



ACTIVATION OF JAK1, JAK2, AND TYK2 KINASES THROUGH IL-6/IL-6R AND gp130 CO-RECEPTOR SIGNALING

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ABSTRACT

Interleukin-6 (IL-6) is a pro-inflammatory cytokine that signals through the gp130 receptor and activates pathways such as Janus kinase (JAK)/ signal transducer and activator of transcription (STAT)3, mitogen-activated protein kinase (MAPK), and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT). It plays a key role in systemic inflammation, fever, and the hepatic acute-phase response, while also activating endothelial cells, increasing vascular permeability, and promoting leukocyte adhesion and tissue edema. During severe systemic inflammation, high IL-6 levels promote coagulation, platelet activation, and thrombus formation, contributing to hypotension, hypoperfusion, organ dysfunction, and, in severe cases such as sepsis, disseminated intravascular coagulation (DIC). IL-6 contributes to the hemodynamic and metabolic alterations associated with systemic inflammation by promoting vasodilation and changes in vascular tone and tissue perfusion in synergy with other pro-inflammatory cytokines, coagulation mediators, complement components, and reactive oxygen species (ROS). IL-6/IL-6R/gp130 signaling activates JAKs and subsequently; the latter translocates to the nucleus and regulates genes involved in immune and inflammatory responses, as well as in cell survival, proliferation, and differentiation. The JAK/STAT pathway rapidly transmits extracellular signals from the membrane receptor to the nucleus, regulating gene expression involved in inflammation, immune responses, and cell growth and differentiation. In the case of IL-6, binding to IL-6R (CD126) promotes interaction with gp130 (CD130), triggering the activation of JAK1, JAK2, and Tyrosine kinase 2 (TYK2) kinases; these phosphorylate gp130, enabling the recruitment and phosphorylation of STAT3. STAT3 dimerizes, translocates to the nucleus, and modulates genes involved in the inflammatory response, the acute-phase response, and cell survival, proliferation, and differentiation, while SOCS3 contributes to the negative feedback regulation of the JAK/STAT pathway. In the central nervous system (CNS), IL-6 is both an immune mediator and regulator of neuronal and glial functions, and is produced by microglia, astrocytes, neurons, and endothelial cells and acting mainly through the IL-6/IL-6R/gp130–JAK/STAT3 pathway. Depending on its concentration and duration, IL-6 can support physiological repair processes or contribute to microglial and astrocyte activation, neuroinflammation, altered neuronal function, and neurodegeneration, while also linking peripheral inflammation, the blood-brain barrier, and CNS immune responses.

KEYWORDS: *JAK1, JAK2, TYK2, kinase, IL-6, gp130, coreceptor signaling*

INTRODUCTION

The interleukin-6 (IL-6) family comprises a group of cytokines that use the gp130 receptor to transduce their signal. IL-6 is a pro-inflammatory cytokine that can be activated by various stimuli and is produced primarily by

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macrophages/monocytes, fibroblasts, endothelial cells, muscle and adipose cells, and lymphocytes (1,2). IL-6 binds to its receptor, IL-6R, and co-receptor, gp130, activating Janus kinases (JAKs). The IL-6 family utilizes the gp130 (IL6ST) signaling receptor and intracellular signaling pathways such as JAK/signal transducer and activator of transcription (STAT)3, mitogen-activated protein kinase (MAPK), and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) (3-5) (Table I).

Table I. *The main members of the IL-6 family.*

<i>IL-6</i>	The best-known member; involved in inflammation, the immune response, and the acute-phase response.
<i>IL-27</i>	Often included in the IL-6 family of cytokines due to its functional association with gp130.
<i>IL-11</i>	Important in hematopoiesis and the inflammatory response.
<i>OSM (Oncostatin M)</i>	Role in inflammation, immune-cell activation, tissue repair, fibrosis, and regulation of cell proliferation/differentiation.
<i>CNTF (Ciliary Neurotrophic Factor)</i>	Promotes neuronal survival, supports motor neurons, regulates glial cells, and contributes to neural repair and regeneration.
<i>CT-1 (Cardiotrophin-1)</i>	Promotes cardiomyocyte survival and hypertrophy, regulates cardiac development, and participates in tissue repair and inflammatory responses.
<i>CT-2 (Cardiotrophin-2)</i>	Supports cell survival and differentiation and may participate in cardiac, neural, and inflammatory processes.
<i>CLC (Cardiotrophin-like cytokine)</i>	Supports neuronal survival and differentiation, particularly in the nervous system, and may influence immune and inflammatory responses.
<i>LIF (Leukemia Inhibitory Factor)</i>	Promotes cell survival and differentiation, regulates stem-cell pluripotency, supports neuronal cells, and participates in immune and inflammatory responses.

