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REVIEW ARTICLE

Inflammation in allergic asthma: Initiating events, immunological response and risk factors

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Abstract: Allergic asthma affects 155 million people worldwide. Currently, it is a disease that can be controlled by diverse therapeutic approaches but that cannot be cured. This means that asthma is one of the most expensive diseases for healthcare systems in developed countries. Efficient prevention strategies are therefore greatly needed to reduce both individual morbidity and national economic burdens. This requires a detailed knowledge of the immunological and physiological mechanisms involved in asthma. This review synthesizes current understanding about the immunobiology of IgE-mediated asthma. It discusses the initiating events, the main immunological and inflammatory processes, and addresses the importance of risk factors in the development and maintenance of allergic diseases. Finally, it integrates these concepts in a theoretical causal model for atopic asthma.

Key words: asthma, immune response, inflammation, risk factors.

INTRODUCTION

Asthma affects nearly 2% of the world's population, having earned the status of an epidemic disease.[1] As a consequence, the cost of treatment has increased to over US$1 billion per annum in Western countries. Although different therapeutic strategies are currently available, asthma can only be controlled, not cured.[2] The emphasis therefore has been that asthma management should focus primarily on prevention.[3] However, efficient prevention requires an accurate knowledge of the mechanisms that trigger asthma. This can only be achieved by dissecting the complex nature of the disease, the manifestation of which involves the interaction between different functional systems of the organism, such as the respiratory, immune, circulatory and neuronal systems. This review provides an updated synthesis of the immunobiology of allergic asthma. It discusses the initiating events, summarizes the main immunological and inflammatory processes thought to take place, and addresses the importance of risk factors in the development of allergic diseases. It concludes by integrating this information into a multifactorial model for atopic asthma.

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ASTHMA: A DISEASE OF IMPAIRED HEALING AND Th2 IMMUNITY

The lung tissue, the cells of the immune system and numerous mediators (e.g. lymphokines, chemokines and growth factors) interact in a specific fashion to cause asthma. However, this interaction must first be triggered. What are the initiating events that lead to the development of allergic asthma? A new paradigm for asthma pathogenesis has recently been proposed.[4] According to this model, asthma develops in individuals who manifest both (i) increased susceptibility to lung epithelial injury and/or impaired healing, and (ii) Th2 allergic sensitization. The interaction between these two conditions seems necessary for the initiation of the disease but other factors are also involved in the perpetuation and amplification of symptoms.

Increased susceptibility to injury and/or impaired healing induces airway remodelling

Over 10 000 L of air flow through the lungs daily. The inhaled gas carries bacteria, viruses, allergens and irritants, which can all cause injury to the lung epi-

thelium. Under normal conditions, the damaged epithelium is able to repair itself rapidly.[5] Indeed, the epithelial cells temporarily acquire a repair phenotype and, by interacting with the myofibroblasts, neural tissue and extracellular matrix of the lamina propria, they promote rapid re-epithelialization and re-innervation of the epithelium. This anatomical and functional interaction between the epithelium and mesenchymal cells defines what is called an epithelial–mesenchymal trophic unit (EMTU).[6] It is suggested that there may be a primary defect in the epithelium in asthma, such that when it is stimulated by specific exogenous factors the epithelium is unable to respond adequately by reconstituting itself.[7] Rather, it becomes blocked in a repair phenotype with a low proliferative rate sustained by the continuous release of growth factors.[8] These mediators can act in concert with Th2 cytokines (discussed later) to cause a functional disturbance of the EMTU, which leads to permanent myofibroblast activation.[4] Once activated, myofibroblasts amplify the inflammatory and airway remodelling processes initiated by the epithelium. They secrete collagen and other reticular and elastic fibres into the extracellular matrix, which contribute to the thickening of the airway wall. In addition, they secrete and express metalloproteinases, which seem to contribute by reducing the integrity of the epithelium through their capacity to disrupt cell–cell and cell–matrix interactions.[9] Finally, they contribute to the build up of inflammatory mediators, which induce epithelial goblet cell hyperplasia and metaplasia, smooth muscle hyperplasia and proliferation of airway blood vessels and nerves.[4,10]

