

Chapter 2

Immune System and Atopic Disorders

2.1 Asthma and Allergy

The terms “complex” or “multifactorial” are used interchangeably to refer to diseases that are obviously not the result of a single mutation or an environmental aggression. The genetic load of these diseases is unquestionable, and numerous studies have demonstrated both its heritability and the influence of certain anti-inflammatory factors, but both have proved to be insufficient to the complete understanding of their prevalence and patterns of heritability.

Allergic rhinitis, atopic dermatitis, allergic asthma, food allergy, anaphylaxis, or contact dermatitis are examples of complex or multifactorial diseases for which much is yet to be understood. The term “allergy” was first used by Clemens von Pirquet in 1906 to define the unusual tendency of some people to develop reactivity symptoms or “hypersensitivity reactions” when exposed to seemingly innocuous substances. Atopic diseases, from the Greek *atopos* meaning “out of place”, are associated with the production of specific IgE antibodies and with the expansion of specific T cell populations, which are reactive against what normally would be harmless substances.

The prevalence of allergic diseases has increased around 75 % during the last three decades [1]. This rise in the epidemiological trend has not found a satisfactory explanation yet, although there is a general consensus that is not due solely to a genetic explanation. This observation has been subject of intense speculation, and the role of certain environmental factors has been studied. To this intriguing scenario we have to add that the pathogenesis of the disease as well as the contribution of genetic factors is still poorly understood [2].

Today it is thought that about 300 million people worldwide suffer from asthma [3, 4]. According to the American Academy of Allergy, Asthma and Immunology (www.aaaai.org), it is thought that more than half (54.6 %) of Americans are positive for one or more allergens [5, 6], and that about 50 millions suffer from some kind of allergy, including allergies to food, drug, latex, insects, pollen, mites, or skin and eye allergic diseases. Allergic diseases in the US occupy the fifth position among the most common chronic diseases, and the third position among the most common chronic diseases in children under 18 years [7]. In a pioneer study that was conducted in Britain in 1992, the comparison of children from 1964 to

those from 1989 showed that asthma prevalence had increased from 4.1 to 10.2 %, respectively, whereas rhinoconjunctivitis to pollen raised from 3.2 to 11.9 %, and atopic dermatitis from 5.3 to 12 % [8]. In European countries like Spain, it has been estimated that the prevalence of allergic diseases in adults is around 21.6 % (about one in five individuals will experience some kind of allergy-related disease during their life time) [9]. The prevalence is higher in women than in men and the number of cases is greater in larger cities. Among the main causes inducing allergy are pollens, domestic dust mites, and drugs. Allergic diseases are one of the most frequent reasons for pediatric medical visits, where children exhibit symptoms that can limit their daily activities in more than 40 % of the cases.

2.2 Classification of the Allergic Reactions

According to the traditional classification proposed by Gell and Coombs in 1963, hypersensitivity reactions can be divided into four groups [10] (Table 2.1). Although our current knowledge of the immune system has widely increased, this classification is still in use, at least in teaching terms. In the clinical practice, however, its use has been challenged since it does not include all possible allergic reactions caused by medical drugs, and sometimes both humoral and cellular responses can occur at the same time [11, 12]. Other scientists have proposed the existence of additional types of hypersensitivity [13, 14]. However, for the clarity and simplicity of our exposition of the fundamental concepts that inspire the classification of hypersensitivity reactions, we will start here by discussing the traditional one, to give a quick overview of the different predominant scenarios (see Table 2.1), and then we will annotate some of the improvements and subtypes.

In a more precise way, anaphylactic **Type I** reactions or immediate reactions those that refer to an IgE-mediated response [15]. These reactions take place in seconds to minutes after contact with the allergen, due to the release of preformed

Table 2.1 Original Gell and Coomb’s classification of hypersensitivity reactions

Antigen-mediated hypersensitivity			Cell-mediated hypersensitivity
Type I	Type II	Type III	Type IV
IgE-mediated release of histamine and other mediators from mast cells and basophils	Involve IgG or IgM antibodies bound to cell surface antigens and complement fixation	Involve circulating antigen/antibody immune complexes and complement fixation	Mediated by T cells rather than by antibodies
↓	↓	↓	↓
Immediate hypersensitivity reactions, allergic rhinitis, bronchial asthma	Cytotoxic hypersensitivity reactions, thrombocytopenia	Immune-complex reactions, serum sickness	Delayed hypersensitivity reactions, contact dermatitis

mediators from mast cells and basophils. Most allergens that can trigger this response have low molecular mass (ranging between 6 and 120 kilodaltons, kDa) [16] and are highly hydrophilic, capable of penetrating the human body through mucosal areas in the respiratory and digestive tracts [11]. In sensitized people, even trace amounts of allergen are capable of triggering an allergic response.

