HISTAMINE AND CYTOKINES AS MEDIATORS RELEASED DURING ASTHMA ATTACK

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Abstract
Lung diseases are amongst the most common medical conditions in the world. Chronic obstructive pulmonary disease (COPD), pulmonary fibrosis and asthma are the result of ongoing inflammatory process. Over three decades the prevalence of chronic inflammatory lung diseases (asthma, COPD, fibrosis) are increasing worldwide. Asthma as a common chronic disorder of the airways, is characterized by variable and recurring symptoms pertaining to airflow obstruction, bronchial hyper-responsiveness, and an underlying inflammation. Clinical manifestations and response to treatment are determined by the interactions of these features of asthma. The symptoms can be controlled by muscle relaxing and anti-inflammatory drugs, however, there is yet no cure available for asthma. An imbalance of cytokines released from T helper cells cause asthma pathogenesis. T lymphocytes (especially T helper lymphocytes) are important in the pathogenesis of asthma and can be divided into two subsets: Th1 and Th2. Histamines inhibit the production of Th1 such as IL2, IL12, and IFN Y. Th1 is known to mediate autoimmune diseases such as type 1 diabetes, inflammatory bowel disease, and multiple sclerosis while Th2 mediates allergic diseases. Th2 cytokines (Interleukins) IL4, IL5, IL9, and IL13 are implicated in the expression and development of airways inflammation and hyperactivity (AHR). This review evaluates the mechanisms and roles of cytokines and histamines in chronic inflammatory conditions of asthma. Knowledge of these factors can lead to identification and enhancement of hidden problems in the management of asthma conditions or lead to other new therapeutic targets in chronic inflammatory processes.

Keywords: Cytokine, Inflammation, Chronic disorder, Histamines, Interleukins

INTRODUCTION
Lung diseases are some of the most common medical conditions in the world. Chronic obstructive pulmonary disease (COPD), pulmonary fibrosis and asthma are the result of ongoing inflammatory process [1]. Asthma, an allergic reaction is a chronic inflammatory disease of the respiratory airways characterized by intermittent reversible obstruction and chronic inflammation of the airways, bronchial hyper responsiveness and infiltration of the lymphocytes and eosinophils into the airway mucosa [2]. The huge infiltration of the bronchial mucosa is by CD4+ T cells. With an altered local T-cells response in favour of Th2 cytokine release (IL4, IL5, IL13) results in B-cell isotope switching to IgE, recruitment of eosinophils, basophiles and mast cells production of inflammatory mediators [3, 1].

Many symptoms have been implicated in asthma attack such as shortness of breath, wheezing and forced inhalation thus, causing the individual in question to gasp for air upon exposure to allergens [2, 4]. Narrowing of the large and small airways causes the shortness of breath, a condition known as bronchospasm. The principle of bronchospasm is dependent on three factors: Histamine, Leukotriene and Prostaglandins which is released by mast cells causing smooth muscle contraction and therefore bronchocostriction. Histamine, an inflammatory mediator and Leukotriene increase mucous secretion of the airways thereby narrowing the free air flow causing congestion of the airway passage [5]. Prostaglandins act mainly and rapidly to cause smooth muscle contraction, increase vascular permeability and mucus secretion inducing an influx and activation of leukocytes which contribute to the late phase of response.

Shortness of breath in asthma and airway inflammation could be linked to two specific cytokines such as interleukin 4 and interleukin 5. IL4 induces immunoglobulin E (IgE) synthesis, mast cell activation...
and eosinophil recruitment. IgE expresses the acute phase of asthma while the chronic or late phase of asthma occurs in the presence of more specific cells such as the CD4+ T cells and the B cells, which sometimes serve as the memory cells if the allergen has previously been encountered in the body.