Thus, asthma is hypothesized to develop in individuals with an inherited or acquired susceptibility to injury, impaired healing or both. This is thought to result in permanent inflammatory and remodelling responses that may be crucial initiating events in asthma. Evidence to support this hypothesis comes from airway BAL and biopsy studies in young children that have shown that both airway inflammation and tissue restructuring may be present before the onset of symptoms.[11,12]

Th2 allergic sensitization

Atopic asthma is a disease that involves the action of the adaptive immune system; specifically, it is thought to involve the development of a specific immune response known as Th2 allergic sensitization. Allergic sensitization develops when dendritic cells (DC) for the first time present allergens taken up in the lung to naïve CD4 T lymphocytes in peripheral lymphoid organs. Given the right conditions (e.g. extremely high doses of allergen), these DC are able to activate naïve CD4 cells that proliferate and differentiate into effector helper cells. As part of their differentiation programme, some of these effector T cells are believed to acquire a helper type-2 phenotype (i.e. they preferentially produce IL-4, IL-5 and IL-13).[13,14]

The activation of naïve CD4 T cells by DC also seems to involve the expansion of another subset of T cells (gcTh) characterized by the expression of the CXC chemokine receptor 5.[15] This gcTh subset migrates to the B-cell areas of the lymph nodes where it provides key help for B-cell differentiation and antibody production in lymphoid tissues. Once both allergen-specific CD4 Th2 cells and B cells are activated, they migrate to the inflamed tissue in the lung where they execute their effector functions under the influence of the local environment. Importantly, once exposed to Th2 cytokines[16,17] and to the co-stimulation provided by accessory molecules such as ICOS,[18] B cells undergo immunoglobulin isotype switching from IgM to IgE. The secretion of high levels of allergen-specific IgE results in the saturation of the high-affinity IgE receptors (FcεRI) expressed on the surface of mast cells that lie beneath the bronchial epithelium. As discussed below, this sensitization of airway mast cells is a determinant of the development of the early asthmatic response.

Finally, the sensitization phase involves the formation of a pool of allergen-specific memory CD4 T cells and B cells. Memory T cells can either home to peripheral lymphoid organs (central memory) or inflamed tissues (effector memory)[19] and require low stimulation from DC to become activated. Therefore, if the lung is exposed for a second time to the same allergen, the interaction between allergen-carrying DC and both central and effector memory T cells can lead to a rapid and strong immune response, even if the DC are poorly stimulatory.[20] If memory T cells are indeed activated, then a prolonged late asthmatic response follows the preceding early reaction. This late response has a prevalence of 30–50% in adults, being perhaps higher in children, and peaks 6–12 h after allergen exposure.[21]

THE ASTHMATIC RESPONSE

In allergic asthma patients, airborne allergens are able to trigger an amplified inflammatory response in the lung, which results in a significant reduction in pulmonary function. This inflammation develops in individuals who manifest both increased susceptibility to injury or impaired healing and Th2 allergic sensitization. This section describes how the tissue, the cells of the immune system and the different mediators interact to cause such debilitating effects. A typical episode of allergic asthma involves an early and a late response.

Early asthmatic response

The early reaction is triggered by allergens that gain access to sensitized mast cells

The lung is equipped with innate defence mechanisms, such as mucociliary clearance, the physical protection provided by the epithelium and macrophage phagocytosis.[22] In healthy individuals, these innate mechanisms are able to minimize the load of allergen that reaches the adaptive immune system. However, if the innate mechanisms become inefficient, as is thought to occur in individuals with

increased susceptibility to injury or impaired healing, then a larger load of allergen reaches the sensitized mast cells. When the allergen reacts with the specific IgE on the surface of mast cells, a series of cellular events are activated that culminate in the release of several mediators, including histamine, tryptase, leukotrienes and prostaglandins.[23,24]

The immediate and widespread release of these mediators triggers an amplified inflammatory response characterized by considerable transient changes in the bronchial wall. The airway smooth muscle that encircles the bronchi contracts, the blood vessels of the lamina propria dilate, plasma exudes and mucus secretion by submucosal glands is significantly increased. These transient changes build upon the more permanent structural changes elicited during earlier remodelling processes; as a result, airway narrowing occurs and a reduction in respiratory function is observed.

