ISSN: 2378-3672

Syabbalo. Int J Immunol Immunother 2020, 7:049
DOI: 10.23937/2378-3672/1410049
Volume 7 | Issue 1
Open Access

International Journal of
Immunology and Immunotherapy

REVIEW ARTICLE

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

Abbreviations

Act1: Adaptor protein nuclear factor (NF)-κ activator; AERD: Aspirin-exacerbated respiratory disease; AHR: Airway hyperresponsiveness; ARDS: Adult respiratory distress syndrome; BAL: Bronchoalveolar lavage; CF: Cystic fibrosis; COPD: Chronic obstructive pulmonary disease; CXCL: C-X-C motif chemokine ligand; DPP-4: Dipeptidyl peptidase-4; FEF25-75%: Forced expiratory flow at 25% to 75% points; FeNO: Fractional expired nitric oxide; FEV1: Forced expiratory volume in 1 sec; FVC: Forced vital capacity; GERD: Gastroeosophageal reflux disease; G-CSF: Granulocyte colony-stimulating factor; GM-CSF: Granulocyte/macrophage colony-stimulating factor; GRO-α: Growth-related oncogeneα; ICS: Inhaled corticosteroids; IFN-γ: interferon-γ; JAK: Janus kinase; LABA: Long-acting beta-agonist; LAMA: Long-acting muscarinic antagonist; IL: Interleukin; ILC-3: Type 3 innate lymphoid cells; LTB4: Leukotriene B4; MAP: Mitogen-activated protein; MIP-1α: Macrophage inflammatory protein 1-α; MMP: Matrix metalloproteinases; MPO: Myeloperoxidase; NETs: Neutrophil extracellular traps; NF-κB: Nuclear factor-κb; NO: Nitric oxide; OCS: Oral corticosteroids; OSA: Obstructive sleep apnea; PAF: Platelet activating factor; PGE2: Prostaglandin E2; RORγt: Retinoic acid-related orphan receptor γ; ROS: Reactive oxygen species; RV: Rhinoviruses; SABA: Short-acting beta-agonist; STAT: Signal transducer and activator of transcription; TGF-β: Transforming growth factor-β; Th2: T-helper type 2 cells; Th17: T-helper type 17 cells; TNF-α: tumour necrosis factor-α; TSLP: Thymic stromal lymphopoietin; TXB2: Thromboxane B2

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 beco-

Citation: Syabbalo N (2020) Role of IL-17 and IL-23 in the Pathogenesis of Neutrophilic Asthma. Int J Immunol Immunother 7:049. doi.org/10.23937/2378-3672/1410049

Accepted: May 19, 2020: **Published:** May 21, 2020

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, 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

Table 1: Mechanisms of airflow obstruction in patients with neutrophilic asthma.

Airway neutrophil recruitment, Migration, and Activation
Release of cytokines, Chemokines, Growth factors, and Adhesion molecules
Airway epithelial damage and further release of cytokines
Goblet cells hyperplasia and Mucus hypersecretion
Airway hyperresponsiveness
Subepithelial fibrosis
Airway smooth muscle proliferation
Airway remodeling
Corticosteroid resistance

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 naïve 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)-γt in mouse [56,57], and RORc in humans [57]. The transcription factor Rorγt 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, δγ 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 pathophysiologic 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. Bullone 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-

gnificant neutrophiliain 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, Bullone 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 Interleulkin-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 coworker [93] have demonstrate 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 hyperesponsiveness, goblet cell metaplasia and hypersecretion of mucus, subepethelial 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
Interleukin-6 (IL-6)
IL-8 (CXCL8)
Granulocyte colony-stimulating factor (G-CSF)
Granulocyte macrophage colony-stimulating factor (GM-CSF)
IL-1β
Transforming growth factor-β (TGF-β)
Tumour necrosis factor-α (TNF-α)
Chemokines(C-X-C motif chemokine ligands)
CXCL1 (Gro-α)
CXCL2 (Gro-β)
CXCL5
CXCL6
CXCL8
CXCL2
CCL20
Prostaglandins
Prostaglandin E2
Leukotrienes
Leukotriene B4

Table 3: Chemoattractant mediators associated with neutrophilic airway inflammation.