Asthma attacks may be triggered by a variety of stimuli, which varies from one individual to the other. Exposure to smoke, perfumes, paints or strong chemical odours, changes in whether or temperature, exposure to moulds, animal danders, grass or tree pollens, sulphites, food colourings like the yellow dye tartazine, trigger the attack. Following exposure to these stimuli, mast cells, basophiles and macrophages are activated to release a variety of mediators (histamine, cytokines, leukotrienes, prostaglandins, bradykinin and tryptase) which produce direct effects on airway smooth muscles and capillary permeability. An intense local reaction (early reaction) is evoked, followed by a more severe or chronic reaction (late reaction) [6, 2].

Asthma could present as extrinsic or intrinsic. As a type 1 hypersensitivity reaction it is induced by an exposure to an extrinsic antigen. Individuals who exhibit extrinsic asthma have a history of atopy, onset of symptoms during childhood or adolescence, predictable seasonal occurrence and response to environmental stimuli [7]. Attacks of this type of asthma may take place seasonally or yearly and maybe precipitated by common household allergens such as dust mites, animal dander and fungal spores. Anxiety, inhalation of airway irritants and exposure to perfumes and strong household odours can also precipitate asthmatic episodes [8].

In intrinsic asthma, triggering mechanism is usually non immune. Stimuli that have little or no effect in normal subjects can trigger bronchospasm. This results from bronchial inflammation leading to characteristic physiologic abnormality of airway hyper responsiveness making the airway narrow [6, 9]. This work reviews the two major mediators- cytokines and histamines released during asthmatic attack with insight into their roles and mechanisms during chronic inflammation that can lead to asthma attack.

MAST CELL ACTIVATION IN ASTHMA

Mast cells are highly specialized cells and prominent resident of mucosal and epithelial tissues in the vicinity of small blood vessels and post capillary venules where they act to protect against invading pathogens. Mast cells are very crucial in the allergic response. Upon exposure to initiating stimuli, mast cells, basophiles and macrophages can be activated to release a variety of mediators which provide direct effects on airway smooth muscles and capillary permeability, thereby evoking an intense local reaction (early) followed by chronic reaction [6, 10].

Activation of mucosal mast cells releases bronchoconstriction mediators (histamine, cysteinyl-leukotrienes, prostaglandin D2) [11, 12, 13]. Lipid mediators like the leukotrienes (C4, D4, E4 are important in sustaining inflammatory responses in the tissue) and platelet activating factors, additional cytokines such as IL4 and IL13 which perpetuate the TH2 response that contribute to both acute and chronic inflammatory response [10, 12]. These mast cells become activated when surface receptor bound antigen-specific immunoglobulin encounters an antigen that the IgE recognizes (sensitization of mast cell). This triggers the mast cell degranulation to the release of inflammatory mediators like histamine, proteoglycans and cytokines.

RELEASE OF HISTAMINE

Histamine is a short lived vasoactive amine that causes an immediate increase in local blood flow and vessel permeability, tryptase, chymase and serine esterase which activate matrix metalloproteinase causing breakdown of matrix proteins thereby leading to tissue destruction [10]. Mast cells and basophiles in the immune system serve as the predominant storage site for histamine in humans. Histamine is released when these cells degranulate in response to both immunologic and non-immunologic stimuli. Apart from the mast cell and basophiles, several other cell types such as myeloid and lymphoid cells (dendritic cells and T cells), which do not store histamine, are also capable of producing histamine [14].

Histamine has several functions such as acting as a neurotransmitter by binding to H1 (histamine type 1 receptors) to decrease appetite and increase wakefulness. When it binds to H2 (histamine type 2 receptors), it induces the release of gastric acid from the parietal cells in the gut and also increases the output of pepsin and intrinsic factors. Dilation of blood vessels by histamine in the cardiovascular system through both H1 and H2 receptors lead to flushing, lowered peripheral resistance, increased capillary permeability and a fall in systemic blood pressure [2].