The early asthmatic response is transient but leads to a prolonged late response

The exaggerated inflammation triggered by mast cell activation will persist while the mediators exert their effects upon the structural cells. When the concentration of these mediators begins to decrease in the tissue, typically 1 h after exposure,[25,26] the inflammation attenuates and normal airflow is gradually restored.

As a result of this early inflammatory response, however, DC that matured under the influence of newly secreted inflammatory cytokines (e.g. granulocyte-macrophage colony-stimulating factor) become increasingly exposed to the inhaled allergen particles. These DC capture the allergen and present it to local effector memory T cells. However, when adjuvants or inflammation are present in peripheral tissues, resident DC are believed to be activated in large numbers and migrate to the draining lymph nodes.[27,28] Indeed, these DC can be viewed as 'disposable packets' of information for central memory T cells, carrying messages in the form of allergen-MHC complexes, costimulatory molecules and cytokines, which reflect the conditions of the tissues where the allergen was captured.[20] By presenting this information to memory T cells, both locally and in the lymph nodes, DC initiate the immunological mechanisms that lead to the late asthmatic response. The important role played by DC in the development of the late asthmatic response is demonstrated by challenge studies in sensitized mice which have been selectively depleted of airway DC. During secondary exposure to inhaled allergen, the inflammation characteristic of the late response is completely suppressed.[29]

Late asthmatic response

Dendritic cells activate memory T cells which migrate to the inflamed tissue

Normal respiratory function is usually restored 1–3 h after allergen exposure. However, working in the background, the immune system is mounting a complex immune response that will cause a relapse in pulmonary function typically 6–12 h after exposure but which can persist for more than 24 h.

This immune response is initiated by DC that activate memory CD4 T lymphocytes both in the lung mucosa and in the peripheral lymphoid organs. Following activation in the lymph nodes, central memory T cells differentiate into Th2-skewed effector cells and enter the bloodstream where they circulate until they receive chemical signals that arrest their migration. Such signals are provided by chemokines (e.g. macrophage inflammatory protein (MIP-1α), regulated upon activation normal T-cell expressed and secreted (RANTES)) released by the inflamed bronchial tissue as a result of the initial mast cell degranulation.[30] These chemokines activate the T-cell integrins, which increase their avidity for adhesion molecules expressed on the surface of the endothelium. In this way, CD4 Th2 cells become anchored to the endothelium which facilitates their movement from the circulation into the inflamed tissue. Here, they join a pool of clonally expanded effector memory cells and exert their effector function. Lymphocyte infiltration into areas of inflammation can be observed as early as 1 h after allergen exposure, though it seems to peak at 6 h.[31]

Activated T cells coordinate the activity of other immune and structural cells

Although the DC is the initiator of the late response, once in the lung wall CD4 T cells play a major role in orchestrating cellular activity.[32] Indeed, by releasing large amounts of IL-4 and IL-13, T cells induce IgE synthesis by B cells while they inhibit mediator release by macrophages and by the structural cells of the tissue. The IgE released by B cells binds to its specific allergen which enhances the phagocytosis by macrophages and neutrophils. This anti-inflammatory activity of T cells is counteracted by the secretion of IL-5. Indeed, IL-5 stimulates eosinophil production in the bone marrow, enhances their migration to the lung and increases their activity and survival once in the bronchi.[33] Although eosinophil infiltration is not essential for the development of the late-phase response,[34,35] if it occurs it further contributes to tissue damage by the release of major basic protein, eosinophil cationic protein, leukotrienes and other inflammatory mediators. Other immune cells that are recruited to the lung wall during the late response as a result of T-cell activity are neutrophils and basophils. Although these cells can potentially amplify the inflammatory response through the release of mediators, their role in asthma is still largely unclear.[36,37]

Thus, at present, CD4 T cells seem to have contradictory effects in the lung. On the one hand, they indirectly contribute to clearing the antigen from the mucosa. However, they can also mediate and directly amplify the inflammation during the late asthmatic response.[35,38]

Prolonged airway inflammation and impaired airflow is maintained by activated leukocytes

