drives RA. One such example is interleukin-6 (IL-6), a multifunctional cytokine that contributes to chronic inflammation in patients with RA.

Regeneron Pharmaceuticals and Sanofi Genzyme are excited to bring you additional educational material describing some of the fundamental immunology as well as clinical pathology we see in RA patients through a series of scientific monographs entitled *The New and Evolving Science of IL-6 in Rheumatoid Arthritis*. In the first installment, we reviewed the signaling mechanisms of IL-6 that allow it to have widespread effects in RA. In the second installment, we reviewed the contributions of the IL-6 pathway to bone resorption, both at the joint and more systemically, in RA. In this installment, we discuss in greater detail how persistently elevated IL-6 signaling may contribute to both articular and systemic manifestations of RA.

We hope you find this latest installment informative and engaging.

Sincerely,

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Introduction

Rheumatoid arthritis (RA) is a chronic, progressive, autoimmune disease characterized by debilitating articular and systemic manifestations.[1] Articular manifestations include pain, tender and swollen joints, and morning stiffness. Although the disease course varies among patients, RA leads to progressive joint destruction and loss of function in most cases, and may lead to physical disability.[1-3] Systemic manifestations may include anemia, fatigue, osteoporosis, rheumatoid nodules, and vasculitis. These manifestations may negatively impact prognosis and survival of patients with RA.[1,4]

It has been established that RA and other inflammatory diseases are driven by a complex network of cytokines, including tumor necrosis factor-α (TNF-α), interleukins (IL)-1, 4, 6, 12, 13, and 17, and interferons (IFN).[1,5] IL-6 is a multifunctional cytokine that performs many diverse functions, including vital pro-inflammatory roles, in response to infection or injury.[1,5] Persistently elevated IL-6 signaling may play a role in disrupting homeostasis in multiple physiologic processes, which can contribute to pathologic conditions observed in autoimmunity and chronic inflammation conditions such as RA.[6,7] Elevated IL-6 signaling plays an important role in RA, and may contribute to both articular and systemic manifestations of the disease.[1,8-11] IL-6 is one of the most abundant cytokines in the serum and synovial fluid of patients with RA and correlates with both disease activity and articular destruction.[1,12,13]

The signaling features of IL-6 allow it to interact with a broad range of cells and tissues including immune cells, fibroblast-like synoviocytes (FLS), hematopoietic stem cells, hepatocytes, adipocytes, endothelial cells, and pancreatic islets.[5,8,14-17] IL-6 can signal through both a membrane-bound receptor and a soluble receptor.[1] The latter differentiates IL-6 signaling from other cytokines such as TNF-α and IL-1, which are also implicated in driving inflammation in RA.[3,18]

This monograph will describe how the broad cell and tissue distribution of IL-6 signaling allows for its contributions to the articular and systemic manifestations seen in RA.

Elevated IL-6 Signaling Plays a Critical Role in Driving Articular Manifestations of RA[1,9,19]

Synovial joint damage is mediated by cells of the pannus. In RA, there is a marked increase in proliferation, or hyperplasia, of cells of the synovial intimal lining, which include FLS, osteoclasts, and macrophages.[20] As a result, the lining increases from a depth of 1 to 2 cells to a depth of 10 to 20 cells.[21] This expansive synovial tissue is referred

