# Recent insights into targeting the IL-6 cytokine family in inflammatory diseases and cancer

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Abstract | The IL-6 family of cytokines consists of IL-6, IL-11, IL-27, IL-31, oncostatin M (OSM), leukaemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF), cardiotrophin 1 (CT-1) and cardiotrophin-like cytokine factor 1 (CLCF1). Membership of this cytokine family is defined by usage of common β-receptor signalling subunits, which activate various intracellular signalling pathways. Each IL-6 family member elicits responses essential to the physiological control of immune homeostasis, haematopoiesis, inflammation, development and metabolism. Accordingly, distortion of these cytokine activities often promotes chronic disease and cancer; the pathological importance of this is exemplified by the successful treatment of certain autoimmune conditions with drugs that target the IL-6 pathway. Here, we discuss the emerging roles for IL-6 family members in infection, chronic inflammation, autoimmunity and cancer and review therapeutic strategies designed to manipulate these cytokines in disease.

Lymphokines
A subset of cytokines that are released by lymphocytes.

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https://doi.org/10.1038/

Cytokines contribute to all aspects of human biology and have evolved to enable the sensing and interpretation of environmental cues relevant to the maintenance of normal host physiology[1]. Although these secretory proteins are best known for their role as custodians of immune homeostasis and the inflammatory response to infection, trauma or injury, their diverse functions also affect embryonic development, cognitive function and behaviour, tissue integrity and ageing. In this regard, cytokines often display pleiotropic or overlapping functional properties[1].

The IL-6 cytokine family comprises IL-6, IL-11, IL-27, IL-31, oncostatin M (OSM), leukaemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF), cardiotrophin 1 (CT-1) and cardiotrophin-like cytokine factor 1 (CLCF1), and among all cytokine families, it arguably displays the highest degree of functional pleiotropy and redundancy in eliciting responses relevant to health and disease[2]. Members of this family play prominent roles in chronic inflammation, autoimmunity, infectious disease and cancer (BOX 1), where they often act as diagnostic or prognostic indicators of disease activity and response to therapy[1,3–6]. Moreover, IL-6 family cytokines are now viewed as major therapeutic targets for clinical intervention[3–9]. This is epitomized by the treatment of chronic immune-related conditions, such as inflammatory arthritis, giant cell arteritis and Castleman disease, with drugs that target IL-6 (REFS[5,10–12]). In this Review, we draw on recent advances to provide and their clinical potential as therapeutic targets or disease modifiers in autoimmunity, inflammation, infection and cancer.

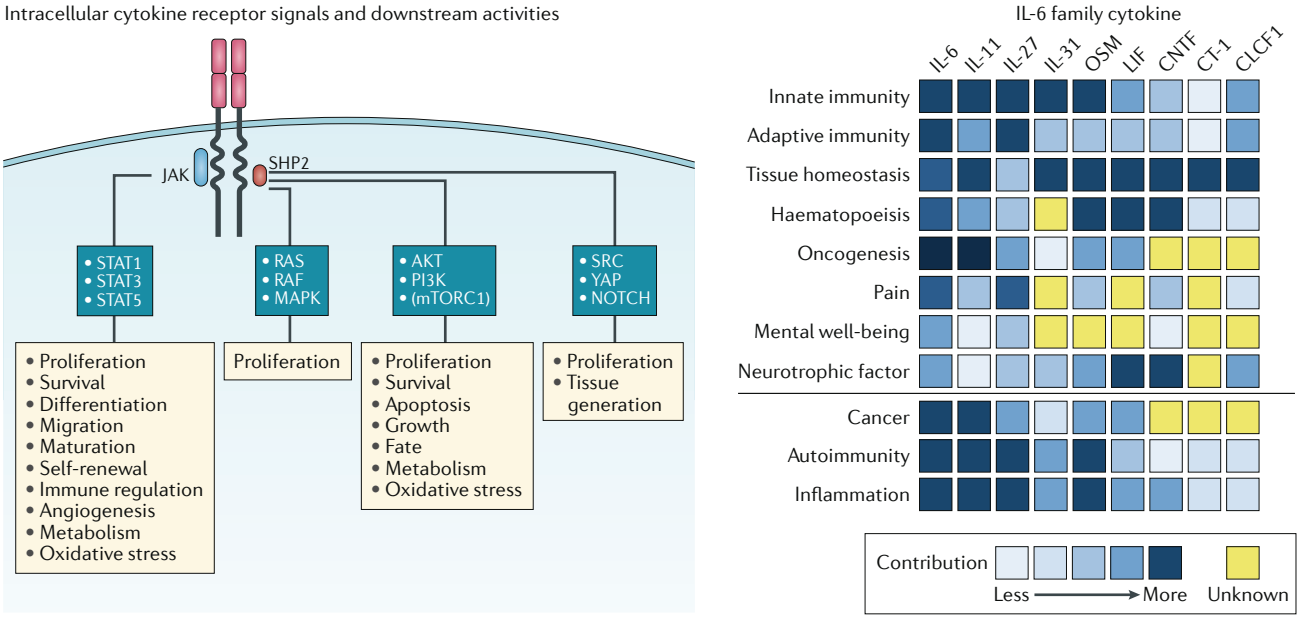
## What constitutes IL-6 family membership?

