The Immunobiology of Interleukin-27

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Abstract

Interleukin-27 (IL-27) is a cytokine with strikingly diverse influences on the immune response. Although it was initially linked with the development of Th1 responses, it is now recognized as a potent antagonist of different classes of inflammation through its ability to directly modify $CD4^+$ and $CD8^+$ T cell effector functions, to induce IL-10, and to promote specialized T regulatory cell responses. Although this aspect of IL-27 biology has provided insights into how the immune system prevents hyperactivity in the setting of infectious and autoimmune inflammation, in vaccination and cancer models the stimulatory effects of IL-27 on $CD8^+$ T cell function appear prominent. Additionally, associations between IL-27 and antibody-mediated disease have led to an interest in defining the impact of IL-27 on innate immunity and humoral responses in different disease states. The maturation of this literature has been accompanied by attempts to translate these findings from experimental models into human diseases and by efforts to define where IL-27 might represent a viable therapeutic target.

INTRODUCTION

Interleukin-27 (IL-27) is a heterodimeric cytokine that contains Epstein-Barr virus–induced gene 3 (*EBI3*) and IL-27p28, which signals through a receptor composed of gp130 (utilized by many cytokines, including IL-6) and IL-27Rα (also known as WSX-1 or TCCR) (1, 2). There are a number of distinct structural motifs that characterize the receptor and cytokine subunits of IL-27 and that highlight their evolutionary relationship to the IL-6, IL-12, and IL-23 signaling cassettes, as well as their ability to engage Janus kinase, signal transducer and activator of transcription (STAT), and mitogen-activated protein kinase (MAPK) pathways (3). Initially, IL-27 was predicted to be proinflammatory, in part because of its ability to promote the production of interferon-γ (IFN-γ) by natural killer (NK) and T cells, as well as its predicted relationship to IL-6 and IL-12, but the past decade has seen a more nuanced appreciation of its biological activities. Early studies with mice that lacked *Wsx-1*, *Tccr*, or *Ebi3* showed altered immune responses in the setting of oxazolone-induced colitis or following infectious challenge, and suggested a role for IL-27 in the balance between Th1 and Th2 immunity (4–6). The discovery that WSX-1/TCCR was part of the receptor for IL-27, and that IL-27 activated STAT1 and T-bet to promote responsiveness to IL-12 and production of IFN-γ, provided a mechanism to explain how IL-27 could promote Th1 cells (1, 5–8). However, when *Il27ra*$^{-/-}$ mice were challenged with different classes of viral, bacterial, or parasitic pathogens (9–23), or utilized in models of tissue-specific autoimmunity (24–31), these experiments identified a role for IL-27 as a negative regulator of T cell responses. Since then, multiple studies have shown that IL-27 can antagonize Th1, Th2, Th9, and Th17 responses, but it has been difficult to reconcile these inhibitory activities with the ability of IL-27 to promote T cell growth and survival, and, under certain circumstances, effector T cell functions (1, 32). This contradiction highlights the idea that cytokines are not intrinsically pro- or anti-inflammatory, and we now realize that IL-27 does not simply block T cell activities. Rather, some of the regulatory properties of IL-27 depend on its ability to stimulate T cells to perform functions necessary to suppress ongoing inflammation. Below, we review the biology of the cytokine and receptor subunits that are necessary to understanding the relationship of IL-27 to IL-6 in particular, and then discuss some of the model systems in which the ability of IL-27 to control inflammation has been prominent. Other sections focus on the progress that has been made in understanding how IL-27 can suppress T cell responses in vivo, and how its role in promoting CD8^{+} T cell activity has become relevant to vaccine development and tumor immunotherapy. Additionally, we review the effects of IL-27 on nonhematopoietic cells and other arms of the innate immune system, and on humoral immunity. Invariably, within each of these sections there are conflicting data sets and conclusions, and it can be difficult to distinguish incongruities that may be resolved through experimentation from those that reflect genuine differences in the biology of IL-27. Lastly, there has also been an increased emphasis on the translation of basic research on IL-27 in disease models into clinical situations, and examples are provided that may help to define whether IL-27 represents a viable target for neutralization or for use as a therapy.

The IL-27 Subunits

EBI3 was identified as a gene that is preferentially expressed in Epstein-Barr virus–transformed B cell lines and that is related to IL-12p40, a cytokine subunit that resembles a soluble receptor and is a component of IL-12 and IL-23 (33). IL-27p28 was recognized as a component of IL-27 based on an in silico search for orphan cytokine-like molecules that could partner with EBI3 (1). Thus, IL-27 is one of four related heterodimeric cytokines composed of a four-α helix bundle subunit (IL-6, IL-12p35, IL-23p19, and IL-27p28) that bind to a soluble receptor-like protein (IL-6Rα, IL-12p40, and EBI3). Within this group, the different subunits can form various homodimers

and heterodimers, and EBI3 also partners with IL-12p35 to form IL-35, a cytokine linked to the activities of regulatory T cells (34, 35). The IL-27p28 subunit has also been reported to bind to cytokine-like factor (CLF) 1 to form a heterodimer that promotes T and NK cell activation (36). Although there is no evidence that IL-27p28 and IL-12p40 can combine naturally, administration of this recombinant heterodimer to mice with experimental autoimmune uveitis resulted in inhibition of Th1 and Th17 cell responses, expansion of T regulatory (Treg) cells, and decreased disease (37).

In current models, IL-27p28 and EBI3 are secreted as a heterodimer, but the observation that IL-27p28 can be secreted independently of EBI3 has raised questions about the biological function of this molecule. Indeed, recombinant IL-27p28 can block the activity of cytokines (IL-6, IL-11, and IL-27) that utilize the type I domain of gp130 to signal (2, 38, 39), and the overexpression of IL-27p28 antagonizes gp130-dependent B cell responses in vivo and can block liver damage, abrogate antitumor responses, suppress graft rejection, and inhibit experimental autoimmune uveitis (37–40). Similarly, mutated versions of IL-27p28 that are unable to interact with gp130 can act as receptor antagonists and limit immune-mediated liver damage (41). Together, these data have led to the proposal that IL-27p28 represents a natural low-affinity receptor antagonist that provides a mechanism to limit cytokine signaling. However, a recent report has suggested that the recombinant IL-27p28 used in some of the previous studies may not have been folded correctly, and when IL-27p28 adopts a more appropriate conformation, it can bind to the soluble IL-6Rα and signal in trans through gp130 homodimers, and, surprisingly, at high concentrations IL-27p28 is able to signal independently of IL-6Rα (42). This literature raises similar questions about whether EBI3 has biological functions of its own, analogous to the ability of the IL-12p40 homodimer to act as an antagonist of signaling through IL-12R. Dissecting the function of these individual subunits from their role as components of IL-27 will not be simple; however, strains of mice that identify the cells producing IL-27p28 or EBI3, or that contain floxed alleles for EBI3 and IL-27p28, will be important tools to help identify the cells that synthesize both of the subunits necessary to produce biologically active IL-27 and those that make the individual subunits. Such identification can help researchers define the effect of the individual IL-27 components on the immune system.