Cytokines
Interleukin-1β (IL-1β)
IL-6
IL-8 (CXCL8)
IL-17 and IL-17F
IL-23
Interferon-γ (IFN-γ)
Tumour necrosis factor-α (TNF-α)
Macrophage inflammatory protein 1-α (MIP-1α)
Chemokines
CXCL1 (GRO-α)
CXCL2 (GRO-β)
CXCL5
CXCL6
CXCL10
Lipids derivatives
Leukotriene B4 (LTB4)
Lipoxin A4
Prostaglandin E2 (PGE2)
Platelet activating factor (PAF)

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 chemoattractant 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, hyperresponsiveness, 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.

References

1. The Global asthma network (2014) The Global asthma report 2014.
2. Masoli M, Fabian D, Holt D, Beasley R (2004) Global initiative for asthma (GINA) program. The global burden of asthma: Executive summary of the GINA dissemination committee report. Allergy 59: 469-478.
3. National asthma education and prevention program (2007) Expert Panel Report 3 (EPR 3): Guidelines for the diagnosis and management of asthma - a summary report. J Allergy Clin Immunol 120: S94-S138.
4. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, et al. (2006) Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phase one and three repeat multi-country cross-sectional surveys. Lancet 368: 733-743.
5. Wenzel SE, Schwartz LB, Langmack EL, Halliday JL, Trudeau JB, et al. (1999) Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. Am J Respir Crit Care Med 160: 1001-1008.
6. Simpson JL, Scott R, Boyle MJ, Gibson PG (2006) Inflammatory subtypes in asthma: Assessment and identification using induced sputum. Respirology 11: 54-61.
7. Moore W, Bleecker E, Curren-Everett D, Erzurum S, Ameredes BT, et al. (2007) National heart, lung, and blood institute's severe asthma research program. Characterization of the severe asthma phenotypes by the National heart, lung, and blood institute's severe asthma research program. J Allergy Clin Immunol 119: 405-413.
8. Anderson GP (2008) Endotypying asthma: New insights into key pathogenic mechanism in a heterogenous disease. Lancet 372: 1107-1119.
9. Moore WC, Meyer DA, Wenzel SE, Teague WG, Li H, et al. (2010) Identification of asthma phenotypes using cluster analysis in the severe asthma research program. Am J Respir Crit Care Med 181: 315-323.
10. Wenzel SE (2012) Asthma phenotypes: The evolution from clinical to molecular approach. Nat Med 18: 716-725.
11. Siroux V, Gonzalez JR, Bouzigon E, Curjuric I, Boudier A, et al. (2014) Genetic heterogenicity of asthma phenotypes identified by a clustering approach. Eur Resp J 43: 439-452.
12. Sutherland ER, Basagana X, Boudier A, Lehman E, Stevens AD, et al. (2012) Cluster analysis of obesity and asthma phenotypes. PLoS One 7: e36631.
13. (2000) Proceeding of the ATS workshop on refractory asthma: Current understanding, recommendations, and unanswered questions. American Thoracic Society. Am J Respir Crit Care Med 162: 2341-2351.
14. Chung K, Godard P, Adelroth E, Ayres J, Barnes N, et al. (1999) Difficult/therapy-resistant asthma: The need for integrated approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies. Eur Respir J 13: 1198-1208.
15. Bousquet J, Mantzouranis E, Cruz AA, Ait-Khaled N, Baena-Cagnani CE, et al. (2010) Uniform definition of asthma severity, control, and exacerbations: Document presented for the world health organization consultation on severe asthma. J Allergy Clin Immunol 126: 926-938.
16. Chung KF (2016) Asthma phenotyping: A necessity for improved therapeutic precision and new targeted therapies. J Intern Med 279: 192-204.
17. Gold M, Hiebert PR, Park HY, MR Starkey, A Deane, et al. (2016) Mucosal production of uric acid by airway epithelial cells contributes to particulate matter-induced allergic sensitization. Mucosal Immunol 9: 809-820.
18. Kim RY, Pinkerton JW, Essilfie AT, Robertson AAB, Baines KJ, et al. (2017) Role of NLRP3 inflammasome-mediated, IL-1β-dependent responses in severe asthma. Am J Respir Crit Care Me 196: 283-297.
19. Pinkerton JW, Kim RY, Robertson AAB, Hirota JA, Wood LG, et al. (2017) Inflammasomes in the lung. Mol Immunol 86: 44-55.
20. Chang HS, Lee T-H, Jun JA, Baek AR, Park JS, et al. (2017) Neutrophil inflammation in asthma: Mechanisms and therapeutic consideration. Expert Rev Respir Med 11: 29-40.
21. Simpson JL, Douwes J, Scott RJ, Boyle MJ, Gibson PG (2007) Innate immune activation in neutrophilic asthma and bronchiectasis. Thorax 62: 211-218.
22. Kim RY, Pinkerton JW, Gibson PG, Cooper MA, Horvat JC, et al. (2015) Inflammasomes in COPD and neutrophilic asthma. Thorax 50: 1-3.
23. Oppemann B, Lesley R, Blom B, Timans JC, Xu Y, et al. (2000) Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. Immunity 13: 715-725.
24. Cua DJ, Sherlock J, Chen Y, Murphy CA, Joyce B, et al. (2003) Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. Nature 421: 744-748.
25. Kastelein RA, Hunter CA, Cua DJ (2007) Discovery and biology of IL-33 and IL27: Related but functionally distinct regulators of inflammation. Annu Rev Immunol 25: 221-242.
26. Vignoli DAA, Kuchroo VK (2012) IL-12 family cytokines: Playmakers. Nat Imunol 13: 722-728.
27. Hsieh CS, Macatania SE, Tripp CS, Wolf SF, O'Garra, et al. (1993) Development of TH1 CD4+ T cells through IL-12