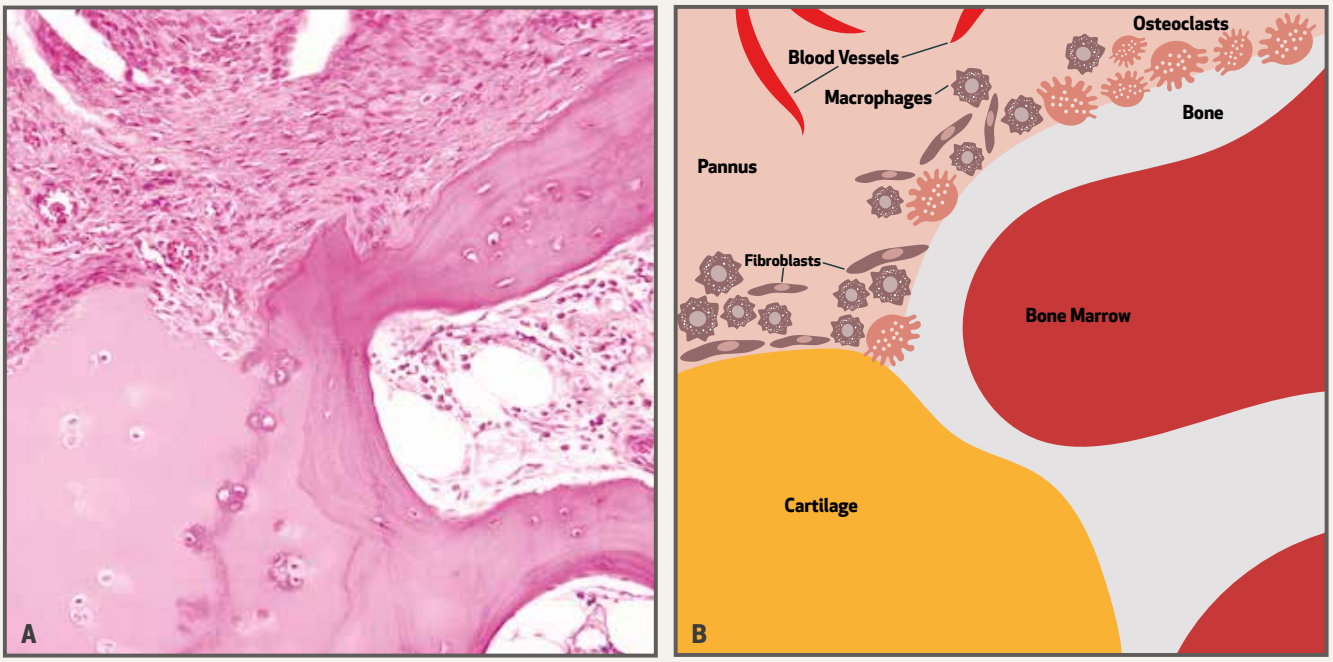

Figure 1. Pathology in a rheumatoid joint. A) A section through the ankle pannus of a patient with rheumatoid arthritis. **B)** Schematic representation. The synovial lining interfaces directly with the cartilage and bone, providing access to effector cells which mediate cartilage and bone destruction. Reprinted from the Clinical Slide Collection on the Rheumatic Diseases, © 1991, 1995, 1997. Used by permission from the American College of Rheumatology.

to as *pannus* and directly interfaces with both cartilage and bone of the joint with pathological consequences. During RA progression, FLS along with chondrocytes degrade cartilage, and the pannus invades bone, causing erosion through increased osteoclast activity **(Figure 1)**.[21,22]

FLS of the synovial intimal, or inner, lining play a key role in chronic inflammation and joint destruction in RA.[15,23,24] The invasive properties of FLS have been shown to correlate with radiographic and histological damage in RA.[25] Under normal conditions, FLS secrete proteins that help build the extracellular collagen network, which is responsible for cushioning in joints.[20] In RA, however, FLS:

- Promote inflammatory cell recruitment and activation, as well as angiogenesis, through expression of immunomodulating cytokines and mediators, including IL-6[15,21,23,24]
- Are the main effectors of cartilage breakdown due to their unique invasive properties and the production of large amounts of matrix metalloproteinases (MMPs)[21,26]
- Contribute to bone erosion and systemic osteoporosis through secretion of factors such as receptor activator of nuclear factor kappa B ligand (RANKL), which promotes osteoclast differentiation, survival, and activity[27,28]

