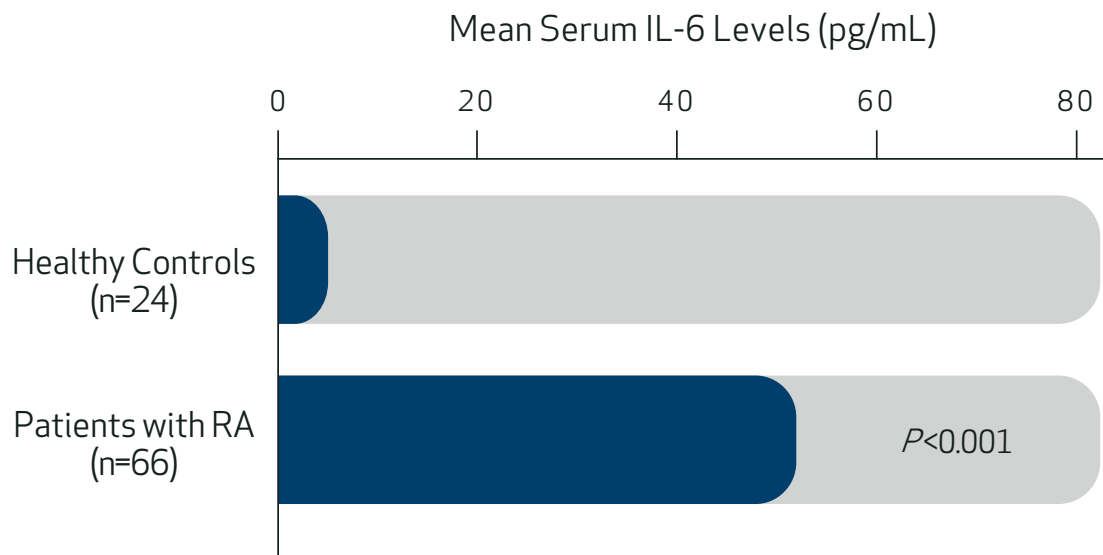


The Importance of IL-6 in Rheumatoid Arthritis

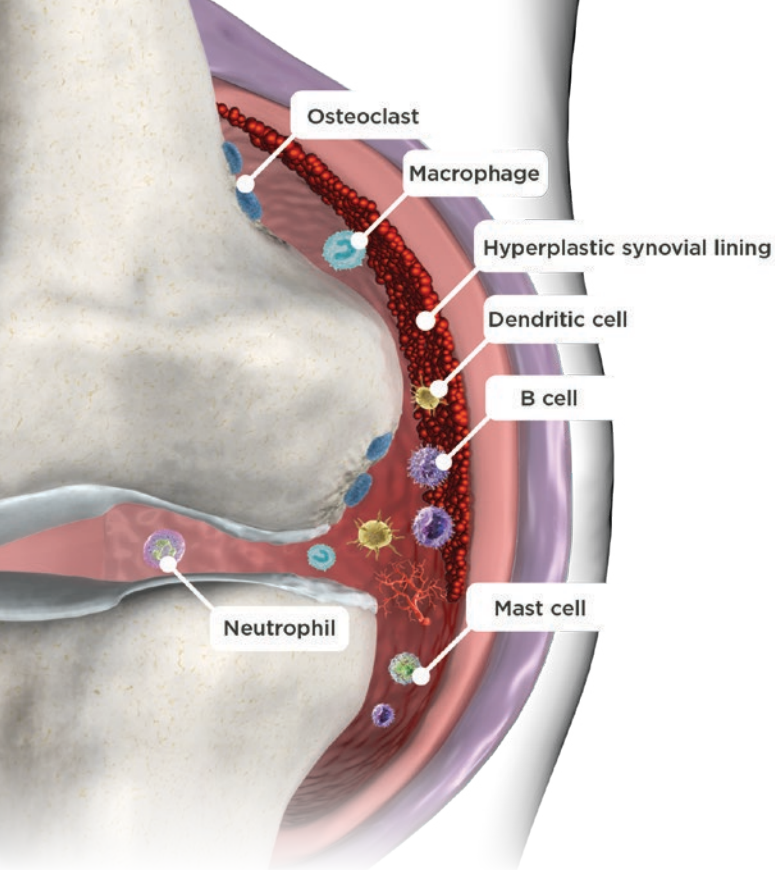
A Key Driver of Articular and Systemic Manifestations

