Role of IL-17 and IL-23 in the Pathogenesis of Neutrophilic Asthma

Nightingale Syabbalo, MB, ChB, PhD, FCCP, FRS*

Professor of Medicine and Physiology, MC Sata School of Medicine, Copperbelt University, Zambia

*Corresponding author: Nightingale Syabbalo, Professor of Medicine and Physiology, MC Sata School of Medicine, Copperbelt University, P.O. Box 21692, Kitwe, Zambia, Tel: +260-966-486-117

Abstract

Asthma is a complex chronic airway disease with several distinct phenotypes characterized by different immunopathological pathways, clinical presentation, physiology, comorbidities, biomarker of allergic inflammation, and response to treatment. Approximately 10% of patients with asthma have severe refractory disease, which is difficult to control on high doses of inhaled corticosteroids and other modifiers. About 50% of these individuals suffer from neutrophilic asthma. Neutrophilic asthma is a phenotype of asthma that is severe and persistent, with frequent exacerbations, and hospitalization. It is characterized by the presence of high levels of neutrophils in the lungs and airways. The IL-23/IL-17 cytokine axis plays an important role in the pathogenesis of neutrophilic asthma. IL-23 is crucial for the differentiation and maintenance of Th17 cells, and it is required for full acquisition of an effector function of Th17 cells. Furthermore, IL-23 prolongs the expression of Th17 cytokines, such as IL-17, IL-17F, IL-22, and GM-CSF which induce tissue pathology and chronic inflammatory diseases. Th17 cells produce IL-17 which plays a key role in the pathogenesis of neutrophilic asthma by expressing the secretion of chemoattractant, cytokines, and chemokines which lead to the recruitment, and activation of neutrophils. Activated neutrophils release multiple proteinases, cytokines, chemokines, and reactive oxygen species which cause airway epithelial cell injury, inflammation, hyperresponsiveness, and airway remodeling. Neutrophilic asthma is unresponsive to high dose inhaled corticosteroids, and probably to novel monoclonal antibody therapies. There is need for targeted precision biologics, and other treatment modalities for these patients, such as macrolide antibiotics, and bronchial thermoplasty.

Keywords

Neutrophilic asthma, Chemokines, Cytokines, Interleukin-17, Interleukin-23

Introduction

Asthma is a complex chronic airway disease with several distinct phenotypes characterized by different immunopathological pathways, clinical presentation, physiology, comorbidities, biomarker of allergic inflammation, and response to treatment [1-4]. It has now become...
me common practice to phenotype asthma for precision, targeted treatment because asthmatic patients respond to the standard treatment differently. There are several proposed distinct clinical phenotypes of asthma, such as childhood-onset allergic asthma, adult-onset eosinophilic asthma, neutrophilic asthma, exercise-induced asthma (EIA), obesity-related asthma, and aspirin-exacerbated respiratory disease (AERD) [5-12]. About 5%-10% of the patients in these different phenotypes of asthma have severe persistent disease [9-11], which is refractory to the standard treatment with high doses of inhaled corticosteroids (ICSs), long-acting β2-agonists (LABAs), and/or other modifier [5,7,9,13-15].

Severe refractory asthma encompasses several cellular and molecular phenotypes of asthma, including eosinophilic, neutrophilic, paucigranulocytic, and mixed cellularity asthma [6]. Neutrophilic asthma comprises about 30%-50% of the patients with symptomatic asthma, and is one of the most severe refractory phenotypes of asthma [16].

The pathogenesis of neutrophilic asthma is not fully understood. Early exposure of the lungs to bacterial and viral infections; allergens; and endogenous factors can lead to neutrophilic airway inflammation. This can cause epithelial cell injury and the release of toll-like receptors (TLR)2, and TLR4 responses, and inflammasomes, such as NLRP3 (nucleotide-binding oligomerization domain-like family, pyrin domain-containing 3) [17-19]. Activation of TLRs has been shown to induce a shift in the innate immune responses toward T helper 1 (Th1) and T helper 17 (Th17) responses, leading to the expression and production of IL-1β, INF-γ, TNF-α, and IL-17A, IL-17F, IL-8, and IL-6 [20]. Simpson, et al. [21] have reported that patients with neutrophilic asthma have increased expression of innate immune receptors, such as TLR2, TLR4 and CD14, as well as pro-inflammatory cytokines, such as IL-1β, and IL-8. Neutrophilic asthma is associated with increased levels of NLRP3 and caspase-1 in the airways, exaggerated IL-1β responses, and Th17 cell differentiation, and IL-17 production. This lead to IL-17-driven neutrophilic inflammation, airway hyperresponsiveness, and severe steroid-resistant asthma [18,19,22].