IL-6 remains the archetypal member of the IL-6 cytokine family and regulates a diverse array of functions relevant to haematopoiesis, tissue homeostasis, metabolism and immunity[5,13] (BOXES 1,2). Since the discovery of IL-6, subsequent investigations have revealed a high degree of functional redundancy among IL-6 family cytokines[14]. As a consequence, cytokines within this family are often described with activities attributed to lymphokines, adipokines or myokines, which reflect their broad expression and cellular distribution among all major cell types within the body. This redundancy is characterized by a precise hierarchical involvement in inflammation, metabolism, development, tissue regeneration, neurogenesis and oncogenesis[15] (BOXES 1,2).

A defining feature of this cytokine family is its usage of common cytokine receptor subunits. These receptor complexes comprise the shared signal-transducing receptor β-subunit, membrane glycoprotein 130 (gp130; also known as IL-6Rβ), together with either a ligand-binding non-signalling receptor α-subunit or a signalling receptor β-subunit that resembles gp130 (REFS[2,15,16]) (FIG. 1). The receptor signalling complexes for IL-6 and IL-11 contain a gp130 homodimer, whereas other family members signal via a heterodimeric receptor com-

Box 1 | **Signalling mechanisms for IL-6 family cytokines and links with physiological and disease processes**

Intracellular signalling mechanisms linked to the membrane glycoprotein 130 (gp130) receptor system are triggered via activation of receptor-associated cytoplasmic tyrosine kinases (Janus kinase 1 (JAK1), JAK2 and non-receptor tyrosine-protein kinase 2 (TYK2)). Activation of these proteins leads to distinct patterns of tyrosine phosphorylation and subsequent activation of the latent transcription factors signal transducer and activator of transcription 1 (STAT1), STAT3 and, to a lesser extent, STAT5. Additional signalling mechanisms associated with cytokine activation of the gp130 receptor system include processes controlled through the tyrosine-protein phosphatase SH-PTP2 (SHP2). The activation of this protein promotes signalling through the RAS–RAF pathway and the SRC–YAP–NOTCH pathway. Activation of the RAS–RAF cascade also regulates several downstream modifiers that include the phosphorylation of mitogen-activated protein kinases (MAPKs) and the RAC serine/threonine-protein kinase (AKT) and mechanistic target of rapamycin complex 1 (mTORC1) pathways and activities associated with the transcription factors nuclear factor NF-IL-6 (a CAAT/enhancer binding protein (C/EBP) family member) and activator protein 1 (AP-1) (a heterodimer of proto-oncogene JUN and proto-oncogene FOS). Other kinases with less defined involvements with this receptor system include serine/threonine-protein kinase SAK (also known as PLK4), tyrosine-protein kinase HCK, tyrosine-protein kinase FES/FPS (FES), tyrosine-protein kinase BTK and tyrosine-protein kinase TEC[16]. Each of these signal transduction mechanisms controls various biological processes, as indicated. The heat map depicted in the right-hand panel details how individual IL-6 cytokine family members contribute to specific physiological and immunological processes and emphasizes their relative importance in certain disease settings (depicted below the blue line).




