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Review Article

IL27: Its Roles in the Induction and Inhibition of Inflammation

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Abstract: IL27 is the newest member of the IL6/IL12 family. It consists of Epstein-Barr virus-induced gene 3 (EBI3) and p28 subunits and signals through the IL27 receptor complex formed by WSX-1 and gp130 subunits. IL27-IL27 receptor interaction was initially shown to induce an early signal for the induction of Th1 responses. Recently other studies indicate that IL27 inhibits inflammatory Th17 lineage development. Despite the overall effects observed, the role of individual IL27 subunits remains controversial and is largely unclear. EBI3, while predominately found with p28 to form IL27, has different expression kinetics than p28. P28 has also been shown to signal independently of EBI3. Moreover, EBI3 has other potential binding partners such as the p35 subunit of IL12 and theoretically may regulate the inflammatory response through yet undiscovered mechanisms. Understanding the inflammatory and anti-inflammatory roles of IL27 and its subunits are essential before the immunological regulatory therapies can be developed.
Key Words: IL27, IL6, IL12, inflammation, induction, inhibition

Introduction

Interleukin-27 (IL27) is a recently discovered cytokine belonging to the IL6/IL12 cytokine family [1]. Due to the heterodimeric nature of these cytokines and their receptors, studies on the IL12 family members have generated exciting stories to follow. Early studies of IL12 (p40/p35) based on the elimination of the p40 subunit yielded conflicting results. Not until the discovery that the p19 subunit of IL23 also binds p40 were the conflicting results resolved into a reasonable model [2]. Subsequent research on p19 or p35 knock out mice further helped resolve the conflicting data [3, 4].

IL27 plays a role in the innate as well as the adaptive immunity. In adaptive immunity, IL27 was shown to synergize with IL12 to promote IFNγ production by CD4, CD8 T cells and NKT cells [5-7]. IL27 was also identified as an early initiator of Th1 differentiation [8]. In innate immune, IL27 was demonstrated to induce the production of IL1, TNFα, IL18 and IL12 in monocytes, and IL1 and TNFα in mast cells [9]. Recent studies have revealed that IL27 inhibits differentiation of Th17 cells [10-12]. This review focuses on the subunits of IL27, IL27 receptor and their roles in diseases models.

IL27 (p28/EBI3)

IL27 is a heterodimeric cytokine comprised of p28 and Epstein-Barr virus-induced gene 3 (EBI3) subunits [7] (**Figure 1A**). EBI3 was initially described as being expressed in B lymphocytes infected by Epstein-Barr virus [13]. It is homologous to IL12p40 subunit with 2 fibronectin-3 motifs, placing it in the hematopoietin receptor family. EBI3 is known to exist in three forms, homodimer [14], p35 heterodimer [15], and p28 heterodimer [7]. EBI3 is expressed in lymphoid blasts of reactive lymphoid organs [17, 18]. In the light zone of germinal centers, EBI3 is secreted where B cells can be found in association with

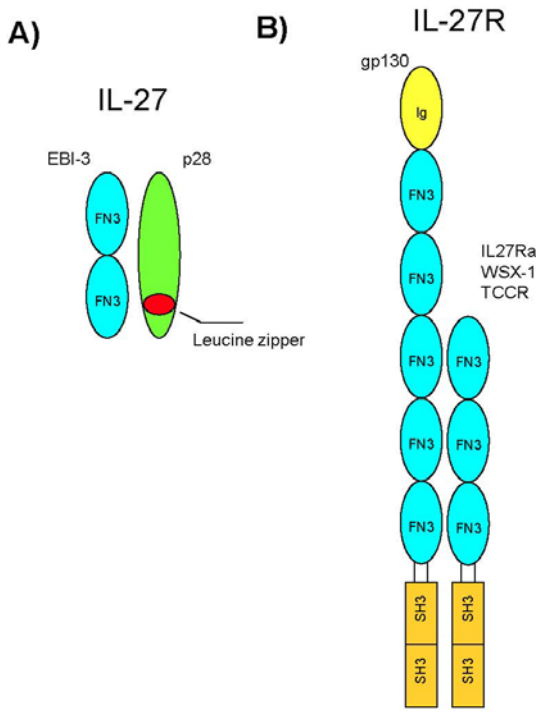

Figure 1 IL27 and IL27 receptor. **A**. IL27 is comprised of two subunits, EBI-3 and p28. EBI-3 has two fibronectin type 3 domains, and p28 has a leuicine zippper motif. **B**. IL27R is comprised of gp130 and IL27Rα. gp130 belongs to the IL6 receptor family. IL27Rα is also called WSX-1 or TCCR. Both chains have intracellular signaling domains.

