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Review

Biology of IL-27 and its Role in the Host Immunity against *Mycobacterium Tuberculosis*

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Abstract

IL-27, a heterodimeric cytokine of IL-12 family, regulates both innate and adaptive immunity largely via Jak-Stat signaling. IL-27 can induce IFN-γ and inflammatory mediators from T lymphocytes and innate immune cells. IL-27 has unique anti-inflammatory properties via both Tr1 cells dependent and independent mechanisms. Here the role and biology of IL-27 in innate and adaptive immunity are summarized, with special interest with immunity against *Mycobacterium tuberculosis*.

Key words: IL-27; IL-27Rα; IL-12 family; *Mycobacterium tuberculosis*; Immunity

Introduction

Tuberculosis remains a leading cause of death worldwide which afflicts approximately one-third of the world's population and claims a death toll around 1.2 million annually [1].

*Myc*obacterium tuberculosis (*Mtb*) is an unusual facultative intracellular pathogen which multiplies within macrophage [2]. Macrophages are crucial for the innate and adaptive immune response to *Mtb* because of their potent antimicrobicidal activities, antigens-presenting abilities, secretion of inflammatory mediators such as the IL-12 family of cytokines [3, 4], and their role in granuloma formation to control the pathogen [5-7]. However, *Mtb* can persist within granuloma lifelong without clinical symptoms [3, 4, 8]. In-depth understanding of the underlying molecular mechanisms can inspire better drug design and treatment of TB.

The interleukin-12 (IL-12) family, including IL-12, IL-23, IL-27 and IL-35, are important for TB pathogenesis and control, which can regulate the Th1 response [9, 10].

Interleukin-27 (IL27) was first discovered in 2002 as a new member of the IL-12 cytokine family [11]. It is a heterodimer, comprised of p28 and EBI3 subunits that are structurally similar to the p35 and p40 subunits of IL-12 [12].

IL-27 is largely secreted from activated antigen-presenting cells (APCs) such as macrophages and Dendritic cells (DCs) [13-15] (Figure 1). The receptor of IL-27 consists of two subunits: IL-27Rα and gp130. Both subunits are essential [16-18] for activating Janus Kinase (Jak) and Transcription factor (Stat). Specifically, Stat1and Stat 3 are predominant mediators of IL-27 effects (figure 2) [19, 20]. IL-27 can mediate Th1 cells differentiation and proliferation [17, 18]. IL-27 has potent antitumor activities by activation of cytotoxic T lymphocytes CD8+ T cells [21-25], Natural killer (NK) cells [26-28], NK T cells [28] and anti-angiogenic factors [29, 30]. However, IL-27R signaling was demonstrated to be involved in the potent antagonizing of Th1, Th2 and Th17 inflammatory responses [31-33] and agonist of Tr1 cell response [34, 35]. IL-27 can ameliorate symptoms of autoimmune diseases in preclinical studies [33, 36, 37].

The expression level of IL-27 in granuloma suggested a role in tuberculosis [38]. The elevated level of IL-27 in tuberculous pleural fluid suggested a potential biomarker for tuberculous pleurisy diagnosis [39, 40]. IL-27 level might be manipulated to benefit pathogen [41-43].

Molecular characteristics of IL-27

IL27 is a heterodimeric cytokine consisting of p28 and Epstein-Barr virus induced gene 3 (EBI3) subunits [16, 44]. EBI3 expression is high in human B lymphoblast cell lines transformed *in vitro* by EBV, activated APCs and placental syncytiotrophoblasts [16, 45]. EBI3 is a 34-kDa glycoprotein similar to the p40 subunits of IL-12 [46]. The EBI3 reversibly binds to IL-12p35-related subunit, namely p28, to form heterodimeric cytokine IL-27[46, 47]. The connection between p28 and EBI3 is labile and these subunits can be secreted independently [16]. EBI3 is also capable of binding to the IL-12p35 to form IL-35 [48]. The human p28 gene encodes a 24.5kDa polypeptide [16]. The p28 is structurally similar to an IL-6/IL-12 family, composed of a long chain of four α helix bundle named A–D from the N terminus to the C terminus[49]. The polypeptide loop connecting the p28 C and D α helices contains a stretch of polyglutamic acids (poly-E) unique among helical cytokines and is highly conserved [50]. The p28 alone can suppress IL-27 mediated Th1 responses [51] and IL-6 mediated signaling [52]. These data suggest a regulatory role of p28 in IL-27-mediated immune response.