CLCF1, cardiotrophin-like cytokine factor 1; CNTF, ciliary neurotrophic factor; CT-1, cardiotrophin 1; LIF, leukaemia inhibitory factor; OSM, oncostatin M; PI3K, phosphoinositide 3-kinase.

β-subunit (FIG. 1). The exception to this 'gp130 rule' is IL-31, which binds a cytokine receptor complex containing the OSM-specific receptor subunit-β (OSMRβ) and a cognate IL-31-binding receptor termed IL-31 receptor subunit-α (IL-31Rα)[17–19].

Phylogenetic analysis of cytokine families reveals that members of the IL-6 family share a close relationship with IL-12 family cytokines[20–22]. This link is illustrated by the heterodimeric composition of IL-27 (comprising IL-27p28 (also known as IL-27α) and Epstein–Barr virus-induced gene 3 protein (EBI3; also known as IL-27β)), which is structurally related to the IL-12 (IL-12p40 (also known as IL-12β)–IL-12p35 (also known as IL-12α)), IL-23 (IL-23p19 (also known as IL-23α)–IL-12p40), IL-35 (IL-12p40–EBI3) and IL-39 (IL-23p19–EBI3) heterodimers[23–25]. Interestingly, both IL-27p28 and IL-35 can also signal via gp130 (REFS[26,27]), although the biological importance of this engagement with gp130 requires further substantiation, and thus their membership to the IL-6 family of cytokines is premature.

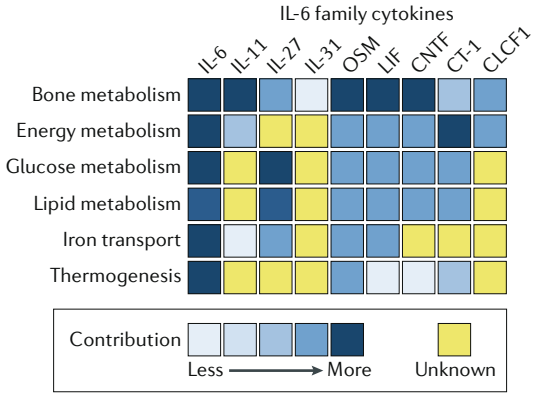
The functional diversity and redundancy associated presence of the ubiquitously expressed common gp130 signal-transducing receptor (FIG. 1). Use of the common gp130 receptor subunit contributes to the regulation of a wide range of overlapping activities that are controlled by IL-6 family cytokines. As a consequence, these cytokines play key roles in many physiological processes, including development, as evidenced by the embryonic lethality of gp130-deficient mice[28]. In contrast to gp130, the receptor subunits specific to individual family members display a more restricted cellular expression profile, and the phenotype of mice lacking individual cytokine family members or their associated receptor subunits is often less severe than their apparent pleiotropic properties would suggest[28–31].

While the tissue distribution of these receptors offers some distinction as to how individual family members act in defined cellular compartments, certain cytokines within the family have evolved several mechanisms that amplify or broaden their cellular activities. For example, human OSM can signal via gp130–LIF receptor (LIFR) or gp130–OSMRβ complexes to mediate responses typi-

Adipokines
A subset of cytokines that are secreted by adipose tissue and are sometimes called adipocytokines.

Myokines
Cytokines produced and released by myocytes in response to muscle

Box 2 | **IL-6 family cytokines as regulators of metabolic processes**




CLCF1, cardiotrophin-like cytokine factor 1.

