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Inflammation in Asthma Pathogenesis: Role of Eosinophil, Basophils, Neutrophil and Mast Cells.

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Abstract

Asthma is a common chronic airway disease worldwide. Recent studies findings suggested that asthma is not a single disease entity, but it is a syndrome that characterised shortness of breath, intermittent attack, cough and wheezing. The disease onset commonly occurred during childhood. The natural history of asthma is variable and the disease not restricted to children, also it affects adults and both gender. Asthma pathogenesis is a complex scenario interplay of sequences of inflammation, immune responses, and airway remodelling. Thus the disease presented with different phenotypes and endotypes which are with variable treatment outcomes. The chronic inflammation is a main corner stone of asthma pathogenesis during attack and during asymptomatic course. The inflammation and immune responses are induced by the inhaled allergens and multiple host cells are involved in asthma pathogenesis. In this review we present the role of eosinophils, basophils and neutrophils in pathogenesis of asthma.
Keywords: Asthma, eosinophil, basophil, neutrophil.

1. Introduction

Asthma is a common chronic airway disease worldwide [1,2].Asthma is not a single disease entity, but it is a syndrome that characterised by shortness of breath, intermittent attack, cough and wheezing. The disease onset commonly occurred during childhood [3]. The natural history of asthma is variable and the disease not restricted to children, also it affects adults and both gender [3]. Asthma pathogenesis is a complex scenario interplay of sequences of inflammation, immune responses, and airway remodelling. [4,5]

The chronic inflammation is a main corner stone of asthma pathogenesis during attack and during asymptomatic course [6]. The inflammation and immune responses are induced by the inhaled allergens, that include house dust mite, moulds, grasses, pollen, animal dander, and trees [7,8]

After the induction phase of the disease, there is possibility of remission or course chronicity with intermittent attacks which lead to smooth muscle hypertrophy, epithelial mucus metaplasia, and glycoprotein deposition in the sub-epithelial matrix [6]. When allergens come in contact with mucus and epithelial barriers penetrate these barriers and induce cytokines that induce subsequent events. Viral infections is a major risk factor for

asthma induction mainly in atopic individuals [9]. Chronic inflammation in asthma was initiated and driven by interplay of innate immune response, adaptive immune response and respiratory epithelium [10].

2. Asthma phenotypes and endotypes

Asthma is not a single entity and it is a heterogenic syndrome. Asthma is defined as a ***''collection of several distinct diseases (endotypes) and varying phenotypes (young atopic, obese middle aged and elderly), all of which manifest with symptoms of wheezing and shortness of breath to cough and chest tightness and accompanied by variable airflow obstruction''[11].***Table 1. Shows the endotypes and phenotypes.

Table 1. Asthma endotypes and phenotypes. [11].

Endotype	Phenotype	Clinical features	Molecular mechanism	Biomarkers	Natural history
T2 high	**Atopic**	**Early onset, well defined, steroid sensitive**	**Allergic sensitisation**	**Blood/sputum eosinophils count, serum specific allergen IgE, high FeNO, high total IgE**	**Identifiable and treatable, preserved lung function**
	Late onset	**± concomitant CRSwNP, steroid refractory**	**Staphylococcus aureus enterotoxin**	**Blood/sputum eosinophils count, high FeNO,**	**Severe from onset, more frequent exacerbation**
	AERD	**Adult onset**	**Dysregulated arachidonic acid metabolism**	**Blood/sputum eosinophils count, urinary LTE4**	**Severe from onset, more frequent exacerbation**
Non-T2	**Non-atopic**	**Adult onset, paucigranuocytic or neutrophilic**	**NLRP3/IL-1ß, altered micro-RNA expression, Th17**	**Induced sputum neutrophil count, MMP-9 in Bal**	**Variable course and lung function**
	Smokers	**Older adult**	**Oxidative stress, mixed Th2 high Th2 low**	**Induced sputum neutrophil count**	**More frequent exacerbation, low lung function**
	Obesity related	**Female sex**	**Oxidative stress, neutrophils, increased innate immune activation,**	**Serum IL-6**	**Severe symptoms, preserved lung function**
	Elderly	**>50 to > 65 years at onset**	**Immunosenescence, Th1/Th17 inflammation**	**Induced sputum neutrophils count**	**Steroid resistant**

CRSwNP= Chronic rhinosinusitis with nasal polyp
FeNO= Fractional excretion of Nitric Oxide

