Interleukin-6 in Surgery, Trauma, and Critical Care: Part I: Basic Science

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Abstract

A variety of cytokines play a role in the response to an inflammatory stimulus. The interleukin-6 (IL-6)-type cytokines are released in response to tissue injury or an inflammatory stimulus. They act locally and systemically to generate a variety of physiologic responses, principal among them is the acute phase response. The IL-6 type cytokines demonstrate pleiotropy and redundancy of actions. This is made possible by the distinctive characteristics of the IL-6 receptor complex, which contains an ubiquitous subunit that is shared by most IL-6-type cytokines, as well as a cytokine-specific subunit.

Keywords

IL-6; cytokine; interleukin; critical care; ARDS; laparoscopy; sepsis; trauma

In the coordination of the response to tissue injury, infection, and pathogen exposure, many cytokines are involved. These mediators function through autocrine, paracrine, and endocrine mechanisms. Several members of the interleukin-6 (IL-6)-type cytokine family play a particularly prominent role in determining the local and systemic inflammatory response. In part I of this review, we examine the basic science of IL-6-type cytokines as it relates to surgery, trauma, and critical care. In part II, we apply these principles to elucidate their role in these clinicopathological conditions.

Interleukin-6 Type Cytokine Biologic Activities

Interleukin-6 and its family members have a variety of effects on a multitude of cell types. In turn, elevated systemic concentrations of IL-6 in the postoperative period or in critically ill patients not only indicate the magnitude of the inflammatory response, but also provide an understanding of the mechanisms responsible for an exaggerated inflammatory response and adverse outcome. This review focuses primarily on IL-6; however, other IL-6 family members are discussed because they provide redundancy for IL-6 actions.

Interleukin-6

Interleukin-6 targets multiple cell types and induces a broad array of responses (Table 1). These responses are often, simplistically, classified as pro- or anti-inflammatory in nature. A key function of IL-6, which was demonstrated in the IL-6 knockout mouse, is mediation of the acute phase response.[1,2] The acute phase response occurs when an inflammatory stimulus is severe enough to generate a large number of accompanying systemic changes that reset normal homeostatic mechanisms.[3] Specifically, tissue injury incites a local reaction that includes activation of leukocytes, endothelial cells, and fibroblasts. This activation results in the release of cytokines that induce a systemic response characterized by fever, leukocytosis, and the release of acute phase proteins (APPs).[4,5] There are at least 40 plasma proteins that are classified as such because their concentrations change by at least 25% after an inflammatory stimulus.[6] Interestingly, the speed of protein concentration change parallels the magnitude of the inflammatory stimulus.[3] Induced proteins include clotting proteins, complement components, antiproteases, and proteins used for transport.[6] Although the acute phase response is classically described as a pro-inflammatory phenomenon, many of the acute-phase reactants have inhibitory effects on the immune system.[1,2,7] For example, the APP haptoglobin inhibits the respiratory burst in neutrophils, inhibits lipopolysaccharide (LPS)-induced tumor necrosis factor-α (TNFα) production in monocytes, and inhibits LPS-induced proliferation of lymphocytes.[7] C-reactive protein (CRP), another APP, has a variety of important pro-inflammatory functions, suchas promoting opsonization, enhancing phagocytosis, activating complement, and stimulating cytokine release and adhesion molecule expression.[6] However, CRP also has anti-inflammatory effects, such as inhibiting the neutrophil respiratory burst and degranulation, and thereby limiting tissue injury.[8]

Interleukin-6 has a variety of effects on the immune system. It plays an important role in immune cell maturation. It induces immunoglobulin production by B cells and differentiation of T cells.[9] Although IL-6 is believed to be essential for antibody production by B cells, it does not affect proliferation of activated B cells.[10] Interleukin-6 activates mitogen-stimulated T cells by inducing IL-2 production and IL-2 receptor expression. It acts synergistically with IL-2 in propelling T cell differentiation into cytotoxic lymphocytes.[10] Interleukin-6 activates endothelial cells and induces chemokine production as well as adhesion molecule expression, leading to the recruitment of leukocytes to sites of inflammation.[11] Additional pro-inflammatory effects of IL-6 include inducing expression of phospholipase A_2 (PLA$_2$).[1] In turn, PLA$_2$ actions generate leukotrienes, prostaglandins, and platelet-activating factor (PAF).[1] Platelet activating factor also acts synergistically with IL-6

to prime polymorphonuclear cells (PMNs).[12] In vitro anti-inflammatory effects of IL-6 include inhibition of TNFα production and IL-1 inhibitor release, as well as induction of tissue inhibitor of matrix metalloproteinase (TIMP).[1,4,9,13,14]

Interleukin-6 also stimulates hemostasis. It stimulates platelet production by megakaryocytes.[9,15] In vitro experiments on human platelets have demonstrated morphologic alterations as well as platelet activation as measured by adenosine triphosphate, P-selectin, and dense granule concentrations.[15] In vivo experiments in dogs have demonstrated that administration of IL-6 reduces the concentration of thrombin required to activate platelets and enhances their responsiveness to PAF.[15] Furthermore, IL-6 induces tissue factor expression in monocytes; in turn, the binding of tissue factor to factor VIIa eventually leads to thrombin and fibrin generation.[16]

