Inflammatory mediators of asthma health essay

Once IgE binds to mast cells (or activated eosinophils), an amplification system operates since the cells not only release the spasmogens and other mediators specified but also can stimulate β cells to produce more IgE. Furthermore, the production of IL-5, IL-4 IL-13 and IL-9 amplifies the Th2-mediated events.

It is believed that asthma symptoms are manifested because of Th2 mediated immune response. Pulmonary allergic inflammation in mice lead to decrease in pulmonary IL-5 concentration, specific IgE, IgG1, and eosinophil and T cell recruitment in wild type mice in the absence of T cells. T cells are important in IL-4 dependent IgG1, IgE and Th2 cell mediated lung inflammation, further more there is evidence that CD4+T cells have a role in asthma process. For example, in murine model external protein induced T cells increases IL-5 production and produces airway eosinophilia. (Larche et al. 2003)

Asthma is a complex chronic inflammatory airway disorder that involves the activation of the inflammatory and structural cells. These released inflammatory mediators cause typical pathophysiological changes of asthma (Peter et al., 2003).

There are several lines of evidence that may implicate a mediator in asthma. Firstly, it may mimic features of clinical asthma. Secondly, the mediator may be produced in asthmatic patients. Thus, mediators or their metabolites may be detected in plasma (e. g. histamine), urine (e. g. LTE4), or more likely, the airways in biopsies, bronchoalveolar lavage fluid, induced sputum or exhaled air.

1. 8. 3. 1. Histamine

Histamine was the first mediator implicated in the pathophysiological changes of asthma (Barnes et al., 1998). Histamine is one of the important mediator of allergy, inflammation and bronchoconstriction. Histamine is synthesized and released by mast cells in the airway wall and by circulating and infiltrating basophils.

Antigen-induced histamine secretion is initiated by the bridging of the adjacent IgE receptors on the mast cell surface. Histamine receptors are among the thousands of members of the 7-transmembrane-spanning family of receptors that couple ligand binding to intracellular reactions through interactions with another large family of guanosine triphosphate (GTP)-binding heterotrimeric proteins. H1-receptors mediate a host of intracellular events most readily characterized by changes in free cytosolic calcium levels.

Histamine show different response in mammalian tissue depends upon presence of receptor on that tissue Kulkarni, (1976).

1. 8. 3. 2. Adenosine

Adenosine can act as an autocoid cause bronchoconstriction in asthmatics and increase immunologically induced mediator release from mast cells of human lung (Cushley et al., 1984; Peachell et al., 1988). Mast cells also release adenosine in response to IgE cross-linking and other stimuli for mast cell activation.

1. 8. 3. 3. Lipid-Derived Mediators

Leukotrienes

Leukotrienes are potent lipid mediators produced by arachidonic acid metabolism in cell or nuclear membrane. Several types of airway inflammatory cells, like eosinophils, macrophages, mast cells, neutrophils, and epithelial cells, can synthesize LTs in response to a variety of stimuli. Leukotrienes are important inflammatory mediators involved in the pathogenesis of asthma. All the Cys-LTs are potent constrictors of bronchial smooth muscle. On a molar basis, LTD4 is 1000 times more active than histamine and constrict bronchioles (Dahlen et al., 1980).

Cys-LTs, acting on Cys-LT1 receptors produce bronchospasm, airway hyper-responsiveness, proliferation of airway smooth muscle, excess production of mucus and mucosal edema and eosinophilia in the airways, and other features in asthma (Sundeep et al., 2001; Peter, 1998).

Platelet Activating Factor (PAF)

PAF is ether-linked phospholipid. The synthesis of PAF occurs in inflammatory cells, including platelet, neutrophils, basophils, macrophages and eosinophils. PAF induces airway smooth muscle contraction by releasing other mediators. PAF-induced bronchoconstriction is not inhibited by H1 receptor antagonist Ketotifen. However, PAF-induced bronchoconstriction can be inhibited by LT antagonists, because of involvement of LTD4 in this response. PAF stimulate chemotaxis and adhesion of eosinophils and neutrophils in-vitro (Peter et al., 2003).

