IL-6 is a multifunctional cytokine that is associated with articular inflammation, synovial fibroblast proliferation, and osteoclastogenesis. It is involved in a variety of cells and physiologic processes throughout the body. Normal levels of IL-6 are vital for homeostasis, but in rheumatoid arthritis, IL-6 plays a role in disrupting homeostasis by affecting the function of a variety of cells and tissues. IL-6 induces the proliferation of synovial fibroblastic cells in the presence of soluble IL-6 receptor.

The role of IL-6 in the pathogenesis of rheumatoid arthritis is well-documented. Interleukin-6 (IL-6) is produced by osteoblasts and induces bone resorption. IL-6 is also produced by circulating monocytes and macrophages, which are activated in the inflammatory synovial fluid of rheumatoid arthritis patients. IL-6 is closely associated with other proinflammatory cytokines, chemotactic activity, and neutrophil activation in rheumatoid synovial fluid. IL-6 is a permissive factor for monocytic colony formation by human hematopoietic progenitor cells.

IL-6 is a key mediator in the development of autoimmune diseases. IL-6 receptors (IL-6R) are expressed on the surface of many cell types, including T cells, B cells, and monocytes/macrophages. IL-6R binding to IL-6 triggers signaling that can lead to the differentiation of Th17 cells and the development of autoimmune diseases. IL-6 signaling can also lead to bone resorption and cardiovascular disease, highlighting the role of IL-6 in the systemic inflammation associated with rheumatoid arthritis.

Therapeutic targets in rheumatoid arthritis include the IL-6 receptor. Inhibiting IL-6 and its receptor has been shown to improve disease activity and control symptoms in rheumatoid arthritis patients. Tocilizumab, a humanized anti-IL-6 receptor monoclonal antibody, is approved for the treatment of rheumatoid arthritis and has been shown to be effective in reducing the signs and symptoms of the disease. The role of IL-6 in rheumatoid arthritis continues to be a focus of research, with the goal of developing new and effective therapeutic strategies.
IL-6 signaling features can impact a wide variety of cells

**IL-6 signals through 2 distinct mechanisms**

- IL-6 can signal through membrane-bound receptors (classical or cis-signaling)
- IL-6 can also signal through soluble forms of its receptors (trans-signaling)

These 2 distinct signaling mechanisms allow IL-6 to interact with cells that do or do not express the IL-6 membrane-bound receptor (mIL-6R).

In RA, multiple cytokines, including IL-6, TNF-α, IL-1, and IL-17, signal through membrane-bound receptors.

- Receptors for tumor necrosis factor (TNF-α) or IL-1 are also expressed as membrane-bound and soluble forms.
- Inflammatory signaling for TNF-α and IL-1 is mediated by the membrane-bound form of the receptor.

**Elevated IL-6 signaling can disrupt homeostasis in multiple physiologic processes**

- The presence of both membrane-bound and soluble receptor’s allows IL-6 to expand its range of biological activity interacting with cells and tissues such as:
  - Immune cells
  - Synovial fibroblasts
  - Hematopoietic stem cells
  - Hepatocytes
  - Adipocytes
  - Endothelial cells
  - Pancreatic islets

- Persistently elevated IL-6 levels contribute to chronic inflammation and have been associated with disease progression in RA.
- May affect metabolism (lipid, glucose), hematopoiesis, the central nervous system, and host defense.

- IL-6 signaling is a major contributor to induction of C-reactive protein (CRP) and other acute-phase proteins.

**In RA, sIL-6R has effects on several cell types, such as fibroblast-like synoviocytes (FLS cells), osteoblasts, and endothelial cells, which helps to explain the broad spectrum of biological activity seen with IL-6.**

---

Adapted from Choy 2004.
IL-6 plays a central role in the articular manifestations of RA\cite{6,11,32,33}

IL-6 is one of the most abundant cytokines in the serum and synovial fluid of the inflamed joints of patients with RA and is associated with disease activity and articular destruction\cite{1,2,22,45,51}.

- Under normal physiologic conditions, IL-6 performs many functions—including vital pro-inflammatory functions in response to infection or injury\cite{11,21,27}.
- Persistently elevated IL-6 levels are a key driver in the dysfunctional and chronic inflammatory milieu in RA\cite{11,12}.

