Review

Biology of recently discovered cytokines: Discerning the pro- and anti-inflammatory properties of interleukin-27

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Abstract

IL-27 is a recently identified heterodimeric cytokine produced in response to microbial and host derived inflammatory cues. Initial studies indicated that IL-27 promotes the generation of Th1 responses required for resistance to intracellular infection and unveiled the molecular mechanisms mediating this effect. However, subsequent work uncovered a role for IL-27 in the suppression of Th1 and Th2 responses. Thus, by discussing its pleotropic functions in the context of infection-induced immunity and by drawing parallels to fellow IL-6/IL-12 family cytokines, this review will attempt to reconcile the pro- and anti-inflammatory effects of IL-27.

Keywords IL-27, WSX-1, Th1, Th2, infection

Introduction

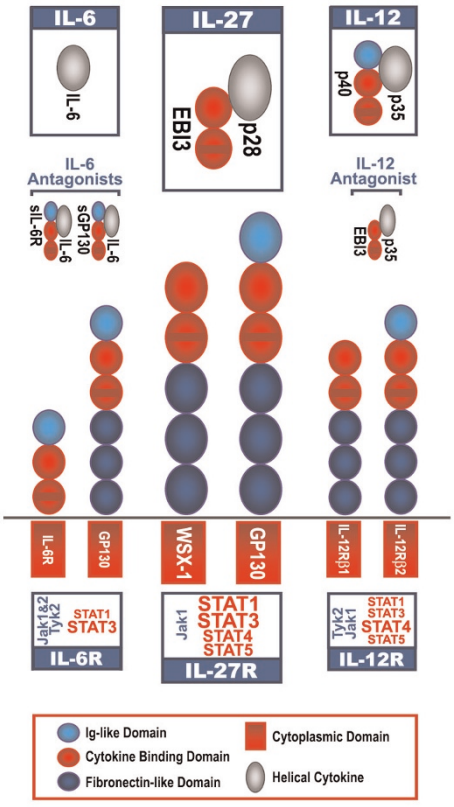
IL-27 is a heterodimeric member of the IL-6/IL-12 family of type I cytokines [1,2]. Like IL-12 and IL-23 [1], IL-27 is the pairing of a helical protein (IL-27p28) with a soluble cytokine receptor-like component (Epstein–Barr virus-induced gene 3 [EBI3]; Fig. 1) [1,3]. Similar to IL-12p40 and soluble forms of IL-6 receptor components [4], EBI3 contains two cytokine binding domains but lacks membrane anchoring motifs and a cytoplasmic tail (Fig. 1) [5]. Originally identified as an IL-12p40 homolog that is secreted by Epstein–Barr virus (EBV) transformed B cells [5], EBI3 is produced by a range of immune cell lineages including B cells, monocytes, dendritic cells (DCs) and epithelial cells [3,5–7].

While typically low or absent in resting cells, EBI3 expression is constitutive in several human lymphomas [8] and can be elicited by pathogen and host derived inflammatory stimuli [3,5,6]. For instance, in B cells, EBI3 production is directly induced by EBV latent membrane protein 1 [9]. Likewise, monocytes and DCs secrete EBI3 in response to lipopolysaccharide (LPS), CD40 ligation or exposure to inflammatory cytokines [3,6,10,11]. Since production of EBI3 is limited to activated immune cells, expression levels are highest in the spleen [3,5,6], lymph nodes [3,5,6], placenta [12,13] and sites of chronic inflammation [7,14–16]. Thus the induction by inflammatory stimuli and its prevalence in lymphoid tissues suggest that EBI3 plays a role in the regulation of immune responses.

Since EBI3 shows no direct activity on its own [5], it is likely that, like IL-12p40, it must associate with other proteins to form bioactive cytokines. One dimeric partner for EBI3 is IL-27p28 (Fig. 1), a helical cytokine that was identified through its homology to IL-12p35 and IL-6 [3]. While it is possible that IL-27p28 can associate with other proteins, expression of this gene is only detected concurrently with that of EBI3 [3,6,10,17–20]. As with IL-12p35, IL-27p28 gene transcription is tightly regulated and the protein is poorly secreted unless it is co-expressed with a soluble receptor-like component (IL-12p40 and EBI3 respectively) [3]. In macrophages, DCs and epithelial cells, the same inflammatory stimuli that promote IL-27p28 transcription also induce

BCG = bacille Calmette-Guérin; DC = dendritic cell; EBV = Epstein–Barr virus; EBI3 = Epstein–Barr virus-induced gene 3; HMDC = human monocyte derived dendritic cell; IFN = interferon; IL = interleukin; IL-27R = Interleukin-27 receptor Jak = Janus kinase; LPS = lipopolysaccharide; NK = natural killer; STAT = signal transducer and activator of transcription; Th = T-helper; TLR = Toll-like receptor; TNF = tumor necrosis factor.