Interleukin-6 plays an important role in the neuroendocrine system. Interleukin-6 binds to the hypothalamus and induces fever.[17] Interleukin-6 is a "robust" stimulant of the hypothalamic-pituitary-adrenal axis, both centrally and at the adrenal gland. It stimulates the release of corticotrophin-releasing factor from the central nervous system (CNS), adrenocorticotrophic hormone (ACTH) release from the pituitary gland, and cortisol release from the adrenal gland.[18–20] Conversely, cortisol inhibits IL-6 production.[20] Interleukin-6 also stimulates vasopressin and growth hormone secretion by the pituitary gland but inhibits thyroid-stimulating hormone secretion.[20] Several IL-6 family members, including IL-6, IL-11, ciliary neurotropic factor (CNTF), and oncostatin M (OSM), also mediate the "immuno-neuroendocrine interface."[21] Interleukin-6 induces hyperglycemia by releasing glucose from hepatic glycogen stores; increased serum concentrations of IL-6 are associated with insulin resistance.[22] Conversely, hyperglycemia increases IL-6 serum concentrations by augmenting IL-6 production by monocytes.[22] In vitro experiments suggest that insulin resistance in a variety of disease states, including infection, may be mediated by IL-6.[23] Interleukin-6 has been shown to inhibit insulin signaling in hepatocytes; this in turn may be mediated by induction of suppressor of cytokine signaling-3 (SOCS-3) proteins (vide infra).[23]

Interleukin-6 is also expressed and secreted by osteoblasts and osteoclasts upon stimulation with parathyroid hormone, Vitamin D, or IL-8; it also activates these cells.[9,14,24,25] Finally, IL-6 stimulates multilineage blast cell colonyformation in hematopoietic stem cells, G0 to G1 cell-cycle progression, differentiation of neural cells, and proliferation of keratinocytes.[9,10,20]

Knowledge of this myriad of actions is essential to understanding the multiple roles that IL-6 plays in surgery, trauma, and critical illness. Serum IL-6 concentrations increase in surgical patients, in proportion to the magnitude of the surgical stress.[19,26,27] Similarly, IL-6 concentrations increase in sepsis, in proportion to the severity of illness and correlate with adverse outcome.[28,29]

Other IL-6 Family Members

The actions of IL-6 are redundant with other members of its family. The IL-6 cytokine family also includes IL-11, IL-27, IL-31, OSM, leukemia inhibitory factor (LIF),

cardiotrophin-1 (CT-1), cardiotrophin-like cytokine (CLC), neuropoietin/cardiotrophin 2 (NP), and CNTF (Table 2). Although these cytokines provide redundancy for IL-6 actions, such as the acute phase response, they also have highly specific actions. For example, LIF, named for its antiproliferative effects in a mouse leukemia cell line, plays important roles in embryogenesis, hematopoiesis, bone metabolism, and inflammation, including the acute phase response.[30–32] Additionally, LIF has protective effects on neurons and peripheral tissues.[21] Elevated LIF concentrations have been noted with sepsis and correlated with adverse outcome.[33,34]

Oncostatin M is also a pleiotropic cytokine that is produced by activated T cells and macrophages; it induces acute phase protein and IL-6 production.[35] Oncostatin M appears to be more closely related to LIF, as opposed to IL-11.[36] Indeed, OSM and LIF are believed to have arisen via a gene duplication event. They compete for binding to the LIF receptor.[36] Oncostatin M effectively recruits stromal, endothelial, and epithelial cells at local concentrations.[37] Its functions include promotion of megakaryocyte differentiation/ thrombocytosis, induction of neurotrophic peptides, mediation of wound healing, and inhibition of tumor cell growth.[35] In addition, it stimulates plasminogen activator and induces TIMP-1.[36] Meanwhile, it also plays a role in limiting inflammation, as suggested by its delayed temporal appearance in the inflammatory response, (indirect) suppression of TNFα, and suppression of certain IL-1 functions.[35] Furthermore, in vitro, elevated concentrations of OSM have been demonstrated to inhibit IL-6-IL-6 receptor complex formation.[38] Systemic OSM concentrations are elevated in patients with septic shock.[35]

Cardiotrophin-1 is cardioprotective and neuroprotective. It induces cardiac myocyte hypertrophy and the acute phase response.[39,40] Experimental data indicates that CT-1 induces atrial natriuretic peptide and brain natriuretic peptide secretion. Cardiotrophin-1 elicits hypotensive effects via a nitric oxide-dependent mechanism.[41] It also increases platelet and red blood cell counts.[30] Like other IL-6 cytokine family members, CT-1 also has anti-inflammatory effects. In animal models, CT-1 has been shown to inhibit TNFα-induced LPS production, and CT-1 administration inhibits both endotoxin-induced neutrophil accumulation in the lung and lung edema.[42] Cardiotrophin-1 expression in the heart is found in myocytes as well as nonmyocytes.[41] Significant concentrations of CT-1 have also been demonstrated in the kidneys, lung, aorta, and skeletal muscle.[41]