Members of the IL-6 cytokine family perform integral roles in health and disease, and their capacity to influence the maintenance of immune homeostasis and well-being can occur via regulation of various metabolic processes. The depicted heat map summarizes the relative contribution of individual members of the IL-6 cytokine family to metabolism and emphasizes the types of metabolic processes that they affect. Certain family members, such as IL-6 and oncostatin M (OSM), elicit these effects in various stromal tissue compartments (for example, muscle, liver, bone and brain) and inflammatory cells (for example, lymphocytes and macrophages)[242–244]. On the other hand, IL-27 displays a more restricted activity profile on select immune cell types, where it controls the expression of enzymes responsible for oxysterol generation in effector and regulatory $CD4^+$ T cells[245]. Importantly, several of these associations with metabolism have been identified through clinical observations in patients receiving biological drugs. For example, hypoferraemia is a common response to systemic infection, and patients with autoimmune conditions, such as rheumatoid arthritis, frequently suffer from inflammatory anaemia[246]. Here, biological drugs against IL-6 (for example, tocilizumab) combat the development of anaemia and inhibit the hepatic-derived generation of hepcidin and haptoglobin[247,248]. These latter responses are also associated with OSM and leukaemia inhibitory factor (LIF)[249]. Further roles for IL-6 in metabolic processes have been identified in *Il6*$^{-/-}$ mice, which develop mature-onset obesity, hypertriglyceridaemia and glucose intolerance, and patients on tocilizumab experience changes in serum cholesterol and triglyceride levels, along with increases in body weight[10,250,251]. The control of adipogenesis and lipolysis is also attributed to other IL-6 family cytokines, and these are reviewed elsewhere[252–254]. For instance, ciliary neurotrophic factor (CNTF) treatment in mice reduced adiposity and body weight and improved various parameters of diabetes and hepatic steatosis, a finding that led to the development of recombinant CNTF therapy (axokine), which suppressed appetite, increased energy expenditure and caused sustained weight loss in humans[255–257]. Consistent with a role for IL-6 family cytokines in regulating energy and glucose metabolism, acute infusion of IL-6 in mice increased glucose uptake and fatty acid oxidation in skeletal muscle, which was associated with improved insulin sensitivity and protection from diet-induced obesity[258]. Here, IL-6 released from contracting muscle drives the production of glucagon-like peptide 1 (GLP-1) within the gut and pancreas and contributes to the maintenance of glucose homeostasis through GLP-1 control of insulin secretion[259]. An important aspect of these metabolic-associated outcomes regulated by IL-6 family members is their link with alterations in mitochondrial activity. These include changes in mitochondrial remodelling because of cachexia, alterations in mitochondrial calcium mobilization and membrane potential and the regulation of thermogenesis through regulation of mitochondrial brown fat uncoupling protein 1 (REFS[260–266]).

Receptor promiscuity can also elicit defined forms of cytokine receptor crosstalk. For instance, CNTF displays a low affinity interaction with IL-6 receptor subunit-α (IL-6Rα) that can lead to the formation and activation of an IL-6Rα–gp130–LIFR signalling receptor complex[2,32]. Such cross-regulation may afford CNTF the capacity to control IL-6-related processes not normally associated with its primary involvement in the nervous system (for example, metabolism, bone remodelling and immune regulation)[33,34] (BOXES 1,2). The complexities of IL-6Rα usage also extend to cytokines beyond the IL-6 cytokine family, with a recent example being IL-27p28, which moderates inflammatory activities through

Janus kinase–signal transducer and activator of transcription pathway (JAK–STAT pathway). A cytokine receptor signalling mechanism used by certain cytokines to sense and interpret environmental cues during inflammation and

In addition to these classical mechanisms of cytokine receptor signalling, several members of the IL-6 family employ alternative modes of gp130 activation termed cytokine *trans*-signalling (relevant to IL-6, IL-11 and CNTF) and *trans*-presentation (relevant to IL-6) (BOX 3). These alternative modes of cytokine signalling are best epitomized by the action of IL-6, and we refer the reader to several recent articles that review the regulation and biological properties of classical IL-6 receptor (IL-6R) signalling and IL-6 *trans*-signalling in health and disease[5,15,17,37–40]. Briefly, classical IL-6R signalling describes activities mediated via the membrane-bound IL-6R complex and is restricted to cells that express both IL-6Rα and gp130 (REF.[37]). By contrast, IL-6 *trans*-signalling denotes a process that involves IL-6 binding to a soluble form of IL-6Rα (sIL-6R), which maintains the circulating half-life of IL-6 and increases its bioavailability[41,42]. Interestingly, sIL-6R shares sequence identity with both IL-12p40 and EBI3, and once bound with IL-6 resembles a heterodimeric cytokine similar to IL-12-related cytokines[5,20,43]. In this regard, the IL-6–sIL-6R complex is able to directly engage and activate membrane-bound gp130 to facilitate IL-6 signalling in cell types that would not normally respond to IL-6 (REF.[37]). Thus, *trans*-signalling serves to broaden the target cell repertoire of IL-6 and is considered the primary mechanism for IL-6 involvement in numerous chronic diseases and cancers[5,37,39]. Intriguingly, similar cytokine *trans*-signalling mechanisms have been described for IL-11 and CNTF, and recent in vitro observations imply that both IL-27p28 and EBI3 can also induce sIL-6R-mediated forms of *trans*-signalling[2,15,36,44–46] (BOX 3). While the in vivo consequences of these latter signalling modes require further evaluation, the identification of soluble variants of gp130 (sgp130) in human serum, urine and inflammatory exudates that antagonize both IL-6 and IL-11 *trans*-signalling emphasizes the biological importance of these alternative signalling mechanisms[17,37,40,46].

