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Role of Various Mediators in Inflammation of Asthmatic Airways

Poonam Arora and S.H. Ansari

Abstract

The degree of airway inflammation is directly related to asthma severity and associated hyper-responsiveness. Airway inflammation is categorized into three types: (a) acute asthmatic inflammation featured by early recruitment of cells into the airways, (b) subacute asthmatic inflammation involving activation of recruited cells in continual inflammation, and (c) chronic inflammation characterized by cellular damage. T-helper lymphocytes, the key factor in the pathogenesis of bronchial asthma, induce B cells to synthesize and secrete IgE through production of IL-4 and induce eosinophil-mediated inflammation. Mediators such as histamine, PG, leukotrienes, and kinins contract airway smooth muscle, increase microvascular leakage, increase airway mucus secretion, and attract other inflammatory cells into airway epithelia that initiate mucociliary clearance signaling pathways through special Toll-like receptor 4 expressed on epithelial cells activated by allergic and infectious triggers. These cells form barrier against mechanical stress, oxidant stress, allergens, pollutants, infectious agents, and leakage of endogenous solutes. Various adhesion molecules and costimulatory factors also promote infiltration of inflammatory cells at the site of inflammation.

Keywords: airway inflammation, hyper-responsiveness, bronchial asthma, T-helper lymphocytes, mediators

1. Introduction

The inflammatory response in asthmatic airways is a complex interplay between respiratory epithelium and immune system. The drive for a chronic inflammatory response initiates with production of bioactive mediators from airway epithelium, which attracts, activates, and recruits the inflammatory cells into lung airways. Infiltrated cells augment inflammatory response through the release of other biochemical mediators. The inflammatory mediators released by these cells are the effectors of chronic inflammation including cytokines classified into lymphokines or immunomodulatory cytokines released by T-helper cells, proinflammatory cytokines that promote and amplify the inflammatory response, chemokines that are chemoattractants for leukocytes, growth factors that promote cell survival, and eicosanoid lipid mediators that have multiple effects in the airway. The products released from leukocytes and epithelial cells induce bronchospasm, damage the epithelium, stimulate airway cells, and recruit additional leukocytes creating a cycle of

inflammation that becomes chronic. In acute cases of allergen exposure, mast cells can provide an early source of proinflammatory mediators such as IL-4 and IL-5. Episodes of acute inflammatory reactions are often accompanied by an underlying chronic inflammation even in the absence of continuous allergen exposure.

2. Airway inflammation in asthma

The degree of airway inflammation and corresponding airway hyper-responsiveness (AHR) is related to clinical symptoms in asthma. Asthmatic inflammation is categorized into three types: (a) acute asthmatic inflammation featured by early recruitment of cells into the airways, (b) subacute asthmatic inflammation involving activation of recruited cells in continual inflammation, and (c) chronic inflammation characterized by cellular damage. Various types of biogenic mediators that play an important part in inflammatory process in asthmatic airways are given in **Figure 1**.

2.1 Cells

2.1.1 Eosinophils

Eosinophil infiltration is a characteristic feature of asthmatic airway inflammation that plays a central role in asthma. Allergen inhalation results in a marked increase in eosinophil count in bronchoalveolar (BAL) fluid at the time of the late asthma response with a decrease in peripheral eosinophil counts with the appearance of eosinophil precursors in the circulation. Recruitment of eosinophils to airways is mediated by interleukin (IL)-13, histamine, prostaglandin type 2, and chemokines, such as RANTES (regulated on activation T-cell expressed and secreted), eotaxins, and macrophage chemotactic protein (MCP)-4, expressed in epithelial cells [1, 2].

