

Immunopathogenesis of allergic disorders: current concepts

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Allergic disorders are a group of immune-mediated disorders that are associated with considerable morbidity and ill health. There has been significant rise in the prevalence of allergy in the last few years. This has heightened interest in uncovering the novel mechanisms involved in etiopathogenesis of allergic disorders. Understanding the pathways underlying allergy will help in developing effective modalities for its prevention and treatment. This review focuses primarily on common IgE-mediated allergic conditions and recent developments in their immunopathogenesis, especially those involving respiratory mucosa.

KEYWORDS: allergic disorders • bronchial asthma • IgE mediated • immunopathogenesis

In the year 1906, Clemens von Pirquet, an Austrian pediatrician, for the first time observed that antibodies that protect us against various ailments may also be responsible for disease [1]. He coined the term ‘allergy’ for this phenomenon and proposed that the term should be used to describe ‘an uncommitted biological response which in an individual may lead either to immunity, (beneficial) or an allergic disease (AD; harmful) [2]. However, over a period of time, the meaning of the word ‘allergy’ has been modified and is now defined as a hypersensitivity reaction mediated by the immune system. Although the majority of ADs are IgE mediated, in some, other mechanisms are also involved, for example, contact dermatitis and celiac disease (TABLE 1).

Allergy versus atopy

The term ‘atopy’ (Greek *atopos* meaning out of place) is sometimes used synonymously for describing IgE-mediated diseases. Atopic individuals may or may not have symptoms of allergy, but are genetically predisposed to develop one or more ADs (i.e., allergic rhinitis [AR], hayfever, asthma, atopic eczema and certain food allergies) and have a strong familial basis. These individuals may produce IgE antibodies against otherwise harmless environmental substances.

Allergic disorders: extent & burden

AR, asthma and atopic dermatitis are among the most common immune-mediated ailments.

According to recent data, worldwide prevalence of allergy ranges from 30 to 40% [3,4]. In Europe and the USA, approximately half of the population is said to be either suffering from allergy or already sensitized to one or more allergens [5,6]. Moreover, ADs are more prevalent in children as compared with adults. According to the ISAAC Phase III study, every third child (<18 years of age) is allergic to one or other allergens [7]. The prevalence of AD in developed societies has doubled in the past two decades and is increasing rapidly in developing countries (e.g., India), which were previously considered low endemic zones for allergy [8].

Etiologic basis of allergy

In a given time frame, besides ethnic variation, the genetic makeup of a stable population does not change. Therefore, frequency of genetically mediated disorders is unlikely to change in that population. However, this is not true for AD; a rapid increase in prevalence clearly indicates that other factors may be equally or more important in etiopathogenesis. In fact, ADs are believed to be caused by a combination of both environmental and genetic factors (FIGURE 1), each accounting for approximately 50% of risk of susceptibility [4].

Environmental factors

A high prevalence in the western population and increasing prevalence in developing countries suggests that factors like western lifestyle, which

Table 1. Common allergic diseases.

Allergic disease	Clinical symptoms	Allergens	Predominant immune response
Allergic rhinitis	Blocked and runny nose, sneezing, itching and streaming eyes Intermittent: <4 days/week or for <4 weeks Persistent: >4 days/week or for >4 weeks	Pollen, house dust mite and animal dander	IgE mediated
Bronchial asthma	Episodic or recurrent breathlessness with cough, wheezing and chest tightness	Pollen, house dust mite, animal dander, molds, food allergens, viral infections, drugs, smoke	IgE mediated
Anaphylaxis	A serious, sometimes fatal, allergic reaction affecting several parts of body	Insect venom, foods and drugs	IgE mediated
Atopic dermatitis (atopic eczema)	Chronic, relapsing, intense itching particularly around skin flexures at wrist, elbow, ankle and knees	Egg, cow's milk, wool	IgE mediated
Sensitivity to insect venom	Temporary irritation or swelling around the site of sting	Wasp or bee sting	IgE mediated
Drug allergy	Rash	Any drug, especially penicillin group of drugs	IgE mediated
Food intolerance	Rash, especially around mouth; sometimes diarrhea	Peanuts, tree nuts, milk, egg, fish	IgE mediated
Oral allergy syndrome	A type of food allergy presenting with itch or burning sensation around lips, mouth, tongue, ear canal or throat	Certain food, vegetables and nuts	IgE mediated
Urticaria and angioedema	Wheals on the surface of skin (urticaria) or deeper in the subcutaneous tissue particularly around mouth and eyes, abdominal organs or upper airway (angioedema)	Foods, drugs, insect sting, sunlight exposure, heat or cold temperature	IgE mediated
Contact dermatitis	Redness, scaling and itching at the site of skin contact with the allergen	Nickel and cosmetics	IgE independent
Celiac disease	Diarrhea, failure to thrive, fatigue, weight loss (in adults)	Gluten (a protein found in wheat)	IgE independent
Hypersensitivity pneumonitis (extrinsic allergic alveolitis)	Shortness of breath with or without cough with muscular aches, fever and lethargy especially during acute phase. Examples are the following: bird fancier's lung, bagassosis, farmer's lung	Avian proteins in feather and bird droppings Thermophilic actinomycetes in processed sugarcane Moldy hay	IgE independent

Data taken from [6,9,94].

is spreading around the globe, could be important. Changes in the level of air pollution, indoor exposure to allergens and general living standards may be additional environmental factors associated with the risk of allergy.

The hygiene hypothesis, a concept related to lifestyle changes, proposes that early and repeated childhood infections reduce the tendency to develop AD [9,10]. This is supported by the fact that children in western countries who are protected from infections due to their cleaner and germ-free surroundings are at an increased risk of developing allergy. On the other hand, infants and children in developing countries are frequently exposed to infections. Problems related to sanitation, clean drinking water, malnutrition, and overcrowding all contribute to early exposure to infections. It has been observed that, in the developing world, besides exposure to parasitic, viral and bacterial infections,

intestinal colonization with Gram-negative bacteria tends to occur early in life. Differences in intestinal flora have also been found between allergic and nonallergic children in Europe [11]. Antibiotic use during the first 2 years of life may also accentuate the risk of developing AD [12].

A balanced exposure to microbes, parasites, allergens and other environmental substances usually promotes normal development of the immune response (Th1 and Th2). However, as exposure to allergens is increased, there is a propensity in genetically predisposed individuals for an exaggerated Th2-cell type response to a variety of environmental allergens. The counter-regulation hypothesis proposed by van den Biggelaar *et al.* showed that, in response to parasitic and bacterial infections, the regulatory T cells (Tregs), monocytes, macrophages and dendritic cells (DCs) secrete IL-10 [13]. IL-10 has an immunoregulatory

role and dampens both Th1 and Th2 responses resulting from activation of either the innate or adaptive immune system (FIGURE 2).

Allergic sensitization is another environmental predisposing factor for the development of allergy. The properties of an allergen (e.g., type, size, dose and route of exposure) are believed to decide the development of the aforementioned phenomenon (Box 1). Concentration in environment and whether the exposure occurs together with the agents that can enhance the sensitization process (i.e., adjuvants) are other factors that may be important [14]. Allergens are almost always proteins (but not all proteins are allergens) and often have enzymatic functions such as proteolytic activity. Abundance of such proteins in the food, high number of linear IgE-binding epitopes and resistance of these proteins to digestion and processing make them powerful allergens [15]. Such properties, besides eliciting a strong IgE-mediated Th2-cell response, may also participate in augmenting mucosal permeability and other aerodynamic properties [16].

