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REVIEW

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The immunomodulatory potentials of interleukin-27 in airway allergies

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Abstract

Allergic airway disorders such as asthma and allergic rhinitis are mainly caused by inhaled allergen-induced improper activation and responses of immune and non-immune cells. One important response is the production of IL-27 by macrophages and dendritic cells (DCs) during the early stage of airway allergies. IL-27 exerts powerful modulatory influences on the cells of innate immunity [eg neutrophils, eosinophils, mast cells, monocytes, macrophages, dendritic cells (DCs), innate lymphoid cells (ILCs), natural killer (NK) cells and NKT cells)] and adaptive immunity (eg Th1, Th2, Th9, Th17, regulatory T, $CD8^+$ cytotoxic T and B cells). The IL-27-mediated signalling pathways may be modulated to attenuate asthma and allergic rhinitis. In this review, a comprehensive discussion concerning the roles carried out by IL-27 in asthma and allergic rhinitis was provided, while evidences are presented favouring the use of IL-27 in the treatment of airway allergies.

1 | INTRODUCTION: IMMUNOPATHOGENESIS OF ASTHMA, RHINITIS AND AIRWAY DISEASE

Atopic asthma and allergic rhinitis are the most prevalent inflammatory airway allergies[1] Approximately, 300 million individuals suffer from asthma worldwide.[2] Asthma is a complex multi-factorial disorder triggered by a cross-regulatory interplay between multiple host factors—genetic, gender, obesity, nutrition and infections. The environmental factors including air pollution, weather, pollens, moulds and allergens (eg dust mites, animal dander, pollens, cockroaches and spores)[1,2] are some additional eliciting factors. The frequency of allergic rhinitis [20%-30% of adults and 40% of children] is greater than asthma and can have a major impact on the quality of life, even to a similar degree as asthma.[3] Through genetic studies (SSCP analysis, heteroduplex analysis, DNA sequencing, etc), it has been shown that gene polymorphisms like those present in the CC16 gene render individuals to acquire inherited predisposition to asthma[4] many more such genes have now been identified.[5]

Asthma is clinically characterized by reduced lung function, wheezing, shortness of breath and coughing. In addition, allergic rhinitis, characterized by sneezing, rhinorrhea, conjunctivitis and itching, represent Type-1 hypersensitivity

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reactions involving mast cells, basophils, eosinophils and Th2 cells.[6] During allergic sensitization, dendritic cells (DCs) take up, process, and present allergens to naïve $CD4^+$ T-helper (Th) cells inducing their differentiation to Th2 cells secreting IL-4, IL-5 and IL-13, the key contributors to the development of allergic reactions. IL-4 and IL-13 induce B cells to secrete IgE that binds to FcεRI on mast cells and basophils in the airways sub-epithelium. Upon re-exposure to the same allergen, the allergen-IgE complexes cross-link and aggregate the FcεRI on mast cells and basophils causing their activation and degranulation to release the vesicle-stored preformed mediators—histamine, serotonin, proteases, heparin and chondroitin sulphates. Apart from these preformed mediators, nascent synthesized lipid-derived mediators which include platelet-activating factor (PAF), prostaglandins, leukotrienes and cytokines[7] also play important role in rapid response to antigenic presence. These mediators reduce airways respiratory function by increasing vascular permeability, smooth muscle cell contraction and mucus secretion. At the same time, PAF, prostaglandins, leukotrienes and proinflammatory cytokines also promote DC migration, maturation, and the late phase inflammation which onsets within 2-10 hours of allergen challenge. An increased recruitment of eosinophils, neutrophils, macrophages and T cells through up-regulation of adhesion molecules on vascular endothelial cells or by inducing chemotactic mediators is observed.[8] Therefore, the frontline drugs like bronchodilators and corticosteroids are prescribed to alleviate the asthmatic reactions since their primary target is immune cells mediating such reactions. A combination of the inhaler with corticosteroid formulation is regarded as reliant 'Gold-Standard' therapy. Here, in this review, we explore the immunomodulatory potentials of IL-27 in context of airway allergies and attempt to provide mechanistic explanations for same (Figure 1A-E).

2 | IL-27 AND IL-27 RECEPTOR SIGNALLING

IL-27, a heterodimer of P28 and Epstein-Barr virus-induced gene 3 (EBI3), is a member of the IL-12 family cytokines; EBI3 collaborates with IL-12-p35 to make IL-35.[9,10] The major IL-27-producing cells are activated antigen-presenting cells (APCs) such as macrophages and DCs, although NK cells, endothelial cells, and microglia also produce lower levels of IL-27.[11] The TLR- and interferon receptor-related signalling pathways play a main role in IL-27 production.[12] Several signalling axes, in particular, TLR4-MyD88-IRF1/IRF8-NF-κBc-Rel,[13] TLR4-MyD88-AP1/c-Fos,[14] TLR3/TLR4-TRIF-IRF3/IRF7,[15] IFN-α/IFN-β-STAT-1/STAT-2-IRF1/IRF9[16] and IFN-γ-MyD88-IRF8, induce p38MAPK-sensitive p28 expression.[11,17] IFN-γ induces IL-27 expression by activating the MAPKs, C-Jun N-terminal kinases (JNK) and phosphoinositide-3-kinase (PI3K) signalling.[18] The expression of EBI3 is triggered by signalling pathways such as TLR2/TLR4/TLR9-MyD88-NF-KB/PU.1.[11] Of an important note, IRAK1 (IL-1 receptor-associated kinase 1) limits TLR3/4- and INFAR-induced IL-27 production by regulating the transcription factors (TFs) STAT1, IRF1 and IRF9.[19]

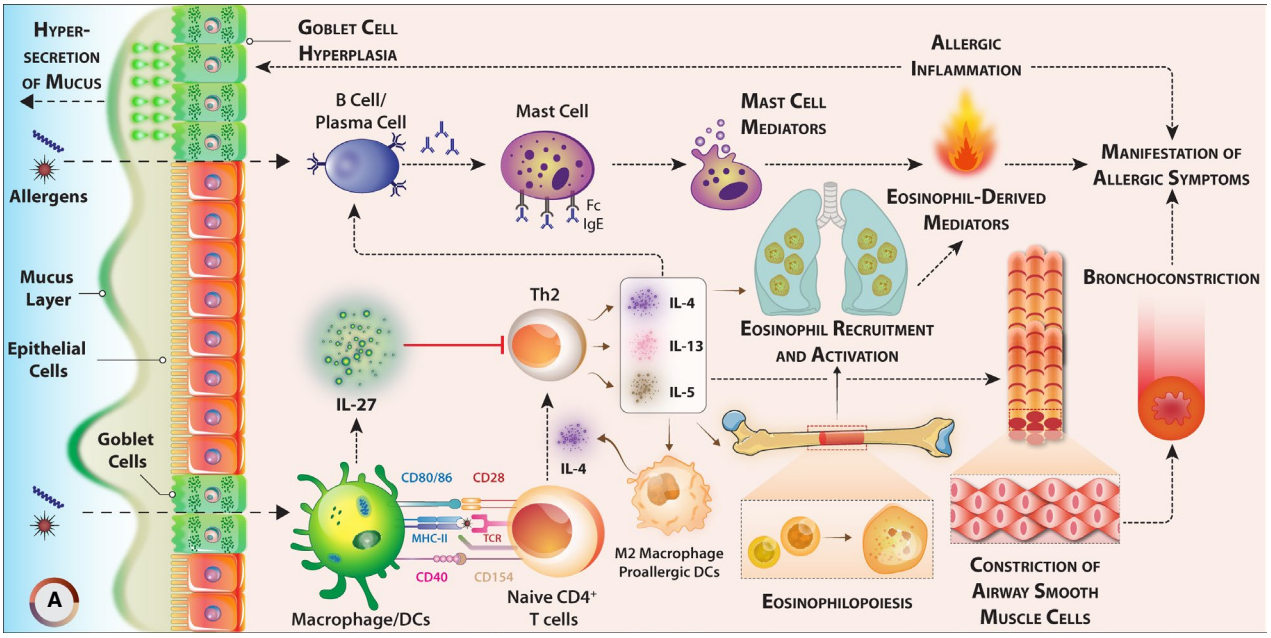
The IL-27 cellular effects are exerted through IL-27 receptor—an IL-27Rα [IL-27Rα or WSX1]-gp130 heterodimer—expressed on activated endothelial cells, mast cells, NK cells, monocytes, macrophages, DCs and naïve T cells.[10,12] The IL-27R signalling shows JAK-STAT isoform selectivity, and its operation is different in the context of the immune cells. Naïve $CD4^+$ T cells utilize JAK-1, JAK-2, Tyrosine kinase-2 (TYK-2), STAT-1, −2, −3, −4 and −5, NK cells utilize JAK-1, STAT-1, STAT-3 and STAT-5, monocytes utilize STAT-1, STAT-3, and NF-κB, and mast cells utilize STAT-3.[12] IL-27-activated STAT-3 induces expression of SOCS3 that binds to Y^{759} (humans) or Y^{757} (mice) on gp130, preventing STAT-3 activation and IL-27 signalling.[20] This SOCS3-dependent negative-feedback mechanism potently regulates the duration and quality of gp130-mediated signalling.[21]

