Hindawi
Journal of Immunology Research
Volume 2018, Article ID 1535194, 9 pages
https://doi.org/10.1155/2018/1535194

Review Article

The Biology and Role of Interleukin-32 in Tuberculosis

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Received 10 May 2018; Revised 8 August 2018; Accepted 29 August 2018; Published 22 October 2018

Academic Editor: Shalini Gautam

Tuberculosis, caused by *Mycobacterium tuberculosis*, remains a leading cause of morbidity and mortality globally, with nearly 10.4 million new cases of incidence and over 1.7 million deaths annually. Drug-resistant *M. tuberculosis* strains, especially multidrug-resistant or extensively drug-resistant strains, have further intensified the problem associated with tuberculosis control. Host-directed therapy is a promising alternative for tuberculosis control. IL-32 is increasingly recognized as an important host molecule against tuberculosis. In this review, we highlight the proinflammatory properties of IL-32 and the mode of action of IL-32 in mycobacterial infections to inspire the development of novel immunity-based countermeasures and host-directed therapies against tuberculosis.

1. Introduction

Mycobacterium tuberculosis, the causative agent of tuberculosis (TB), latently infected one-third of the global population. TB is a global public health threat, with 10.4 million new cases and 1.7 million TB-associated deaths reported worldwide in 2016. New classes of effective anti-TB antibiotics are urgently needed [1] largely due to the occurrence of drug-resistant *M. tuberculosis*. Six hundred thousand new cases are rifampin resistant, including four hundred and ninety thousand patients exhibiting multidrug-resistant infection (http://www.who.int/tb/publications/global_report/en/). Host-directed therapy is a promising direction for the treatment of TB. Interleukin-32 (IL-32), originally called NK cell transcript 4 (NK4), can be produced by human NK and T cells stimulated with IL-2 [2]. IL-32 is a pleiotropic cytokine that can induce proinflammatory cytokines such as TNF-α and IL-1β via activation of NF-κB and p38 MAPK signaling [3]. IL-32 is primarily found only in primates [3, 4]; in humans, this gene is located on chromosome 16p13.3 and consists of eight exons [3, 5]. The presence of IL-32 mRNA in both immune and nonimmune tissues and cells, including NK cells, T cells, dendritic cells, endothelial cells, and epithelial cells [6, 7], suggests that this gene has multiple functions [7–10], such as inflammatory response [3], apoptosis [11], cell death [12], differentiation [8, 9], and in the pathogenesis of inflammatory disorders, including rheumatoid arthritis [13, 14], allergic rhinitis [15, 16], neuromyelitis optica [17], inflammatory bowel disease [18], chronic rhinosinusitis [19], osteoporosis [20], atherosclerosis [21], cardiovascular diseases [22], pulmonary diseases [23], Crohn's disease [24], Behçet's disease [25], hidradenitis suppurativa [26], cancer [27], and myeloid leukemia [28]. IL-32, as a proinflammatory cytokine, has been extensively studied [29], and the mechanisms of action and functions of IL-32 during bacterial and viral infection as well as in cancer have been reviewed [30–32]. IL-32 plays protective roles in multiple infectious diseases, such as HIV [33–35], influenza [36], cytomegalovirus [37], HBV [38, 39], *Leishmania braziliensis* [40, 41], *Mycobacterium avium* [42], and *M. tuberculosis* [43, 44]

infection. In this review, we highlight the immunomodulatory effects and signaling pathways of IL-32 during mycobacterial infection.