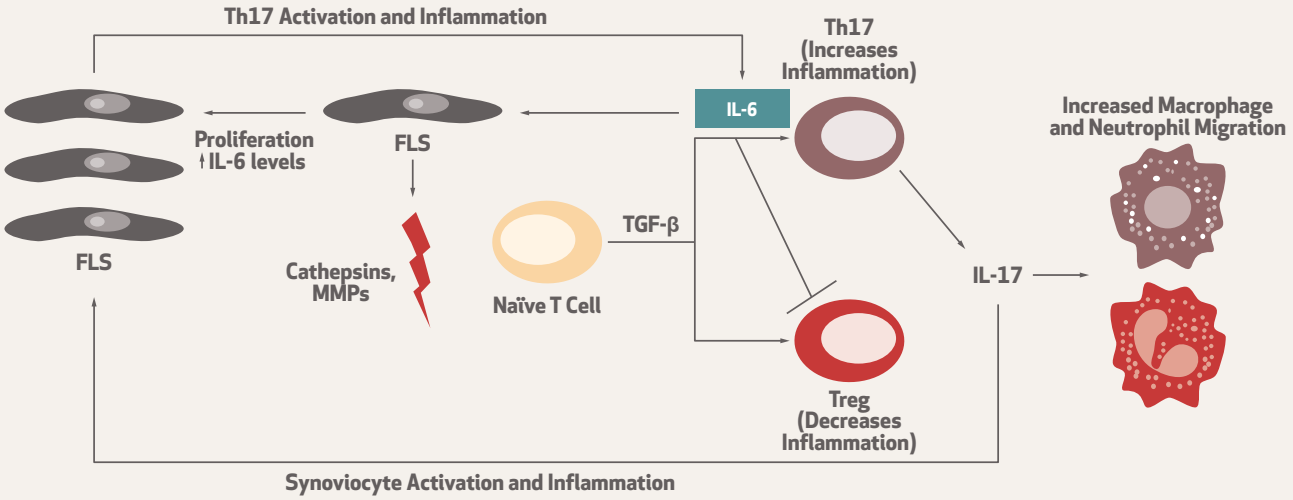

Figure 2. IL-6 forms a positive feedback loop through its effects on FLS and Th17 cells. FLS release cathepsins and matrix metalloproteases (MMPs), which degrade cartilage. In concert with TFG-β, IL-6 can induce naïve T-cells to differentiate into Th17 cells instead of Treg cells. Th17 cells in turn secrete IL-17, which has proinflammatory effects on macrophages and neutrophils. IL-17 also stimulates FLS to produce more IL-6, enhancing a feedback loop that increases inflammation.

Elevated IL-6 contributes to chronic inflammatory synovitis and promotes joint damage in RA by:

- **Activating pro-inflammatory cells and mediators both at the joint and extra-articularly,** such as neutrophils, macrophages, FLS, T cells, and B cells, and increasing the production of pro-inflammatory molecules, such as cytokines and chemokines[12,15,23,24,29-36]

- **Activating and increasing proliferation of FLS.** IL-6 both activates and is produced by FLS, establishing a positive feedback loop.[15,23,24] FLS in the intimal lining are the primary source of IL-6 in synovial joints, as shown by *in situ* hybridization and immunohistochemistry studies.[21] Because most synovial cells do not express transmembrane IL-6R in the joint, it is thought that *trans*-signaling mediates IL-6 effects on synoviocytes[37]

- **Activating Th17 cells, in combination with effects on FLS, sets up a positive feedback loop of IL-6 expression.** The combined presence of IL-6 and TGF-β stimulates naïve T cells to differentiate into Th17 cells.[38] Th17 cells in turn release more IL-6, which further promotes Th17 differentiation.[39] Th17 cells produce IL-17, which also contributes to RA pathogenesis, in part by increasing RANKL expression on osteoblasts **(Figure 2)** [5,40]

- **Stimulating osteoclastogenesis and osteoclast activity, leading to structural damage through bone resorption.** There is also evidence that IL-6 and/or sIL-6R may be implicated in the regulation of osteoclast precursors in the bone marrow (hematopoietic stem cells) before and during inflammatory arthritis[12,41,42]

- **Increasing VEGF levels synergistically with TNF-α and IL-1β.** VEGF is central to the formation and maintenance of the pannus through stimulation of angiogenesis[1,43,44]

- **Contributing to the shift from acute to chronic inflammation in RA.** The transition from acute to chronic inflammation in RA is

characterized by a shift from neutrophil to monocyte infiltration of the synovia. During acute inflammation, IL-6 is initially released by monocytes, macrophages, and endothelial cells; IL-6 signaling mediates neutrophil recruitment through activation of a subset of chemokines by endothelial cells, and by increasing expression of adhesion molecules on these cells. Soluble IL-6 receptor is in turn released from neutrophils, which increase the amounts of monocyte-specific, but not neutrophil-specific, chemoattractants secreted by endothelial cells.[45-48] It has been proposed that IL-6 and its soluble receptor may regulate the leukocyte recruitment transition through a shift in chemokine production.

