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Directing Transition from Innate to Acquired Immunity: Defining a Role for IL-6[1] FREE

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BRIEF REVIEWS

Directing Transition from Innate to Acquired Immunity: Defining a Role for IL-6[1]

Simon A. Jones[2]

***Appropriate control of leukocyte recruitment and activation is a fundamental requirement for competent host defense and resolving inflammation. A pivotal event that defines the successful outcome of any inflammatory event is the transition from innate to acquired immunity. In IL-6 deficiency, this process appears defective, and a series of in vivo studies have documented important roles for IL-6 in both the resolution of innate immunity and the development of acquired immune responses. Within this review, particular attention will be given to the regulatory properties of the soluble IL-6 receptor and how its activity may affect chronic disease progression. The Journal of Immunology,* 2005, 175: 3463–3468.**

Inflammation[1,2] represents a highly orchestrated process designed to combat infection or tissue injury. When affective, the inflammatory response ensures successful resolution of the condition and restoration of normal tissue architecture. However inappropriate control of this natural defense mechanism ultimately contributes to chronic disease progression. Although the events that trigger development of a chronic inflammatory state remain unclear, it is evident that communication between leukocytes and cells resident to a site of infection or injury affects the outcome of the inflammatory episode. Consequently, mediators that alter the pattern of the immune response ultimately direct the healing process.

A pivotal event in the resolution of any inflammatory episode is the transition from innate to acquired immunity. In acute inflammation, this process is defined by a precise regulation of leukocyte recruitment and clearance (Fig. 1), which during chronic disease becomes distorted and results in the retention of an activated mononuclear cell population within the affected tissue. It is therefore conceivable that inappropriate regulation of the "immunological switch" from innate to acquired immunity may affect disease outcome (1). Consequently, an increased understanding of the processes directing this transition may lead to a better understanding of disease progression.

Although innate and acquired immunity were classically considered to be self-governing entities, recent advances in TLR signaling, cytokine biology, and complement activation have identified a network of regulators that direct a shift from innate to acquired immunity (1). One such factor is the inflammatory cytokine IL-6, which through differential control of leukocyte recruitment, activation, and apoptosis has recently emerged as a regulator of this immunological switch.

IL-6 in disease

IL-6 is traditionally considered an activator of acute phase responses and a lymphocyte stimulatory factor (2). However, recent advances have documented a series of IL-6 activities that are critical for resolving innate immunity and promoting acquired immune responses (Fig. 1). Identification of these activities has largely been achieved through an increased understanding of the regulatory properties of its soluble receptor (3–5), while a fuller appreciation of IL-6 signaling has led researchers to reflect on the interplay between IL-6 and other inflammatory mediators (6–9). Collectively, these studies emphasize a central role for IL-6 in inflammation and highlight the therapeutic potential of targeting IL-6 activities. Significantly, IL-6-deficient ($IL\text{-}6^{-/-}$) mice remain resistant to the induction of a number of experimental autoimmune conditions (10–13), while agents that inhibit IL-6 or its receptor have shown considerable promise in clinical trials (14–18). This is exemplified by the application of the blocking anti-IL-6 receptor Ab MRA (Atlizumab, Tocilizumab), which has proven highly effective in the treatment of rheumatoid arthritis and Crohn's disease (16, 17). The detrimental consequences of IL-6 bioactivity in chronic disease must however be balanced by its capacity to protect against septic shock and to direct resolution of acute inflammation (19–23). What causes IL-6 to be seduced to the "dark side" of the inflammatory response is currently unclear.

IL-6 and its soluble receptor

IL-6 belongs to a family of cytokines that promote cellular responses through a receptor complex consisting of at least one subunit of the signal-transducing glycoprotein gp130 (24). Although gp130 activation classically occurs through IL-6 binding to a membrane-bound cognate receptor (IL-6R), many of the biological activities assigned to IL-6 are mediated via a naturally occurring soluble (s)[3] IL-6R (Fig. 2, *A* and *B*). This soluble receptor forms an agonistic complex with IL-6 that binds gp130 to trigger cellular responses (Fig. 2*B*). Regulation of this

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[3] Abbreviations used in this paper: s, soluble; SOCS, suppressor of cytokine signaling.