2. The Isoforms and Secretion of IL-32

Many cytokines have multiple splicing isoforms. IL-17, IL-15, and vascular endothelial growth factor (VEGF) as well as IL-32 possess differently spliced isoforms. IL-15 has two alternatively spliced isoforms with identical biological properties but distinct modes of regulation and expression patterns [45]. There are nine alternatively spliced isoforms of IL-32 in the GenBank database (https://www.ncbi.nlm.nih.gov/genbank/), namely, IL-32α, IL-32β, IL-32γ, IL-32δ, IL-32ε, IL-32ζ, IL-32η, IL-32θ, and IL-32s, generated by alternative mRNA splicing [46]. These isoforms interact with each other to control their biological activities [46]. IL-32 isoforms IL-32δ and IL-32β can interact. IL-32δ interacts with IL-32β and inhibits IL-32β-induced production of IL-10 [47]. The sequence of IL-32β is similar to that of IL-32γ which is spliced into IL-32β in different cell lines, such as THP-1, HeLa, and human synovial fibroblast cells [48, 49]. IL-32α is frequently observed in the cytosol but not in the culture supernatants of epithelial cells, including primary keratinocytes, intestinal epithelial cell lines, and colonic subepithelial myofibroblasts [18, 50, 51]. IL-32α specifically binds to proteinase-3 with high affinity, and this binding is independent of enzyme activity [52]. IL-32α has been reported to interact with PKCε and STAT3 [53] and with focal adhesion kinase 1 (FAK1) and integrins [54]. IL-32β and IL-32γ can induce caspase-8- and caspase-3-dependent apoptosis [54, 55]. IL-32β interacts with C/EBPα and PKCδ, culminating in increased IL-10 production [56]. IL-32γ, without exon deletions, is the most active isoform [46, 57].

The secretion of IL-32 isoforms remains to be investigated. IL-32γ possesses an N-terminal hydrophobic signal peptide, which is a typical feature of secreted cytokines. IL-32 is expressed in peripheral blood mononuclear cells (PBMCs) by LPS stimulation or *M. tuberculosis* infection, instead of *Staphylococcus aureus* and *Candida albicans* [58]. The IL-32α isoform was detected as an intracellular fraction, whereas the IL-32β isoform was found in the cell culture supernatant of Cos7 cells under transient transfection [3]. However, when performing transient transfection of IL-32β into bovine aortic vascular endothelial cells (BAVECs), IL-32β was found mainly in the cytosol and localized in the endoplasmic reticulum [6]. In addition, IL-32β was detected in the supernatant derived from the cytoplasm of apoptotic T cells but not secreted in anti-CD3 antibody-activated human T cells [12]. However, IL-32 can bind to the RGD motif of integrin, and IL-32 isoforms contain predicted tyrosine sulfation sites, which are prevalent in secreted proteins [2, 5, 59]. In HT-29 cells stimulated with TNF-α and IFN-γ, IL-32 was associated with membrane vesicles, and the release of IL-32 depended on exosome-like vesicle release mechanisms [60]. Therefore, IL-32 may be secreted via a nonclassical protein secretion pathway, similar to IL-33 and HMGB1, without typical signal peptides and are released via ER/Golgi-independent means [60, 61].

3. The Cellular Source and Expression of IL-32

IL-32 does not share homology with known cytokines. IL-32 expression has been detected in multiple human tissues and organs, including spleen, thymus, leukocytes, lungs, heart, placenta, liver, muscle, kidneys, pancreas, prostate, small intestine, colon, and brain [3]. The IL-32 mRNA is highly expressed in immune cells, and IL-32 expression has also been detected in nonimmune tissues and cells [6, 55, 62]. NK cells [2, 3, 63], monocytes/macrophages [3, 62, 64], dendritic cells (DCs) from PBMCs [58, 62, 65], neutrophils [66], T lymphocytes [62], epithelial cells [67], endothelial cells [68], fibroblasts [69], and hepatocytes [64] can express IL-32. IL-32 is also expressed and released in both cancer and noncancer cell lines, including the HepG2 human cancer cell line [3, 70], A549 cells [71, 72], pancreatic cancer cell lines such as MIA PaCa-2, PANC-1, and BxPC-3 [73, 74], the human hepatoma cell line Huh-7.5 [64], cervical cancer cells and tissues [75], the HEK293T cell line [34, 57], the HT-29 human colon cell line [60], the human colon neuroendocrine LCC-18 cell line [34], human colonic subepithelial myofibroblasts [51], human primary keratinocytes [50], synovial cells and fibroblast-like synoviocytes (FLS) [14, 69], and the marrow stromal cell lines HS-5 and HS-27A [76].