3 | IL-27 THERAPY OF AIRWAY ALLERGIES TARGETS THE INNATE IMMUNE SYSTEM

Evidences suggest that IL-27 exhibits both pro- and anti-inflammatory effects in case of asthma. In the experimental asthma models, endogenous IL-27 or treatment with IL-27 attenuates the Th2 cell-mediated lung inflammation. The asthmatic symptoms—goblet cell hyperplasia, massive eosinophil infiltration, elevated IgE levels and airway hyperresponsiveness (AHR)—are exacerbated in OVA-primed IL-27Rα$^{-/-}$ mice following OVA challenge.[22] While the intranasal IL-27 administration ameliorates established allergic rhinitis,[22] the intranasal administration of OVA and IL-27 into OVA-sensitized mice prevents the OVA-induced airway inflammation[22] suggesting IL-27 as a therapeutic agent for airway allergies.

3.1 | IL-27 effects on respiratory epithelial cells modulate airway allergies

The respiratory epithelial cells from atopic allergic patients secrete IL-25, IL-33 and thymic stromal lymphopoietin protein (TSLP) which support the development of Th2- and ILC2-promoting pro-allergic DCs[23] (Figure 1A-E). In atopic patients, as the inhaled allergens pass through the inflamed epithelial barrier, epithelial cells secrete CCL2 and CCL20 that attract immature DCs.[24] The activated DCs carry the allergens to the local lymph nodes and



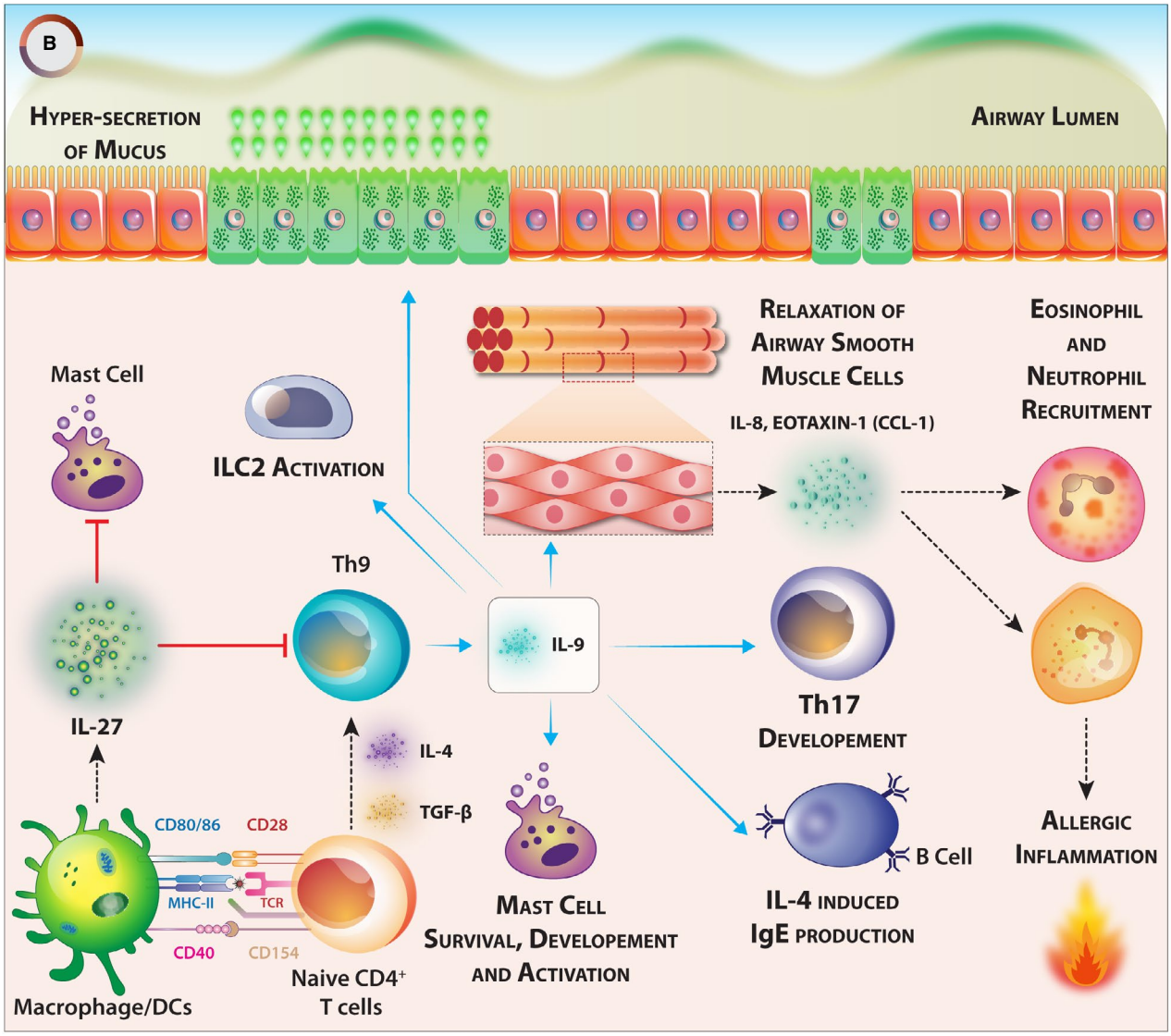


FIGURE 1 (Continued)