CD3+ T cells [19]. A splice variant of EBI-3 has been recently found and expressed in the spleen, liver and kidney [16]. The expression pattern of EBI3 reveals that EBI3 has important functions in the immune system. It has been suggested that free EBI3 or EBI3/p35 might be an antagonist to IL12 family signaling [20], but this role has yet to be confirmed.

P28 is related to the IL12p40 subunit [7], containing a long-chain four-helix bundle typical of the IL6/IL12 family. P28 contains a leucine zipper motif indicative of homo-or heterodimerization. P28 is normally found to be co-expressed with EBI3 in activated macrophages and dendritic cells, forming a non-covalently linked heterodimer [7, 17, 21]. In the normal central nervous system (CNS), IL27p28 and EBI3 are detected at very low levels if at all [22]. But in the brain during chronic toxoplasmic encephalitis, EBI3 levels were increased by 3 folds while p28 increased 500 folds. Furthermore, in response to lipopolysaccharide (LPS) and IFNγ induction, the expression of p28 increased more than 2000 folds while EBI3 levels remained unchanged [10, 23]. In viral-transformed neoplastic cells, there is a dissociated expression of EBI3 and p28 in which EBI3 is expressed while p28 is not [19, 21]. EBI3 was up-regulated during the induction of septic peritonitis, but returned to normal levels within 20 hours, while p28 remained elevated [24].

IL27 Receptor (gp130/IL27Rα)

Class I cytokine receptors are usually comprised of α and β heterodimers. The α subunit is the primary cytokine binding protein, while the β subunit is for high affinity binding and signal transduction. IL27 receptor (IL27R) is comprised of two signaling molecules, IL27Rα and gp130 (**Figure 1B**).

IL27Rα, also know as WSX-1 or TCCR, has 2 tyrosine residues that can be phosphorylated in humans. In mice it has 3 tyrosine residues, one of which is conserved. Human IL27Rα has 63% sequence match with murine IL27Rα. Human IL27Rα contains 7 N-linked glycosylation sites, while murine IL27Rα has only 5. IL27Rα is very similar to IL12β1R in that it also lacks an Ig domain, indicating that

IL12βR1 might also be a signaling partner with gp130 [25].

GP130 subunit belongs to the IL6 receptor family and is shared by many other cytokine receptor partners such as IL6, IL11, CT-1, CNTF, LIF, and OM [26]. IL6 signaling through gp130 is well understood. IL6 first binds to IL6R and then dimerizes with gp130 to induce signal transduction in leukocytes and hepatocytes [27]. A soluble form of IL6R also exists which can bind IL6 and trans-signal through gp130 on non-immunological cells [28]. Soluble gp130 can effectively block trans-signaling in this IL6 pathway [29]. Experiments that utilized soluble gp130 to block signaling through IL27Rα suggest that IL27Rα is not expressed in a soluble form [30].

Both IL27Rα and gp130 receptor subunits have signaling domains, but they do not signal independently [31]. IL27Rα expression is found in naïve and memory B cells but not in germinal center B cells [32]. Alternatively activated macrophages, induced by IL4 and IL13, express IL27Rα while classically activated macrophages do not [33]. In naïve T cells, IL27Rα expression is low. Its expression is high in effector and memory T cells. IL2 suppresses the expression of IL27Rα nn activated CD4 T cells in a dose-dependent manner [34]. Resting NK, NKT, and TReg cells express high levels of IL27 receptors. Upon stimulation, naïve T cells greatly enhance the expression of IL27Rα, while NK and NKT reduce IL27Rα expression [34].