Four major isoforms (IL-32α, IL-32β, IL-32γ, and IL-32δ) were found in IL-2-stimulated human NK cells [3]. IL-32β, IL-32ε, and IL-32ζ were isolated from activated T cells [12], and IL-32s expression was first observed in Jurkat human leukemia T cells [70]. IL-32ε, IL-32ζ, IL-32θ, and IL-32s are also found in T cells, and the IL-32β isoform is mainly expressed in activated T cells [2, 12, 46]. IL-32θ and IL-32s were identified from monocyte-derived dendritic cells purified from human PBMCs and Jurkat T cells via 5′ RACE [46]. The function of different IL-32 isoforms in different cell types was summarized in Table 1. IL-32 mRNA levels increased after stimulation with Con A and monoclonal antibodies against CD3 and CD28 [62]. TNF-α reciprocally induced the expression of IL-32 mRNA in monocyte-derived dendritic cells, T cells, and synovial fibroblasts [62]. Intracellular IL-32 is constitutively expressed in human umbilical vein endothelial cells (HUVECs). The IL-32α and IL-32γ isoforms are the most prominently expressed IL-32 mRNAs in unstimulated endothelial cells [6, 60, 68, 77], while TNF-α and IL-1β induced the expression of IL-32β in endothelial cells [4]. Studies have shown that GM-CSF induces the expression of the IL-32α, IL-32β, IL-32γ, and IL-32δ isoforms in a caspase-1-dependent manner in eosinophils [15, 16]. Synovial fibroblasts isolated from patients with rheumatoid arthritis express IL-32γ after stimulation with IL-1β and TNF-α [48]. TNF-α can also promote the expression of the IL-32α, IL-32β, IL-32δ, and IL-32γ isoforms by activating the Syk/PKCδ/JNK/c-Jun signaling pathway [69]. The cell or tissue-specific expression patterns and functions of each isoform of IL-32 remain to be determined.

Table 1: The function of IL-32 isoforms in different cell type.

Cell type	IL-32 isoform	Targets	Function	Reference
U937 and monocyte-derived DCs	IL-32β	Increase in IL-10 production	Anti-inflammatory effects	[65]
Tumor cells	IL-32β	Decrease IL-1β, IL-6, TNF-α, and increase IL-10 production	Tumor growth	[78]
Myeloid cells and U937 cells	IL-32β	Increase in IL-10 production	Anti-inflammatory effects	[56]
Eosinophils	IL-32γ	Induces production of IL-6, TNF-α, IL-8, and VEGF	Inflammation of allergic rhinitis	[15]
Eosinophils	IL-32γ	Induces IL-1β, TNF-α, CXCL8, CCL3, CCL4, CD18, and ICAM-1	Interacts with NOD1 or NOD2; PR3 activation	[79]
Monocytes or monocyte-derived macrophages	IL-32γ	TNF-a, IL-1b, IL-6, GROa/CXCL1, and MCP-1/CCL2, IL-10, and IL-1ra	Activation of ERK1/2, Akt, and Fyn signaling pathways	[80]
PBMC	IL-32α/β	TNF-α, IL-6	—	[57]
Murine macrophage	IL-32α/β	TNF-α, CXCL2	—	
THP-1 and RAW264.7	IL-32α/β	TNF-α, IL-8, and, CXCL2	—	[3, 62]
THP-1 cells	IL-32γ	Induces TNF-a, IL-1b, IL-8, and IL-6	Activation of p38, caspase-1 and NF-κB pathways	[16]
THP-1 cells	IL-32γ	TNF-α, IL-23, CXCL1, CXCL8, and IL-1β	PI3K/Akt/P300/NF-κB signaling pathways	[81]
Endothelial cells	IL-32$\alpha/\beta/\varepsilon$	ICAM-1, IL-1α, IL-8, and IL-6	Vascular inflammation	[68]
PBMC/precursors	IL-32α	Activates Akt, JNK, ERK1/2, and NF-κB pathways	Cell differentiation	[10]
Murine DC	IL-32γ	Suppresses the production of CCL5	Driving acquired immunity	[82]
Murine bone marrow–derived DCs	IL-32γ	IL-6 and IL-12	Driving acquired immunity	[83]
PBMCs, $CD4^+$ T cells, $CD163^+$ macrophages, Treg cells, and DCs	IL-32γ	IDO and ILT4	Immunosuppression	[35]
Monocyte-derived macrophages	IL-32γ	Induce cathelicidin and β-defensin 2 (DEFB4)	Microbicidal activity	[84]
PBMC	IL-32γ	IFNλ1	Antiviral activity	[85]
T cells, epithelial cells, THP-1, and tumor cells	IL-32γ/β	Caspase-3, Caspase-8	Cell apoptosis	[12, 27]
THP-1 cells	IL-32θ	Suppresses the production of CCL5	Modulators of inflammation	[86]
THP-1 cells	IL-32θ	Decreases TNF-α	p38 and NF-κB signaling pathways	[28]