## Regulation of intracellular signalling

All IL-6-related cytokine receptor complexes transduce intracellular signals via the Janus kinase–signal transducer and activator of transcription pathway (JAK–STAT pathway), where receptor-associated JAKs (namely, JAK1, JAK2 and TYK2) activate the latent transcription factors STAT1, STAT3 and (to a lesser extent) STAT5 (REFS[6,9,16]) (BOX 1). Other signalling intermediates activated in response to IL-6 family cytokines include, first, the protein tyrosine phosphatase SH-PTP2 (SHP2; also known as PTPN11), which promotes activation of the RAS–RAF–extracellular-signal-regulated kinase 1 (ERK1)/ERK2 mitogen-activated protein kinase (MAPK) and the phosphoinositide 3-kinase (PI3K)–protein kinase B (PKB; also known as AKT) pathways, and, second, the transcription factor nuclear factor NF-IL-6 (also known as C/EBPβ)[16] (BOX 1). Recently, IL-6-induced and IL-11-induced activation of PI3K was shown to regulate the mechanistic target of rapamycin (mTOR) complex 1 (mTORC1) system, which controls telomerase activity and protein synthesis and influences various cellular

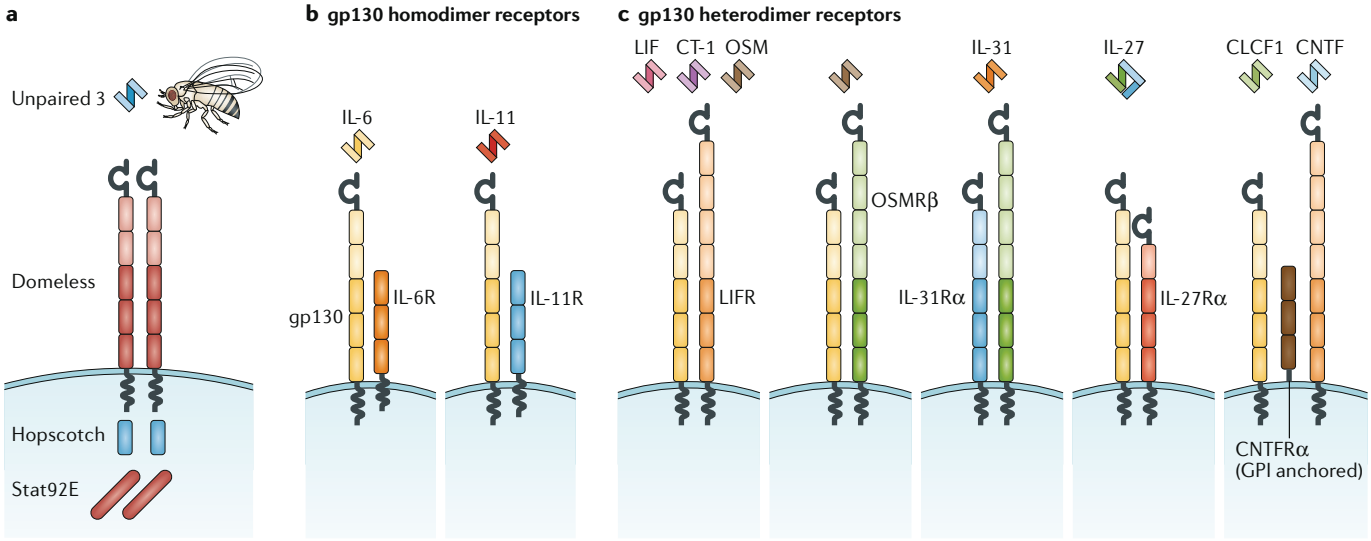



Fig. 1 | **Cytokine receptor usage by the IL-6 family of cytokines.** Members of the IL-6 cytokine family share a common ancestral link to an innate immune sensing mechanism found in *Drosophila melanogaster* (part **a**). This system consists of Unpaired 3 (IL-6-like), Domeless (gp130-like), Hopscotch (*Drosophila melanogaster* homologue of mammalian Janus kinase (JAK)) and signal transducer and activator of transcription protein at 92E (Stat92E; also referred to as Marelle). In mammals, all cytokines within the family activate cells through receptor complexes that contain the signal-transducing receptor β-subunit