3. Eosinophils role in induction of inflammation in asthma

The role of eosinophils in pathogenesis of asthma was reviewed in last decade [12-15]. The measurement of the inflammation of airway that was induced by eosinophils can be achieved invasively by bronchoscopic sampling or non-invasive sputum analysis [13]. Sputum and bronchoalveolar lavage examined for eosinophils counts, cytology, FeNO, eosinophil cationic protein, eosinophil-derived neurotoxin, eosinophil peroxidase, and major

basic protein. Eosinophil recruitment from blood to tissue required eosinophils activation [16-18]. Allergic diseases including asthma were associated down-regulation or up-regulation of surface eosinophils proteins and Fc receptors or integrins activation [16-19]. Eosinophils surface proteins such as CD44, CD45RO, CD48, CD137, CD89, CD16, IL-2Rα, IL-17RA, CD25, IL-17RB, regulated in asthma and involved in disease pathogenesis [16, 20,21].

The eosinophils surface proteins that serve as a target for therapy in asthmatic patients include activated ß2 integrin, CD162, CD125, CD25, CD18, CD11a, and CD11b [16,21]. However, eosinophils express several inhibitory receptors [22].

The mediators that were released by eosinophils had the capacity for induction of airway hyperresponsiveness [15]. Human eosinophils major basic proteins and eosinophils peroxidase induced airway hyperresponsiveness (AHR) in animal models [23,24]. However, eosinophils cationic proteins and eosinophils-derived neurotoxins did not [23]. The mechanism by which AHR was induced by bradikinin production [24]. In addition, major basic proteins cause histamine release by basophils and mast cells [25,26].

Eosinophils count in sputum and bronchoalveolar lavage fluid was lower in none asthmatic as compared to asthmatic subjects [27]. Th2 cytokines expression like IL-5 as an indicator of eosinophilc inflammation increased in bronchoalveolar lavage fluid from asthma patients [28]. Eosinophilia of blood correlated with asthma exacerbation frequency and severity [27,29], however, there was none eosinophils asthma phenotype and presence of other causes for peripheral eosinophilia [30,31]. Several cytokines such as IL-13 produced by eosinophils and thus IL-13 lead to AHR and induce mucus secretion [24]. Th2 cells and ILC2s also produced IL-13. In addition, eosinophils produced leukotrienes which induce AHR [32].

Eosinophils development from CD34+ hematopoietic progenitor cells were promoted by IL-5, IL-3 and granulocyte-macrophage colony stimulating factor, however, only IL-5 was specific for eosinophils development [12]. Proinflammatory mediators are produced by eosinophils which included eosinophils cationic proteincytokines and newly synthesised eicosanoids [33-35]. Previous studies [12-15]suggested that eosinophils play a role in asthma pathogenesis through release of mediators, cytokines and chemokines such as MBP, ECP, EDN,EPO, galectin-10, LTC4, PEG2, platelet-activating factor, thromboxane, TGF-ß, IL-3, IL-4, IL-5, IL-8,IL-10, IL-12, IL-13, IL-16, IL-18, TNF-α, CCL5 and CCL11. Airway remodelling was a potential change that was caused by eosinophils inflammation induction and release of fibrogenic mediators and multiple growth factors such as transforming growth factor (TGF-ß), matrix metalloproteinase-9, tissue inhibitor of mettaloproteinase-1, vascular endothelial growth factor, basic fibroblast growth factor, angiogenin, MBP, ECP, IL-17, IL-13, heparin-binding epidermal growth factor, nerve growth factor, cystinyl leukotrines, and stem cell factor [36-55]. In asthma exacerbation, eosinophila of the airway was the early feature [56]. In addition, eosinophils released cytokines were responsible for induction of various immunomodulation in asthma patients [26,57-70]. Fig1. Illustrate the role of eosinophils in asthma pathogenesis.

4. Basophils role in induction of inflammation in asthma

Recent studies indicated that basophils play a potential role in induction of allergic inflammation in both IgE dependent and none-dependent. [71]. Basophils migrated to the site of allergic inflammation and secreted chemokines, proteases and cytokines [12]. The mediators that were produced by basophils divided in to cytokines/chemokines, preformed mediators, and newly synthesised lipid mediators [72]. In allergic inflammation basophils induced its effect through histamine that is stores in granules, rapid production of LTC4, LTD4, and LTE4 which cause bronchoconstriction and increase vascular permeability [12,14].