Allergic sensitization, usually to food substances such as egg or milk, begins early in life and occurs primarily in high-risk infants who have a parent with underlying AD. This sensitization may lead to mild symptoms, but by 3–5 years of age tolerance to food has often developed. Sensitization to aeroallergens, such as house dust mites, generally beginning at 1–2 years of age may lead to future development of an AD.

Genetic and epigenetic factors

Genetic factors were believed to be one of the important etiological factors in allergy. With widespread use of genome-wide association studies, hundreds of genes associated with asthma or other ADs have been identified in recent years. Although a definitive etiological link remains to be drawn, these genes have helped us in understanding several pathways crucial in the etiology of allergy. Depending upon their association with the innate or adaptive immune response, the genes can be divided into those regulating the immune function or those affecting the structural tissues like epithelium or connective tissue (TABLE 2).

Epigenetic regulation could also be an important mechanism by which environmental factors may interact with genes involved in the development of AD [17,18]. Recently, it has been shown that DNA methylation and histone modification are involved in effector T-cell polarization and differential secretion of Th1 and Th2 cytokines [19,20]. As epigenetic modifications may be inherited, besides altering immune response in allergy in an individual, they may also influence development of allergy in the subsequent generations [21].

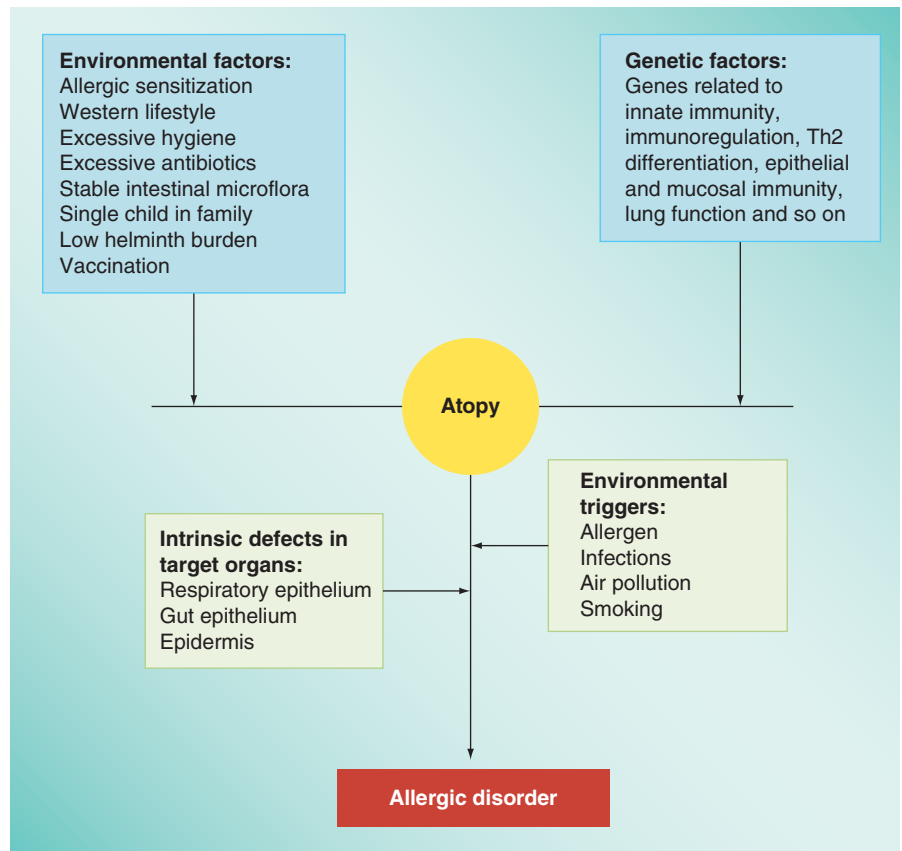


Figure 1. Factors predisposing to allergy.

Cells & chemical messengers in allergy

An allergic inflammatory response is a sequential interaction between various inflammatory and structural cells through their chemical messengers, which together lead to symptoms of allergy.

IgE & its receptors

IgE plays a central role in allergic inflammation and is part of a protein network that includes its two principal receptors FcRI (high-affinity receptor for IgE) and FcRII (low-affinity receptor also known as CD23).

During an allergic response, the allergen is captured by a pre-existing complex of an IgE antibody bound to its high-affinity receptor FcRI on the membrane of mast cells and basophils. This leads to crosslinking of the IgE–FcRI complex, which then triggers activation of these cells and release of substances causing symptoms of allergy. The high affinity of FcRI for IgE facilitates rapid IgE–FcRI interaction, a step critical for IgE-mediated mast cell activation [22].

Recently, it has been proposed that an allergen may not be required for certain IgE-mediated allergic responses, and IgE by itself can display such activity. This phenomenon has been designated as cytokinergic activity of IgE [23,24]. This allergen-independent cytokinergic crosslinking of IgE–FcRI complexes involves contact sites in the N-terminal (Fv) domains of IgE for binding to FcRI on the mast cells. The conformational isomerism of the Fv domain provides the opportunity for additional

