UNIT NO. 2

PATHOPHYSIOLOGY OF ASTHMA

A/Prof Lee Bee Wah, A/Prof Goh Lee Gan

ABSTRACT

The understanding of the pathophysiology of asthma has moved from bronchoconstriction to airway inflammation as the initiator of disease and perpetuation of disease. The use of tools such as bronchoscopy, bronchoalveolar lavage (BAL), airway biopsy, and measurement of airway gases helped to provide an understanding of the pathogenesis of asthma. The pathophysiological processes in asthma begin with various triggers in susceptible individuals causing an airway inflammation. Asthma triggers can be allergens (specific triggers) or non-allergens which are mostly irritants (non-specific triggers). Prolonged inflammation induces a state of airway hyperactivity, which might progress to airway remodeling unless treated effectively. Pathologically, airway remodeling appears to have a variety of features, namely, (a) an increase in smooth muscle mass, (b) mucus gland hyperplasia, (c) persistence of chronic inflammatory cellular infiltrates, (d) release of fibrogenic growth factors along with collagen deposition, and (e) elastolysis. Environmental influences and genetic predisposition may explain the susceptibility in individuals to the pathophysiological processes of asthma.

INTRODUCTION

Asthma is not a single disease. Many forms exist. The understanding of the pathophysiology of asthma has moved from bronchoconstriction to airway inflammation as the initiator of disease and perpetuation of disease[1,2] (Holgate, 1997; Sezefler, 2002). Much progress has been made in the fundamental understanding of asthma pathogenesis in the last decade through the use of tools such as bronchoscopy, bronchoalveolar lavage (BAL), airway biopsy, and measurement of airway gases.

A brief review of normal structure and function is given to provide the necessary background information. The pathophysiological processes in asthma begin with various triggers in susceptible individuals causing an airway inflammation. Prolonged inflammation induces a state of airway hyperactivity, which might progress to airway remodeling unless treated effectively. Environmental influences and genetic predisposition may explain the susceptibility in individuals to the pathophysiological processes of asthma.

LEE BEE WAH, The Child & Allergy Clinic, Mount Elizabeth Centre

GOH LEE GAN, Senior Consultant Family Physician, Department of Community, Occupational and Family Medicine, National University of Singapore

NORMAL STRUCTURE AND FUNCTION

Gaseous exchange

The main function of the respiratory system is in the gaseous exchange of oxygen across the alveoli into the circulation and carbon dioxide out of the circulation. The alveoli have very thin walls to allow oxygen and carbon dioxide to cross between the lung capillaries and the alveolar spaces.

Breathing

The action of breathing is the concerted efforts of both the respiratory muscular system and the neural control. The respiratory muscular system is made up of the diaphragm and the intercostal muscles. Neural control of breathing is achieved by the respiratory centre, the parasympathetic nerves, and the sympathetic nerves.

The respiratory muscular system. During normal breathing, inspiration is an active process that involves the contraction of the diaphragm (to expand the chest cavity downward) and the intercostal muscles (to expand the chest cavity up and outward). Expiration is largely passive in normal breathing, during which time the diaphragm and intercostal muscles relax.

Neural control. The respiratory centre controls the rate and depth of breathing. An increase in carbon dioxide levels will stimulate an increase in the rate or depth (or both) of breathing. A decrease in oxygen levels will cause an increase in the rate of breathing.

The vagus nerve sends motor parasympathetic fibres to innervate the smooth muscle cells in the bronchial walls. Stimulation of the vagus nerve releases acetylcholine which binds to specific "cholinergic" receptors on the smooth muscle cells and causes bronchoconstriction.

The sympathetic nerves innervate the blood vessels and glandular cells in the lungs, but not the bronchial smooth muscle. Thus, sympathetic nerves cannot directly control airway diameter. Instead, the sympathetic nerves cause its effects of bronchodilation to the bronchial smooth muscle through the release of catecholamines by the adrenal glands into the bloodstream.

