Changing Concepts on Pathogenesis of Asthma*

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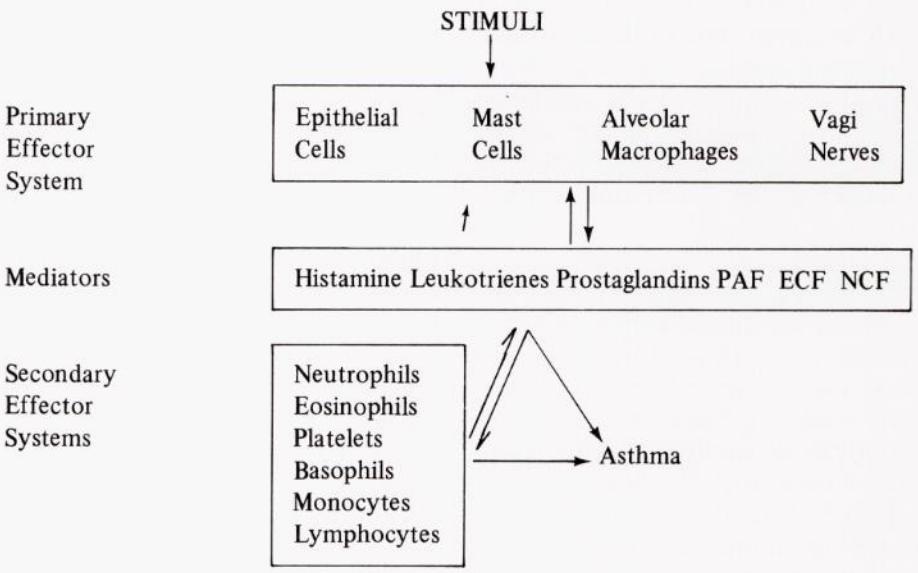
Asthma is a common disease. In Singapore, for example, the cumulative prevalence of asthma in adults is about 5 per cent, and the current prevalence in children is approximately 1 per cent.[1] In Shanghai, the point prevalence of asthma in adults is 0.7 per cent,[2] whereas in Hong Kong, the cumulative prevalence in adults is 0.5 per cent.[3] Asthma is not only common, but also important because of its socio-economic impact, as patients need treatment and may lose time at school or work.

Recent research has elucidated the mechanisms of asthma in greater detail and, more importantly, has changed our concepts on the pathogenesis of asthma. This may have the potential of promoting the development of more effective anti-asthmatic therapy. We shall attempt to summarise recent findings in this article.

Asthma is a heterogeneous disease, the pathogenesis of which is complicated. Table 1 shows our concepts on the pathogenesis of asthma. Multiple mechanisms are likely to be operative, and these may vary from one patient to another. We shall discuss firstly the Primary Effector Systems, which include mast cells, the vagi, airway epithelial cells and alveolar macrophages.

Table 1. Pathogenesis of asthma



Mast cells

The mast cells have long been thought to be important in the pathogenesis of asthma. The binding of an allergen with two IgE molecules on the surface of mast cells will lead to the release of chemical mediators of inflammation from the mast cells with resultant asthma. Interestingly, degranulation of mast cells has only been recently demonstrated *in vivo* in human beings,[4] as previous experiments with chopped human lung preparations did not pin-point the source of mediators. There is now evidence to suggest that non-allergic stimuli such as exercise[5] and exposure to sulphur dioxide[6] may also activate mast cells. Therefore, degranulation of mast cells should be no longer regarded as a purely allergic phenomenon.