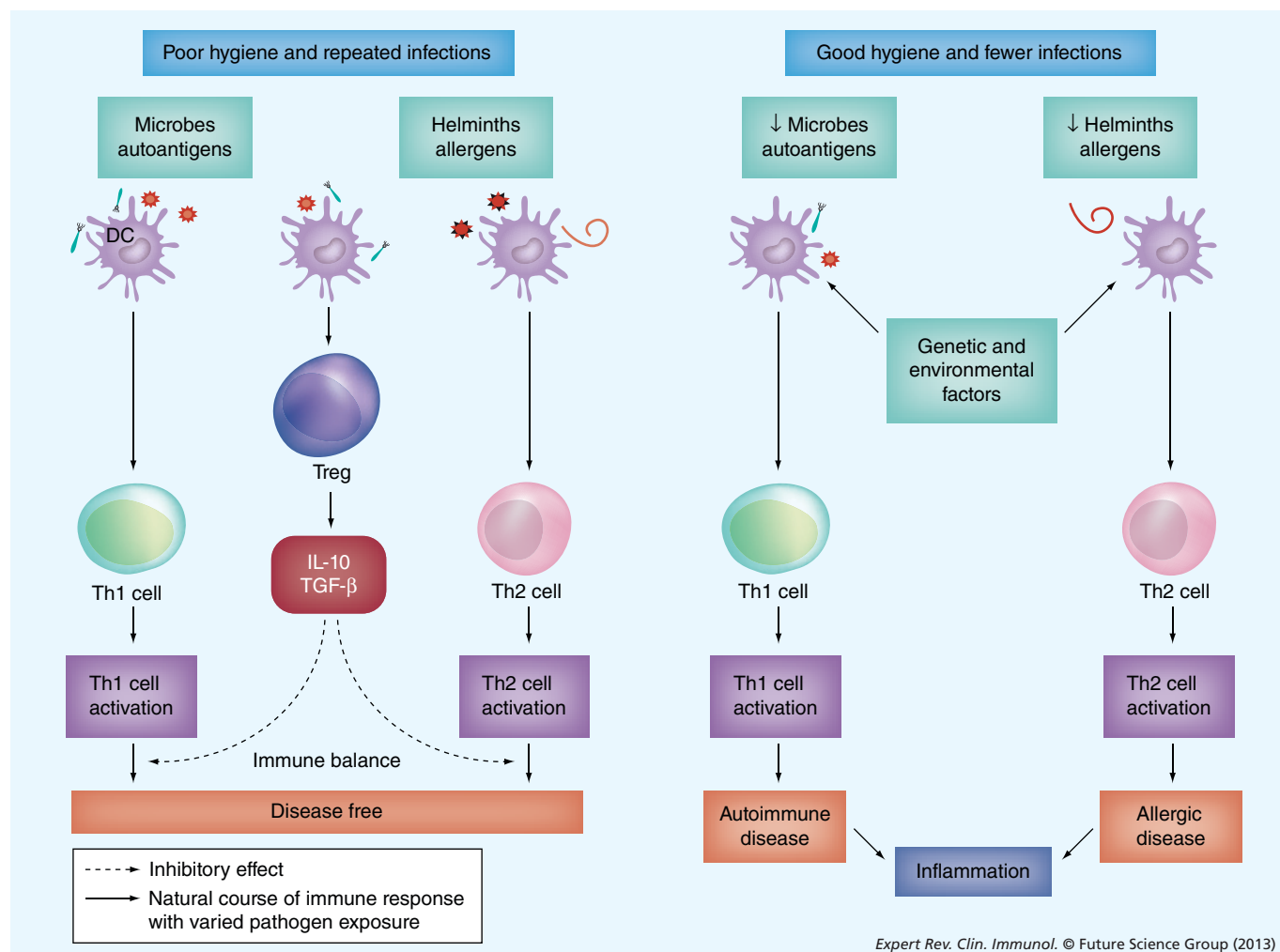


Figure 2. Hygiene hypothesis and counter-regulation theory for allergy. Poor hygiene is associated with frequent infections, which result in strong Th1 and Th2 type of immune responses. However, this also favors the development of Tregs, which maintain a balance between Th1 and Th2 immune responses, thus preventing their harmful effects. On the other hand, reduction in pathogen burden due to excess hygiene shifts immune response against environmental allergens or self antigens, especially in atopic individuals. Moreover, the regulatory check by Tregs is minimal or absent, making individuals more prone to allergic or autoimmune disorders. DC: Dendritic cell.

Data taken from [9–10].

protein-binding interactions. This could be via a new protein, free IgE, or a self-protein, thereby leading to a bridge formation between two IgE–FcRI complexes. Rarely, adjacent IgE–FcRI complexes may contact each other directly [25].

The low-affinity receptor CD23 exists in two splice variants; CD23a and CD23b. CD23a is expressed by antigen-activated B cells before differentiation into antibody-secreting plasma cells, whereas CD23b expression is induced by IL-4 on a variety of inflammatory cells, B cells and epithelial cells. CD23 is primarily involved in regulation of IgE synthesis and maintenance [26].

Allergic functions of IgE include the following: immediate hypersensitivity by forming an IgE–FcRI complex on mast cells leading to their degranulation, thereby causing allergy in skin (atopic dermatitis or eczema), nose (AR), eyes (conjunctivitis), lungs (asthma) or gut (food allergy); antigen presentation by binding to APCs; helping eosinophils and monocytes in lysis

and phagocytosis of the resulting cell fragments and transport of allergen across the epithelium, and thereafter binding to mast cells and DCs via FcRI.

Mast cells

On activation, the mast cells release three classes of biologically active products: those stored in cytoplasmic granules; lipid-derived mediators; and newly synthesized cytokines, chemokines (CCs) and growth factors. During degranulation, the membrane of mast cell granules fuses with the plasma membrane and exposes the contents into the external environment. The important mediators released include histamine, heparin, chondroitin sulfate, tryptase, chymase, carboxypeptidase, certain cytokines and growth factors.

The mediators released lead to bronchoconstriction, vasodilatation and plasma exudation, thus leading to symptoms of asthma (wheezing and dyspnea) or AR (nasal blockage and mucus

secretion). The mast cells are maintained in the tissue and mucosal surfaces by cytokines such as IL-9 and stem cell factor [27].

Dendritic cells

Human DCs can be subdivided into CD11c⁻ (CD123⁺ CD303⁺CD304⁺) plasmacytoid DCs and CD11c⁺ myeloid DCs. The myeloid DCs have further subsets on the basis of differential expression of CD1c, CD141 and CD16 [28]. DCs extend their processes between the epithelial cells lining the airway lumen or surface [29]. They form tight junctions with adjacent epithelial cells and detect allergenic molecules without disturbing the epithelial barrier. Pathogen-associated molecular patterns of allergens are recognized by Toll-like receptors (TLRs) on DCs, which initiate their maturation and augment their homing by upregulating CC receptors, which then direct them towards the T-cell zone of the lymph nodes. The myeloid-type DCs act mainly as APCs, whereas plasmacytoid DCs are responsible for acquisition of tolerance and antiviral defense. Depending on the stimulus, the DCs produce CCs including CCL2, CCL3, CCL4, CCL17, CCL22 and CXCL8, thereby leading to the recruitment of various inflammatory cells at the site of allergen exposure [30].

Th2 cells

Th2 cells orchestrate allergic inflammation through the release of interleukins such as IL-4, IL-5, IL-9 and IL-13 [31]. The APCs process and present the allergic peptides to naive T cells. The CCs such as CCL17 and CCL22 together with IL-4 secreted by eosinophils, mast cells or T cells lead to differentiation of naive T cells into Th2 cells, which promote B-cell proliferation and IgE production [32].

Invariant natural killer T cells

Invariant natural killer T cells have an invariant variable region T-cell receptor α -chain 14 – joining region 18 (V(α)14–J(α)18) [33]. These cells have a unique property of responding to glycolipid antigens, rather than the peptide antigens presented by the nonpolymorphic class I MHC-like protein CD1d expressed on APCs. They are proposed to be responsible for the development of allergen-induced airway hyperreactivity, cell lysis and tissue damage [34].

Th17 cells

Th17 cells are a distinct T-cell lineage with a different developmental pathway from either Th1 or Th2 cells. Their production is inhibited by IL-4 and IFN- γ . Th17 cells play a role in neutrophil and monocyte recruitment leading to phagocytosis and removal of allergens and progression into chronic allergic inflammation [31]. They have also been shown to be responsible for corticosteroid resistance in bronchial asthma [35]. These cells produce IL-17A, IL-17F and IL-22. IL-17A and IL-17F induce IL-6, GM-CSF, CXCL10 and CXCL8 secretion in epithelial and endothelial cells, fibroblasts, neutrophils and eosinophils [36].

Th9 cells

Th9 cells are IL-4- and TGF- β -dependent, IL-9-producing subsets of Th2 cells [37]. These cells do not express T-bet, GATA3,

Box 1. Some of the common allergens responsible for allergic symptoms.

- Plant pollens
- Rye grass
- Timothy grass
- Ragweed
- Plantago weed
- Birch trees
- Hazel tree
- Proteins
- Foreign serum
- Vaccines
- Semen
- Foods
- Nuts
- Wheat
- Milk
- Eggs
- Vegetables
- Seafood
- Animal products (e.g., hair/fur)
- Dander
- Wool
- Insect products
- House dust mite feces
- Bee venom
- Wasp venom
- Ant venom
- Cockroach calyx
- Mosquito sting
- Mold spores
- Thermophilic actinomycetes
- *Aspergillus* species
- Drugs
- Penicillin
- Sulfonamides
- Salicylates
- Local anesthetics
- Contrast dye
- Cosmetics
- Latex
- Poison ivy
- Nickel
- Gold
- Sunlight
- Heat or cold

Data taken from [4,14].

ROR γ t and Foxp3 transcription factors, and hence are different from Th1, Th17 or inducible Tregs. IL-9 expression is markedly increased during allergen challenge [38]. Production of IL-9 by mast cells, basophils and eosinophils has also been noted

Table 2. Some of the important genes involved in allergic disorders.

