REVIEW

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IL-6 as a keystone cytokine in health and disease

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Interleukin 6 (IL-6) has a broad effect on cells of the immune system and those not of the immune system and often displays hormone-like characteristics that affect homeostatic processes. IL-6 has context-dependent pro- and anti-inflammatory properties and is now regarded as a prominent target for clinical intervention. However, the signaling cassette that controls the activity of IL-6 is complicated, and distinct intervention strategies can inhibit this pathway. Clinical experience with antagonists of IL-6 has raised new questions about how and when to block this cytokine to improve disease outcome and patient wellbeing. Here we discuss the effect of IL-6 on innate and adaptive immunity and the possible advantages of various antagonists of IL-6 and consider how the immunobiology of IL-6 may inform clinical decisions.

Biological response modifiers ('biologics') that inhibit inflammatory cytokines and small molecules that target kinases associated with cytokine signaling are used in the treatment of chronic inflammation, autoimmunity and cancer[1]. Unlike drugs that have broad immunosuppressive qualities, these newer approaches represent a more targeted strategy that has the potential to promote clinical remission[2]. However, their efficacy can be hard to predict and clinical trials have produced unexpected outcomes. For example, therapies that block interleukin 1 (IL-1) or IL-17 display robust efficacy in the treatment of auto-inflammatory conditions and psoriasis, respectively, but show limited efficacy in rheumatoid arthritis and, in patients with inflammatory bowel disease, can actually make the disease worse[2–4]. These situations highlight the challenge of understanding which drug is most appropriate for a particular patient or disease activity. This has led to the suggestion that in some immune system–mediated diseases there may be a limited number of keystone cytokines that support disease progression[1] and that targeting these factors should offer the best opportunity for remission. The success of the monoclonal antibody tocilizumab, which targets the receptor for IL-6 (IL-6R), in the treatment of inflammatory arthritis and a subset of other immunological conditions has identified IL-6 as a keystone cytokine in these processes[5,6]. This has fuelled the design of other biologics that target IL-6, its receptor or signaling pathways. Here we review the complex biology associated with the IL-6 signaling cassette (i.e., the individual cytokine and receptor components that transduce IL-6 signals), its role in many infectious and inflammatory processes and the various modes of action for biologics that target IL-6.

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The identification of a truly pleiotropic cytokine

When IL-6 was first identified, it was characterized according to its ability to promote the population expansion and activation of T cells, the differentiation of B cells, and regulation of the acute-phase response[7–13]. Thus, IL-6 is pleiotropic, and it is now appreciated that IL-6 has hormone-like attributes that affect vascular disease, lipid metabolism, insulin resistance, mitochondrial activities, the neuroendocrine system and neuropsychological behavior[1,4,5,14–17]. Almost all stromal cells and cells of the immune system produce IL-6, and while IL-1β and tumor-necrosis factor are major activators of *IL6* expression, other pathways such as Toll-like receptors, prostaglandins, adipokines, stress responses and other cytokines can promote the synthesis of IL-6. IL-6 is controlled at multiple levels by microRNAs (for example, let-7a), RNA-binding proteins (for example, Lin28B and Arid5a), RNases (for example, regnase-1) and circadian control factors such as the product of the 'clock gene' *Per1* (refs. 18–20). Normal physiological concentrations of IL-6 in human serum are relatively low (1–5 pg/ml), but these are rapidly elevated in disease settings and in extreme circumstances, such as meningococcal septic shock, can reach quantities in the μg/ml range[21]. Thus, *IL6* expression is subject to both homeostatic basal regulation and rapid induction in the context of infection, autoimmunity or cancer in which increases in IL-6 are often a better predictor of disease activity than is C-reactive protein[22–24].

Consistent with the early description of IL-6 as a lymphocyte-stimulating factor, IL-6 deficiency leads to impaired innate and adaptive immunity to viral, parasitic and bacterial infection[25–32]. Indeed, children with inhibitory autoantibodies to IL-6 develop recurrent staphylococcal cellulitis and subcutaneous abscesses[33]. Similarly, patients with autosomal mutations in the gene encoding the transcription factor STAT3 (Job's syndrome) show impaired IL-6 activity and are susceptible to recurrent infections of the skin, lung and gut and often die prematurely from pneumonia caused by Gram-negative bacteria or filamentous fungi[34]. Another way to gauge the importance of a cytokine in pathogen control is whether these microorganisms have evolved ways to mimic or disrupt this immunological pathway. For example, human cytomegalovirus can

antagonize *IL6* expression[35], whereas human herpesvirus 8 expresses a viral form of IL-6 that shares ~60% amino acid similarity with its human counterpart and can block the recruitment of neutrophils[36]. This viral form of IL-6 has the unusual ability to signal through a single chain of the heterodimeric IL-6 receptor[37], and in conditions associated with human herpesvirus 8, such as B cell lymphoma, primary effusion lymphoma and multicentric Castleman's disease, it promotes cellular proliferation and prevents apoptosis. The viral IL-6 also inhibits antiviral immunity through inhibition of type I interferons, which allows HHV8 to evade immune detection[38–40].

While IL-6 has a protective role in many infections, the same activities can be key to the maintenance of chronic inflammation that includes models of arthritis, experimental autoimmune encephalomyelitis, multicentric Castleman's disease and pristane-induced lupus and plasmacytomas[41–46]. Conversely, mouse strains with transgenic expression of IL-6 develop various disorders, including multiple myeloma; neurological disease when IL-6 is overexpressed in the central nervous system; pulmonary fibrosis and hypertension when IL-6 is expressed in the lungs; and plasmacytosis when IL-6 is expressed under control of the enhancer of the gene encoding the human immunoglobulin chain[47–50]. Other studies have identified links between IL-6 activity and tumor development, metastasis and tumor-associated inflammation[51,52]. Furthermore, genome-wide association studies and analyses of single-nucleotide polymorphisms and microarray data have identified links between IL-6 and disease outcome. For example, a G-to-C mutation proximal to the transcriptional start of *IL6* (rs1800795) causes elevated *IL6* expression, and carriers of this mutation have an increased incidence of coronary heart disease, idiopathic juvenile arthritis and other inflammatory conditions[53–56]. In the following sections we will emphasize the importance of IL-6 as an orchestrator of innate and adaptive immunity and as therapeutic target for treatment.