Figure 1



IL-27 and the IL-27 receptor complex. Heterodimeric IL-27 is the association between a helical protein, IL-27p28, and a soluble cytokine receptor-like component, EBI3. Through engagement of its cognate receptor, (IL-27R: GP130/WSX-1), IL-27 can activate a heterogeneous Jak/STAT signaling cascade. In order to emphasize structural similarities, IL-27 is depicted with fellow IL-6/IL-12 family cytokines and the conserved WSXWS motif is represented by a dark band within cytokine binding domains. To indicate functional parallels, the relative ability to activate STAT transcription factors is reflected by differences in font size. However, in this figure, the physical size of cytokine/receptor pairings or their components does not have physiological relevance. IL, interleukin; Jak, Janus kinase; STAT, signal transducer and activator of transcription.

expression of EBI3, thus prompting secretion of heterodimeric IL-27 [3,6,7,17–20]. Pathogenic *Streptoccocus pyogenes* can elicit IL-27 production from human monocyte derived DCs (HMDCs) but commensal Gram-positive bacteria do not [19,20]. Conversely, exposure of HMDCs to non-pathogenic Gram-negative bacteria promotes strong IL-27 expression [19] and, correspondingly, LPS induces production of IL-27 by HMDCs, murine bone marrow derived macrophages and murine DCs [3,6,17]. Many of the stimulatory effects of LPS are mediated through Toll-like receptor 4 (TLR4) but other host pattern recognition receptors can also trigger IL-27 expression. Ligation of TLR9 with double stranded DNA leads to strong induction of IL-27 in murine bone marrow derived DCs and engagement of TLR2 with its synthetic ligand (Pam3Cys) promotes a similar but weaker IL-27 response in these cells [18]. Together, these studies demonstrate that bacterial products can directly induce IL-27 production but do not account for the elevated expression of this cytokine during infection with eukaryotic pathogens, such as *Toxoplasma gondii* and *Trichuris muris* [21–23]. However, since a variety of host derived factors, including CD40 ligation, IFN-β, and IFN-γ, can promote IL-27 expression [3,6,10,17], it is unclear whether the appearance of this cytokine can be directly attributed to parasite elements or the host response to infection. Nonetheless, these findings indicate that IL-27 is generated in response to various inflammatory stimuli and imply a role for this cytokine in the regulation of infection-induced immunity.

Because they promote inflammatory processes, the production of heterodimeric IL-6/IL-12 family cytokines is tightly regulated. However, for both IL-12 and IL-27, transcription of the soluble receptor component (IL-12p40/EBI3) is always greater than that of the helical subunit (IL-12p35/IL-27p28) [3,6,24,25]. In the case of IL-12p40, it can also dimerize with the IL-6/IL-12 family protein IL-23p19 to form IL-23, a cytokine that promotes the development of infection induced and autoimmune inflammatory responses [24–28]. Therefore, since it can be expressed in the absence of IL-27p28, it is tempting to speculate that, like IL-12p40, EBI3 can participate in multiple cytokines. While an association between EBI3 and IL-12p35 was described several years prior to the identification of IL-27, no distinct function has been ascribed to this hematopoietin [29]. It is possible that, like the sequestering of IL-6 by soluble receptor components (e.g. soluble IL-6 receptor and soluble GP130) [4], this EBI3 heterodimer acts as a molecular sink that limits the availability of IL-12p35 for inclusion in bioactive IL-12 (Fig. 1) [29]. However, since IL-27 can have dramatic and direct effects on a variety of cell types (Detailed discussion below), it is likely that IL-27p28 is the more biologically relevant partner for EBI3.