2.1.2 Neutrophils

Neutrophils are predominantly observed in the airways and sputum of patients with severe asthma [3], especially during acute exacerbations of asthma and in some patients with long-lasting or corticosteroids dependent or unresponsive to inhaled steroids. They are recruited through Th17 pathways and lead to increased concentrations of IL-8 in sputum, which in turn may be due to the increased levels

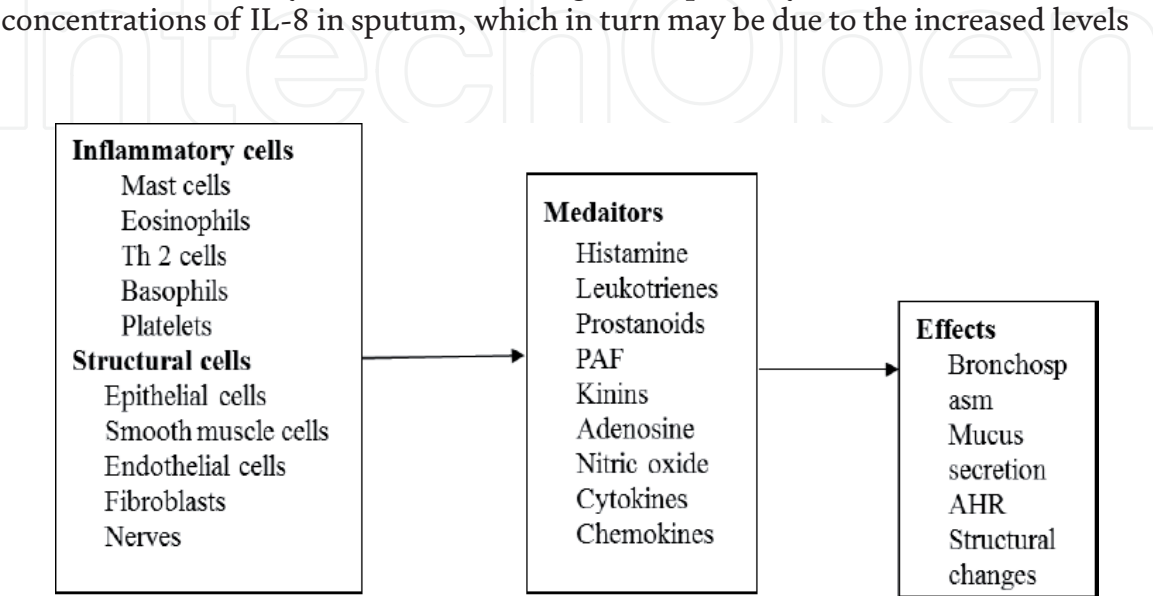


Figure 1.
Inflammatory mediators in asthma.

of oxidative stress in severe asthma [4]. Neutrophils contribute to BHR and airway inflammation through the release of mediators like PAF, thromboxanes, and leukotrienes and tissue damage through secretion of proteases and oxygen radicals [5].

2.1.3 Macrophages

Macrophages, derived from blood monocytes, extend inflammatory process in asthma through production of a variety of cytokines, after being activated by allergen via low-affinity IgE receptors (FcεRII) [6]. Macrophages may both increase and decrease inflammation, depending on the stimulus. Alveolar macrophages normally have a suppressive effect on lymphocyte function, but this may get impaired in asthma after allergen exposure [7]. Macrophages secrete an anti-inflammatory protein IL-10 which is reduced in alveolar macrophages from patients with asthma [8]. Macrophages may, therefore, play an important anti-inflammatory role, by preventing the development of allergic inflammation [9].

2.1.4 Mast cells

Mast cells are central to the development of type I hypersensitivity reaction. Mast cells are bone marrow-derived cells widely distributed in the body predominantly near blood vessels, subepithelial cells and nerves, mucosal lining of the gut, and upper and lower respiratory tract. Increased numbers of degranulated mast cells have been found in asthma exacerbation [10]. Mast cells contain membrane-bound granules filled with biologically active mediators.

After re-exposure, mast cells get activated by cross-linking of high-affinity IgE Fc receptors present on mast cell surface or by stimuli such as C5a and C3a (anaphylatoxins) and release a wide variety of mediators that result in acute bronchospasm or perpetuate underlying inflammation through cytokines [11]. Mast cells are an important source of histamine, cysteinyl leukotrienes, prostaglandins, cytokines, and platelet-activating factor, after getting activated by binding of stem cell factor to the surface receptor c-kit, IgE cross-linking, or binding of tyrosine kinase [12], and the process is called degranulation of mast cells (**Figure 2**).