Pathway involved	Genes	Functions	Ref.
Innate immunity and immunoregulation	TLR-2, -4, -6, -9, -10	Triggering immune response	[106–111]
	<i>CD14</i>	Immunoregulatory	[112–114]
	<i>NOD1</i> and <i>NOD2</i>	Antigen presentation	[110]
	IL-10		
	TGF- α 1		
	<i>STAT3</i>		
Th2-cell differentiation and effector functions	IL-13, IL-33, IL-18	Th2-mediated responses	[115–120]
	<i>STAT6</i>		
	IL-4, IL-4R		
Epithelial biology and mucosal immunity	<i>CCL5</i> , <i>CCL11</i> , <i>CCL24</i> and <i>CCL26</i>	Chemoattractants	[110]
	Filaggrin	Epithelial integrity	[121]
	<i>COL29A1</i>	Protection against proteases	[122]
	<i>ORMDL3</i>		[64]
	<i>SMAD3</i>		[123]
	<i>SPINK5</i>		
Lung function, airway remodeling and disease severity	<i>ADAM33</i>	Formation of epithelial–mesenchymal trophic unit	[124]
	<i>IRAKM</i>	Negative regulation of the TLR and IL-1R pathway	[125]
	<i>ADRB2</i>	Bronchial smooth muscle relaxation	[110]
	TGF- α 1	Allergic airway inflammation and airway remodeling	[126]

TLR: Toll-like receptor.

particularly in ADs such as asthma. The predominant role of IL-9 is mucus production, subepithelial fibrosis and release of inflammatory mediators [39].

Nuocytes

A recently recognized cell known as the nuocyte, an innate, Th2 immune effector leukocyte, has been suggested to form a link between the innate and adaptive Th2 response in AD [40]. They proliferate in response to epithelial-derived IL-25, IL-33, Notch signaling and activation of the ROR γ t [41]. They have been claimed to be an early source of IL-13, especially in helminthic infestation. Their role in ADs needs to be defined further.

Tregs

Tregs are responsible for dampening of allergic response and tolerance. They express transcription factor Foxp3, CD4 and CD25, and exist in either naturally occurring (thymus-derived) or inducible (Tr1 or iTreg) forms [42]. Naturally occurring Tregs secrete IL-10 and TGF- β , which suppress DCs that are involved in programming effector T cells. They inhibit Th1, Th2 and Th17 cells, allergen-specific IgE and induction of IgG4, mast cells, basophils and eosinophils and also prevent effector T-cell migration into the target tissue [43]. Increased number of circulating Tregs has also been linked to protection against allergy in prenatal exposures [44].

B lymphocytes

Under the influence of IL-4, IL-13 and IL-9, B cells generate IgE in the draining lymph nodes, in the mucosal lymphoid tissue or at the site of inflammation [45]. They may also function as APCs or may play a regulatory role through secretion of IL-10.

Eosinophils

Eosinophils are common at the site of allergic inflammation and are regulated by Th2 cells through release of IL-5. They can be primed by a number of other factors including IL-3, IL-5, GM-CSF, CC (CCL2, CCL3, CCL5, CCL7, CCL8, CCL11, CCL13) and platelet-activating factor (PAF) [46]. Eosinophils contribute to the pathophysiology of allergic symptoms by release of cysteinyl leukotrienes (Cyst-LTs), which are also produced by mast cells and basophils. These lipid mediators interact with Cyst-LT receptors on the target cells (i.e., epithelial cells) and promote allergic inflammation by adhesion, migration and survival of eosinophils and by generation of certain proinflammatory cytokines [47].

Basophils

Like mast cells, the basophils also degranulate after re-exposure to allergens. Mediators such as CCL11, CCL24, CCL26, CCL7, CCL13, CCL5, IL-3, IL-5, GM-CSF and histamine releasing factor potentiate FcRI effects leading to basophil mediator release [46]. In addition, CCL11 and CCL24 also act as chemoattractants for basophils. Basophils secrete many mediators including histamine, eicosanoids, leukotrienes (LTs), IL-4 and IL-13 [48]. The cytokines released are important in the later phase of allergic inflammation.

Neutrophils

Neutrophil levels are increased at the site of allergic inflammation under the influence of LTB $_4$, CXCL1, CXCL8 and IL-17 [49]. They can produce a wide range of products including lipids (LTA $_4$, LTB $_4$, PAF, Thromboxane A $_2$), cytokines (IL-1, IL-6, TNF- α , TGF- β , CXCL8), proteases (elastase, collagenase, matrix

metalloproteinase 9), microbicidal products (lactoferrin, myeloperoxidase, lysozyme), reactive oxygen species such as superoxide, hydrogen peroxide, OH⁻ and nitric oxide (NO). Neutrophil products cause airway narrowing and increased mucus secretion [50].

Inflammatory mediators & cytokines

Many different mediators are implicated in allergic inflammation, and each of these has multiple effects (TABLE 3). Because of this overlapping, it is difficult to pinpoint the exact role of a particular mediator in the pathophysiology of allergic inflammation. Their functions may vary depending upon the phase of inflammatory cascade [51–53].

Epithelium & other structural cells

Although infiltrating and resident inflammatory cells are important sources of inflammatory mediators, it is now apparent that structural cells also play a critical role in their secretion, and hence in maintaining chronic allergic inflammation.

Allergic inflammation is closely related to breakdown of the barrier function of the epithelium. Incomplete formation of the tight junction leads to defective or leaky epithelium facilitating the penetration of allergens. Environmental stimuli such as tobacco smoke, air pollutants or certain viruses disrupt tight junctions and impair the barrier function [25]. This type of defective epithelial barrier has been observed in asthma, food allergy, allergic rhinosinusitis and conjunctivitis, and atopic dermatitis. The defective epithelial cells interact with the environment and get activated by pathogens and bacterial toxins through TLR. Activated cells then interact with DCs and release key mediators such as GM-CSF, thymic stromal lymphopoietin (TSLP) and IL-33 that promote a Th2 response [32].

Airway smooth muscle cells are responsible for luminal narrowing in asthma due to release of histamine, Cyst-LTs and prostaglandins D₂ from mast cells [54]. Several CCs such as CCL5, CCL7, CCL11, CCL13 and CXCL8 are produced by airway smooth muscle cell upon stimulation by cytokines (IL-4, IL-13, IL-1, TNF- α and PAF). These CCs are involved in recruitment of inflammatory cells to lungs and upregulation of adhesion molecules on the cell surface.

Other structural cells such as fibroblasts and myofibroblasts may also migrate towards the surface, especially during the chronic phase, and may promote subepithelial fibrosis. Similarly, endothelial cells

under the influence of NO, prostaglandin or Cyst-LTs may lead to microvascular leakage and vasodilatation, thereby leading to plasma exudation, edema and vasodilatation [55].

Goblet cells that are responsible for mucus secretion are also a part of the innate immune response. Several inflammatory cells stimulate mucus secretion and cause goblet cell hyperplasia [56]. IL-13 is the most potent cytokine that leads to goblet cell hyperplasia. Furthermore, the mucus glycoproteins (MUC5AC and MUC5B) may interact with exuded plasma proteins and cause airway blockage or mucus plugging seen in fatal asthma [57].

Neural cells

Sensory nerves in the respiratory tract and skin play a key role in producing cough, sneezing and itch, which are prominent symptoms of AD. Mediators like bradykinin and histamine are potent activators of unmyelinated C fibers, which are responsible for these symptoms [58].