Cardiotrophin-like cytokine plays a role in embryogenesis and neuronal support. Neuropoetin plays a role in nervous system development in rodents.[43] Ciliary neurotropic factor is a survival factor for neuronal cells that prevents degeneration of motor axons after axotomy.[40,43]CNTF also regulates the acute phase response and down-regulates pro-inflammatory cytokines such as IL-1 and IL-8.[30] Elevated systemic concentrations of CNTF, LIF, and OSM have been noted in patients with septic shock, but these cytokines were undetectable in normal patients.[44]

Interleukin-11 is produced bya variety of stromal cells, including fibroblasts, epithelial cells, and osteoblasts.[45] Interleukin-11 stimulates acute phase protein production, immune cell development, erythropoesis, and megakaryopoesis.[14,40] It also plays an important role in bone metabolism, tissue remodeling, and protection of mucosal surfaces.[46] It limits tissue

injury via protection of clonogenic stem cells, regulates epithelial cell proliferation, inhibits apoptosis, and modulates cytokine production by macrophages.[45,46] Like IL-6, OSM, and LIF, it upregulates TIMP-1.[30] Furthermore, IL-11 has anti-inflammatory functions similar to Th2 cytokines.[47] Specifically, it inhibits IL-12 and interferon-γ (IFN-γ) production.[46] Significant elevations of IL-11 have been demonstrated in trauma.[45,46] Although IL-11 concentration elevations did not appear to correlate with injury severity in a study of 216 patients by Schinkel et al,[45] IL-11 concentrations were significantly higher in nonsurvivors.

Interleukin-27 is produced mainly by macrophages and dendritic cells; it has pro- and anti-inflammatory activities with white blood cells, including T cells.[48,49] Finally, IL-31 has been shown to play a role in skin inflammation and bronchopulmonary inflammation.[50–54]

Interleukin-6 Type Cytokine and Receptor Pathophysiology

Interleukin-6 is produced by a wide variety of immune and nonimmune cell types, especially macrophages, dendritic cells, lymphocytes, endothelial cells, and fibroblasts.[10,14,20,55,56] More recently, muscle cells were shown to produce IL-6, giving IL-6 the designation "myokine."[57] Indeed, virtually every tissue studied has cells that can produce IL-6.[58] Besides the immune cells that play an important role in the inflammatory response that accompanies surgery and critical illness, stromal cells would also be expected to play an important role, not only in the production of IL-6, but also in responding to it.

Interleukin-6 Synthesis, Regulation, and Measurement

The IL-6 type cytokines belong to the long-chain 4α-helix hematopoietic cytokine family. Interleukin-6 is a 212 amino acid cytokine; its gene maps to chromosome 7p21 and contains 4 introns and 5 exons.[10,14,20,55] It is observed as a 22- to 28-kDA phosphorylated and variably glycosylated protein.[30] The *IL-6* gene contains a variety of single nucleotide polymorphisms (SNPs); the role of these SNPs in generating physiologically relevant differences in IL-6 expression in inflammation and outcome is under intense investigation. One commonly evaluated SNP is the G to C transition at position – 174 base pair (bp) of the IL-6 promoter; it has been variably associated with outcome in critical illness.[59] In some reports, patterns of several SNPs that are in linkage disequilibrium (haplotypes) were investigated. Evolutionarily related haplo-type groups comprise haplotype clades.[59] Various IL-6 haplo-type clades have been associated with increased mortality in critical illness.[59]

The *IL-6* gene has glucocorticoid-responsive elements; cortisol suppresses IL-6 production.[10,20] Conceivably, these glucocorticoid-responsive elements and the effects of IL-6 on the HPA axis could begin to explain the adverse effects of relative adrenal insufficiency in patients with septic shock and consequently, the reported benefits of corticosteroid administration in this circumstance.[60] The *IL-6* gene is not constitutively expressed, but its expression can be induced by a myriad of stimuli, including viral infections, LPS, IL-1β, TNFα, platelet-derived growth factor (PDGF), and IFN-γ.[10] Catecholamines also stimulate IL-6 production, whereas the sex steroids suppress its production.[20]

A key component of IL-6 production during the inflammatory response is the recognition of structures that are shared among infectious agents, that is, pathogen-associated molecular

patterns (PAMPs), by Toll-like (TLRs) receptors.[61] In humans, greater than 10 TLRs have been described. They are expressed primarily on monocytes/macrophages, dendritic cells, and neutrophils.[61–63] They are also expressed on B cells.[64] Recognition of PAMPs by TLRs activates dendritic cells and represents a key step in the innate and adaptive immune response. Although TLR2 signaling is elicited by gram-positive bacterial products, TLR4 signaling is induced by LPS and the lipid A component of gram-negative bacteria.[62,64] Toll-like receptors 4 and 8 stimulate IL-6 production; TLR2 also appears to contribute to IL-6 production.[62,64]

