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Understanding the Pro- and Anti-Inflammatory Properties of IL-27

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The recent identification of IL-27 (IL-27p28/EBV-induced gene 3) and IL-27R (WSX-1/gp130) has provided new insights for the biology of IL-6/IL-12 family cytokines. Initial studies indicated that IL-27 can directly regulate T cell functions and suggested an important role for it in promoting Th1 type responses. However, subsequent studies have revealed that IL-27R signaling influences a variety of immune cell types and can inhibit either Th1 or Th2 type responses. Though elucidation of the Jak/STAT signaling pathways activated by IL-27R ligation has unveiled some of the molecular mechanisms used by IL-27 to promote inflammation, little is known about the anti-inflammatory activities of this cytokine. Thus, the aim of this review is to discuss the pleotropic nature of the IL-27/IL-27R interaction and attempt to reconcile the pro- and anti-inflammatory properties of this immunomodulator. The Journal of Immunology, 2004, 173: 715–720.

Upon ligation of their cognate receptors, cytokines initiate intracellular signaling cascades that play essential roles in development, homeostasis, and immunity. Type I cytokines are defined by a common helical tertiary protein structure and, due to poor sequence homology, are separated into families according to receptor specificity (1). In contrast, type I cytokine receptors are grouped according to sequence phylogeny (1). Though 29 type I cytokines and 35 corresponding type I cytokine receptors have been described in mice (1), this review discusses only those pertinent to the biology of IL-27 and IL-27R. IL-27 is a member of the IL-6/IL-12 family of cytokines, a group that is critical in fundamental processes like neuronal growth, bone maintenance, cardiac development and immune regulation (Fig. 1) (1, 2). Though some pair with soluble group 3 cytokine receptors to form stable heterodimers, all IL-6/IL-12 family cytokines propagate intracellular signaling through membrane complexes that include either IL-12Rβ1 or gp130, the canonical group 2 cytokine receptor (Fig. 1) (1). Because gp130 is expressed ubiquitously during development and by a variety of immune and nonimmune cells in adult animals, distinct functions and tissue tropisms of gp130-associated cytokine receptors are determined by the tightly regulated expression of ligand specific coreceptors (2).

Recent studies have found that WSX-1 can associate with gp130 to form a functional signaling complex (Fig. 1) (3). Similar to gp130 and its ligand-binding coreceptors, WSX-1 is a type I, group 2 cytokine receptor with four positionally conserved cysteine residues and a C-terminal WSXWS protein sequence motif, but unlike promiscuously expressed gp130, WSX-1 is expressed primarily in lymphoid tissues (Fig. 1) (2–6). Though levels are highest in naive T and NK cells, a range of cells are capable of coexpressing WSX-1 and gp130, including endothelial cells, mast cells, activated B cells, monocytes, Langerhan’s cells, activated dendritic cells, and polarized Th cells (3–6).

Ligands for gp130-associated cytokine receptors comprise a subgroup of the IL-6/IL-12 cytokine family that includes oncostatin, LIF, IL-6, and IL-11 (Fig. 1) (1, 2). The only known ligand for the gp130/WSX-1 receptor pairing is the cytokine IL-27, a heterodimer of EBV-induced gene 3 (EBI3) (1) and its associated ligand IL-27p28 (Fig. 1) (7). The former subunit was originally described as a factor secreted by EBV-transformed B cells, while the latter was identified through its homology to the IL-6/IL-12 cytokine family (7, 8). Produced mainly by macrophages and dendritic cells, IL-27 can activate a heterogeneous Jak/STAT signaling cascade that includes phosphorylation of Jak1, STAT1, STAT3, STAT4, and STAT5 in T cells, STAT1 and STAT3 in monocytes, and STAT3 in mast cells (Fig. 1) (3, 9–12).