IL-6 is a key cytokine in systemic inflammation and the acute-phase response. It contributes to fever, induces the hepatic acute-phase response, and modulates the immune response (6,7). Prolonged high levels of IL-6 can contribute to the transition from low-grade inflammation to a harmful systemic response that may lead to organ dysfunction. A strong inflammatory stimulus triggers high IL-6 levels, leading to JAK/STAT3 pathway activation, endothelial activation, and the production of other cytokines (4,8). Systemic inflammation alters endothelial function, increases vascular permeability, and causes fluid leakage into tissues, leading to edema and impaired perfusion. During a generalized inflammatory response, mediators such as cytokines, histamine, and nitric oxide can induce endothelial dysfunction, resulting in the loss of normal regulatory functions regarding vascular tone, coagulation, and the blood-tissue barrier (8,9). In inflammation, the junctions between endothelial cells widen, increasing permeability and causing the leakage of fluids and proteins into the tissues, which leads to edema. These reactions result in fluid loss from the blood vessels and reduced oxygen delivery to the tissues. If the inflammatory response is systemic, the aforementioned reactions can contribute to hypotension, hypoperfusion, and organ dysfunction (8,10,11).

In the systemic inflammatory response, IL-6 can mediate endothelial dysfunction and promote inflammation. IL-6 increases the expression of adhesion molecules on the endothelium, promotes increased vascular permeability, and facilitates leukocyte adhesion and migration into tissues (9,12). IL-6 induces hepatic production of acute-phase proteins, including serum amyloid A (SAA), amplifies the systemic response, and causes impaired perfusion. This cytokine can also act indirectly on endothelial cells by inducing tumor necrosis factor (TNF), IL-1, complement, ROS, and other mediators (6,8,13). In cases of significant systemic inflammation, IL-6 activates the endothelium and induces a procoagulant state. IL-6 triggers an increase in hepatic fibrinogen, thereby raising the availability of the substrate needed to generate fibrin (14,15). IL-6 promotes the expression of tissue factor, and consequently, the activation of the extrinsic coagulation pathway, either directly or through the activation of endothelial and immune cells (15). It also fosters platelet activation and thrombus formation during the inflammatory process, contributing to a state of hypercoagulability (16,17). In serious conditions of sepsis, the interaction between inflammation and coagulation can play a crucial role, contributing to disseminated intravascular coagulation (DIC) and organ damage (8).

IL-6 SIGNALING RECEPTORS AND INTRACELLULAR SIGNALING PATHWAYS

IL-6 contributes to hemodynamic alterations in which the systemic inflammatory response can be associated with vasodilation and changes in vascular tone, leading to reduced effective tissue perfusion (18). These inflammatory reactions can result in damage to organs such as the lungs, heart, kidneys, liver, and brain (18). In the lungs, disruption of the alveolocapillary barrier can cause edema, respiratory failure, and even death, while cardiac effects may include impaired myocardial function and altered vascular response. In the kidneys, liver, and brain, the consequences may include, respectively, altered perfusion and tubular damage, impaired metabolic function with the production of acute-phase proteins, particularly C-reactive protein (CRP), fibrinogen, and SAA, and neurological damage (18,19). In addition, at a metabolic level, during systemic inflammation, IL-6 alters glucose, lipid, and protein metabolism (20,21).

It should be noted that IL-6 is generally not directly responsible for organ dysfunction. In severe forms of inflammation, it acts in concert with other pro-inflammatory cytokines, coagulation mediators, the complement system, and ROS. Thus, IL-6 mediates inflammatory conditions by activating immune cells and, together with other pro-inflammatory compounds, can cause organ damage. Although IL-6 is an important mediator, multiorgan damage results from the interaction of multiple inflammatory, endothelial, coagulation, and metabolic pathways, rather than from IL-6 alone (18).