2.1.5 T-lymphocytes

Several types of T-lymphocytes (especially, Th1, Th2, Th9, and Th17) play an important role in coordinating the inflammatory response in asthma through release of a number of cytokines. Traditionally, Th2 cells have been thought to predominate, with characteristic raised levels of IL-4, IL-5, and IL-13. High proportion of T_H1 cells that can develop under the influence of IL-18 and interferon γ (IFN- γ) associated with further production of IFN- γ is found in some asthmatics. Th17 cells, expressing IL-17, also play an unusual role in asthmatic patients [13]. Th17 are CD4-positive T cells and result in neutrophils influx. Th9 levels are raised in people with atopy cells, secrete IL-9, and promote allergic responses, probably through activation of mast cells. T-regulatory cells, characterized by secretion of transforming growth factor β (TGF- β) and IL-10, are thought to be important because of their role in blunting atopic responses [14].

2.1.6 B-lymphocytes

B cells are important in asthma associated with atopy because they produce IgE. Their survival is supported by IL-5 and a B-cell-activating factor. B cells need to bind to T cells under the influence of IL-4 or IL-13. Secreted IgE are primarily bound through the

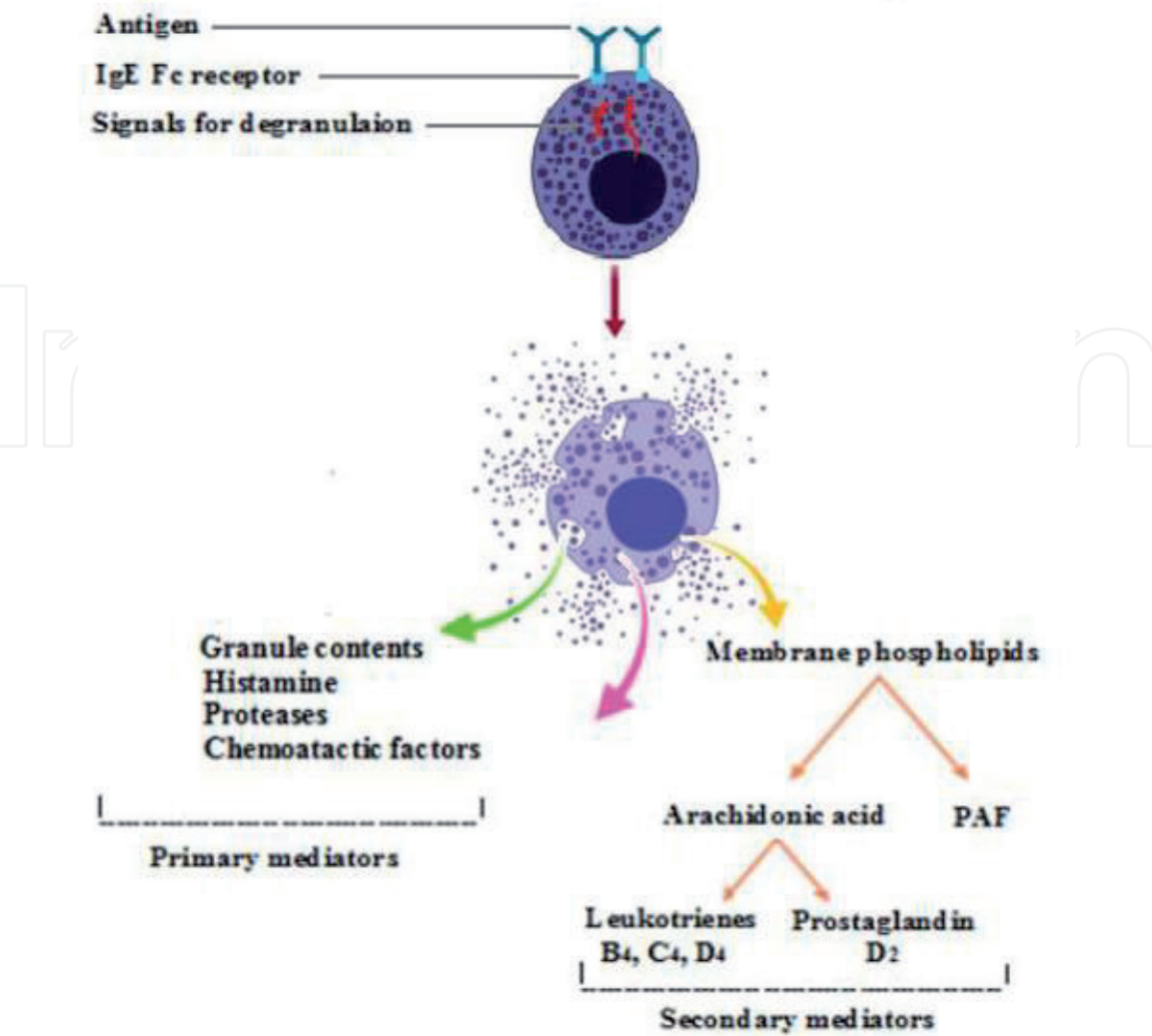


Figure 2.
Activation of mast cells and release of mediators in allergic asthma.

high-affinity Fc receptors on mast cells and basophils, and when cross-linked by aeroallergen, it causes these cells to degranulate and release their mediators [15].

2.1.7 Innate lymphoid cells

ILCs are a family of immune cells that are defined by several features including the absence of recombination-activating gene (RAG)-dependent rearranged antigen receptors, their lymphoid morphology, as well as lack of myeloid phenotypic markers and are therefore called cell lineage marker-negative (Lin[−]) cells. These ILCs are present in the skin, adipose tissues, mesenteric lymph nodes, tonsils, and spleen and mediate inflammatory pathways in various diseases of the lungs and skin. ILCs are classified into three groups according to their transcription factors and cytokine production profile that resembles T-helper (TH) cell subsets [16]. Among these cells, group 2 innate lymphoid cells (ILC2s) are known to play a role in pathogenesis of type 2 inflammatory diseases of the lungs and skin such as asthma and atopic