produced by Listeria-induced macrophages. Science 260: 547-549.

28. Hua Z, Yi B, Fang W, Xiaojing M (2016) Regulation of interleukin-12 production in antigen-presenting cells. Adv Exp Med Biol 941: 117-138.

29. Aggarwal S, Ghilardi N, Xie MH, de Sausage FJ, Gurney AL (2003) Interleukin-23 promotes a distinct CD4 T cell activation state characterized by production of interleukin-17. J Biol Chem 278: 1910-1914.

30. Duvallet E, Semerano L, Assier E, Falgarone G, Boissier MC (2011) Interleukin-23: A key cytokine in inflammatory disease. Ann Med 43.

31. Langrish CL, Chen Y, Blumenschein WM, Mattson J, Basham B, et al. (2005) IL-23 drives a pathogenic T cell population that induces autoimmue inflammation. J Exp Med 201: 233-240.

32. McGeachy MJ, Bak-Jensen KS, Chen Y, Tato CM, Blumenschein W, et al. (2007) TGF-beta and IL-6 drive the production of IL-17 and IL-10 by T cells and restrain T(H)17 cell-mediated pathology. Nat Immunol 8: 1390-1397.

33. Gaffen SL, Jain R, Garg AV, Cua DJ (2014) The IL-23-IL-17 immune axis: From mechanisms to therapeutic testing. Nat Rev Immunol 14: 585-600.

34. Chabaud M, Durand JM, Buchs N, Fossiez F, Page G, et al. (1999) Human interleukin-17: A T cell-derived proinflammatory cytokine produced by the rheumatoid synovium. Arthritis Rheum 42: 963-970.

35. Robert M, Miossec P (2018) IL-17 in rheumatoid arthritis and precision medicine: From synovitis expression to circulating bioactive levels. Front Med (Lausanne) 5: 364.

36. Di Cesare A, Di Meglo P, Nestle PO (2009) IL-23/Th17 axis in the immunopathogenesis of psoriasis. J Invest Dermatol 129: 1339-1350.

37. Nakajima K (2012) Critical role of the interleukin-23/T-helper 17 cell axis in the pathogenesis of psoriasis. Dermatol 39: 219-224.

38. Mannon PJ, Fuss IJ, Mayer L, Elson CO, Sandborn WJ, et al. (2004) Anti-IL-12 crohn's disease study group. Anti-IL-12 antibody for active Crohn's disease. N Engl J Med 351: 2067-2079.