Activated basophils expressed cytokines such as GM-CSF, IL-13 and IL-4, but IL-4 was secreted by activated basophils in high concentration and rapid response [12]. In animal model, basophils production of none mediated IgE IL-4 was the early differentiation of Th2 [73]. IgE synthesis amplification under the control of expression of IL-13, IL-4 and CD154 by basophils [12]. A novel mediator, granzyme B (protease) was secreted in asthma following challenge with inhalation allergens [74]. The predominant source of IL-4 in allergen activated polymorphonuclear cells and in mouse models [12]. Post-mortem studies on patients die due to asthma show increased number of basophils in lung tissue [73,75-77]. Studies in animal models suggested that basophils play direct role as antigen presenting cell that lead to Th2 responses induction, IL-4and MHC class II molecule expression [78-80]. CD63 and CD203C are the well-described human basophils activation markers [81-83]. Similar up-regulation exhibited by CD107a, CD164 and CD13 [84]. Identification of basophils can be achieved by expression of CCR3, CD123, or CRTH2 cell surface markers [82,83]. Additionally, basogranulin was a the specific basophils marker [85] and secreted after both non- IgE and IgE- mediated stimuli [86]. Basophils identification in tissue can be done using immunohistochemical technique to detect basogranulin as specific marker [87].

5. Neutrophils role in induction of inflammation in asthma

Neutrophilic asthma is one of the refractory asthma phenotype, which characterised by course severity, fixed obstruction of the airway, poor response to treatment and frequent exacerbation [88-91]. Neutrophilic asthma was not fully understood phenotype, however, this phenotype was complex and form about 30-50% of symptomatic asthma [92]. Obesity, gastrointestinal reflux disease, respiratory infections, and obstructive sleep apnoea were associated with neutrophilic asthma [93].

Better outcomes of severe asthma treatment were achieved recently by the phenotypes characterization which contribute to personalized therapy of asthma through the development of novel biologics [88,92,94,95,96,97]. Th2 driven eosinophic asthma in about 50% of asthma cases, while the remaining half were none eosinophils asthma phenotypes and were subdivided into paucigranulocyte and neutrophilc subtypes [94,95,98].

Phenotype of neutrophilic asthma was less well defined [99,100], while the eosinophils asthma phenotype was well defined [96,98-105]. Neutrophilic asthma pathophysiology was complex. High neutrophils count in sputum from neutrophilic asthma in 40-76% of sputum cells [99,100,106] and less sputum eosinophils count [95,104]. Presence of high number of neutrophils in sputum was associated with persistant asthma severity [88,95,97,106,107], low FEV1 [108] and fixed airway obstruction [106,108,109]. Exacerbation was more frequent in neutrophilic asthma phenotype, but the severity was less than that in eosinophilic phenotype [110-113].

Neutrophilic asthma was characterised by nocturnal worsening which associated with high number of BAL granulocytes [114] and this guide the treatment of cases [115]. Neutrophilic asthma was with poor prognosis, worse quality of life, none responsive to high dose of inhaled corticosteroids and newly developed biologic therapy [88-90,97,102,108,116-122].

To date, there was no specific biomarkers for neutrophilic asthma diagnosis, however, the phenotype was adult onset, mainly not atopic, and with bronchoprovacation test weak responsiveness to methacholine [103,108,123-125]. Innate immune response alteration and Th17 cells activation drive the neutrophilic asthma [126-128]. IL-17A and IL-17F were play a potential role in neutrophilic asthma pathogenesis and neutrophilic inflammation. However, other cytokines and chemochines such as TGF-ß, TNF-α, IL-1ß, IL-23, IL-8 and IL-6 which act with IL-17A in induction of neutrophilic inflammation in severe cases [129-132].

Pathogens elimination from the airway was done by neutrophils. But persistent neutrophilia and protease secretion will lead to airway injury, hypersecretion of mucus, and airway obstruction and remodelling [133]. Neutrophils recruitment to lung tissue in asthma patients and induce neutrophilic inflammation include the following cytokines, lipids, chemokines and complements: IL-1α, IL-1ß, IL-1Ra, IL-6, IL-10, IL-17, IL-23, INF-γ, TNF-α, LTB4, Lipoxin A4, Resolvin D1/E1, PGD2, CXCL1, CXCL5, CXCL6, CXCL8, C5a, and FMLP [134-163]. However, IL-1Ra, IL-10, Lipoxin A4, Resolvin D1/E1, and PGD2 were decreased while others were increased. The most potent neutrophils chemoattractant in the lung was CXCL8 [164] and was increased in asthmatic nasal secretions and sputum [165,166]. Asthmatic patients neutrophils express the high affinity IgE receptor (FcsR1) which induct release of CXCL8 from neutrophils [167]. It was suggested that Th17, Th1 and neutrophils form a network communication in airway and cause severe attack that refractory to corticosteroids [133].