**Elevated IL-6 perpetuates chronic synovitis**\cite{13,34,35,9}:

- Activates pro-inflammatory cells and mediators within the joints, such as neutrophils, macrophages, FLS cells, T cells, and B cells\cite{33,36-42}.
- Degrades cartilage by activating FLS cells and chondrocytes to release cathepsins and MMPs\cite{23,43-46}.
- Stimulates osteoclastogenesis and osteoclast activity leading to structural damage through bone resorption. There is also evidence that IL-6 and/or sIL-6R is implicated in the regulation of osteoclast precursors in the bone marrow (hematopoietic stem cells) before and during inflammatory arthritis\cite{32,33,39,46-48}.
- Activates pro-inflammatory cells and mediators within the joints, such as neutrophils, macrophages, FLS cells, T cells, and B cells.
- Degrades cartilage by activating FLS cells and chondrocytes to release cathepsins and MMPs.
- Stimulates osteoclastogenesis and osteoclast activity leading to structural damage through bone resorption.

Serum IL-6 levels are at their highest in the early morning hours, when patients with RA most often experience articular pain and stiffness, as well as functional disability\cite{3,49,50}.

- In one study, samples were taken every hour over a 24-hour period in 5 patients with RA and 5 without\cite{3}.
- Serum IL-6 levels spiked dramatically in patients with RA—peaking in the early morning—compared to people without RA\cite{3}.

*Based on pre-clinical, ex-vivo, and clinical data.

Fibroblast-like synoviocytes play a key role in chronic inflammation and joint destruction in RA\cite{11,45,51}.

There is an influx of immune cell mediators and increased cytokine signaling between the cells in the synovium that leads to inflammation and eventual structural joint damage through increased osteoclast activity\cite{11}.

Serum IL-6 levels are at their highest in the early morning hours, when patients with RA most often experience articular pain and stiffness, as well as functional disability\cite{3,49,50}.

- In one study, samples were taken every hour over a 24-hour period in 5 patients with RA and 5 without\cite{3}.
- Serum IL-6 levels spiked dramatically in patients with RA—peaking in the early morning—compared to people without RA\cite{3}.

*Based on pre-clinical, ex-vivo, and clinical data.
Effects of persistently elevated IL-6 levels may play a role in systemic manifestations of RA\textsuperscript{1,3,31}

Elevated IL-6 levels may contribute to anemia, fatigue, and other systemic manifestations of RA\textsuperscript{1,3,11}

- Lipid metabolism through interactions with adipose tissue\textsuperscript{53,54}
- Low-density lipoprotein (LDL) cholesterol metabolism\textsuperscript{55}
- Systemic inflammation through its actions on the liver, which increases CRP and serum amyloid A (SAA)\textsuperscript{1}
- Inducer of CRP\textsuperscript{11}
- Vascular endothelial dysfunction\textsuperscript{11,56}
- Hypoferremia through induction of hepcidin—a potential cause of anemia\textsuperscript{1}
- Anemia of chronic disease\textsuperscript{1}
- Fatigue\textsuperscript{1}
- Osteoclast activation\textsuperscript{1}
- Generalized bone mineral density loss\textsuperscript{39}
- Auto-antibody production\textsuperscript{11}
- Dysregulation of T cells and B cells\textsuperscript{11,39,41}

IL-6 contributes to articular destruction and has been associated with the systemic manifestations of RA\textsuperscript{1,3,11,39,41}
THE ROLE OF IL-6 IN RHEUMATOID ARTHRITIS

- RA is a chronic systemic disease driven by a complex network of cytokines.
- IL-6 is a multifunctional cytokine that is associated with articular and systemic manifestations of RA.
- IL-6 has signaling features that can impact the functions of a wide variety of cells and physiologic processes throughout the body.

THE ROLE OF IL-6 IN RHEUMATOID ARTHRITIS

- Rheumatoid arthritis (RA) is a chronic systemic disease driven by a complex network of cytokines.
- Interleukin-6 (IL-6) is a multifunctional cytokine that has been associated with articular and systemic manifestations of RA.
- While normal levels of IL-6 are vital for homeostasis in the inflammatory process, persistent, elevated IL-6 levels may play a role in disrupting homeostasis by affecting the function of a broad range of cells.

SANOFI GENZYME

© 2017 Sanofi and Regeneron Pharmaceuticals, Inc. All Rights Reserved. 12/19/09 03:16. REV:03/19/10