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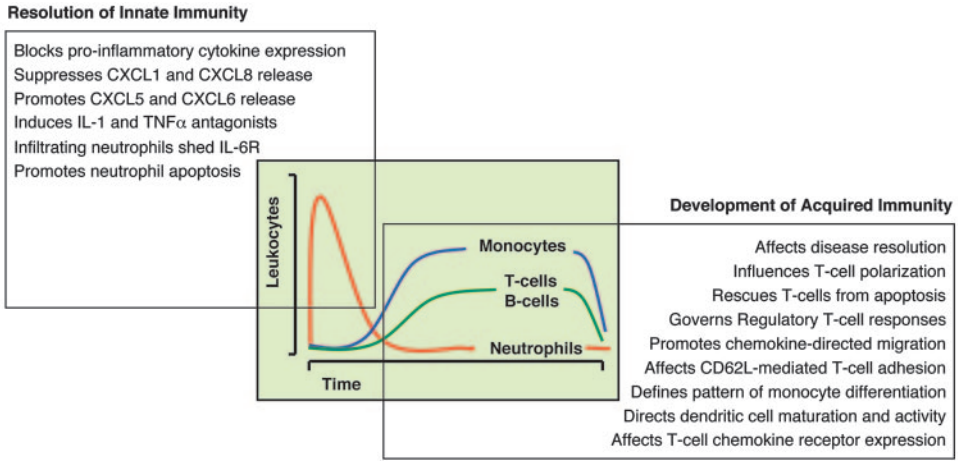

FIGURE 1. IL-6 regulates innate and acquired immune responses. The profile of leukocyte recruitment observed following inflammatory activation is depicted in the *middle* illustration. The transition from a neutrophil to mononuclear cell population defines a switch from innate to acquired immunity. IL-6 directs this immunological switch by influencing both arms of the immune response. A series of IL-6-mediated events are listed which overall support a role for IL-6 in the resolution of innate immunity and development of acquired immunity.

activity is termed "IL-6 *trans*-signaling" and the biological significance of this mode of activation is only fully appreciated when you consider the restricted cellular distribution of IL-6R (3, 5). In contrast to the ubiquitous expression of gp130, the cognate IL-6R exhibits a highly defined pattern of expression and is largely confined to hepatocytes and leukocytes (25). Consequently, IL-6 *trans*-signaling affords IL-6 with the capacity to trigger responses in cell types that would remain unresponsive to IL-6 itself (Fig. 2*D*). This is particularly evident at sites of inflammation where resident tissue stromal cells exhibit a predominantly gp130$^+$ IL-6R$^-$ phenotype (11, 26–28). Therefore, to unlock the secrets of IL-6 bioactivity during inflammation, it has become essential to define the pathological regulation and contribution of sIL-6R (25).

Although the relevance of IL-6 *trans*-signaling in vivo is only now emerging (7, 8, 11, 19, 28–32), studies show that sIL-6R influences leukocyte migration, activation, and apoptosis (9, 11, 19, 27–37). Documentation of these activities has been aided by the demonstration that IL-6 *trans*-signaling is selectively counteracted by a soluble form of gp130 (sgp130), which prevents signaling via membrane-bound gp130 (Fig. 2C). Soluble gp130 antagonism therefore distinguishes between activities coordinated by IL-6 *trans*-signaling and those controlled by IL-6 itself (3, 5, 10, 38). The selective nature of sgp130 antagonism has therefore been invaluable in experimental models of disease, where its application has implicated IL-6 *trans*-signaling in a number of inflammatory events (9, 11, 19, 30–32).