IL-6, its receptor, and its co-receptor

IL-6/IL-6R and gp130 co-receptor signaling constitutes a fundamental cellular signaling pathway involved in inflammatory and immune responses, as well as in the regulation of cell survival and proliferation (4,5). IL-6 binds to its specific receptor, IL-6R (CD126), and the IL-6–IL-6R complex interacts with gp130 (CD130), a transmembrane protein that acts as a co-receptor and signaling component (22,23). Dimerization of gp130 leads to the activation of associated JAKs. JAKs phosphorylate gp130, generating docking sites for STAT3 and, to a varying extent, STAT1. STAT3 is phosphorylated, forms a dimer, and translocates into the nucleus. Inside the nucleus, STAT3 modulates the expression of genes involved in immune and inflammatory responses, cell survival, proliferation, and differentiation (4,5) (Fig.1).

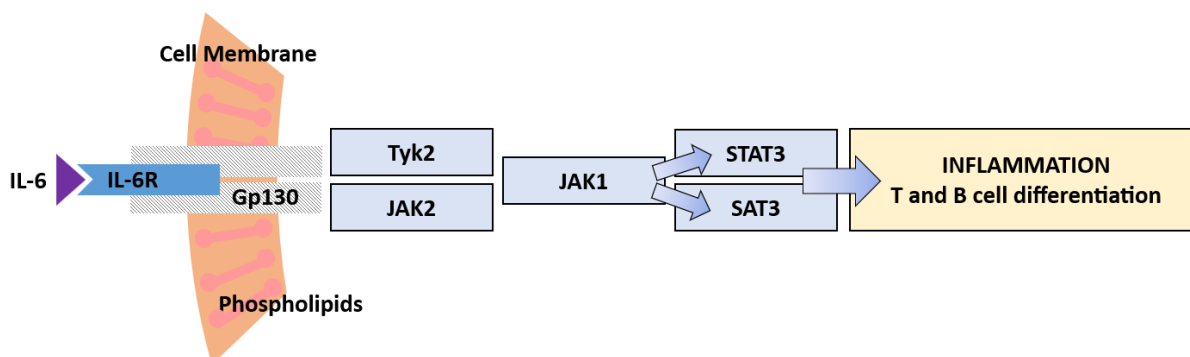


Fig. 1. IL-6 binds to the IL-6 and the gp130 co-receptor, activating the JAK/STAT signaling pathway through JAK1, JAK2, and TYK2. This leads to STAT3 activation, promoting T- and B-cell differentiation and contributing to inflammation.

IL-6R is known to exist in two forms: membrane-bound and soluble. Membrane-bound IL-6R (mIL-6R) is expressed on the surface of certain cells, including hepatocytes, leukocytes, and some epithelial cells. When IL-6 binds to mIL-6R, the complex interacts with gp130, triggering intracellular signaling. In contrast, soluble IL-6R (sIL-6R) is a free form of the receptor found in extracellular fluids that can bind to IL-6 to form an IL-6/sIL-6R complex, which subsequently associates with gp130 on the cell surface (4,23).

Canonical signaling occurs through the binding of IL-6 to membrane-bound IL-6R and gp130, leading to JAK/STAT3 activation, whereas trans-signaling involves IL-6 binding to soluble IL-6R and gp130, also resulting in JAK/STAT3 activation (4,5). Trans-signaling thus enables IL-6 to act on cells that do not express membrane-bound IL-6R, provided

they express gp130 (22,23). Trans-signaling is frequently associated with the pro-inflammatory effects of IL-6, while classical signaling can also mediate physiological and regenerative functions.

In the bone marrow, IL-6 contributes to the hematopoietic response and thrombocytosis, while in the hypothalamus, in conjunction with IL-1, it causes fever (24,25). IL-6 is a key cytokine for the immune system, as it promotes B-cell differentiation and, along with other cytokines, facilitates the differentiation of Th17 lymphocytes (26). At a metabolic level, during systemic inflammation, it alters glucose, lipid, and protein metabolism (20,21).

JAK-STAT

The JAK–STAT pathway is involved in cellular signaling. It allows a cell to receive an external signal and translate it into an intracellular response. When a protein (for example, an inflammatory cytokine) binds to its receptor on the cell membrane, the binding activates the JAKs associated with the receptor. The JAK/STAT pathway rapidly transmits a signal from a cytokine, moving from the cell membrane to the DNA in the nucleus. Thus, the protein, which may be a cytokine, follows this pathway: the protein binds to its receptor, triggering JAK/STAT activation and the subsequent regulation of nuclear gene transcription (3).