A polymorphism (-964A>G) in the p28 promoter has been noted in certain diseases such as asthma [53], inflammatory bowel diseases [54], chronic obstructive pulmonary disease[55], and epithelial ovarian cancer [56], which seems to be associated with an increase in disease susceptibility. However, the effects of SNPs on the expression of IL-27 remain elusive.

IL-27 is mainly produced by activating APCs such as DCs and macrophages (figure 1). Macrophages-stimulated with TLRs agonists, (polyinosinic: polycytidylic acid (poly (I:C)), Lipopolysaccharide (LPS), or R848 can induce both subunits of IL-27 [13]. It has been reported that p28 production is completely dependent on the TLR4-associated myeloid differentiation factor 88 (MyD88) mediated pathway and partially dependent on NF-κBc-Rel transcription factor [14]. MyD88 also regulates p28 expression through binding of AP-1/c-Fos to the p28 promoter in both human and mouse macrophages. However, the binding of c-Fos to the p28 promoter can be blocked by overexpression of p38 MAPK [57]. In addition, TLR4 can induce the expression of p28 subunit through activating the TIR domain-containing adaptor inducing IFN-β (TRIF) and IFN regulatory factor 3 (IRF3) pathways [58]. TLR2, TLR4, and TLR9-associated MyD88 are required for the induction of EBI3 expression through binding of NF-kB subunits (p50/p65) and PU.1 to the EBI3 promoter [59].