The proinflammatory properties of IL-27

Despite a shared receptor subunit and strong sequence identity, the group of cytokines that signal through gp130 can have disparate, even paradoxical, functions. For instance, IL-6 has been reported to promote and antagonize the inflammatory responses associated with rheumatoid arthritis and diabetes (13). A key inflammatory mediator in both these autoimmune disorders is IFN-γ, the signature cytokine of type I (Th1) inflammatory responses (13). Though dysregulated IFN-γ production can, as in the cases noted in this review, contribute to...
serious disease, appropriate induction of Th1 responses is essential for resistance to intracellular pathogens (14, 15). Many factors coordinate the generation of type I immunity, but the heterodimeric cytokine IL-12 has emerged as a central figure in promoting IFN-γ production (16, 17). IL-12 is required for optimal differentiation of naive CD4⁺ T cells into mature Th1 effector cells and can also induce the secretion of IFN-γ by NK cells and CD8⁺ T cells (16, 17). Based on a significant degree of sequence and structural homology, it was surmised that, like IL-12, IL-27 can promote Th1 responses. In accord with this hypothesis, rIL-27 can augment proliferation and secretion of IFN-γ by naive CD4⁺ T cells and, when combined with IL-12, can synergize to induce IFN-γ production by human NK cells (7, 9, 12). Naive WSX-1-deficient CD4⁺ T cells produce less IFN-γ than wild-type counterparts when cultured under non-polarizing conditions (4, 5, 9–12, 18). Similarly, during in vitro Th1 differentiation with IL-12 and high doses of either Con A or polyclonal anti-TCR Abs, WSX-1⁻/⁻ CD4⁺ T cells produce less IFN-γ than wild-type cohorts (4, 5, 9, 10, 12).

The ability of IL-27R signaling to promote IFN-γ production can be largely attributed to the induction of T-bet, a transcription factor whose target genes, particularly IL-12Rβ2 and IFN-γ, are essential components of Th1 responses (Figs. 2 and 3) (9, 11, 12). Although activation of STAT1 can directly induce T-bet expression, IL-27 can also promote STAT1-independent T-bet transcription (Fig. 2) (12, 19). Because IL-27 production by macrophages and dendritic cells precedes that of IL-12 and naive CD4⁺ T cells express only IL-12Rβ1, it was postulated that IL-27 can sensitize lymphocytes to the polarizing influences of IL-12 (7, 12). In fact, IL-27R ligation can also activate STAT4, the signaling pathway used by IL-12 to polarize effector cell populations (Figs. 1 and 2) (12).

In agreement with in vitro studies indicating a role for IL-27 in promoting IFN-γ production, initial studies also showed that WSX-1⁻/⁻ mice have enhanced susceptibility to infection with intracellular pathogens (4, 5, 20). Although resistance to infection with the protozoan parasite Leishmania major requires the development of a CD4⁺ T cell-dependent Th1 response, after 2 wk of infection, WSX-1⁻/⁻ mice display deficient IFN-γ production and advanced lesion development (5, 20). Similarly, reduced production of IFN-γ is noted upon challenge of WSX-1⁻/⁻ mice with an avirulent strain of mycobacterium (baccillus Calmette-Guérin; BCG) and infection of receptor-deficient mice with Listeria monocytogenes results in defective bacterial clearance and IgG2a Ab class switching, both functions that are promoted by IFN-γ (4, 5). In one model of murine carcinoma, transgenic overexpression of IL-27 in immortalized colon cells leads to increased CD8⁺ T cell-dependent IFN-γ production, cytotoxicity, and tumor clearance (21).

Despite evidence that IL-27/IL-27R can enhance IFN-γ production, the requirement for this cytokine/receptor pairing in the development of protective Th1 responses is not absolute. After L. major or BCG infection, defects in pathogen-induced IFN-γ production are transient and as each disease progresses, WSX-1⁻/⁻ mice generate Th1 type responses and control infection like wild-type cohorts (5, 20). Nevertheless, based on defects in the generation of type I immunity in WSX-1⁻/⁻ mice and in vitro evidence supporting a role for IL-27/WSX-1 in promoting IFN-γ production, a consensus emerged that, like IL-12, IL-27 is necessary for the efficient induction of Th1 responses (16, 17, 22–27).
The anti-inflammatory properties of IL-27

Although many IL-6/IL-12 family cytokines can have critical proinflammatory effects, it is becoming clear that some, particularly those that signal through gp130, can also suppress inflammatory responses (2, 13). Thus, it is not surprising that despite the literature supporting a role for IL-27 in promoting Th1 responses, there is also evidence that WSX-1 signaling can inhibit inflammatory processes (Fig. 3). Several groups have reported increased proliferation of WSX-1-deficient CD4+ T cells during in vitro culture (4, 5, 10). Similarly, both the CD4+ and CD8+ T cell compartments of WSX-1−/− mice display enhanced proliferation and IFN-γ production during infection with *Toxoplasma gondii* (4, 5, 10). Although both wild-type and receptor-deficient mice can control parasite replication through the generation of robust Th1 responses, WSX-1−/− mice develop a lethal, CD4+ T cell-dependent inflammatory disease during acute toxoplasmosis (10). Thus, the pathogenic accumulation of activated Th1 effector cells and elevated inflammatory cytokine production observed in *T. gondii*-infected receptor-deficient mice suggest that WSX-1 signaling may have an inhibitory effect on parasite-induced type I immune responses (10).