Chemokine-directed leukocyte recruitment

During a successfully resolving acute inflammatory episode, leukocyte recruitment is defined by an initial influx of neutrophils, followed by their clearance and replacement by a more sustained population of mononuclear cells (39). This pattern of infiltration relies on IL-6 *trans*-signaling (Fig. 1). Although IL-6 does not affect the initial rate of neutrophil infiltration (7), studies in IL-6-deficient (IL-6$^{-/-}$) mice show that IL-6 blocks neutrophil accumulation at sites of infection or inflammation (40). IL-6 control of neutrophil infiltration is however susceptible to inhibition by sgp130 (7, 19, 28). Given that stromal cells display a predominantly gp130$^+$IL-6R$^-$ phenotype, IL-6 bioactivity is governed by the local concentration of sIL-6R. Significantly, increases in sIL-6R levels correlate with the degree of neutrophil infiltration (19), and in vitro activation of human neutrophils with C-reactive protein, inflammatory chemokines, or other chemotactic agents promotes IL-6R shedding (19, 27, 28, 30, 36, 41, 42). The emergence of the neutrophil infiltrate subsequently drives IL-6 *trans*-signaling in resident tissue cells and directs transition from neutrophil to mononuclear cell recruitment (19, 22). In this respect, in vitro studies confirm that IL-6 *trans*-signaling blocks the TNF-α- or IL-1β-induced control of CXCL1, CXCL8, and CX3CL1, while directly enhancing CXCL5, CXCL6, CCL2, and CCL8 secretion (7, 11, 19, 22, 27–29, 33, 36). This highly orchestrated chemokine response is complemented by the ability of IL-6 *trans*-signaling to direct CD62 ligand adhesion (32) and to modulate expression of ICAM-1 and VCAM-1 (27, 29, 35).

The importance of this IL-6-directed process was recently emphasized in an in vivo model of bacterial infection (22). Specifically, reconstitution of IL-6 *trans*-signaling in IL-6$^{-/-}$ mice improved the rate of mortality and led to reduced neutrophilia and increased bacterial clearance (22). The IL-6 control of these activities may have particular relevance in the development of septic shock where IL-6 has proven to be protective (20, 23). Successful resolution of these conditions is however also reliant on the development of an acquired immune response. Here again we see that IL-6 performs a prominent role, and in vivo models of disease or infection reveal that IL-6 *trans*-signaling affects the inflammatory outcome by influencing mononuclear cell recruitment and clearance (11, 22, 30, 32).

Although early studies noted that sIL-6R directs mononuclear cell recruitment (19, 29, 36), a recent investigation showed that *trans*-signaling preferentially promotes trafficking of CD3$^+$ T cells (43). This response seems somewhat surprising given the nature of the chemokines induced by IL-6 (19, 43). However, the selectivity of IL-6 for T cell migration is also evident in the regulation of T cell adhesion. Specifically, during a febrile response, IL-6 *trans*-signaling has been shown to enhance T cell adhesion through activation of CD62 ligand (32). A similar response could not however be replicated in CD14$^+$ monocytic cells (32). Collectively, these studies suggest that sIL-6R controls the homing capacity of T cells by affecting both T cell migration and adhesion. Such dysregulation of T cell trafficking is seen in IL-6$^{-/-}$ mice where acute inflammation is associated with impaired local chemokine secretion (CCL2, CCL4, CCL5, CCL11, CCL17, CXCL10) and reduced chemokine receptor (CCR3, CCR4, CCR5, CXCR3) expression on the CD3$^+$ infiltrate (43).