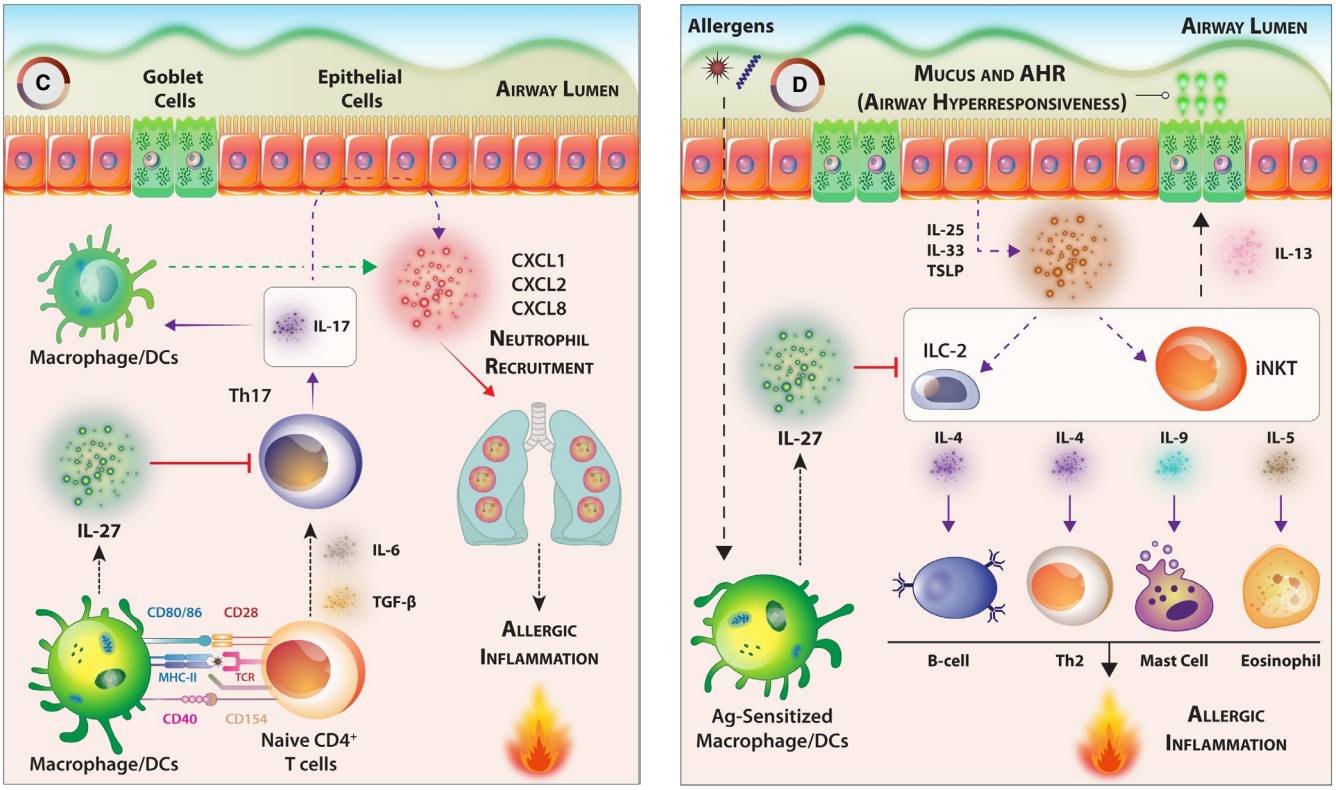


FIGURE 1 (Continued)

polarize naïve $CD4^+$ T cells to pro-allergic effector Th2 cells.[8,25] The DC movement is primed by ILC2-secreted IL-13 and mast cells- and basophils-secreted IL-4. In addition, the movement is further guided by the expression of CCR2 chemokine receptor which controls the release of monocytic DC precursors into the bloodstream of allergic subjects.[26] The STAT-1 and STAT-3 regulate the IL-27 effects on epithelial cells subsequently, inhibiting CXCL8 and CCL20 production in TNF-α-stimulated epithelial cells, reducing neutrophil and Th17-cell migration, enhancing CXCL10 and CXCL11 generation in oral epithelial cells. CXCL10 and CXCL11 in synergy with IL-13 augment CXCL9 production by airway epithelial cells.[27-30] As these chemokines attract Th1 cells, IL-27 may increase the infiltration of Th1 cells that exert suppressive effects on pro-allergic Th2 cells (Figure 1E). IL-27 further regulates the expression of inflammatory chemokines and cytokines such as CXCL1, CCL2, CCL3, CCL4, IL-6, GM-CSF and TNF-α from intestinal and bronchial epithelial cells.

3.2 | IL-27 effects on dendritic cells

DCs are functionally categorized into pro-allergic DCs and tolerogenic DCs that potentiate the allergic inflammation or support the immune tolerance to allergens, respectively, depending on the local cytokine microenvironment and maturation stage.[8,31] While the pro-allergic DCs express GATA-3, OX40 ligand, CD141 and receptor-interacting serine/threonine-protein kinase 4 (RIPK4) and primarily promote Th2 cell-dependent responses, the tolerogenic DCs express PD-L1 and inhibit allergen-specific T-cell response.[32,33] WSX-1-deficient DCs augment IFN-γ production by NK cells and T cells whereas IL-27 reduces LPS-induced expression of MHC-II molecules and costimulatory molecules CD86 and CD40. IL-27 stimulates the DCs to up-regulate the B7-H1 (PD-L1) expression and the binding of T-cell-expressed PD-1 to DCs-expressed PD-L1 diminishes the responses of the antigen-specific T cells[34,35] (Figure 2). Similarly, IL-27 may act on DCs to suppress T-cell response in the context of autoimmune disease by inducing the expression of the NTPDase CD39.[36] The above observations are however context-specific as there are also reports describing that IL-27 may also increase the surface expression of MHC-I (β2m and TAP-1) and enhance the expression of CD80, CD86, and CD54 in THP-1 cells.[37] These observations collectively reflects a cell-specific/disease-model dependent functional pleiotropy in the function of IL-27.

The IL-27-mediated PD-L1 up-regulation on DCs thus converts these cells functionally tolerogenic.[38] While IL-27Rα deficiency exacerbates the lung pathology and airway hyperresponsiveness in the Th2 cell-dependent asthma,[22,39] IL-27 produced by alveolar macrophages and DCs during airway allergy or a viral infection-directly exerts tolerogenic effects on DCs[40,41] by enhancing the expression of the immunosuppressive molecules such as PD-L1 and CD39. In