Antibodies of the IgG or IgM isotypes mediate **Type II** or cytotoxic reactions. These antibodies are able to recognize antigens that are located on cellular surfaces. Type II reactions involve the formation of immune complexes and the interaction of these complexes with the complement system, Fc-IgG receptors present on macrophages and Natural Killer cells, among others. The affected cells are removed in minutes. Among the diseases associated with complement activation and type II hypersensitivity responses are drug-induced cytopenias [12]. The new improvements in the original classification from Gell and Coomb, now consider that **Type IIa** corresponds to the former Type II, where the inflammatory response results in cell death mediated by activation of the complement, phagocytosis, or cytolysis following the binding of antibodies to cell surface antigens on the target cell. On the other hand, the newly defined **Type IIb** is mechanistically distinct and refers to the inflammatory response resulting in cell death which is mediated by the direct binding of antibodies to cellular receptors [14].

Type III reactions are mediated by antigen–antibody immune complexes that are insoluble in the bloodstream. Despite being itself a physiological process, if these complexes are not properly removed by phagocytosis in the spleen or other lymphoid organs, they may be deposited on the walls of the circulatory system, skin, or joints. Remaining immune complexes are able to trigger the activation of the complement system and the recruitment of other immune cells.

In the pathophysiology of hypersensitivity **Type IV** reactions or delayed reactions, T cells react independently of antibodies against self or foreign antigens associated with tissues or cells. This type of reaction has been later subdivided into four subtypes according to the type of T cells involved [17, 18]:

- **Type IVa** hypersensitivity reactions are mediated by CD4⁺ Th1 T lymphocytes, which activate macrophages through the secretion of INF- γ (probably including also other cytokines such as TNF or IL-18), promoting the B cell-mediated production of antibodies related to the complement system (IgG1, IgG3), stimulating the inflammatory response, and activating CD8⁺ mediated T cell responses [17, 18].
- **Type IVb** hypersensitivity reactions are mediated by CD4⁺ Th2 T lymphocytes, which secrete IL-4, IL-5, and IL-13. These cytokines promote the production of IgE and IgG4 by B cells and have the potential to activate eosinophils and mast cells [17, 18]. High levels of secreted IL-5 promote eosinophilic inflammatory responses characteristic of many adverse drug reactions [19].
- In **Type IVc** hypersensitivity reactions, the cytotoxic CD8⁺ T cells act as effectors by secreting cytolytic proteins (e.g. perforin) and serine proteases (e.g. granzyme B), thereby inducing apoptosis of the targeted cells [20]. In general, hypersensitivity reactions mediated by CD8⁺ cytotoxic T lymphocytes

are considered more dangerous, since all cells expressing MHC-I complexes may be potential targets, as opposed to those reactions involving CD4⁺ helper T lymphocytes that regulate the targeting of fewer cells expressing MHC-II complexes.

- **Type IVd** hypersensitivity reactions are characterized by the coordination of T cell-mediated neutrophilic inflammation. The principal mediators of this type of response are CXCL-8 and GM-CSF [17, 18].

2.3 Asthma Phenotypes

The first problem faced by epidemiological studies on asthma is its definition, which combines medical history and physical examination. The Global Initiative for asthma (GINA, www.ginasthma.org) defines the disease as “a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment” [21].

This disease is found in both sexes and all ethnic groups, with variations both in symptoms and severity [22]. It has been proposed to consider asthma as a set of overlapping syndromes rather than as a single disease. The clinical features of the disease allow us to distinguish two types of asthma: atopic and non-atopic. Apart from being pathologically indistinguishable, both types of asthma are characterized by reversible airflow obstruction, wheeze with exertion, diurnal variation of bronchial tone and eosinophilia in sputum and peripheral blood [23].