These reactions enable the JAK/STAT pathway to rapidly transmit a signal from a ligand protein at the cell membrane to the nuclear DNA. The JAK/STAT pathway plays a crucial role in immune and inflammatory responses, as well as in cell growth and differentiation (4,5). Upon binding to its receptor, IL-6R (CD126), IL-6 acts as a key activator of the JAK/STAT pathway, which involves JAK1, JAK2, and Tyrosine kinase 2 (TYK2). The IL-6–IL-6R complex then interacts with gp130 (CD130), a transmembrane glycoprotein that serves as a co-receptor and the primary signaling subunit (3,4). Although gp130 does not bind IL-6 directly, it works alongside IL-6R to facilitate ligand recognition and induce the assembly of the receptor complex. Assembly of this complex induces the dimerization and reorganization of gp130, promoting activation (4,23).

JAKs undergo trans-phosphorylation, increase their catalytic activity, and phosphorylate specific tyrosine residues located on the cytoplasmic tail of gp130. The phosphorylated tyrosines on gp130 serve as docking sites for proteins containing SH2 domains, particularly STAT3, which is subsequently phosphorylated and activated (4,27).

IL-6 canonically activates STAT3, though STAT1 can also be activated. STAT3 activation leads to the induction of various genes, including those involved in immune and inflammatory responses, the acute-phase response, differentiation, cell survival, and proliferation (4,5).

IL-6 can also induce genes such as the suppressor of cytokine signaling 3 (*SOCS3*) gene, which are inhibitors of the JAK/STAT pathway. *SOCS3* represents an important negative-feedback regulator of IL-6 signaling and interacts with gp130 and JAK proteins to limit the duration and intensity of signaling (27).

The dimerization and reorganization of gp130 can activate JAK1, JAK2, and TYK2; these kinases phosphorylate gp130, leading to the recruitment, phosphorylation, and dimerization of STAT3, followed by nuclear translocation and the regulation of gene expression (4,27).

JAK1 is the most important kinase in gp130 signaling, whereas JAK2 and TYK2 can contribute to complex activation depending on the cellular context. Experimental studies have demonstrated that JAK1 plays a predominant role in IL-6 signaling, since loss of JAK1 markedly reduces gp130 phosphorylation and STAT1/STAT3 activation, whereas JAK2 and TYK2 appear to have ancillary roles (5,28).

IL-6 and the central nervous system

IL-6 plays an important role in the central nervous system (CNS), where it acts both as a mediator of the immune response and as a modulator of neuronal and glial function. In the CNS, IL-6 can play both physiological and pathological roles, depending on various factors such as concentration, duration of the effect, species, and temperature (29,30).

In the CNS, IL-6 is produced by various cell types, including microglia, astrocytes, neurons, and endothelial cells (29,30). In the brain, IL-6 can exert its effects through canonical signaling, wherein IL-6 binds to its receptor (IL-6R) and, together with gp130, triggers the JAK1/JAK2/TYK2 and STAT3 pathways. STAT3 activation leads to the regulation of genes involved in stress responses, inflammation, cell survival, and differentiation (4,5).

The relationship between IL-6 and the CNS is particularly interesting regarding microglial activation. Elevated IL-6 levels can mediate and amplify the inflammatory response, modulate astrocyte activity, alter neuronal survival and function, and influence synapses (30,31). Physiologically, the IL-6–IL-6R/gp130 complex can participate in the response to cellular damage and in certain repair mechanisms (29).

IL-6/JAK/STAT3 signaling mediates the cerebral inflammatory response; an inflammatory stimulus activates microglia and astrocytes, leading to increased IL-6 levels, STAT3 induction, altered gene expression, and neuroinflammation (30).

In neurodegenerative conditions such as Alzheimer's disease, an increase in IL-6 does not necessarily imply that IL-6 is the primary cause of pathology; rather, it may also be considered a consequence of the inflammatory response (30,32). IL-6 is also involved in the interaction between the peripheral immune system and the CNS. It serves as one of the potential molecular links connecting peripheral inflammation, the blood-brain barrier, microglia, and neuroinflammation (33).

CONCLUSIONS

IL-6 is a central mediator linking systemic and CNS inflammation through IL-6R/gp130-dependent JAK/STAT3 signaling, with dysregulated activation contributing to vascular, metabolic, immune, and neurological dysfunction. Its effects are highly context-dependent, as transient IL-6 signaling can support protective and regenerative responses, whereas sustained or excessive activation promotes chronic inflammation, tissue damage, and organ dysfunction.

Conflict of interest

The author declares that they have no conflict of interest.

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