Leukocyte infiltration and activation in the airways is believed to be the primary cause underlying the impaired airflow observed during the late response. By analogy with the effects of inflammatory mediators released by mast cells in the early response, the mediators released by activated T cells, B cells, eosinophils and other leukocytes trigger smooth muscle contraction, vasodilation, plasma exudation and mucus secretion. Again, this inflammatory process, together with the structural changes already present in the bronchial wall as a result of previous airway remodelling events, causes a significant reduction in the internal airway diameter. Nevertheless, unlike the early phase, these changes can now persist for several hours and cause a prolonged drop in respiratory function.[21]

The amplified inflammation and therefore the impaired airflow associated with it, is thought to persist as long as an increased number of leukocytes is maintained in an activated state in the airways. Dif-

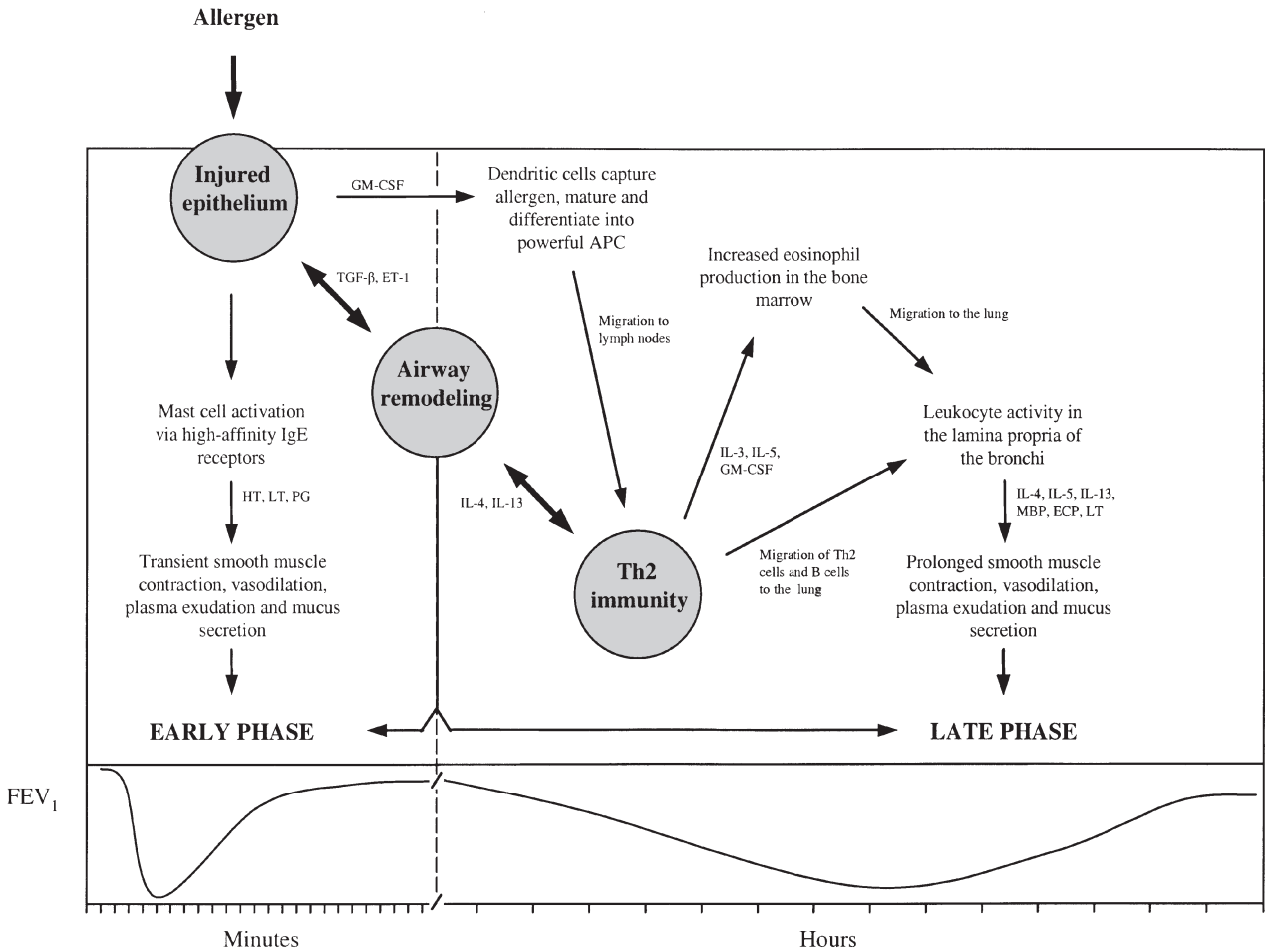

Figure 1 Summary of the main immunological and inflammatory events thought to occur during the early and late responses in an asthmatic patient. Prior to allergen challenge, the patient has developed an injured epithelium, airway remodelling and Th2 allergic sensitization. These phenotypes are likely to be maintained by the secretion of growth factors and cytokines, namely transforming growth factor (TGF)-β, endothelin 1 (ET-1), IL-4 and IL-13. After challenge, allergens break the innate defence mechanisms and react with IgE on sensitized mast cells. This triggers the immediate release of histamine (HT), leukotrienes (LT), prostaglandins (PG) and other mediators that cause transient inflammation of the bronchial wall. The development of this inflammatory process in bronchi already affected by airway remodelling results in a considerable transitory reduction of FEV_1, a measure of lung function. Simultaneously, as a result of the early allergic inflammation, resident dendritic cells capture allergen, mature under the influence of granulocyte-macrophage colony-stimulating factor (GM-CSF) and differentiate into powerful antigen presenting cells (APC). They activate memory T cells in the lung and migrate to the lymph nodes where they regulate the differentiation of central memory Th2 cells and memory B cells. Th2 cytokines (IL-3, IL-5) and GM-CSF stimulate eosinophil production in the bone marrow. Activated Th2 cells and B cells then migrate to the lamina