4. The Function of IL-32 in the Activation of Signaling Pathways

Although proinflammatory activities are key features of IL-32 and are enhanced by the different IL-32 isoforms, which induce the expression of cytokines such as TNF-α [3], IL-1β [87], IL-6 [53], IL-8 [88], and COX-2 [75], the mechanism of IL-32-based signaling remains unknown. The potential signaling pathways of macrophages induced by IL-32 are summarized in Figure 1. IL-32α, IL-32β, and IL-32γ are the main isoforms of IL-32 and have been shown to enhance the inflammatory response, suggesting that IL-32 can mediate diverse responses by interacting with different signaling molecules [53, 54, 56]. Intracellular IL-32α interacts with PKCε and STAT3, leading to phosphorylation of STAT3 and induction of IL-6 production after PMA stimulation [53]. Induction of TNF-α by IL-32α is mediated by phosphorylation of inhibitor kappaB (IkB) and ERK1/2 [89], NF-κB activation, and p38 MAPK phosphorylation in macrophage cell lines such as THP-1 and RAW264.7 [3]. Both IL-32α and IL-32β induce the expression of TNF-α, IL-8, and CXCL2 in THP-1 and RAW264.7 cells [3, 62] and induce the expression of TNF-α and CXCL2 in peritoneal murine macrophages [57]. Treatment of THP-1 cells with IL-32γ induced TNF-α, IL-6, IL-1β, and IL-8 expression via activation of the p38, caspase-1, and NF-κB pathways [16]. In addition, IL-32γ-stimulated monocytes and macrophages, such as THP-1-derived macrophages and monocyte-