dermatitis [17]. They have the capacity to produce type 2 (TH2) cytokines and interact with both immune and nonimmune cell populations in the local tissue environment. ILC1s produce TH1 inflammatory cytokines, particularly IFN- γ and tumor necrosis factor (TNF- α). They play their role in the pathogenesis of chronic obstructive pulmonary disease (COPD) and human inflammatory bowel (IBD). ILCs generally differentiate into macrophages and granulocytes while stimulating eosinophils and producing Th2 cytokines [18].

2.1.8 Airway epithelial cells

Airway epithelial cells play an important role in mucociliary clearance signaling through special receptors Toll-like receptor 4 expressed on epithelial cells activated by allergic and infectious triggers. These cells form barrier against mechanical stress, oxidant stress, allergens, pollutants, infectious agents, and leakage of endogenous solutes. In asthma, epithelial cell-derived cytokines and chemokines (including IL-25, IL-33, thymic stromal lymphopoietin [TSLP], and granulocyte-macrophage colony-stimulating factor [GM-CSF]) signal effector cells (including basophils, eosinophils, mast cells, and lymphocytes) and dendritic cells are of importance in developing characteristic asthmatic immune response patterns to various types of allergic stimuli [19].

2.1.9 Dendritic cells

Like airway epithelial cells, pulmonary dendritic cells are also directly exposed to the external environment. These dendritic cells act as antigen-presenting cells and are directly stimulated by allergens or infectious agents directly after binding with recognition receptors or indirectly stimulated by airway epithelial cells (by mediators such as IL-25, IL-33, GM-CSF); dendritic cells can recruit eosinophils in allergen-presenting regions [20]. Dendritic cells are also found to effect T-cell differentiation and generate Th2 response commonly seen in atopic asthma [21].

2.2 Adhesion molecules

These molecules promote infiltration of inflammatory cells at the site of inflammation, recruitment of leukocytes from vascular lumen to tissues, and cell activation [22]. Adhesion molecules are upregulated in allergic inflammation and play a critical role in pathogenesis inflammation. More than 35 adhesion molecules have been identified, for example, integrins, immunoglobulin supergene family, selectins, and carbohydrate ligands including ICAM-1 and VCAM-1.