Interleukin-17 is produced mainly by Th17 cells, but other cells in the lung can also secrete the IL-17 family members. It plays a key role in the pathogenesis of neutrophilic asthma by expressing the secretion of chemoattractant cytokines, chemokines, and adhesion molecules which lead to the recruitment, and activation of neutrophils. Activated neutrophils produce oxidative bursts, releasing multiple proteinases, cytokines, chemokines, and reactive oxygen species (ROS) which cause airway epithelial cell injury, inflammation, hyperresponsiveness, and airway remodeling.

This article discusses about the role of IL-23 and other cytokines in promoting IL-17 secretion by Th17 cells; and the role of IL-17 in inducing the expressing cytokines, and chemokines which cause neutrophil recruitment, and activation; and the immunopathology of neutrophilic asthma.

**Interleukin-23**

Interleukin-23 (IL-23) is a pro-inflammatory heterodimeric cytokine composed of two subunits, p19 and p40 [23]. It shares the p40 subunit with interleukin-12 a family member cytokine [24,25]. The interleukin-12 family comprises of four members, IL-12, IL-23, IL-27, and IL-35 [25]. IL-23 is more closely homologous to IL-12, but they have different receptors, and different immunopathological effects [24,25]. IL-12 is involved in inducing the development of Th1 cells [26]. It stimulates the production of interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α) from T cells, and natural killer (NK) cells, and reduces IL-4 mediated suppression of interferon-γ (IFN-γ) [27]. On the other hand, IL-23 is involved in the development, maintenance, and stabilization of Th17 cells after induction by transforming growth factor-β (TGF-β) and IL-6 [28]. Signal transducer and activator of transcription (STAT) are also involved in the final differentiation, and maturation of the Th17 cells.

Interleukin-23 signals through it complex receptor consisting of IL-23Rα and IL-12R β1, the latter also serves as a subunit for the IL-12 receptor [23,24]. The biological effects of IL-23 on its target cells are mediated through activation of tyrosine kinase2 (TYK2), Janus kinase 2 (JAK2), STAT3, and STAT4 [23,24]. The high affinity IL-23 receptor is expressed in many cell types, including dendritic cells, macrophages, activated T cells, Th17 cells, γδ T cells, natural killer (NK) T cells, and innate lymphoid cells (ILCs) [29]. Interleukin-23 is secreted by hematopoietic and non-hematopoietic cell such as macrophages, activated antigen presenting cells (APCs), B cells, and endothelial cells [29]. Activated macrophages, and other immune cells also produce other cytokines, such as IL-1β, and TNF-α, and IL-17 itself, which are important in Th17 cell function [30].

Interleukin-23 is crucial for the maintenance of Th17 cell [31], and it is required for full acquisition of an effector function of Th17 cells [32]. Furthermore, IL-23 prolongs the expression of Th17 cytokines, such as IL-17A, IL-17F, IL-22, and GM-CSF that induce tissue pathology and chronic inflammatory diseases [33]. These effects identify IL-23 as a key cytokine in the Th17 cells/IL-17 inflammatory axis in the pathogenesis of many autoimmune and chronic inflammatory diseases [30]. IL-23 is implicated in several chronic inflammatory diseases, such as rheumatoid arthritis [34,35], psoriasis [36,37], inflammatory bowel disease [38,39], and neutrophilic asthma [40,41].