In support of an anti-inflammatory role for IL-27, infection of WSX-1−/− mice with *Trypanosoma cruzii* leads to the development of immune-mediated liver necrosis (28). Because hepatic T and NK cells from infected WSX-1−/− mice produce more IFN-γ and TNF-α than wild-type cohorts and in vivo neutralization of IFN-γ can ameliorate liver damage in receptor-deficient animals, it is likely that dysregulated Th1 responses, and not elevated parasitemia, incite the liver pathology (28). Likewise, WSX-1−/− mice display enhanced sensitivity to Con A-induced hepatitis, resulting in enhanced liver disease and increased T and NK cell production of IFN-γ when compared with wild-type counterparts (29). In these studies, depletion of IFN-γ, CD4+ or NK1.1+ cells leads to a reduction of liver pathology in Con A-treated WSX-1−/− mice (29). In vitro enhanced IFN-γ production has been noted when WSX-1−/− or *EBI3*−/− T cells are stimulated with IL-12 and low-dose TCR ligation (10, 18). Together, these data suggest that in the presence of strongly polarizing inflammatory responses, such as those during acute toxoplasmosis, the ability of WSX-1 to promote Th1 responses becomes secondary to its role in the suppression of effector cell functions like proliferation and cytokine production.

Given the Jak/STAT signaling cascade initiated by WSX-1 ligation, several molecular mechanisms can be proposed to account for the inhibitory properties of IL-27. Although STAT1 activation has been traditionally associated with promoting inflammation, it has become apparent that this signaling pathway can also inhibit T cell responses (Fig. 3). Type I (IFN-αβ) and type II (IFN-γ) IFNs, which signal primarily through STAT1, can inhibit T cell production of IFN-γ and proliferation, respectively (30, 31). Also, when compared with wild-type counterparts, T cells from *T. gondii*-infected STAT1-deficient mice display enhanced proliferation, activation marker expression, and IFN-γ production (32). However, currently, the molecular mechanisms that mediate the inhibitory properties of STAT1 signaling remain poorly understood.

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Although STAT3 phosphorylation has been well characterized as an inhibitory event in monocytes, a role for this pathway in the suppression of effector T cells has also emerged (Fig. 3) (33, 34). For instance, the ability of IL-6 to inhibit CD4+ T cell production of IFN-γ during in vitro Th1 differentiation is dependent on STAT3 (35). Furthermore, like WSX-1−/− animals, mice deficient in IL-10, a powerful anti-inflammatory cytokine that also activates STAT3, succumb to a lethal inflammatory disease during acute toxoplasmosis (36). However, as IL-10 acts primarily on macrophages and dendritic cells to limit the expression of factors that promote Th1 responses, it is likely that IL-27 signaling represents a novel and direct means by which infection-induced T cell functions can be suppressed.

Although WSX-1 signaling can suppress Th1 responses elicited by T. gondii and T. cruzi, it has also surfaced that IL-27 can negatively regulate the generation of type II (Th2) inflammatory responses. Appropriate differentiation of CD4+ Th2 effectors, classically associated with the production of IL-4, IL-5, and IL-13, is indispensable for resistance to helminth infection, but dysregulated Th2 responses are pathogenic in several diseases, including asthma and allergy (14). Because the increased parasitemia associated with T. cruzi infection of WSX-1−/− mice can be ameliorated through in vivo neutralization of IL-4 and is not associated with a corresponding defect in IFN-γ production, it is likely that aberrant Th2 responses contribute to the increased mortality in these animals (28). In support of this hypothesis, T. cruzi infection induces elevated levels of IL-4, IL-5, and IL-13 in WSX-1−/− CD4+ and NK1.1+ T cells when compared with wild-type counterparts (28). Likewise, WSX-1−/− NKT cells produce more IL-4 than wild-type cohorts during Con A-induced hepatitis and the enhanced liver pathology noted in these animals can be curbed through systemic administration of anti-IL-4 Ab (29).