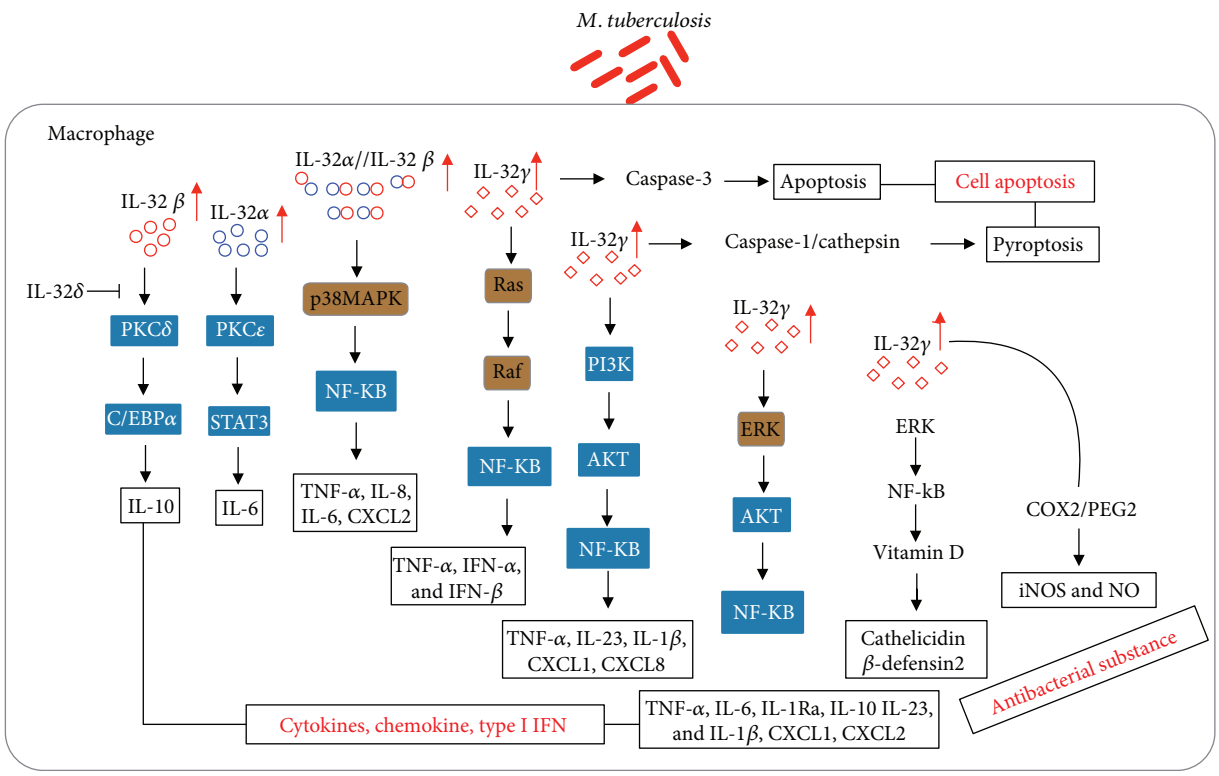

Figure 1: Endogenous IL-32-induced signaling pathway activation in macrophages and the potential roles of this pathway in *M. tuberculosis* infection.

derived macrophages, induce the expression of TNF-α, IL-1β, IL-6, CXCL1, and CXCL2 along with IL-1Ra and IL-10 via the ERK1/2 and Akt signaling pathways [80]. Moreover, IL-32γ triggers the production of TNF-α, IL-1β, IL-23, CXCL1, and CXCL8 via the PI3K/Akt/P300/NF-κB signaling pathway [81]. PR3 cleaves IL-32α and increases the activity of IL-32, which subsequently activates PAR2 and triggers the TRIF and Ras/Raf pathways, resulting in increased type I IFN (IFN-α and IFN-β) and TNF-α production [90]. However, IL-32 isoforms can reduce cellular inflammation [47, 65]. IL-32δ inhibits the binding of IL-32β to PKCδ, resulting in decreased IL-10 production [47]. In monocyte-derived DCs and human macrophages, endogenous IL-32β promotes IL-10 expression, resulting in decreased expression of proinflammatory cytokines, such as IL-12, TNF-α, and IL-1β [65]. IL-32β promotes IL-10 production via interaction with PKCδ, which phosphorylates C/EBPa, an inhibitor that binds to the IL-10 promoter [56]. Moreover, low-severity arthritis was observed in a human IL-32β transgenic mouse model [91]. In summary, IL-32 regulates the expression of inflammatory cytokines.

5. IL-32 Regulates the Expression of MicroRNAs

IL-32 isoforms were shown to induce inflammation by regulating the expression of microRNAs [20, 37, 92, 93]. The expression of IL-32 is activated by human cytomegalovirus infection and functionally downregulated by hcmv-miR-UL112-1 [37]. MiR-23b-3p directly targets and induces the expression of PTEN, resulting in reduction in PI3-kinase, total Akt, and IL-32 levels [93]. IL-32α promotes the expression of the atheroprotective-associated genes Timp3 and Reck by downregulating the Rprd2-Dgcr8/Ddx5-Dicer1 biogenesis axis downstream of microRNA-205 [92]. Overexpression of human IL-32γ in transgenic mice led to increased bone formation, reduced bone loss with advancing age, and high osteogenic capacity of osteoblasts by upregulation of microRNA-29α [20]. Therefore, IL-32 is a novel protective cytokine that acts against mycobacterial infection. Elucidating the complex interactions between the IL-32 isoforms, microRNA-based regulation of the isoforms and the function of IL-32 will provide novel insight into the novel mechanism of the protective roles of IL-32 in multiple diseases.

6. The Function of IL-32 in Mycobacterial Infection

M. tuberculosis, the causative agent of human TB, can subvert host immune defenses to promote its own intracellular survival. Infection of human macrophages or PBMCs with *M. tuberculosis* H37Rv induced IL-32 production [11, 58], suggesting a role for IL-32 in the control of *M. tuberculosis* infection. *M. tuberculosis* and *Mycobacterium bovis* induced the release of IL-32 from PBMCs via IFN-γ, which was produced after caspase-1-activated IL-18 release [58]. Silencing of endogenous IL-32 in differentiated THP-1 human macrophages significantly decreased TNF-α, IL-1β, and IL-8 production and simultaneously increased the *M. tuberculosis* burden in infected macrophages [11].