Ciprandi and colleagues [42,43] have found that serum IL-23 levels were increased in allergic asthmatic children not on corticosteroids treatment, compared
with non-allergic children, and IL-23 levels were strongly and inversely correlated with lung function (FEV1), and airflow limitation in small airways (FEF25-75%). Interleukin-23 can be used as a biomarker of airflow obstruction in patients with neutrophilic asthma [43] (Table 1). Targeting IL-23 has a potential for the development of biologics for precision medicines to treat IL-23/IL-17 axis-mediated diseases.

### T Helper 17 Cells

T helper 17 (Th17) cells were first identified in 2005 as the main producer of the IL-17 [44,45]. Th17 cells also produce IL-17, IL-17F, IL-22, IL-21, and IL-26, and to a lesser extent IL-6, GM-CSF, and TNF-β [46-53]. The differentiation of Th17 cells from naive T cells is regulated by the combination of IL-6, and transforming growth factor (TGF)-β [54-60]. The presence of both IL-6, and TGF-β is required for the upregulation of a specific Th17 cell transcription factor, retinoic acid receptor-related orphan receptor (ROR)-yt in mouse [56,57], and RORc in humans [57]. The transcription factor RORyt is necessary for Th17 cytokine production and for the expression of the IL-23 receptor complex [57]. Interleukin-23 is required for expansion, stabilization, proliferation, and survival of Th17 cells to produce more IL-17, and other cytokines, and chemokines [61,62]. In addition, IL-23 prolongs the expression of type 17 signature cytokines, such as IL-17, IL-22, and GM-CSF which induce tissue pathology and mediates chronic inflammation. Interleukin-21 produced by Th17 cells, acts in a positive feedback loop to differentiate more Th17 cells [63]. Signal transducer and activator of transcription 3 (STAT3) is required for the stages of differentiation of Th17 cells [53,64]. Interleukin-1β is essential in the early differentiation and conversion of Forkhead transcription factor P3 (Fox3+) T cells into IL-17-producing cells [65,66].

### Other IL-17 Producing Cells

Interleukin-17 is also secreted by other activated immune cells, such as dendritic cells, CD8+ T cells, 6γ T cells, natural killer cells, invariant natural killer T cells, lymphoid tissue inducer cells, and type 3 innate lymphoid cells (ILC3) [67-71]. Additionally, hematopoietic and non-hematopoietic cells, such as eosinophils, neutrophils, monocytes, macrophages, and bronchial fibroblasts can secrete IL-17, under certain circumstances [72-75]. Because of the large number of cells producing IL-17, it becomes very difficult to target any specific cell type. Moreover, most of these cells produce a plethora of inflammatory mediators, which can make precision therapeutic targeting difficult.

### Interleukin-17

Interleukin-17 (synonymous to IL-17A) plays a key role in the pathogenesis of neutrophil asthma, via induction and expression of cytokines, chemokines, adhesion molecules, and growth factors which propagate neutrophil recruitment and activation into the airways. Interleukin-17 was initially identified as cytotoxic T-lymphocyte-associated antigen 8 (CTLA-8) in 1993 by Rouvier and colleagues [76]. Subsequent characterization revealed that this cytokine was produced by a special type of T helper cells different from Th1 and Th2 known as Th17 cells, and thus renamed as IL-17 [77,78]. Latter genomic sequencing led to the discovery of additional IL-17 family members totaling six, namely IL-17A (synonymous to IL-17), IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25), and IL-17F [79-81].

IL-17 is disulfide-linked homodimeric glycoprotein consisting of 155 amino acids with a molecular weight of 35 kDa; but heterodimers composed of IL-17A and IL-17F, as well as IL-17F homodimers exist [79-81]. IL-17A homodimer produce more pathophysiological responses than the heterodimer or the IL-17F homodimer [80-82]. Among the IL-17 family members, IL-17F has the highest homology (55%) with IL-17A [80,81] and IL-25 has the least homology (17%) [80]. Moreover, IL-25 immunopathologically behaves as a Th2 cytokine similar to the other “alarmin” cytokines [83], such as IL33 and thymic stromal lymphopoietin (TSLP). IL-17A and IL-17F have similar pathophysiological roles, although IL-17 is about 10-30 times as potent as IL-17F [80]. Both IL-17 and IL-17F are implicated in the pathogenesis of many autoimmune diseases, and neutrophilic asthma.