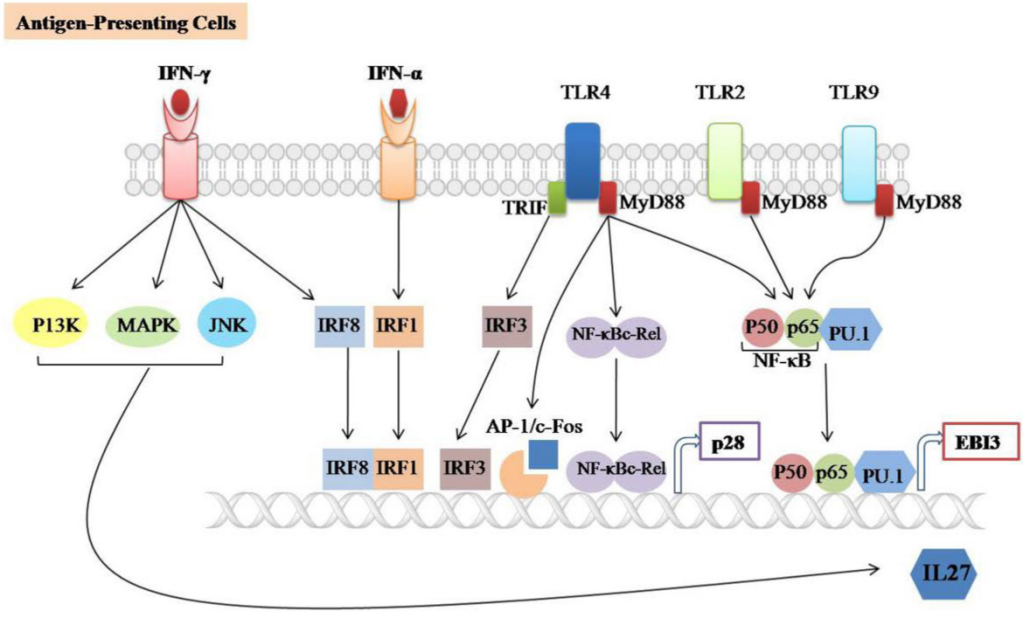

Figure 1. Signaling involved in IL-27 expression. IL-27 is largely produced by Antigen-presenting cells (APCs) such as Dendritic cells (DCs) and macrophages upon stimulation with TLRs agonists, IFN-α, IFN-γ or microbial infections. It consists of two subunits (p28/EBI3) which are expressed independently. TLR2, TLR4 and TLR9-associated MyD88 can induce EBI3 expression through the binding of NF-κB subunits (p50/p65) and PU.1 to the EBI3 promoter. TLR4-associated MyD88 induces p28 expression through binding of NF-κB-c-Rel and AP-1/c-Fos to the p28 promoter, TLR4-associated TRIF induces p28 expression by binding of IRF3 to the p28 promoter. The IFN-α and IFN-γ induces p28 expression through the binding of IRF3 and IRF8 to the p28 promoter, respectively. In addition, IFN-γ-mediated IL-27 instead of IL-27p28 gene expression is positively regulated by the C-Jun N-terminal kinases (JNK), mitogen-activated protein kinases (MAPKs) and the phosphoinositide 3-kinase (PI3K).