Interleukin-6 is a normally circulating plasma protein.[58] However, measurement of IL-6 levels is problematic. Although large (nanomolar) quantities are present in the blood in healthy individuals, it may be undetectable by various assays, including bioassays and enzyme-linked immunosorbent assays (ELISAs).[58] Part of the difficulty in IL-6 measurement arises because IL-6 exists as monomer, dimers, and multimers. Furthermore, although IL-6 is present in blood at concentrations sufficient to elicit the whole gamut of IL-6 effects in the healthy individual, it remains relatively inert. This suggests the presence of chaperone proteins which modify or limit its biologic activity and camouflage it from assay systems. Interleukin-6 can exist in high-molecular-weight complexes with various proteins such as CRP, complement components, and the soluble IL-6 receptor. Finally, some individuals may also have IL-6 autoantibodies, which may also function as chaperones. The various assays may have trouble detecting IL-6 in these multiple forms.[38,58,65] Because of these chaperones, depending on the assay used, concentrations may differ by more than 10-fold.[38] These findings suggest that free IL-6 may have only a transient presence in blood.[65]

Interleukin-6-Type Cytokine Receptors

The IL-6 type cytokines engage receptors that share overall structural organization characteristics with the long-chain type I hematopoietic receptor family. Generally, the IL-6-type cytokines are recognized by ligand-specific binding receptor subunits (α subunits) that associate with a common receptor (β) subunit to transduce signal (vide infra).[37] Similar to other hematopoietic cytokines, the IL-6 cytokines are recognized by receptor systems based on structural motifs formed by loop and helical elements (termed sites I, II, and III). These cytokines coordinate the formation of a complex signaling competent unit, by forming complementary interfacing contacts with sites within the cytokine recognition site of the extracellular domain of the receptor subunits.[66]

The α and β subunits share a common cytokine homology domain (cytokine binding module) that is formed from 2 fibronectin type III domains (Figure 1). Note that a domain is defined as an element of protein structure that stabilizes itself and often folds independently of the remaining portions of the protein.[68] These domains have conserved β sheet structures that are stabilized by 2 pairs of cysteine residues at their *N*-terminus and have a tryptophan-serine-x-tryptophan-serine (WSXWS) sequence motif at their C-terminus. Additional conserved structural modules in the extracellular receptor portion include an immunoglobulin-like domain, a single transmembrane domain, and an intracellular domain that lacks intrinsic enzymatic activity. This intracellular domain is longer in β subunits. All signaling-capable (ie, β) subunits have 3 additional fibronectin type III domains that separate

the cytokine homology domain from the transmembrane region, thereby providing a larger cytokine interaction site to the extracellular milieu.[30] Although the tertiary structure of the IL-6 cytokines and their engagement of shared receptor subunits results in functional overlap, there is also considerable specificity. Factors responsible for this specificity include the different spatial and temporal expression of the cytokines as well as tissue localization of their receptors.[69]

The receptor subunits may be present in membrane-bound or soluble forms. The soluble forms are generated via alternative mRNA splicing or proteolysis of fully processed and cell-surface exposed receptor subunits. This latter mode of production is often observed as a consequence of tissue injury and inflammation. Soluble forms of receptor subunits have been reported for many different receptor systems including growth factors, hormones, and cytokines. Depending upon the requirement for forming a signaling-competent receptor complex on cell surface, in particular the recruitment of subunits with cytoplasmic domains that contribute to signal-transduction reactions, the soluble receptors in combination with cytokines can assume agonistic or antagonistic actions (Figure 2).

α Subunits.—The alpha subunits are the nonsignaling components of the IL-6 receptor complex. They include IL-6Rα, IL-11Rα, CT-1Rα, and CNTFRα. These components exhibit tissue-specific expression and therefore contribute to specificity of cytokine action.[69] Interleukin-6Rα (gp80, CD126) has a molecular weight of 80 kDa, maps to chromosome 1, and is primarily expressed by hepatocytes and lymphocytes but is also detectable in low concentrations (and thus low activity) in other cells such as mesenchymal, endothelial, epithelial, and neural cells.[38,55,73,74] Interleukin-6Rα exists in membrane-bound and soluble forms.

Soluble IL-6Rα serves as an IL-6-binding component; it cannot transduce signal on its own. [25] Soluble IL-6Rα (sIL-6Rα) is generated via proteolysis or alternative mRNA splicing. [14,19] Various stimuli can induce shedding of IL-6Rα from the cell surface including CRP, f-met-leu-phe (fMLP), phorbol myristate acetate (PMA), bacterial pore-forming toxins, and neutrophil degranulation.[25,73,75] Soluble IL-6Rα complexes with IL-6 and gp130 with an affinity that is similar to membrane-bound IL-6Rα. This complex in combination with the membrane-bound form of gp130 can induce signaling in cells that do not express IL-6Rα, that is, "trans-signaling."[73] The complex of IL-6 bound to soluble IL-6Rα acts as a potent agonist on any cell type that expresses gp130. Considering that essentially every cell type in the body expresses gp130, but not always the membrane from of IL-6Rα, the IL-6-sIL-6Rα complex assumes a very potent signaling function.[66,73,76,77] Trans-signaling helps explain the myriad of previously described IL-6-mediated functions noted in multiple cell types. For example, IL-6 facilitates erythropoiesis and it also stimulates chemokine production in endothelial cells.[38]