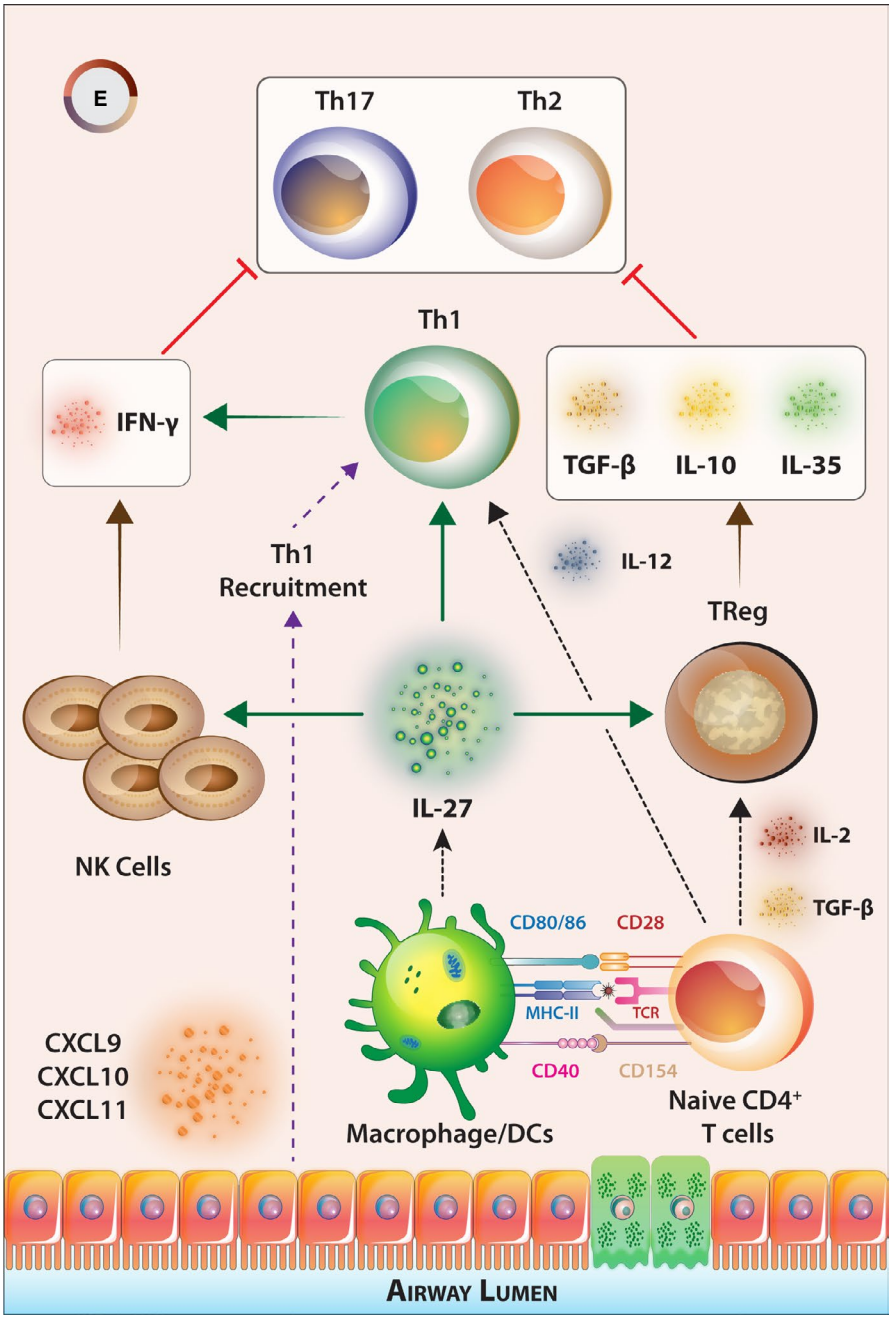


FIGURE 1 Major immunopathological pathways contributing to the development of airway allergies. (A) Th2-cell-derived cytokines directly and/or indirectly play a fundamental role in the development of allergic asthma via isotype-switching to IgE in B cells, employment of mast cells, recruitment of eosinophils, induction of the bronchoconstriction, triggering of the Goblet cell hyperplasia and mucosal secretion. IL-27 can interfere with asthma development through direct inhibitory effects on the Th2 cells, mast cells, Goblet cell and eosinophils. (B) Th9-cell-derived IL-9 directly and/or indirectly plays a key role in the development of allergic asthma via supporting the mast cell development, survival and activation, promoting the IL-4-mediated isotype-switching to IgE in B cells, inducing the chemokine production in airway smooth muscle cells, and increasing the ILC2 and Th17-cell activities. IL-27 can interfere with asthma development through direct inhibitory effects on Th9-cell development and activity. (C) Th17-cell-derived cytokines directly and/or indirectly play a principal role in the development of allergic asthma largely via the recruitment of neutrophils. IL-27 suppresses Th17-cell differentiation and can reduce Th17-cell activity. (D) ILC2-cell-derived cytokines and some iNKT-cell-derived cytokines directly and/or indirectly play an important role in the development of allergic asthma via similar pathways explained for Th2 cells. IL-27 reduces the expansion of ILC2 and decreases the production of pro-allergic cytokine by ILC2 and iNKT cells. (E) Treg-cell- and Th1-cell-derived cytokines exert anti-allergic impacts mainly via suppressing the Th2- and Th17-cell-mediated pro-allergic activities. NK-cell-derived IFN-γ can inhibit Th2-cell-related pro-allergic responses. IL-27 reinforces Treg-, Th1- and NK-cell-mediated anti-allergic effects

chronic obstructive pulmonary disease (COPD) patients, tolerogenic DCs enhance Treg-cell activity, whether IL-27 remains as an activator of tolerogenic or immunosuppressive DCs remains to be identified.[42] However, in the case of the autoimmune (EAE) model, this observation can be verified.[43]

3.3 | IL-27 reduces group 2 innate lymphoid cells (ILC2)

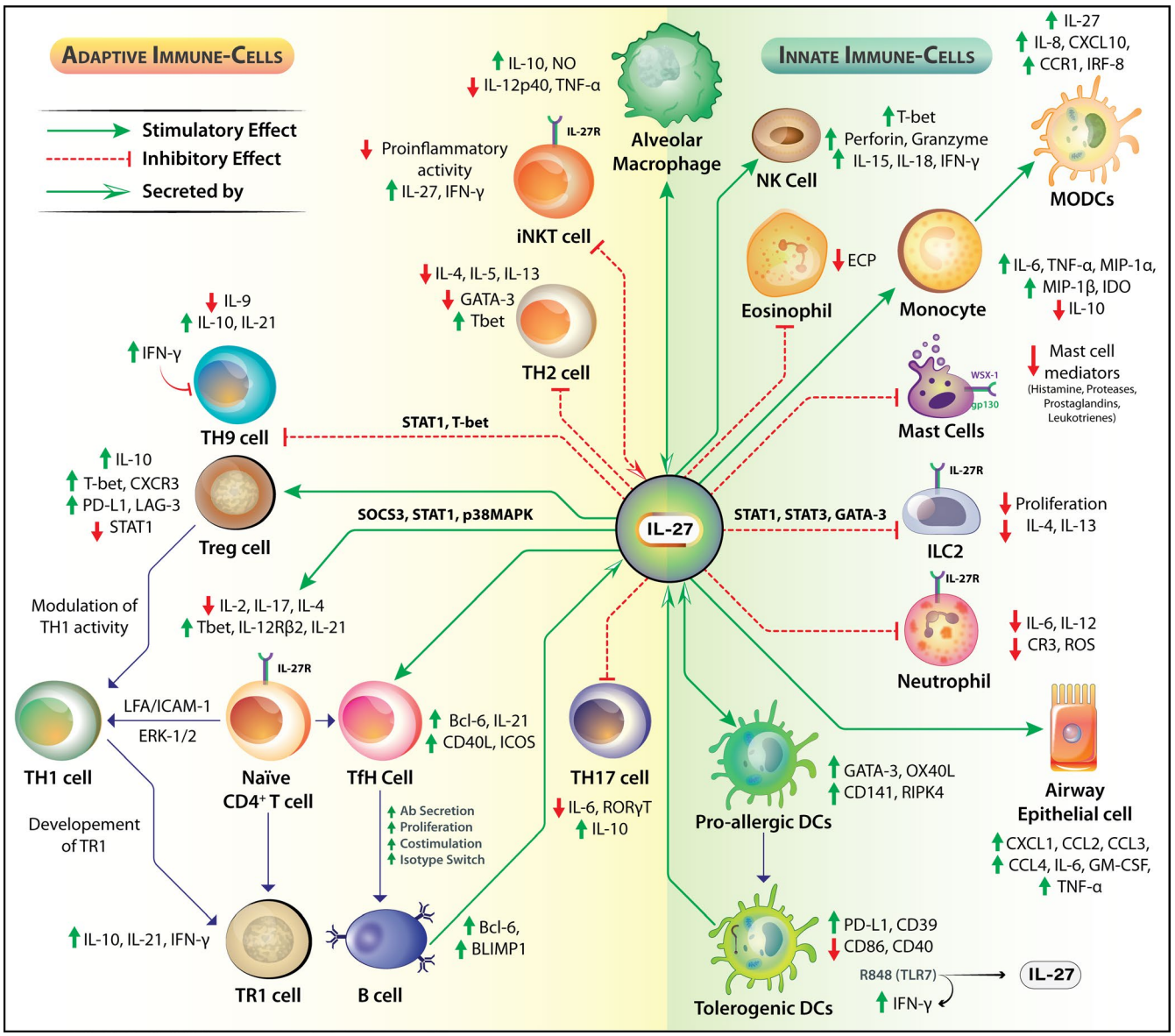
The ILCs lack antigen-specific receptors and secrete high amounts of Th cell-related cytokines via antigen-independent stimulation such as cytokines and lipid mediators. ILCs are classified into 3 subgroups: Group-1 ILCs (ILC1) constitutively expressing T-bet, IFN-γ and TNF-α for defence against intracellular pathogens. ILC2 expressing GATA3, IL-4, IL-5, IL-9 and IL-13 provides immunity against helminth parasites and the airway inflammation. ILC3 expressing RORγt, IL-17A and/or IL-22 functions as a part of defence system against extracellular bacteria, and tissue repair processes.[44]

The ILCs—ILC1 expressing T-bet, IFN-γ and TNF-α, ILC2 expressing GATA3, IL-4, IL-5, IL-9 and IL-13, and ILC3 expressing RORγt, IL-17A and/or IL-22—lack antigen-specific receptors and secrete high amounts of Th cell-related cytokines via antigen-independent stimulation.[44] The patients with asthma and allergic rhinitis and the individuals challenged with a cat allergen show higher frequencies of ILC2 in peripheral blood.[45] IL-27 reduces ILC2 expansion (Figure 1D) and IL-4 and IL-13 production by a STAT-1- and STAT-3-dependent and GATA-3-targeted mechanism.[46,47]