Airway defence

Besides conducting air to and from the alveoli, the bronchi also protect the alveoli from damage from specific allergens, irritants, and other noxious agents. This is achieved through the following mechanisms:

- bronchoconstriction by the smooth muscles in the bronchial wall;
- muco-ciliary clearance; and
- Immunological processes.

Bronchoconstriction. The calibre of the bronchial wall is controlled by smooth muscle in the wall. In response to an inhaled noxious stimulus e.g., smoke of irritant, the smooth muscle will clamp down. This mechanism protects the delicate alveoli from toxic damage.

Muco-ciliary clearance. The bronchi have a self-cleaning mechanism to remove small, inhaled airborne particles. Among the cells that line the mucosa from the nasal lining through the trachea and bronchi, are cells that secrete mucus. This coats the lining of the airway to create a sticky surface that can collect foreign particles in the inhaled air. In addition, most cells that line the airway have cilia on their free surface. These move constantly in a sweeping fashion. Fine airborne particles that land on the airway lining are trapped in the mucus. The mucus and foreign particles are swept upwards by the cilia. Eventually, the mucus is brought far enough to be coughed out of the respiratory system or more commonly swallowed. Any particles not removed by the muco-cillary clearance can reach the alveoli. These are removed by phagocytosis by large scavenging cells called alveolar macrophages.

Immunological processes. Antibodies, inflammatory cells and inflammatory mediators acting together constitute the immunological processes to eliminate the noxious antigen that has entered the airway.

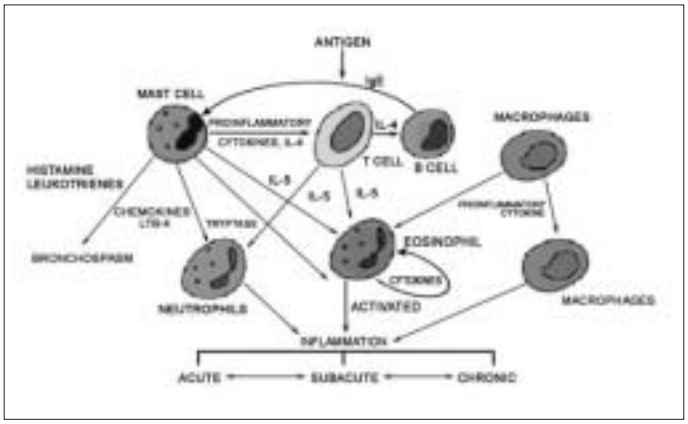
Antibodies. These are immunoglobulins created and secreted by B cells. The presence of an antigen in the airway causes the B cell that is secreting an antibody that has a close structural "fit" to the surface of this antigen to bind to it. Once that occurs, the B cell is activated to divide repeatedly (termed B cell proliferation). IgE immunoglobulins are central to the allergic immune response in asthma.

Inflammatory cells. These are the mast cells, the eosinophils, and the lymphocytes. The mast cell is fixed in a particular tissue location e.g. bronchial wall. It becomes sensitized to an allergen when the IgE specific for that particular allergen circulating in the bloodstream binds on its surface. The cross-linking of the surface IgE by the allergen molecule triggers a rapid activation (within 15 minutes) of the mast cell to release numerous inflammatory mediators into the tissue surrounding the mast cell.

The eosinophil is the inflammatory cell most closely associated with asthma. Unlike the mast cell, it is mobile. It can move from the bloodstream into the bronchus. When activated, it releases pre-formed mediators residing in the granules within the cell.

The lymphocyte manufactures proteins involved in the inflammatory process. There are two kinds of lymphocytes. The B lymphocyte manufactures antibodies. The T lymphocyte releases a variety of cytokines that communicate with inflammatory cells (B cells, eosinophils, and neutrophils) involved in the inflammatory process (Figure 1).

Figure 1. Schematic diagram showing inflammatory cell participation in airway inflammation in asthma.