2.3 Costimulatory factors

A number of costimulatory factors are known to play an important role in the development of immunity such as inducible costimulator (ICOS) and ligand for ICOS. ICOS is known to regulate production of Th2 cytokines and to have a significant role in lung mucosal inflammatory responses [23, 24].

2.4 Inflammatory mediators

A number of mediators that account for pathophysiological features of allergic diseases have been implicated in asthma. Mediators such as histamine, PG, leukotrienes, and kinins contract airway smooth muscle, increase microvascular leakage, increase airway mucus secretion, and attract other inflammatory cells.

2.4.1 Histamine

Histamine was the first mediator known to be implicated in pathophysiology of asthma. Histamine is synthesized and released by mast cells and basophils in the airways. Histamine causes mucus secretion and bronchoconstriction which is partially mediated by vagal cholinergic reflex. Histamine also acts as a chemoattractant for eosinophils and activates eosinophils [25].

2.4.2 Leukotrienes

The cysteinyl leukotrienes, LTC₄, LTD₄, and LTE₄, are eicosanoids derived from arachidonic acid by 5-LOX (lipoxygenase) pathway. They are potent constrictors of human airway and have been reported to increase AHR and play an important role in asthma [3]. They constitute the slow-reacting substance of anaphylaxis. [26]. Potent LTD₄ antagonists protect (by 50%) against exercise- and allergen-induced bronchoconstriction, suggesting that leukotrienes contribute to bronchoconstrictor responses.

2.4.3 Platelet-activating factor

Platelet-activating factor (PAF) is a potent inflammatory mediator that mimics many features of asthma, including eosinophil recruitment and activation and induction of AHR, plasma exudation, and mucus hypersecretion. The high level of lyso-PAF (metabolite of PAF) is analyzed in BALF of patients with allergic asthma [27].

2.4.4 Prostaglandin

Prostaglandins are generated from arachidonic acid by cyclooxygenase (COX) pathway. Increased concentration of PGF₂, PGD₂, and thromboxane B₂ in bronchoalveolar (BAL) fluid of asthmatics is found. When inhaled, they cause bronchoconstriction [28] and increase airway responsiveness to spasmogen.

2.4.5 Proteases

Tryptase is a mast cell serine protease and plays a role in hemostasis, mucus secretion, and vascular permeability. Elevated levels of tryptase have been found in BAL fluid and sputum of asthmatic patients after allergen challenge [29]. Elevated levels of MMP-9 (matrilysin-9), a protease released by eosinophils and alveolar macrophages, are found in bronchoalveolar fluid from asthmatic patients [30].

2.4.6 Kinins

Kinins are vasoactive peptides secreted from kininogens by the action of kininogenase during the inflammatory response. Bradykinin is an important kinin that has many effects on airway functions mediated by direct activation of B₂ receptors of airway smooth muscles. Bradykinin activates alveolar macrophages to release LTB₄ and PAF and activates nociceptive nerve fibers in the airways of asthmatic patients only which may mediate cough and chest tightness characteristic features of asthma [31].

2.4.7 Cytokines

Cytokines are extracellular signaling proteins secreted by almost every cell under certain conditions and play a critical role in orchestrating all types of inflammatory response in asthma [32]. They act on target cells to cause a wide range of cellular functions like activation, proliferation, chemotaxis, immunomodulation, release of inflammatory mediators, growth and cell differentiation, and apoptosis. In contrast to acute and subacute inflammatory responses, cytokines play a dominant role in maintaining chronic inflammation in allergic diseases. The important cytokines in asthma are lymphokines secreted by T-lymphocytes: IL-1 β , IL-3, IL-4, IL-5, IL-6, IL-9, IL-13, TNF- α , etc. where IL-3 is reported to be crucial for

the survival of mast cells in tissues, but IL-4 plays an important role in switching B-lymphocytes to produce IgE and expression of VCAM-1 on endothelial cells. IL-5 plays a critical role in differentiation, survival, and priming of eosinophils, thus promoting eosinophilic inflammation, and present in BAL fluid during allergen-induced late-phase asthma [33]. Airway macrophages are important source of IL-1 β , TNF- α , and IL-6 which act on epithelial cells to release GM-CSF, IL-8, and RANTES and amplify the inflammatory response leading to influx of secondary cells like eosinophils [34].