Most agents such as exercise, infections, allergens, atmospheric pollutants and occupational chemi-

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cals stimulate asthma directly through contact with airway epithelium. However, the airway epithelium is impermeable to proteins of high molecular weight such as allergens under normal conditions,[7] and mast cells are mainly distributed in the submucosa of airways.[8] This would make it difficult for one to understand how asthma could be initiated since the mast cells are shielded from the stimuli. Recently it was found that asymptomatic asthmatics possess more mast cells in the bronchoalveolar lumen than control subjects.[9] It is not known how mast cells migrate into the airway lumen from the submucosa, but it is likely that these luminal mast cells may come into contact with allergens and initiate asthma. The mediators so released would then open up the tight epithelial junctions, allowing an influx of mediators and allergens into the submucosa with resultant amplification of asthma.[10]

The vagi

The irritant receptors distributed among the airway epithelial cells may also be stimulated by mediators such as histamine with resultant rapid shallow breathing and bronchospasm via vagal reflex action.[11] Stimulation of the vagi has been implicated in the pathogenesis of asthma owing to allergens,[12] respiratory infections,[13] exercise,[14] exposure to ozone[15] and psychological factors.[16] Vagal stimulation causes not only bronchospasm, but also increased mucus secretion.

Airway epithelial cells

It is now know that non-specific bronchial hyper-reactivity to histamine can develop in normal subjects following respiratory tract infection[17] and exposure to ozone.[15] This would imply that inflammation of airways is a cause of bronchial hyper-reactivity. Since bronchial hyperreactivity is a characteristic feature of asthma, it is possible that airway epithelial damage or inflammation may cause the exaggerated responses seen in asthma. Recently, Anderson and her coworkers found that bronchoconstriction may be induced in asthmatics by an aerosol generated from either hypo- or hyper-osmolar solutions, while isotonic solutions had no effect and normal subjects responses to none of the aerosol.[18] This may suggest that a basic defect responsible for asthma could be in the epithelium and may be related to an inability to control the osmolarity and ion concentration of the fluid lining the airway surface.[19] Also, there is now evidence to suggest that inflammatory stimuli may interact initially with airway epithelial cells, causing these cells to generate and release chemotactic factors (e.g. leukotriene B). These factors attract neutrophils from the circulation to the airway epithelium where, in turn, neutrophils may also interact with the stimuli and become activated. The neutrophils then generate and release cyclo-oxygenase and lipoxygenase products to cause asthma.[20] It should be recalled that airway epithelial cells are made more permeable by mediators, and yet they also generate mediators.

Alveolar macrophages

These have been implicated in the pathogenesis of asthma because they are able to bind IgE,[21] they can respond to activation by anti-IgE and specific allergens with the release of lysosomal enzymes, PAF-acether and arachidonic metabolites.[22] Recently, it has also been shown that a human macrophage-derived product can activate basophils and mast cells to release histamine.[23] The role of alveolar macrophages probably has been underestimated in the past.

THE MEDIATORS

Two recent findings about chemical mediators of inflammation are important in the understanding of pathogenesis of asthma.

New mediators

Attention has now been directed away from the traditional mediator such as histamine to the more potent and longer acting ones such as arachidonic acid metabolities, platelet activating factor (PAF-acether) and chemotactic factors. These "new" mediators cause not only bronchospasm, but also airway mucosal edema and mucus plugging. Hence they can account for all the pathological features of asthma.

a. Arachidonic acid metabolites

Over the last 10 years, a series of inflammatory mediators originated from the metabolism of arachidonic acid derived from membrane phospholipids have been identified. Arachidonic acid is metabolised along two major pathways. The first is the cyclo-oxygenase pathway. In this, arachidonic acid is converted to prostanoids such as prostaglandin (PG) F_2, PGE_2, thromboxane (Tx) A_2 and prostacyclin (PGI_2). The second pathway is the recently described lipoxygenase pathway, which leads to the formation of monohydroxylated derivatives such as 5-hydroxyeicosatraenoic acid (5-HETE) and leukotrienes (LTs). Varying proportions of three leukotrienes, LTC_4, LTD_4 and LTE_4, constitute the slow reacting substance of anaphylaxis (SRS-A). Unlike histamine, these arachidonic acid metabolites are not pre-formed and stored in the granules, but are newly formed upon activation of mast cells in the presence of calcium ions.