IL27 Signal Transduction

Engagement of the IL27 receptor recruits several Jak family kinases, which induces phosphorylation of STAT1 and STAT3 [35]. Some evidence indicates that STAT2, STAT4 and STAT5 are phosphorylated as well [32, 36-38]. In activated T cells, IL27 predominantly signals through STAT3 [23], while in memory B cells it signals predominately through STAT1 [32]. It has been shown that IL27Rα co-precipitates with JAK1 and STAT1 interacts with the conserved Y609 residue [36]. IL27 signaling induces Tbet expression in T cells in a STAT4-independent manner, which results in up-regulation of IL12Rβ2 expression even

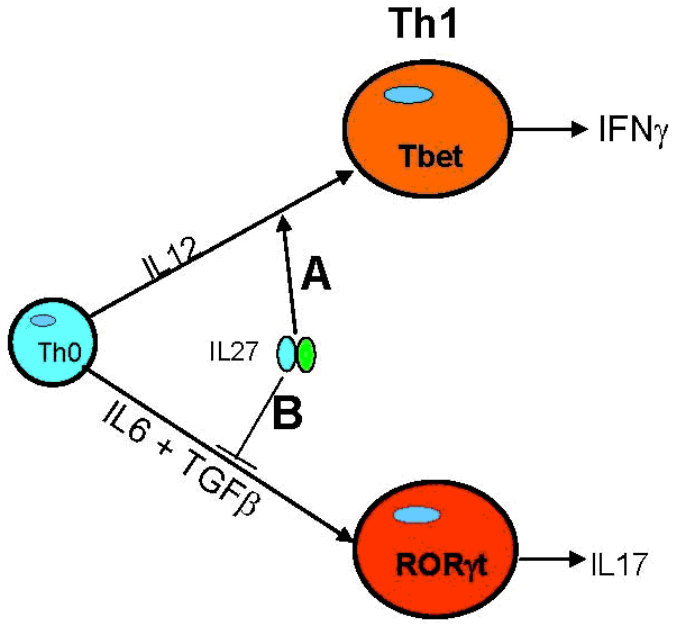

Figure 2 IL27 promotes Th1 but inhibits Th17 cell differentiation. **A**. IL27 promotes näive T cells (Th0) to differentiate into Th1 effectors characterized by expression of transcription factor Tbet and IFNγ. **B**. IL27 inhibits CD4 T cell differentiation into Th17 effectors characterized by expression of transcription factor RORγt and IL17. This model is largely based on the results obtained from IL27Rα$^{-/-}$ mice.

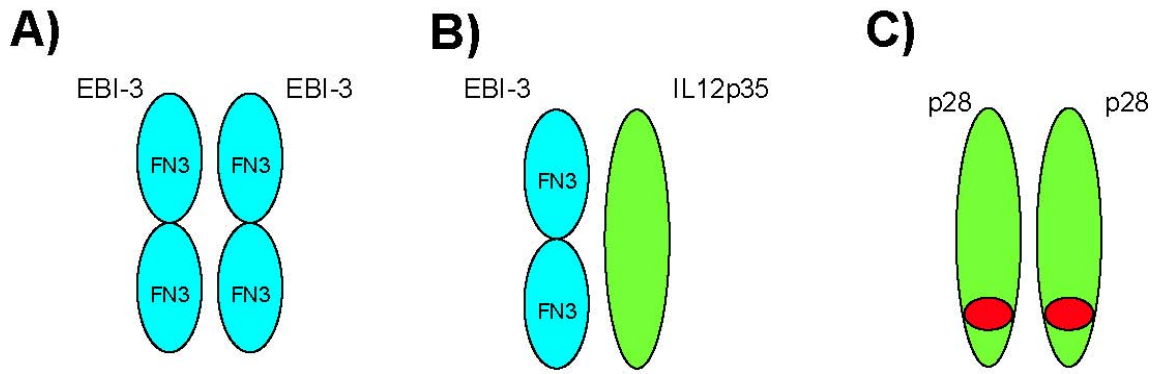

Figure 3 EBI3 and p28 associations other than IL27. **A**. EBI3 exists as a homodimer but its function is not yet known. **B**. EBI3 is associated with IL12p35 and is expressed during human pregnancy by syncytial trophoblasts. **C**. p28 has a leucine zipper motif and can homodimerize with each other.