Prostanoids

Prostanoids include prostaglandins (PGs) and thromboxane (Tx), which are generated from arachidonic acid, usually by the action of COX. In general PGF2 and PGD2 contract and PGE relax tracheal muscle. Asthmatic individuals are particularly sensitive to PGF2α, which may cause intense bronchospasm. Although both PGE1 and PGE2 can produce bronchodilatation when given to such patients by aerosol, bronchoconstriction sometime is observed. Tx analogue U 46619 is a potent constrictor in asthmatic patients, and this effect is mediated in part via acetylcholine release. Prostanoids stimulate airway mucus secretion in various animal species. It inhibits the release of mediators from mast cells, monocytes, neutrophils and eosinophil inflammatory cells (Peter et al., 2003).

1. 8. 3. 4. Cytokines

Cytokines are small protein mediators that play an integral role in the coordination and persistence of inflammation in asthma. Many inflammatory cells macrophages, mast cells, eosinophils and lymphocytes) are capable of synthesizing and releasing these proteins. Th2 lymphocytes produce a panel of cytokines, including IL-5, IL-4, IL-13 and IL-9 (Barnes et al., 1998).

1. 8. 3. 4. 1. Interleukin-4

IL-4 is critical for the synthesis of IgE by B-cells and for eosinophils recruitment. IL-4 is also involved in Th2 cell differentiation. IL-4 is a key factor in the development of allergic inflammation, and they may also play a major role in exacerbating asthmatic symptoms (Adcock and Caramori, 2003).

Figure 11. Role of CD4+Th2cells and Various cytokines in asthma pathogenesis.

1. 8. 3. 4. 2. Interleukin-5

It play important role in allergic asthma. IL-5 promote the maturation of eosinophils from bone marrow processor, prolongs their survival by inhibition of apoptosis, activates mature eosinophil recruitment to tissue via synergistic effect with chemoattractants such as eotaxin and promote eosinophil adhesion of vascular endothelium. IL-5 can also promote basophils to release exaggerated amounts of histamine and leukotrienes, mediators that contribute to allergic bronchospasm and congestion in asthma (Fred et al., 2000).

1. 8. 3. 4. 3. Interleukin-9

Its major actions include maturation of eosinophils, airway inflammation, airway hyper-responsiveness and mucus over production (Adcock and Caramori, 2003).

1. 8. 3. 4. 4. Interleukin-13

IL-13 is critical for the synthesis of IgE by B-cells. Activates eosinophils, monocyte. IL-13 is a key factor in the development of allergic inflammation and they may also play a major role in exacerbating asthmatic symptoms (Barnes et al., 1998).

1. 8. 3. 5. Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF)

GM-CSF is one of the colony-stimulating factor that acts to regulate the growth, proliferation and maturation of hematopoietic cells. GM-CSF can

enhance the release of superoxide anions, also induce eosinophil apoptosis and activation, induces release of LTs, endothelial cell migration (Barnes et al., 1998).

1. 8. 3. 6. Reactive Oxygen Species in Asthma

Reactive oxygen species (ROS) are generated by various enzymatic reactions and chemical processes or they can directly be inhaled. ROS are essential in many physiological reactions and are important for the killing of invading microorganisms. However, when airway cells and tissues are exposed to oxidative stress elicited by environmental pollutants, infections, inflammatory reactions or decreased levels of anti- oxidants, enhanced levels of ROS can have a variety of deleterious effects within the airways thereby inducing several pathophysiological conditions.

It has been shown that ROS can damage DNA, lipids, proteins and carbohydrates leading to impaired cellular functions and enhanced inflammatory reactions. ROS are known to play a prominent role in the pathogenesis of various airway disorders such as adult respiratory distress syndrome (ARDS), cystic fibrosis, idiopathic fibrosis, chronic obstructive pulmonary diseases (COPD) and asthma (Gillissen and Nowak, 1998; Repine et al., 1997).