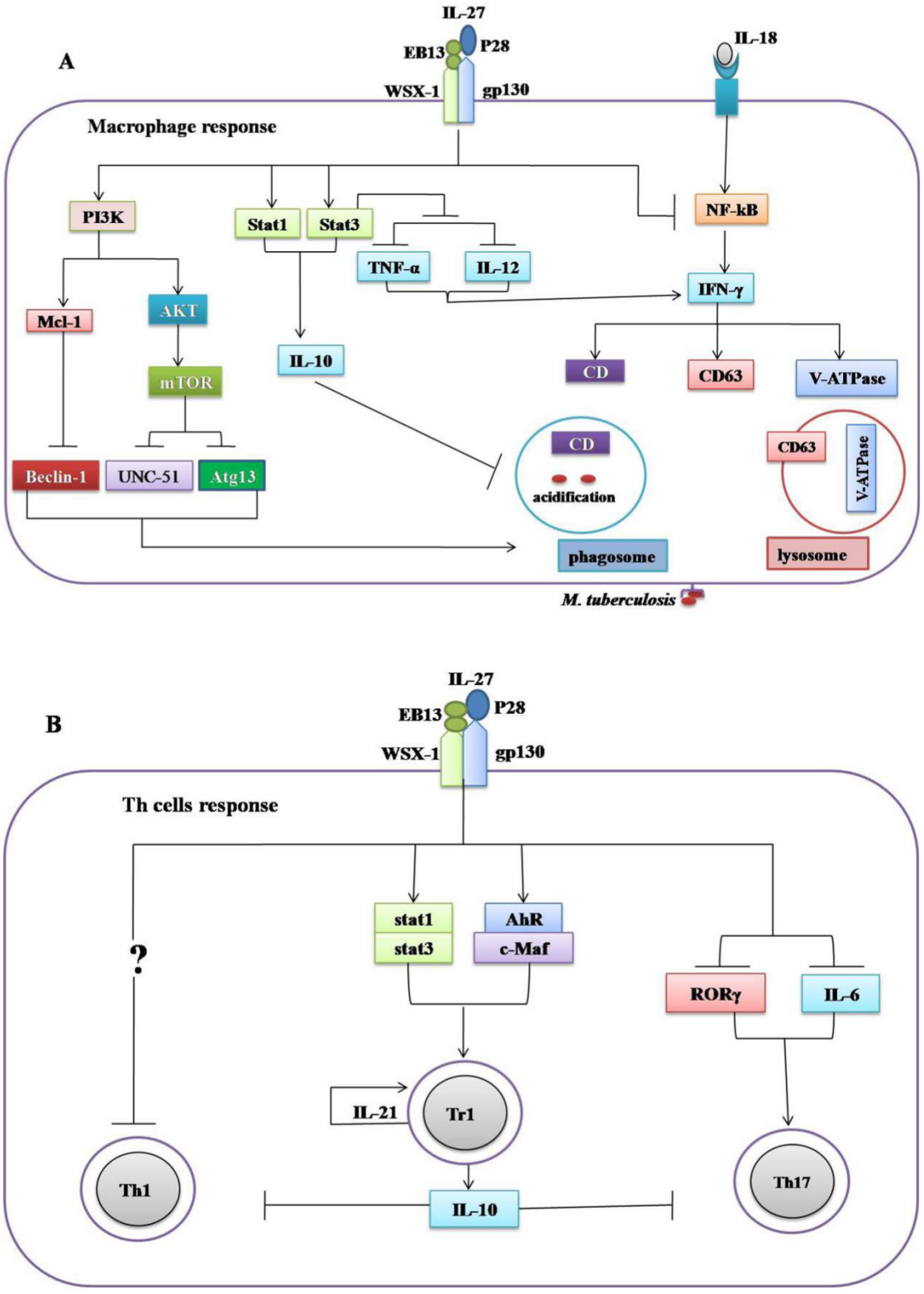

Figure 2. Regulatory role of IL-27 in the immune response against Mycobacterium tuberculosis. (A) IL-27 induced by *Mtb* infection modulates macrophage response. IL-27 inhibits autophagy by inducing negative regulator factors of autophagy mTOR and Mcl-1 through PI3K/AKT and PI3K, respectively. IL-27 induces IL-10 production through Stat1/Stat3, which in turn blocks phagosomal maturation. It also suppresses TNF-α and IL-12 via Stat3 and both cytokines required for augmenting IFN-γ production by macrophages. In addition, IL-27 targeting NF-kB to inhibit IL-18 mediated IFN-γ production. Suppression of IFN-γ led to down-regulation of V-ATPase and CD63 and Capethsin D (CD) and subsequently suppression of phagosomal acidification. (B) IL-27 induced IL-10-producing type 1 regulatory T cells (Tr1) cell via Stat1/Stat3 and AhR/c-Maf pathway, which in turn suppress Th1 and Th17 cells. IL-27 directly inhibits Th17 cells by inhibiting ROR-γ expression and IL-6 signaling.

IFN-alpha can promote the production of IL-27 by enhancing the expression and binding of IRF-1 to the IFN-stimulated response element (ISRE) in the p28 gene promoter [13]. Likewise, IFN-γ induced IRF-8 expressions can upregulate p28 gene transcription in synergy with IRF-1 [15]. IFN-γ can selectively induce IL-27 expression via activating the C-Jun N-terminal kinases (JNK), MAPKs and the phosphoinositide-3-kinase (PI3K) signaling in primary human monocyte[60]. Many molecular details of the negative regulation of IL-27 expression remain to be determined.

IL-27 signaling pathways

IL-27R is indispensable for the IL-27 signaling. IL-27R consists of the class I cytokine receptor family (TCCR) (also known as WSX-1) and gp130 [16-18]. IL-27R is expressed in various cell types including naïve T cells, NK cells, activated B cells, monocytes, dendritic cells, activated endothelial cells, and mast cells [61]. IL-27 induced intracellular signaling involves phosphorylation of different isoforms of Jak and Stat, which varies with immune cell types: Jak1, Jak2, Tyrosine kinase 2 (Tyk2), Stat1, 2, 3, 4 and Stat5 in naïve CD4 T cells [62], Jak-1, Stat1, Stat-3 and Stat5 in NK cells[61, 63] , Stat1, Stat3, and NF-κB activation in monocytes [20], and Stat-3 in mast cells [64]. Interestingly, the effect of the IL-27 can be both pro-inflammatory and anti-inflammatory via same Stat1/Stat3 signaling.