2.4.7.1 Proinflammatory cytokines

IL-9 and IL-13 are considered as proinflammatory cytokines. IL-9 is known to stimulate proliferation of activated T cells, enhancing IgE production from B cells, promoting proliferation and differentiation of mast cells, upregulating the α -chain of the Fc ϵ RI receptor, and inducing CC chemokine expression in lung epithelial cells contributing in allergen-induced airway changes. IL-13 is present in increased amounts in asthmatic airways and possesses biological activities similar to IL-4 [35]. Unlike IL-4 which is central to development of Th2 cells during primary sensitization, IL-13 release is more important during secondary antigen exposure [36].

Another group of proinflammatory cytokines are TNF- α that help in leukocyte recruitment through upregulation of adhesion molecules on vascular endothelial cells and induction of cytokine and chemokine synthesis airway hyper-responsiveness and pathogenesis of airway remodeling [37].

2.4.7.2 Immunomodulatory cytokines

IL-10, IL-12, IL-18, and interferon gamma (IFN- γ) are known as immunomodulatory cytokines. IL-10 is a pleiotropic cytokine that has the potential to downregulate both Th1- and Th2-driven inflammatory processes [38] and beneficial effect on airway remodeling [39]. IL-12 is released by antigen-presenting cells and is known to play an important role in Th1/Th2 differentiation during primary antigen presentation [40]. IL-18 is secreted by macrophages [41], and IFN- γ is reported to

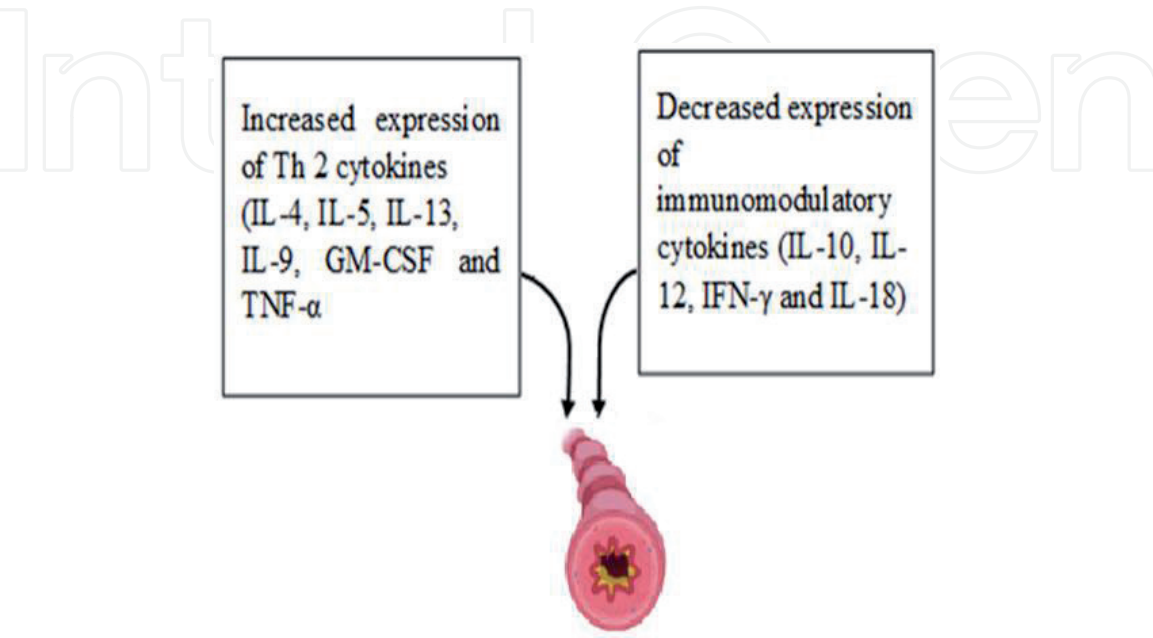


Figure 3.
Cytokines involved in the pathogenesis of bronchial asthma.