IL-17 is the most studied family member [79-81], particularly in the pathogenesis of rheumatoid arthritis [84,85], and psoriasis [86,87], and to a lesser extent in the immunopathology of neutrophilic asthma [5,6,10,16,20].

### Th17 Cells and IL-17 Protein Expression in the Airways

Histopathologically, neutrophilic asthma is associated with increase in neutrophils, and Th17 staining cells in the airways. Null and coworkers [88] characterized the prevalence of neutrophilic asthma using bronchial biopsy specimens from the entire bronchial tree (lobar, segmental and subsegmental) in patients with asthma. Analysis of their bronchial biopsies revealed si-
significant neutrophils in the lamina propria of the airway wall [88]. Neutrophil-high patients had a 3-fold increase in cells staining positive for IL-17F+, which correlated with neutrophil numbers. After excluding smokers, Boltone and colleagues [88] found an increase in the numbers of cells staining for IL-17A+ and IL-22+ in the lamina propria of the bronchial biopsies.

Soluble Interleukin-17A protein expression has been shown to be increased in induced sputum and bronchoalveolar (BAL) fluid obtained from patients with moderate-severe neutrophilic asthma [75,89-92] particularly during exacerbations. IL-17 protein expression also correlates with the severity of asthma [91,92]. Bullens and coworkers [93] have demonstrated a modest increase in mRNA for IL-17 in sputum cells in patients with moderate-to-severe asthma compared to health control subjects. The above findings suggest that increased expression of Th17 cells, IL-17 protein, and mRNA for IL-17 play an important role in the recruitment of neutrophils into the allergic airways. Additionally, IL-17 has been shown to be a potent activator of endothelial cells, which promotes transmigration of neutrophils to the sites of allergic inflammation, thus promoting neutrophil diapedesis into the airways [94].

**Immunopathological Roles of IL-17**

Interleukin-17 per se, plays an important role in airway inflammation, and hyperresponsiveness. IL-17 has been shown to stimulate bronchial fibroblasts, epithelial cells, and airway smooth muscle cells proliferation which can lead to airway remodeling, and severe steroid-resistant neutrophilic asthma [92]. Most important, the cytokines, chemokines, and growth factors induced by IL-17 are responsible for the airway hyperresponsiveness, goblet cell metaplasia and hypersecretion of mucus, subepithelial fibrosis, airway smooth muscle proliferation, and airway remodeling [95].

**Cytokines, and Chemokines Expressed by Interleukin-17**

Interleukin-17 induces the expression of several chemoattractant cytokines, chemokines, adhesion molecules, and growth factors in asthmatic airways [96-98]. The mediators include IL-6, IL-8, IL-1β, TNF-α, G-CSF, GM-CSF, TGF-β, and many more other cytokines, and chemokines [96-98]. The proinflammatory mediators act synergistically with IL-17 in orchestrating neutrophilic airway inflammation in patients with severe neutrophilic asthma [97,98]. Some of the mediators, such as IL-6, IL-23, TGF-β, and IL-1β are essential for the induction, propagation, and stabilization of Th17 cells to secret more IL-17, and further perpetuating neutrophilic airways inflammation. (Table 2 and Table 3) shows the list of the chemoattractant cytokines, and chemokines induced by IL-17 which are implicated in neutrophilic airway inflammation.

The cytokines, and chemokines induced by IL-17, which are involved in the recruitment, and activation of neutrophils in lung parenchyma, and airway epithelium, include IL-1β, TNF-α, CXCL1,CXCL2, CXCL5, CXCL6, LTB4, PAF, MIP-1α, and most important, CXCL8 also known as IL-8.

| Table 2: Cytokines and Chemokines expressed by Interleukin-17. |
|---------------------------------------------------------------|
| **Cytokines** | **Chemokines** |
| Interleukin-6 (IL-6) | Interleukin-1β (IL-1β) |
| IL-8 (CXCL8) | IL-6 |
| Granulocyte colony-stimulating factor (G-CSF) | IL-8 (CXCL8) |
| Granulocyte macrophage colony-stimulating factor (GM-CSF) | IL-17 and IL-17F |
| IL-1β | IL-23 |
| Transforming growth factor-β (TGF-β) | Interferon-γ (IFN-γ) |
| Tumour necrosis factor-α (TNF-α) | Tumour necrosis factor-α (TNF-α) |