The IL-6 receptor complex

The fully competent IL-6R is composed of an 80-kilodalton type 1 cytokine α-receptor subunit (IL-6R; also known as CD126), which binds IL-6, and a universally expressed 130-kilodalton signal-transducing β-receptor subunit (gp130; also known as CD130; encoded by *IL6ST*)[57–60]. Structure-function studies predict that a functioning IL-6 receptor requires the formation of an IL-6–IL-6R–gp130 complex that is clustered into a dimer structure[61]. Although gp130 was initially characterized as the signaling subunit of the IL-6 receptor, signaling via gp130 is also essential for development, hematopoiesis, cell survival and growth and functions as the β-cytokine receptor for IL-11, IL-27, oncostatin-M, ciliary neurotrophic factor, cardiotrophin-1, leukemia inhibitory factor and cardiotrophin-like cytokine[5,62,63]. Thus, gp130 is ubiquitously expressed on cells of the immune system and those not of the immune system, and deletion of *gp130* in mice results in embryonic death[63]. In contrast, IL-6R expression is restricted largely to hepatocytes, leukocytes and megakaryocytes, and both *Il6ra*$^{-/-}$ mice and *Il6*$^{-/-}$ mice are viable[28,64]. Interestingly, *Il6*$^{-/-}$ and *Il6ra*$^{-/-}$ mice display some phenotypic differences that include alterations in wound healing and differences in the severity of colitis, as well as differences in insulin sensitivity and glucose tolerance[25,65–67]. Here, low-affinity interactions among IL-6R and the p28 subunit of IL-27 (IL-30), ciliary neurotrophic factor, and a heterodimeric cytokine complex consisting of p28 and cardiotrophin-like cytokine[68–71] might explain these differences, but this requires further investigation.

Once the IL-6 receptor complex is engaged there are multiple downstream events that allow IL-6 to mediate its diverse effects (**Fig. 1**). While this includes the pathway of the GTPase Ras and its effector Raf, and the mitogen-activated protein kinase cascade, which controls cellular proliferation and differentiation, the pathway that is perhaps best understood involves tyrosine kinases of the Jak family and transcription factors of the STAT family[62]. Dimerization of gp130 activates kinases of the Jak family (Jak1, Jak2 and Tyk2) and promotes the recruitment and phosphorylation of STAT1, STAT3 and, to a lesser extent, STAT5 (ref. 62). Jak-STAT's signaling through gp130 is tightly controlled, and the PIAS inhibitors of activated STATs, the SOCS suppressors of cytokine signaling (for example, SOCS1 and SOCS3) and members of the CIS ('cytokine-inducible SH2-domain–containing') family of cytokine receptor inhibitors act to limit IL-6 signaling[62]. Interestingly, in the absence of SOCS3, the effects of IL-6 are altered to resemble those of IL-10, which is a potent inhibitor of macrophages and dendritic cells[72,73]. This may produce a situation analogous to that of an ongoing inflammatory response in which the early production of IL-6 promotes inflammation, while sustained levels of IL-6 can limit inflammation (discussed below). Mice expressing mutant gp130 (generated by knock-in mutation of *Il6st*) that is unable to bind SOCS3 display more sustained signaling via STAT1 and STAT3 and develop exacerbated inflammation, chronic disease and cancer[74–78]. Thus, IL-6 signatures, based in part on the activity of STAT1 and STAT3, are viewed as predictors of outcomes or indicators of response to therapy in patients with autoimmune disease or cancer.

Classical and trans-activation of IL-6 receptor signaling

Over the past decade it has become clear that IL-6 utilizes two mechanisms to mediate its biological effects (**Fig. 1**). 'Classical' IL-6 receptor signaling denotes activities mediated via the membrane-bound IL-6R subunit and is relevant only to cells that express both receptor subunits[5]. In contrast, IL-6 'trans-signaling' refers to a process in which a soluble form of IL-6R (sIL-6R) binds secreted IL-6 to form a complex that increases the circulating half-life of IL-6 and promotes its bioavailability[79,80]. Interestingly, sIL-6R shares 60% identity with the IL-12p40 subunit and may represent an ancestral link to the heterodimeric cytokines IL-12, IL-23 and IL-27 (ref. 81). Nevertheless, any cell that expresses gp130 may acquire responsiveness to IL-6 and thus IL-6 trans-signaling widens the cell types that are affected by IL-6. While more work is anticipated in this area, classical IL-6 receptor signaling seems to control central homeostatic processes and immunological outcomes such as the acute-phase response, glucose metabolism, hematopoiesis and regulation of the neuroendocrine system, as well as hyperthermia, fatigue and loss of appetite[82]. In contrast, models of colitis, tissue fibrosis, inflammatory arthritis, allergy, infection, neuroinflammation, cardiovascular disease and inflammation-induced cancers have shown that IL-6 trans-signaling is important for the recruitment and apoptosis of leukocytes, maintenance of the effector function of T cells, and the inflammatory activation of stromal tissues[5,83,84]. sIL-6R is released by monocytes and activated T cells[64,78,85,86], but studies of human neutrophils have shown that C-reactive protein, inflammatory chemokines, bradykinin, N-formyl peptides, complement regulators and lipid mediators, including platelet-activating factor and leukotrienes, activate the shedding of IL-6R[87–92]. Thus, sIL-6R may be classified as an alarmin that, when released by neutrophils, promotes IL-6 trans-signaling within the local milieu as a potential danger response to disease that affects innate and adaptive immunological outcomes[5,83]. Further consideration now needs to be given to the importance of regulating the IL-6 receptor on CD4$^+$ T cells: IL-6R expression in CD4$^+$ T cells is largely restricted to naive and central memory populations[64,86]; CD4$^+$ T cells recovered from sites of disease typically lack IL-6R but remain responsive to IL-6 trans-signaling[64,78,86,93,94].