The dominant cellular sources of IL-27 are considered to be myeloid cell populations, which include macrophages, inflammatory monocytes, microglia, and dendritic cells (DCs), although plasma cells, endothelial cells, and epithelial cells express IL-27 (43). A range of microbial (Toll-like receptor–dependent; TLR-dependent) and immune stimuli—including the tumor necrosis factor (TNF) family members CD40 and CD137 (44, 45), as well as the type I and type II IFNs (46–50)—promote the expression of IL-27. The studies that identified these stimuli have led to a model in which early NF-κB signals initiate the transcription of IL-27p28, but when combined with the IFNs promote sustained production of IL-27p28 (**Figure 1*a***); the MyD88-dependent and -independent signaling pathways involved in these events are reviewed in detail elsewhere (51). The observation that during toxoplasmosis DCs are an acute source of IL-12, while a secondary wave of inflammatory monocytes makes IL-27p28, implies that these cells have very different functions during this infection. In contrast, the use of transgenic mice in which *Cd11c-Cre* was used to delete a floxed allele of IL-27p28 identified DCs as a key source of IL-27 in a model of concanavalin A–induced hepatitis (31). These examples suggest that different temporal profiles or cellular sources of IL-27 may determine whether IL-27 affects T cell populations during priming or at sites of inflammation, and questions remain about how the sources of IL-27 impact on the generation and function of activated T cell populations.

There has been interest in understanding the pathways that limit the production of IL-27 and purinergic receptors, and complement pathways have been implicated in this process (**Figure 1*a***). The release of adenosine triphosphate (ATP) from dead cells and local complement activation are

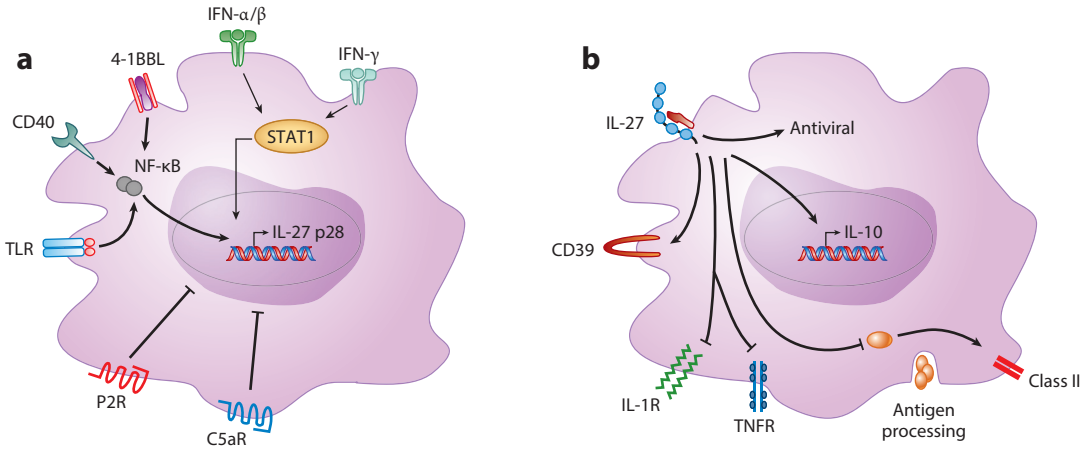

Figure 1

The production of IL-27 and its impact on macrophages and dendritic cells (DCs). (*a*) Pathways involved in the production of IL-27. Signaling through Toll-like receptors (TLRs) or the tumor necrosis factor (TNF) family receptors CD40 or 4-1BBL leads to the activation of NF-κB, which synergizes with the signal transducer and activator of transcription 1 (STAT1) pathway that is engaged by type I and II interferons (IFNs) to promote the transcription of IL-27. These events are antagonized by the ability of adenosine triphosphate (ATP) to bind to purinergic receptors (P2R) and by the binding of the complement cleavage product C5a to the C5aR. (*b*) IL-27 has been linked to multiple biological effects on macrophages and DCs, including the inhibition of viral replication and the downregulation of the receptors for IL-1 and TNF. The ability of IL-27 to upregulate CD39 expression, which can hydrolyze ATP, is associated with the depletion of ATP and reduced inflammasome activation, and IL-27 can also reduce the ability of DCs to present antigen.

characteristic features associated with innate activation at local sites of inflammation, and these pathways are most commonly associated with providing chemotactic signals to attract inflammatory cells. However, whereas the combined enzymatic action of CD73 and CD39 to convert ATP to adenosine is prominently linked to inhibition of inflammation, in vitro experiments have shown that ATP acts through purinergic receptors to limit the production of IL-27p28 (52). Similarly, activation of the complement cascade generates C5a, and ligation of C5aR inhibits IL-27 secretion (53–55). The physiological relevance of these events is illustrated by studies in which mice deficient in C5aR that are treated with pristane to induce lupus nephritis have elevated levels of IL-27 and reduced disease (56). The activation of these pathways could provide a way whereby acute innate responses limit the local production of IL-27, but as a lesion resolves the reduced levels of cell death and complement activation allow the local production of IL-27, perhaps to aid in the resolution of local tissue inflammation and associated damage. However, some of these inhibitory effects of C5a are not specific to IL-27, as IL-12 and IL-23 are also downregulated by this cleavage product; additional studies are needed to evaluate whether there are specific circumstances in which these pathways can preferentially inhibit IL-27.

Composition and Regulation of IL-27R

Although gp130 is considered the main partner for IL-27Rα, there is evidence that IL-27Rα can form homodimers that activate the JAK-STAT pathway associated with the transformation of myeloid cells (57, 58). Early studies that examined tissue expression of the IL-27Rα chain indicated a broad role for this receptor in immune function (5, 59). NK cells express high levels of IL-27Rα, but their activation leads to its downregulation, whereas naive $CD4^+$ T cells express low amounts

of IL-27Rα, but activation leads to increased surface expression. These results suggest that IL-27 has different effects on resting and activated NK and T cells, which may result in different patterns of signaling and biological outcomes. This was illustrated in work that showed that naive and activated $CD8^+$ T cells are responsive to IL-27, but memory $CD8^+$ T cells downregulate expression of gp130 and are rendered nonresponsive to IL-27, and consequently do not produce IL-10 during a secondary response (60).