The interleukin-27 receptor complex

All IL-6/IL-12 family cytokines propagate intracellular signaling through transmembrane receptor complexes that include either IL-12Rβ1 or GP130 [1]. Restricted to mature lymphoid cells, IL-12Rβ1 is a component in the heterodimeric receptors for IL-12 and IL-23 [24,25]. Accordingly, IL-12Rβ1 defects result in enhanced susceptibility to intracellular infection and compromised adaptive immunity [30,31]. In contrast, GP130 is expressed throughout development by a range of immune and non-immune cells [32]. Because GP130 is a component in heterodimeric receptors for several cytokines, including IL-6, IL-11, LIF (leukemia inhibitory factor), G-CSF (granulogyte colony-stimulating factor) and Oncostatin M [4,32], germline deletion of this gene leads

to gross developmental defects [33]. Therefore, due to the broad distribution of this shared receptor component, the distinct functions and tissue tropisms of GP130 associated cytokines are determined by the availability of ligand specific co-receptors [32].

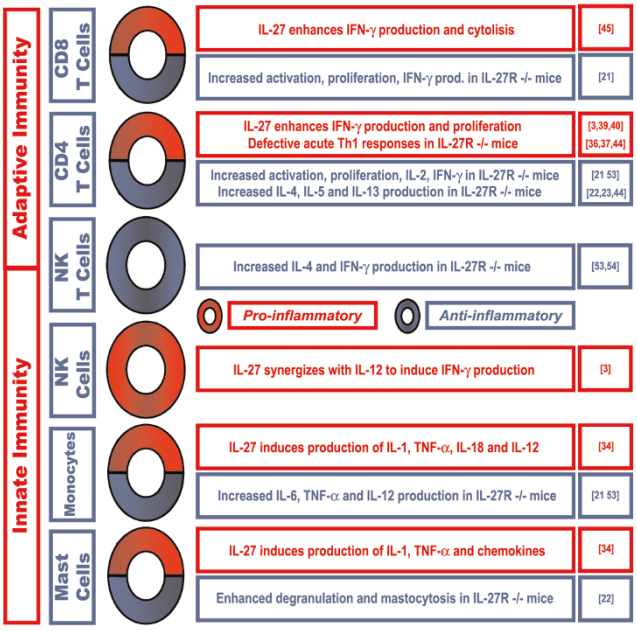
Recent studies have reported that GP130 can associate with WSX-1 (TCCR), a type I cytokine receptor with four positionally conserved cysteine residues and a C-terminal WSXWS protein sequence motif (Fig. 1) [34]. WSX-1 binds to IL-27 with high affinity [3] but requires cooperation with GP130 to form an IL-27 receptor (IL-27R) complex that is capable of propagating intracellular signaling [34]. Coexpression of GP130 and WSX-1 (IL-27R) can be found in a variety of immune cell types including activated endothelial cells, activated epithelial cells, activated DCs, monocytes, mast cells and B cells. However, expression of IL-27R is greatest in the lymphoid lineage, particularly in NK and T cells (Fig. 2) [34–37]. Thus, like its ligand IL-27, IL-27R is restricted mainly to sites of immune involvement like the spleen, thymus, lungs, intestine, liver, peripheral blood and lymph nodes [35,36].

As with other type I cytokine receptors [1,38], ligation of IL-27R by its cognate ligand results in the activation of a heterogeneous Janus kinase (Jak)/signal transducer and activator of transcription (STAT) signaling cascade (Fig. 1). The binding of IL-27 to IL-27R induces phosphorylation of: Jak1, STAT1, STAT3, STAT4 and STAT5 in T cells [6,21,34,39,40]; Jak1, STAT1, STAT3 and STAT5 in NK cells [6,40]; STAT1 and STAT3 in monocytes [34] and STAT3 in mast cells [34]. Together with the limited distribution of WSX-1, the ability to activate Jak/STAT signaling pathways implies that the principal function of the IL-27R, like that of fellow GP130 user IL-6R (Fig. 1), is in the regulation of immune processes.

Interleukin-27 can promote type I inflammatory responses

IL-6/IL-12 family cytokines play key roles in the generation and regulation of inflammatory responses [24,25,32]. For instance, IL-12 promotes resistance to intracellular infection by inducing the production of IFN-γ, the signature cytokine of type I (Th1) immune responses [24,25,41,42]. Though many factors coordinate the generation of type I immunity, IL-12 is a central figure; required for optimal differentiation of naïve CD4+ T cells into mature Th1 effector cells and able to induce the secretion of IFN-γ by NK cells and CD8+ T cells [24, 25]. Thus, based on a significant degree of sequence and structural homology, it was predicted that, like IL-12, IL-27 could promote Th1 responses [3]. In accord with this hypothesis, recombinant IL-27 can augment proliferation and secretion of IFN-γ by naïve CD4+ T cells [3,39,40] and when combined with