3.4 | The IL-27 effects on the mast cells

The inhaled allergens cross-link the membrane-bound IgE on mast cells inducing the release of mast cell-derived mediators—histamine, proteases, prostaglandins and leukotrienes. These mediators are responsible for vasodilation, smooth muscle contraction, mucous secretion and the late phase accumulation of inflammatory cells—eosinophils, basophils, neutrophils and $CD4^+$ T cells causing bronchial wall thickening and accelerated histamine release[48] (Figure 1A). IL-10-stimulated bone marrow-derived mast cells express WSX-1, gp130 and SOCS3, which inhibits gp130 signalling, explaining the IL-27-modulated pro-inflammatory cytokines production[49] and negative regulation of the immediate hypersensitivity reactions. In mast cell-dependent passive cutaneous anaphylaxis, IL-27Rα-deficient mice display higher mast cell activities suggesting that IL-27 reduces the mast cell responses.[39]

FIGURE 2 The Role Of IL-27 In The Development Of Immune Cells Producing Pro- And Anti-Allergic Effects Is Illustrated. INHIBITORY EFFECTS OF IL-27: Eosinophils: IL-27 contributes to the regulation of eosinophil-related activities. ILC2: IL-27 reduces the ILC2 expansion and the IL-4 and IL-13 production by ILC2. iNKT cells: iNKT cells express IL-27R and IL-27 blocks the pro-inflammatory activity of NKT cells. Mast cells: IL-27 reduces the mast cell responses (production of pro-inflammatory cytokines and mast cell mediators). Neutrophils: The IL-27R heterodimer is constitutively expressed on human neutrophils. IL-27 also reduces IL-6 and IL-12 secretion from neutrophils and decreases their recruitment. TH17 cells: IL-27 prevents the Th17-cell differentiation by variety mechanisms including interference with IL-6 signalling and suppression of RORγt expression through induction of the IL-10 production, and induction of PD-L1 on naïve T cells. TH2 cells: IL-27 suppresses Th2-cell development and Th2 cytokines production from polarized Th2 cells. IL-27 inhibits the expression of GATA-3, a fundamental transcription factor of Th2 cell thereby reinforces the Th1-cell differentiation but prevents the Th2-cell polarization. The inhibitory effects of IL-27 on the IL-4 secreting Th2 cells down-regulate IL-4-induced IgE production. TH9 cells: IL-27 prevents Th9-cell development and enhances Tr1 cells cytokines IL-10, IL-21 and IFN-γ and represses IL-9 production by these cells. STIMULATORY EFFECTS OF IL-27: Airway Epithelial Cells: IL-27 regulates the expression of CXCL1, CCL2, CCL3, CCL4, IL-6, GM-CSF and TNF-α from intestinal and bronchial epithelial cells. B cells: Tfh secreted IL-21, along with CD40L and ICOS signals are required for B-cell proliferation and differentiation. IL-21 promotes Blimp-1 expression in B cells that are essential for plasma cell differentiation. DCs: IL-27 is produced by alveolar macrophages and DCs during airway allergy. The IL-27-mediated PD-L1 up-regulation on DCs thus converts these cells functionally tolerogenic phenotype also contributed by reduced expression of costimulatory molecules CD86 and CD40. IL-27 may serve as an activator of tolerogenic or immunosuppressive DCs. Macrophage: IL-27 enhances macrophage capability to generate NO. Production of IL-27 occurs through APCs (macrophages and dendritic cells) during the early stage of airway allergies. Monocyte-Derived Dendritic Cells (MODCs): IL-8, IL-27, CXCL10, chemokine receptor (CCR1) and IFN-stimulated genes. Monocytes: IL-27 enhances the monocyte differentiation into macrophages. IL-27-pretreated monocytes display elevated TLR4 expression through STAT-3 and NF-κB, and additional LPS-induced NF-κB activation resulting in more IL-6, TNF-α, MIP-1α and MIP-1β expression. NK Cell: IL-27 strengthens the NK cell cytotoxicity via increasing the expression of granzyme B and perforin. Tfh Cells: IL-6 and IL-21 guided differentiation of the antigen-specific naïve $CD4^+$ T cells to effector Tfh cells are promoted by IL-27. B-cell-derived IL-27 promotes differentiation of Tfh cells. TH1 cells: The interaction of IL-27 with IL-27R on the $CD4^+$ T cells induces the p38/MAPK signalling-mediated and STAT-1-dependent expression of T-bet. IL-27 enhances the surface expression and interaction of LFA-1/ICAM, which then induces the ERK1/2 that supports Th1 differentiation. Tr1 Cells: IL-27 facilitates the development of $CD4^+$ Tr1 cells. Treg cells: IL-27 induces Treg cells to express LAG-3, supports the development of IL-10-secreting T-bet^+ $CXCR3^+$ Treg cells. However, IL-27 can interfere with TGF-β-induced generation of Treg cells. *IL-6 and IL-27 are shown to inhibit human Treg-cell-related suppressive functions



3.5 | IL-27 reduces granulocytes infiltration and functions in airways

The massive airway infiltration with eosinophils and neutrophils is independently correlated with the severity of airflow obstruction and intense histamine release in asthma pathogenesis. The ILC2 and Th2 cell-derived IL-5 enhance eosinophil differentiation and prevent eosinophil apoptosis during airway allergies. The IL-5-Eotaxin synergy enhances lung and circulatory eosinophilia aggravating asthma in patients.[50] The eosinophil-derived mediators, for example, major basic protein (MBP), and leukotrienes cause bronchoconstriction but the eosinophil-derived TGF-β may contribute to airway remodelling.[51] Human eosinophils express IL-27R and the IL-27 quantities are negatively correlated with the eosinophil numbers, serum IgE concentrations and eosinophil cationic protein in allergic rhinitis patients suggesting IL-27 regulation of eosinophil-mediated airway allergy[52] (Figure 1A).

Neutrophil frequency is increased in airway secretion, sputum and bronchial alveolar lavage in patients with acutely aggravated asthma. It is positively correlated with the severity of airflow obstruction and progressive pulmonary failure,[53] perhaps associated with the CXCL1, CXCL2 and CXCL8 production by epithelial cells and/or alveolar macrophages (Figure 1C). The neutrophil-derived cytokines and mediators—GM-CSF, IL-6, TNF-α, IL-17A, CXCL8, LTB4, elastase and MMP-9—rise in bronchoalveolar lavage and plasma from patients with severe neutrophilic asthma.[53,54] Human neutrophils express IL-27R and IL-27-exposed human neutrophils exhibit low Mac-1 expression, reduced adhesion, diminished ROS, IL-6 and IL-12 secretion and reduced recruitment[55] whereas IL-27 deficiency reinforces neutrophil activity.[56] *Cryptococcus neoformans*-infected

IL-27R-deficient mice exhibit unchanged Th1 and Th17 cytokines but elevated Th2-related cytokines—IL-4, IL-5 and IL-13—along with increased lung neutrophil infiltration. However, neutrophil depletion improved the outcome in infected IL-27R-deficient mice and IL-27 reduces the neutrophil-mediated pathological reactions during lung *Cryptococcus neoformans* infection.[57]

3.6 | IL-27 modulates NK and NKT cells in asthma

NK cells and NKT cells modulate immune responses by rapidly mobilizing the effector cytokines following the infection or vaccination. While the number of IL-4-producing NK cells increases, the frequencies of the IFN-γ-secreting NK cells diminish, in asthmatic patients. In an OVA-induced asthma model, NK cells depletion before OVA-priming inhibits IL-4 expression, reduces the production of the OVA-specific IgE and prevents the T-cell and eosinophil accumulation in the lungs.[58] As NK cells express IL-27R, IL-27 enhances NK cell expansion and strengthens cytotoxicity by increasing granzyme B and perforin expression. IL-27 induces T-bet expression promoting the IL-15- and IL-18-induced IFN-γ production by NK cells[59] (Figure 2). The IL-27-induced NK cells IFN-γ production suppress the Th2-cell-mediated inflammation during airway allergies.

