INTERLEUKIN-6: AN INFLAMMATORY REGULATOR

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ABSTRACT

IL-6 is an important cytokine in the early steps of inflammation. It is secreted by various cells including endothelial cells and plays a key role in the acute phase response and in the immune response through T and B cell activation, thus favouring chronic inflammation. IL-6 directs transition from acute to chronic inflammation by changing the nature of leucocyte infiltrate i.e., from polymorphonuclear neutrophils to monocyte/macrophages. The prevention and treatment of chronic inflammatory diseases can be achieved by targeting IL-6 and IL-6 signalling.

KEYWORDS

IL-6, Inflammation, IL-6R, sIL-6R, gp130, Tocilizumab.


INTRODUCTION

Inflammation

Inflammation is the body defense against infection or injury or as a consequences of disease. It can be acute or chronic inflammation. Acute inflammation is transient beneficial response in which initially the leucocyte infiltration mostly with neutrophils and monocyte infiltration occurs after 24-48 hours. (1-3) Chronic inflammation is persistent phenomenon with the presence of mononuclear cells such as macrophages and lymphocytes. (1,2) The transition from neutrophil to monocyte/macrophage recruitment during the transformation of acute to chronic inflammation is possibly due to IL-6 and its receptor complex. (4)

IL-6 (INTERLEUKIN-6)

IL-6 is a cytokine with variety of biological activities. (5) It is the member of the gp130 related cytokine family. It is also called as Interferon-β2,26-kd protein, B cell stimulatory factor-2, and hybridoma growth factor. (6) Its functions in cells are carried out through receptor called IL-6Rα or CD126 (7) IL-6 is a complex receptor consisting of transducing protein gp 130 which is present on almost all cell types. (8) IL-6R may present as a membrane-bound protein which is expressed by hepatocytes, neutrophils and mononuclear cells. (9) and a soluble form (sIL-6Rα) which is present in circulation and at inflammatory sites. sIL-6Rα are formed through membrane shedding or alternative splicing can bind IL-6 and protect it against enzyme inactivation. (9-11) IL-6 signalling through membrane-bound IL-6R as classical IL-6R signalling and IL-6/sIL-6Rα complex can bind to gp 130 on a cell membrane and activate cells in a mechanism called trans-signalling. (12) Trans-signalling leads to activation of receptor associated kinases (JAK1, JAK2 and Tyk2) within the cell after dimerization of gp 130.

In turn these leads to phosphorylation of proximal tyrosine residues within the intracellular portion of gp 130, and subsequent control of STAT1 and STAT3 activity and Src homology region 2 domain containing phosphatase 2 cascade. (13)

IL-6 has dual action even though it is traditionally considered as a regulator of acute phase inflammatory responses and a lymphocyte stimulatory factor. (13) It also control homeostatic function such as glucose metabolism. (14,15) and hypothalamic-pituitary-adrenal axis. (16) It has anti-inflammatory and proinflammatory properties in vivo and in vitro. (17)

IL-6 AND ACUTE INFLAMMATION

The acute phase response in acute inflammation leads to numerous changes such as the concentration of plasma proteins (Acute phase proteins), behavioural, physiological, biochemical and nutritional changes. (18) Acute phase protein changes are due to changes in their production by hepatocytes. The acute phase proteins are produced by stimulation of cytokines which are produced during inflammatory process. These cytokines are IL-6, IL-1β,TNF-α, Interferon-γ, transforming growth factor-β, (19) and IL-8, (20) by variety of cells. The important sources for cytokines are macrophages and monocytes at inflammatory sites.

IL-6 is the most important stimulator for the production of acute phase proteins. (21) The acute phase proteins which are produced by stimulation of IL-6 depends on the nature and site of the inflammation. (22) IL-6 is critical in controlling the extent of local and systemic acute inflammatory responses, particularly the level of proinflammatory cytokines in the local and systemic circulation. IL-6 induced during acute phase response will act as anti-inflammatory by suppressing the level of proinflammatory cytokines without change in the level of anti-inflammatory cytokines. (17,23) It also stimulates the production of IL-1 receptor antagonist which act as anti-inflammatory mediator. (24) Therefore IL-6 has a protective effect in acute inflammation.

IL-6 AND CHRONIC INFLAMMATION

IL-6 plays an important role in the development of specific cellular and humoral immune responses including end-stage B cell differentiation, immunoglobin secretion and T cell activation. The recruitment of monocyte to the area of
inflammation is the main switch from acute to chronic inflammation. IL-6 acts as important transition between the acute and chronic inflammation.\(^{(17)}\) The IL-6/IL-6Rα complex favours the transition from neutrophil to monocyte in inflammation.\(^{(23,26)}\) This transition may be secondary to a shift in the type of chemokine produced by stromal cells, inflammatory macrophages or neutrophils.\(^{(17)}\) After several hours, neutrophils with inflammatory cytokines will selectively produce MCP-1, which leads to late monocyte recruitment.