Source: Spahn J, Covar R, Stempel DA. Asthma: addressing consistency in results from basic science, clinical trials, and observational experience. J Allergy Clin Immunol 2002;109:S492.

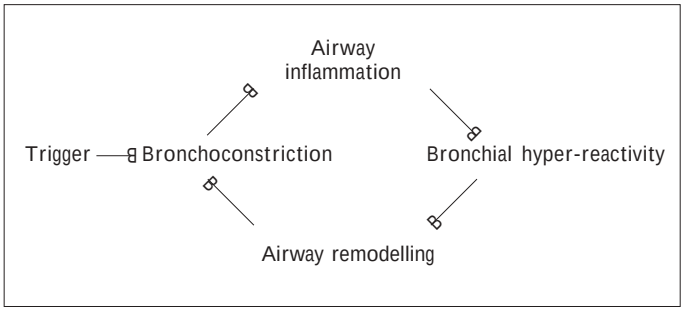
Cytokines from the T cell initiate and orchestrate a cascade of cytokine-mediated airway inflammation. T cells and their cytokines provide a common pathway for allergic (i.e., IgE-mediated) and non-allergic asthma. The T cell is however, not a source of mediators of immediate hypersensitivity reactions and thus does not participate in the acute (within 15 minutes) response to allergen that can cause an acute asthmatic attack. The latter is accomplished by the mast cell.

Inflammatory mediators. These are substances released by activated inflammatory cells to result in an inflammatory reaction. Examples of such substances are histamine, cytokines, prostaglandins, eosinophil cationic protein, and leukotrienes.

PATHOPHYSIOLOGICAL PROCESSES IN ASTHMA

Figure 2 shows how the important pathophysiological processes in asthma are linked. Briefly, various triggers in susceptible individuals initiate an airway inflammation. Prolonged inflammation induces a state of airway hyperactivity, which might progress to airway remodeling unless treated effectively. Environmental influences and genetic predisposition may explain the susceptibility in individuals to the pathophysiological processes.

Figure 2. Pathophysiological processes in asthma



Asthma Triggers

Asthma symptoms may be activated or aggravated by triggers. It is important to note that not all asthmatics react to the same triggers. Also, the effect that each trigger has on the individual varies from person to person. It is also noteworthy that triggers that activate asthma can also worsen nasal or eye symptoms.

Asthma triggers can be divided into two broad categories:

- Allergens (specific triggers)
- Non-allergens – mostly irritants (non-specific triggers).

Table 1 shows a list of allergens and irritants. About 80% children and 50% of adults with asthma have allergies. The many potential triggers of asthma explain the different ways in which asthma can present. In most cases, the disease starts in early childhood – age 2 to 6 years. In this age group, the cause of asthma is often linked to exposure to allergens, such as dust mites, and viral respiratory infections, or irritants like tobacco smoke. In the very young children, less than 2 years of age, asthma can be difficult to diagnose with certainty. Wheezing at this age often follows a viral infection and might disappear later, without ever leading to asthma. On the other hand, the asthma can develop again in adulthood. Adult onset asthma occurs more often in women, mostly middle-aged, and frequently follows a respiratory tract infection. The triggers in this group are usually non-allergic in nature.

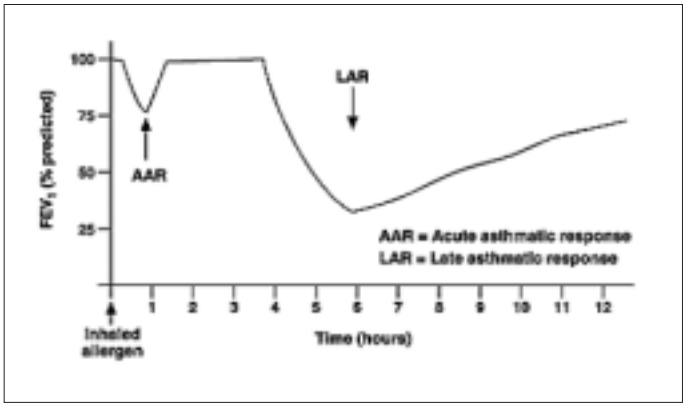
Table 1 Allergens and irritants in asthma