2.3.1 Atopic Asthma

The inflammatory response in atopic asthma is associated with sensitization to certain allergens and, in most cases, with an elevation of total serum IgE. As we will review later, the asthmatic response is orchestrated by a typical Th2 T cell response, which is able to regulate and activate a wide range of other cells (B cells, mast cells, or eosinophils, among others) or by direct interaction with structural cells of the lung.

The Th2 response is mainly associated with the secretion of a set of interleukins, including IL-4, IL-5, and IL-13. The secretion of these cytokines results in the activation of adhesion molecules and the production of other cytokines and chemokines, which can trigger a process of recruitment and subsequent cellular

degranulation of eosinophils, mast cells, and basophils, as well as B cell activation and concomitant production of IgE [11].

Many patients initially present only one type of allergic disease such as atopic dermatitis, but will eventually develop others such as allergic rhinitis, allergic asthma, or food allergy. This feature of allergic diseases is known as “atopic march” [24–26]. Rhodes and colleagues [27] conducted a study in the UK where they assessed the disease outcome of 100 infants on the basis that at least one parent was atopic. This study, which began in 1976, continued for a total of 22 years. The prevalence of atopic dermatitis was 20 % after the first year, dropping to 5 % at the end of the study. Meanwhile, the prevalence of allergic rhinitis was increasing over time, from 3 to 15 %. The respiratory distress described by the parents arose from 5 to 40 % at the end of the study. Allergic sensitization to a battery of common allergens reached 36 % of the participants. This study concluded that adults with asthma could begin wheezing at any age, but tended to be sensitized early in life. This typical sequence of clinical manifestations, characterized by the development of atopic dermatitis at an early age and later development of other diseases has been observed in numerous studies [28, 29].

2.3.2 Non-Atopic Asthma

Non-atopic asthma is characterized by the absence of specific IgE to a particular antigen in peripheral blood or bronchial mucosa. The serum IgE levels are often found within the normal range. It usually develops during middle age; remission is rare and generally tends to be more severe than atopic asthma. In this sense, there is a higher incidence of hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) [23].

Non-atopic asthma pathogenesis is also characterized by the development of an eosinophilic response, where eosinophils have important roles as proinflammatory cells driving the bronchoconstrictive response through the release of leukotrienes, oxygen metabolites, and toxic proteins, among other factors. Although this topic is out of the scope of this chapter, understanding the molecular mechanisms involved in non-atopic asthma is an exciting field for which other interesting reviews have been recently published and that we recommend to the interested reader [30, 31].

2.4 Pathophysiology of Allergy and Asthma

2.4.1 Immunological Basis of Allergic Reactions

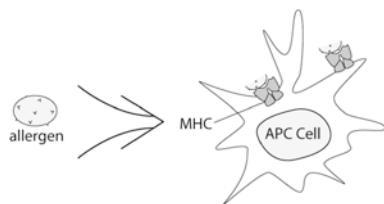
Although there are different allergic reactions, all the allergic inflammatory responses are the result of a complex interplay of chemical and molecular signals

and different immune cells, including dendritic cells, mast cells, basophils, eosinophils, and lymphocytes (further discussed below). These cells produce a huge variety of cytokines, chemokines, and reactive oxygen species that target other cells like epithelial, vascular, or airway smooth muscle cells, which will also become an important source of inflammatory mediators and signals. Depending on the affected cellular compartment, the associated symptoms will vary from asthma to allergic rhinitis/rhinosinusitis or atopic dermatitis.