There appears to be some promiscuity in the ability of IL-27Rα to interact with other surface receptors, and the mitochondrial-derived peptide humanin may also utilize IL-27Rα as part of a complex with gp130 and CNTFRα to promote neuronal survival (61). Whether this activity is physiologically relevant during neuroinflammation is unclear, and the ability to compare mice that lack IL-27p28 or Ebi3 with mice deficient in IL-27Rα should help to define the importance of these pathways in the brain. IL-27Rα has also been reported to form a complex with gp130 and IL-6Rα that allows binding of the p28-CLF heterodimer (36). However, there are conflicting reports on whether the IL-27Rα chain is part of the receptor for IL-35: One report has indicated that IL-35R on T cells is composed of IL-12Rβ2 and gp130 or homodimers of these chains but that it does not require IL-27Rα (62); another has proposed that in B cells the IL-35R is composed of IL-12Rβ2 and IL-27Rα (63). The biology of IL-27R is further complicated by a recent report that T and B cells, as well as macrophages, release a soluble version of IL-27Rα that can block the ability of IL-27 to signal (64). This combinatorial biology remains a fascinating topic that has broad implications for thinking about the effects of IL-27 on the immune system, but one of the biggest challenges faced in this area is the lack of reliable reagents to study receptor expression and the lack of commercial sources of cytokines (IL-27p28, p28-CLF, IL-35) that have robust activity in multiple laboratories. In addition, the crystal structure of IL-27 binding to its receptor remains to be resolved, and this information might inform the development of altered versions of IL-27 that could act as receptor agonists or antagonists, similar to the approaches that have been used to generate an IL-2 superkine with enhanced biological activities (65).

THE ANTI-INFLAMMATORY PROPERTIES OF IL-27

Although early studies on the individual components of the IL-27 signaling cassette led to a focus on the role of IL-27 in promoting Th1-type immunity, there were two keystone studies that highlighted its function in limiting immune hyperactivity. In one report, *Il-27rα*$^{-/-}$ mice infected with *Toxoplasma gondii* efficiently controlled parasite replication, but failed to downregulate the infection-induced $CD8^+$ and $CD4^+$ T cell responses and developed a lethal $CD4^+$ T cell–mediated immune pathology associated with elevated levels of IFN-γ (9). This model has proved useful during the past decade in helping to understand the ability of IL-27 to limit the production of IL-2 and granulocyte-macrophage colony-stimulating factor, inhibit Th17 responses, induce IL-10, and promote a subset of Treg cells specialized to limit Th1 cells (66–70) (**Figure 2**). Similarly, *Il-27rα*$^{-/-}$ mice challenged with *Trypanosoma cruzi* developed exacerbated IFN-γ production and a lethal inflammatory disease (11). However, this is an infection that also promotes a mixed Th1 and Th2 response, and these *Il-27rα*$^{-/-}$ mice also produced enhanced levels of IL-4 that led to an increased parasitemia, an observation that foreshadowed the recognition that IL-27 limits many classes of the Th cell response.

In the setting of helminth infection, IL-27 has emerged as an important negative regulator of Th2 responses, with *Il-27rα*$^{-/-}$ mice exhibiting enhanced resistance to these organisms (12, 71, 72). The molecular basis for the effects of IL-27 on developing Th2 responses has been revealed by studies showing that IL-27 antagonized expression of GATA3, a key transcription factor that promotes Th2 responses (8). With the emergence of the Th17 paradigm, which showed that

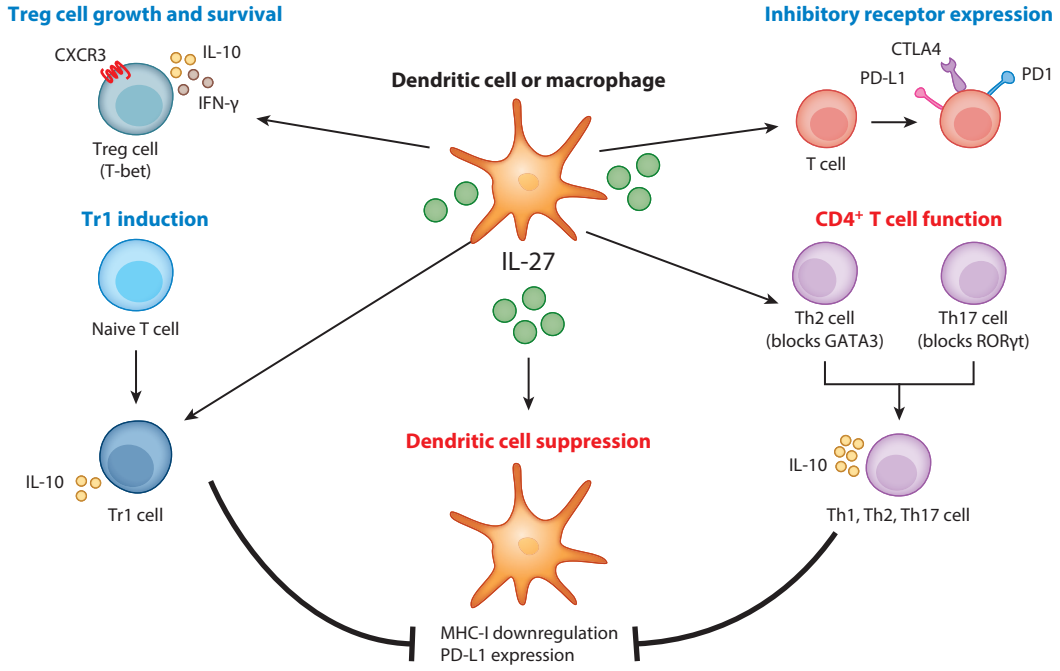

Figure 2

A central role for IL-27 in the control of multiple regulatory activities. IL-27 promotes Treg expression of T-bet and CXCR3 and the induction of Tr1 cells, both of which produce IL-10. IL-27 has also been linked to increasing expression of inhibitory receptors by T cells, antagonizing the development of Th2 and Th17 cell subsets, and promoting their ability to produce IL-10, a potent antagonist of many functions of dendritic cells. IL-27 alone has been reported to inhibit the ability of dendritic cells to present antigen and to promote their expression of PD-L1. Abbreviations: IFN, interferon; MHC-I, MHC class I molecule; Treg, T regulatory.

T cell production of IL-17 contributed to autoimmune inflammatory conditions (73), there has been an interest in defining the signals that promote this T cell subset. Although IL-6 and IL-23 have been shown to support Th17 development (74), their cousin IL-27 emerged as a potent inhibitor of IL-17 production (15, 29, 75, 76). Data from murine models indicate that IL-27 does not affect fully differentiated Th17 cells (67, 75), but for many human lymphocytes it is effective in suppressing the ability of human naive and memory T cells to produce IL-17 (77). Although IL-27 may be a promising therapeutic target for the treatment of pathological Th17 effectors, understanding the effects of IL-27 on developing and existing pathogenic $CD4^+$ T cells will be critical in determining how to tailor its use therapeutically. Nevertheless, the suppressive effects of IL-27 on Th17 cells are dependent in part on STAT1/STAT3 and T-bet signaling, which contributes to reduced expression of RORα and RORγt, two transcription factors involved in Th17 development (23, 29, 67, 78). Further insights into the impact of IL-27 on Th17 cells come from a study that used microarrays to compare the effects of IL-6 and IL-27 on $CD4^+$ T cells (79). This analysis revealed that despite the shared use of gp130 and similar signaling pathways, IL-27 specifically upregulated expression of PD-L1, which allows these cells to act in trans to limit Th17 cells and ameliorate the development of experimental allergic encephalomyelitis (EAE) (79). The PD-1–PD-L1 interaction has emerged as a major mediator of exhaustion in T cells, most prominently in the setting of chronic viral infections and cancer (80, 81), and this work has provided an important link between two apparently distinct mechanisms that limit T cell activities.