Histamines in the immune system are important mediators of allergic disease which occurs in excessive production of histamine. Histamine modulates the activity of immune-competent cells (T lymphocytes inclusive) by binding to histamine receptors on their cell surface. Response to histamine between human T lymphocytes subsets are based on receptor distribution. For example, suppressor T cells are more responsive to histamine than T helper cells or cytotoxic T cells. Again, the response to histamine in T helper cells and cytotoxic T cells is always increased after mitogenic stimulation. An imbalance of cytokines released from T helper cells causes asthma pathogenesis. T lymphocytes (especially T helper lymphocytes) are important in the pathogenesis of asthma and can be divided into two subsets: Th1 and Th2 (Figure 1) based on their role in the development, initiation and regulation of immune response [2].
Th1 is involved in delayed type of hypersensitivity and cytotoxic response. This secretes primarily IL2, IFN gamma, IL3, granulocyte monocyte colony stimulating factor, GM-CSF. While Th2 cells on the other hand regulate allergic disease by activating B cells and regulating IgG and IgE secretion. Histamine acts to down regulate the proliferation of T helper type 1 lymphocytes, which control cytotoxic response and delayed-type hypersensitivity and regulates the development of an allergic state by enhancing the secretion of Th2 cytokines such as IL4, IL5, IL10, and IL13. Histamines inhibit the production of Th1 such as IL2, IL12, and IFN Y.

**CYTOKINES INVOLVED IN ASTHMA**

Cytokines are lower molecular weight proteins released from cells that regulate important biological processes including growth, cell activation, inflammation, immunity, tissue repair and fibrosis [2]. Cytokines when made by lymphocytes are called lymphokines or interleukins (IL) and act on specific cytokine receptors on the cells that they affect [10]. These cytokines trigger the differentiation of Th1 into Th2 cells to secrete IL4, IL5, IL10 and IL13. Th1 response mature gradually during the first years of life but not until 18 months of age so that responses during this period are relatively skewed towards the Th2 pattern which normally characterize allergic diseases (Fig 1). Th1 mediates autoimmune diseases such as type 1 diabetes, inflammatory bowel disease, and multiple sclerosis while Th2 mediates allergic diseases. There is accumulating evidence that Th2 cytokines (Interleukins) IL4, IL5, IL9, IL13 are implicated in the expression and development of airways inflammation and hyperactivity (AHR) [15].

Th1 cells are involved in the allergic inflammation in local tissues, failing to counterbalance Th2 responses in airways in inflammation, suggesting that atopic response may develop as a result of a more fundamental failure of underlying immune regulation other than just skewing of immune response along Th1-Th2 (Fig 1). The immune system is capable of defensive responses in both allergic asthma and in autoimmune diseases. This immune haemostasis is achieved by a group of diverse cells with important regulatory functions, examples are CD4, CD25, T regulatory cells, epithelial cells, dendritic cells and a whole lot of antigen presenting cells. When these cells are activated upon infection, both the innate and cognate response is orchestrated via direct cell contact (CD4 CD25 T reg. Cells) or by production of cytokines (IL10 and TGFβ). The action inhibits inappropriate or excessive responses. Dendritic cells play roles in the allergic asthma as well. These cells are essential for the priming and differentiation of naïve CD4+ T cells towards allergens. During infection with antigens, respiratory tract dendritic cells migrate to the draining mediastinal lymph nodes where activation and differentiation of antigen-specific T cells are controlled. Migration of activated dendritic cells is accelerated, enabling fast transfer of information about the pathogen to the lymphoid organs [16].

Recent studies in animal models have observed that, resting dendritic cell stimulates Th2 immune development when they receive obligatory Th1 tropic signals during infection or other local stress evoking protective Th1 effectors T cell responses [15]. The role

Figure 1: Numerous factors that may affect the balance between Th1-type and Th2-type cytokine responses and increase the likelihood that the immune response will be dominated by Th2 cells and thus will ultimately lead to the expression of allergic diseases such as asthma. Adopted from US NAEPP Report, 2007.
of dendritic cells can be found to be the generation of regulatory T cells that actively suppresses immune responses. IL4 and IL5 are the major cytokines involved in the local infiltration and activation of eosinophils. The infiltrating eosinophils cause damage of the airways and hyper responsiveness by releasing cytotoxic granules and membrane mediated products [17]. The night time worsening of the asthmatic condition is associated with increase of eosinophils in the airways as well as increased presence of chemical messengers of inflammation. IL4 is involved in the development of allergic inflammation as well as IgE isotype switch, promotion of eosinophil transmigration across endothelium, mucus secretion and differentiation of T helper type 2 lymphocytes [18, 19]. IL4 is capable of directing the migration of T. lymphocytes, monocytes and basophils and eosinophils to inflammatory loci but inhibits eosinophil apoptosis by maintaining levels of the survival-promoting protein BCL2 in T cells.