Interleukin-6 (IL-6) is one of the most abundant cytokines in the serum and synovial fluid of patients with rheumatoid arthritis (RA) and plays a pivotal role in chronic inflammation¹⁻³

Mean serum IL-6 levels were approximately 10 times higher in patients with RA⁴



In a single-center controlled study, serum concentrations of IL-6 were measured in healthy subjects and adult RA patients, and the levels were correlated with disease activity⁴

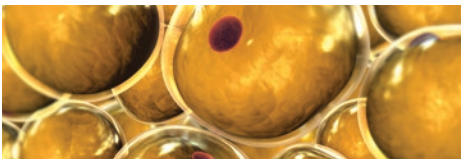


Elevated IL-6 perpetuates chronic synovitis and promotes joint destruction through^{1,5}:

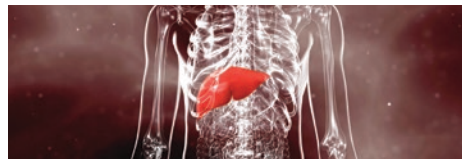
- Activation of proinflammatory cells and mediators within the joints, such as neutrophils, macrophages, fibroblast-like synoviocytes (FLS), T cells, and B cells^{1,6-10}
- Activation of FLS and chondrocytes, leading to degradation of cartilage^{1,5}
- Stimulation of osteoclastogenesis and osteoclast activity, leading to structural damage through bone resorption^{1,6}

Adapted from Choy 2012.⁵

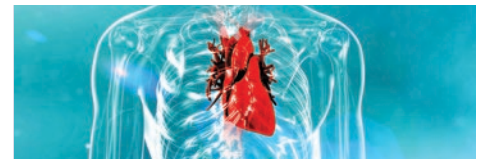
Persistently elevated IL-6 levels may contribute to structural damage, fatigue, morning stiffness, and other systemic manifestations of RA^{5,10,11}



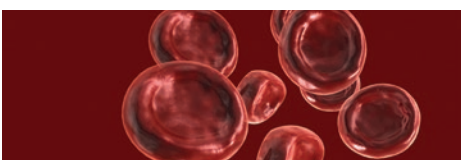
- Lipid metabolism through interactions with adipose tissue^{12,13}



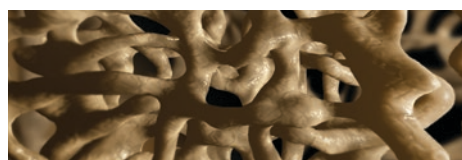
- Increased hepatocyte production of C-reactive protein (CRP) and serum amyloid A (SAA)⁵



- Contributes to vascular endothelial dysfunction^{1,14}



- Induction of hepcidin, leading to hypoferremia⁵
- Lower hemoglobin levels and fatigue⁵