39. Sarra M, Pallone F, McDonald TT, Monteleone G (2010) IL-23/IL-17 axis in IBD. Inflamm Bowel Dis 16: 1808-1813.

40. Nakajima H, Hirose K (2010) Role of IL-23 and Th17 cells in airway inflammation in asthma. Immune Network.

41. Syabbalo N (2020) Neutrophilic asthma: A complex phenotype of severe asthma. J Lung Pulm Respir Res 7: 18-24.

42. Ciprandi G, Cuppari C, Salpeitro AM, Tosca MA, Rigoli L, et al. (2012) Serum IL-23 strongly and inversely correlates with FEV1 in asthmatic children. Int Arch Allergy Immunol 159: 183-186.

43. Ciprandi G, Cuppari C, Salpietro C (2012) Serum IL-23: A surrogate biomarker for asthma? Clin Exp Allergy 42: 1416-1417.

44. Harrington LE, Hatton RD, Mangan PR, Turner H, Murphy TL, et al. (2005) Interleukin 17-producing CD4+ effector T cell develop via a lineage distinct from the T helper type 1 and type 2 lineages. Immunology 6: 1123-1132.

45. Park H, Li Yang XO, Chang SH, Nurieva R, Wang Y, et al. (2005) A distinct lineage of CD+ T cells regulates tissue inflammation by producing interleukin 17. Nat Immunol 6: 1133-1141.

46. Korn T, Betteli E, Oukka M, Kuchroo VK (2009) IL-17 and 17 cells. Annu Rev Immunol 27: 485-517.

47. Wilson NJ, Boniface K, Chan JR, Mckenzie BS, Blumenschein WM, et al. (2007) Development, cytokine profile and function of human interleukin 17-producing helper T cells. Nat Immunol 8: 950-957.

48. Chen Z, Tato CM, Muul L, Laurence A, O'Shea JJ (2007) Distinct regulation of interleukin-17 in human T helper lymphocytes. Arthritis Rheum 56: 2936-2946.

49. Liang SC, Tan XY, Luxenberg DP, Karim R, Dunussi-Joanopoulos K, et al. (2006) Interleukin (IL)-22 and IL-17 are coexpressed by Th7 cells and cooperatively enhance expression of antimicrobial peptides. J Exp Med 203: 2271-2279.

50. Chung Y, Yang X, Chang SH, Ma L, Tian Q, et al. (2006) Expression and regulation of IL-22 in the IL-17-producing CD41 T lymphocytes. Cell Res 16.

51. Zheng Y, Danilenko DM, Valdez P, Eastham-Anderson J, Wu J, et al. (2007) Interleukin-22, a T(H)17 cytokine mediates IL-23-induced dermal inflammation and acanthosis. Nature 445: 648-651.

52. Tesmer LA, Lundy SK, Sarkar S, Fox DA (2008) Th17 cells in human disease. Immunol Rev 223: 87-113.

53. Bettelli E, Korn T, Oukka M, Kuchroo VK (2008) Induction of effector functions of T(H)17 cells. Nature 453: 1051-1057.

54. Mangan PR, Harrington LE, O'Quinn DB, Helms WS, Bullard DC, et al. (2006) Transforming growth factor-β induces development of TH17 lineage. Nature 441: 231-234.

55. Veldeon M, Hocking RJ, Atkins CJ, Locksley RM, Stockinger B (2006) TGTbeta in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing cells. Immunity 24: 179-189.

56. Miossec P, Korn T, Kuchroo VK (2009) Interleukin-17 and type 17 helper T cells. N Engl J Med 361: 888-898.

57. Ivanov II, McKenzie BS, Zhou L, Tadokoro CE, Lepelley A, et al. (2006) The orphan nuclear receptor RORgammat directs differentiation program of proinflammatory IL-17+ T helper cells. Cell 1262: 1121-1133.

58. Noack M, Miossec P (2014) Th17 and regulatory T cell balance in autoimmune and inflammatory diseases. Autoimmune Rev 13: 668-677.

59. Stockinger B, Veldhoen M (2007) Differentiation and function of Th17 T cells. Curr Opin Immunol 19: 281-286.

60. McGreachy MJ, Cua DJ (2008) Th17 cells differentiation: The long and winding road. Immunity 28: 445-453.

61. Haines CJ, Chen Y, Blumenschein WM, Jain R, Chang C, et al. (2013) Autoimmune memory T-helper 17 cell function and expansion are dependent on interleukin-23. Cell Rep 3: 1378-1388.