The original identification of gp130 as the β-subunit of the IL-6 receptor was aided by the observation that IL-6 binds gp130 in the presence of recombinant sIL-6R[57]. The importance of these findings was highlighted by the purification of a biologically active form of sIL-6R

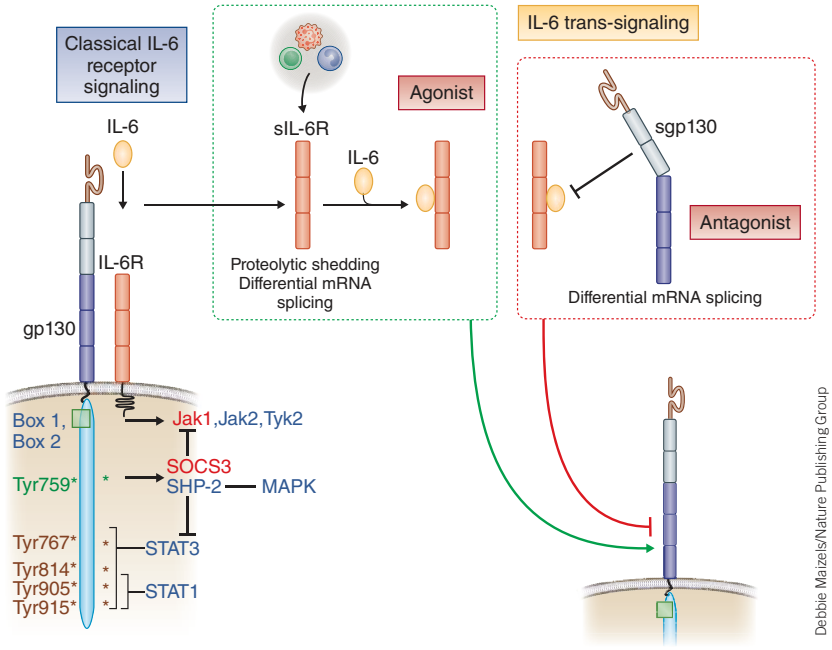

Figure 1 Two distinct modes of IL-6 receptor signaling. Classical IL-6 receptor signaling occurs in cells that express IL-6R (CD126) and gp130 (CD130). IL-6R is a non-signaling receptor that binds IL-6. The gp130 subunit is the signal-transducing receptor for IL-6 and its related family members. A soluble form of IL-6R is released from the cell surface by proteolysis and splicing of *IL6R* mRNA, and can bind IL-6 to form an agonistic complex that signals through gp130. This mechanism of trans-signaling allows IL-6 to act on cells that lack IL-6R. A fully functioning IL-6 receptor complex consists of a hexameric structure in which IL-6, IL-6R and gp130 exist in a 2:2:2 stochiometry. Both modes of IL-6 receptor signaling lead to gp130 activation of Jak1, Jak2 and Tyk2, which bind box 1 and box 2 sites within the gp130 sequence and a series of proximal tyrosine residues (bottom left) within the intracellular carboxy-terminal sequence that activate STAT1 and STAT3 and the mitogen-activated protein kinase (MAPK) cascade. The tyrosine residues included here relate to defined biological roles (position numbers are for the human gp130 sequence). Tyr759 (the mouse equivalent is Tyr757) is pivotal for docking of the tyrosine phosphatase SHP-2 and the cytokine receptor signaling inhibitor SOCS3. Both factors act as negative regulators of gp130-STAT signaling. In the context of infection, trauma and injury, sIL-6R is released from infiltrating neutrophils, monocytes and T cells, but IL-6 trans-signaling is antagonized by sgp130.

from human urine and plasma and the realization that normal serum concentrations of sIL-6R (25–35 ng/ml) are enhanced during inflammation[95–97]. Such observations led to the recognition that in humans, proteolytic shedding of membrane-bound IL-6R and differential splicing of *IL6R* mRNA control sIL-6R production (in mice, sIL-6R is generated solely as the product of proteolytic shedding)[95]. Human IL-6R is shed by the adamalysin proteases ADAM17 and ADAM10 (ref. 98), while in mice only ADAM10 promotes IL-6R shedding[99]; these enzymes cleave a site in the IL-6R that is proximal to the plasma membrane[98]. These enzymes are potentially activated differentially, and ADAM17 has been implicated in the release of sIL-6R in response to apoptosis or bacterial toxins, while ADAM10 cleaves IL-6R following depletion of cholesterol or stimulation of the purinergic receptor P2X7 (refs. 98,100). The physiological importance of the generation of sIL-6R in humans is exemplified by the observation that the rs2228145 mutation in *IL6R* results in elevated circulating levels of sIL-6R associated with reduced levels of C-reactive protein, a greater risk of cardiovascular disease and enhanced susceptibility to insulin resistance, obesity, type 2 diabetes and diabetic nephropathy[101–103]. Given the inherent complexity of IL-6R signaling, it is perhaps not surprising that are three, or possibly four, forms of soluble gp130 (sgp130) that are released by cells as the products of differential splicing of *IL6ST* mRNA[104–109]. While no unique function has been assigned to any of these sgp130 isoforms, they all retain ligand-binding properties. Although sgp130 does not bind IL-6 or IL-6R alone, sgp130 interacts with the IL-6–sIL-6R complex to block IL-6 trans-signaling[110] (**Fig. 1**). Biochemical studies have shown that sgp130 has no effect on classical IL-6 receptor signaling and has a limited effect on other gp130-activating cytokines. For example, ciliary neurotrophic factor and IL-27 responses are unaffected by sgp130, and the inhibitory effect of sgp130 on leukemia inhibitory factor and oncostatin-M requires 100-fold higher concentrations of sgp130 than those used to block IL-6 trans-signaling[5,106,110]. Indeed, the high concentrations of sgp130 in human serum (200–400 ng/ml) remain largely unaltered during inflammation and may function as a physiological buffer of IL-6 trans-signaling[78,111,112]. Thus, in clinical settings in which a surge in the levels of IL-6 and sIL-6R is observed, the level of sgp130 would be inadequate to counteract IL-6 trans-signaling.