During acute inflammation, IL-6 may favor the resolution of the neutrophilic infiltrate and the initiation of the immune response; in chronic inflammation, IL-6 may increase the mononuclear cell infiltrate and participate in disease pathogenesis[1,49,50]

- **Regulating B-cell differentiation and autoantibody production.** IL-6 stimulates plasmablasts to differentiate into mature plasma cells.[29,51] IL-6 can also stimulate antibody production by increasing the production of IL-21 to provide $CD4^+$ T cell-mediated B-cell help.[52,53] These functions increase B-cell interactions, sustain B-cell survival, and lead to ectopic germinal-center

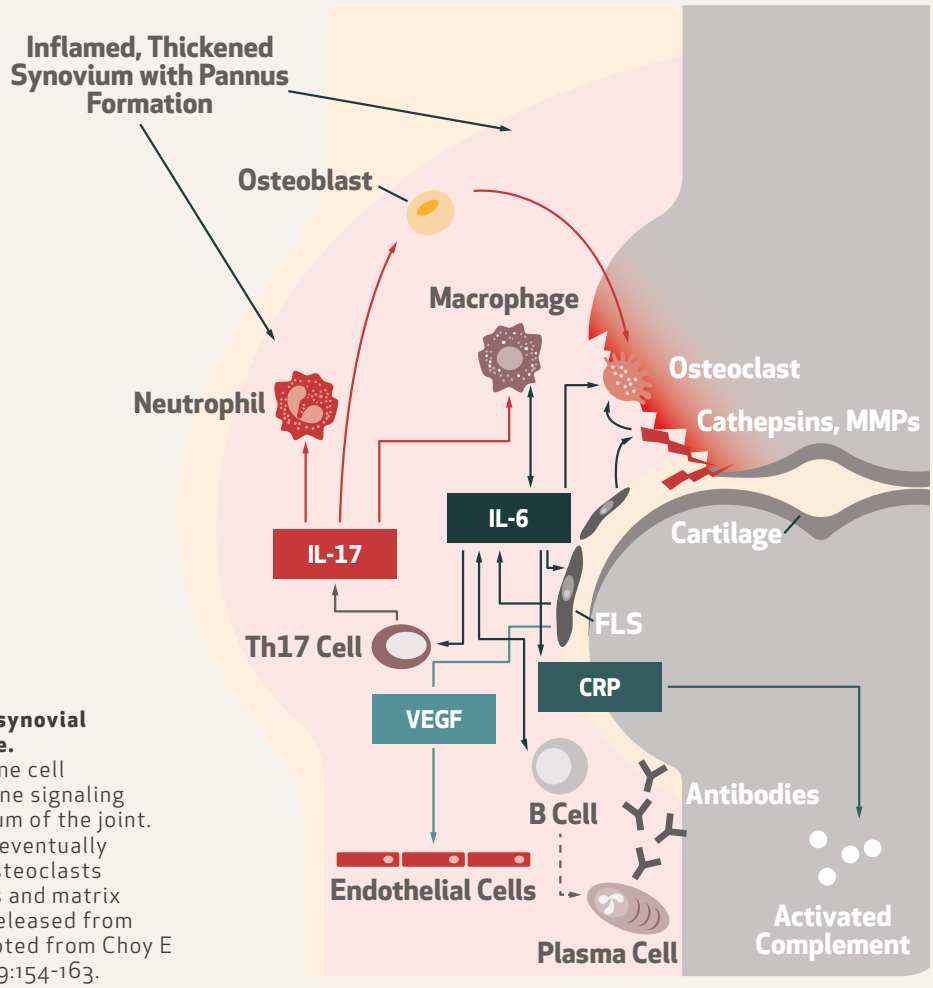

Figure 3. Pathogenesis of RA: synovial inflammation and joint damage.
In RA there is an influx of immune cell mediators and increased cytokine signaling between the cells in the synovium of the joint. This leads to inflammation and eventually joint structural damage, with osteoclasts destroying bone and cathepsins and matrix metalloproteinases (MMPs)—released from FLS—degrading cartilage. Adapted from Choy E et al. *Nat Rev Rheumatol.* 2013:9:154-163.