2.4.1.1 Presenting the Allergen: Antigen Presenting Cells (APC)

Half of the 2011 Nobel Prize in Physiology or Medicine was awarded to Ralph M. Steinman for his discovery of the dendritic cells and their role in activating the adaptive immune response (www.nobelprize.org). These cells, which are derived from hematopoietic progenitors, can be found in most tissues and are specialized in taking antigens by endocytosis, processing them into smaller peptides, and presenting them to other immune cells through the major histocompatibility complexes (MHC) [32] (Fig. 2.1). Such antigen-presenting cells (APCs) have an exceptional ability to activate T lymphocytes, and they have opened to scientists new fields of research through the development of new ways of vaccination and treatment of diseases by boosting the immune response [33]. During allergic responses (see later in Fig. 2.6), APCs contribute to the progression of the sensitization against the allergen by presenting the allergenic complexes peptide/MHC to T cells and activating its cytokine production. Interestingly, recent studies on the maternal transmission of asthma risk suggest that dendritic cells and DNA methylation changes within these antigen-presenting cells might play a role in the congenital susceptibility to allergic disease [34–36].

Fig. 2.1 The antigen presenting cell and the processing of allergens



2.4.1.2 Mast Cells, Eosinophils, Basophils, and Neutrophils

Mast cell activation plays a pivotal role in initiating allergic reaction in the airways (Fig. 2.2), and their activation is responsible of the early phase of allergic reaction. It has been shown that monomeric IgE molecules have the ability to activate mast cells in several ways, from full mast cell activation (including degranulation) to enhanced mast cell survival [15, 37]. IgE can form clusters crosslinking FcεRI receptors and activate mast cell signaling, leading to a rapid

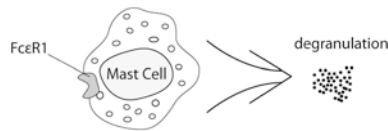


Fig. 2.2 Mast cell degranulation. Like mast cells, eosinophils, basophils, and neutrophils have shown to play a role during allergic responses mainly through the release of soluble mediators

release of inflammatory mediators (see later in Fig. 2.6). This activation will result in bronchoconstriction, vasodilatation, and plasma exudation, leading to the symptoms of asthma (wheezing and dyspnea) or allergic rhinitis. The role of mast cells during the development of late allergic responses remains still obscure [38].

Infiltration and accumulation of eosinophils in the bronchial mucosa are also responsible of many of the asthmatic symptoms. Eosinophilic activation depends on the release of IL-5 by Th2 cells [38], which leads to the release of cysteinyl leukotrienes. However, eosinophils are a less important source of inflammatory mediators when compared with mast cells. Interestingly, eosinophils are also able to act as APCs, producing several Th1 and Th2 cytokines [39].

Basophils are involved in the initiation as well as the maintenance of Th2 responses. Several studies show a role for basophils as APCs and it is known that they can release histamine, IL-4 and IL-13, or lipid mediators such as leukotrienes and prostaglandins, and express cysteinyl leukotriene mediators upon stimulation. Moreover, its presence in inflamed tissue during the allergic reaction clearly reveals a key role for basophils that has been underestimated [40]. Upon activation, basophils are able to skew Th2 responses toward allergens, secreting cytokines that support the development of IL-4-producing CD4⁺ T cells and of IgE-secreting B cells associated with the Th2 immune response [41].

Finally, the neutrophilic infiltration that is found in some patients with bronchial asthma might be driven by Th17 cells through the secretion of IL-17A, IL-17F, IL-21, IL-22, and IL-26, among other mediators [42, 43]. Although these observations support an important role of neutrophils in allergic reactions, their exact role is not completely understood yet and further studies are required.

2.4.1.3 T cells

In 1986, Mosmann and Coffman first described the existence of two different types of CD4⁺ populations, which are called T cell helper cell type 1 (Th1) or T cell helper cell type 2 (Th2) according to their pattern of cytokine secretion [44] (Fig. 2.3). The prevalent idea is that the immunological basis of atopic sensitization and allergic disease are the result of an inappropriate Th2 response to usually



Fig. 2.3 T cells (Th1 and Th2) and the secretion of cytokines. Regulatory T cells (Treg), both through cell-to-cell interactions and cytokine secretion, also play a critical role modulating the immune response and tolerance

harmless substances known as allergens. Some of the cytokines associated with this response are IL-4 and IL-13, important in the regulation of IgE production; IL-5, which contributes to the eosinophilic inflammation characteristic of allergic reactions; or IL-9 and IL-13, which are believed to be important for bronchial hyperresponsiveness [45] (see later in Fig. 2.6).