The pro-inflammatory role of IL-27 as key inflammatory mediator for Th1 differentiation and IFN-γ production has been intensively explored [16, 63, 65]. Stimulation of Th0 in the presence of IL-27 induces the expression of the key signature Th1 cytokine IFN-γ via up-regulating of the transcription factor T-bet and IL-12Rβ2 chain which is essential for responding to IL-12 and the differentiation of a Th1 phenotype [61, 62, 65]. This effect of IL-27 on Th cell depends on multiple transcription factors such as Stat-1 and Stat-3 [61, 62, 65]. *In vivo* studies demonstrated the role of IL-27 in Th1 responses. In this context, it was shown that WSX-1−/− mice were more susceptible to *Leishmania major* infection and impaired IFN-γ production [17]. Similarly, reduced Th1 responses and IgG2a production was demonstrated in WSX-1-deficient mice infected with *Listeria monocytogenes* [18]. Moreover, it was shown that IL-27R signaling is vital *in vivo* for the IFN-γ production by CD8+ T cells [66]. IL-27 can enhance the proliferation of naïve CD8+ T cells and IFN-γ and granzyme B production dependent on Stat1 and Stat3 [22].

IL-27 can stimulate human monocyte to express TLR4 through activation of Stat-3, and NF-κB which subsequently respond to LPS-inducing IL-6, TNF-α, MIP-1α, and MIP-1β expression [67]. IL-27 increased the production of nitric oxide from peritoneal macrophages via activation of Stat-1, NF-κB and MAPKs [68]. IL-27 also enhanced monocyte derived dendritic cells (moDCs) to express IL-27, IL-8, CXCL10, chemokine receptor (CCR1), IFN-stimulated genes, IRF8 and other genes involved in antigen presentation [69]. IL-27 negatively regulated Tr1 cells by induction of metallothioneins (MTs) which in turn reduced stat1 and stat3 phosphorylation resulting in impaired IL-10 production [70]. Taken together, IL-27 positively regulates both innate and adaptive immune responses.

IL-27 can negatively modulate inflammatory processes. Improved control of *Leishmania donovani* correlates with massive inflammatory responses were reported in IL-27R-deficient mice [71]. Similarly, WSX-1-/- mice infected with *Toxoplasma gondii* or *Trypanosoma cruzi* generated robust IFN-γ responses and developed lethal T cell-mediated inflammation [31, 72]. Greater effector and memory CD4+ T cells responses were noted in IL27R lacking mice challenged by *Plasmodium berghei* [73].

The negative feedback of IL-27 largely depends on the induction of type 1 regulatory T cells (Tr1). IL-27 can induce Tr1 cells via various mechanisms including activation of Stat1, Stat3 [75-76], upregulation of Blimp1 [77], aryl hydrocarbon receptor (AhR), transcription factor c-Maf, inducible T cell costimulator (ICOS), and IL-21 production, which is indispensable for the expansion and maintenance of Tr1 cells [34, 35]. Furthermore, the anti-inflammatory effect of IL-27 needs more than the induction of Tr1 cells. IL-27R-/- CD4+ T cells produce more IL-2 than wild-type during *in vitro* differentiation. The addition of recombinant IL-27 suppressed the expression of IL-2 both transcriptionally and translationally [78]. IL-27 suppresses CD28-mediated IL-2 production by Stat 1 which in turn induces the expression of the suppressor of cytokine signaling 3 (SOCS3) [79]. Moreover, it was observed that WSX-1-deficient macrophages are more efficient in inducing IFN-γ and IL-17A production by CD4+ T cells than control. IL-27 can activate stat1 which in turn suppresses cyclooxygenase (COX) expression and followed by reducing prostaglandin (PG2) secretion, which can affect the CD4+ T cell responses [80].

IL-27 was also reported to suppress Th2 cells development and their cytokines production by downregulation of Gata3 and upregulation of T-beta in differentiated Th2 cells [32]. In addition to suppress both Th1 and Th2 cells, IL-27 can inhibit the development of Th17 cells. Consistently, it was demonstrated that IL-27 can inhibit Th17 cell development through various mechanisms including the suppression of IL-6 signaling mediated IL-17 production [33],

retinoid-related orphan receptor γ (RORγ) expression (Th17-specific transcription factor) [36], and also via induction of the IL-10 production [81], and programmed death ligand 1 (PD-L1) on naïve T cells [37]. IL-27 upregulates the expression of Blimp1 in pre-committed Th17 cells and acquired a Tr-1-like phenotype characterized by the production of IL-10 and IFN-γ [77].