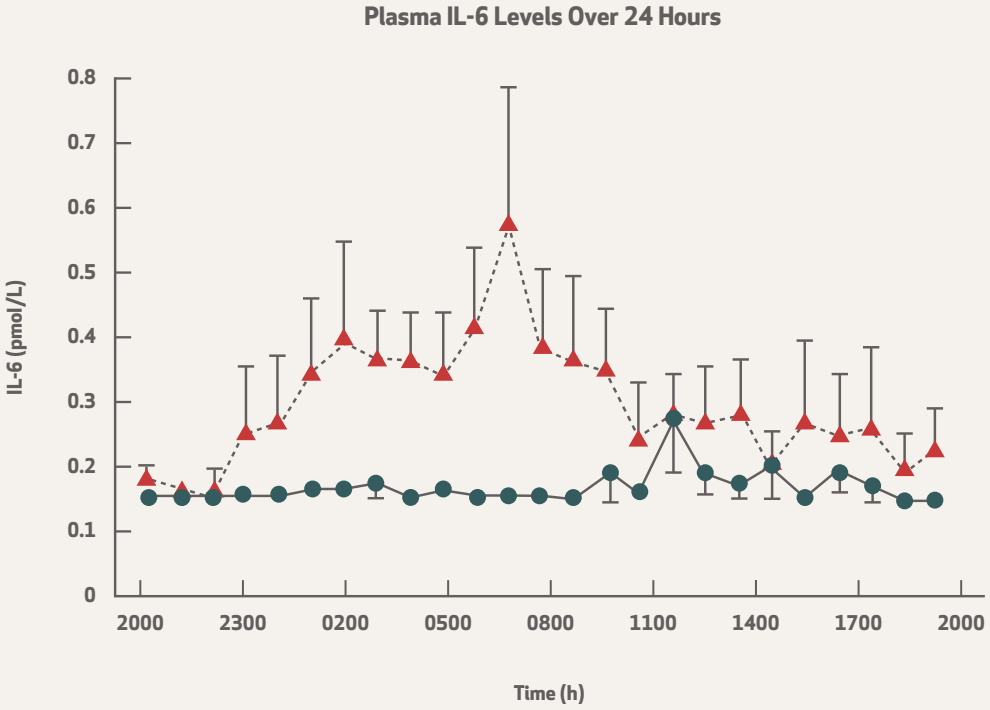

Figure 4. Diurnal variation in plasma IL-6 concentrations in 5 normal subjects (●) and 5 RA patients (▲). Samples were taken every hour over a 24-hour period.[32] Exaggerated circadian variation with respect to amplitude and timing in serum IL-6 levels was seen in patients with RA when compared with healthy subjects. The data showed that serum IL-6 levels significantly increased and were at their highest in the early morning. Adapted from Crofford LJ et al. *J Clin Endocrinol Metab.* 1997;82:1279-1283.

formation in synovial tissue.[54] Activated mature B cells trigger inflammatory and mesenchymal cells to produce cytokines, chemokines, and other pro-inflammatory factors. They also produce autoantibodies that contribute to chronic inflammation[1,5]

- **Activating and targeting the complement system to healthy tissue.** Abundant, activated complement is found in the synovial fluid of RA patients.[55] C-reactive protein (CRP), a major acute-phase protein induced by IL-6, enhances sIL-6R shedding and can activate the complement system.[56] Complement, in conjunction with autoantibody immune complexes, places a target on healthy tissues for destruction.[57] The complement cascade also contributes to inflammation by increasing cytokine production[58]

Through these diverse mechanisms, IL-6 contributes significantly to the articular pathology associated with RA (summarized in **Figure 3**).

Elevated IL-6 levels in diurnal sway and morning stiffness

Serum IL-6 levels are at their highest in the early morning hours when patients with RA particularly experience articular pain and stiffness, as well as functional disability **(Figure 4)**.[32,59,60] This morning stiffness is related to both increased levels of IL-6 and decreased levels of cortisol.[61] Diurnal variation of IL-6 levels is thought to be controlled at a systemic level through signaling pathways originating from the central circadian clock, and at a local level by autonomous clocks in inflammatory cells and tissues.[60] In

vitro, macrophages and synoviocytes both demonstrate rhythmic IL-6 responses or circadian oscillations.[62,63]

In humans, levels of cortisol are downregulated during the evening and upregulated in the early morning. In patients with RA, the ratio of serum cortisol to serum pro-inflammatory cytokines is reduced compared with healthy subjects, leading to articular pain and stiffness in the early morning, when IL-6 levels are increased. In healthy subjects and cancer patients, investigational administration of exogenous IL-6 leads to a dose-dependent increase in plasma cortisol levels; however, repeated IL-6 administration leads to a blunting of this response.[61]

Elevated IL-6 Signaling and Its Potential Correlation With Systemic Manifestations of RA

As mentioned, IL-6 is one of the most abundant cytokines in the serum and synovial fluid of patients with RA.[1,12,13] In RA, IL-6 is synthesized and secreted by cells of the synovia of inflamed joints including FLS, monocytes/macrophages, and neutrophils.[5,16,19] IL-6 originating from articular sources can then diffuse into circulation and affect a broad range of distal cells/tissues due to its dual signaling mechanism. Consistent with this, increased IL-6 levels may be associated with systemic manifestations of RA, which are described below **(Figure 5)**.