A new variety of T cells known as regulatory T cells (Treg) has recently entered in scene. This “new” cell type develops naturally in the thymus, through the stimulation of IL-2, TGF β , and CD28 among others, and can also be induced in the periphery from naïve CD4 T cells (adaptive Treg) [46]. The best-characterized Tregs are CD4⁺ lymphocytes that constitutively express high levels of surface receptor CD25 (the receptor for α chain of the IL-2: CD25hi T cells) [47]. Unlike CD4⁺ lymphocytes, the lymphocytes CD25hi Treg do not proliferate or produce any cytokine after stimulation, but actively suppress the proliferation and cytokine production of other effector T cells. This “suppressor phenotype” is partly due to the expression of high levels of the transcription factor FOXP3 and expression of IL-10 and TGF β [48, 49]. It is believed that these cells could play an important role in allergic diseases. Indeed, after separating the lymphocyte subsets CD4⁺CD25⁺ and CD4⁺CD25⁻ from peripheral blood of healthy individuals, it was found that in vitro the population CD4⁺CD25⁻ responded rapidly to antigenic stimulation, whereas in the presence of the CD4⁺ CD25⁺ population, the allergic response was inhibited [50].

2.4.1.4 B Cells

As mentioned before, humans, mice, and other vertebrate species are able to generate a highly diverse antibody response to protect themselves from infections and toxic substances in the environment. After B cells generate a large repertoire of antigen binding sites through combinatorial rearrangement of germline variable (V), diversity (D), and joining (J) elements [51] (see VDJ recombination later in Fig. 2.5), two processes called somatic hypermutation (SHM) and class switch recombination (CSR) further diversify the germline-encoded antibodies, which are often not protective, to produce high-affinity antibodies of all of the immunoglobulin isotypes. CSR to IgE is induced by the cytokines IL-4 or IL-13 secreted by T helper 2 (Th2) cells in humans [15] and CD40L or LPS plus IL-4 in mice [52]. In allergy and asthma, there is a significant bias toward the production of IgE by B cells and plasma cells in the respiratory tract mucosa [53, 54] (Fig. 2.4).

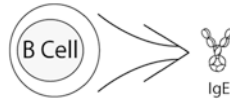


Fig. 2.4 The B cell and the production of IgE antibodies

Until recently, CSR had been thought to occur primarily in the germinal centers of lymphoid tissue, where the B cell expresses large amounts of the mutagenic enzyme activation induced deaminase (AID) [55, 56]. AID then induces mutation at the IgH and L chain V regions to initiate SHM, and at the switch regions (SRs) to initiate CSR. With the help of selection for B cells making higher affinity antibodies, these AID-induced mutations are responsible for affinity maturation and changes in specificity of the antibody response [57–63] and for the expression of different Ig isotypes that can carry out different effector functions throughout the body and in the mucosal spaces [64]. CSR to IgE and IgE synthesis, clonal selection and affinity maturation can also occur locally in the B cell population of local tissues and mucosas [65–68]. Both IgE and mast cells, which are concentrated in mucosal tissues, are thought to be a central part of that defense against pathogens [15]. Crosslinking of IgE and FcεRI, which is a high-affinity Fc receptor for IgE on mast cells and antigen-presenting cells (APCs), sensitizes these cells to allergens and promotes feedback mechanisms to produce more IgE by B cells [15]. These immune responses, however, may also result in immediate hypersensitivity, which characterizes allergic responses in different target organs such as the skin