Table 3. Important chemical messengers in allergic inflammation.

Chemical messenger	Predominant source	Actions
Histamine, leukotrienes, PAF	Mast cell, eosinophil and basophil	Allergic reactions (i.e., urticaria, rhinorrhea, wheeze due to bronchoconstriction)
Prostaglandins	Mast cell	Bronchoconstrictors
Cyst-leukotrienes	Eosinophil and basophil	Bronchoconstrictors
LTB ₄	Eosinophil and basophil	T-cell activation, chemotaxis
Cytokines		
IL-4, IL-9, IL-13	Th2 cell	IgE synthesis Development of mast cells Overproduction of mucus
IL-4, IL-5, IL-9, IL-13	Th2 cell	Differentiation, survival and priming of eosinophils
IL-9, IL-13	CD4 ⁺ T cell	Airway hyperresponsiveness
IL-33	Epithelial cells Endothelial cells	NF- κ B and MAP kinase pathway activation and Th2 cell function
IL-1 β , IL-6, TNF- α , GM-CSF	Macrophages and epithelial cells	Proinflammatory
IL-10	Tregs, monocytes, macrophages, DCs and B cells	Immunoregulatory
TSLP	Epithelium	DC stimulation and Th2 differentiation Suppression of Th1
Chemokines		
CCL5, CCL7, CCL11, CCL13, CCL24, CCL28	Endothelial cell, epithelial cell and smooth muscle	Chemotaxis Persistence of inflammation Upregulation of adhesion molecules

DC: Dendritic cell; PAF: Platelet-activating factor; TSLP: Thymic stromal lymphopoietin.
Data taken from [53,127].

IgE-mediated allergic disorders

Bronchial asthma

Bronchial asthma is a chronic inflammatory disorder of the airways that causes recurrent episodes of wheezing, breathlessness, chest tightness and cough particularly at night and/or at early morning. The hallmarks of the disease are increased airway responsiveness to a variety of stimuli resulting in episodic bronchoconstriction, inflammation of bronchial walls and increased mucus secretion. Previously, the disease used to be categorized as extrinsic (allergic with evidence of allergen sensitization) and intrinsic (nonallergic or without evidence of allergen sensitization) [59]. However, several years of research have improved our knowledge on asthma and it is now considered to be a broad entity that includes several disease variants, further subdivided into phenotypes or endotypes. The phenotypes describe clinical and morphologic characteristics and also the responses to treatment while endotypes describe disease subtypes based on their cellular and molecular mechanisms [60]. Based on disease onset, allergic response, histological findings, aggravating or associated factors and response to treatment, several phenotypes of asthma have been described [60,61]. Of these, atopic or allergic and eosinophilic phenotypes are usually associated with a Th2 response. Clinical phenotype of exercise-induced asthma (EIA) may also have a component of Th2 inflammation related to eosinophils and mast cells [62].

Early-onset allergic Th2 asthma

Early-onset allergic asthma has strong family history, originating in childhood. These patients typically have other associated atopic diseases such as AR and atopic dermatitis [63]. Recent genome-wide association studies have shown that there are stronger genetic links to early age of onset than to atopy and IgE [64]. The levels of total and allergen-specific IgE and Th2 cytokines are higher in these patients than those with later-onset asthma. Successful relief with molecules that target components of the Th2 pathway, that is, antibodies to IgE, IL-4R α receptor blockers and IL-13, confirms the relationship of Th2 cytokines to specific allergic asthmatic responses.

Late-onset persistent eosinophilic asthma

Late-onset or eosinophilic asthma is an adult-onset, less allergic form of asthma characterized by the presence of an increased number of eosinophils in sputum and blood of the patients. It is often associated with sinusitis, nasal polyps and sometimes aspirin-exacerbated respiratory disease (AERD). A family history is less commonly observed than in early-onset disease but is often severe with onset [64,65]. Being a less allergic phenotype, the Th2 process in this type of asthma is slightly different from early-onset asthma, as there is interaction of additional immune pathways including activation of pathways related to IL-33 and IL-17 [66–68]. AERD, a subphenotype, is a non-IgE-mediated response to aspirin and other cyclooxygenase-1 inhibitors. The Cyst-LT pathway in AERD is upregulated due to increased Th2 cytokines in cells associated with Th2 inflammation (eosinophils, basophils and mast cells) [69].

Exercise-induced asthma

EIA refers to asthma where patients' symptoms are experienced primarily after exercise. Although it is a very old entity, its pathogenesis is still not very clear. It is a milder form of the disease, frequently seen in cold and dry conditions. EIA is generally noted in atopic athletes and generally associated with high percentages of eosinophils in both sputum and tissue, suggesting a role of Th2 inflammation, although the relationship is not established [70].

Non-Th2 asthma

Non-Th2 asthma includes a large proportion of all asthma. Many people with mild-to-moderate adult-onset asthma and without history of childhood allergic features possibly belong to this category [71]. Poor response to Th2-targeted therapies and the existence of multiple other pathways that lead to airway hyper-responsiveness strongly suggest that there is no Th2 immunity in this subset of asthma [72].

Obesity-related asthma

Obesity has been seen to be associated with development, control and severity of asthma. Although a distinct obesity-related asthma phenotype has been suggested to exist by several studies, the exact role of obesity in pathogenesis remains controversial. In early-onset allergic Th2 asthma, the disease duration correlates with BMI [73]. Moore *et al.* found a later onset, non-Th2 obesity-related phenotype in a group of obese women who had a milder form of allergic asthma with little need for high-intensity healthcare [63].

Neutrophilic asthma

Neutrophilia may sometimes be noted in asthma generally in corticosteroid-treated patients. Neutrophilia may be associated with lower lung function, excessive trapping of air, thickening of airway walls and overexpression of matrix metalloproteinases. Th17 inflammation has been strongly linked with neutrophilia [67].

Allergic rhinitis

AR is one of the most common ADs, afflicting approximately 20% of the world's population. Patients develop a symptom complex that consists of sneezing, nasal congestion, itching and rhinorrhea with involvement of eyes (rhinoconjunctivitis), ears, sinuses (rhinosinusitis) and throat [74]. Approximately 10–40% of patients have asthma comorbidity, while most patients with asthma have rhinitis. Previously, AR was classified based on the time and type of exposure and symptoms as seasonal, perennial and occupational; however, the Allergic Rhinitis and its Impact on Asthma (ARIA) initiative has revised this classification by introducing the terms 'intermittent' and 'persistent' [75,76]. Some patients with AR display symptoms comparable with IgE-mediated AR, yet lack increased serum IgE levels and/or antigen-specific IgE. Such phenomena of localized nasal allergy and existence of Th2 disease pathway in the absence of systemic atopy was termed as 'entopy' by Powe *et al.* [77,78]. Recently, it has been suggested that localized IgE switching is upregulated in AR mucosa as a result of selective B-cell proliferation. This could give rise to a localized IgE-mediated Th2 inflammatory response in

such cases of allergic inflammation. A similar phenomenon has also been observed in food allergies, dermatitis and asthma [79].

Atopic dermatitis

Atopic dermatitis is a chronic inflammatory skin disease that commonly begins in early infancy, runs a course of exacerbations and remissions and is associated with a characteristic distribution and morphology of skin lesions. It results from a complex interplay between strong genetic and environmental factors. Genes involved may be divided into those involved in the epidermal barrier function and those involved in the regulation of the innate and adaptive immune systems including the regulation of IgE sensitization [80]. Moreover, there are chromosomal regions that overlap with other skin diseases, such as inflammatory and autoimmune diseases. This may be one of the reasons that atopic dermatitis is often associated with asthma, AR (hayfever) and food allergy.