Induction of acute-phase proteins

C-reactive protein (CRP)

IL-6 signaling is a major contributor to induction of CRP and other acute-phase proteins. The acute-phase response is the change in the concentration of certain plasma proteins, such as CRP, hepcidin, and serum amyloid A, which are produced by the liver in response to infection, tissue injury, neoplastic growth, or immunological disorder.[1,8,64,65] IL-6 is a major inducer of acute phase protein levels, although other cytokines such as IL-1, TNF-α, TGF-β1, and IFN-γ also have stimulatory effects.[4,64] Peak values of CRP usually occur within 24 to 72 hours after experimental induction with IL-6 and last for several days, although circulating levels remain elevated in cases of chronic inflammation.[64]

A prospective study found that an elevated baseline CRP level was a significant predictive factor for radiographic damage at 3 years in patients with RA.[66] Several studies investigating the relationship between CRP levels and cardiovascular disease (CVD)

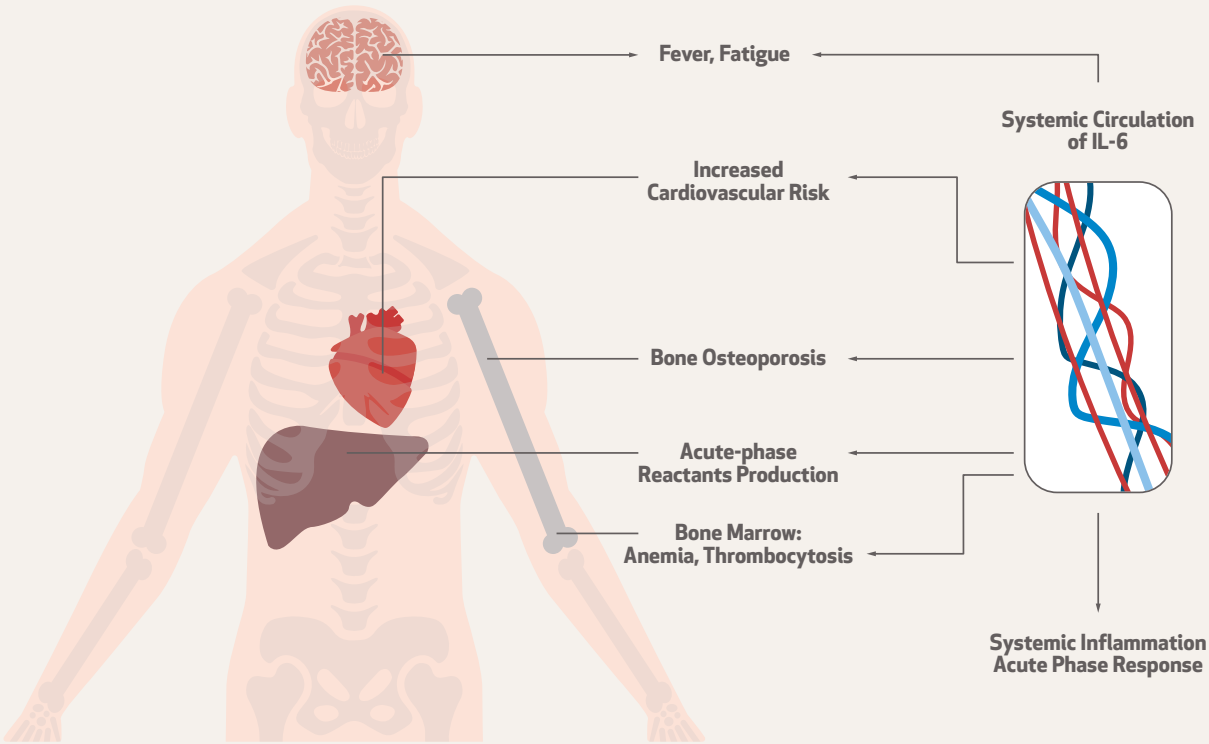

Figure 5. Potential association of IL-6 and RA systemic effects.
Persistently elevated IL-6 signaling may be associated with several systemic manifestations of RA.

have found that CRP is associated with an increased risk of myocardial infarction, stroke, sudden death from cardiac causes, and peripheral arterial disease. RA patients are at higher risk for cardiovascular illness (standardized mortality rate, ~1.5) which includes myocardial infarction, cerebrovascular events, and heart failure.[67] Data suggest that CRP levels are a strong predictor of cardiovascular events, as evidenced by improved clinical outcomes in a general patient population with lowered CRP levels following statin therapy compared to those with higher CRP levels, regardless of the resultant level of low-density lipoprotein (LDL) cholesterol.[4,5,68-70]

Hepcidin

Elevated IL-6 signaling may lead to hypoferremia through induction of hepcidin.