Pro- and anti-inflammatory properties of IL-6 in innate immunity

Literature from the past 30 years has emphasized links among IL-6 and mononuclear phagocytes, the complement system and pattern-recognition receptors. However, a fundamental role for IL-6 in innate immunity is illustrated by the identification of an ancestral IL-6-like cytokine system in *Drosophila melanogaster*. Explicitly, unpaired-3 (IL-6-like), when induced as a response to bacterial infection, forms a signaling network with domeless (gp130-like), hopscotch (Drosophila homolog of mammalian Jak) and marelle (a Drosophila homolog of a STAT protein; also called stat92E) to promote innate immunity[113–115]. Moreover, unpaired-3 from plasmatocytes (Drosophila phagocytic macrophages) has been linked the control of glucose and tissue homeostasis[116], similar to the effects of IL-6 on macrophages that promote glucose intolerance and obesity-associated insulin resistance[66]. Nevertheless, as noted above, the most compelling evidence for the involvement of IL-6 and IL-6 receptor–mediated outcomes in innate immunity is derived from models of infection and susceptibility to endotoxin challenge[28,117,118].

There is extensive literature showing that IL-6 modulates almost every aspect of the innate immune system, including hematopoiesis and the accumulation of neutrophils at sites of infection or trauma through the control of granulopoiesis[119,120]. This is attributed to the regulation of neutrophil-activating chemokines and neutrophil apoptosis by IL-6, and while *Il6*$^{-/-}$ neutrophils show impaired respiratory burst and degranulation, these defects seem to be secondary to the effects of IL-6 trans-signaling on endothelial, smooth muscle, epithelial and mesothelial cells and fibroblasts[83]. For example, IL-6 trans-signaling inhibits expression of the chemokines CXCL1, CXCL8 and CX3CL1, promotes secretion of the chemokines CXCL5, CXCL6, CCL2 and CCL8 and cellular adhesion controlled by the lymph node–homing receptor CD62L, and modulates expression of the adhesion molecules ICAM-1 and VCAM-1 (refs. 87–89,121–123). Regulation of these activities requires an initial influx of neutrophils, which then shed IL-6R to promote IL-6 trans-signaling in stromal tissue cells[89,122,124]; thus, following activation of Toll-like receptors, *Il6*$^{-/-}$ mice display a heightened and prolonged profile of neutrophil accumulation[89,124–126]. These types of events are also relevant to other experimental systems; IL-6 limits influenza virus–induced inflammation and protects against fatal lung pathology[127]. This retro-

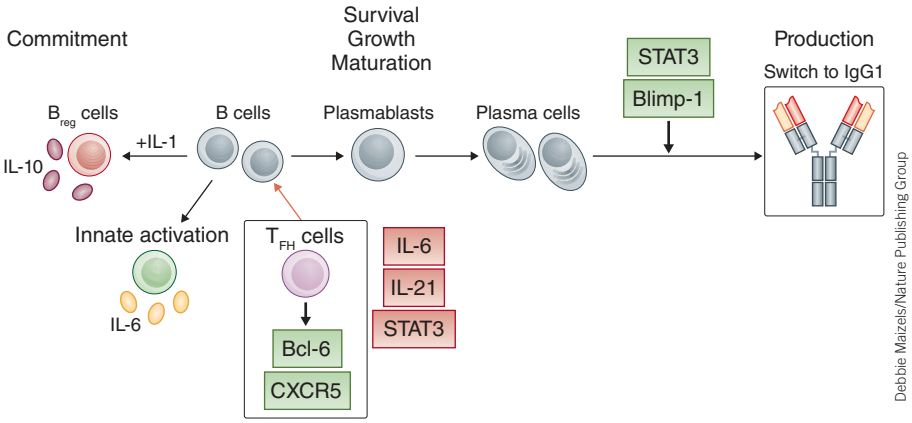

Figure 2 IL-6 control of B cells and humoral immunity. IL-6 controls the survival, population expansion and maturation of B cells and plasmablasts. For example, regulation of the transcription factor Blimp-1 by STAT3 is linked to antibody secretion and is associated with long-lived plasma cells that produce large amounts of immunoglobulin. IL-6 also controls the expression of IL-21 in T cells, and the activation of STAT3 by IL-6 and IL-21 enhances Bcl-6 expression and the generation of T_{FH} cells. The activities of Blimp-1 and Bcl-6 counteract each another, and this reciprocal relationship affects both lymphocyte differentiation and lymphocyte function. Innate activation of B cells through defined Toll-like receptors also controls the production of IL-6 by B cells, and IL-6 in combination with IL-1β provides the necessary commitment signals for the generation of IL-10-secreting regulatory B cells. B_{reg} cells, regulatory B cells; IgG1, immunoglobulin G1.

grade signaling mechanism ensures competent host defense, prevents excessive tissue damage and drives the transition from the recruitment of neutrophils to the recruitment of mononuclear cells[83,128]. *In vitro*, IL-6 promotes macrophage differentiation and restricts the formation of dendritic cells[129,130], which may relate to the ability of IL-6 to control the macrophage colony-stimulating factor receptor (encoded by *Csf1r*)[131]. IL-6 also inhibits activation of the transcription factor NF-κB and expression of the chemokine receptor CCR7 in dendritic cells and induces expression of the IL-1 receptor antagonist and the soluble p55 receptor for tumor-necrosis factor[132,133]. These findings are consistent with the ability of IL-6 to promote an alternatively activated macrophage phenotype associated with wound healing[66] and its ability to inhibit the microbicidal activities of macrophages and the production of pro-inflammatory cytokines[118,134,135]. Hence, IL-6 has clear pro-inflammatory effects (for example, in acute innate responses), but these effects are context dependent, and IL-6 also coordinates anti-inflammatory activities essential for resolution of inflammation.