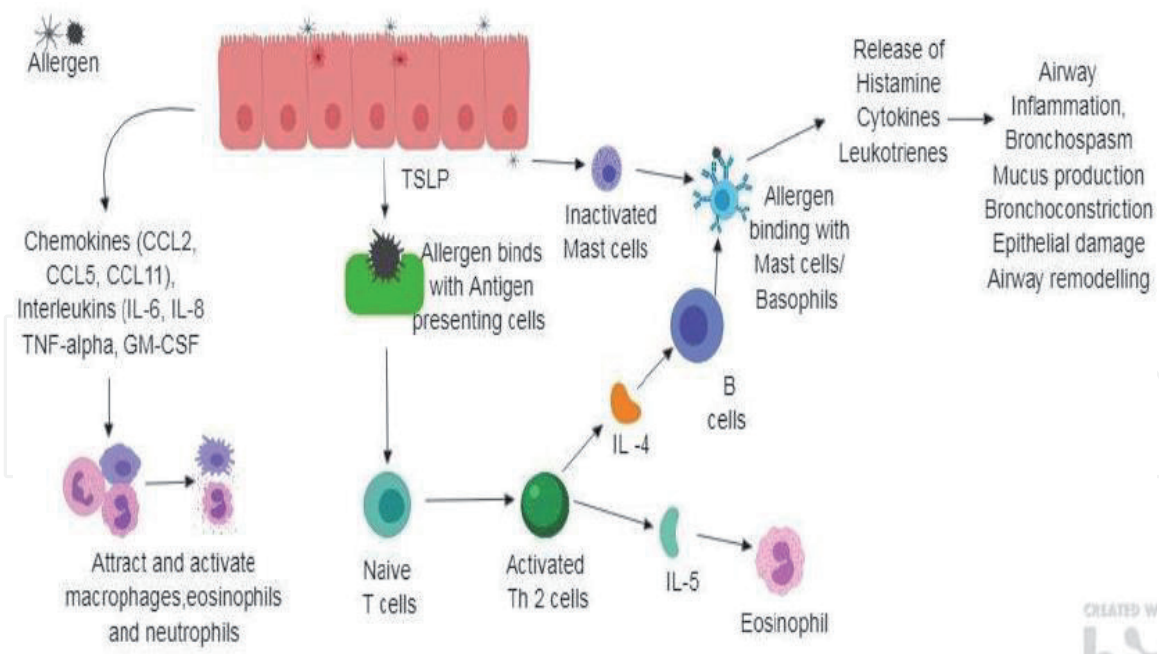


Figure 4.
Release of mediators after allergen exposure to airway epithelia.

prevent the development of antigen-induced airway eosinophilia and hyper-responsiveness [42]. IL-12 and IL-18 act synergistically for inducing IFN- γ and inhibiting IL-4-dependent IgE synthesis as well as inhibiting allergen-induced airway hyper-responsiveness [43]. Balance between Th1 and Th2 cells is thought to be determined by locally released cytokines, such as IL-12, which favor emergence of Th1 cells; contrary to this, IL-4 and IL-13 favor the growth of Th2 cells (**Figures 3 and 4**).

2.4.8 Chemokines

Chemokines are chemotactic cytokines responsible for recruitment of inflammatory cells in the airways. Chemokines have been categorized into two main groups, (a) CXC (α -type) and CC (β -type) chemokines, and exert their effects through G-protein-coupled chemokine receptors (CCR) [44]. Exacerbation of asthma leads to the synthesis and release of a number of chemokines. Increased expression of eotaxin, eotaxin-2, MCP-3, MCP-4, and CCR3 in the airways of asthmatic patients is found, and this can be correlated to increased AHR [45].

2.4.9 Tachykinins

Tachykinins are neuropeptides derived from preprotachykinins (PPTs). They are released by sensory nerves of airways and stimulate mucus secretion, plasma exudation, neural activation, bronchoconstriction, and structural changes. These peptides activate macrophages and monocytes to release inflammatory cytokines, IL-6 [46]. Higher concentration of a tachykinin, substance-P (SP), has been found in BALF of asthmatic lungs [47].