Soluble IL-6Rα prolongs the half-life of IL-6 and makes detection of IL-6 easier as the antibodies used to measure IL-6 concentrations in clinical studies often detect both free and bound IL-6.[78] Responses that are generated by the IL-6-sIL-6Rα complex can in part be mimicked by other IL-6-type cytokines, such as CT-1, IL-11, LIF, and OSM.[78] Soluble IL-6Rα acts as an agonist for IL-6 activities, in contrast to soluble gp130 or other receptor

subunits for LIF or OSM, which act as antagonists (vide infra).[70,78] Soluble forms of IL-6Rα and gp130 can be detected in the circulation of healthy persons.[25] Decreased circulating concentrations of sIL-6Rα have been reported in sepsis, along with an alteration of the IL-6-IL-6 receptor "axis."[25,71,79] In contrast, serum sIL-6Rα concentrations have been reported to be elevated in several inflammatory diseases, but its levels did not change after stroke.[78,80]

β Subunits.—The signaling-capable β subunits for the IL-6-type cytokines include gp130, LIFR, and OSMRβ. Interleukin-31Rα, although often classified as a β subunit, can only transduce signal when combined with another β subunit.[52] The β subunits may combine with another β subunit or with the α subunits of selected IL-6 cytokines to form dimeric or multi-meric complexes.[70,81] The shared subunit for the IL-6 cytokines, with the exception of IL-31, is gp130.[30,70,82] The gp130 subunit (molecular weight 130 kDa) maps to chromosome 5q11 and a pseudogene maps to chromosome 17; it is expressed by nearly all cells in the body.[38,70,74,83] It is a transmembrane protein, whose cytoplasmic domains can engage STAT proteins and *Jak* kinases to transduce signal.[66] Again, the ubiquitous expression of gp130 as well as its shared use by nearly all members of the IL-6 family helps account for the pleiotropic effects and redundancy of action of the IL-6 type cytokines. [30,69,82]

Like IL-6Rα, gp130 can also exist in a soluble form (sgp130).[72,73] However, unlike sIL-6Rα, sgp130 is a biologic response inhibitor. Soluble gp130 binds only to sIL-6Rα-IL-6 complexes and inhibits their biologic response. Similarly, it inhibits the actions of LIF and OSM. It does not bind to free IL-6 or to membrane-bound IL-6/IL-6Rα complexes, that is, it inhibits "trans-signaling," but not classical signaling via membrane-bound IL-6Rα.[14,72,73] Concentrations of sgp130 vary in various clinical conditions, for example stroke and cardiac surgery are associated with decreased sgp130 concentrations.[80,84]

Interleukin-6 – IL-6 receptor component "axis.".—Variations in the concentration of IL-6 and its receptors suggest that tissue injury and inflammation are associated with perturbations of the IL-6-IL-6 receptor component axis. Alterations in this axis have been demonstrated in experimental endotoxemia. Marsik et al[55] in 2005 measured serum cytokine concentrations in 9 healthy male volunteers following LPS injection in a randomized, double-blinded, placebo-controlled trial. They found that LPS infusion significantly increased plasma IL-6 concentrations and significantly increased the percentage of gp130-positive neutrophils. However, monocyte and neutro-phil IL-6Rα concentrations were not significantly altered in low-grade endotoxemia. Dekkers et al,[25] in 2000, measured cell-surface and systemic cytokine concentrations in 8 healthy participants before and after LPS infusion. Plasma sIL-6Rα and sgp130 were detected at baseline in healthy volunteers and were not significantly influenced by LPS injection. At baseline, IL-6Rα, gp130, and LIFR were detectable on the surface of peripheral blood monocytes and granulocytes. However, LPS infusion significantly reduced IL-6Rα expression on both cell types, whereas gp130 and LIFR expression were unchanged. Interleukin-6 concentrations, while undetectable at baseline, peaked at 3 hours postinjection at 5.99 pg/mL. It should be noted that this degree of IL-6 elevation is below detection threshold by some IL-6 enzyme-linked-immunosorbent

serologic assays (ELISAs) and could be considered as background noise, suggesting that the concentration of LPS infused had minimal systemic effects, perhaps intentionally.