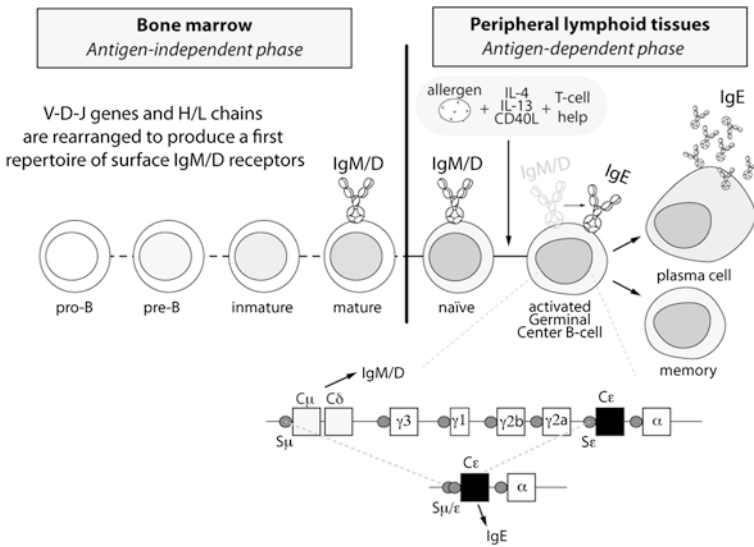


Fig. 2.5 B cell development and specific class-switch recombination processes to produce IgE antibodies

(atopic dermatitis or eczema), the nose (rhinitis), the lungs (asthma), and the gut (food allergic reactions) [37, 69].

Because AID is required for triggering switching to IgE production, it is important to understand not only how AID preferentially targets Ig genes to generate antibody diversity and why the rates of AID-induced mutation are higher in Ig genes than in most other genes [70], but also what regulates AID targeting specifically to the repetitive noncoding S μ and S ϵ switch regions (SR, see Fig. 2.5) during CSR to produce IgE antibodies. A number of not mutually exclusive mechanisms have been suggested to explain the targeting of AID [62, 71] including associated proteins, changes in chromatin structure to provide accessibility or specific recruitment through a histone code, and particular cis-acting sequences that bind transcription factors or other proteins that in turn recruit AID and its associated error-prone repair processes. Although some proteins that have been reported to interact physically with AID, including replication protein A (RPA), RNA polymerase II (RNA Pol II), MDM2, DNA PKcs, PKA, PTBP2, SPT5, the RNA exosome, or the spliceosome-associated factor CTNNBL1 [72–82], all of these have very general functions and it is not immediately clear how they might be responsible for the preferential targeting of AID to V(D)J and SRs.

The molecular analysis of cis-acting regulatory elements in the human and murine IgE germline promoter region has identified several motifs that are bound by transcription factors upon IL-4 treatment. STAT6 binds one of these motifs [83, 84]. Recently, a cis-acting element with a PU.1 binding site that overlaps a NF- κ B binding sequence was described and it has been suggested that the cooperation of either NF- κ B or PU.1 with STAT6 mediates the IL4-induced activation of IgE germline gene transcription [85–87]. Germinal center IgG1⁺ cells and memory IgG1⁺ cells can undergo sequential switching to IgE after stimulation with IL-4 and this can be inhibited by IL-21 [88]. This result suggests that high-affinity IgE⁺ cells can be generated in a sequential program with a pre-IgE phase in which SHM and affinity maturation take place in IgG1⁺ cells, followed by a sequential switching to IgE⁺ cells that will quickly differentiate into plasma cells [88]. Consistently, it has been recently shown that mice deficient in IgG1 production cannot produce IgE after immunization [89].

2.4.2 Allergic Sensitization

In Type I allergic responses, there is always a preliminary stage of sensitization (Fig. 2.6). Thus, in a first contact, the allergen is taken up by antigen-presenting cells and processed to generate peptides that are expressed in molecules of the Major Histocompatibility Complex class II (MHCII). This complex is presented to T cells and recognized through their TCR/CD3 receptors. Next, expression occurs of certain co-stimulation molecules such as CD154 (surface CD40 ligand, CD40L) located on the surface of T cells. CD40L molecules will bind to their corresponding receptor, CD40, present in the surface of B lymphocytes. This