Allergens
o "Seasonal pollens
o Year round allergens – dust mites, moulds, pets, and insect parts
o Foods – fish, egg, peanuts, nuts, cow's milk, and soy
o Additives – sulphites
o Work related agents – latex, flour
Irritants
o Respiratory infections – viral colds, bronchitis, and sinusitis
o Drugs – aspirin, NSAIDs, betablockers
o Tobacco smoke
o Outdoor factors – haze and smog, weather changes, exhaust fumes from vehicles
o Indoor factors — paint, detergents, deodorants, chemicals and perfumes
o GERD
o Temperature change – night-time
o Exercise in cold dry conditions
o Work-related factors – chemicals, dusts, gases, and metals
o Emotional factors – laughing, crying, yelling and distress
o Hormonal factors – premenstrual syndrome

Airway Inflammation

Figure 2 shows the inflammatory cells involved in the airway inflammation in asthma[3] (Spahn et al, 2002). The focus of the inflammatory mechanisms underlying asthma is the alteration of the balance between the T-helper type 1 (Th1) and Th2 lymphocytes towards the latter. There is now overwhelming evidence to suggest allergen-induced airway inflammation is orchestrated by the activation of Th2 cells[4] (Suresh Babu & Hasan Arshad, 2003). The Th2 lymphocytes mediate allergic inflammation in atopic asthmatics by a cytokine profile that involves IL-4 (which directs B lymphocytes to synthesize IgE), IL-5 (which is essential for the maturation of eosinophils), and IL-3 and granulocyte-macrophage colony-stimulating factor[5,3] (Boride, 2001; Spahn et al, 2002).

Figure 3. Early and late asthmatic response to an allergen



Source: Merck & Co, Inc, 1998

Eosinophils are frequently present in the airways of asthmatics (more commonly in allergic but also in non-allergic patients), and these cells produce mediators that can exert damaging effects on the airways. Recent knockout studies and anticytokine studies suggest that lipid mediators are products of arachidonic acid metabolism. They have been implicated in the airway inflammation of asthma, and therefore have been the target of pharmacologic antagonism by a new class of agents called antileukotrienes.

Prostaglandins (PGs) are generated by the cyclooxygenation of arachidonic acid, and leukotrienes are generated by the lipoxygenation of arachidonic acid. The proinflammatory prostaglandins (PGD_2, PGF_2, and TXB_2) cause bronchoconstriction, whereas other prostaglandins are considered protective and elicit bronchodilation (PGE_2 and PGI_2, or prostacyclin). Leukotrienes C_4, D_4, and E_4 compose the compound called "slow-reacting substance of anaphylaxis," a potent stimulus of smooth muscle contraction and mucus secretion. Ultimately, mediators lead to degranulation of effector/proinflammatory cells in the airways that release other mediators and oxidants, a common final pathway that leads to the chronic injury and inflammation noted in asthma.

The observation of the focus towards the Th2 lymphocyte mediated pathway, the higher prevalence of asthma in industrialized Western societies compared to less technologically advanced societies, and the observation that asthma often occurs in early childhood, with persistence of the asthmatic syndrome into later childhood and adulthood, has led to the proposal of the "hygiene hypothesis"[6,7] (Dompeling et al, 2000; Weiss, 2002).