propria of the lung where they enhance the recruitment and activity of other leukocyte populations. The secretion of leukocyte-derived mediators, including major basic protein (MBP) and eosinophil cationic protein (ECP), is likely to be responsible for the prolonged airway inflammation. This, together with previous airway remodelling, results in late, long-lasting impaired airflow. Adapted from Lacy and Moqbel.[95]

Table 1 Risk factors associated with asthma and possible mechanisms of action. Environmental risk factors are classified as protective, predisposing or both. This classification has not been applied to genetic risk factors because there is limited functional data on the polymorphisms of these genes

Risk factors	Possible mechanisms of action	References
Environmental		
Allergen exposure	Predisposing: IgE dependent or independent (via PAR-2 receptors) inflammation	43
Breast feeding	Protective: allergen avoidance, immune and inflammatory regulation	44, 45
Cold air, exercise	Predisposing: airway inflammation/constriction	46–48
Diet	Protective: epithelial integrity. Predisposing: inflammation	49, 50
Endotoxin exposure	Protective: Th1 immune-modulation. Predisposing: inflammation	51, 52
Helminth infections	Protective: Th1 immune-modulation	53
Pet exposure	Protective: modified Th2 response. Predisposing: allergen exposure	54–56
Air pollution	Predisposing: epithelial damage, inflammation, airway remodelling	57–59
Active/passive smoking	Predisposing: epithelial damage, inflammation	60–62
Virus/bacteria infections	Protective: Th1 immune-modulation. Predisposing: epithelial damage, inflammation, reduced mucociliary clearance	49, 63
Genetic		
ADAM-33	Regulation of airway remodelling and inflammation	4, 64
ADRB2	Regulation of smooth muscle response to endogenous ligands	65
AICDA	Immunoglobulin class switching	66
CC16, UGRP1	Modulation of airway inflammation, susceptibility to oxidant lung injury	67, 68
CD14, CTL4, IL-12, TIM	Regulation of T cell differentiation	69–72
CFTR	Mucociliary clearance	73, 74
ECP	Cytotoxicity	75
Fc∈RI	Sensitivity to ligands, regulation of IgE production	76
GSTP1	Response to oxidative stress	77
IFN-γ, IL-10	Modulation of leukocyte function	78, 79
IL-4, IL-4R, IL-13, MHC	Regulation of IgE production	80–83
MCP-1, RANTES, TNF	Leukocyte infiltration and activation	84–86
MUC2	Regulation of mucus viscoelastic properties	87
NO synthases	Modulation of airway inflammation	88
PAI-1	Regulation of fibrinolytic enzyme system	89
ET-1, TGF-β	Airway remodelling	90, 91