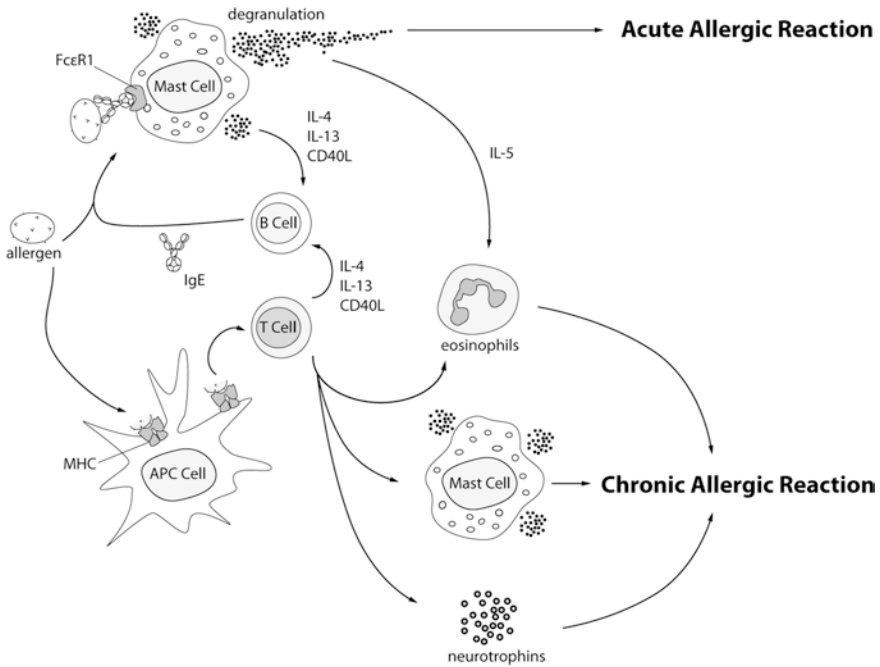


Fig. 2.6 Schema of the major cellular and signaling players during the allergic reaction. IgE production by B cells is activated by allergens and maintains mast cell and APC sensitization during allergic reaction

lymphocyte stimulation by TCR/CD3, MHCII/antigen, and CD40 and its ligand triggers a series of reactions that will culminate in the secretion of IgE by the B cell. Many B cell responses are governed by an integration of signals received by the B cell receptor (BCR) and other surface molecules. While *in vivo* studies have shown that the antigen recognition is necessary for a proper activation of B cells, the presence or absence of these other surface molecules determine the response of the cell after binding to the antigen through BCR [90]. One of the signaling cascades activated in B cells involve the induction of CD80/86, which will interact with CD28 on T lymphocytes and promote the expression of essential cytokines in the allergic response, such as IL-4, and IL-13 [15].

The binding of IL-4 and IL-13 to its corresponding receptor (IL-4R and IL-13R, respectively) present on the cell surface of B cells, activates the signaling cascade of STAT6 (Signal Transducer and Activator of Transcription 6). It is known that STAT6, in synergy with NF- κ B, can activate the expression of AID, promoting class-switch recombination, and isotype switching from IgM to IgE [85, 87, 91, 92]. The IgE will then bind to the high sensitivity Fc ϵ R1 receptors that are present in mast cells and basophils, triggering the release of inflammatory mediators responsible of the characteristic symptoms in allergic reactions. In patients with allergic diseases, the population of B lymphocytes and plasma

cells in the respiratory tract mucosa is mostly committed to the production of IgE. Approximately, 4 % of B lymphocytes and 12–19 % of plasma cells express IgE in allergic rhinitis patients, whereas in healthy individuals these frequencies drop to 1 % or < 1 %, respectively [53].

2.4.3 Effector Response in the Allergic Reaction

Following the sensitization phase, a second contact with the allergen can rapidly trigger an effector response. Allergic reactions may occur in a two-phase mode: an initial phase or immediate response, which appears from seconds to minutes after exposure to antigen, and a late phase reaction that occurs between 4 and 8 h later. Furthermore, inflammation may occur as a result of chronic allergic reactions after repeated exposure to allergen [45, 93] (Fig. 2.6).