IL-27 Promotes IL-10

In models of parasitic diseases, there has been a long-standing recognition that IL-10 has an important role in limiting infection-induced inflammation, and studies in *Il-27rα*$^{-/-}$ mice infected with *T. gondii*, *T. cruzi*, *Leishmania* species, or malaria (9, 11, 14, 21) were reminiscent of the phenotypes observed with these parasites in the absence of IL-10 (82). However, although *Il-10*$^{-/-}$ mice develop spontaneous colitis and display overt susceptibility to cancer (83), this is not the case for mice that lack IL-27 or *Il-27rα*. This difference between mice deficient in IL-10 and those deficient in IL-27 suggests that IL-10 has a prominent role in the homeostatic processes that control the immune response to commensals, whereas both cytokines have a critical role in the setting of systemic inflammation. In addition, the observation that IL-10 mediates its suppressive activities largely through its effects on the function of macrophages and DCs, and that IL-27 may directly inhibit T cells, indicates that these pathways have distinct cellular targets. In 2007, a series of studies in the context of infectious and autoimmune conditions established that IL-27 could activate Th1, Th2, Th17, Treg and Tr1 cell subsets to produce IL-10 (68, 84, 85). The ability of IL-27 to induce a wide range of T cells to produce IL-10 illustrates the plasticity within T cell responses. Since 2007, there have been many more examples of situations in which IL-27 contributes to the development of IL-10-producing T cells (see Translational Implications of IL-27) (15, 19, 22, 60, 76, 86–88).

The ability of IL-27 to promote IL-10 is due to a complex process, and early studies highlighted the role of STAT1 and STAT3 signaling (68) and suggested that these events also require costimulation through the inducible costimulator (ICOS) (89). A more molecular approach showed that IL-27 activates MAPK signaling and induces the AP-1 transcription factor, which promotes IL-21 production that sustains IL-10 expression (89, 90). Furthermore, the ability of the aryl hydrocarbon receptor to partner with c-Maf has been implicated in the optimal production of IL-10 and IL-21 (91). While IL-21 can potentiate some of the activities of IL-27, it is not essential for the production of IL-10 following challenge with *T. gondii* or influenza (60, 92). Although IL-10 is also a potent antagonist of the antimicrobial activities of macrophages, there is also the need to control its production, as exemplified by the studies that showed that the inability of memory CD8^{+} T cells to make IL-10 is linked to the loss of IL-27 responsiveness (60). In addition, IL-27 promotes the expression of two isoforms of metallothionein, proteins involved in metal homeostasis and the regulation of oxidative stress. In the absence of these targets, IL-27 is a more potent activator of STAT3 and induces higher levels of IL-10 (93), but whether this pathway impacts the expression of IL-27R has not been tested. Taken together, these studies identify the existence of networks that limit the ability of IL-27 to drive T cell production of IL-10, but they will also likely be relevant to other properties of IL-27. Indeed, the consequence of aberrant IL-27 production is illustrated by its deleterious effects on hematopoiesis and Treg populations (94, 95).

IL-27 and Treg Cells

The description of the suppressive effects of IL-27 and the observation that Treg cells expressed IL-27Rα brought to light an obvious problem: How does IL-27 intersect with the biology of Foxp3^{+ve} Treg cells, a major arm of the immune system dedicated to the maintenance of tolerance? This is complicated by a literature in which Treg cells can promote DCs that make IL-27, which in turn can promote Foxp3^{-ve} Tr1 cells (84). More direct links of IL-27 to Treg cell biology were provided by reports that IL-27 inhibited the generation of inducible Treg cells in vitro (68, 96, 97), and by in vivo studies in which the absence of IL-27Rα led to increased conversion of Treg cells that ameliorated colitic disease more efficiently than wild-type cells (98). These early works

led to the notion that IL-27 limited Treg activities, and this idea was strengthened by studies in which the transgenic overexpression of IL-27 resulted in the loss of Treg cell populations and autoimmunity similar to the scurfy disease present in mice that lack *Foxp3* (95). In this nonphysiological model, the loss of Treg cells is not due to a direct inhibitory effect of IL-27 on Treg cells, but is most closely associated with the IL-27-mediated suppression of IL-2, an essential factor for Treg cell maintenance. However, mice that lack Ebi3, IL-27p28, or IL-27Rα have normal Treg cell frequencies, and IL-27 does not downregulate Foxp3 expression nor does it antagonize the ability of Treg cells to function in suppression assays (98, 99). As work on this topic has matured, it has become apparent that IL-27 promotes Treg cell growth and survival (32, 69), and studies that have revisited the impact of IL-27Rα in the transfer model of colitis have concluded that IL-27 was required for the expansion of populations of Treg cells (32). Additional insight into the impact of IL-27 on Treg cells has been provided by the identification of a subset of Treg cells associated with intracellular infections that, in response to IFN-γ/STAT1 signals, expressed T-bet and the chemokine receptor CXCR3, which allows these cells to operate in areas of Th1 inflammation (100, 101). IL-27 has now been shown to engage this same STAT1–T-bet transcriptional pathway in Treg cells, and following challenge with *T. gondii*, *L. major*, or *Salmonella*, IL-27 is required for the emergence of a T-bet$^+$, CXCR3$^+$ Treg population at local sites of inflammation, which produce IL-10 and suppress parasite-specific effector responses (69). The idea that IL-27 promotes the activities of Treg cells is reinforced by the observation that IL-27 promotes Treg cell expression of the inhibitory receptors PD-1 and CTLA-4 in collagen-induced arthritis (102). These findings raise new questions about how broadly the effects of IL-27 extend into other tissue-specific Treg cell populations or into those associated with different classes of Th cell responses.

IL-27 PROMOTES T CELL RESPONSES

The section above focuses on the ability of IL-27 to limit inflammation, but IL-27 is also a growth and survival factor for T cells and can positively influence many aspects of their function (1, 32). The finding that IL-27 upregulates T cell expression of lymphocyte function-associated antigen-1, intercellular adhesion molecule-1 (ICAM-1), and sphingosine-1-phosphate but inhibits CCR5 expression (103–105) suggests a need for additional studies to understand the impact of IL-27 on trafficking and behavior of lymphocyte populations. However, the stimulatory effect of IL-27 appears most reproducible in the context of CD8$^+$ T cells, where IL-27 enhances proliferation and the expression of T-bet, EOMES, and IL-12Rβ2 associated with increased production of IFN-γ and cytolytic activity (106–108). The efficacy of IL-27 in promoting the effector function of CD8$^+$ T cells is illustrated by a number of in vivo studies that used different cancer cell lines engineered to express IL-27. In these experiments, IL-27 promoted tumor-specific cytotoxic T cell responses, tumor regression, and, in some cases, complete remission with memory responses to subsequent challenge (109–114).