More recently, it was recognized that IL-27 can inhibit the development of Th9 cells and limit its related encephalitis by mechanism partly depending on Stat-1 [82]. Taken together, IL-27 induces an immunosuppressive effect by both Tr1 cells dependent and independent mechanisms. However, the contribution of IL-27 in the induction of IL-35-producing T regulatory cells remains unknown.

Role of the IL-27 in innate and adaptive immune response to *Mtb* infection

The innate immunity plays a decisive role in the early clearance of *Mtb* via the recognition of the antigen and subsequent induction of pro-inflammatory cytokines and antimicrobial peptides [83]. The production of IL-27 in response to *Mtb* infection modulates macrophage responses [41-43]. The combination of IL-12 and anti-IL-27R can limit *Mtb* growth via upregulation of pro-inflammatory cytokines such as TNF-α, IFN-γ, and IL-18[41, 84]. However, the molecular mechanisms by which IL-27 negatively regulated macrophages during *Mtb* infections remain unclear. It was demonstrated that IL-27R singling in mice peritoneal macrophages suppresses IL-12 and TNF-α production by Stat3 [43]. IL-27 can antagonize IL-18 signaling in human macrophages challenged with *Mtb* by inhibiting the expression of the IL-18 receptor beta-chain and IL-18R downstream signaling component NF-kB [42]. IL-18 and IL-12, synergistically induced IFN-γ production by human macrophages and promoted the killing of *Mtb* [84]. It has been shown that IL-27 can inhibit the expression of the phagosomal vacuolar ATPase (V-ATPase) and lysosomal integrated membrane protein-1 (CD63), resulted in the suppression of phagosomal acidification and cathepsin D maturation [85]. IL-27 signaling is necessary for the IL-10 production by macrophages through enhancing the activity and binding of Stat1/Stat3 to the IL-10 promoter [86]. Recently, it was found that IL-10 induced by *Mtb* during macrophage infection can manipulate phagosomal maturation to enhance its own intracellular growth [87]. Most recently a study demonstrated that IL-27 suppresses IFN-γ mediated autophagy in human macrophages infected with *Mtb* by inducing autophagy negative regulatory factors mTOR and Mcl-1 through JAK/PI3-K/Akt and PI3-K pathway, respectively [88]. In brief, *Mtb* can subvert the normal bactericidal function of macrophages by inducing IL-27 (Figure 2A, Table 1).

Table 1: The consequence of IL-27 signaling in tuberculosis

Immune cells involved	Consequence of IL-27 signaling	References
Macrophages	Inhibits the production of pro-inflammatory cytokines	[43-42]
	Induces the production of anti-inflammatory cytokine.	[86]
	Inhibits phagosomal acidification.	[85, 87]
	Suppresses the autophagy formation.	[88]
T cells	Suppresses Th1 cell responses.	[43, 89-90].
	Induces the IL-10 producing Tr1 cells, promotes proliferation and maintenance of Tr1 cells.	[34-35, 75-77, 94].
	Suppresses the Th17 cell development.	[33, 36, 37, 81].

Ablation of IL-27, either by disruption of the IL-27R gene in mice or by an antibody blockade of the IL-27R, implicates an important role of IL-27 in adaptive immunity against mycobacteria infections. WSX-1-deficient mice have impaired IFN-γ production and granuloma formation when challenged with *M. bovis* BCG [89]. However, there are no differences in liver pathology and bacterial load between mutant and wild type mice [89]. Significant elevation of IL-27 throughout the infanthood and neutralization of IL-27 in neonatal macrophages improved control of bacterial replication [90]. Furthermore, blockade of IL-27 during incubation with the *M. bovis* (BCG) augmented the IFN-γ production by allogeneic CD4+ T cells [90]. Similarly, it has been demonstrated that improved control of *Mtb* growth in the lungs results from increased production of pro-inflammatory cytokines in WSX-1-knockout mice [43]. These results suggest that IL-27 negatively regulated Th1 response (Figure 2B, Table 1), however, the underlying mechanisms remain elusive.