membrane glycoprotein 130 (gp130) (parts **b** and **c**). Three distinct forms of cytokine receptor arrangements are utilized by these cytokines. Receptor complexes for IL-6 and IL-11 (part **b**) contain a cognate non-signalling receptor α-subunit and gp130 (termed a gp130 homodimer receptor complex), with gp130 existing as a homodimer to elicit signalling. On the basis of the proposed structural arrangement of the IL-6 receptor (IL-6R), a functioning receptor is composed of an IL-6–IL-6R–gp130 complex that is clustered into a dimer structure[16,268]. By contrast, receptor complexes for leukaemia inhibitory factor (LIF), cardiotrophin 1 (CT-1), oncostatin M (OSM) and IL-27 (part **c**) comprise gp130 and a second receptor subunit, which contains structural features similar to gp130 (termed a gp130 heterodimer receptor complex). These include LIF receptor (LIFR), OSM-specific receptor subunit-β (OSMRβ) and IL-27 receptor subunit-α (IL-27Rα). The receptor for ciliary neurotrophic factor (CNTF) and cardiotrophin-like cytokine factor 1 (CLCF1) comprises three individual receptor subunits formed between CNTF receptor subunit-α (CNTFRα), LIFR and gp130. Currently, IL-31 remains the only exception to this 'gp130 rule', and the IL-31 receptor consists of IL-31 receptor subunit-α (IL-31Rα) and OSMRβ. These alternative receptors provide cytokine specificity and couple directly to signal transduction pathways required for cellular activation (BOX 1). GPI, glycosylphosphatidylinositol; IL-11R, IL-11 receptor.

(BOX 1). The diverse signalling networks activated by IL-6 also extend to NOTCH and Yes-associated protein (YAP), which upon gp130–SRC kinase-dependent activation facilitate epithelial cell proliferation and tissue remodelling or regeneration[49] (BOX 1).