The activated iNKT cells worsen the symptoms of allergic asthma independently of Th2-cell-mediated pathways. NKT cells are activated following antigenic stimulation in a CD1d-dependent manner, as CD1d-dependent antagonists or anti-CD1d antibodies suppress OVA-induced airway inflammation and histamine release.[60] The iNKT cells produce various cytokines such as IL-4, IL-5, IL-13 and IL-17.[61] Along with ILC2, iNKT2 possesses the ability to respond to IL-25 and produce IL-13.[62,63] IL-13 in the lung may promote histamine release and airway inflammation,[64] which is considerably attenuated in the absence of iNKT cells.[65] The patients with asthma exhibit a great number of iNKT cells in their bronchoalveolar lavage as compared to healthy controls.[66] Although, many reports draw the consensus that invariant NKT cells increase the pathology of asthma. It has been shown in a mouse model of airway allergen challenge of OVA-sensitized mice that 1 hour pretreated mice with chemical agent α-galactosylceramide (α-GalCer) may attenuate airway hyperresponsiveness and induces accumulation of iNKT cells in the lungs. Moreover, this treatment also polarizes accumulating NKT cells cytokine profile from IL-4 to protective IFN-γ production.[67] iNKT cell may produce IL-27 in an activation-dependent manner and IFN-γ inhibits the Th2 cell-related responses and allergic inflammation in a mouse model of OVA-induced asthma.[68] This observation also opens up the possibility that IL-27 may also be contributed from the other innate cells as PMA and ionomycin stimulation in vitro may incite the IL-27p28 transcripts in culture supernatants unambiguously. On the other hand, in vivo scenario is much more complex. One must not override the possibility that both the subunits of IL-27 (IL-27p28 and EBI3) could be differentially expressed in various immune cell types following the nondiscriminatory stimulation with agents such as α-GalCer or others. This may overall affect the available pools of IL-27 and IFN-γ which may further be controlling the suppression of Th2 and thereby affecting the progression of allergic inflammation.

4 | IL-27 THERAPY OF AIRWAY ALLERGIES TARGETS THE ADAPTIVE IMMUNE SYSTEM

4.1 | The IL-27 effects on the Th1 cells

The Th1 cells support the defence against intracellular pathogens and the elimination of malignant cells through activating NK cells, macrophages and CTLs. The interaction of IL-27 with IL-27R on the Naïve $CD4^+$ T cells induces the p38/MAPK signalling-mediated and STAT-1-dependent expression of T-bet[69,70] resulting in the Th1-cell differentiation. IL-27 inhibits the expression of GATA-3,[71] which mediates Th2 differentiation, and reinforces the Th1-cell differentiation. In a T-bet-independent process, IL-27 enhances the surface expression and interaction of LFA-1/ICAM, which then induces the ERK1/2 that supports Th1 differentiation.[69] By contrast, IL-27 induces SOCS3 that inhibits IL-2 production by $CD4^+$ T cells reducing the T-cell growth, diminishing Th1-cell responses due to reduced survival and expansion of Th1 cells,[72] and inducing the immunosuppressive cytokine IL-10[73] that further suppresses Th1-cell response.

Evidently, in an OVA-induced allergic asthma model, the prophylactic intranasal IL-27 administration in mice before the OVA challenge imparts therapeutic benefits. Mechanistically, it up-regulates the STAT-1 expression and activation, promotes the Th1, Tmem and Treg-cell differentiation in lung tissue. Further down-regulates the STAT-6 expression and concomitantly decreases Th2-cell-related cytokines altogether inducing a protective Th1 lung microenvironment.[74] An imidazoquinoline compound namely R848 (resiquimod) induces IL-27 and IFN-γ production from alveolar macrophages and DCs and enhances the PD-L1 expression and effectively mitigate the Th2-cell-mediated airway inflammation.[41,75] Administration of the R848 before the OVA challenge effectively prevents the expression of the total symptoms of allergic asthma, and the IL-27 neutralization completely abolishes the therapeutic

impacts of R848 this asthma model. The R848-mediated improvement of airway inflammation is thus performed in an IL-27 dependent manner.

4.2 | The IL-27 effects on the Th2 cells

Upon antigenic activation in the presence of IL-4, the naive $CD4^+$ T cells undergo GATA3-dependent differentiation into effector Th2 cells. These cells produce IL-4, IL-5, IL-6, IL-9 and IL-13. Th2 cells stimulate B cells to secrete antibody aggravating allergic disorders.[76] Th2-cell-derived cytokines facilitate the accumulation of different inflammatory cells—eosinophils, basophils, neutrophils, B cells, and plasma cells—that contribute to the pathogenesis of airway allergies (Figure 1A). Elevated serum IL-4 levels and enhanced expression of the GATA3 and GATA3/FOXP3 ratio in the PBMCs from asthmatic patients indicate an imbalance in the Th2/Treg-related transcription factors and a skewed Th2 predominance.[77] The Th2-cell-originated IL-4 and IL-13 promote isotype-switching to IgE in B cells and up-regulate the expression of vascular cell adhesion molecule-1 (VCAM-1) on the vascular endothelium, supporting the adhesion of very late antigen-4 (VLA4)-expressing eosinophils.[78] Both cytokines stimulate mucus secretion from goblet cells in the airways. IL-5 contributes to the final eosinophils differentiation and mobilization and prolongs their survival by preventing apoptosis, causing tissue eosinophilia within 4-12 hours after allergen challenge.

Although highly expressed in naïve $CD4^+$ T cells, WSX-1 expression declines upon Th subset differentiation.[79,80] As the circulating concentrations of Th2-cell-related cytokines—IL-4, IL-13, IL-5—are significantly increased but the serum IL-27 significantly reduced in allergic rhinitis patients in comparison with healthy controls.[81] The IL-27 quantities are negatively correlated with Th2-cell-related cytokines concentrations, suggesting a role for IL-27 in Th2-cell-mediated inflammation.[71,74] Indeed, IL-27 suppresses the generation of the Th2-cell-derived cytokines by PBMCs from allergic rhinitis patients, while the Th1-cell-derived cytokines expression is not changed after IL-27 treatment. IL-27 does not alter the expression of the Th2- and Th1-cell-derived cytokines in PBMCs collected from healthy individuals, indicating that the immunomodulatory impacts of IL-27 are exerted in inflammatory conditions. These differences may be attributed to the higher levels of IL-27R expression by T cells from allergic rhinitis patients and also on Th2 cells in comparison with Th1 cells.[52] In a model of OVA-induced airway allergy, IL-27Rα deficiency increases the lung levels of Th2-cell-related cytokines, mucus secretion and histamine release. This enhanced Th2-cell response was not due to cross-suppression by IL-27-induced Th1 cells since the OVA-specific Th1-cell-related responses were also up-regulated in these mice. The OVA-specific Th2 responses, but not Th1 response, were potentiated in the intra-nasally OVA-sensitized $EBI3^{-/-}$ mice. Severe eosinophilia and higher production of Th2 cell-associated cytokines were also observed in $EBI3^{-/-}$ mice upon OVA challenge.[82] As EBI3 is also a part of the IL-35 heterodimer, the findings from the $EBI3^{-/-}$ mice suggest some roles for IL-35. A similar relationship between IL-27 and suppression of Th2 response was reported in ragweed pollen-induced experimental allergy in WSX-$1^{-/-}$ mice.[83] However, the $CD4^+$ T cells from the patients with chronic asthma patients are resistant to the IL-27-mediated inhibition of IL-4 production perhaps due to a much larger number of effector Th2 cells in asthma patients and due to low expression of IL-27R on these effectors. IL-27 could inhibit the Th2 polarization of naïve $CD4^+$ T cells but could not induce re-differentiation of terminally differentiated Th2 cells. In an OVA-induced asthma model, preventive IL-27 administration can improve the pathological outcome dependent on GADD45γ and p38-MAPK pathways along with reversal of impairment of STAT1. This study advocates the fact that preventive intervention with IL-27 is successful over therapeutic intervention because of presence of differentiated Th2 population that resist IL-27 inhibition.[84] In contrast to this another group, utilizing the cockroach antigen-induced allergic inflammation model in mice elucidated that Treg cells are predominant target of IL-27 (through the induction of immunosuppressive molecule LAG-3) in vivo to exert its anti-inflammatory functions.[85]