62. Zhou L, Ivanov II, Spolski R, Min R, Shenderov K, et al. (2007) IL-6 programs T(H)-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathway. Nat Immunol 8: 967-974.

63. Korn T, Betteli E, Gao W, Awasthi A, Jager A, et al. (2007) IL-21 initiates alternative pathway to induce T(H)17 cells. Nature 448: 484-487.

64. Wei L, Laurence A, Elias KM, O'Shea JJ (2007) IL-21 is produced by Th17 cells and drives IL-17 production in a STAT3-dependent manner. J Biol Chem 282: 34605-34610.

65. Acosta-Rodriguez EV, Napolitani G, Lanzaveocchia A, Sal-

lusto F (2007) Interleukins 1beta and 6 but not transforming growth factor-beta are essential for the differentiation of interleukin 17-producing cells. Nat Immunol 8: 942-949.

66. Chung Y, Chang SH, Martinez GJ, Yang XO, Nurieva R, et al. (2009) Critical regulation of early Th17 cell differentiation by interleukin-1 signaling. Immunity 30: 576-587.

67. Michel ML, Mendes-da-Cruz D, Keller AC, Lochner M, Schneider E, et al. (2008) Critical role of ROR-gammat in a new thymic pathway leading to IL-17-producing invariant NKT cell differentiation. Proc Natl Acad Sci USA 105: 19845-19850.

68. Roark CL, Simonian PL, Fontenot AP, Born WK, O'Brien RL (2008) Gammadelta T cells: An important source of IL-17. Curr Opin Immunol 20: 353-357.

69. Rachitskaya AV, Hansen AM, Horai R, Li Z, Villasmil R, et al. (2008) Cutting edge: NKT cells constitutively express IL-23 receptor and RORgammat and rapidly produce IL-17 upon receptor ligation in an IL-6-induced fashion. J Immunol 180: 5167-5171.

70. Takatori H, Kunno Y, Watford WT, Tato CM, Weiss G, et al. (2009) Lymphoid tissue inducer-like cells are an innate source of IL-17 and IL-22. J Exp Med 206: 35-41.

71. Cua DJ, Tato CM (2010) Innate IL-17 producing cells: The sentinel of the immune system. Nat Rev Immunol 10: 479-489.

72. Brodlie M, McKean MC, Johnston GE, Anderson AE, Hilkens CM, et al. (2011) Raised interleukin-17 is immunolocalised to neutrophils in cystic fibrosis lung disease. Eur Respir J 37: 1378-1385.

73. Ramirez-Velazquez C, Castillo EC, Guido-Bayardo L, Ortiz-Navarrete V (2013) IL-17-producing peripheral blood CD177+ neutrophils increase in allergic subjects. Allergy Asthma Clin Immunol 9: 23.

74. Song C, Luo L, Lei Z, Li B, Liang Z, et al. (2008) IL-17A-producing alveolar macrophages mediate allergic lung inflammation related to asthma. J Immunol 181: 6117-6124.

75. Molet S, Hamid Q, Davoine F, Nutku E Taha R, et al. (2001) IL-17 is increased in asthmatic airways and induces human bronchial fibroblasts to produce cytokines. J Allergy Clin Immunol 108: 430-438.

76. Rouvier E, Luciani MF, Mattei MG, Denoit F, Golstein P (1993) CTLA-8, cloned from activated T cell, bearing AU-rich messenger RNA instability sequences, homologous to a herpes virus saimari gene. J Immunol 150: 5445-5456.

77. Yao Z, Maraskovsky E, Spriggs MK, Cohen JI, Armitage RJ, et al. (1996) Herpesvirus saimari open reading frame 14, a protein encoded by T lymphotropic herpes virus, binds to MHC class II molecules and stimulates T cell proliferation. J Immunol 156: 3260-3266.

78. Yao Z, Fanslow WC, Seldin MF, Rousseau AM, Painter SL, et al. (1995) Herpesvirus Saimiri encodes a new cytokine, IL-17, which binds to a novel cytokine receptor. Immunity 3: 811-821.