The impact of IL-27 on CD8$^+$ T cell responses has been confusing in part because of the observation that in many instances when *Il-27rα*$^{-/-}$ mice are challenged with intracellular pathogens, the result is hyperactive CD8$^+$ T cell responses, but in other instances, the expression of IL-27Rα is required for the induction of T-bet and IFN-γ and for optimal CD8$^+$ T cell activity (19, 115). In some of the latter studies, this cell-intrinsic requirement for IL-27Rα was assessed using radiation chimeras, and it is possible that indirect effects of the loss of the IL-27Rα result in less competitive T cell populations. However, there are models in which even outside the competitive setting, IL-27 is required for optimal CD8$^+$ T cell responses (60). A major advance in this area has been the finding that the ability of vaccines that include an adjuvant composed of agonistic anti-CD40

antibodies combined with TLR ligands to elicit $CD4^+$ and $CD8^+$ T cell responses depends on the ability of IL-27 to promote T cell survival (116). These studies are notable because in parallel experiments the authors have shown that IL-27 limits infection-induced $CD8^+$ T cell responses. The dependence of these vaccine-elicited T cell responses on IL-27 has significant translational potential and suggests that IL-27 may be a useful adjuvant itself or that adjuvants that preferentially induce IL-27 may represent a strategy to generate $CD8^+$ T cell memory populations associated with cell-mediated immunity.

Although there have been some contradictory reports about the effects of IL-27 on $CD8^+$ T cells, a common feature of many of these studies is that IL-27 is required for $CD8^+$ T cells to make IL-10. Interestingly, IL-10 can act as a direct inhibitor of $CD8^+$ T cell responses (117), although under other circumstances it is required for optimal $CD8^+$ T cell memory responses (118). At present no reports have been able to distinguish the direct effects of IL-27 on the quantity and quality of the $CD8^+$ T cell response from those effects that might be secondary to its ability to induce IL-10 or IL-21, both of which are growth factors for $CD8^+$ T cells. The dependence on $CD4^+$ T cell help (normally attributed to the production of IL-2) is another variable that affects the generation of optimal $CD8^+$ T cell responses, but it is unclear how the ability of IL-27 to inhibit $CD4^+$ T cell production of IL-2 (66) influences the generation of an effector or memory $CD8^+$ T cell response. Interestingly, IL-12 shares many properties with IL-27, and it is a potent stimulator of $CD8^+$ T cells, is an inhibitor of IL-2 production, and can promote T cell production of IL-10 (119, 120). These shared properties, and the observation that IL-12 and IL-27 are both produced during Th1 responses, raise questions about how their signals are integrated to control $CD8^+$ T cell functions. Differences in the temporal and cellular profiles of their production may dictate which cytokine is most biologically relevant at different points during an immune response. Alternatively, the original concept that the ability of IL-27 to promote Th1 activities is most apparent when IL-12 is limited, whereas during a strong Th1 response the inhibitory activities of IL-27 are prominent (121), may explain some of the context-dependent effects of IL-27.

IL-27 AND HUMORAL IMMUNITY

IL-27 signaling is not required to generate antibody responses in multiple models of infection, allergy, and autoimmunity. The report that the overexpression of IL-27Rα in the MRL/*lpr* mouse model of lupus ameliorated autoantibody responses suggests that IL-27 can antagonize antibody production (6, 24, 122–124). Nevertheless, IL-6 has a key role in directly promoting the Tfh and B cell responses necessary for germinal center (GC) formation (125), and because IL-6 and IL-27 both signal through gp130, it seems likely that IL-27 would have some impact on these events. Indeed, in $CD4^+$ T cells, IL-27 can activate c-Maf and upregulate IL-21 synthesis, events considered critical for Tfh cell responses (89, 126, 127). IL-21 also promotes B cell expression of Blimp-1 and Bcl-6, which are important for plasma cell differentiation and B cell function (128, 129). This axis may be relevant in several in vivo models, including a model of proteoglycan-induced arthritis in which the loss of IL-27Rα leads to decreased IFN-γ, reduced disease, and low levels of proteoglycan-specific immunoglobulin (Ig) G2a (130). In other studies, after immunization of *Il-27rα*$^{-/-}$ mice with ovalbumin linked to the hapten trinitrophenyl (TNP), IL-21 expression was compromised, and these mice exhibited fewer GC B cell antibodies and lower titers of TNP-specific antibody (131). These authors concluded that the differentiation of Tfh cells did not require IL-27, but its ability to induce IL-21 promoted Tfh survival. Similarly, it has been proposed that in the chronic stage of lymphocytic choriomeningitis virus (LCMV) infection IL-27 is not required for the generation of Tfh responses but does

contribute to the long-term survival of virus-specific $CD4^+$ T cells, including Tfh cells (132). These loss-of-function studies suggest a role for IL-27 in promoting Tfh responses, but the interpretation of these data may be complicated by the fact that IL-27 is a negative regulator of IL-2, which is a potent inhibitor of Tfh generation (133–135), and it is possible that the elevated levels of IL-2 detected in the absence of IL-27 influence Tfh responses.

Although B cells were the first identified source of EBI3, these cells are also responsive to IL-27, and various B cell subsets differentially express IL-27Rα and gp130 (136, 137). It is not clear from the studies described above whether the altered humoral responses observed in the absence of IL-27Rα reflect any direct effects of IL-27 on B cells. Indeed, polyclonal stimulation of naive and GC B cells in the presence of IL-27 increases their proliferation, but it does not favor formation of memory B cells (136, 138, 139). IL-27 can also upregulate B cell expression of ICAM-1 and CD86, molecules that promote productive interactions with T cells, and through the ability of IL-27 to activate STAT1 and T-bet in B cells, it can promote the production of IgG2a and IgG1 by human B cells (136–138, 140). IL-17 has also been linked to the survival and proliferation of B cells (141), but whether the ability of IL-27 to suppress IL-17 influences B cell activity is unclear. Despite many in vitro experiments that have directly implicated IL-27 in the control of B cell responses, there is a paucity of studies that specifically address the direct effects of IL-27 on B cells in vivo.