2.4.3.1 Immediate Reactions

The reactions of type I hypersensitivity occur within minutes after the exposure to a particular antigen, and involve the secretion of inflammatory mediators from mast cells in the affected sites. In sensitized persons, these cells expose their FcεRI surface receptors for high-affinity IgE. When several IgE molecules bind to antigens, FcεRI receptors aggregate and trigger a complex network of intracellular signaling which results in the release of mast cell granules. This process is known as degranulation and involves the merging of the cytoplasmic granules with the mast cell plasma membrane. These granules contain different types of biologically active products, including biogenic amines (e.g. histamine), proteoglycans (e.g. heparin), or serine proteases (e.g. triptasas or carboxypeptidases). Cytokines such as IL-4 and IL-13, or growth factors such as the tumor necrosis factor alpha (TNF-α) or Vascular Endothelial Growth Factor A (VEGFA) are also released as the degranulation progresses [94–97]. In addition, de novo synthesis of lipid mediators such as prostaglandins and leukotrienes also occurs in a matter of minutes. Arachidonic acid is metabolized by cyclooxygenases and lipoxygenases, and give rise to compounds known as prostaglandins such as prostaglandin D2 (PGD2), leukotrienes such as LTB4, and cysteinyl leukotrienes (cys-LTs) [94, 95].

The release of all these mediators is responsible for the characteristic symptoms of the immediate phase of allergic reactions: vasodilation (reflection of the activity of mediators acting in local nerves, causing erythema of the skin and conjunctiva), increased vascular permeability (resulting in the formation of edemas and tearing), bronchial smooth muscle contraction (and consequently airway obstruction and coughing), and increased mucus secretion (exacerbating the obstruction of the airways). In addition, these mediators may also stimulate nociceptors and nerve sensitivity of the nose [98], skin [99], or respiratory track [100], resulting in symptoms as characteristic as sneezing, itching, or coughing.

2.4.3.2 Late Stage

The allergic response stimulated by the IgE/allergen interaction in mast cells involves not only the immediate release of chemotactic factors, cytokines, chemokines, and growth factors previously synthesized, but also the synthesis of new inflammatory mediators that are released in a more gradually manner, constituting a delayed response [101]. During this late phase of allergic reactions, additional *de novo* synthesis of prostaglandins, leukotrienes, and various cytokines are induced in activated mast cells and basophils. Among the molecules that are released at this stage are TNF α , LTB₄, IL-8 (also known as CXCL8) or CC2 chemokine ligand (CCL2). These factors are capable of recruiting other immune cells, activating cells responsible for innate immunity (through TNF α and IL-5), or activating various biological mechanisms that affect dendritic cells, T cells, and B cells through the activity of IL-10, TNF α , TGF β or histamine [96, 102]. The clinical characteristics of these reactions highlight the contribution of both resident cells located at the damaged tissue and circulating cells that were recruited during the course of the inflammatory reaction. As an example, the associated vasodilation that occurs at late stages in atopic asthmatics by allergen-derived T cells peptides could be explained, at least in part, by the secretion of calcitonin and the recruitment of immunoreactive infiltrating inflammatory cells [103].

Late reactions usually occur 2–6 h after allergen exposure, with an elapsed peak around 6 or 9 h. The fact that such reactions do not appear in all sensitized individuals is not entirely clear, as it is not clear why in other patients there is not a clear distinction between the end of one phase and the beginning of the next [45].

2.4.3.3 Chronic Allergic Inflammation

When exposure to an allergen is produced in a continuous or repeated manner, many cells of the innate and adaptive immunity that are normally found in the bloodstream, may chronically infiltrate the affected tissues. The persistent inflammation that characterizes this type of exposures may cause structural changes in the tissues, compromising the correct functioning of the affected organs [104].

Although both the immediate and the delayed phase of allergic reactions can be studied relatively easily in human patients, most studies of chronic allergic inflammation have been performed in animal models. Therefore, it is yet not well understood how, after persistent exposure to an allergen, local tissue inflammation switches from an early or late phase to a chronic phase [102]. It is known that individuals with chronic asthma may have affected all layers of the respiratory tract, exhibiting changes in the epithelium and the number of goblet cells. This results in increased production of mucus, cytokines, and chemokines by epithelial cells, and ends up inducing tissue damage in the epithelium [105]. Respiratory viral infections with rhinovirus or influenza viruses are capable of producing a marked exacerbation of signs and symptoms of asthma [106], and might constitute an additional risk factor for subjects already at risk of developing allergies and

asthma [107–109]. In cases of atopic dermatitis [110] and allergic rhinitis [111], as well as in asthma, chronic allergic inflammation is associated with tissue remodeling. In all cases, this remodeling may lead to persistent changes in the structural elements of the affected sites (such as increased vascularity) and substantially introduce alterations in the epithelial barrier function.

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