**Table 3: Chemoattractant mediators associated with neutrophilic airway inflammation.**

| Cytokines | Chemokines | Lipids derivatives |
|----------|------------|--------------------|
| Interleukin-1β (IL-1β) | Interleukin-1β (IL-1β) | Interleukin-1β (IL-1β) |
| IL-6 | Interleukin-1β (IL-1β) | Interleukin-1β (IL-1β) |
| IL-8 (CXCL8) | Interleukin-1β (IL-1β) | Interleukin-1β (IL-1β) |
| IL-17 and IL-17F | Interleukin-1β (IL-1β) | Interleukin-1β (IL-1β) |
| IL-23 | Interleukin-1β (IL-1β) | Interleukin-1β (IL-1β) |
| Interferon-γ (IFN-γ) | Interleukin-1β (IL-1β) | Interleukin-1β (IL-1β) |
| Tumour necrosis factor-α (TNF-α) | Interleukin-1β (IL-1β) | Interleukin-1β (IL-1β) |
| Macrophage inflammatory protein 1-α (MIP-1α) | Interleukin-1β (IL-1β) | Interleukin-1β (IL-1β) |
| Chemokines | Lipids derivatives |
| CXCL1 (GRO-α) | Leukotriene B4 (LTB4) |
| CXCL2 (GRO-β) | Lipoxin A4 |
| CXCL5 | Prostaglandin E2 (PGE2) |
| CXCL6 | Platelet activating factor (PAF) |
| CXCL10 | which are involved in the recruitment, and activation of neutrophils in lung parenchyma, and airway epithelium, include IL-1β, TNF-α, CXCL1,CXCL2, CXCL5, CXCL6, LTB4, PAF, MIP-1α, and most important, CXCL8 also known as IL-8. |
Interleukin-8

Interleukin-8 (synonymous known as CXCL8) is an 8.4 kDa non glycosylated protein consisting of 69, 77, and 79 amino acid residues depending on the length, and physiological functions of the protein. Interleukin-8 (IL-8) is prototype cysteine-X-cysteine (CXC) chemokine; it was initially discovered as a leukocyte chemoattractant [99,100]. Interleukin-8 is one of the most potent chemotactic cytokine for neutrophil recruitment, activation, and degranulation, and the response is NF-kB dependent [101,102]. There is evidence that IL-8 prolong neutrophil survival by suppressing neutrophil apoptosis [103], thus promoting airway neutrophilia, and neutrophilic asthma. IL-8 differs from other cytokines due to its ability to specifically activate neutrophils. It causes a transient increase in cytosolic Ca$^{2+}$, which causes release of enzymes and ROS from granules. IL-8 also enhances expression of ROS, and of adhesion molecules, further promoting neutrophil chemotaxis [104]. IL-8 levels have been reported to be increased in induced sputum and bronchoalveolar lavage fluid in patients with neutrophilic asthma, thus implicating IL-8 in neutrophil recruitment, activation, and in the pathogenesis of neutrophilic asthma [105-108].

Activated Neutrophils in Neutrophilic Asthma

Neutrophils are polymorphonuclear leukocytes that have a fundamental role to play in innate immune response [109,110]. Neutrophils act as the first line of defense against pathogens, such as bacteria, fungi, and viruses, and participate in the resolution of inflammation and tissue repair [110]. However, neutrophils also contribute to immunopathology of many diseases including respiratory diseases, such as bronchiectasis [111], cystic fibrosis [112], COPD [113], ARDS [114], and neutrophilic asthma [5,6,15,20].

Activated neutrophils produce oxidative bursts, releasing multiple proteases, cytokines, chemokines, lipid mediators, elastase, metalloperoxidases, and cytotoxic reactive oxygen species that lead to airway epithelial cell injury, inflammation and hyperresponsiveness. The mediators are also responsible for goblet cell hyperplasia, and mucus hypersecretion, airway smooth muscle proliferation, and airway remodeling [115,116].