This hypothesis proposes that airway infections and higher levels of exposures to animal allergens (egg, farm animals, cat, dog) is important in affecting the relative balance of the Th1 versus the Th2 airway immunologic profile. Specifically, early

exposure to the various triggers that may occur with higher frequency in a rural setting may tilt this balance to a Th1 paradigm and hence be protected against the allergic diathesis that is characteristic of the Th2 paradigm. In a "cleaner" urban Western society, such early childhood exposure is lacking, and the paradigm therefore shifts closer to the allergic diathesis of Th2, which results in a higher incidence of asthma and other allergic diseases. Although this notion remains speculative, it is the basis for emerging therapeutic options that attempt to shift the balance in favor of the Th1 immunologic profile. Oral supplementation with Lactobacillus ruminus[8,7] (Kalliomaki et al, 2001; Weiss, 2002); the presence, from birth onward, of a dog or other pet in the home[9,7] (Reijonen et al, 2000; Weiss, 2002); and attendance at day care during the first year of life[10,7] (Celedon et al, 2002; Weiss, 2002) are all environmental factors that may protect against the development of allergies and allergic asthma in childhood[7] (Weiss, 2002).

Bronchoconstriction

Inhalation of an allergen solution by a patient with allergic asthma causes a prompt bronchoconstriction. There is a rapid decline in forced expiratory volume in 1 second (FEV1) and this begins within 15 minutes and generally subsides within the first hour. This bronchial manifestation of an immediate reaction has been termed the early asthmatic reaction (EAR). This is also called the early phase response.

This EAR results from binding of inhaled allergen to mast cell membrane-bound IgE with subsequent release of mediators (e.g., histamine, leukotrienes, and prostaglandins). Amongst these mediators, the cysteinyl leukotrienes appear to account for a significant part of the early bronchoconstriction response. After this phase resolves, either spontaneously or with a beta-agonist, the FEV1 reaches a level that is at or close to the pre-challenge baseline (Figure 3).

In about 50% of patients, a late phase response is observed. This is termed the late asthmatic response (LAR). There is a spontaneous return of bronchoconstriction several hours after the allergen challenge and after EAR has resolved. This late phase response usually occurs 6-24 hours after exposure to the allergen. The LAR is typified by a decline in FEV1 as well as the influx of inflammatory cells, most notably eosinophils, and airway edema. The intensity of the LAR inflammation correlates with the degree of airflow obstruction that occurs during the LAR. The repeated or prolonged episodes of LAR approximate the events in the airways in both chronic allergic and non-allergic asthma.

Bronchial Hyper-reactivity

Airway inflammation also results in bronchial hyper-reactivity (BHR). Studies have shown that the degree of BHR correlates with the number of inflammatory cells recovered in the BAL fluid from the airways of asthmatic patients. Clinically, the degree of BHR (measured by metacholine challenge) has been shown to correlate with general asthma severity, with morning peak expiratory flow rate (PEFR), and with the degree of diurnal variation of the PEFR. The degree of BHR appears to decrease when asthma is well controlled with medication. The ultimate result and significance of BHR is the airflow obstruction that occurs when an asthmatic is exposed to a trigger.

Airway remodeling

Clinically, it has been observed that in some patients, there is persistent airflow obstruction despite aggressive anti-inflammatory therapies, including inhaled corticosteroids (ICs) and systemic corticosteroids. This has led to the concept of airway remodeling as a long term result of airway inflammation and hence the need to prevent this from occurring.

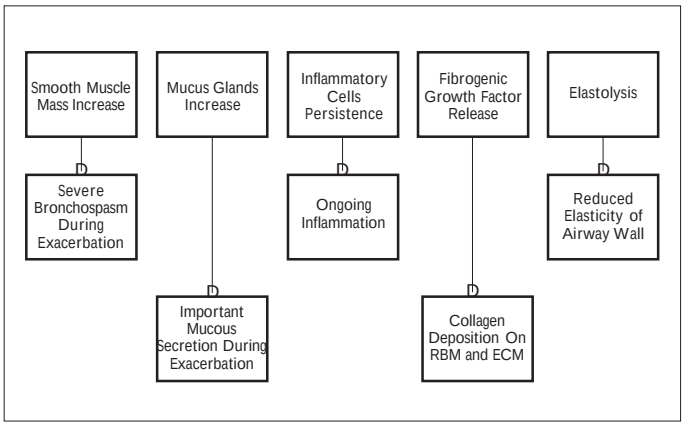
THE CONCEPT OF AIRWAY REMODELLING

The relation between the several types of airway inflammation (both early-phase and late-phase events) and the concept of airway remodeling, or the chronic nonreversible changes that may happen in the airways, remains a source of intense research[11] (Bousquet J et al, 2001). The natural history of airway remodeling is poorly understood, and although airway remodeling may occur in some patients with asthma, it may not be a universal finding.