More recently, it was recognized that IL-27 positively regulates IL-10 producing Tr1 cells during chronic inflammation [34, 35, 75-77] (Figure 2B, Table 1). It has been demonstrated that IL-10 suppressed the immune response to *Mtb* infections without immunopathology observed in both C57BL/6 and CBA/J mice [91, 92]. Moreover, it was shown that IL-10-deficient mice were more resistant to *M. bovis* (BCG) challenge in comparison to control mice [93]. Blocking of IL-10R in CBA/J mice improved *M. bovis* (BCG) evoked protection against *Mtb* characterized by enhanced Th1 and Th17 responses and increased IFN-γ and IL-17A production in the mice lungs [94]. Taken together, these data indicate IL-27 can modulate immune response against mycobacteria by inducing IL-10.

IL-27 directly mediated the suppression of the

development of Th17 cells in chronic inflammation models [33, 36, 37, 81] (Figure 2). Th7 cells induce T cell chemokines (CXCL9, CXCL10 and CXCL11) in the lungs of infected mice to recruit IFN-γ-producing CD4+ T cells to limit *Mtb* growth [95]. BCG-induced Th17 cells which can downregulate IL-10 and generate Th1 immune response resulted in protection upon *Mtb* challenge [96]. IL-17-deficient mice were more susceptible to mycobacteria, evidenced by the impaired granulomas formation and decreased IFN-γ production [97]. Vaccination will elicit Th17 cells response associated with increased pro-inflammatory cytokines, granulocytes infiltration and severe lung damage in mice [98]. The higher amount of Th17 cells and related cytokines in active tuberculosis patients implicated a role in immunopathogenesis [99, 100].

As an exceptional successful silent killer, *Mtb* can manipulate the host signaling to persist and reactivate at opportune occasion. Knowledge about the emerging player, namely IL-27, will inform better countermeasures against this hideous threat of global health public.

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Competing Interests

The authors have declared that no competing interest exists.

Abbreviations:

IL: Interleukin; IL-27Rα: Interleukin-27 receptor alpha; TCCR: class I cytokine receptor family; gp130: glycoprotein 130; Mtb: *Mycobacterium tuberculosis*; TIR: Toll-Interleukin receptor; AhR: aryl hydrocarbon receptor; EBI3: Epstein-Barr virus induced gene 3; SNPs: single nucleated polymorphisms; DCs: Dendritic cells; moDCs: monocyte derived dendritic cells; Th cell: T helper cells; CTL: cytotoxic T lymphocyte; NK cells: Natural Killer cells; Tr1 cells: type 1 regulatory T cells; Tr35 cells: T regulatory type 35 cells; KO: Knockout; APCs: antigen-presenting cells; TLRs: Toll-Like Receptors; IFN: Interferon; Jak: Janus Kinase; Stat: Transcription factor; Tyk: Tyrosine kinase; NF-κB: nuclear factor-kappa beta; MAPK: mitogen activated protein kinase; MyD88: myeloid differentiation factor 88; IRF: IFN regulatory factor; JNK: C-Jun N-terminal kinases; PI3K: phosphoinositide 3-kinase; ICAM-1: intercellular adhesion molecule-1; c-Maf: transcription factor c-Maf; ICOS: inducible T cell costimulator; MIP: Macrophage inflammatory protein; SOCS: Suppressor of cytokine signaling; CD: cathepsin D; mTOR: mammalian target of rapamycin; PI3 K: phosphatidylinositol-3-kinase class I; Mcl-1: Myeloid cell leukemia 1.

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