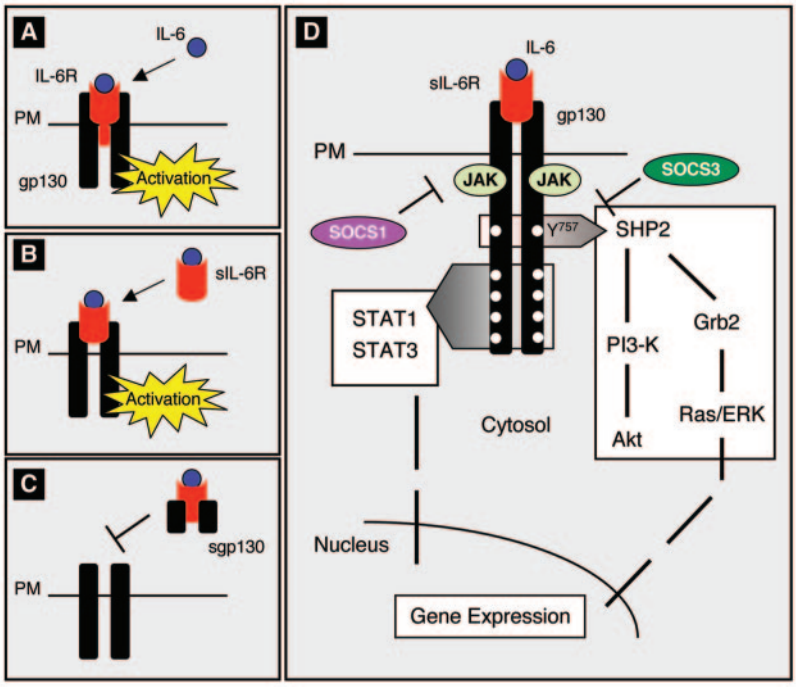

FIGURE 2. Mechanisms of IL-6 activation. *A,* IL-6 classically activates cells by binding a nonsignaling cognate receptor (IL-6R), which then dimerization with the signal-transducing receptor subunit gp130 to transmit its signal. *B,* IL-6 responses can also be elicited through IL-6 *trans*-signaling. This mode of activation relies on a sIL-6R, which is generated via both differential IL-6R mRNA splicing and proteolytic shedding of the cognate receptor (25). The IL-6/sIL-6R complex binds directly to gp130 and triggers a response. *C,* sgp130 selectively blocks IL-6 *trans*-signaling by preventing binding of the IL-6/sIL-6R complex to membrane-bound gp130. *D,* Engagement of gp130 leads to activation of the receptor-associated kinases JAK1, JAK2, and Tyk2 (JAK), and the subsequent phosphorylation of proximal tyrosine residues (white circles) that control STAT1/STAT3 activity and the Src homology region 2 domain-containing phosphatase 2 (SHP2) cascade. As part of the transcriptional events controlled by IL-6, a series of negative regulators including suppressor of cytokine signaling (SOCS) 1 and SOCS3 are induced. In particular, SOCS3 counteracts STAT3 activation by interaction with a tyrosine residue that also directs Src homology region 2 domain-containing phosphatase SHP2 signaling (Y^{757} in mice, Y^{759} in humans). For a more detailed review of gp130 signaling, the reader is referred elsewhere (24).

Regulation of leukocyte apoptosis

Transition from innate to acquired immunity is not only promoted by control of chemokine-directed leukocyte recruitment, but also by efficient activation of leukocyte apoptosis. Any alteration in the apoptotic response may lead to a delay in neutrophil clearance and retention of an activated mononuclear cell population within the affected tissue (30, 44, 45). This is clearly evident in the synovium of rheumatoid arthritis patients where T cells isolated from the inflamed joint show increased expression of anti-apoptotic regulators such as Bcl-x_L (46). In this respect, a series of studies have heavily implicated IL-6 in the control of these apoptotic events.

In vitro, IL-6 rescues T cells from entering apoptosis, and protects cells from Fas-mediated cell death (35, 47, 48). Control of these events appears to rely on STAT3 (Fig. 2*D*), which drives expression of anti-apoptotic regulators (Bcl-2, Bcl-x_L) and modulates surface Fas expression (49, 50). Such mechanisms for evading apoptotic cell death are also evident in vivo, with development of autoimmune arthritis in mice displaying exaggerated gp130-mediated STAT3 activity being associated with an inability of T cells to enter apoptosis (51). Indeed, blockade of sIL-6R signaling in experimental models of colitis prevents disease onset by suppressing Bcl-2 and Bcl-x_L expression (30). In contrast to the induction of these rescue signals, IL-6 *trans*-signaling also promotes neutrophil apoptosis through a mechanism involving caspase-3 (7). These studies imply that gp130 signaling initiates normal resolution of acute neutrophil infiltration, whereas aberrant control of lymphocyte apoptosis would lead to their retention within inflamed tissue. How IL-6 coordinates the balance between these pro- and anti-apoptotic signals remains unclear. Such differential control of leukocyte apoptosis precisely complements the IL-6-mediated management of leukocyte recruitment, and taken together supports a role for IL-6 in directing transition from innate to acquired immunity.

IL-6 control of mononuclear cell activities

It is increasingly evident that gp130 signaling influences the nature of the mononuclear cell response. In vitro studies suggest that IL-6 is involved in skewing the differentiation of human monocytes away from a dendritic lineage to a more macrophage phenotype (52, 53). Channeling of this IL-6-directed differentiation might relate to the ability of IL-6 to induce expression of M-CSF receptors on monocytes (52). Studies in signaling defective gp130 knock-in mice have subsequently shown that gp130-mediated control of M-CSF receptor expression is reliant on enhanced signaling via the ERK-MAPK cascade (54). However, these studies also highlight that the differentiation pathway adopted may depend on the nature of the signal transmitted via gp130, since M-CSF receptor expression is inversely related to the quality of the gp130-mediated STAT3 signal (54). Although this certainly complicates the manner by which monocyte differentiation is governed, it is evident that expansion of bone marrow-derived dendritic cells from IL-$6^{-/-}$ mice results in a 10-fold higher number of $CD11c^{+}$ dendritic cells than IL-$6^{+/+}$ mice (55). The impaired secretion of IL-6 by these expanded cells, however, significantly affects dendritic cell function (55). Indeed, IL-6 has been shown to inhibit NF-κB activity and to suppress CCR7 expression in dendritic cells (56), suggesting that IL-6 may influence their maturation or trafficking. Although the significance of these findings in chronic disease remain to be clarified, the demonstration that IL-6 secretion by dendritic cells following TLR activation blocks the immunosuppressive activities of regulatory T cells may provide valuable clues for further consideration (57).