Figure 2

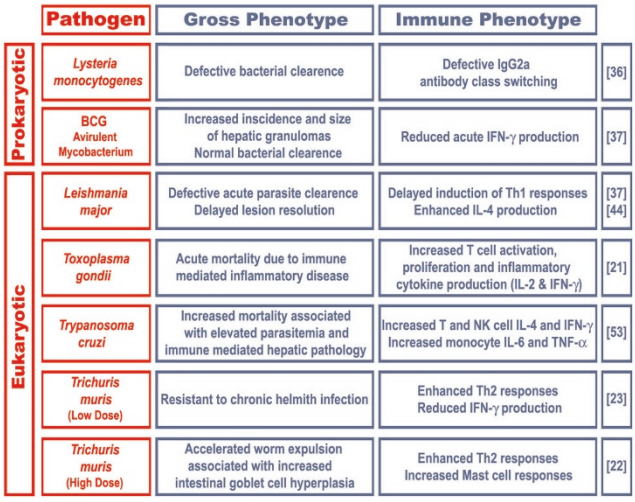


The paradoxical pro- and anti-inflammatory properties of IL-27. Through ligation of its cognate receptor, IL-27 influences a range of immune cell lineages. This figure summarizes the effects of IL-27 treatment or IL-27 receptor deficiency on mast cells, monocytes, NK cells, NK T cells, CD4+ T cells and CD8+ T cells. References are listed as bracketed citations in the far right column of the figure. IFN, interferon; IL, interleukin; NK, natural killer; TNF, tumor necrosis factor.

IL-12, can synergize to induce IFN-γ production by human NK cells (Fig. 2) [3]. Correspondingly, naïve WSX-1 deficient CD4+ T cells produce less IFN-γ than wild-type counterparts when cultured under non-polarizing conditions (Fig. 2) [21,36,37,39,40]. Likewise, during *in vitro* Th1 differentiation with IL-12 and high doses of either αT-cell receptor antibody or ConA, *WSX-1*$^{-/-}$ CD4+ T cells produce less IFN-γ than wild-type counterparts (Fig. 2) [36,37,39,40].

Consistent with *in vitro* experiments demonstrating the ability of IL-27 to promote IFN-γ production, early studies also showed that *WSX-1*$^{-/-}$ mice have enhanced susceptibility to infection with intracellular pathogens (Fig. 3). In resistant mouse strains, infection with protozoan parasite *Leishmania major* results in the development of CD4+ T cell dependent Th1 responses that mediate parasite clearance [43]. However, *L. major* infected *WSX-1*$^{-/-}$ mice display acute defects in IFN-γ production and lesion resolution (Fig. 3) [37,43,44]. Similarly, in *WSX-1*$^{-/-}$ mice, reduced Th1 responses are evident upon challenge of an avirulent strain of mycobacterium (bacille Calmette-Guérin [BCG]; Fig. 3) [37]. During infection with *Listeria monocytogenes*, receptor deficient animals exhibit defective bacterial

Figure 3



	Pathogen	Gross Phenotype	Immune Phenotype	
Prokaryotic	*Lysteria monocytogenes*	Defective bacterial clearance	Defective IgG2a antibody class switching	[36]
	BCG Avirulent Mycobacterium	Increased inscidence and size of hepatic granulomas Normal bacterial clearence	Reduced acute IFN-γ production	[37]
Eukaryotic	*Leishmania major*	Defective acute parasite clearence Delayed lesion resolution	Delayed induction of Th1 responses Enhanced IL-4 production	[37] [44]
	Toxoplasma gondii	Acute mortality due to immune mediated inflammatory disease	Increased T cell activation, proliferation and inflammatory cytokine production (IL-2 & IFN-γ)	[21]
	Trypanosoma cruzi	Increased mortality associated with elevated parasitemia and immune mediated hepatic pathology	Increased T and NK cell IL-4 and IFN-γ Increased monocyte IL-6 and TNF-α	[53]
	Trichuris muris (Low Dose)	Resistant to chronic helmith infection	Enhanced Th2 responses Reduced IFN-γ production	[23]
	Trichuris muris (High Dose)	Accelerated worm expulsion associated with increased intestinal goblet cell hyperplasia	Enhanced Th2 responses Increased Mast cell responses	[22]