Interleukin-6-IL-6 Receptor Interactions and Signaling

To generate a signal, site I on IL-6 binds to the cytokine binding domain of IL-6Rα. Then, IL-6 site II binds to the cytokine binding module of gp130. Intekeukin-6 site III binds to the immunoglobulin-like domain of a second gp130 receptor subunit that is recruited, and thereby generates a functional complex.[14,66] Stoichiometric experiments suggest that the functional complex is hexameric, composed of 2 units each of IL-6, IL-6Rα, and gp130. Analogous, although subunit- specific, combinations are coordinated between other members of the IL-6 family and their receptors.[66,70] Whereas signaling involves the combination of an α subunit with a β subunit for several IL-6 cytokines, 2 β subunits may combine to transduce signal also, for example, OSM can signal via OSMRβ/gp130 or LIFR/gp130.[70] Leukemia inhibitory factor signals via LIFR/gp130. Interleukin-31 signals via IL-31Rα/OSMRβ.[52] Finally, CNTF and CLC signal via the CNTFRa/LIFR/gp130 complex. [70]

Ligand-binding by the receptor leads to activation of cytoplasmic Janus tyrosine kinases (*Jak*). Specifically, IL-6 activates *Jak*1, *Jak*2, and *Tyk*2. [56,85,86] Of these, *Jak*1 is believed to play a key role.[66] Activation of *Jak* kinases leads to phosphorylation of signal transducer and activator of transcription (STAT) proteins (Figure 2). The IL-6 type cytokines, via gp130, activate STAT3 potently and to a lesser extent, STAT1.[66] In animal models, STAT3 activation is believed to be an important regulator of neutrophil trafficking in inflammation. [87] LIFR and OSMR can also activate STAT5.[64] As classically described, phosphorylation of STATs induces their dimerization and translocation into the nucleus and thereby results in activation of gene transcription. However, it should be noted that much of the information about the STATs is in a state of flux, where the manner of existence of these proteins, importance of dimerization in nuclear translocation, and a variety of other fundamental observations about them is being challenged.[88] It appears that rather than simply existing as monomers or dimers, STAT proteins associate with a variety of cytoplasmic proteins including chaperones, regulatory proteins, and trafficking proteins.[88] Various STAT proteins, *Jak* kinases, and IL-6 receptor components at least partially exist in caveolin-1 containing, cholesterol-rich, detergent-resistant plasma membrane raft (microdomains) fractions, which limit their bioavailability.[89,90] These raft microdomains represent the unit of function for signaling.[89]

Interleukin-6 receptor complexes also activate the mitogen-activated protein kinase/ extracellular signal-regulated kinase (ERK) pathway, with the assistance of the tyrosine phosphatase, *Src* homology phosphatase (SHP2; Figure 2).[66,86,87] Specifically, ERK 1/2 is activated.[56] This in turn leads to activation of transcription factors and gene expression. Finally, IL-6 can also transduce signal via the PI3K/Akt pathway.[70]

Interleukin-6 signaling also has a negative feedback system that is mediated by phosphatases, namely, the inducible suppressors of cytokine signaling (SOCS) system and the constitutively active protein inhibitors of activated STATs (PIAS) system.[10,70] It appears

that the SOCS proteins play an important role in inhibiting IL-6 signaling, mediated by TNFα.[70]

Conclusions

Expression of membrane receptors for IL-6 determines IL-6 actions on target cells. The relative number of receptor molecules defines the limits of signaling. Cells that lack membrane-bound IL-6Rα can be rendered sensitive to IL-6 via trans-signaling. The coexistence of sIL-6Rα and sgp130 determines the extent to which trans-signaling can occur. The production and action of all components of the IL-6-IL-6 receptor axis is strongly regulated by trauma and inflammation.[91] Elevated concentrations of IL-6 are found in nearly every case that involves infectious, traumatic, and inflammatory states, rising within minutes of an insult and remaining elevated for days. In general, greater tissue trauma is associated with greater mediator production and inflammatory response.[92] In turn, the systemic dissemination of circulating IL-6 promotes the widespread development of focal areas of inflammation. The temporal change in IL-6 concentrations renders certain predictions possible regarding the regulation of cell responses. Consequences of this systemic action include the induced expression of C-reactive protein, which has been used as the assay par excellence for grading inflammation severity in patients.[91,93] In considering the functions of IL-6-regulated genes in the progression of trauma and/or septic response and recovery, an understanding of a cause-effect relationship of tissue damage, IL-6 expression, and the inflammatory response provides important diagnostic and predictive information in surgery, trauma and critical care, as discussed in part II of this review.