- Osteoclast activation that leads to bone resorption^{5,15}

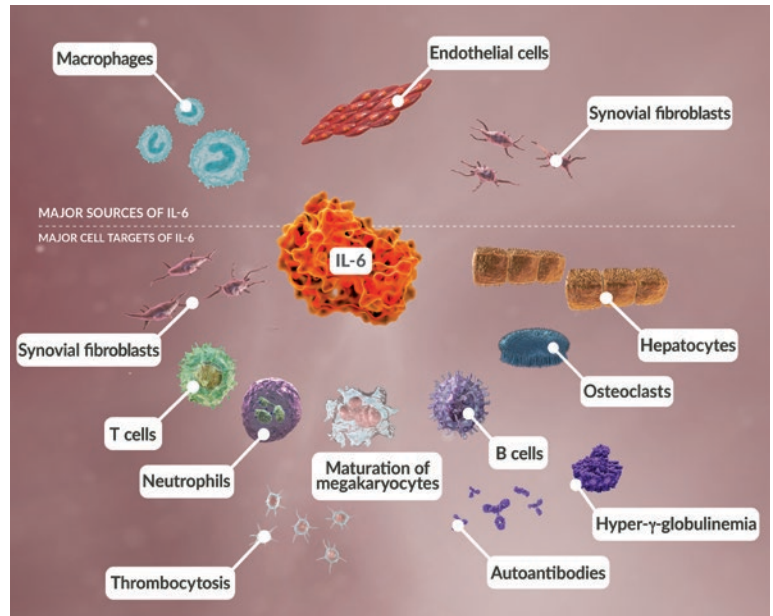


- Regulation of T cells and B cells^{1,15}
- Autoantibody production¹

IL-6 Is a Multifunctional Cytokine That Is Vital for Maintaining Immunological Homeostasis¹⁶

In the Inflammatory Process, IL-6 Has Various Roles, Including²:

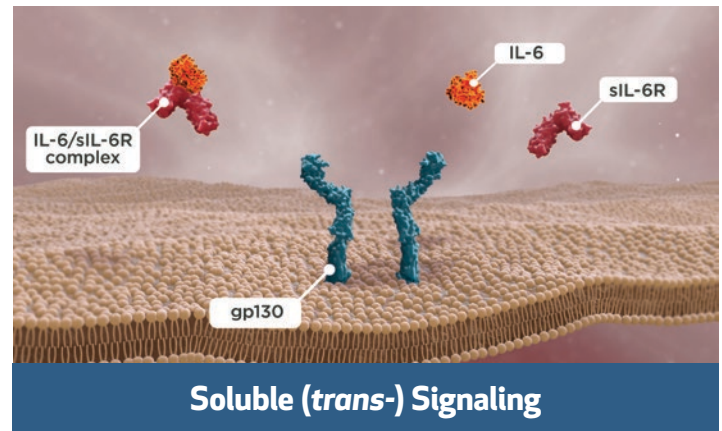
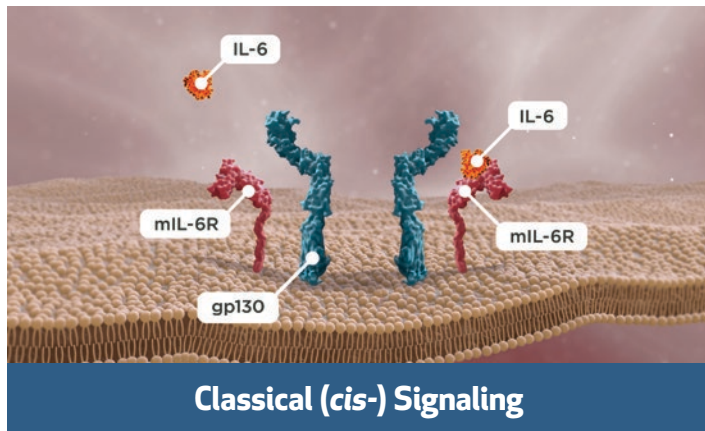
- IL-6 levels are greatly increased in response to infection or injury, helping to promote and coordinate the proinflammatory activities of cells throughout the body^{16,17}
 - Once the infection or injury is resolved, circulating IL-6 levels are restored to basal levels¹⁶
- In RA, persistently elevated IL-6 may disrupt homeostasis in multiple physiologic processes through its actions on a broad range of cells^{1,5}



Adapted from Choy 2004.¹⁸

IL-6 signals through 2 distinct mechanisms³

- 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 expand its range of biological activity and interact with cells that do or do not express the IL-6 membrane-bound receptor (mIL-6R)



In RA, the widespread effects of elevated IL-6 stem from its ability to signal via both soluble and membrane-bound receptors, thereby impacting a wide variety of cells¹

IL-6—a multifunctional cytokine that:

- Is one of the most abundant cytokines in the serum and synovial fluid of patients with RA¹
- At normal levels, is vital for maintaining immunological homeostasis¹⁶
- Has various roles in the inflammatory process²
- At persistently elevated levels, is a key driver of articular and systemic manifestations and chronic inflammation of RA^{1,5}
- Impacts a wide variety of cells and physiologic processes throughout the body due to its unique dual signaling mechanism^{1,5}

References

1. Dayer J-M, Choy E. Therapeutic targets in rheumatoid arthritis: the interleukin-6 receptor. *Rheumatology (Oxford)*. 2010;49:15-24.
2. Tutuncu Z, Kavanaugh A. Anticytokine therapies. In: Firestein GS, Budd RC, Gabriel SE, McInnes IB, O'Dell JR, eds. *Kelley's Textbook of Rheumatology*. 9th ed. Philadelphia, PA: Elsevier/Saunders; 2013:chap 63.
3. Rose-John S, Scheller J, Elson G, Jones SA. Interleukin-6 biology is coordinated by membrane-bound and soluble receptors: role in inflammation and cancer. *J Leukoc Biol*. 2006;80:227-236.
4. Robak T, Gladalska A, Stepień H, Robak E. Serum levels of interleukin-6 type cytokines and soluble interleukin-6 receptor in patients with rheumatoid arthritis. *Mediators Inflamm*. 1998;7:347-353.
5. Choy E. Understanding the dynamics: pathways involved in the pathogenesis of rheumatoid arthritis. *Rheumatology (Oxford)*. 2012;51(suppl 5):v3-v11.
6. Wong PK, Quinn JM, Sims NA, van Nieuwenhuijze A, Campbell IK, Wicks IP. Interleukin-6 modulates production of T lymphocyte-derived cytokines in antigen-induced arthritis and drives inflammation-induced osteoclastogenesis. *Arthritis Rheum*. 2006;54:158-168.
7. Hashizume M, Hayakawa N, Mihara M. IL-6 trans-signalling directly induces RANKL on fibroblast-like synovial cells and is involved in RANKL induction by TNF-alpha and IL-17. *Rheumatology (Oxford)*. 2008;47:1635-1640.
8. Chomarat P, Banchereau J, Davoust J, Palucka AK. IL-6 switches the differentiation of monocytes from dendritic cells to macrophages. *Nat Immunol*. 2000;1:510-514.
9. de Hooge ASK, van De Loo FAJ, Arntz OJ, van Den Berg WB. Involvement of IL-6, apart from its role in immunity, in mediating a chronic response during experimental arthritis. *Am J Pathol*. 2000;157:2081-2091.
10. Tanaka T, Kishimoto T. Targeting interleukin-6: all the way to treat autoimmune and inflammatory diseases. *Int J Biol Sci*. 2012;8:1227-1236.
11. Gibbs JE, Ray DW. The role of the circadian clock in rheumatoid arthritis. *Arthritis Res Ther*. 2013;15:1-9.
12. Trujillo ME, Sullivan S, Harten I, Schneider SH, Greenberg AS, Fried SK. Interleukin-6 regulates human adipose tissue lipid metabolism and leptin production in vitro. *J Clin Endocrinol Metab*. 2004;89:5577-5582.
13. Hashizume M, Mihara M. The roles of interleukin-6 in the pathogenesis of rheumatoid arthritis. *Arthritis*. 2011;2011:765624. doi:10.1155/2011/765624.
14. Sattar N, McCarey D, Capell H, McInnes IB. Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. *Circulation*. 2003;108:2957-2963.
15. Maggio M, Guralnik JM, Longo DL, Ferrucci L. Interleukin-6 in aging and chronic disease: a magnificent pathway. *J Gerontol A Biol Sci Med Sci*. 2006;61:575-584.
16. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol*. 2014;6:a016295. doi:10.1101/cshperspect.a016295.
17. Chaudhry H, Zhou J, Zhong Y, et al. Role of cytokines as a double-edged sword in sepsis. *In Vivo*. 2013;27:669-684.
18. Choy E. Clinical experience with inhibition of interleukin-6. *Rheum Dis Clin North Am*. 2004;30:405-415.