THE ROLE OF IL-27 IN INNATE RESPONSES

The focus of the sections above has been on the impact of IL-27 on T and B cells, but there is increasing evidence that many hematopoietic and nonhematopoietic cells associated with innate immune function are sensitive to the effects of IL-27 (94, 142–145). It has been reported that IL-27 promotes the survival of eosinophils by reducing apoptosis and can facilitate eosinophil adhesion and accumulation in vivo and induce their release of cytokines and chemokines (146). Although in vitro studies have shown that IL-27 enhances the ability of human mast cells to produce IL-1 and TNF (2), the in vivo data indicate that IL-27 can limit the activity of mast cells. Thus, MRL/*lpr* mice that lack IL-27Rα have increased numbers of dermal mast cells (147), and in a model of passive cutaneous anaphylaxis, or when challenged with a helminth, *Il-27rα*$^{-/-}$ mice have elevated circulating levels of mast cell protease (12). Enhanced neutrophil activity has been a common characteristic of the absence of IL-27 in multiple experimental systems, including models of peritoneal sepsis (148) and infection with respiratory syncytial virus (RSV) (149, 150); however, administering IL-27 to mice acutely infected with influenza reduced neutrophil accumulation and was associated with impaired viral clearance (20). Indeed, in mice infected with LCMV, the absence of IL-27Rα results in increased early viremia that may be due to a role of innate cells, but whether this is related to the situation seen with influenza is unclear (132). Regardless, it has been difficult to distinguish whether the exacerbated neutrophil responses that have been observed in the absence of IL-27 signals occur because neutrophils are directly inhibited by IL-27 or occur as a secondary consequence of altered inflammatory responses. For example, IL-17 has a key role in promoting neutrophil responses, and IL-27 can inhibit innate NK and γδ T cell production of IL-17 (151, 152), an activity that could contribute to control of neutrophil responses. Additionally, there have been reports that IL-27 blocks the proinflammatory activities of NKT cells in a model of hepatitis (30), but it can activate NK and NKT activities to promote antitumor responses and to secrete IL-10 (153, 154). This literature emphasizes that many lymphocyte populations associated with innate immunity (NK, NKT, γδ T cells) are sensitive to IL-27, but little is known about whether any of the emerging populations of innate lymphoid cells associated with barrier function are influenced by IL-27.

Although macrophages and DCs can make IL-27, whether these cells have the ability to respond to IL-27 is less clear; **Figure 1*b*** summarizes some of the literature related to this topic. There is evidence for the ability of IL-27 to inhibit murine DCs during leishmaniasis, and in the absence of IL-27Rα, DCs are more potent activators of T cells (155). In agreement with this literature, IL-27 has been shown to promote murine DC expression of CD39, which can deplete extracellular ATP and therefore limit inflammasome activation (156). In other studies, the ability of IL-27 to promote human DC expression of PD-L1 provides another mechanism for suppressing T cell activation (157), and there is evidence that IL-27 cripples the ability of DCs to present antigen (158). There have been reports that resting mouse macrophages are not responsive to IL-27 (159), but others have found that IL-27 inhibits the ability of murine macrophages to produce IL-12 and TNF-α (13). In vitro studies have suggested a complex model in which macrophages treated with lipopolysaccharide produce type I IFNs, which in turn stimulate the synthesis of IL-27 that acts in an autocrine fashion to promote IL-10 (160). Consistent with this observation, the ability of IL-27 to induce type I IFNs can inhibit the replication of HIV in monocytes (161), a process that involves the ability of IL-27 to promote monocyte differentiation into macrophages, which are resistant to HIV (162). IL-27 has also been shown to engage the antiviral responses of macrophages to hepatitis and influenza (163, 164), and this may occur at the level of microRNAs associated with antiviral activities (165). In contrast to these activities, in human macrophages, IL-27 can downregulate the receptors for IL-1 and TNF-α (166) and promote the growth of *Mycobacterium tuberculosis* (16). Some of these findings appear contradictory, and in our own experience, identification of robust effects of IL-27 on murine macrophages and DCs has been difficult. Nonetheless, as examples of the diversity of macrophage and DC subsets increase, knowledge about their unique functions and perhaps even their ability to respond to IL-27 will also increase. This is an area that would benefit from using a systematic approach to define which of these accessory cell populations are directly influenced by IL-27.

TRANSLATIONAL IMPLICATIONS OF IL-27

Multiple reports have shown basal levels of circulating IL-27p28 in humans; these levels are altered in many disease states, including bacterial infections, sepsis, aplastic anemia, and ankylosing spondylitis (167–171). The interpretation of what the changes in levels of IL-27 mean is not straightforward; increased production could indicate causality or simply be a secondary host response to ongoing disease. In many instances, it remains unclear whether available reagents can reliably distinguish the IL-27 heterodimer from circulating IL-27p28, which may make it difficult to interpret these data sets. Nevertheless, with multiple reports finding that IL-27 suppresses human Th17 cell responses and promotes the production of IL-10 (76, 91, 172), it seems obvious that researchers might be able to use IL-27 as a therapy to manage T cell–mediated diseases associated with the overproduction of IL-17 or the absence of IL-10. Indeed, there are many studies in murine models of autoimmune conditions demonstrating that IL-27 treatment can prevent disease, but the opportunity to apply this information to human disease is complicated by the possible negative side effects of altering levels of bioactive IL-27. The loss of IL-27 could lead to hyperinflammation and bystander damage, but treatment with IL-27 could limit protective immune responses. These types of concern are relevant to the clinical use of all recombinant cytokines or cytokine-neutralizing antibodies. Nevertheless, what has emerged during the past five years are links among the murine models and relevant clinical conditions that may help in understanding how IL-27 influences these inflammatory processes. The remainder of this section reviews some of the anatomical sites and human disease states wherein IL-27 has been implicated in limiting or contributing to disease pathogenesis.

IL-27 and Infectious Disease

Murine models of parasitic infections have provided some of the most tractable systems for studying the impact of IL-27 on T cell responses, and there are now reports linking IL-27 to the outcome of these infections in humans. For example, visceral leishmaniasis is caused by *L. donovani*, and in mice challenged with this parasite, the ability of IL-27 to promote T cell production of IL-10 is linked to its ability to limit infection-induced pathology (14). In the clinical setting, leishmaniasis is a spectral disease in which progression is associated with the presence of IL-10, and this is thought to support parasite growth because of its ability to inhibit the microbicidal activities of macrophages (173, 174). In patients infected with *L. donovani*, the observation that circulating levels of IL-27 are elevated and correlate with the production of IL-10 suggests that IL-27 may be a key determinant in the outcome of this infection (87). In murine malaria, endogenous IL-27 promotes IL-10, limits T cell responses, and prevents immune pathology (21, 86), and in malaria patients those with the lowest levels of IL-27 have elevated inflammatory responses and the most severe symptoms (175). In mice infected with influenza, IL-27 promotes $CD8^+$ T cell responses and their production of IL-10 (19, 60), and although human infection is associated with increased IL-27, it is not clear whether this correlates with disease outcome (164). Relatively little is known about the impact of IL-27 on models of fungal infection, but in patients with gain-of-function mutations in STAT1, the enhanced ability of IL-27 to antagonize IL-17 is associated with an increased susceptibility to mucocutaneous candidiasis (176). Taken together, these studies in humans imply that IL-27 is likely operational in these diverse infections, but there is not enough information to determine whether there would be benefits to neutralizing IL-27 to boost the immune response or to use it as a therapy to ameliorate the collateral damage that may accompany these microbial challenges.