During the early stages of Leishmania infection, neutralization of IL-4 restores the ability of WSX-1−/− mice to control parasite replication and promotes the resolution of inflammatory lesions (20). Because blockade of IL-4 also results in complete recovery of IFN-γ production in WSX-1−/− animals, it is clear that the ability of IL-27 to enhance Th1 differentiation is not required for resistance to this parasite. Instead, an alternative interpretation for Leishmania susceptibility in receptor-deficient mice is that an enhanced acute Th2 response inhibits the initial expansion of protective Th1 cells (20). Accordingly, lymphocytes from WSX-1−/− mice that have been infected for 7 days produce significantly more IL-4 than wild-type cohorts after ex vivo stimulation with Leishmania Ag (5, 20). Furthermore, maintained IL-4 transcription and elevated Th2-dependent Ab titers are detected in infected WSX-1−/− mice even after they have developed protective Th1 responses (5).

Further demonstrating an inhibitory role for IL-27/IL-27R in type II inflammatory responses are studies that assess the role of WSX-1 during infection with the intestinal dwelling helminth Trichuris muris.4 Though wild-type animals do not generate the Th2 responses required for parasite clearance until ~3 wk postinfection, by day 14, all WSX-1−/− animals have eradicated larval worms.5 At this early time point, receptor-deficient mice display increased Th2-dependent intestinal goblet cell hyperplasia, mastocytosis, and enhanced production of IL-4, IL-5, and IL-13 during ex vivo lymphocyte recall assays.5 Because wild-type animals do not acquire this hyperresistant phenotype when Th1 responses are effectively blocked in vivo, it is unlikely that the accelerated development of Th2-type immunity in WSX-1−/− mice is the secondary consequence of an intrinsic defect in IFN-γ production.4 Instead, these data suggest that IL-27 signaling can regulate the kinetics and intensity of protective type II immunity through the suppression of helminth-induced Th2 responses.

Several in vitro experiments support the hypothesis that IL-27 can directly down-regulate Th2 processes and provide possible cellular and molecular mechanisms for this effect. In CD4+ T cells, rIL-27 can inhibit expression of GATA-3, a transcription factor that mediates the acquisition of several important Th2 attributes in differentiating CD4+ T cells (Fig. 3) (12). When treated with IL-27, reduced GATA-3 transcription is reflected in decreased IL-4 production by naive CD4+ T cells that have been cultured under Th2-polarizing conditions (12).4 Concurrent with these findings, WSX-1−/− CD4+ T cells produce more IL-5 and IL-13 than wild-type counterparts during in vitro Th2 differentiation.6 Because at least one complete cell cycle is required for CD4+ T cells to become Th2 effectors, it is likely that the elevated proliferation noted in WSX-1−/− CD4+ T cells, in combination with a lack of IL-27-dependent GATA-3 inhibition, allow for a more rapid outgrowth of mature Th2 cells from a pool of naive precursors (37). Thus, by limiting the proliferative capacity of naive CD4+ T cells and inhibiting the expression of a key Th2 transcription factor, IL-27 appears to regulate the potency of nascent type II inflammatory responses.

Although lymphoid cells display the highest levels of WSX-1, other immune cell lineages express both IL-27R components (Fig. 1) (3). It has been reported that rIL-27 can activate STAT3 in purified human monocytes and mast cells (Fig. 3) (3). Furthermore, during T. cruzi infection, hepatic WSX-1-deficient macrophages produce more IL-6 and TNF-α than wild-type counterparts (28). Because ablation of STAT3 in myeloid cells results in elevated production of IL-6, TNF-α, and IL-12 (38), it is possible a lack of IL-27-induced STAT3 phosphorylation contributes to the enhanced secretion of inflammatory cytokines observed in T. cruzi-challenged WSX-1−/− animals. Similarly, in WSX-1−/− mice, deficient STAT3 activation may factor in the enhanced IL-12 production and increased mast cell activation that is observed during T. gondii and T. muris infection, respectively (Fig. 3) (10).4 Though many questions remain about the functional consequences of IL-27 signaling in myeloid cells, it is becoming clear that this cytokine may be critical in the suppression of a variety of inflammatory processes.