ferent factors contribute to the persistence of large number of leukocytes in the lung wall, namely increased production and migration,[39] increased survival[40] and increased retention.[41] On the other hand, the activation state of these leukocytes is to a great extent modulated by the microenvironment (e.g. cytokine concentrations). It can be seen then that remission of the late-phase asthmatic response will depend on the suppression of some or all of these mechanisms. Indeed, corticosteroids, which are the most effective asthma treatment currently available, suppress the expression of multiple inflammatory genes, including cytokines, inflammatory enzymes, adhesion molecules and inflammatory mediator receptors.[2] In this way, they efficiently attenuate the late-phase response. However, how these mechanisms subside spontaneously without treatment is still poorly understood.[42] Figure 1 summarizes the different steps thought to be involved in the allergic asthmatic response.

RISK FACTORS FOR ASTHMA

The immune response described above takes place when inhaled allergens gain access to IgE-coated mast cells (initial effector cell of the early-phase response) and immunoregulatory DC (initial effector cell of the late-phase response). If this takes place then an asthmatic response follows, typically characterized by two events of amplified inflammation. This amplified inflammatory process causes debilitating secondary effects and therefore is non-adaptive. Why, then, does this response affect one in four children in Western countries? Why is asthma triggered in some individuals but not others?

Genetic and environmental risk factors for asthma

There is not a unique immune cell or a unique mediator that alone can cause all pathological changes that characterize asthma. In the same way, there is no unique factor, be it environmental or genetic, that alone is responsible for the development of asthma in all individuals. Indeed, a number of different factors have been demonstrated to influence the relative risk of developing asthma, either by conferring protection or by increasing the likelihood of developing the disease (Table 1). Some of these risk factors are derived from personal lifestyles and others from the family environment, while some are genetic.