Neuroinflammation

Although there are many examples that illustrate how the immune system operates in the brain, this site is still considered immune privileged, and there are many mechanisms that control local inflammatory processes to mitigate the impact of inflammation on the function of the brain. The production of IL-27 and the expression of IL-27Rα have been reported in the central nervous system (CNS) (177); thus, it is tempting to speculate that IL-27 contributes to the local immune privilege. During toxoplasmic encephalitis, IL-27Rα has an important role in limiting brain inflammation, and this role has been linked to the ability of IL-27 to limit Th17 responses and to support IL-10 (67, 68). Similarly, in murine models using the JHM strain of the mouse hepatitis virus, IL-27 promotes IL-10 production, which is required to control CNS inflammation, but in these mice, a failure to clear the virus can lead to more extensive demyelination (17, 18). Although no data sets have indicated how these observations relate to CNS infections in humans, these studies are relevant to other immune-mediated conditions that affect the brain. In murine models of multiple sclerosis (MS), treatment with IL-27 can delay the onset of EAE and ameliorate established CNS disease, and in some models of EAE, the absence of IL-27Rα results in more severe disease (25, 85, 178). These protective effects of IL-27 are associated with the inhibition of pathological Th17 and Th9 responses with and the induction of IL-10 (25, 85, 179). Interestingly, type I IFNs, which are used to treat MS, are potent inducers of IL-27 (48, 180), and the ability of type I IFNs to block disease in EAE depends on IL-27 (181, 182). A clinical correlate of this result was provided by a report that in patients with MS, the ability of type I IFNs to stimulate IL-27 predicts the efficacy of IFN therapy (183). In other words, the clinical efficacy of IFN-β in patients with MS may be attributed to its ability to induce IL-27; therefore, IL-27 may represent an additional therapeutic strategy for managing this condition. However, it remains to be determined whether these

neuroprotective effects of IL-27 are mediated locally within the CNS and/or through events in the periphery that are manifested in the brain. In addition, with the growing recognition that other CNS disorders, such as traumatic brain injury and neurodegenerative states, have an immunological component, there is a good rationale for assessing whether IL-27 may be used to modulate these conditions.

B Cell– and Antibody-Mediated Autoimmune Diseases

B cells and antibodies contribute to disease pathogenesis in a wide range of autoimmune conditions, including rheumatoid arthritis, Sjögren's syndrome, and systemic lupus erythematosus (SLE). Some of the earliest studies showing that treatment with IL-27 might be a useful therapy were performed in models of collagen-induced arthritis, and these protective effects were associated with the inhibition of IL-17 (184, 185). However, in a model of proteoglycan-induced arthritis, endogenous IL-27 promoted a Th1-like response that was associated with elevated antibodies and increased joint damage (130). In the clinical setting, a polymorphism in IL-27p28 has been associated with the severity of rheumatoid arthritis (186), and increased levels of IL-27 have been observed in the synovial fluid of patients with rheumatoid arthritis, which correlates with reduced local levels of IL-17 and IL-6 (184, 187). The literature on Sjögren's syndrome parallels that of arthritis, in that IL-27 can be used to inhibit disease in a murine model (188), and elevated IL-27 is associated with this condition in humans (189). For both of these diseases, it has largely been assumed that the protective effects of IL-27 revolve around its ability to limit Th17 responses; what needs to be determined is whether IL-27 has a direct or indirect impact on pathological B cell responses.

In MRL/*lpr* mice, which have a mutation in Fas and exhibit a spontaneous disease similar to human SLE, the overexpression of IL-27Rα leads to decreased titers of self-reactive antibody and reduced skin disease (190, 191), whereas mice that lack IL-27Rα develop exacerbated disease and more severe skin lesions (147). These data support the idea that IL-27 inhibits autoantibody responses, and this is reinforced by the observation that deletion of *Ebi3* in MRL/*lpr* mice resulted in increased titers of autoantibodies but, incongruously, improved disease scores (192). In a model of pristane-induced lupus there is evidence that links the ability of IL-27 to promote GC responses with increased disease (131), but this conclusion is at odds with work that correlated the presence of IL-27 with less severe disease in the same model (56). This variance in the role of IL-27 in lupus-like conditions may indicate different roles for IL-27 in the distinct models that reflect the spectrum of lupus conditions. A better understanding of the impact of endogenous IL-27 on spontaneous (MRL/*lpr*) models compared with those induced by pristane may inform decisions about how best to target IL-27. One paradox in this area is that SLE is associated with high amounts of type I IFNs (193), which are known to promote IL-27 production. However, in these patients there is a strong inverse correlation between the amount of circulating IL-27 and active disease (194). Insight into this phenotype has been provided by the recognition that C5a inhibits IL-27 synthesis and by the observation that in lupus patients there are elevated levels of C5a that correlate inversely with the amount of circulating IL-27 (56). These observations have led to speculation that reduced IL-27 in some lupus patients allows pathological T and B cell responses to emerge.

IL-27 at Barrier Surfaces

Aberrant T cell responses are characteristic of several diseases that affect the skin, lungs, and gut. Little is known about the role of IL-27 in murine models of skin disease, but in humans with chronic eczema, keratinocytes express IL-27 and respond to IL-27, which triggers increased MHC class I

expression, the production of β-defensin-2, and the production of the chemokine CXCL10 (195–197). In human psoriasis, IL-27 has been associated with disease progression (197–199); in patients with systemic sclerosis, a condition characterized by the abnormal accumulation of collagen and vascular damage in the skin, elevated levels of IL-27Rα are expressed in fibroblasts, and IL-27 promotes fibroblast proliferation and the production of collagen (200). These observations may indicate a role for IL-27 in tissue repair (a topic not yet addressed experimentally), but in these conditions this response is dysregulated.

Many studies have considered the impact of IL-27 on inflammation in the gut and have used chemically induced models of Crohn's disease (CD) or inflammatory bowel disease, often with apparently contradictory outcomes. Thus, *Ebi3*$^{-/-}$ mice are more resistant to oxazolone-induced colitis (4); similarly, mice deficient in IL-27Rα that are treated with a low dose of dextran sodium sulfate (DSS) have reduced disease (201). These two reports indicate a proinflammatory role for IL-27 in the gut. In contrast, *Il-27rα*$^{-/-}$ mice given a high dose of DSS develop more severe colitis that is associated with elevated Th17 cell activity (26); and in a model of acute colitis induced by 2,4,6-trinitrobenzene sulfonic acid (TNBS), treatment with IL-27 can ameliorate disease (202). The ability of IL-27 to stimulate intestinal epithelial cells to express the scavenger receptor DMBT1, which can act as an antimicrobial peptide (203), may help to explain the beneficial role of IL-27 in the maintenance of barrier function. Although evidence links a single-nucleotide polymorphism (SNP) in IL-27 to inflammatory bowel disease, no studies have examined how this SNP influences levels of IL-27 (204). The most comprehensive study in this area utilized genome-wide association studies and high-density SNP analysis of a pediatric cohort and identified *IL-27p28* as a candidate gene for susceptibility to CD (205). This SNP correlated with reduced IL-27 production (205), consistent with the idea that IL-27 (or IL-27p28) may play a role in limiting inflammation in the gut. Together with a recent report that the IL-27Rα chain can be shed and that serum levels of sIL-27Rα were elevated in patients with CD (64), it is possible that IL-27p28 or sIL-27Rα may be useful as biomarkers for disease progression. It should be noted that the bacterium *Citrobacter rodentium* had the ability to induce inflammation in mice deficient in IL-10, but this effect was ameliorated by IL-27 (206). This finding provides evidence that, in addition to its ability to induce IL-10, IL-27 has other suppressive effects in the gut, further strengthening the rationale for using IL-27 to treat these conditions. Indeed, the bacterium *Lactococcus lactis* has been engineered to express IL-27, and in a model of colitis, it has shown significant protective effects (207).