Analysis of infection-induced immune responses in IL-27 receptor deficient mice. The availability of receptor deficient mice has allowed researchers to explore the role of IL-27 *in vivo*. This figure summarizes the immune response of *WSX-1 -/-* mice upon challenge with various prokaryotic and eukaryotic pathogens. References are listed as bracketed citations in the far right column of the figure. BCG, bacille Calmette-Guérin; IFN, interferon; IL, interleukin, TNF, tumor necrosis factor.

clearance and IgG_{2a} antibody class switching, both functions that are associated with IFN-γ production (Fig. 3) [36]. Furthermore, since many of the effector mechanisms required for resistance to intracellular infection are also crucial in immunity to cancer, it is not surprising that in a model of murine carcinoma, transgenic overexpression of IL-27 leads to increased *in vivo* $CD8^+$ T cell IFN-γ production, cytotoxicity and tumor clearance (Fig. 2) [45]. Thus, due to the evidence that IL-27R signaling can promote type I inflammatory responses, a consensus emerged that, like IL-12, IL-27 is necessary for the efficient induction of Th1 responses [25,46–50].

Although the molecular mechanisms controlling IFN-γ production are complex, it is well established that activated STAT transcription factors play a vital role. IL-27 can induce limited phosphorylation of STAT4, the same signaling pathway employed by IL-12 to polarize Th1 effector cell populations [40]. Furthermore, by activating STAT1, IL-27 promotes expression of T-bet, a transcription factor whose target genes, particularly IL-12Rβ2 and IFN-γ, are essential components of Th1 responses [6,39,40]. However, since other cytokines, such as IFN-α and IFN-γ, also induce T-bet, the requirement for IL-27/IL-27R in the development of Th1 responses is not absolute [41]. In fact, despite acute defects in pathogen induced IFN-γ production, *WSX-1*$^{-/-}$ mice eventually develop the Th1 responses required for control of *L. major* and BCG infections (Fig. 3) [37,44]. Thus, in spite of evidence that IL-27 can promote IFN-γ production, a requirement for this cytokine in the development of protective type I immunity appears transient.

Interleukin-27 can inhibit immune effector cell functions

Although many IL-6/IL-12 family cytokines have proinflammatory effects, it is becoming clear that some, particularly those that signal through GP130, can also suppress inflammatory responses [32,51]. Thus, despite the literature that describes a role for IL-27 in the development of Th1 responses, there is also evidence that WSX-1 signaling can inhibit inflammatory processes. Several groups have reported increased proliferation of WSX-1 deficient $CD4^+$ T cells during *in vitro* culture (Fig. 2) [21,22,36,37]. However, since treatment with recombinant IL-27 can also enhance the expansion of activated $CD4^+$ T cells, the role of this cytokine/receptor pairing in the regulation of proliferation remains unclear (Fig. 2) [3].

A similar paradox exists regarding the effects of IL-27R signaling on the production of IFN-γ by $CD4^+$ T cells. When activated with a high mitogenic dose (ConA or αT-cell receptor monoclonal antibodies), WSX-1 deficient $CD4^+$ T cells produce reduced amounts of IFN-γ during *in vitro* Th1 differentiation (Fig. 2) [36,37,39,40]. In contrast, with low dose antigenic stimulation in the presence of IL-12, *WSX-1*$^{-/-}$ and *EBI3*$^{-/-}$ $CD4^+$ T cells produce significantly more IFN-γ than wild-type counterparts (Fig. 2) [21,52]. Because a similar percentage of wild-type and *WSX-1*$^{-/-}$ cells become IFN-γ positive during these studies, the increased accumulation of IFN-γ in WSX-1 deficient Th1 cultures is likely to be a secondary consequence to enhanced $CD4^+$ T cell proliferation [21]. Thus, in the presence of IL-12, IL-27 is not required for optimal Th1 differentiation but, instead, appears to regulate the proliferation of effector T cells.

Although production of IFN-γ is necessary for immunity to intracellular pathogens, aberrant Th1 responses can lead to the development of inflammatory diseases [2,24,25,41, 42]. While it may be dispensable for the generation of *in vivo* Th1 responses, several studies suggest that IL-27R signaling is crucial for the suppression of infection-induced immunity. Following challenge with the intracellular protozoan *Toxoplasma gondii*, *WSX-1*$^{-/-}$ mice generate robust Th1 responses and control parasite replication (Fig. 3) [21]. However, during the acute phase of infection, these animals develop a lethal, $CD4^+$ T cell-dependent inflammatory disease that is characterized by immune-mediated pathology and elevated splenocyte production of IFN-γ and IL-2 (Fig. 3) [21]. Together with the increased T cell activation and proliferation observed

in *T. gondii* infected *WSX-1*$^{-/-}$ mice, these findings suggest that IL-27 may have inhibitory effects on parasite induced Th1 responses [21].