IL-6 shapes adaptive immunity

Early studies identified IL-6 as a lymphokine that induces the maturation of B cells into antibody-secreting cells and showed that it promotes the survival and maintenance of long-lived plasma cells (**Fig. 2**). That link was reinforced by early reports that *Il6*$^{-/-}$ mice immunized with a T cell–dependent antigen have lower immunoglobulin G production than wild-type mice and that IL-6 deficiency often correlates with diminished antibody responses and susceptibility to infection[28]. The clinical situation in which a link between IL-6 and B cells might be most apparent is Castleman's disease[136]. This complex condition is characterized by increased concentrations of IL-6, B cell hyperplasia associated with anemia, increased concentrations of C-reactive protein and fevers; the role of IL-6 in the pathogenesis of this disease is illustrated by the clinical efficacy of tocilizumab[137]. Published studies have described additional links between IL-6 and B cells (**Fig. 2**) that include the control of regulatory B cells and B cell production of IL-6, which affects autoimmunity and defense against *Salmonella* species[138–140]. In addition, the ability of IL-6 to promote humoral immunity has been linked to its effects on follicular helper T cells (T_{FH} cells), a specialized subset of CD4$^+$ T cells that express the chemokine receptor CXCR5 and localize to B cell follicles, where they promote B cell proliferation and immunoglobulin class switching[141]. In this context, IL-6 promotes commitment to the T_{FH} cell lineage through induction of the transcriptional repressor Bcl-6 and control of IL-21 activity; thus, IL-6 serves as a central link between T cell responses and B cell responses[142–144]. Surprisingly, beyond its role during infection with lymphocytic choriomeningitis virus, little is known about the IL-6 control of T_{FH} cell responses in infection and whether this paradigm is broadly relevant to other pathogens for which antibody-mediated resistance is relevant. Similarly, it is not clear whether blockade of IL-6 in a clinical situation affects pre-existing T_{FH} cell and B cell populations and whether this contributes to the efficacy of IL-6-directed interventions in diseases such as rheumatoid arthritis. Head-to-head comparisons of tocilizumab and rituximab, a B cell–depleting monoclonal antibody (to the B cell–specific surface antigen CD20), may offer some interesting insights.

As for the differentiation of CD4$^+$ T cells (**Fig. 3**), early reports linked IL-6 to the control of T helper type 2 (T_H2) cell responses and the inhibition of T_H1 cell activities[145], but there are examples in which IL-6 supports the population expansion of interferon-γ–secreting CD4$^+$ T cells that promote peritoneal fibrosis[146]. It appears that IL-6 does not direct the commitment to the T_H1 or T_H2 cell lineage; instead the inflammatory context is important, and IL-6 controls the proliferation and survival of these cells. Where IL-6 is important in lineage commitment is with the T_H17 subset of helper T cells. While IL-1β, IL-21 and IL-23 are linked to the generation or maintenance of T_H17 cell effector functions, IL-6 is considered a key driver of IL-17-secreting CD4$^+$ or CD8$^+$ T cells[147–151]. Specifically, the activation of STAT3 by IL-6 in naive CD4$^+$ T cells in the presence of the morphogen TGF-β promotes the population expansion of T_H17 cells that express the transcription factors RORγt and AhR and secrete IL-17A[76,78,118,152–154]. The recognition that T_H17 cells are pathogenic in various diseases, as well as the realization that IL-6 is essential for the generation of these cells in mice and humans, has rekindled interest in IL-6 as a therapeutic target. Here, interest in T_H17 cells centers on three key aspects: their link to barrier function[155], their role in resistance to fungal infections[156,157], and how dysregulated responses of T_H17 cells contribute to local tissue damage in chronic inflammatory diseases[155]. However, caution should be taken in the extrapolation of links between IL-6 and IL-17 with inflammation, since IL-6 promotes the production of IL-10 by T cells[158,159], which would restrict many inflammatory processes.

One topic that requires consideration is the relationship between T_H17 cells and Foxp3$^+$ regulatory T cells (T_{reg} cells); IL-6 can inhibit T_{reg} cell function and prevents T_H17 cells from converting into T_{reg} cells[160,161], while overexpression of IL-6 *in vivo* inhibits the generation of inducible T_{reg} cells but does not seem to affect natural T_{reg} cells[162]. At sites of inflammation, T_{reg} cells seem to be able to be reprogrammed to acquire effector characteristics without loss of the transcription factor

Foxp3. Specifically, IL-6 promotes the generation of Foxp3-expressing T cells that coexpress either T-bet or RORγt and restricts expression of the transcription factor Eos (encoded by *Ikzf4*), which is the co-repressor for Foxp3 (ref. 163). In contrast, IL-6 blocks expression of the transcription factor GATA-3 by Foxp3$^+$ T_{reg} cells, which may be relevant in determining the outcome of graft-versus-host disease or mucosal infection[31,164,165]. In another example, during experimental autoimmune encephalomyelitis, IL-6 could promote IL-17 expression in Foxp3$^+$ T_{reg} cells from the periphery but not those from the central nervous system[166]. The event that determines these outcomes probably occurs at the transcriptional and epigenetic level, where the interaction of transcription factors and co-activators might serve to modify the effector characteristics of these cells. For example, the absence of *Stat3* impairs the suppressor properties of T_{reg} cells *in vivo*, which indicates a potential interaction between STAT3 and Foxp3 (ref. 167). More-detailed understanding of how IL-6 helps cells adapt to their environment is needed, and the application of functional genomic approaches is now helping to formulate fresh ideas about the dynamic nature of effector T cell function and the involvement of defined cytokine signatures[168].