On the alternative, apoptosis of T cells is induced through signals mediated by fas ligand through the fas (CD95) receptor expressed on these cells and this IL4 promotes eosinophilic inflammation thereby, causing eosinophilic chemo taxis and activation through increased expression of eotaxin from fibroblasts. IL4, act mostly in the development of allergic inflammation by driving the differentiation of naïve T helper type 0 (Th0) lymphocytes into Th2 lymphocytes. IL5, a Th2 cytokine is usually increased in the airways of atopic asthma and plays an important role in allergic disease by controlling movement. Th2 cytokines comprising of IL10 and IL13 are important in inducing airway hyper reactivity and allergic inflammation with IL10 acting as inflammatory cytokines that suppresses the secretion of proinflammatory cytokines (Th1) allergen induced airway inflammation and nonspecific airway responsiveness. IL13 plays the role of inhibition of product of inflammatory cytokines, and induces B-cell proliferation and differentiation including IgE production and enhances expression of CD23 and MHC class II molecules [2, 20]. Cytokines action is by binding to cytokine receptors on cells. IL13 and IL4 act directly on the airway epithelium to induce AHR and goblet-cell metaplasia and IL4R- deficient mice that were engrafted with bone marrow derived from IL4R- expressing mice failed to develop goblet-cell metaplasia. The goblet-cell metaplasia and mucus production that is induced by allergic inflammation is strictly dependent on the expression of IL4R- and STAT6 in non-airway epithelium.

A search for the downstream signalling pathways that mediate the effectors functions of IL13 and IL4 airway epithelium tissues implicates the calcium activated chloride channel 3 (human CLCA1 or murine CLCA3 or Gob-5). This induction is necessary and sufficient for goblet cell metaplasia and possible AHR. Such an induction of CLCA3 involves the activation of STAT6 and mitogen activated protein kinase pathways. IL13 triggered epithelial-cell pathway also mediates the production of the profibrotic cytokine transforming growth factor β (TGFβ) produced by the epithelium and other cells, including macrophages, transform fibroblasts into myofibroblasts. These cells initiate a program of airway remodelling by secreting matrix proteins and enzymes which include metalloproteases [21].

Figure 2: Th1 and Th2 cells: role of cytokines and their effector functions. Various cytokines can control the differentiation of naïve T helper cells into Th1 and Th2 cells. Th1 cytokine IFNy and monokine IL-12 are important for the differentiation into Th2 cells. Each T helper subset plays its own role. Th1 cells secrete predominantly IL-2, IL-3, IFNy, TNFB and GM-CSF that ultimately, leads to tissue inflammation, cytotoxic response and delayed hypersensitivity. Th2 cells secrete IL-3, IL-4, IL-5, IL-10, IL-13 and GM-CSF that ultimately perpetuate allergic disease and asthma. Diagram adopted from Packard and Khan, 2003.
CYTOKINE SIGNALING IN ALLERGIC RELATION

IL4 and IL 13 are key pathways that regulate allergic inflammation and tissue remodelling in the airway. IL4, produced by TH2 and mast cells along with IL13 are responsible for the induction of IgE synthesis. IL4 acts on the Th0 cells to promote the differentiation into Th2 cells. In the hematopoietic cells, IL4 acts by interacting with a specific cell surface receptor composed of a binding component, IL4R and the common y-chain (yc), which is shared by multiple cytokine receptors.