Further supporting an anti-inflammatory role for IL-27, is the finding that *WSX-1*$^{-/-}$ mice develop immune-mediated liver necrosis during infection with *Trypanosoma cruzii* (Fig. 3) [53]. Since hepatic T and NK cells from infected *WSX-1*$^{-/-}$ mice produce more IFN-γ and tumor necrosis factor (TNF)-α than wild-type cohorts and *in vivo* neutralization of IFN-γ can ameliorate pathology in receptor deficient animals, it is likely that dysregulated Th1 responses mediate the liver damage (Fig. 3) [53]. Likewise, when compared with wild-type counterparts, *WSX-1*$^{-/-}$ mice display enhanced sensitivity to ConA induced hepatitis [54]. In this model of acute inflammation, *WSX-1*$^{-/-}$ mice display enhanced T and NK T cell production of IFN-γ and the severe liver pathology observed in these animals can be curbed through depletion of IFN-γ, CD4$^+$ cells or NK1.1$^+$ cells [54]. Together, these studies suggest that in the presence of strongly polarizing inflammatory responses, such as those elicited by systemic parasitic infection, the ability of IL-27 to promote Th1 responses becomes secondary to its role in the suppression of effector cell proliferation and cytokine production.

Given the Jak/STAT signaling cascade initiated by WSX-1 ligation, several molecular mechanisms can be proposed for the inhibitory effects of IL-27R signaling on Th1 responses. While the proinflammatory effects of STAT1 activation were recognized first, it has also become apparent that this signaling pathway can inhibit T cell responses [38]. Type I (IFN-α/β) and type II (IFN-γ) interferons, which signal primarily through STAT1, can inhibit T cell production of IFN-γ and proliferation, respectively [55,56]. 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 [57]. However, currently, the molecular mechanisms that mediate the inhibitory properties of STAT1 signaling remain poorly understood.

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. 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 activation and its induction of SOCS (suppressors of cytokine signaling) family proteins [58]. 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 [59]. However, because IL-10 acts primarily on macrophages and DCs 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.

While the studies described above indicate that WSX-1 signaling can inhibit infection-induced Th1 responses, it has also been reported that IL-27 negatively regulates the generation of type II (Th2) inflammatory responses. Appropriate differentiation of CD4$^+$ Th2 effector cells, classically associated with the production of IL-4, IL-5 and IL-13, is indispensable for resistance to helminth infection, while dysregulated Th2 responses are pathogenic in several diseases, including asthma and allergy [42]. Several pieces of evidence suggest that the increased susceptibility of *WSX-1*$^{-/-}$ mice to intracellular pathogens is associated with the development aberrant Th2 responses. For example, the elevated parasitemia associated with *T. cruzi* infection of receptor deficient animals can be reduced through *in vivo* neutralization of IL-4 and is not associated with a corresponding defect in IFN-γ production (Fig. 3) [53]. Accordingly, *T. cruzi* infection of *WSX-1*$^{-/-}$ mice leads to increased production of IL-4, IL-5 and IL-13 by CD4$^+$ and NK1.1$^+$ T cells (Fig. 3) [53]. Moreover, *WSX-1*$^{-/-}$ NK T cells produce more IL-4 than wild-type cohorts during ConA induced hepatitis and the enhanced liver pathology noted in these animals can be curbed through systemic administration of anti-IL-4 antibody [54].

Since the morbidity associated with *T. cruzi* infection of *WSX-1*$^{-/-}$ mice is mediated, in part, by the development of aberrant Th2 responses, it is possible that a similar mechanism may contribute to the delayed resolution of *Leishmania* infection in these animals. During acute leishmaniasis, neutralization of IL-4 restores the ability of *WSX-1*$^{-/-}$ mice to control parasite replication and promotes the resolution of inflammatory lesions (Fig. 3) [44]. Since 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 [44]. Thus, an alternative interpretation for *Leishmania* susceptibility in receptor deficient mice is that enhanced acute Th2 responses inhibit the initial expansion of protective Th1 cells [44]. Accordingly, lymphocytes from *WSX-1*$^{-/-}$ mice that have been infected for seven days produce significantly more IL-4 than wild-type cohorts after *ex vivo* stimulation with *Leishmania* antigen (Fig. 3) [37,44]. In fact, even after infected *WSX-1*$^{-/-}$ mice have developed protective Th1 responses, IL-4 transcription is maintained and elevated Th2 dependent antibody titres are detected [44].