As IL-13 mediates the airway allergies, acting independently of IL-4 on epithelial cells and smooth muscle, it is possible that the stoichiometry of IL-13R and IL-27R expression on Th2 cells, determining the strengths of pro-allergic and anti-allergic signalling, respectively, will also control the alternative fate of allergy. However, whether receptor desensitization can be another mechanism of the observed effect warrants further investigation. From the above discussions, it is apparent that IL-27 has multiple cellular targets for its mediating its immunoregulatory functions in the context of airway allergy and allergic inflammation. Some common patterns encompassing its actions can be summarized as: (a) $CD4^+$ T-cell polarization to Th2 effector phenotype can be directly suppressed by IL-27 stimulation[39]; (b)induction of protective lung microenvironment via Th1 responses[74]; (c) inhibition of ILC2 responses by IL-27 within lung mucosa[86]; (d) Tregs are important mediators of immunosuppression via IL-27 and the effect could be dependent on molecules like CD39, CD73, ICOS, LAG3 and others[85]; (e) may further intensify the immunosuppression via induction of IL-10 producing TR1 cells.[87] However, TF c-Maf is required for the optimal IL-10 production by TR1 cells, and it been shown that IL-27 is instrumental in inducing ligand-activated transcription factor aryl hydrocarbon

receptor which acts cooperatively with c-Maf for development of TR1 cells.[88] Many such mechanisms controlled by IL-27 which are of immunoregulatory importance relevant in case allergic asthma are discussed in detail in the following sections.

4.3 | IL-27 suppresses Th9 cells expansion and differentiation and functions

The presence of IL-4 along with TGF-β directs the polarization of the antigen-induced naïve $CD4^+$ T cells to IL-9 secreting Th9 cells. IL-9 induces the differentiation, maturation and activation of mast cells. It potentiates the IL-4-induced IgE production, promotes the IL-5-mediated eosinophil maturation and induces mucin secretion in the respiratory airways[89] (Figure 1B). STAT-6, SMAD2 and PU.1 are the main signalling elements in the IL-4R/TGF-βR pathways which are critical for the Th9-cell development and the pathogenesis of allergic asthma. In experimental models of asthma and allergic rhinitis, IL-9 neutralization attenuates the OVA-induced airway inflammation mainly by modulating the Th2- and Th17-cell-related responses.[90,91] IL-27 suppresses the development of Th9 cells and the IL-27-mediated inhibition of Th9 cells is partly dependent on the STAT-1 and T-bet (Figure 1B). IL-27 treatment of Th9 cells enhances the expression of the Tr1 cells signature cytokines IL-10, IL-21 and IFN-γ but represses IL-9 production.[89] IFN-γ suppresses Th9 differentiation and induces DCs to express IL-27 that prevents Th9-cell development.[89]

4.4 | IL-27 facilitates Treg cells development and functions

Approximately 5%-10% of the total blood $CD4^+$ T cells are Treg cells, comprising two separate sub-populations that contribute to the induction and maintenance of immunological tolerance.[92] The natural Treg (nTreg) cells differentiate in the thymus from immature precursors, while induced Treg (iTreg) cells emerge extrathymically from antigenic stimulated-naive $CD4^+$ T cells in the presence of TGF-β and IL-2.[93] Treg cells express FOXP3 transcription factor and are characterized by the secretion of immunomodulatory cytokines IL-10, TGF-β and IL-35. The iTreg has Tr1- and Th3-cell subsets producing abundant quantities of IL-10 and TGF-β, respectively.[94,95] Particularly in asthma, corticosteroids effectiveness may be a function of potentiation of nTreg cells activity. In this regard, it has been shown that pre-treatment of $CD4^+CD25^+$ nTreg cells may potentize their anti-proliferative effects on T cells.[96] Additionally, IL-27 pretreated human iTregs are superior in protecting the recipients in the xenogenic Graft versus Host Disease (GvHD) model.[97] The conserved non-coding sequence 2 (enhancer of FOXP3 locus) is hypermethylated in the case of induced Tregs than normally generated Tregs.[98] One could hypothesize that it may be possible that IL-27 stimulation may bring changes in the transcriptional landscape of Tregs which may control their effector profiles in case of allergies as observed with GvHD. Treg-cell activity is compromised in allergic disorders[78,99] as evident from patients of immune dysregulation, polyendocrinopathy and enteropathy syndrome (IPEX).[100] Data from the preclinical study show that mutations in the FOXP3 gene leads to the development of allergic inflammation,[101] representing that Treg cells play an essential role in controlling the Th2-cell-mediated allergies.[102] The circulating Treg cells in children with mite-allergy exhibit lower suppressor activity in comparison with non-asthmatic individuals. In the bronchoalveolar lavage from asthmatic subjects, the counts of Treg cells are lower compared with healthy individuals, indicating a reduced ratio of Treg- to effector T cells in patients.[103] The in vivo elimination of Treg cells before antigen challenge promotes the generation of Th2-cell-related cytokines, IgE generation, airway eosinophilia and histamine release in an animal model of OVA-induced asthma whereas adoptive transfer of allergen-specific Treg cells efficiently reduces these asthmatic symptoms.[104] Corroborative with the finding that depletion of $CD4^+CD25^+$ Treg cells before Ag-sensitization is sufficient to accentuate the severity of AHR in lungs contributing towards disease susceptibility.[105]

IL-27 facilitates the development of $CD4^+$ Tr1 cells.[73] IL-27 enhances the IL-10 production by effector $CD4^+$ Tr1 cells which attenuate the Th17-cell-induced inflammation in an EAE model.[106] In a model of cockroach antigen-induced airway allergy, IL-27 reduced total counts of the lung-infiltrated cells perhaps due to the IL-27 effects on the iTreg-cell development.[85] IL-27 also supports the development of IL-10-secreting T-bet^+ $CXCR3^+$ Treg cells. The DC-RA (retinoic acid-skewed dendritic cells)-derived IL-27 induces tolerance to a food allergen by replacing the allergen-specific Th2-cell responses with $CD25^+LAG3^+CD49b^-FOXP3^-$ Treg-cell responses.[107] The $EBI3^{-/-}$ DC-RAs are insufficient for inducing tolerance to food allergens. While Treg-cell stimulation in the presence of IL-27 improves their suppressive activity, IL-$27R\alpha^{-/-}$ Treg cells are deficient in their repressive capacity to inhibit the inflammatory responses.[108]

In the OVA-induced asthma model, intranasal IL-27 ameliorates the clinical symptoms, decreases the eosinophilia in the nasal mucosa, reduces the IL-4 and IL-5, but increases IL-10 and IL-35, production by OVA-specific T cells, increases the FOXP3 expression and the numbers of $CD25^+$ $FOXP3^+$ Treg cells in cervical lymph node and decreases the serum concentrations of OVA-specific IgE.[109] IL-27 induces Treg cells to express LAG-3, which is necessary for IL-27-mediated inhibition of allergic inflammation, concurring

with the low suppressive activity of LAG-3$^{-/-}$ Treg cells[108,110] (Figure 2).