Several studies have documented increased concentrations of neutrophil active mediators, such as IL-8, elastase, matrix metalloproteinase-9 (MMP-9), leukotriene B4 (LTB4), IL-17A, GM-CSF, and TNF-α in plasma, BAL fluid, and bronchial epithelial-conditioned media derived from patients with severe neutrophilic asthma [115-118].

Role of NETosis in Neutrophilic Asthma

Activated neutrophils due to viral, bacterial and fungal infections or immunopathological inflammation, such as asthmatic responses, can undergo a process known as NETosis [119]. NETosis is a process by which neutrophils can extrude cytosolic and nuclear material, referred to as neutrophil extracellular traps (NETs) via a conserved cell death process distinct from apoptosis and necrosis [120]. NETosis are web-like scaffolds of extracellular DNA (eDNA) in complex with histones and antimicrobial neutrophil granular proteins, such as neutrophil elastase, and myeloperoxidase [121-124]. During NETosis neutrophils can transform into enucleated cells with chemokinesis known as cytoplasts [122,123].

NETs play a vital role in host defense against bacteria and fungi [121,122,125] but NETs and cytoplasts are associated with organ injury and chronic inflammation. NETs and cytoplasts have been implicated in several chronic inflammatory and non-infectious diseases [126-128]. Excessive NET production have been reported in patients with respiratory diseases, such as cystic fibrosis [129] and acute respiratory distress syndrome (ARDS), [125,130] and asthma [131].

Excessive NETs and cytoplast production during neutrophilic airway inflammation may cause epithelial injury, and impair epithelial function barrier during respiratory viral infection [131,132]. Furthermore, NETosis induces Th17 differentiation and promotes neutrophilic airway inflammation in patients with asthma, and increased NETs and cytoplasts are associated with severe neutrophilic asthma [132,133]. Furthermore, extracellular DNA (eDNA) mediate inflammasome (e.g., NLRP3) activation, and secretion of IL-1β, and IL-17, which causes further neutrophilic inflammation and epithelial injury [132].

Viral-Induced Exacerbations in Neutrophilic Asthma

A major contributor of asthma morbidity and mortality is an exacerbation usually caused by viral respiratory infection [134] Systemic, [135] and respiratory viral infections can induce production of NETs from neutrophils [130,136], Influenza viruses and rhinoviruses (RVs) are the most common cause of asthma exacerbations [130,137]. Toussaint, et al. [137] have identified neutrophils capable of forming neutrophil extracellular traps in asthmatic airways during infection with RVs. They have shown that activated neutrophils are capable of releasing NETs, and double-stranded DNA (dsDNA), which is major players in orchestrating the underlying airway inflammation and initiating RV-provoked asthma exacerbation [137]. It has been suggested that NETosis and the release of dsDNA, histones, and granule enzymes, such as neutrophil elastase, may be one of the mechanisms responsible for the exacerbations observed in asthmatic patients [138].

Conclusion

Neutrophilic asthma is a complex phenotype of asthma that is severe and persistent, with frequent exacer-
bations, hospitalization, and fixed airway obstruction. Immunopathologically, it is characterized by the presence of high levels of neutrophils, and Th17 staining cells in the lungs and airways. Interleukin-23 plays a pivotal role in the development and maintenance of Th17 cells which produce IL-17. Interleukin-17 plays a key role in the pathogenesis of neutrophilic asthma by expressing the secretion of cytokines, and chemokines responsible for the recruitment and activation of neutrophils. Activated neutrophils release multiple proteinases, cytokines, chemokines, and reactive oxygen species which cause airway epithelial cell injury, inflammation, hyper-responsiveness, and airway remodeling. NETs generated during viral respiratory infections may be responsible for the observed exacerbations in patients with neutrophilic asthma. Neutrophilic asthma is unresponsive to the standard care, including high dose inhaled corticosteroids, and probably to precision novel anti-IgE, interleukin and interleukin monoclonal antibodies therapies. There is need for targeted precision biologics, and other treatment modalities for these patients, such as long-acting phosphodiesterase-4 inhibitors, macrolide antibiotics, and bronchial thermoplasty.

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