Pathologically, airway remodeling appears to have a variety of features, namely, (a) an increase in smooth muscle mass, (b) mucus gland hyperplasia, (c) persistence of chronic inflammatory cellular infiltrates, (d) release of fibrogenic growth factors along with collagen deposition, and (e) elastolysis (Figure 4). Many biopsy studies show these pathological features from the airways of patients with chronic asthma.

There are many unanswered questions, including whether features of remodeling are related to an inexorable progression of acute or chronic airway inflammation or whether remodeling is a phenomenon separate from inflammation altogether. It is known that the airway epithelium is an active regulator of local events, and the relation between the airway epithelium and the subepithelial mesenchyme is thought to be a key

Figure 4. Clinical consequences of airway remodeling in asthma



Source : Bousquet J, et al. Asthma : From Bronchoconstriction to Airways Inflammation and Remodelling, Am J Repir Crit Care Med 2000; 161:1720-1745. RBM = respiratory bronchiolar mucosa; ECM = extracellular mucosa

determinant in the concept of airway remodeling. A hypothesis by Holgate et al[12] (Holgate et al, 2000) suggests that airway epithelium in asthma functions in an inappropriate "repair phenotype" in which the epithelial cells produce proinflammatory mediators as well as transforming growth factor-ß to perpetuate remodeling.

GENETIC PREDISPOSITION

Studies suggest a genetic basis for bronchial hyper-reactivity, including linkage to chromosomes 5q and 11q. However, asthma clearly does not result from a single genetic abnormality, but is rather a complex multigenic disease with a strong environmental contribution. For example, allergic potential to inhalant allergens (dust mites, mold spores, cat dander, etc) more commonly is found in asthmatic children as well as asthmatic adults whose asthma began in childhood, compared with adult-onset asthmatics.

ADAM33 on chromosome 20p12 from positional cloning has been implicated as a candidate gene involved in the pathogenesis of airway remodeling. The cellular and mediator responses underpinning airway remodeling involve aberrant communication between the airway epithelium and underlying mesenchyme, involving the generation of growth factors that lead to proliferation of fibroblasts and smooth muscle and the deposition of matrix proteins to cause airway thickening linked to bronchial hyper-reactivity and fixed airway obstruction. The association of ADAM33 with progressive asthma and in predicting reduced lung function in young children suggest that this gene has an important role in the natural history and possibly the origins of asthma, a disease unique to humans[13] (Cakebread et al, 2004).

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LEARNING POINTS

- **The understanding of the pathophysiology of asthma has moved from bronchoconstriction to airway inflammation as the initiator of disease and perpetuation of disease.**
- **The use of tools such as bronchoscopy, bronchoalveolar lavage (BAL), airway biopsy, and measurement of airway gases helped to provide an understanding of the pathogenesis of asthma.**
- **The pathophysiological processes in asthma begin with various triggers in susceptible individuals causing an airway inflammation.**
- **Asthma triggers can be allergens (specific triggers) or non-allergens which are mostly irritants (non-specific triggers).**
- **Prolonged inflammation induces a state of airway hyperactivity, which might progress to airway remodeling unless treated effectively.**
- **Pathologically, airway remodeling appears to have a variety of features, namely, (a) an increase in smooth muscle mass, (b) mucus gland hyperplasia, (c) persistence of chronic inflammatory cellular infiltrates, (d) release of fibrogenic growth factors along with collagen deposition, and (e) elastolysis.**
- **Environmental influences and genetic predisposition may explain the susceptibility in individuals to the pathophysiological processes of asthma.**