Acknowledgments

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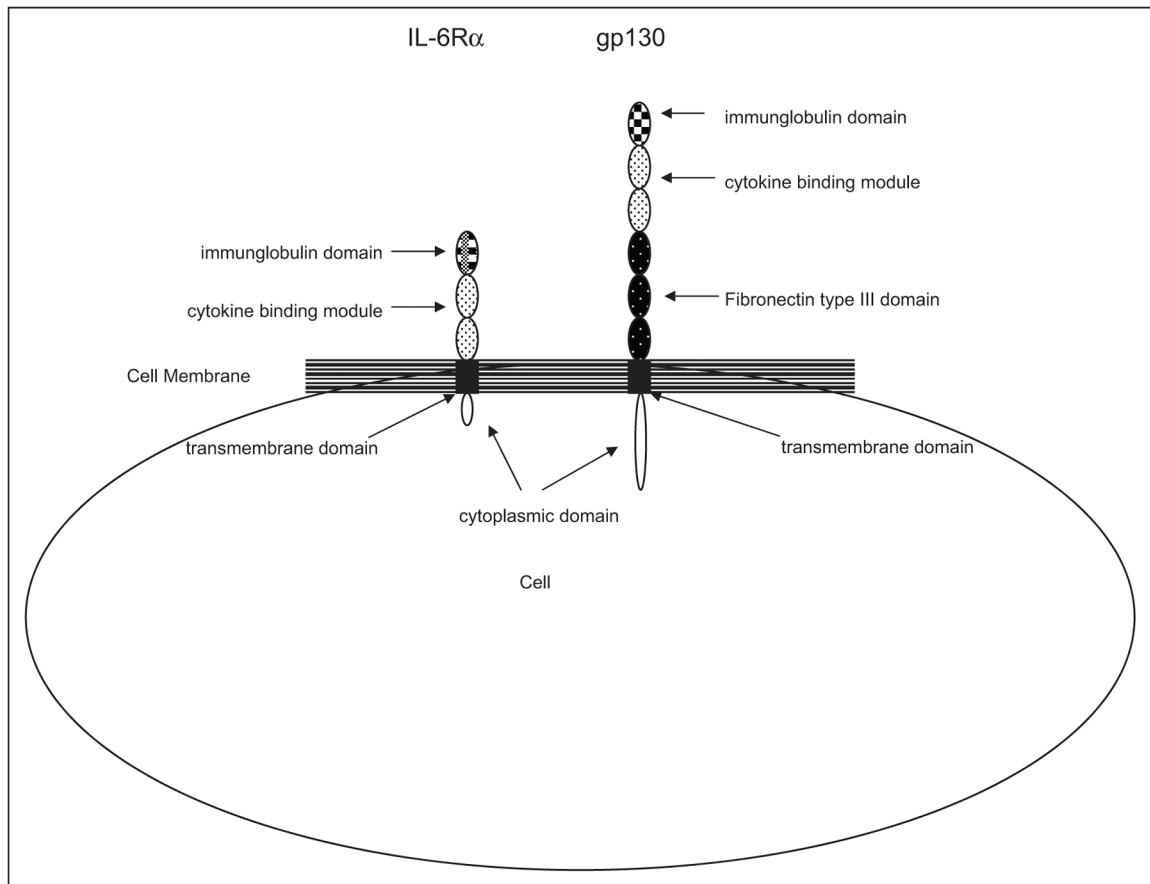
Figure 1.
A schematic of membrane-bound IL-6 receptors: IL-6Rα and gp130. These receptors engage with IL-6 in multimeric complexes to transduce signal. Both have a cytokine-binding module which has 2 pairs of conserved cysteine residues at the *N*-terminus as well as the WSXWS motif in the extracellular domain, at the C-terminus. This cytokine-binding module is composed of 2 fibronectin type III domains. Additionally, both receptors have an immunoglobulin-like domain, a single transmembrane domain, and an intracellular domain that lacks intrinsic enzymatic activity. The intracellular domain is longer in gp 130. The gp130 subunit also has 3 additional fibronectin type III domains. Adapted from *Biochem J.* 1998; 334 (pt 2): 297–314[30] and *Clin Rev Allergy Immunol.* 2005; 28(3): 177–186[67]. IL indicates interleukin; gp, glycoprotein; WSXWS, tryptrophanserine-x-tryptophan-serine.
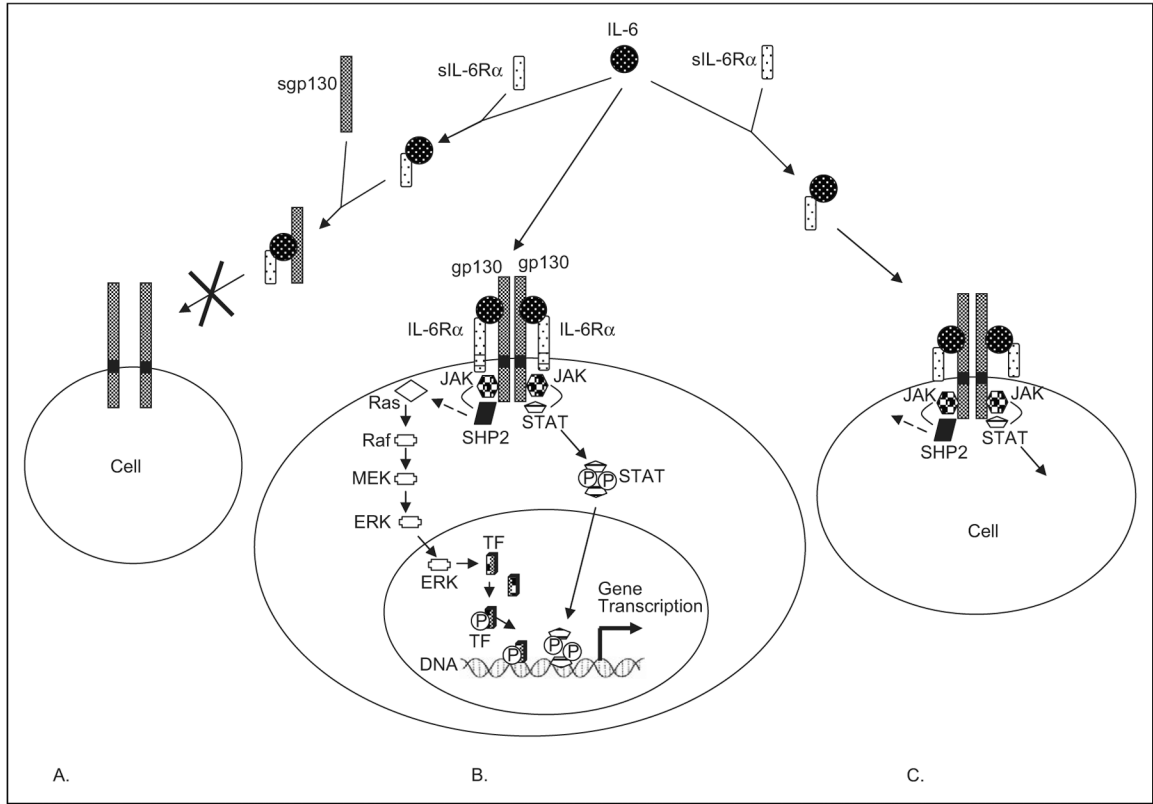
Figure 2.
A schematic of IL-6 and IL-6 receptor interactions. A. Soluble gp130, an antagonist of IL-6 activity. Serum IL-6 binds with sIL-6Rα. This complex in turn binds to sgp130. Soluble gp130 thereby competitively antagonizes the binding of the IL-6-sIL-6Rα complex to membrane-bound gp130, and thereby inhibits IL-6 effects on this cell. B. Membrane-bound gp130 and membrane-bound IL-6Rα. Membrane-bound IL-6Rα is restricted in location and is found in only select cell types, whereas gp130 is ubiquitous. In this case, serum IL-6 complexes with membrane-bound IL-6Rα and then associates with membrane-bound gp130, to generate a signaling-capable hexameric complex. As classically described, signaling is mediated proximally by the *Jak* kinases and STAT proteins. Phosphorylation of STAT proteins by the *Jak* kinases and their subsequent translocation to the nucleus induces gene transcription. The *Jak* kinases, with the help of tyrosine phosphatase, SHP2, also activate a series of additional kinases (Ras, Raf, Mek, and ERK), which in turn eventually phosphorylate a transcription factor (TF) and thereby induce gene transcription. A third pathway, not illustrated involves PI3K (see text for details). C. Soluble IL-6Rα, an agonist for IL-6 activities. Soluble IL-6Rα binds to serum IL-6. This complex then engages membrane-bound gp130, which is found on most cells, to transduce signal in those cells that lack membrane-bound IL-6Rα. This phenomenon, termed "trans-signaling," allows IL-6 to target multiple cell types. Adapted from *Arthritis Res.* 2002; 4(suppl 3): S233-S242,[9] *Biochem J.* 2003; 374(pt 1):1–20,[70] *Crit Care Med.* 2005; 33(8):1839–1844,[71] and *Acta Biochim Pol.* 2003; 50(3):603–611.[72] IL indicates interleukin; gp, glycoprotein; sIL-6Rα, soluble IL-6Rα STAT, signal transducer and activator of transcription.