IL-6 control of lymphocyte activities

The original classification of IL-6 as IFN-β2, cytotoxic T cell differentiation factor, B cell differentiation factor, and B cell stimulatory factor 2 clearly defines IL-6 as a prominent regulator of T cell proliferation, differential, survival, and Ig secretion

by B cells. IL-6 deficiency is not however associated with gross differences in the phenotype or composition of T cell subsets (12, 58), and induction of acute inflammation does not significantly affect the activation status (as gauged by CD25 and CD28 expression) of the infiltrating T cell population (43). However, with the emergence of IL-6 *trans*-signaling as a prominent mechanism of IL-6 regulation in vivo, researchers have begun to reconsider the relationship between IL-6 and T cell responses.

The induction of anti-apoptotic regulators by IL-6 in both naive and activated T cell populations (47, 59, 60) may for instance have considerable clinical relevance, since anti-IL-6R Abs reduce the severity of experimental colitis by negating IL-6 control of these rescue signals (30, 61). The control of these apoptotic processes is not only governed by IL-6 (47, 59), but also IL-6 acting via its soluble receptor (30, 37). Collectively, these findings suggest that T cells do not universally express the cognate IL-6R (Fig. 3). Indeed, T cells recovered from sites of inflammatory challenge predominantly lack IL-6R (9, 30, 37). Thus, inflammation results in either the homing of a $CD3^+$IL-$6R^-$ T cell subset to the affected tissue or a selective down-regulation of IL-6R expression. The presence of a $CD3^+$IL-$6R^-$ T cell subset within these sites also suggests that activated T cells lose their capacity to respond directly to IL-6 and infers that cognate IL-6R expression relates to either a naive or memory T cell phenotype (59, 60, 62). Activated T cells following in vivo stimulation with superantigen show significantly lower levels of IL-6R, and although this down-modulation in receptor expression does not affect STAT3 phosphorylation, IL-6-induced STAT1 activity was markedly impaired in activated vs resting T cells (59). This skewing of the gp130-mediated activation of STAT1 and STAT3 might influence the balance in induction of pro- and anti-apoptotic signals (6) and may ultimately affect inflammatory outcome. Identification of these $CD3^+$IL-$6R^+$ (IL-$6R^{high}$ or IL-$6R^{low}$) and $CD3^+$IL-$6R^-$ T cell subsets therefore leads us to question the functional characteristics of these populations. Figure 3 summarizes what is currently known about IL-6 responses in T cells and distinguishes between those events triggered by IL-6 and IL-6 *trans*-signaling.

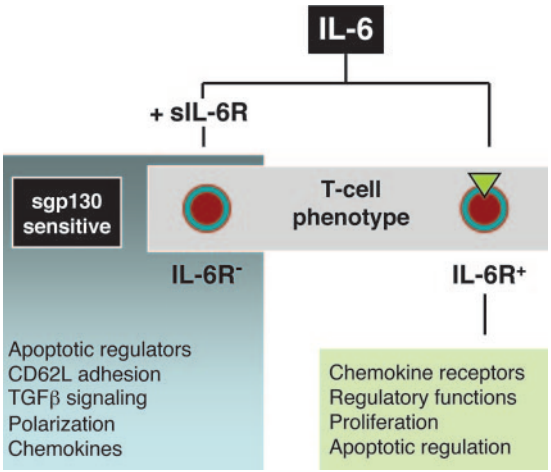

FIGURE 3. IL-6 and T cell regulation. Cognate IL-6R is not universally expressed among T cells and therefore defines a distinct T cell population. Activation of T cells by IL-6 therefore occurs both directly and via IL-6 *trans*-signaling. This figure summarizes IL-6-mediated T cell responses that are either sensitive to sgp130 antagonism (i.e., rely on sIL-6R) or remain unaffected by its action and are considered regulated by IL-6 itself.