Concluding remarks

Although initial studies identified a role for IL-27R/IL-27 in promoting Th1 responses, recent evidence suggests that this receptor/ligand pair is also required to suppress a variety of immune cell effector processes, including proliferation and cytokine production (Fig. 3). Contributing to the difficulty in resolving the principal function of IL-27/IL-27R interaction is the fact that, for several key cellular parameters, the introduction of recombinant cytokine has similar effects to receptor ablation. For instance, while addition of IL-27 induces the proliferation of naive CD4+ T cells in vitro, enhanced proliferation is noted in CD4+ T cells from WSX-1−/− mice in vivo and in vivo (4, 5, 7, 10). Similarly, though IL-27 can enhance the production of IFN-γ from T cells and NK cells, WSX-1 is not
strictly required for the generation of Th1 responses (7, 9, 10). Stimulated under weakly polarizing conditions in vitro, WSX-1−/− T cells are deficient in IFN-γ production, but in a strongly polarizing environment, they produce elevated levels of the same cytokine (4, 5, 9, 10). In accord with this dichotomy, WSX-1−/− mice show a transient, early defect in IFN-γ production when infected with L. major or BCG but infection with T. gondii or T. cruzi leads to aberrantly elevated Th1 responses (5, 10, 20, 28). A key difference between these diseases is the induction of IL-12, a principal mediator of rapid type I immunity (16). Whereas T. gondii and T. cruzi promote strong innate immune responses that lead to systemic IL-12 levels early during infection, acute leishmaniasis induces much less IL-12 production (39). Still, the accelerated type II immunity noted during infection of WSX-1−/− mice with T. muris is not secondary to a defect in Th1 responses.4 In fact, the simultaneously elevated Th1 and Th2 responses noted in receptor-deficient mice have been infected with T. cruzi or L. major indicate that while IL-27 may not dictate the polarity of T cell responses, WSX-1 signaling is essential in regulating the kinetics and intensity of parasite-induced adaptive immunity (5, 20, 28). Because a range of cell lineages can express IL-27R, and enhanced myeloid cell functions are noted upon infection of WSX-1−/− mice with T. cruzi and T. muris (3, 28), IL-27 may also play a role in the regulation of nonlymphoid cells. In sum, these data indicate that IL-27 may act as a general immunosuppressant by dampening inflammatory processes associated with innate and adaptive immunity.

Given the mounting evidence that WSX-1 signaling can inhibit immune cell processes, the increased transcription of EB13 in EBV-transformed B cells and lymphoid cancer cells may represent a previously unidentified strategy for these cancer cells to avoid eradication by cytotoxic lymphocytes (8, 40, 41). In this context, it can be further proposed that detection of IL-27 at sites of inflammation may not be indicative of disease etiology. Instead, detection of IL-27 components in tuberculosis, sarcoidosis, inflammatory bowel disease, colitis, and Crohn’s disease may reflect a protective cellular response against the dysregulated inflammation associated with all these disorders (42–44). Inherent in this hypothesis is the idea that IL-27/WSX-1 signaling initiates new therapeutic targets to suppress inflammatory disease and that neutralization of IL-27 signaling may be useful to boost immune responses. Alternatively, the ability of IL-27 to enhance T cell production of IFN-γ while inhibiting that of IL-4 may allow it to be used as an adjuvant to promote type I immunity (21).

Although paradoxical pro- and anti-inflammatory properties are common in cytokines that use gp130-associated receptors, it is acknowledged that gp130 signaling is required during development (2). However, while gp130 deficiency leads to embryonic death during midgestation in mice (45), WSX-1−/− and EB13−/− animals are viable and fertile (4, 5, 18). Even so, the prevalence of IL-27 transcripts in uterine NK cells, lymphocytes that promote immune tolerance and placental development, suggests a role for this cytokine in cell migration and homeostatic immune regulation (46–48). In addition, the presence of IL-27 mRNA in pluripotent human mesenchymal stem cells suggests a role in early lymphoid ontogeny (49). Despite these observations, the lack of invariant NKT cells in EB13−/− mice may not be the immediate result of deficient IL-27R signaling during lymphoid maturation (18). Because normal numbers of NK and NKT cells are found in WSX-1−/− mice (18, 29), it is possible that EB13, bound to either IL-27p28 or another cytokine component, may signal through a different receptor complex to promote the development of these cells. One alternative is the heterodimeric pairing of group 3 soluble receptor EB13 with the IL-6/IL-12 family member IL-12p35 (41). Though this association has been known for several years, no function or receptor specificity has yet assigned for this potential cytokine. In turn, though IL-27 is the only known ligand for WSX-1, it is feasible that there are others. Such a finding could explain discrepancies between in vitro experiments using rIL-27 and those using receptor-deficient animals. Moreover, while much of the early work has attempted to identify the function of IL-27 in isolation, it is likely that the effects of IL-27R signaling are influenced by its interaction with other pro- and anti-inflammatory cytokines. Nevertheless, though much remains enigmatic about the biology of IL-27, the recognition that it belongs in the subfamily of cytokines that signal through gp130 dictates that future research must consider the pleotropic nature of this immune mediator.

References