Table 1.

Overview of IL-6 Actions

Acute phase response
Hypothalamic-pituitary-adrenal axis
Fever
Hormone release
Immune cell maturation and activation
Immunoglobulin production by B cells
Proliferation and differentiation of T cells
Hemostasis
Platelet production from megakaryocytes
Hematopoesis
Endothelial cell activation
Neuronal cell differentiation
Keratinocyte proliferation
Cardiac muscle hypertrophy
Osteoclast activation

Abbreviation: IL-6, interleukin-6.

Table 2.

Overview of Actions of Several Members of the IL-6 Cytokine Family[a]

IL-11	OSM	LIF
Acute phase response	Acute phase response	Acute phase response
Neurogenesis	Megakaryocyte differentiation	Neuronal survival factor
Hematopoiesis	Adhesion molecule expression	Hematopoiesis
Immune cell development	Mediates wound healing	Bone metabolism
Bone metabolism		
CNTF	**CT-1**	**CLC**
Acute phase response	Acute phase response	Neuronal support
Activates acetylcholine transferase in motor neurons	Neuronal survival factor	Embryogenesis
	Increases platelet and erythrocyte counts	
Anti-apoptotic effects after nerve injury	Cardiac myocyte hypertrophy	
IL-27	**IL-31**	**NP**
Pro- and anti-inflammatory activities on white blood cells	Role in skin inflammation	Nervous system development in rodents
	Role in bronchopulmonary inflammation	

Abbreviations: IL, interleukin; CNTF, ciliary neurotrophic factor; OSM, Oncostatin M; CT-1, cardiotrophin-1; LIF, leukemia inhibitory factor; CLC, cardiotrophin-like cytokine; NP, neuropoetin/ cardiotrophin 2.

[a] Modified from Biochem J. 1998; 334(pt 2): 297–314.[30]