It has been observed that in the absence of common y-chain, IL4 is capable of using the type II IL4R, comprised of IL4Ra and the IL-13Ra1 chain [22]. The paring of IL4R with IL13R1 makes the cytokines to have high affinity for IL13 and IL4 binding heterodimeric complex that is expressed on both hematopoietic and non-hematopoietic cells such as airway epithelium. The binding of yc, IL4R and IL13R1 (receptor dimerization) trigger the activation of the member of Janus family of protein kinases (JAKS) that are constitutively associated with IL4R (jak1), the yc (jak3) and the IL13R1 chain (JAK2) [21]. JAKS are one of the eleven non-receptor tyrosine kinase families that are essential mediators of cellular signalling through cytokine receptors. JAKS consist of Jak1, Jak2, Jak3 and Tyrk2 and this mediate phosphorylation of invariant tyrosine residue on the receptor-bound STAT monomer that induces STAT homodimerization [23].

Activated JAKs initiate several intracellular signalling cascades by phosphorylating specific tyrosine residues in the cytoplasmic domain of closely spaced tyrosine residues of the human receptor. This enables the recruitment of IL4Ra dedicated transcription factor signal transducer and activator of transcription 6 (STAT6) through the SH2 domain of the later [21, 24]. STAT consist of seven structurally and functionally related cytokine functions as diverse as cellular proliferation, differentiation, death and embryonic development. The strength and duration of STATs is under stringent regulation by a family of endogenous negative feedback regulators, called the suppressors of cytokine signalling (SOCs). These are proteins that bind to tyrosine-phosphorylated receptors and prevent recruitment of STATs to the activated receptor complex. These proteins as well inhibit responses of factors that are different from those that induce their expression and there is a belief that they serve to integrate extracellular signals that converge on a target cell [25].

JAK mediated phosphorylation of an invariant tyrosine residue on the receptor-bound STAT monomer induces STAT homodimerization which results in STAT activation. Then the activated STAT dimmers translocate to the nucleus where they bind to specific DNA-response elements in the promoters of target genes and induce gene expression programs. Well, some receptors such as activated growth factor receptor like EGFR and platelet-derived growth factor receptor (PDGFR) with intrinsic tyrosine kinase activity can bypass JAK activation and directly phosphorylate STAT proteins. And activated STAT proteins perform different functions such as growth arrest and promotion of apoptosis and serving as tumor suppressor protein found as the major role of STAT1. STAT3 and STAT5 when activated contribute to malignant progression by stimulating cell proliferation and regulating the expression of genes known to be involved in cell cycle control and preventing apoptosis [23].

IL13R1 consist of two closely located tyrosine residues which bind STAT3 in its cytoplasmic domain and the deletion of c-terminal cytoplasmic tail of IL13R1 (including its STAT3 binding site impairs the activation of Tyk2, STAT1, STAT3 and IL4R associated signalling molecules which includes JAK1, insulin receptor substrate family (IRS1) and STAT6. IL13R1 initiates dual function, amplifying IL4R signalling as well as initiating independent signalling pathways involving other STAT proteins, which include STAT3 and STAT1. STAT3, STAT1 and STAT6 are found to be involved in the induction of lipogenase, the regulatory function of which in allergic airway inflammation is yet to be defined [21].

CONCLUSION

Presently only the symptoms of asthma can be controlled by muscle relaxing and anti-inflammatory drugs. There is as yet no cure available for asthma. However, the risk of complications and identification of genetic and environmental factors (tobacco smoke, air pollution, occupation and diet), managing allergens and respiratory infection can ameliorate the condition. There exists a reciprocal interaction between the two subpopulations in which Th1 cytokines can inhibit Th2 generation and vice versa. Allergic inflammation may be the result of an excessive expression of Th2 cytokines. Additionally, [15] have suggested an alternative possibility that the loss of normal immune balance results from a cytokine dysregulation in which Th1 activity in asthma is diminished. Further focus on the roles of cytokines, histamines and chemokine to regulate and activate the inflammatory profile in asthma may provide further new insight into the pattern of airway injury that may lead to new therapeutic targets.

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