IL-27P28- or IL-27Rα-deficient mice are highly susceptible to allergic disorders.[111] As immune tolerance is an active process, the healthy individuals generate Tr1 (CD49^{+}LAG3^{+}) cells as a response to normally inhaled allergen. The generation of these cells is closely dependent on semi-mature-DC-derived IL-10, IL-27 and TGF-β along with ICOS expression by DCs.[112,113] It may be possible that IL-27-induced-Tr1 cells suppress pro-allergic Th2-cell-related cytokines; however, the number of these cells generated in vivo greatly determines their capability to effectively dampen the detrimental Th2 responses which may affect the clinical outcome in allergic patients.[114] Tr1-like cells can also be induced by immunosuppressant drugs like Vit-D3 and glucocorticosteroids from CD4^{+} T cells justifying one of many reasons for the clinical success of these drugs.

The Treg cells from asthmatic subjects exhibit low STAT-1 phosphorylation in response to IL-27 stimulation,[85] due to IL-4-mediated SOCS3 expression. Similarly, weak STAT-1 phosphorylation in CD4^{+} T cells from asthmatic subjects was reported following in vitro IL-27 stimulation. IL-27 stimulates the STAT-3 pathway, and the IL-27/STAT-3 axis is essential for IL-27-mediated PD-L1 expression and prevention of iTreg-cell development.[115] The IL-27-mediated STAT-3 phosphorylation is diminished in conventional CD4^{+} T and Treg cells from asthmatic subjects, although the extent of reduction is lower than STAT-1 phosphorylation suggesting a compromised IL-27-mediated activation in Treg cells in asthmatic patients.[85] Since IL-27 may be considered as a novel therapeutic tool for inflammatory disorders, improvement and/or restoration of the Treg-cell responsiveness to IL-27 may be an important objective to be investigated in future studies.

4.5 | IL-27 prevents Th17 cells differentiation and function

IL-6 along with TGF-β guides the RORγt-mediated polarization of the antigen-induced naïve CD4^{+} T lymphocytes to IL-17 and IL-22 secreting Th17 cells that effectuate CXCL1-, CXCL2- and CXCL8-directed neutrophil chemotaxis in airway inflammation (Figure 1C). Increased numbers of Th17 cells and neutrophil-mediated bronchiolar inflammation were reported in asthmatic patients and correlated with the severity of childhood asthma[116] where these cells mediate acute allergic inflammation. Th17 cells promote allergen-specific Th2-cell-mediated eosinophilic airway inflammation by enhancing eotaxin-1 and eotaxin-2 expression.[117] The IL-17A neutralization before the antigen challenge attenuates neutrophilic airway inflammation.[118] Consistently, the antigen-induced neutrophilic airway inflammation is attenuated in IL-17A-deficient mice. IL-17A but not IL-17F has a direct effect on muscle contraction, potentiating antigen-induced histamine release and exacerbating the pathology of asthma. It is also evident that the IL-17A is a potent inducer of Th2 immune responses in the murine atopic dermatitis model.[119]

IL-27 prevents the Th17-cell differentiation by interference with IL-6 signalling and suppression of RORγt expression through induction of IL-10 production by Th17 cells and PD-L1 expression on naïve T cells[120] (Figure 2). IL-27 suppresses the RORγt expression and Th17-cell development and increases the production of IL-10 from Treg cells.[52,106,120] Evaluation of the IL-27 on the Th17-cell-mediated responses during the airway allergies may be an important objective to be investigated in the future.

5 | IL-27 AFFECTS ANTIBODY PRODUCTION

In the lymph node, allergen-specific Th cells are differentiated into T cells follicular helper-T (Tfh) cells that secrete IL-4 and IL-21 promoting IgE class-switching in B cells.[121] It has been shown that an important subset of Tfh is enriched in the experimental mouse model of asthma. Moreover, these particular subsets of T cells show elevated levels of Bcl-6, inducible T-cell costimulator (ICOS), ICOS ligand and IL-21 expression both at protein and mRNA level. These cells were also enriched in the expression of CD4^{+} CXCR5^{+} as compared to the control group.[122] It is important to consider that a high frequency of Tfh cells in the circulation of patients with bronchial asthma may control the outcome of chronic airway inflammatory disease through modulating the activities of B cell in the germinal centre. There are more important players in uncovering the biology of the generation of pro-allergic IL-4-producing Tfh cells during many diseases and BTAF (basic leucine zipper transcription factor ATF-like) transcription factor may be the actual player to be considered for therapeutic targeting.[123] During allergen re-exposure, allergen recognition by FcεRI-bound IgE on DCs and FcεRII on B cells amplifies the Th2-cell-mediated responses.

IL-27 promotes IL-6- and IL-21-directed differentiation of the antigen-specific naïve CD4^{+} T cells to effector Tfh cells that express the IL-21-inducing transcription factor Bcl-6. IL-21, CD40L and ICOS signals are required for B-cell proliferation and differentiation [121] (Figure 2). IL-21 promotes Blimp-1 expression in B cells that are essential for the plasma cell differentiation but not the memory B-cell formation. The B-cell-derived IL-27 promotes differentiation of Tfh cells. The number of Tfh cells and the IL-21 expression are reduced in mice with B-cell-specific EBI3 deficiency.[124] The inhibitory effects of IL-27 on the IL-4 secreting Th2 cells down-regulate IL-4-induced IgE production. In patients

with allergic rhinitis, the IL-27 quantities are negatively correlated with the total serum IgE concentrations. IL-27 treatment lowers allergen-specific IgE levels in mice with airway allergy. Taking together, the aforementioned literature into account the effects of IL-27 in the development of immune cells producing pro- and anti-allergic effects is summarized in Figure 2.

6 | PRO-ALLERGIC EFFECTS OF IL-27

IL-27 is shown to exert pro-inflammatory functions in both allergic and non-allergic conditions. IL-27 is generated in response to allergens and causes resistance to steroids.[125] Elevated IL-27 concentrations in asthmatic patients suggest that the extent of IL-27 production can have different effects on different target cells affecting the development of allergy-related inflammatory responses. IL-27 enhances the monocyte differentiation into macrophage, activates macrophages to generate nitric oxide and triggers monocyte-derived DCs to express IL-8, IL-27, CXCL10, chemokine receptor (CCR1) and IFN-stimulated genes. IL-27-pretreated monocytes display elevated TLR4 expression through STAT-3 and NF-κB, and additional LPS-induced NF-κB activation resulting in more IL-6, TNF-α, MIP-1α and MIP-1β expression.[126] IL-27 can interfere with TGF-β-induced generation of Treg cells and the adoptive transfer of IL-27Rα$^{-/-}$ Treg cells into lymphopenic mice ameliorate colitis due to increased Treg-cell activity.[127] IL-27 over-expressing transgenic mice exhibit lower survival rates due to spontaneous inflammation linked to a reduced Treg-cell repertoire.[128] IL-6 and IL-27 inhibit human Treg-cell-related suppressive functions.[129] These inconsistencies could be due to the differences between the organisms—mouse or human—studied, airway allergy models, in vivo, or in vitro experimental systems. Notwithstanding these few inconsistencies, IL-27 serves as a dampening factor in airway allergies that may stratify its consideration for therapeutic employment.

7 | CONCLUSION

IL-27 affects airway allergies by its immunomodulatory activities on several target cells—epithelial cells, DCs, mast cells and basophils, monocytes and macrophages, neutrophils and eosinophils, NK and NKT cells, ILC2, Th1-, Th2, Th9, Th17, Treg and B cells. The resultant effects of IL-27 on allergic inflammation and the pathogenesis of airway allergies depend on the relative contributions of these cells. The molecular basis of the defects in IL-27R signalling in patients with airway allergies remains to be understood. The timing, dosing and the route of IL-27 administration potently influence the IL-27-related functions and are therefore required to be standardized for consistent therapeutic outcomes. The preventive IL-27 administration seems to be more effective than therapeutic as chronic airway allergies show resistance to IL-27, a phenomenon that merits further investigation.

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CONFLICT OF INTEREST

The authors declare that they do not have any conflict of interest.

AUTHOR CONTRIBUTIONS

AJ conceptualized the manuscript, MN and SJ reviewed the literature prepared and compiled the manuscript, BS and PC proofread and edited the MS. PC drew the illustrations.

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