The lungs represent another important barrier surface, and in murine models of asthma the absence of IL-27Rα results in exacerbated lung pathology that is characterized by goblet-cell hyperplasia, infiltration of eosinophils, elevated serum IgE titers, and airway hyperresponsiveness (28, 122, 124). During the induction of experimental asthma, endogenous IL-27 or treatment with IL-27 can limit Th2 responses and protect against lung inflammation, an effect that has been linked to the ability of invariant NKT cells to produce IL-27 (28, 124, 208, 209). This Th2-like asthma appears distinct from steroid-resistant asthma, which is associated with a Th1-like response and increased numbers of neutrophils. Interestingly, treating mice with IL-27 and IFN-γ in the lungs leads to a condition characterized by airway hyperresponsiveness that is not affected by glucocorticoids (210). The different role for IL-27 in antagonizing or promoting asthmatic inflammation is clearly model dependent and illustrates the pleiotropic effects of this cytokine on a single tissue.

The report that IL-27 can directly activate human bronchial epithelial cells associated with increased expression of ICAM and cytokine production indicates a broad role for IL-27 in the lungs (211). There is clear evidence of increased expression of IL-27 in the lungs in the context of human tuberculosis, influenza, and sarcoidosis, in chronic obstructive pulmonary disease, and in neutrophilic asthma (164, 210, 212, 213). One of the first SNPs identified in *IL-27p28* was

linked with susceptibility to asthma, increased IgE, and eosinophilia (214); similar links have been reported for polymorphisms in *IL-27p28* in chronic obstructive pulmonary disease and rhinitis (215, 216). As noted above, IL-27 has a role in controlling inflammation in several viral infections that affect the lung, in particular respiratory syncytial virus (RSV). It is now recognized that even after these challenges (notably RSV) are cleared, they have established an environment that promotes the long-term development of asthmatic inflammation. As IL-27 has already been linked to preventing Th17 responses and to producing mucus during RSV infection (149), there should be interest in understanding whether the impact of IL-27 on the response to infection, or at a later time, influences this progression.

IL-27 and Cancer

Given the contributory role of inflammation to the development of cancer, and in particular the links to the IL-23–Th17 axis (217), it seems likely that IL-27 may impact the immunological processes that contribute to these events. Indeed, there are reports that IL-27Rα expression on different tumor cell lines is associated with the inhibition of effector responses and the promotion of tumor growth (143). However, there is a well-developed literature that shows that IL-27 can be used to promote antitumor immunity mediated by NK, NKT, and $CD8^+$ T cells (109, 111–113). Tumor cell expression of IL-27Rα has also been associated with the ability of IL-27 to increase the expression of MHC class I–related chain A, a ligand for NKG2D, an activating receptor expressed on NK and $CD8^+$ T cells that promotes cytotoxicity (142). IL-27 can also inhibit the growth of leukemic B cells and has antiangiogenic properties (218–221) that can limit tumor growth. The anticancer properties of IL-27 have been illustrated in studies in which B16 melanoma expression of IL-27Rα slowed tumor growth, whereas mice deficient in IL-27Rα were more susceptible to this challenge (114, 144). In other models of carcinogen-induced fibrosarcoma and oncogene-driven mammary cell carcinoma, mice that lack IL-27Rα have an increased incidence of disease, which has led to the suggestion that IL-27 promotes immunity against endogenous tumors (222). The literature indicates that IL-27 has a direct inhibitory effect on some tumor cells and that it can promote antitumor surveillance.

In patients with breast cancer, elevated levels of IL-27 are associated with disease progression (223), and in human patients with acute myeloid leukemia the ability of IL-27Rα to dimerize has been linked to transformation (58). However, IL-27 can have a direct inhibitory effect on tumor cells, even in the context of acute myeloid leukemia (224, 225). The studies described above appear contradictory, with IL-27 promoting the growth or the killing of tumors, but these effects are likely context dependent and may be shaped by the individual tumor microenvironment, how the cancer cells have evolved to evade the immune system, and the degree to which inflammation underlies the development of different types of cancer. Lastly, there is an increasing appreciation of the role of inhibitory receptors in promoting immune exhaustion in cancer; the observation that IL-27 induces PD-L1 and PD-1 (79, 102) implies that IL-27 may be an important molecule in controlling immune checkpoint mechanisms that are relevant to cancer.

CONCLUSIONS AND FUTURE DIRECTIONS

One of the challenges that the field now faces is to determine whether IL-27 can be manipulated to be used therapeutically to modulate inflammation that occurs during various human disease states. For example, IL-27 or agonists of IL-27R could be used directly to limit tissue damage; additionally, the effects of IL-27 on $CD8^+$ T cells suggest that this cytokine may be useful as an adjuvant to promote $CD8^+$ T cell responses, which has been a long-term goal of the vaccine

community. One difficulty in this area is making decisions about which diseases to target and the type of intervention that would be most appropriate. Many of the human studies described above help to synthesize how the immunobiology of IL-27 may be translated, but there is now a wealth of experience with host-targeted therapies that may also be useful. Thus, IL-27 may useful as a therapy or as an adjunct for treating those conditions where antagonists of IL-6, IL-17, and IL-12p40 have been effective (i.e., pathways linked to Th17 cells), but in conditions where these antagonists have had limited efficacy, the use of IL-27 may not be the most attractive strategy.

There has been a profound evolution in our understanding of the immunobiology of IL-27: from the initial studies that described it as a driver of Th1 cell responses to realizing that it is a factor that engages multiple lymphocyte populations to participate in a program of diverse regulatory mechanisms that prevent immune hyperactivity (**Figure 2**). In particular, the abilities of IL-27 to antagonize Th17 populations while promoting IL-10 expression are common themes in many experimental and clinical settings. Additionally, the abilities of IL-27 to promote the expression of PD-1 and PD-L1 and to activate Treg cells indicate that IL-27 acts as a regulatory hub that coordinates multiple regulatory pathways; thus, this may strengthen the rationale for targeting this cytokine therapeutically. Models of infectious and autoimmune systems continue to identify new effects of IL-27, but IL-27 is implicated in disease outcome in other areas—such as metabolic diseases (226, 227) and diabetes (228, 229)—that are relatively unexplored. Regardless, there is still a need to better understand the context-dependent functions of what IL-27 does to T cells to promote regulatory activities versus inflammatory functions, and there remains a need for data sets that utilize genomic approaches to further our understanding of the impact of IL-27 on different immune populations.

DISCLOSURE STATEMENT

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