In asthma patients, neutrophils form the first line defense mechanism against pulmonary infection [168], however, it release mediators that attract macrophages/monocytes to infection site [169].Additional side effects were excerted by neutrophils and cause mucus hypersecretion, and airway obstruction, airway smooth muscle responsiveness increase, and airway remodelling [170-172]. Studies in children and adults with asthma not confirmed the association between neutrophilic inflammation and airway remodelling [173,174]. Persistence of neutrophils in airway of asthma patients may be contributed to that corticosteroids inhibition of neutrophils apoptosis [175-178],release of ATP from dying cells [179-181], LTB4 inflammatory mediators [182], and pathogen-induced mechanisms [183].

6. Mast cells role in induction of inflammation in asthma

Mast cells activation as a response to IgE antigen binding receptor with Th2 cell activation initiate the chronic inflammation in asthma [184]. Mast cells contain high affinity IgE receptors and localised in connective tissue and mucosal membrane and blood vessels [185]. Mast cells play a potential key role in induction of inflammation and modulation of production of mediators and activated by cytokines, viral and bacterial antigens, hormones and growth factors [186]. Local production of monocytes/mast cells (MCP-1 and RANTES) chemotactic factors lead to accumulation of mast cells in inflamed tissues [187].

Mast cells with two phenotypes, the mucosal mast cells and tissue mast cells [188]. Tissue mast cells contain chymase and tryptase, while mucosal mast cells contain tryptase only, additionally, both phenotypes were differ in their number, secretary granules type and stimuli responsiveness [188]. Mucosal mast cells contain more chondroitin, while tissue mast cells contain heparin and responded to neuropeptides while mucosal mat cells not respond [188].

Mast cells play a role in asthma pathophysiology [189], and mast cells express many receptors such as CD117, Fc€R1, CD32a, CD64, PGE2 receptors, C3a and C5a receptors, adenosine receptor, ß2 adrenergic receptor, IL-10R, IL-9R, IL-5R, IL-4R, IL-3R, IFN-γR, GM-CSFR, CXCR4, CXCR2, CCR5, CCR3, Toll-like receptor, and nerve growth factor receptor [190-192]. Mast cells release or generate PGD2, platelets activating factor, histamine, leukotrines, and others as a immediate inflammation responses [193]. The above mediators induce spasmogenic and vasoactive action in asthmatic patients.

Proinflammatory cytokines such as IL-8, IL-6, IL-1 and TNF-α which are innate immunity important factors and mast cells the only cells that release preformed TNF-α [194].Theoharides et al [195] reported that asthma worsen by stress, a process that mediated by mast cells activation that infiltrate bronchial smooth muscle and cytokines secretion. IL-9 target mast cells and expanded the population of mast cells [196]. Independent of IgE, mast cells activated by IL-18 and produce histamine and Th2 cytokines [197]. Several

inflammatory cells were detected in bronchial biopsy and BAL including mast cells [198]. Mast cells synthesise IL-17 in response to signals through TLR9, TLR7, TLR4, TLR3, TLR2, and TLR1 [199]. IL-33 augmented the release of vascular endothelia growth by mast cells in response to substance P [200]. Mast cells participation in asthma development is through surface high affinity receptors for IgE cross-linking which lead to production of proinflammatory and vasoactive materials [184].

Mast cells released mediators that were classified into cytokines/ chemokines, newly synthesized lipid mediators, and preformed mediators [12], however, this categorization not absolute as that TNF-α included in newly synthesized and preformed mediators. The preformed mediators include tryptase, chymase, histamine, proteoglycans (heparin and chondroitin sulphates) carboxypeptidase A and their storage was in cytoplasmic granules [12]. These mediators play a role in the pathophysiology of asthma [14].