79. Aggarwal S, Gurney AL (2002) IL-17: Prototype member of an emerging cytokine family. J Leukoc Biol 71: 1-8.

80. Kolls JK, Linden A (2004) Interleukin-17 family members and inflammation. Immunity 21: 467-476.

81. Gaffen S (2009) Structure and signaling of the IL-17 receptor family. Nat Rev Immunol 9: 556-567.

82. Pappu BP, Angkasekwinai P, Dong C (2008) Regulatory mechanisms of helper T cell differentiation: New lesson learned from interleukin 17 family cytokines. Pharmacol Ther 117: 374-384.

83. Angkasekwinai P, Park H, Wang YH, Wang YH, Chang SH, et al. (2007) Interleukin 25 promotes the initiation of proallergic type 2 response. J Exp Med 204: 1509-1517.

84. Metawi S, Abbas D, Kamal M, Ibrahim M (2011) Serum and synovial fluid levels of interleukin-17 in correlation with disease activity in patients with RA. Clin Rheumatol 30: 1201-1207.

85. Park J, Park M, Lee S, Oh H, Lim M, et al. (2012) TWEAK promotes the production of interleukin-17 in rheumatoid arthritis. Cytokine 60: 143-149.

86. Arican OAM, Sasmaz S, Ciragil P (2005) Serum levels of TNF-alpha, IFN-gamma, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. Mediators Inflamm 2005: 273-279.

87. Martin DA, Toune JE, Kricorian G, Klekotka P, Gudjonsson JE, et al. (2013) The emerging role of IL-17 in the pathogenesis of psoriasis: Preclinical and clinical findings. J Invest Dermatol 133: 17-26.

88. Bullone M, Carriero V, Bertolini F, Anna Folino, Alessandro Mannelli, et al. (2019) Evaluated serum IgE, oral corticosteroid dependence and IL-17/22 expression in a highly neutrophilic asthma. Eur Respir J 54.

89. Trevor JL, Deshane JS (2014) Refractory asthma: Mechanisms, targets, and therapy. Allergy 69: 817-827.

90. Barczyk A, Pierzchala W, Sozanska E (2003) Interleukin 17A in sputum correlates with airway hyperresponsiveness to methacholine. Repir Med 97: 726-733.

91. Sun Y-c, Zhau Q-t, Yao W-z (2005) Sputum interleukin-17A is increased and associated with airway neutrophilia in patients with severe asthma. Chin Med J 118: 953-956.

92. Al-Ramli W, Prefontaine D, Chouiali F, Martin JG, Olivenstein R, et al. (2009) T(H)17-associated cytokines (IL-17A and IL-17F) in severe asthma. J Allergy ClinImmunol 123: 1185-1187.

93. Bullens DMA, Truyen E, Coteur I, Dilissen E, Hellings PW, et al. (2006) IL-17 mRNA in sputum of asthmatic patients: Linking T cell driven inflammation and granulocytic influx? Respir Res 124: 45-51.

94. Roussel L, Houle F, Chan C, Yao Y, Berube J, et al. (2010) IL-17 promotes p38 MAPK-dependent endothelial activation enhancing neutrophil recruitment to sites of inflammation. J Immunol 184: 4531-4537.

95. Chang Y, Al-Alwani L, Risse P-A, Halayko AJ, Martin JG, et al. (2012) Th17-associated cytokines promote human airway smooth muscle proliferation. FASEB J 25: 5152-5160.

96. Jovanovic DV, Di Battista JA, Martel-Pelletier J, Jolicoeur FC, He Y, et al. (1998) IL-17 stimulates the production and expression of proinflammatory cytokines, IL-beta and TNF-alpha, by human macrophages. J Immunol 160: 3513-3521.

97. Linden A (2001) Role of interleukin-17 and the neutrophil in asthma. Int Arch Allergy Immunol 126: 179-184.

98. Linden A, Laun M, Anderson GK (2005) Neutrophil, interleukin-17A and lung disease. Eur Respir J 25: 159-172.

99. Baggliolini M, Walz A, Jundel SL (1989) Neutrophil-activating peptide-1/interleukin-8, a novel cytokine that that activates neutrophils. J Clin Invest 84: 1045-1052.