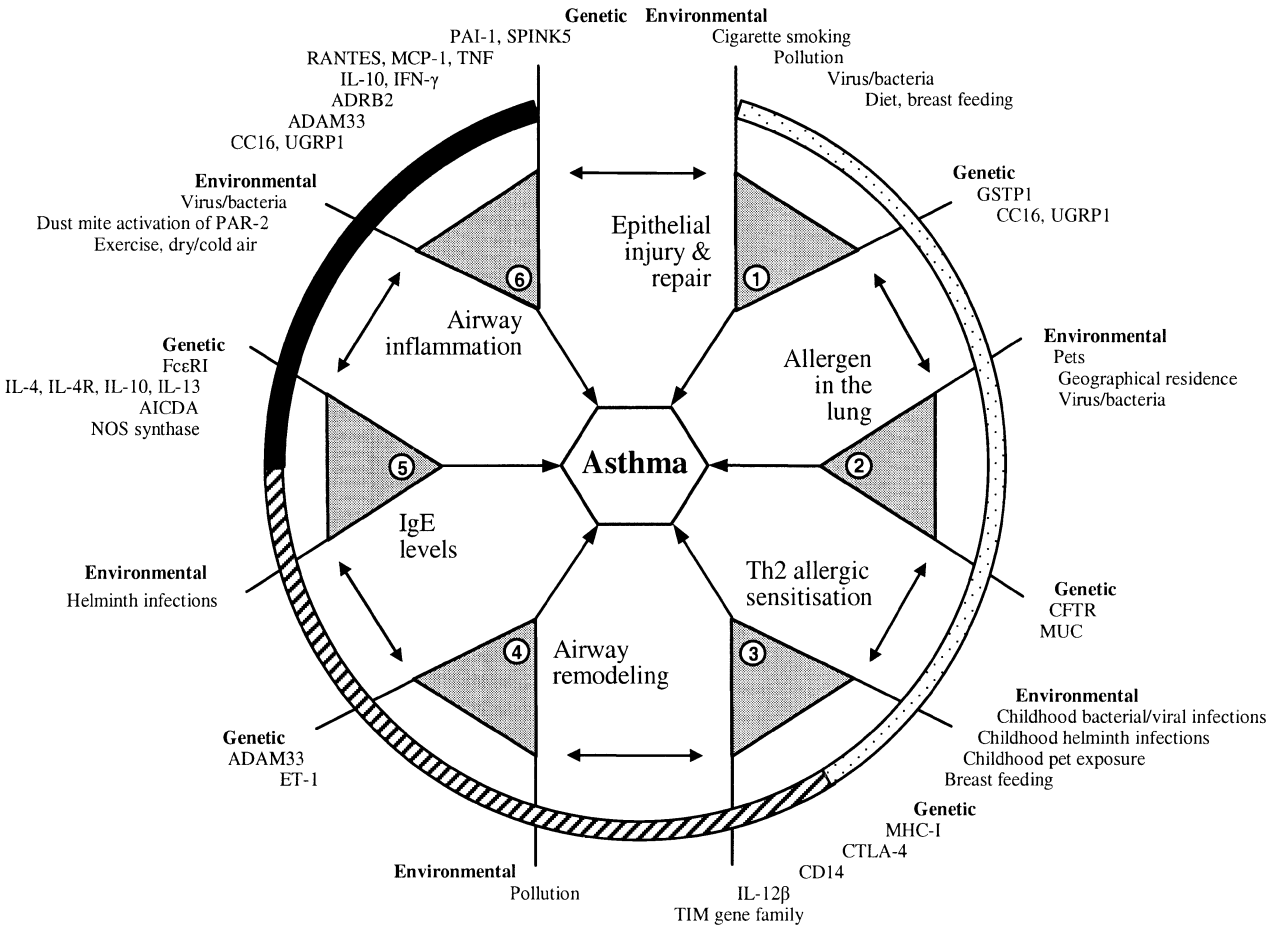

Figure 2 A multifactorial model for asthma. The model is composed of three levels: risk factors associated with asthma, intermediate phenotypes and the final trait. The risk factors, which can collectively be grouped as environmental or genetic risk factors, determine the extent to which the intermediate phenotypes are expressed. The intermediate phenotypes are necessary but not sufficient conditions for the development of allergic asthma. The extent to which these phenotypes are expressed determines the likelihood of the initiation of the disease (dotted), as well as the likelihood of persistence (hatched) and the severity of the disease (black).

Although extensive literature has demonstrated associations between environmental and genetic factors and asthma or related phenotypes, it is still not clear how most of them contribute to the disease manifestation. In fact, some factors fail to show association with asthma but nevertheless are associated with asthma severity,[65,70,71] or with specific phenotypes known to be involved in the disease, such as increased IgE levels.[82,83,88] Together, these results suggest the involvement of independent intermediate phenotypes in asthma that can interact to modulate the onset, recurrence and severity of the disease.

A multifactorial model for allergic asthma

Figure 2 proposes a model to describe how the various genetic and environmental risk factors shown to be associated with asthma may interact to cause the disease. This model involves six intermediate phenotypes that are likely to be necessary but not sufficient for the development of allergic asthma. These include: (i) increased susceptibility to epithelial injury and/or impaired healing; (ii) an allergen load that accumulates in the lung; (iii) sensitization to a common allergen with the development of a Th2-skewed response; (iv) airway remodelling; (v) level of IgE; and (vi) the degree of airway inflammation. Other intermediate phenotypes could be involved. The extent to which these phenotypes are expressed will be determined by the underlying genetic and environmental risk factors. The extent to which they are expressed is likely to determine the degree of disease manifestation.

The task of dissecting the multifactorial nature of asthma into a small number of independent phenotypes is complex but extremely useful. Indeed, defining these 'black boxes' is a necessary step in increasing our ability to detect both environmental and genetic risk factors involved in asthma.[92] Failure to consider the appropriate phenotypes may result in false negative association results. In addition, it

decomposes a complex trait into individual components which can then be targeted by specific therapies.[2,93]

The model presented here provides a practical approach to represent intermediate phenotypes involved in the aetiology of allergic asthma. If the model fails to provide a valid causal mechanism for a given risk factor, then it may be necessary to refine it or include new intermediate phenotypes. Finally, similar models can be derived for other allergic diseases by declaring intermediate phenotypes that are specific for each disease.

CONCLUSION

This review provides an updated synthesis of the pathogenesis of asthma. Still, numerous questions remain unanswered.[94] As asthma research elucidates these questions, our understanding of the immunological and physiological mechanisms of allergic diseases gradually becomes more complete. Although this is unlikely to yield a 'cure' for asthma, it provides an invaluable insight into the factors and mechanisms necessary to trigger and maintain the disease. The identification of these factors is very likely to make asthma preventable.

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