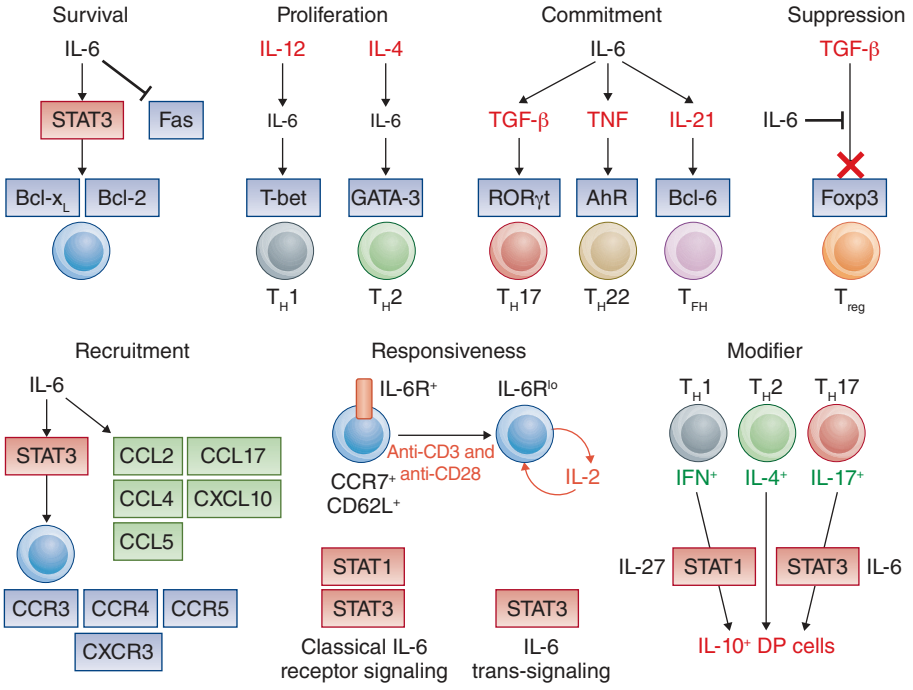

Figure 3 Effect of IL-6 on T cell activities. IL-6 governs the proliferation, survival and commitment of T cells and modulates their effector cytokine production. The examples here highlight the supporting role of IL-6 in maintaining T cell responses (for example, governing the proliferation and survival of T_H1 or T_H2 cells) and where IL-6 is critical for the either the development of defined effector populations (for example, the T_H17, T_H22 and T_{FH} subsets of helper T cells) or their inhibition (for example, T_{reg} cells). IL-6 also regulates T cell infiltration by controlling the expression of chemokine receptors, and IL-6 trans-signaling acting on stromal tissues regulates several inflammatory chemokines responsible for the recruitment of T cells. Cognate IL-6R expression is associated mainly with naive or central memory T cells that express CCR7 and CD62L. Activation of the T cell antigen receptor promotes shedding of the IL-6 receptor and is accompanied by a loss in IL-6-mediated STAT1 activity. The presence of IL-2 prevents the presentation of IL-6R on the T cell surface. This suggests that activation of T cells leads to an alteration in the responsiveness of T cells to IL-6 and a switch from classical IL-6R signaling to IL-6 trans-signaling. IL-6 also modifies the effector characteristics of defined T cell populations. For example, signaling interplay between IL-27 and IL-6 (involving the activation of STAT1 and STAT3) promotes the secretion of IL-10 by defined effector T cell subsets. Similarly, IL-6 is also instrumental in acquisition of the expression of T-bet or RORγt by inducible T_{reg} cell populations. Fas, cell surface receptor (CD95); Bcl-x_L, antiapoptotic factor; TNF, tumor-necrosis factor; anti-CD3, antibody to the invariant signaling protein CD3; anti-CD28, antibody to the coreceptor CD28. DP refers to CD4$^+$ T cells expressing either IFN and IL-10, IL-4 and IL-10, or IL-17 and IL-10.

Hurdles in clinical translation

For IL-6, the participation of two modes of receptor signaling in health and disease means that inhibitors that target IL-6 or the cognate IL-6R or selectively block IL-6 trans-signaling are in development (**Fig. 4**). However, there is still a need for understanding the basis of contraindications for the use of such agents and better appreciation of the roles of IL-6 in various disease states. Such information will provide clearer understanding of why blocking IL-6 in some clinical situations is not effective and whether different intervention strategies might have unique benefits for specific clinical indications or defined patient subgroups. One major issue is whether the therapeutic inhibitors of IL-6 or IL-6R have different effects. The efficacy of IL-6 inhibitors was first evaluated in multiple myeloma, in which IL-6 and sIL-6R are prognostic of tumor severity[95,169]. A monoclonal antibody to IL-6 has been shown to improve tumor outcome and suppress the acute-phase response, but because this antibody traps IL-6 in the circulation, this regime caused gross increases in systemic IL-6 concentrations[170]. As a consequence, IL-6 inhibitors were directed away from the cytokine, and a humanized monoclonal antibody specific for IL-6R was developed[171], but now pharmaceutical companies are reconsidering the potential of blocking IL-6. Early trials adopted an antibody to IL-6 that recognizes an epitope within site I of IL-6 that is essential for the binding of IL-6 to IL-6R (**Fig. 4**). However, a functioning IL-6 receptor complex also engages gp130, which interacts with IL-6 (once bound to IL-6R) at two distinct regions within its structure: site II and site III. Site II pulls gp130 into the receptor complex, and site III anchors the IL-6–IL-6R–gp130 structure into a functional dimer[61,62,172,173]. An antibody that binds site III of IL-6 has generated promising data in a phase IIb clinical trial of its use in the treatment of rheumatoid arthritis; this antibody shares an efficacy and safety profile similar to that of other inhibitors of IL-6 and IL-6R[174,175]. Notably, the inherently high circulating concentrations of sIL-6R suggest that a higher concentration of blocking antibody to IL-6R may be needed to sustain long-term inhibition of IL-6R, and this may afford an intervention involving an antibody to IL-6 an advantage based on pharmacodynamics.