100. Matsushima K, Baldwin ET, Mukaida N (1992) Interleu-

kin-8 and MCAF: Novel leukocyte recruitment and activating cytokines. Chem Immunol 51: 236-265.

101. Baggiolini M, Clark-Lewis I (1992) Interleukin-8, a chemotactic and inflammatory cytokine. FEB Lett 302: 97-101.

102. Hammad ME, Lapointe GR, Feucht PH, Hitts S, Gallegos CA, et al. (1995) IL-8 induces neutrophil chemotaxis predominantly via type 1 IL-8 receptors. J Immunol 155: 1428-1433.

103. Dunican AL, Leuenroth SJ, Grutkoski P, Ayala A, Simms HH (2000) TNFα-induced suppression of apoptosis is mediated through interleukin-8 production. Shock 14: 284-288.

104. Nocker RE, Schoonbrood DF, van de Graaft EA, Hack CE, Lutter R, et al. (1996) Interleukin-8 in airway inflammation in patients with asthma and chronic obstructive pulmonary disease. Int Arch Allergy Immunol 10: 183-191.

105. Chanez P, Enander I, Jones I, Godard P, Bousquet J (1996) Interleukin 8 in bronchoalveolar lavage of asthmatics and chronic bronchitis patients. Int Arch Allergy Immunol 111: 83-88.

106. Gibson PG, Simpson JL, Saltos N (2001) Heterogeneity of airway inflammation in persistent asthma: Evidence of neutrophilic inflammation and increased sputum interleukin-8. Chest 119: 1329-1336.

107. Jatakanon A, Uasuf C, Maziak W, Lim S, Chung KF, et al. (1999) Neutrophilic inflammation in severe persistent asthma. Am J Respir Crit Care Med 160: 1532-1539.

108. Liu W, Liu S, Verma M, Zafar I, Good JT, et al. (2017) Mechanism of Th2/Th17 predominant and neutrophilic Th2/Th17-low subtypes of asthma. J Allergy Clin Immunol 139: 1548-1558.

109. Monteserin J (2009) Neutrophils and asthma. J Investig Allergol ClinImmunol 19: 340-354.

110. Bruijnzeel PLB, Uddin M, Koenderman L (2015) Targeting neutrophilic inflammation in severe neutrophilic asthma: can we target the disease-relevant neutrophil phenotype. J Leukoc Biol 98: 549-556.

111. Fuschillo S, De Felice A, Balzano G (2008) Mucosal inflammation in idiopathic bronchiectasis: Cellular and molecular mechanisms. Eur Resp J 31: 396-406.

112. Gilfford AM, Chalmers JD (2014) Neutrophils in cystic fibrosis. Curr Opin Hematol 21: 16-22.

113. Hoenderdos K, Condliffe A (2013) The neutrophil in chronic obstructive pulmonary disease. Too little, too late or too much, too soon? Am J Respir Cell Mol Biol 48: 531-539.

114. Scott BNV, Kube P (2018) Death to the neutrophil! A resolution for acute respiratory syndrome. Eur Respir J 52.

115. Teran LM, Campos MG, Begishvilli BT, Schroder JM, Djukanovic R, et al. (1997) Identification of neutrophil chemotactic factors in bronchoalveolar lavage fluid of asthmatic patients. Clin Exp Allergy 27: 396-405.

116. Wenzel SE, Larsen GL, Johnston K, Voelkel NF, Westcott JY (1990) Elevated levels of leukotriene C4 in bronchoalveolar lavage fluid from atopic asthmatics after endobronchial allergen challenge. Am Rev Respir Dis 142: 112-119.

117. Cundall M, Sun Y, Miranda C, Trudeau JB, Barnes S, et al. (2003) Neutrophil-derived metalloproteinase-9 is increased in severe asthma and poorly inhibited by glucocorticoids. J Allergy ClinImmunol 112: 1064-1071.

118. Grunwell JR, Stephenson ST, Tirouvanzanian R, Brown LAS, Brown MR, et al. (2019) Children with neutrophilic-predominant severe asthma have proinflammatory neutrophils with enhanced survival and impaired clearance. J Allergy Clin Immunol 7: 516-525.

119. Brinkmann V, Zychlinsky A (2012) Neutrophil extracellular trap. Is immunity the second function of chromatin? J Cell Biol 198: 773-783.