Numerous trigger factors for atopic dermatitis have been identified over recent decades, including food allergens, inhalable respiratory allergens, irritant substances and infectious microorganisms such as *Staphylococcus aureus* and *Malassezia furfur*. Atopic dermatitis manifests itself by means of the heightened capacity of B lymphocytes to produce IgE antibodies against allergens, which trigger the immune response after contact. This may be due to defective regulation of the T lymphocytes, which is associated with inadequate function of the CD8⁺ lymphocytes in suppressing IgE [81,82].

Normally, the food antigens that are ingested enter the gut and encounter the intestinal immune system (gut-associated lymphoid tissue). Here, they are captured by the APCs, which then cause apoptosis among the antigen-specific T cells or differentiation in the suppressor T cells, which produce suppressive TGF- β . A breach in the gut immunity and crossreactivity of the IgE antibodies with skin antigens or direct interaction with specific IgE, Fc receptors on Langerhans cells, mast cells, monocytes, basophilic granulocytes or skin-infiltrating T lymphocytes leads to skin allergy [83].

Cow's milk, eggs, wheat, maize, crustacea, hazelnuts, almonds and peanuts are the most common allergens implicated in atopic dermatitis and may cause sensitization and an outbreak or worsening of skin changes. Some vegetable gums, carmine red, ethyl-vanillin, vanilla and tartrazine can also trigger an IgE-mediated response. In addition to the aforementioned food items, the way in which a food is cooked also influences its level of allergenicity. In general, allergens of animal origin continue their activity for longer, whereas vegetable allergens are more easily broken down by cooking or by other processes [84].

Breastfeeding for at least the first 6 months of life is considered to be an important measure in prevention of atopic dermatitis. During breastfeeding, atopic mothers' diets should consist of frequently varied organic foods on the basis of their individual food intolerances. Moreover, as a therapeutic measure, patients with atopic dermatitis should strictly use foods of strictly organic origin, particularly for fruit, vegetables and whole grains. Frequent use of sunflower oil is also useful due to its high content of -3 and -6 polyunsaturated fatty acids. Topical corticosteroids are still a mainstay of treatment for atopic dermatitis.

Food allergy

Food allergy is a specific immune response that occurs reproducibly on exposure to a food. It can be broadly categorized on a pathophysiologic basis into IgE-mediated (immediate), non-IgE-mediated (cell-mediated, delayed) and mixed responses. Acute allergic responses such as urticaria, vomiting, wheezing and anaphylaxis to food are generally due to IgE antibody directed against various food allergens [58]. In the human gut, there is a complex immune system that can discriminate between pathogens and harmless food antigens to avoid an uncontrolled immune response to food antigens or the components of the commensal microbiota [85]. The gut epithelial barrier is generally protected by immune exclusion of foreign antigens via secretory antibodies and by anti-inflammatory tolerance mechanisms. Efficient removal of foreign antigens requires IgA and IgM. IgA is the most abundant immunoglobulin secreted across the mucosa. It is constantly exposed to pathogenic or harmless microbes and also food antigens, hence it provides an immunological defense by transporting antigens across the intestinal layer to the lumen. Besides IgA, DCs and Tregs also play an important role in the allergic response. DCs in the intestinal mucosa are considered to be crucial mediators as they drive T-cell polarization towards Th1 and regulatory phenotypes. DCs migrate from the intestinal mucosa to mesenteric lymph nodes where they produce retinoic acid and TGF- β , which in turn induce Tregs involved in tolerance induction [86]. A profound shift of DC population may be seen in intestinal tissue towards a more inflammatory and less regulatory phenotype in a person sensitized to food allergens [87]. Moreover, there appears to be a link between Tregs and commensal flora, which are likely to promote the development of Tregs, thereby causing food tolerance [88].

Intraepithelial lymphocytes, particularly T cells, are the other cells supposed to play a role in food allergy. They facilitate cross-talk between epithelial cells and immune cells. Reduced number of T cells has been correlated with intestinal epithelial injury after sensitization [89].

Drug allergy

Drug allergy is another immunologically mediated hypersensitivity reaction. Like food allergy, it also may be either an IgE-mediated or a non-IgE-mediated hypersensitivity reaction. These reactions generally occur after prior development of an immune response to a hapten-carrier complex. On subsequent encounter with the drug, a hapten-carrier complex is formed again, which then crosslinks preformed drug-specific IgE on mast cells, activating a cascade for allergic reaction. However, in 50% of patients with immediate reactions and 80% with lethal anaphylaxis, there may be no prior contact with the drug. This may be due to silent sensitization to a crossreactive compound or due to presence of preformed IgE [90].

Common drugs associated with IgE-mediated allergies include β -lactam antibiotics (e.g., penicillin and cephalosporin), immunoglobulin preparations (IgA, IgE), pyrazolones, quinolones, neuromuscular blocking agents and foreign proteins (chimeric antibodies). In non-IgE-mediated drug allergy, different

mechanisms are involved. These include cytotoxic/cytolytic reactions involving the interaction of IgG or IgM antibodies and complement with a drug allergen (e.g., immune hemolytic anemia and thrombocytopenia), drug-immune complex reactions (e.g., serum sickness and drug-induced lupus) and T-cell-mediated reactions, which are generally the most prevalent type of reaction [91].

Anaphylaxis

Anaphylaxis is a life-threatening, systemic, IgE-mediated allergic reaction caused by sudden release of mast cell- and basophil-derived mediators into the circulation [6]. Anaphylaxis occurs within seconds or minutes of allergen exposure. Besides IgE, other mechanisms including IgG-antigen interaction and complement activation may also play an important part in the pathophysiology of this fatal condition [92].

In younger individuals, food is the most common trigger, while medications and insect sting are more common in middle-aged and older adults [93]. The symptoms of anaphylaxis range in severity from those that are mild and resolve spontaneously to those that are fatal within minutes, termed 'anaphylactic shock'. The anaphylactic shock involves multiple organs such as the respiratory and cardiovascular system, GI tract, skin and CNS and is characterized by rapid fall in blood pressure, swelling in throat and mouth, chest tightness, difficulty in breathing and unconsciousness [94]. Prompt injection of epinephrine is life saving in such cases [95]. Anaphylactic responses to insect stings, injected medications, foods and other agents are thought to be caused by IgE/antigen-dependent mast cell activation. In addition to this classic pathway of systemic anaphylaxis, IgG antibodies can also induce anaphylaxis in a basophil-dependent manner in the mouse. Histamine is primarily responsible for the development of shock in the classic pathway. By contrast, PAF is responsible in the alternative pathway [96].