KIT (CD117) and Fc€R1activated mast cells and contribute to rapid synthesis of eicosanoid mediators from arachidonic acid that was stored in endogenous membrane and subsequent synthesis of cysteinyl leukotrienes which induce bronchoconstriction, attract eosinophils, mucus production induction and initiate vascular permeability. PGD2 as newly synthesized mediators induce basophils and eosinophils attraction and bronchoconstriction [12]. Additionally, TNF-α stored and produced by mast cell and cause increase in hyperresponsiveness and upregulation of epithelial and endothelial adhesion molecules. Also mast cells release other cytokines (such as GM-CSF, IL-3, IL-5, IL-13, 1L-10, IL-6) and chemokines [CCL3, CXCL8 (IL-8)] [190-192].

Based on animal studies it was suggested that mast cells to play function in adaptive immunity, innate immunity, and homeostasis [12].

Allergic diseases (asthma, allergic rhinitis and anaphylaxis) pathogenesis central action was the activation of mast cells through Fc€R1 [12]. Atopic asthma specificity is the Fc€R1 expression robust upregulation on nasal and alveolar mast cells and the changes of alveolar mast cells skewed toward Th2 profile that was correlated with clinical outcome [201,202].

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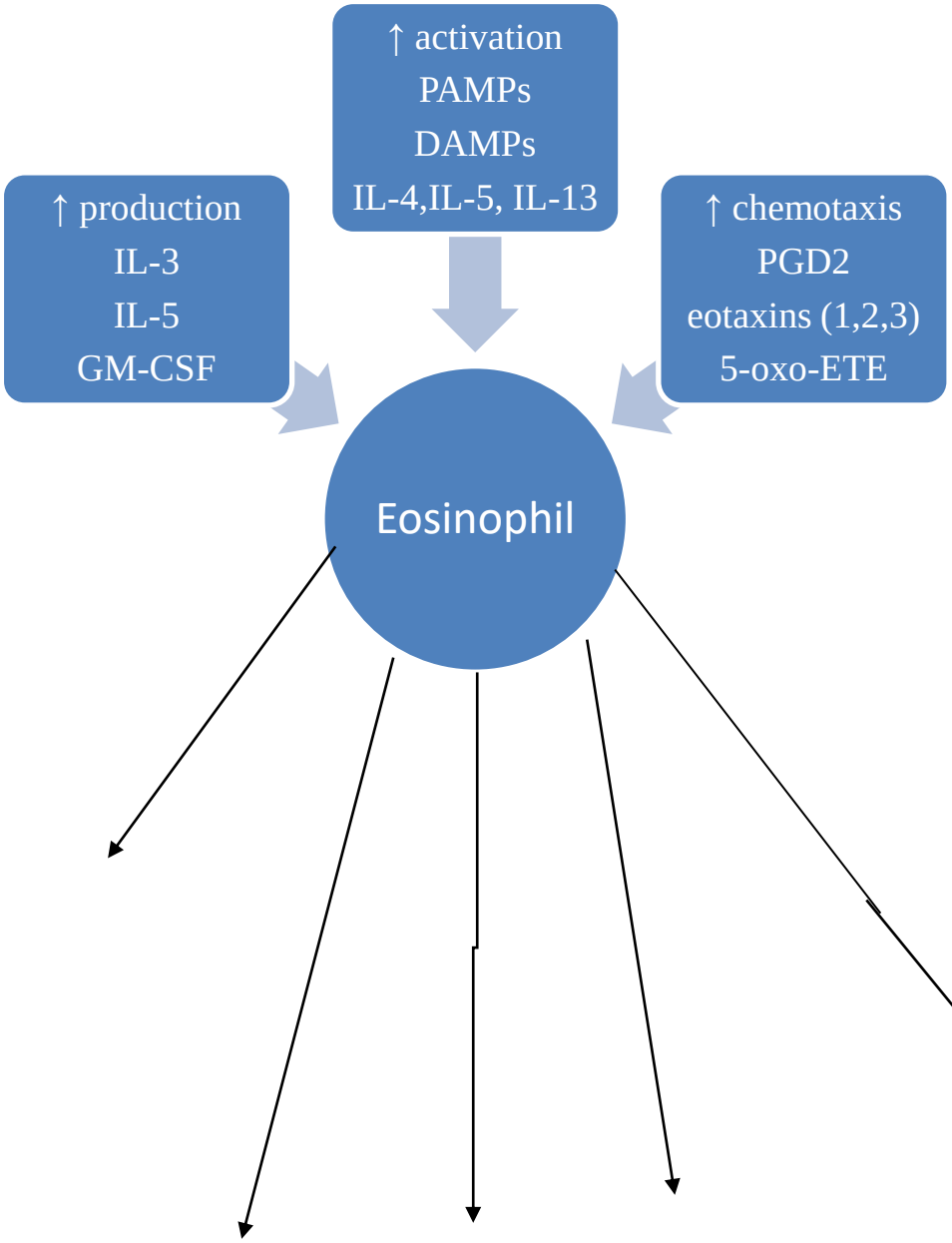