The antimycobacterial effect of IL-32 may be partly due to enhanced cell apoptosis in infected macrophages. IL-32γ is a potent inducer of apoptosis; both IL-32γ and IL-32β can induce caspase-3- and caspase-8-dependent apoptosis [12, 27]. Endogenous IL-32 mediated *M. tuberculosis*-induced apoptosis of macrophages, suggesting that apoptosis of infected macrophages is a mechanism to protect against mycobacterial infection. IL-32γ decreased the *M. tuberculosis* burden within macrophages via classic caspase-3-mediated apoptosis [11] and caspase-1- or lysosomal-cathepsin-mediated apoptosis [94]. Our previous study showed that *M. tuberculosis* PE/PPE (Pro(P)-Glu(E) and Pro(P)-Pro(P)-Glu(E)) family antigen PPE32 induced ER-stress-mediated cell apoptosis via the stimulation of IL-32 production [95]. In addition, IL-32 serves as a mediator of IFNγ-vitamin D-related antimicrobial activity and a marker for latent TB infection (LTBI), as determined via the mining of TB transcriptomic datasets [96]. IL-32γ was also found to be associated with the vitamin D antimicrobial pathway in human macrophages [84]. IFN-γ-induced IL-32γ increases the expression of the vitamin D receptor, leading to the expression of cathelicidin and β-defensin 2 (DEFB4), which are potent antimicrobial peptides that act against intracellular infection in macrophages [84]. IFN-γ treatment activates the production of NO in macrophages, which is the main microbicidal molecule involved in the control of *M. tuberculosis* infection [97]. Human THP-1 cells express iNOS and produce NO after differentiation into macrophages by treatment with IL-32γ [98]. The production of reactive oxygen species (ROS) is required to induce the microbicidal activity mediated by vitamin D and cathelicidin, and cathelicidin enhances the production of ROS and proinflammatory cytokines, such as TNF-α, IL-8, and IL-6 [99]. *M. tuberculosis*-induced GM-CSF can promote NO production and phagolysosomal fusion against *M. tuberculosis* infection [100, 101]. GM-CSF might kill intracellular *M. tuberculosis* via induction of IL-32 as GM-CSF increases the expression of IL-32 in other cell types [15, 16]. In summary, IL-32γ is a protective molecule that enhances the microbicidal activity of macrophages against *M. tuberculosis* via increased apoptosis and pyroptosis, and antimicrobial peptides induced by vitamin D and GM-CSF are involved in protection against *M. tuberculosis* infection (Figure 1).

IL-32, lacking sequence homology with known cytokine families, is a novel proinflammatory cytokine [3]. The expression of IL-32 was increased in patients with *M. avium* infection [42]. IL-32γ significantly reduced the intracellular survival of *M. avium* in human monocyte-derived macrophages [42]. Moreover, the expression of endogenous IL-32 and NOD2 was increased in patients with the restrictive tuberculoid form of leprosy, which is caused by *Mycobacterium leprae* infection [102], suggesting that both NOD2 and IL-32 are associated with leprosy. IL-32 expression was increased in surgically resected lungs of active TB patients, particularly in airway epithelial cells and granuloma macrophages [43], suggesting a protective role of IL-32 against *in vivo M. tuberculosis* infection. However, there was a decrease in the protective response of IL-32γ against *M. tuberculosis* at later time points of infection as IL-32γ mRNA is spliced into IL-32β, leading to increased levels of IL-10-expressing macrophages or DCs in the lungs [43].

Conflicts of Interest

The authors declare that they have no competing interests.

Acknowledgments

This work was supported by the National Natural Science Foundation (81701979, 81371851, 81071316 and 81601740), the general program of Chongqing Science and Technology Commission (cstc2017jcyjA0560), the Venture & Innovation Support Program for Chongqing Overseas Returnees (cx2017106), the National Megaprojects for Key Infectious Diseases (2008ZX10003-006 and 2008ZX10003-001), the Applied Basic Research Program of Science & Technology Department of Sichuan Province (2018JY0108), and the Doctoral Scientific Research Foundation of Neijiang Normal University.

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