Immune response in allergic disorders

Allergic sensitization

Most ADs begin after sensitization to allergens derived from house dust mites, cockroaches, animal dander, fungi and pollens. Sensitization is a phase of immune reaction occurring after an atopic individual is exposed to an allergen for the first time. Microbes and irritants damage and activate the respiratory epithelium, which then secretes GM-CSF and a variety of chemo-attractants such as CCL20, CCL19 and CCL27. As a result, the DCs migrate from the bone marrow to epithelium and underlying mucosa. GM-CSF and other structural and immune cells under the influence of IL-4 and TNF- α also induce DC maturation and their differentiation into fully mature and competent APCs [79,97]. The activated APCs then process the allergen, further mature and migrate to draining lymph nodes or to the site of local mucosal lymphoid tissue. The processed small peptides are then presented via the class I and II MHCs to the naive T-cell receptors. The presentation of processed allergic peptides to naive T cells stimulates their differentiation into Th2 cells. Excess of IL-4 (produced by accessory cells like mast cells or basophils or by

naive T cells) and low levels of IL-12 are critical for this differentiation. Some epithelial cell-derived cytokines secreted as a result of activation of TLR3 and TLR5 or following epithelial injury also exert Th2-polarizing action, namely, IL-1, IL-25 and IL-33 [44,98]. Activation of receptors for IL-33 and IL-1 on T cells leads to Th2 cell expansion. Th2 cells then produce IL-3, IL-4, IL-5, IL-9, IL-13 and GM-CSF. Nuocytes possibly also assist Th2 cells in secreting these cytokines [40,98]. IL-25 mediates a Th2 memory response initiated by TSLP-primed DCs [99].

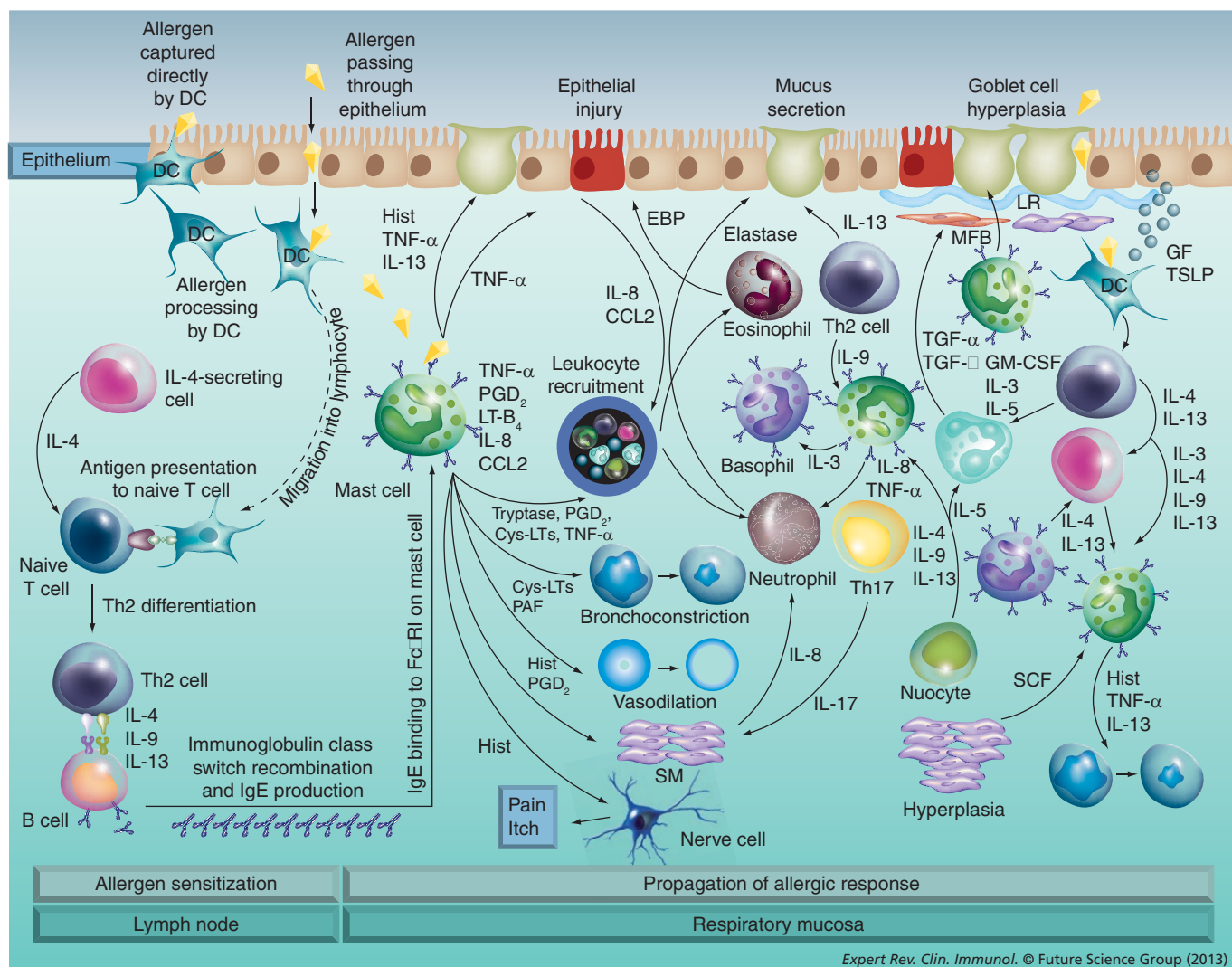
Th2 polarization is also to some extent under epigenetic check. Certain miRNAs are supposed to set a balance between Th1 and Th2 responses. Reduction in levels of miRNAs induce production of increasing amounts of IL-12 by DCs and IFN- γ by allergen-challenged T cells, but inhibit production of IL-4, thus enhancing the Th1 response [100].

Once the Th2 polarization process is complete, IL-4 and IL-13 promote binding of costimulatory molecules (CD40 with CD40 ligands and CD80 or CD86 with CD28) on Th2 cells and B cells, thereby leading to differentiation of B cells into plasma cells and immunoglobulin class switch recombination. In class switch recombination, the gene segments that encode the immunoglobulin heavy chain are rearranged such that antibody of the IgE class is produced. IgE then diffuses locally and enters the lymphatic vessels. It subsequently enters the circulation and is distributed systemically. After gaining access to the interstitial fluid, allergen-specific IgE binds to FcRI on tissue-resident mast cells, priming them (FIGURE 3). Upon re-exposure to allergen, these mast cells respond immediately and release their preformed mediators, resulting in allergy-related symptoms [101].

Propagation of allergic response

After sensitization, re-exposure to allergens leads to an ongoing allergic response driven by memory T cells after they interact with activated DCs. This immediate immune response may be further enhanced by defective barrier function of epithelium, proteolytic and other biological activities of allergens. Moreover, the multi-valent and bivalent nature of the allergens results in binding of more than one IgE molecule resulting in their crosslinking. This results in aggregation of FcRI, which in turn triggers a complex intracellular signaling process causing release of preformed mediators from mast cells. These secreted mediators then result in bronchoconstriction, increased mucus production, vasodilatation, increased vascular permeability (leading to tissue swelling and epiphora) and erythema (reddening of skin in case of atopic dermatitis). The mast cells also contribute to transition to late-phase reaction by promoting influx of inflammatory leukocytes, both by upregulating adhesion molecules on vascular endothelial cells and by secretion of chemotactic factors (FIGURE 3) [102,103].