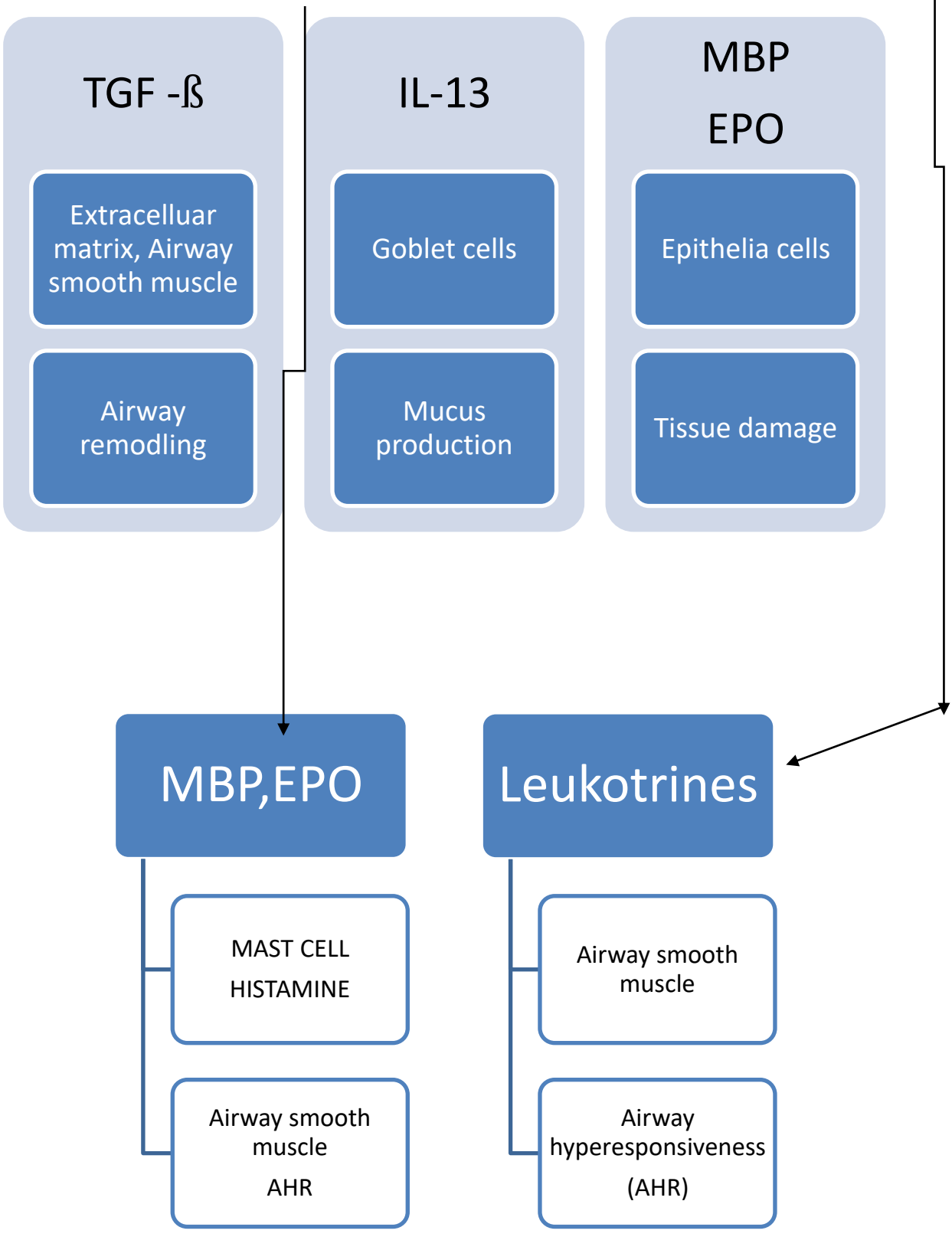

Fig.1. Eosinophils role in asthma pathogenesis [15]