2.4.10 Endothelins

Endothelins are peptide mediators secreted via endothelin-converting enzyme (ECE) through mRNA present in airway epithelial cells and regulated by a number of proinflammatory cytokines in asthma. The biological effects of endothelins are mediated by two receptors: ET_A and ET_B. Endothelins are potent

bronchoconstrictors and induce airway smooth muscle cell proliferation and fibrosis and play an important role in chronic inflammation of asthmatic airways [48]. After the allergen challenge, endothelins (ETs) are secreted de novo. Higher levels of endothelin-1 are found in the sputum of asthmatic patients [49].

2.4.11 Neural mediators

Several nonadrenergic-noncholinergic (NANC) nerves and neuropeptides have been identified in the respiratory tract. Airway nerves may also release neurotransmitters that have inflammatory effects such as substance P (SP), neurokinin A, and calcitonin gene-related peptide, may be released from sensitized inflammatory nerves in the airways, and perpetuate the ongoing inflammatory response. Thus, chronic asthma may be associated with increased neurogenic inflammation, which may provide a mechanism for prolonging the inflammatory response even in the absence of initiating inflammatory stimuli.

2.5 Antibodies

Antibodies are protein molecules released by immune system in response to foreign bodies, allergens. Five classes of antibodies, namely, IgM, IgG, IgA, IgD, and IgE [48], are known. Of these IgE is the predominant antibody in asthma in humans. IgE is the antibody responsible for all types of allergic reaction and pathogenesis of allergic asthma and development of inflammation in the human body. Elevated levels of IgE are found in bronchial asthma. Monoclonal antibodies against IgE have shown the reduction of IgE and associated asthma symptoms in asthmatics [50].

2.6 Oxidative stress

The increased level of oxidative stress found in airways of people with allergic asthma activates circulatory inflammatory cells, such as macrophages and eosinophils. Activated inflammatory cells produce more number of reactive oxygen species causing increased concentrations of 8-isoprostane (a product of oxidized arachidonic acid) [51] and ethane (a product of oxidative lipid peroxidation) in exhaled breath of asthmatic patients [52]. Increased oxidative stress can be related to disease severity and may amplify the inflammatory response and reduce responsiveness to corticosteroids, particularly in severe disease and during exacerbations. Mechanism underlying the role of oxidative stress in asthma severity may be due to reaction of superoxide anions with nitric oxide (NO) forming reactive radical peroxynitrites that may modify several target proteins.

2.7 Nitric oxide (NO)

Measurement of the level of NO in exhaled air of asthmatic patients is increasingly being used as a noninvasive way of monitoring the inflammatory process [53]. NO is produced by NO synthase, but in epithelial cells of asthmatic patients, the enzyme inducible of NO synthase (iNOS) is present. Recent studies report the higher level of NO in the exhaled air of patients with asthma than the level of NO in the exhaled air of normal subjects. The combination of increased oxidative stress and NO may lead to the formation of the potent radical peroxynitrite that may result in nitrosylation of proteins in the airways [54]. Since NO is a potent vasodilator, this may increase plasma exudation in airways, and it may also amplify the Th2-mediated response.

3. Airway remodeling

The acute and chronic allergic inflammatory responses in asthmatic lungs result in epithelial shedding, goblet cell hyperplasia, basal membrane thickening, subepithelial fibrosis in peribronchial interstitial tissue, hyperplasia of airway smooth muscle cells, angiogenesis, and dysfunctioning of bronchial blood vessels [55]. These changes contribute to alteration in lung anatomy termed as airway remodeling and are represented by increased thickness of the basement membrane and increased volume of airway smooth muscle associated with increases in growth factors, including TGF- β_1 and platelet-derived growth factor, in Th2-driven models of asthma [56–58]. Overexpression of Th2 interleukins, especially IL-4, IL-5, and IL-13, is known to produce demonstrative changes in asthmatic airways. Increased expression of IL-13 causes subepithelial fibrosis, mucus metaplasia, and infiltration of eosinophils and macrophages, whereas increased expression of IL-4 and IL-5 induced airway eosinophilia, mucus metaplasia, and subepithelial fibrosis.

4. Conclusion

Complex interactions among various bioactive mediators in asthmatic lungs make it a complex disease and therefore need a more detailed research studies to discern its complete physiology.

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Conflict of interest

The author declares no conflict of interest.

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