Mast cells responding to IgE and allergen also release a broad range of newly synthesized cytokines, CCs and growth factors, albeit much more slowly than the preformed mediators. Some mast cell products have the potential to recruit other immune cells either directly or indirectly (TNF- α , LTB $_4$, IL-8, CCL2 and many other CCs) to activate innate immune cells and to affect many aspects of DC, T- and B-cell biology. Some products of mast



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Figure 3. Sequence of events in IgE-mediated immune response. Allergic sensitization is the first step in the development of IgE-mediated immune response. There is continuous screening of all the molecules coming in contact with surface epithelium or skin cells. After antigen capture, antigen-presenting cells process them and migrate to draining lymph nodes, where they present allergic peptides to naive T cells and promote their activation and differentiation into Th2 cells under the influence of cytokines such as IL-4. The Th2 cells then bind with B cells and induce class switch recombination and plasma cell differentiation, thereby leading to production of IgE immunoglobulins. These allergen-specific immunoglobulins via circulation reach the site of allergen exposure and bind to FcεRI receptors on resident mast cells. Subsequent allergen exposure leads to crosslinking of the IgE–FcεRI complex on mast cells, thereby causing degranulation of preformed mediators. After immediate effects of preformed mediators, cells are recruited at the site of the immune response to sustain inflammatory reaction. Persistence of stimulus or repeated exposure causes continuous recruitment of cells, leading to complex interaction between innate, adaptive, epithelial and other structural cells. In respiratory mucosa, an epithelial–mesenchymal trophic unit is established, which sustains Th2 response, leads to goblet cell hyperplasia, mucus hypersecretion, smooth muscle hyperplasia, myofibroblast migration in the subepithelium and deposition of fibronectin and collagen and thickening of lamina reticularis. The aforementioned events increase severity of allergic symptoms such as bronchoconstriction, mucus secretion, cough, rhinorrhea, itching and pain.

Cys-LT: Cysteinyl leukotriene; DC: Dendritic cell; EBP: Eosinophil basic protein; GF: Growth factor; GM-CSF: Granulocyte–monocyte-colony stimulating factor; Hist: Histamine; LR: Lamina reticularis; LT: Leukotriene; MFB: Myofibroblast; PAF: Platelet-activating factor; PGD₂: Prostaglandins D₂; SCF: Stem cell factor; SM: Smooth muscle; TSLP: Thymic stromal lymphopoietin.

cells can influence the biology of structural cells including vascular endothelial cells, epithelial cells, fibroblasts, smooth muscle cells and nerve cells. Other products that contribute to late-phase reactions are derived from resident or recruited T cells that recognize allergen-derived peptides. Therefore, late-phase reactions are coordinated by activated mast cells and antigen-stimulated T cells

(FIGURE 3); the clinical features reflect the activities of both resident cells and circulating leukocytes that are recruited to the site [103].

Chronic or persistent allergic inflammation

In the case of continuous or repetitive allergen exposure, inflammation persists, and many innate and adaptive immune

cells derived from blood are found in the tissues at the site of allergen challenge [104]. This persistent inflammation is associated with changes in stimulated cells at the affected site and in many cases with markedly altered functions of the affected organs. There is an increase in the number of goblet cells in the respiratory epithelium leading to copious mucus production, increased production of cytokines and CCs by epithelial cells, excessive epithelial injury and repair and inflammation of the submucosa. The latter includes increased deposition of extracellular matrix molecules in the lamina reticularis, changes in fibroblasts, increased numbers of myofibroblasts, increased vascularity and hypertrophy and hyperplasia of the muscular layer of the airway (FIGURE 3) [31]. Repetitive epithelial injury due to chronic allergic inflammation can be exacerbated by exposure to pathogens or environmental factors, and the consequent repair response ultimately results in establishment of an epithelial–mesenchymal trophic unit. This unit is thought to sustain Th2 cell-associated inflammation to promote sensitization to additional allergens or their epitopes (e.g., epithelial cell-derived TSLP can upregulate the expression of costimulatory molecules such as CD40 and CD80 by DC) and to regulate the airway remodeling process [105].

A number of *in vitro* tests can be used to confirm the involvement of allergens in allergic inflammation. Some of the commonly used tests include skin-prick test, patch test or direct challenge with an allergen. Allergen-specific antibody test, basophil activation assay, measurement of inflammatory mediators released, (i.e., mast cell tryptase) and lymphocyte stimulation studies are other tests used as common laboratory methods for detection of allergy.

Future research

Despite extensive research, allergy still remains an unsolved mystery for clinicians and researchers. New discoveries in allergy have greatly enhanced our knowledge; however, they have also given rise to many new questions. The role of genetic factors described years previously has been verified, yet many of the potential genes involved in its etiology remain to be explored. The identification of miRNA and their regulatory effects on immune responses has opened a new vista in molecular pathogenesis of allergy. Although therapeutic means have also progressed, we remain far from our goal to cure and prevent AD. Recent efforts directed on understanding the epigenetic regulation of allergic response, mechanisms of immunologic tolerance breakdown, role of extracellular vesicles in the development of allergy, impact of environment and lifestyle factors, discovery of new therapeutic targets and immune modulation, and personalized medicine, among others, may further help to answer many queries related to the enigma of AD.

Expert commentary

AD disorders are increasing all over the world and also affecting the developing nations, which were previously considered to be low endemic zones. However, more recently, there has been tremendous progress in our understanding of the genetics and

pathophysiology of these disorders. A number of molecules contributing to allergy have been identified. Moreover, the immune mechanism involved in allergy is also better understood due to new discoveries in IgE- and Th2-mediated immune pathways. This development has helped us in redefining clinical, immunological and molecular aspects of allergy. With ongoing progress it is likely that, in future, AD will be characterized on the basis of genetic and epigenetic information and the endophenotype that includes all available biomarkers and the clinical phenotype of diseases.

Five-year view

We are proceeding into a postmodern age of allergology – stage 4 – and we anticipate that new discoveries related to AD will be utilized for early diagnosis, treatment and improving the disease outcome. Contrary to prior belief, IgE and mast cells are not the only contributors to the pathology of allergy. In fact, the other components of both innate and adaptive immune response have also been found to be actively involved. Hence, there is a need to formulate criteria for subcategorization of patients according to the most dominant pathway involved so that they can be given individualized pathway-targeted treatment. A better understanding of the role of epithelial dysfunction in asthma could provide a framework by which new therapeutic strategies can be planned to prevent exacerbations and alter the natural course of the disease. So far, clinicians mainly rely on skin test or laboratory quantification of specific IgE in serum to confirm suspected IgE-mediated allergy. Due to certain limitations of these tests, identification of allergen and confirmation of allergy is not easy. Recently, flow-assisted allergy diagnosis by measuring the expression of basophilic activation markers has been shown to be valuable in the diagnosis of IgE-mediated disorders. The spectrum of the aforementioned test may be expanded further to also include non-IgE-mediated hypersensitivity reactions. Progress in nanotechnology and DNA recombination techniques such as microarray opens the door to component-based diagnosis and patient-specific treatment by improving diagnostic accuracy and defining individualized immunotherapy for each patient. Allergen-specific immunotherapy has been used for atopic diseases, especially AR. With improved understanding of asthma pathogenesis, the rationale for considering immunotherapy for its treatment is expanding. With use of bioengineering, it may be possible to have optimal immune response modifiers, and their combination with allergen-specific immunotherapy might provide a means for efficient immunomodulation of AD. The efforts are multidirectional, but the ultimate goal is to bring the possibility of a cure for AD closer to reality.

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Key issues

- Allergic disorders (AD) are increasing all over the world, particularly in developing countries.
- Besides genetic and environmental factors, changing lifestyle could be responsible for increasing allergy prevalence.
- Prior exposure to allergen is a prerequisite for allergic phenomena, but sometimes a person may develop symptoms similar to allergy even in the absence of contact with an allergen.
- Recent genome-wide association studies have contributed significantly to our knowledge on pathophysiology of AD.
- IgE, mast cells and dendritic cells are key players that drive an allergic immune response; however, the response is significantly influenced by microbial exposure and defective epithelial barrier.
- Recent studies have highlighted that the epithelium particularly in airway allergy plays a crucial role in bridging innate and adaptive immunity.
- These discoveries have uncovered many novel targets, and in the near future, therapeutic interventions affecting these may reduce the morbidity and disease burden related to AD.

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