IL-6 increases production of hepcidin, an acute-phase protein that is a key regulator of iron homeostasis with antimicrobial properties.[71-73] In a study of six healthy human volunteers infused with IL-6, urinary hepcidin levels rose 7.5-fold within 2 hours.[72] IL-6 induces hepcidin expression in the liver via the JAK-STAT signaling pathway. Hepcidin reduces iron bioavailability, which is critical for new hemoglobin synthesis, by inhibiting iron uptake in the duodenum and iron release from macrophages in the spleen and elsewhere.[1,5,72] As a result, when hepcidin levels are increased, concentrations of iron in the blood are limited, a condition referred to as hypoferremia.[65]

Effects of persistent elevated hepcidin levels in RA and the prevalence of anemia, sleep disturbances, and fatigue

Hepcidin is a potential contributing cause of anemia in patients with chronic inflammatory disease.[1,65] Anemia is one of the most frequent systemic manifestations of RA, occurring in approximately one-third of patients, and has been associated with more severe joint disease.[74,75] In addition, anemic patients with RA tend to have greater radiographic progression than non-anemic patients.[76,77] In humans, serum hepcidin levels have been shown to be highest in patients with RA and anemia, whereas healthy adults have been reported to have the lowest levels.[78] Baseline hepcidin levels also correlated with CRP levels.[79,80]

Anemia is a common contributor to fatigue.[4,81] 40% to 80% of rheumatoid arthritis patients report fatigue as their most disabling symptom.[82] In addition to its role in hepcidin production, IL-6 has also been associated with other causes of fatigue.[83] IL-6–induced effects have been linked to functions of the HPA (hypothalamic-pituitary-adrenal) axis, including fatigue, and elevated levels of IL-6 have been positively correlated with fatigue in RA.[1,4,84,85] Studies have also shown that circulating levels of IL-6 may contribute to sleep disturbances in several different patient populations.[83]

Contributing effects of elevated IL-6 signaling on energy homeostasis in RA

IL-6 functions as an energy sensor. Prolonged myocyte activation during sustained exercise depletes glycogen stores, thus triggering a cascade of compensatory responses. Glycogen depletion induces myocytes to produce and secrete IL-6 into plasma.[86] Following exercise, plasma IL-6 concentration may increase up to 100-fold, but less dramatic increases are more frequent.[86] Circulating IL-6 promotes the conversion of hepatic glycogen into glucose, and subsequent glucose uptake and utilization by skeletal muscle. In contrast, TNF-α levels are not increased by myocytes in response to sustained exercise.[87,88] In the context of muscle tissue, IL-6 also stimulates the production of anti-inflammatory cytokines and actually suppresses TNF-α production, which suggests IL-6 offers protection against TNF-induced insulin resistance.[89-91] A recent study also suggests that IL-6 may have a beneficial role in the prevention of obesity-associated insulin resistance through a polarization of macrophages from a pro-inflammatory to an anti-inflammatory phenotype.[92]

IL-6 plays important roles in the endocrine functions of pancreatic islet cells, specifically α and β cells.[93] The IL-6 receptor is expressed by α cells, and IL-6 treatment of α cells promotes their proliferation and acutely regulates pro-glucagon gene expression and glucagon secretion.[93] β cells are a source of IL-6, and experimental models have shown

that IL-6 protects the β-cell population from TNF-α- and IFN-γ–induced apoptosis, and preserves insulin secretory functions.[14,94]

Adipose tissue stores triglycerides and is an active endocrine organ with a central role in maintaining normal energy homeostasis.[95,96] Adipocytes communicate with other cells involved in energy homeostasis through release of adipokines—cytokines secreted by adipose tissue—such as leptin and adiponectin.[97,98] IL-6 also functions as an adipokine; it can increase adipose cell size, and modulate leptin production and lipid metabolism.[99,100]