Another issue is whether selective blockade of IL-6 trans-signaling offers a clinical advantage over a more global inhibition of IL-6. Blockade of IL-6 trans-signaling has the potential to inhibit the 'danger' component of IL-6 signaling but might leave certain IL-6-regulated homeostatic processes intact[5,100]. For example, targeting IL-6 or IL-6R rapidly controls systemic increases in C-reactive protein, but studies of mice have shown that increases in serum amyloid A (equivalent to C-reactive protein in humans) are not controlled by inhibition of IL-6 trans-signaling[5,6,176]. Other common clinical features of the inhibition of IL-6 include neutropenia, liver transaminases, serum lipid levels and alterations in cholesterol composition[2]. The relative effects of classical

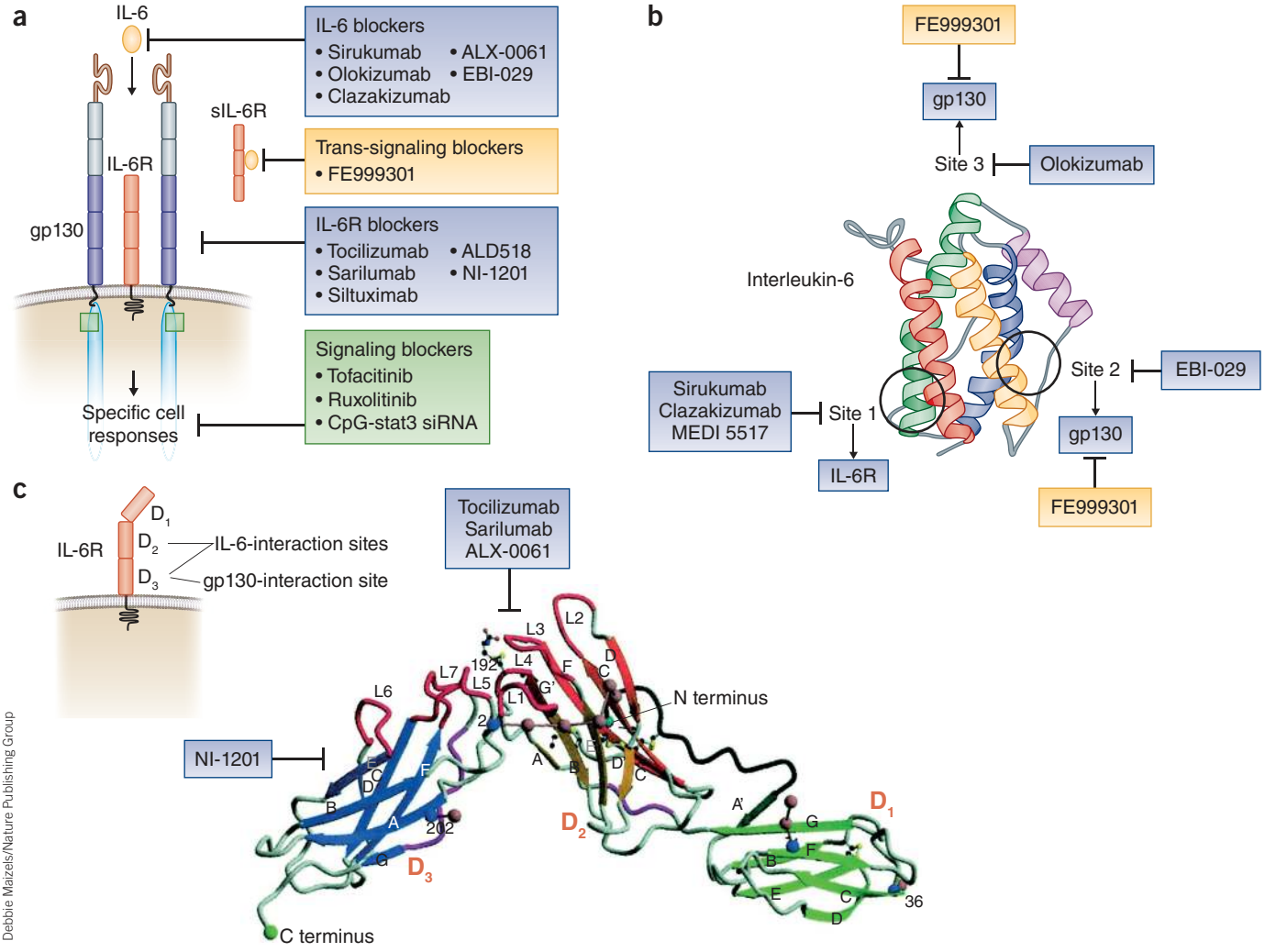

Figure 4 Therapeutic targeting of IL-6 and its receptor. (**a**) Various drugs that block the IL-6 pathway are in pre-clinical testing, clinical trial development or routine clinical practice. Drugs that target IL-6 and IL-6R during classical IL-6 receptor signaling (blue) or IL-6 trans-signaling (orange) and small-molecule agents that inhibit intracellular signaling molecules are listed along the right margin. Monoclonal antibodies that bind IL-6 or its receptor show a high degree of specificity for IL-6, whereas inhibitors of intracellular signaling also affect other cytokine-mediated pathways other than IL-6. (**b**) Inhibitory antibodies that bind IL-6, IL-6R or gp130 target defined epitope regions and display distinct modes of action. Inhibitory agents that bind IL-6 either block the binding of IL-6 to IL-6R (site 1) or interfere with the fully functioning receptor complex by blocking the interaction with gp130 (site 2 or site 3). The action of these antibodies yields differences in efficacy and pharmacokinetics. Inhibitors of site 1 cause more pronounced increases in systemic IL-6 amounts than do inhibitors of IL-6 that bind site 2 or site 3. Blue indicates blocking agents that prevent the binding of IL-6 to the membrane-bound IL-6R complex (classical IL-6 receptor signaling); orange indicates those that interfere with the binding of sgp130 to the soluble IL-6–IL-6R complex (IL-6 trans-signaling), such as the Fc-linked version of sgp130 (FE999301). (**c**) The structure of IL-6R, showing the sites of its interaction with IL-6 and gp130; inhibitory agents that block these interactions are listed along the periphery (right). Letter and number labels refer to structural features described in ref. 173.

IL-6 receptor signaling verses IL-6 trans-signaling on these outcomes, however, remains unclear. Nevertheless, experimental evidence supports the proposal of the therapeutic inhibition of IL-6 trans-signaling. An engineered sgp130-Fc fusion protein has shown promise in animal models and is in development for the clinical treatment of inflammatory bowel disease[5,100]. Pre-clinical studies have also described the generation of monoclonal antibodies with a 'preferential' efficacy for blocking IL-6 trans-signaling over classical IL-6 receptor signaling[26,176]. Unlike tocilizumab or sarilumab, these antibodies do not block the binding of IL-6 to its receptor; instead, they interfere with the docking of gp130 into the receptor complex. The potential therapeutic advantage of blocking IL-6 trans-signaling while leaving classical IL-6 receptor signaling intact is best illustrated in settings in which classical IL-6 receptor signaling is essential for the control of barrier function (for example, maintenance of gut mucosal integrity and epithelial regeneration)[51,177–179]. It is perhaps relevant that infections associated with tocilizumab intervention typically affect the upper and lower respiratory tracts and the urinary and gastrointestinal tracts—tissues in which IL-6 controls barrier function or tissue integrity (either directly or indirectly, through cytokines such as IL-22 or IL-17) (ref. 1). Such observations might explain why inhibition of IL-6 in conditions such as atopic dermatitis improves clinical outcome but leads to contraindications such as bacterial super-infection[180]. It is anticipated that future research will consider whether inhibition of IL-6 provides a therapeutic benefit in conditions in which IL-6R-directed interventions promote adverse reactions (for example, gastric perforations associated with diverticulitis). Clearly this is an interesting topic, and studies of the control of tissue homeostasis by IL-6 have identified a link between gp130 and a novel signaling mechanism that promotes mucosal regeneration and maintenance of barrier function through the transcriptional regulators YAP and Notch[181].