Leukotriene C_4 is 100 times more potent than histamine in causing bronchoconstriction; TxA_2 and PGF_2, 300 times; and LTD_4, 1,000 times.[24] Recently, LTC_4 has been shown to be released into the circulation of allergic asthmatics following the antigen bronchial provocation test.[25]

The prostaglandins D_2, PGI_2 and PGE_2 dilate the microvasculature, whereas LTC_4 and LTD_4 are vasoconstrictors.[24] At low concentrations, LTC_4 and LTD_4 increase

capillary permeability.[24] Together they cause airway mucosal oedema.

The leukotrienes C_4 and PGD_2, PGF_2, metabolite of PGI_2, 5-HETE and LTB_4 all stimulate the secretion of mucus and impair bronchial clearance of mucus,[26] resulting in mucus plugging of airways.

b. Platelet activating factor (PAF-acether) or acetyl glyceryl ether phosphorylcholine (AGEPC). Morley *et al* recently proposed that PAF-acether plays a vital role in the pathogenesis of asthma, because its administration to experimental animals and man has reproduced an impressive spectrum of anaphylactoid and inflammatory reactions and it has been shown to be released *in vivo*.[27] Furthermore, many anti-asthmatic drugs such as cromoglycate, theophylline, ketotifen and steroid modify PAF-acether-dependent bronchospasm.[27] More work on platelets and PAF-acether in asthma is expected.

c. Chemotactic factors These include eosinophilic chemotactic factors of anaphylaxis (ECF), high molecular weight neutrophil chemotactic factor (HMW-NCF), LTB_4 and mono-HETES. They attract eosinophils and neutrophils from the circulation into the airways. They have assumed more importance nowadays as these inflammatory cells contribute significantly to the persistence of asthma by virtue of the enzymes and other chemicals they released.[28]

New sources of mediators

The mast cells have traditionally been regarded as the only source of inflammatory mediators. However, recent experiments cast some doubt about this. For example, antigen challenge of enzymatically dispersed human lung cells (which contain 3-8 per cent mast cells) releases predominantly PGD_2 and TxA_2, with only small amounts of other PGs.[29] Thus, most of the PGI_2, PGE_2 and PGF_2 released from lung tissue with antigen challenge may be derived from the stimulation of vascular endothelium (PGI_2), smooth muscle (PGE_2) and fibroblasts (PGE_2 and PGF_2).[24] Other sources of mediators include alveolar macrophages[21,27] and airway epithelial cells.[20]

Secondary effector systems

These include all inflammatory cells such as neutrophils, eosinophils, monocytes, lymphocytes, platelets and basophils. Airway inflammation with infiltration by such cells is a characteristic feature of asthma. These cells, by virtue of their released proteins, damage the airways and may be responsible for the persistence of late asthmatic reaction and the development of non-specific bronchial hyperreactivity.[30]

CONCLUSIONS

The pathogenesis of asthma is now more complicated. There is evidence to suggest that allergic as well as non-allergic stimuli may activate mast cells. It is the luminal and surface epithelial mast cells that initiate asthma as they first come into contact with inhaled stimuli. The resultant release of inflammatory mediators from mast cells opens up the tight epithelial junctions, allowing an influx of stimuli and mediators into the submucosa of airways which contain more mast cells, which then amplify asthma. The sensory nerve endings among the epithelial cells are also stimulated by mediators with resultant vagal reflex bronchospasm. Moreover, airway epithelial cells when inflamed or stimulated by osmotic changes can elaborate mediators. This is also true for alveolar macrophages when they are exposed to allergens or endotoxins. The inflammatory mediators such as leukotrienes, prostaglandins, thromboxanes and PAF-acether not only cause bronchospasm, mucosal oedema and mucus plugging of airways, but also attract secondary inflammatory cells such as neutrophils and eosinophils to sustain asthma. It is this inflammatory reaction that may be responsible for the late asthmatic reaction and non-specific bronchial hyperreactivity. Future anti-asthma therapy should be directed not only against mast cells, but also against other effector cells and those having significant anti-inflammatory activity.

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