The persistently elevated levels of circulating cytokines such as IL-6 in RA could be one of the contributing factors to muscle and adipose tissues becoming insulin-resistant during chronic inflammation, a condition referred to as an "inflammatory metabolic" state.[67,101,102] In addition, the biochemical composition of lipids is altered in response to chronic inflammation. Rheumatoid arthritis is associated with reduced serum levels of total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL), cholesterol. Although effective therapies raise HDL, LDL, and total cholesterol levels as a consequence of reducing inflammation, these therapies also reduce the risk of cardiovascular events in patients with RA.[67,103]

Circulating levels of IL-6 are elevated in some insulin-resistant states such as obesity.[104] Higher inflammatory activity and a reduced functional activity are associated with obesity in RA patients.[105] Growing evidence suggests that IL-6 is not only produced by adipocytes but is also capable of inducing insulin resistance in these cells.[106-110]

Effects of elevated IL-6 signaling on bone metabolism in RA

RA leads to increased bone destruction, which places patients at risk for fractures.[1,111] In the clinical evaluation of synovial fluid from patients with RA, it was determined that the ratio of RANKL to osteoprotegerin (OPG), a protein that binds directly to RANKL and inhibits it from interacting with its receptor, reflects osteoclast function, and a higher ratio of RANKL to OPG is correlated to osteoclast hyperactivity and bone resorption in joints in patients with RA.[23,42,112-115]

Similar to more general cases of inflammation, IL-6 can affect the RANKL/OPG ratio through two mechanisms during RA inflammation. First, IL-6 directly stimulates osteoblasts to increase expression of RANKL, which can be bound by osteoclasts and drive their activation. Second, IL-6 directly stimulates Th17 cells, which produce IL-17; IL-17 levels are significantly higher in the synovial fluid of patients with RA.[116,117] IL-6 induces macrophages/monocytes to produce IL-1 and TNF-α. IL-17, IL-1, and TNF-α all stimulate effector T-cell proliferation and activation, which contribute to tissue damage in patients with RA. Importantly, these newly formed, activated T cells can express RANKL.[118] Therefore, the increased number of T cells expressing RANKL increases the ratio of RANKL to OPG and thereby enhances osteoclast function.[119,120] The increased

osteoclast function shifts the balance of bone resorption/formation toward resorption, resulting in reduced bone mineral density in patients with RA. Elevated IL-6 signaling also inhibits bone regeneration by affecting osteogenesis.[1,23,112,113,115] The increased bone resorption activity associated with RA translates to articular bone damage and systemic bone loss.[121-123]

Elevated IL-6 levels are associated with generalized bone mineral density loss, a common systemic manifestation of RA.[1,5,124-126] The prevalence of bone mineral density loss in the overall RA patient population has been reported as between 20% and 56%.[123,124,127-129] The disruption of homeostasis caused by elevated IL-6 signaling, and the resultant increase in bone resorption, can lead to overall bone mineral density loss, bone weakening, cartilage destruction, and an increased susceptibility to fracture.[130]

Bone mineral density loss is especially prevalent in postmenopausal women with RA; generalized bone mineral density loss occurs in >50% of this population compared with ~15% in postmenopausal women without RA.[131] Studies have shown that estrogen blocks the synthesis of IL-6 by bone-forming osteoblasts and may also interfere with expression of IL-6 receptors. Elevated serum levels of IL-6 and sIL-6R have also been associated with bone mineral density loss in postmenopausal women with RA, independent of glucocorticoid (GC) use.[132] Elevated serum levels of sIL-6R have also been shown to be the main predictor of bone mineral density loss in a study of postmenopausal women with RA, independent of well-known risk factors of generalized bone loss such as age, disease duration, low body mass index, and cumulative GC dose.[125,133]

Conclusions

IL-6 is a multifunctional cytokine mediating key functions within the complex cytokine network.[1,5] The broad range of IL-6 activities is due in large part to its ability to signal through both transmembrane and soluble forms of its receptors, allowing for interaction with cells that do not express the IL-6 receptor, resulting in expanded biological activity.[1] As a result, IL-6 performs many diverse functions, including vital pro-inflammatory functions, in response to infection or injury under normal physiological conditions. Conversely, persistent elevated IL-6 signaling may have a negative impact that can disrupt homeostasis across multiple physiologic processes. Particularly in RA, IL-6 contributes to articular destruction and may be associated with systemic manifestations that culminate in functional disability.[1,3-5,9,134] Continued research on the many functions of IL-6 may further delineate the pathological origins and underpinnings of RA.

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