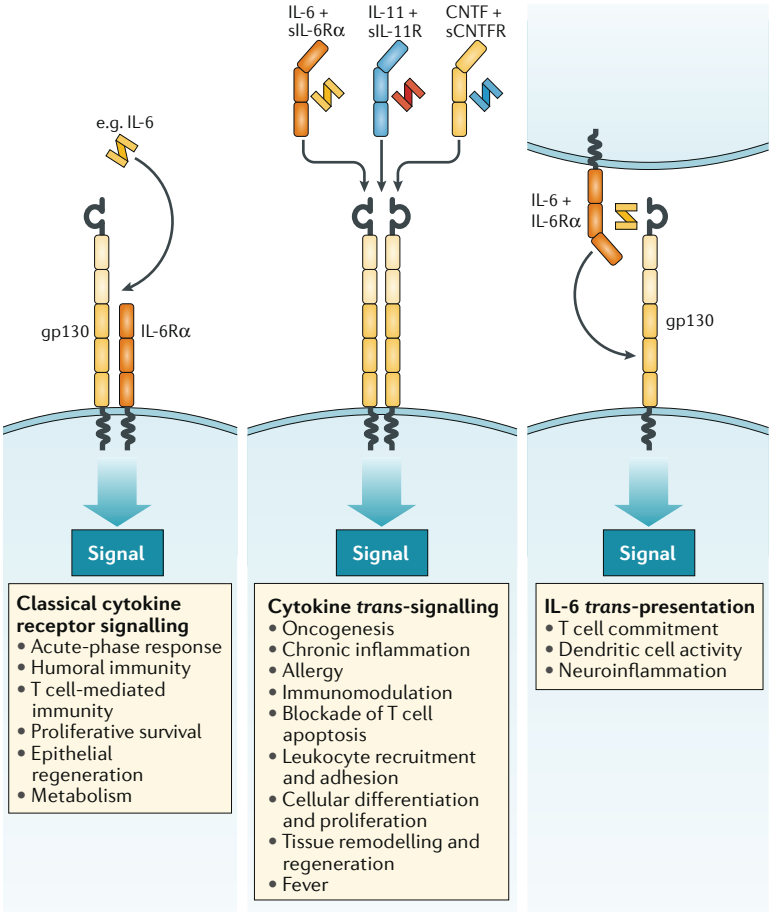
The pathophysiological consequences of dysregulated gp130 activation on immune homeostasis and susceptibility to infection, autoimmunity or cancer have been widely reported, thus highlighting the importance of restricting the magnitude or duration of IL-6 cytokine family signalling in disease[50–54]. In this respect, multiple negative regulatory mechanisms have evolved to curtail gp130-dependent signalling. These include receptor internalization, deactivation of receptors and signalling intermediates by protein tyrosine phosphatases, microRNA (miRNA)-mediated translational repression and degradation of target mRNAs encoding cytokines or their receptors and the STAT-driven induction of protein inhibitor of activated STAT protein (PIAS) and suppressor of cytokine signalling (SOCS) factors[9,16,55,56]. Among these, SOCS3 plays the predominant negative regulatory role by inhibiting JAK–STAT3 activation and targeting cytokine receptor complexes for proteasome degradation[55].

Considering the global cellular processes activated that IL-6 family cytokines display widespread functional pleiotropy (BOX 1). So, how do individual family members acquire unique biological specificity? Early investigations of STAT factors and their interaction with the genome provided evidence of cooperative mechanisms with other transcription factors, competition for overlapping transcription factor binding sites in gene promoter regions and interaction with other transcriptional co-activators or co-repressors[9,55,57]. For example, the STAT3-mediated transcriptional output of IL-6 family cytokines can be influenced by the interaction of STAT3 with co-activators (such as p300–CREB-binding protein (CBP)) and other transcription factors, including nuclear factor-κB (NF-κB). NF-κB complexes with STAT3 in an unphosphorylated state to drive a distinct transcriptional signature enriched for genes involved in oncogenic and immune responses[58]. Interestingly, there is also an alternative mode of transcriptional control employed by STAT3. This occurs downstream of IL-6 and IL-11 and involves the induction of specific miRNAs implicated in tumorigenesis and epithelial–mesenchymal transition (EMT) (for example, miR-21 and miR-200 family members)[59,60].

Another mechanism by which individual IL-6 fam-

Box 3 | **Receptor signalling mechanisms used by the IL-6 family of cytokines**

Several members of the IL-6 family adopt alternative modes of cellular activation via membrane glycoprotein 130 (gp130). For example, IL-6 classical cytokine receptor signalling transduced via a gp130 homodimer is facilitated by membrane-bound forms of IL-6 receptor subunit-α (IL-6Rα) and gp130 (for schematic purposes, only one gp130 molecule is shown). Soluble forms of the cognate non-signalling receptor α-subunits for IL-6 (sIL-6Rα), IL-11 (sIL-11R) and ciliary neurotrophic factor (CNTF) (sCNTFR) are readily detected in serum. These soluble receptors retain cytokine-binding kinetics and form receptor–ligand complexes that activate cells through binding interactions with cell-associated gp130. Cytokine binding to soluble receptors also increases the circulating half-life of the cytokine and offers protection from proteolytic degradation[40]. These forms of cellular activation are termed cytokine *trans*-signalling and provide a mechanism to broaden the types of cells that are responsive to IL-6, IL-11 or CNTF[2]. Recent evidence has identified another form of receptor engagement termed IL-6 *trans*-presentation[267]. Here, IL-6 bound to membrane-bound IL-6Rα is displayed on the surface of cells (for example, specialized dendritic cells) and presented to gp130 expressed on a nearby cell type (for example, a lymphocyte) to elicit signalling via a gp130 homodimer (for schematic purposes, only one gp130 molecule is shown). These additional forms of cytokine receptor signalling contribute to the regulation of innate and adaptive immunity and direct responses in target cells that lack specific receptors for these cytokines. Also shown are the numerous cellular processes associated with each of these signalling modes.