A series of in vivo studies indicate that IL-6 influences T cell polarization (12, 61, 63–66). However the literature does not universally define IL-6 as being selective for the induction of a Th1- or Th2-type response. Examination of cytokine production by lymph node cells derived from IL-$6^{-/-}$ mice indicates that IL-6 may favor IL-2 production and promotion of a Th1 phenotype (12, 61). Such findings correlate with the IL-6 regulation of CD25 and IFN-γ (65–67). By contrast, IL-6 is also known to suppress IL-12-mediated T cell polarization and to direct Th2 differentiation of naive T cells into IL-4-secreting cells (64). This is particularly evident in experimental asthma where IL-6 promotes not only the initial differentiation toward a Th2 phenotype, but affects local Th2 responses in lung $CD4^+CD25^-$ T cells (31). These latter responses were elicited via IL-6 *trans*-signaling and suggest that direct IL-6 activation of $CD3^+$IL-$6R^+$ T cells occurs within the periphery, whereas sIL-6R orchestrates local responses in $CD3^+$IL-$6R^-$ T cells. Such differential control of T cells by IL-6 and IL-6 *trans*-signaling also applies to the chemokine-directed recruitment of the $CD3^+$ infiltrate (43). In this study, sgp130 antagonism only blocked chemokine expression and did not alter T cell chemokine receptor expression (43). Significantly, IL-6 deficiency was associated with a disruption in the expression of chemokine receptors defined as Th1 (CXCR3, CCR5) and Th2 (CCR3, CCR4) subset markers (68). Thus, IL-6 is also prominent in Th1-mediated responses. This is borne out by the presence of a cognate IL-6R on both Th1 and Th2 cells (64) and by the therapeutic management of Th1-driven inflammatory conditions with strategies that block IL-6 signaling (11, 30, 61).

Future perspectives and conclusions

Over the years IL-6 has been assigned both pro- and anti-inflammatory characteristics (9, 30, 40, 69). On reflection, IL-6 should be defined as a resolution factor that balances pro- and anti-inflammatory outcomes to further the immunological response. This is clearly depicted by its ability to orchestrate transition from innate to acquired immunity. Appropriate control of this immunological switch is essential for the successful resolution of any inflammatory episode, and IL-6 activity appears to be critical for the effective management of acute inflammation (19–22). In chronic disease, IL-6 takes on a more sinister function, and blockade of IL-6 signaling is proving to be therapeutically beneficial (13–18). It remains to be established whether transition from acute to chronic inflammation occurs in association with a breakdown in the IL-6 control of innate to acquired immunity (Fig. 1). To fully appreciate the processes involved however, it is important to place IL-6 in its inflammatory context. Recent studies have examined how IL-6 interacts with other inflammatory mediators and the observed interplay between IL-6-mediated signals, and STAT1 (6), IFN-γ (6, 7), TGF-β (9), GATA-3 (31), and NF-κB (57) requires fuller consideration. The potential significance of such interactions is highlighted by a study of colorectal cancer, where TGF-β secretion by tumor-infiltrating T cells was found to block IL-6 *trans*-signaling and to prevent tumor expansion (9). Interplay of this nature might impact chronic disease progression. For instance, the cytostatic properties of TGF-β might affect the sIL-6R-mediated induction of vascular endothelial growth factor (70) and thereby influence tissue fibrosis, hyperplasia, or angiogenesis.

The therapeutic application of novel biologics such as the anti-TNF-α agents has validated the targeting of inflammatory cytokines as a strategy for treating chronic inflammatory diseases. Agents that inhibit IL-6 signaling have now entered clinical trials (16, 17). However, it remains to be determined whether blockade of IL-6 bioactivity offers a true advantage over anti-TNF-α regimes. One area of consideration is the question of whether global inhibition of a given cytokine is an acceptable approach. Within the IL-6 field, researchers are now beginning to address such issues, and selective blockade of IL-6 *trans*-signaling is providing not only valuable insight into the IL-6 regulation of inflammation, but is also validating sgp130 as a therapeutic modality (9–11, 30, 31).

Disclosures

The authors have no financial conflict of interest.

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