While it appears that IL-27R signaling is required to suppress the development of pathogenic Th2 responses in several disease models [21, 53, 54], studies assessing the role of WSX-1 during infection with the intestinal

dwelling helminth *Trichuris muris* suggest that it may also regulate the development of protective type II immunity (Fig. 3) [22]. Genetically resistant wild-type animals do not generate the Th2 responses required for worm expulsion until approximately 3 weeks post infection but, by day 14, all *WSX-1*$^{-/-}$ animals have eradicated larval worms (Fig. 3) [22]. 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 [22]. Since wild-type animals do not acquire this hyper-resistant 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 [22]. Instead, IL-27 appears to have direct inhibitory effects on the generation of mucosal Th2 responses that are independent of its ability to enhance IFN-γ production.

While appropriate induction of mucosal Th2 responses is required for resistance to *T. muris*, production of type I cytokines results in chronic infection [60,61]. In resistant mouse strains, inoculation with a high dose of parasites leads to the generation of protective type II immunity but low dose infection results in the development of Th1 responses and persistent infection [61]. However, a low dose *T. muris* infection does not result in the predominance of Th1 responses in *WSX-1*$^{-/-}$ mice and, instead, these animals develop protective Th2 responses that mediate parasite clearance (Fig. 3) [23]. Although neutralization of IL-12 and IFN-γ can lead to worm expulsion in low-dose infected wild-type mice [60], defective IL-27 dependent Th1 responses are not solely responsible for the enhanced helminth resistance of WSX-1 deficient animals. In fact, since *in vivo* administration of IL-12 restores parasite-specific IFN-γ responses but does not lead to chronic infection [23], it is likely that, as in the case of high dose infection, elevated mucosal Th2 responses mediate enhanced resistance in low dose infected *WSX-1*$^{-/-}$ animals. In sum, these data suggest that IL-27 signaling can directly regulate the kinetics and intensity of protective type II immunity through the suppression of helminth induced Th2 responses.

While these *in vivo* studies support the hypothesis that IL-27 can directly down-regulate Th2 processes, several *in vitro* experiments provide possible cellular and molecular mechanisms for this effect. In CD4$^+$ T cells, recombinant IL-27 can inhibit expression of GATA-3 [40], a transcription factor that mediates the acquisition of several important Th2 attributes in differentiating CD4$^+$ T cells [42]. When treated with IL-27, reduced GATA-3 transcription is reflected in decreased IL-4 production by naïve CD4$^+$ T cells that have been cultured under Th2 polarizing condition [22,40]. 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 [22]. Because at least one complete cell cycle is required for CD4$^+$ T cells to become Th2 effectors [62], 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 naïve precursors. Therefore, by limiting the proliferative capacity of naïve 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.

While the studies discussed here clearly demonstrate that IL-27 has profound effects on T cells and NK cells, expression of IL-27R on other immune cell lineages suggests that it may also regulate myeloid cell functions (Fig. 2) [34]. During *T. cruzi* infection, hepatic WSX-1 deficient macrophages produce more IL-6 and TNF-α than wild-type counterparts (Figs 2 and 3) [53]. Since ablation of STAT3 in myeloid cells results in elevated production of IL-6, TNF-α and IL-12 [63], it is possible that 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 (Figs 2 and 3) [21, 22]. Although *in vivo* studies suggest that IL-27R signaling can suppress monocyte and mast cell functions, *in vitro* experiments propose that it can also have proinflammatory effects in these cells (Fig. 2). IL-27 can directly induce expression of IL-1 and TNF-α by primary mast cells and production of IL-1, TNF-α, IL-12p35 and IL-18 by monocytes [34]. Therefore, while many questions remain about the functional consequences of IL-27 signaling in myeloid cells, it is becoming clear that this cytokine is critical in the regulation of both innate and adaptive elements of parasite induced immunity.