Finally, in what type of disease is IL-6 blockade most likely to be effective? Current IL-6-targeted therapies display robust safety profiles; however, they show strong efficacy in some clinical indications but less in others[6]. Many of the diseases in which inhibition of IL-6 is clinically beneficial are often associated with dysregulated adaptive immunity. However, even in conditions such as rheumatoid arthritis, for which inhibition of IL-6 is an effective therapy, some patients fail to display an adequate response to treatment[6]. Since early intervention with the most appropriate biologic provides the best opportunity for remission[2], it is necessary to understand how IL-6 contributes to the underlining pathology. Such information will enhance patient stratification for IL-6-directed intervention, and researchers should consider the effect of genetic and epigenetic factors and differences in histopathology, which may affect disease severity and rate of progression and response to treatment[182]. In model systems in which T cell priming is required for disease induction, it is notable that *Il6*$^{-/-}$ mice often display impaired involvement of innate cells[78]. This may reflect the ability of IL-6 to regulate a reciprocal connection between innate immunity and adaptive immunity. Notably, effector cytokines (for example, IL-17, IL-22 and interferon-γ) controlled by the action of IL-6 on CD4^{+} T cells have a direct bearing on the activities of neutrophils, macrophages and stromal tissues, which perpetuate inflammatory activation, promote retention of cells of the immune system, and shape the pathology observed within tissues.

Concluding remarks

IL-6 represents a keystone cytokine in infection, cancer and inflammation, in which it drives disease progression or supports the maintenance of immunological reactions. In these cases, the inflammatory context in which IL-6 functions is all about 'location, location, location'. For example, IL-6 produced during T cell priming in a lymph node may potentially control very different effects than those elicited by sustained IL-6 signals in a peripheral site of inflammation where the T cells are already activated. While clinical trials designed to test the efficacy of biologics in patients with defined pathologies are eagerly awaited, it may be equally important to consider why IL-6-directed interventions fail to meet their endpoints in some diseases, such as psoriasis, ankylosing spondylitis, ulcerative colitis and Crohn's disease[1]. Notably, these diseases often show some form of disrupted barrier function as part of the underlining pathology[1]. It is therefore essential to establish how IL-6 contributes to normal homeostasis in these tissue compartments. The challenge is to identify where and when IL-6 is active in inflammation to understand how the pleiotropic effects of IL-6 determine the progression, severity and duration of disease. Identifying the molecular basis of the participation of IL-6 in various conditions will ultimately help define the role of IL-6 and the relevance of classical IL-6 receptor signaling and IL-6 trans-signaling in autoimmunity, infectious disease, barrier function and cancer. This will provide an opportunity to guide treatment and improve rates of clinical remission for some of these conditions.

COMPETING FINANCIAL INTERESTS
The authors declare competing financial interests: details are available in the online version of the paper.

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