under Th2-inducing conditions [39]. It is known that IFNγ production through Tbet is modulated by estrogen [40]. IL12 does not synergize with estrogen, but IL27 does to induce IFNγ [41]. IL27 induces granzyme B and perforin production in CD8 T cells in a STAT1-dependent, but Tbet-independent manner [42]. In mature B cells, IL27 induces Tbet expression, IL12Rβ1 up-regulation, and class switch recombination (CSR) [38]. IL27 induces phosphorylation of STAT1 and subsequently blocks IL4-dependent CSR to IgG1, and induces IgG2a independent of IFNγ [38].

In Vivo Functions of IL27-IL27R Interaction in Inflammation

A number of studies support a proinflammatory role of IL27 in pathogen-induced or autoimmune inflammation models. p28 blockade resulted in suppression of ongoing adjuvant-induced arthritis [43] and experimental autoimmune encephalomyelitis (EAE) [44]. However, these results were challenged by later studies using blocking antibodies and IL27Rα$^{-/-}$ mice [1, 11]. WSX-1$^{-/-}$ mice show impaired IFNγ production and are susceptible to intracellular pathogens, such as *Leishmania major* and *Listeria monocytogenes* which are best combated by Th1 responses [5, 6]. Th1-mediated clearance of *Mycobacterium tuberculosis* and resistance to the disease are dependent upon the production of IFNγ and WSX1-/- mice had prolonged bacterial clearance [45]. WSX-1$^{-/-}$ mice show a skewed profile towards Th2 in response to infection by *Trichuris muris* [9, 46] and exhibit enhanced asthmatic phenotypes [47]. Interestingly, a p28 polymorphism (964A>G) in a Korean population was shown to be associated with susceptibility to asthma [48]. WSX-1$^{-/-}$ mice have also been shown to be less susceptible to experimental autoimmune uveitis [49], another T cell mediated autoimmune disease model.

A number of other studies also reported inhibitory roles of IL27-IL27R interaction in inflammation. Infection of EBI3$^{-/-}$ mice resulted in a massive infiltration of neutrophils and macrophages that resulted in a faster clearance of bacteria in a septic peritonitis model [24]. *Toxoplasma gondii* infection in WSX-1$^{-/-}$ mice generated a robust Th1 response. However, these mice succumb to an acute lethal CD4 mediated inflammatory disease [10]. WSX-1$^{-/-}$ mice mount a robust Th1 response to *Listeria donovani* and control parasite burden faster than WT mice; but the mice still suffer significant liver damage and diffuse inflammation [50]. WSX-1 deficient mice are hypersusceptible to EAE [11].

In inflammation models such as EAE, the IL17-producing CD4 T cells (Th17) have been identified as being better correlated with the severity of the disease than the Th1 subset [51, 52]. The Th17 subset is characterized by the expression of transcription factor RORγt [53] and cytokines including IL17A, IL17F, IL6, TNF, and GM-CSF, but not IFNγ or IL4. TGFβ and IL6 induce Th17 lineage of cells, which then become responsive to IL23 by expressing IL23 receptor [54, 55]. Recent studies suggest that Th17 response during inflammation is critically suppressed by IL27 [10-12] (**Figure 2**). We have recently found that EAE can be

induced in EBI3$^{-/-}$ mice; however we did not observe significant difference between wild type and EBI3$^{-/-}$ mice in Th17 response (our unpublished observations). Thus, considerable conflicting data still exists in the field and more research is required to delineate the role of IL27 in inflammation.

Concluding Remarks and Future Perspective

IL27 is comprised of p28 and EBI3 subunits that functions through interaction with IL27R. IL27 has been shown to have both pro-inflammatory and anti-inflammatory properties. Recent studies revealed that IL27 signaling inhibits the generation of Th17 lineages of cells. Since p28 and EBI3 can be independently expressed (**Figure 3**), one should be careful in interpreting the results of IL27 studies. For instance, opposing results were obtained when studying IL27 subunit P28 and its receptor subunit WSX-1, suggesting different partners may have different functions as shown in the IL12/IL23 case. Future experiments using P28 or EBI3 knockout mice are required to resolve these conflicting results.

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