cross-regulation between individual STAT proteins[9,61–64]. For example, in cells lacking STAT1, STAT1-activating cytokines (for instance IFNγ) show enhanced STAT3-type responses, such as increased cell survival, proliferation and induction of immune tolerance. Conversely, in STAT3-deficient cells, IL-6 induces STAT1-associated cellular effects, such as inhibition of cell proliferation, immunity[9,62,64]. Notably, a series of studies investigating the differential transcriptional responsiveness of T cells to IL-6 and IL-27 has uncovered novel insights into how cross-regulation between STAT1, STAT3 and STAT5 can determine the effector characteristics of $CD4^+$ T helper cells[9,65,66]. Specifically, while both cytokines transcriptionally regulate a comparable number of genes, a small number of immunoregulatory genes was differentially expressed (for example, *Ifng*, *Ccl5* and *Rorc*), which reflect the opposing pro-inflammatory and immunosuppressive functions assigned to IL-6 and IL-27 (REF.[66]). In this setting, STAT3 provided the bulk of the overall transcriptional responsiveness to each cytokine, while STAT1 shaped the transcriptional programme specific to either IL-6 or IL-27.

## Critical modulators of innate immunity

During inflammation, IL-6 family cytokines regulate innate immunity through direct effects on innate immune cells and indirectly via activation of stromal tissue cells resident to the site of inflammation (BOX 1). These activities influence changes in leukocyte recruitment, their functional activation, differentiation and survival and the development of a more sustained adaptive immune response[5,15,17,67]. Importantly, such roles illustrate why therapeutic targeting of IL-6 family members has been often associated with clinical benefit in inflammatory diseases, where these processes are distorted or skewed.

The capacity of IL-6 family cytokines to regulate almost every aspect of the innate immune system is facilitated, at least in part, by their signalling interplay with the complement system and pattern recognition receptors[68,69]. For example, IL-6R, complement component C5a receptor 1 (C5AR1) and Toll-like receptor 4 (TLR4) signalling pathways share a complex interaction that is relevant to the control of bacteraemia and sepsis[70–72]. Such interactions may include the collaborative crosstalk that exists between STAT3 and NF-κB[73,74]. Thus, IL-6 and other IL-6-related cytokines often work in association with innate sensing systems to link innate and adaptive immunity and to control antimicrobial defence.

Studies on IL-6, IL-27, OSM and LIF highlight important roles for these cytokines in antimicrobial and antiviral immunity, where they provide tissue protection from infection-related injury[30,67,70,75–77]. These cytokines often control the recruitment, adhesion, survival and effector activities of neutrophils, tissue-resident and inflammatory monocytes, and innate lymphoid cell populations (for example, natural killer (NK) cells). Specifically, these activities include the regulation of neutrophil-activating chemokines (for example, CXC-chemokine ligand 1 (CXCL1), CXCL5, CXCL6 and CXCL8), adhesion molecules (for example, intercellular adhesion molecule 1 (ICAM1), vascular cell adhesion protein 1 (VCAM1) and L-selectin) and apoptotic regulators (for example, apoptosis regulator BCL-2 and apoptosis regulator BCL-$X_L$ (also known as BCL2L1))[39,78]. In this regard, several in vivo studies have shown that IL-6 family cytokines affect the accumulation of specific immune cell subsets within

Pattern recognition receptors
Innate sensors that detect bacteria, viruses, fungi and other endogenous ligands generally associated with

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