120. Takei H, Araki A, Watanabe H, Ichinose A, Sendo R (1996) Rapid killing of human neutrophils by the potent activator phorbol 12-myristate 13-acetate (PMA) accompanied by changes different from typical apoptosis or necrosis. J Leukoc Biol 59: 229-240.

121. Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y, et al. (2004) Neutrophil extracellular traps kill bacteria. Science 303: 1532-1535.

122. Yipp BG, Petri B, Salina D, Jenne CN, Scott BNV, et al. (2012) Infection-induced NETosis is a dynamic process involving neutrophil multitasking in vivo. Nat Med 18: 1386-1393.

123. Fuchs TA, Abed U, Goosmann C, Hurwitz R, Schutze I, et al. (2007) Novel cell death program leads to neutrophil extracellular traps. J Cell Biol 176: 231-241.

124. Papayannopoulos V, Metzler KD, Hakkim A, Zychlinsky A (2010) Neutrophil elastase and myeloperoxidase regulate formation of neutrophil extracellular traps. J Cell Biol 191: 677-691.

125. Remijsen Q, Kuippers TW, Wirawan E, Lippens S Vandenabeele P, et al. (2011) Dying for a cause: NETosis, mechanisms behind an antimicrobial cell death modality. Cell Death Differ 18: 581-588.

126. Thomas GM, Carbo C, Curtis BR, Martinod K, Mazo IB, et al. (2012) Extracellular DNA traps are associated with the pathogenesis of TRALI in humans and mice. Blood 119: 6335-6343.

127. Jorch SK, Kubes P (2017) An emerging role for neutrophil extracellular traps in noninfectious diseases. Nat Med 23: 279-287.

128. Kaplan MJ, Radic M (2002) Neutrophil extracellular traps: Double-edged sword of innate immunity. J Immunol 189: 2689-2695.

129. Dwyer M, Shan Q, D'Ortana S, Maurer R, Mitchell R, et al. (2014) Cystic fibrosis sputum DNA has NETosis characteristics and neutrophil extracellular trap release is regulated by migration-inhibitory factor. J Innate Immun 6: 765-779.

130. Narasaraju T, Yang E, Samy RP, Ng HH, Poh WP, et al. (2011) Excessive neutrophils and neutrophil extracellular traps contribute to acute lung injury of influenza pneumonitis. Am J Pathol 179: 199-210.

131. Krishnamoorthy N, Douda DN, Bruggerman TR, Ricklefs I (2018) National heart, lung, and blood institute severe asthma research program-3 investigators. Neutrophil cytoplasts induce Th17 differentiation and skew inflammation towards neutrophilia in severe asthma. Sci Immunol 3.

132. Lachowicz-Scroggins ME, Dunican EM, Charbit AR, Raymond W, Looney MR, et al. (1999) Extracellular DNA, neutrophil extracellular traps, and inflammasome activation in severe asthma. Am J Respir Crit Care Med 199: 1076-1085.

133. Pham DL, Bon GY, Kim SH, Shin YS, Le YM, et al. (2017)

Neutrophil autophagy and extracellular DNA traps contributes to airway inflammation in severe asthma. Clin Exp Allergy 47: 57-70.

134. Busse WW, Lemanske RF, Jr Gern JE (2010) Role of viral respiratory infection in asthma and asthma exacerbations. Lancet 376: 826-834.

135. Saitoh T, Komano J, Saitoh Y, Misawa T, Takahama M, et al. (2012) Neutrophilic traps mediate host-defense response to human immunodeficiency virus-1. Cell Host Microbe 12: 101-116.

136. Schonrich G, Raftery MJ (2016) Neutrophil extracellular traps go viral. Front Immunol.

137. Toussaint M, Jackson DJ, Swieboda D, Guedan A, Tsorouktsoglou T-D, et al. (2017) Host DNA related NETosis promotes rhinovirus-induced type-2 allergic asthma exacerbations. Nat Med 23: 1384.

138. Jackson JD, Makrinioti H, Rana BMJ, Shamji BWH, Trujillo-Tarralbo M-B, et al. (2014) IL-33-dependent type 2 inflammation during rhinovirus-induced asthma exacerbations in vivo. Am J Respir Crit Care Med.