Conclusion

Initial studies indicated that IL-27, like IL-12, can promote T and NK cell IFN-γ production while, similar to IL-12R deficiency in humans and mice, *WSX-1*$^{-/-}$ T cells are defective in the generation of Th1 responses (Fig. 2). However, subsequent work has reported that the IL-27/IL-27R interaction is not strictly required for the generation type I immunity. Thus, while *WSX-1*$^{-/-}$ mice exhibit acute defects in the production of IFN-γ during infection with *L. major,* these animals also develop exaggerated Th1 responses upon infection with *T. gondii* and *T. cruzi* (Fig. 3). One key difference between these infections is the prevalence of innate immune cell activation and the abundance of IL-12, a key factor for the optimal development of Th1 responses [43]. The acute response

to *L. major* is localized to the site of infection and is not associated with NK cell activation or systemic IL-12 production [43]. In contrast, *T. gondii* and *T. cruzi* are disseminating infections that induce strong innate immune responses and high serum levels of inflammatory cytokines [43]. In these infectious diseases, innate involvement promotes the secretion of IL-12 by macrophages and DCs and thereby creates a highly polarizing, Th1 environment for T cell priming [43]. Under such conditions, the ability of IL-27 to enhance IFN-γ production may be secondary to its effects on clonal expansion and contraction. In support of this hypothesis, infection of *WSX-1*$^{-/-}$ mice with *T. gondii* leads to acute mortality mediated by a pathogenic accumulation of activated Th1 cells (Fig. 3) [21]. Furthermore, the accelerated helminth resistance observed in *WSX-1*$^{-/-}$ mice indicates that IL-27 may also suppress infection induced Th2 responses (Fig. 3) [22, 23]. Thus, it can be hypothesized that while IL-27 may not dictate the polarity (i.e. Th1 vs. Th2) of a nascent response, it may be essential in regulating the kinetics and intensity of infection induced immunity.

Many of the cytokines produced to combat pathogenic challenge are also characteristic of chronic inflammatory disorders. Accordingly, production of IL-6/IL-12 family cytokines is associated with the development of rheumatoid arthritis [4,51,64]. In murine models, IL-6 can promote the onset and severity of joint inflammation [51,64] but deficiencies in this cytokine can also exacerbate arthritic pathology [65]. Early studies identified the ability of IL-12 to aggravate disease [66,67] but recent work has determined that IL-23, and not IL-12, is required for the development of arthritis [68]. Thus, similar to the paradoxic functions of IL-27 during parasitic infection, it is apparent that IL-6/IL-12 family cytokines can have both pro- and anti-inflammatory effects on the development of autoimmune pathology.

While the detection of IL-27 in granulomatous tissues from individuals with sarcoidosis and Crohn's disease suggest that it may factor in the regulation of immune mediated pathologies [7], the pleotropic nature of this cytokine makes its role in arthritis difficult to predict. By enhancing Th1 responses directed towards self-antigens, it is possible that IL-27 may promote disease. In agreement with this hypothesis, a recent study indicated that *in vivo* neutralization of IL-27 reduces the severity of adjuvant-induced arthritis in rats and, in this model, amelioration of disease is associated with a reduction in T-cell proliferation and inflammatory cytokine production [69]. However, it is also possible that IL-27 can have inhibitory effects on the inflammatory responses associated with arthritis. By increasing the amount of GP130 available for inclusion in the IL-6 receptor, *WSX-1*$^{-/-}$ animals may display increased rheumatoid pathology. Furthermore, since STAT1 deficiency is associated with increased chronic pathology in zymosan induced arthritis [70], it is possible that signaling through the IL-27R may provide a direct inhibitory signal to curb disease progression. Similarly, reports of spontaneous colitis and arthritis in mice lacking the STAT binding sites of GP130 support a role for IL-27 in protection from autoimmune disease [71]. Since IL-6 is closely associated with the development of arthritis and mice deficient in this cytokine do not develop inflammatory disease unless prompted by exogenous mitogens [51,64], it is likely that the heterodimeric IL-27R mediates some of the inhibitory effects associated with GP130 dependent STAT activation. When considered in the context of the aberrant adaptive immune responses noted in pathogen challenged *WSX-1*$^{-/-}$ mice (Fig. 3), these studies suggest that IL-27 may be a general suppressor of cell mediated inflammatory responses. Thus, given the viability of WSX-1 deficient animals, IL-27 and the IL-27R may represent safe and effective targets for future inflammatory therapeutics.

Competing interests

Amgen, DNAX and Genentech have provided reagents and support for studies on IL-27 and WSX-1.

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