Chemo attractants released from endothelium or other cells recruit neutrophils and induce IL-6Rα, IL-6Rα with IL-6 bind with gp 130 on the endothelial cell membrane and increases the IL-6 and MCP-1 secretion, which favours the transition from neutrophil to monocyte recruitment.\(^{(25,26)}\) Also, the phagocytosis of apoptotic polymorph nuclear neutrophils by macrophages increases transforming growth factor-β and MCP-1 secretion and decreases IL-8 production, leading to a chemokine shift favouring monocyte recruitment. After several days the monocyte and macrophages migrate to the local lymphnodes.\(^{(26)}\) During this migration, monocytes differentiate into dendritic cells, upregulate HLA class II antigen membrane expression and acquires costimulatory molecules such as CD80 and CD86.\(^{(27)}\) These cells present antigenic peptides to lymphocytes, contributing to the immune response generation. Thus IL-6 is proinflammatory in chronic inflammation.

**IL-6 AND DISEASES.**\(^{(4)}\)

IL-6 not only maintains inflammation but also modifies the immune responses in Autoimmune diseases. Elevated levels of circulating IL-6 are seen in several inflammatory diseases such as Rheumatoid arthritis, juvenile idiopathic arthritis, systemic lupus erythematosus, ankylosing spondylitis, psoriasis and Crohn’s disease. IL-6 levels are elevated in lupus without having any relation to levels of C-reactive protein. In Systemic juvenile idiopathic arthritis there is a correlation between disease activity and levels of IL-6. In other diseases mentioned above, IL-6 levels are elevated and correlate with markers of the diseases.

**IL-6 AND THERAPEUTICS**

Predclinical models have emphasized the involvement of numerous cytokines in the pathology of various inflammatory diseases and cancers. As a consequence, cytokines have become major therapeutic targets for clinical intervention. These agents work by either targeting the cytokine directly or by inhibiting cytokine binding to their specific receptors on the surface of cells. In this regard, they are designed to prevent cytokine signaling within cells. Cytokines that signal via this pathway (e.g., IFN-γ, GM-CSF, IL-6, IL-10, IL-15, IL-23) have become increasingly linked with the pathogenesis of chronic inflammatory diseases and cancers.\(^{(28,29)}\) IL-6 is one of the most highly expressed mediators of inflammation. Despite these apparent roles for other gp130-related cytokines in autoimmunity, therapies that target IL-6 or its receptor remain the most developed strategies. IL-6 as a therapeutic target for autoimmunity and led to the development of agents such as tocilizumab.

A renewed interest in IL-6 was sparked in 2006, when IL-6, in combination with TGF-β, was shown to promote the differentiation of IL-17-secreting T helper (Th17) cells.\(^{(30)}\) Although Th17 cells are associated with the pathogenesis of various autoimmune/chronic inflammatory states,\(^{(31)}\) it is presumptuous to assume that anti–IL-6 therapies would be effective because they block Th17 development. Indeed, the anti–IL-6R mAb tocilizumab may be viewed more broadly as a robust inhibitor of IL-6/STAT3 activity. Tocilizumab intervention in rheumatoid arthritis leads to a rapid and sustained improvement in disease activity, a reduction in radiographic joint damage, and inhibition of B cell hyperactivity.\(^{(22,23)}\) These changes are also associated with a dramatic normalization of the acute phase response (including C-reactive protein [CRP]) and improvements in both pain and fatigue.\(^{(32)}\) IL-6 remains the only example of a cytokine that in vivo uses both classical membrane-bound receptor signalling and trans-signalling through its soluble receptor.\(^{(24,25)}\)

Consequently, those who implement therapeutic strategies need to consider the impact of blocking classical membrane-bound signalling and IL-6 trans-signalling. The anti–IL-6R antibody tocilizumab globally blocks IL-6 activities since it inhibits both modes of IL-6 signalling. The clinical efficacy of tocilizumab suggests that IL-6/STAT3 signalling actively contributes to the pathology of autoimmune disorders, including rheumatoid arthritis.\(^{(29)}\) Tocilizumab is not recommended for patients with a pre-existing history of diverticulitis. Although these are rare occurrences and tocilizumab displays a robust safety profile. A soluble form of gp130 (sgp130) selectively inhibits IL-6 trans-signalling without affecting the classical pathway. Using sgp130 as a molecular tool, various in vivo studies have now documented roles of IL-6 trans-signalling in experimental models of arthritis, colitis, infection, allergy, and inflammation-induced cancer.\(^{(25,36,37,38)}\) This finding has opened up the possibility of using sgp130 as a therapeutic modality for the treatment of inflammation. Sgp130 linked to the Fc portion of IgG (sgp130Fc) is currently in preclinical development and shows efficacy in animal models of inflammatory arthritis, peritonitis, inflammatory bowel disease, and colon cancer.

**CONCLUSION**

IL-6 plays an important role in both in acute and chronic inflammation. It has also got a role in sepsis and wound vitality. Therefore, targeting against IL-6 and its signalling pathway may be an add on value in the therapeutic armamentarium of inflammatory reactions and diseases. As the targeting molecules are still under study, it will likely to broaden in coming years.

**REFERENCES**


