

Physiopathology of Allergy

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I. Introduction

Allergy is defined by an *immunological hypersensitivity* to one or several defined antigens, called *allergens*, which trigger symptoms in the skin, the upper or lower airways, or the oral and digestive mucosae upon exposure, according to the mechanisms and the target organ(s) involved. Classification of hypersensitivity reactions (summarized in Table I) can be based on the delay between the eliciting exposure, i.e. immediate *versus* delayed, and/or by the mechanisms involved, i.e. non immune ('intolerance') *versus* immunological (IgE or non-IgE) (Johansson et al, 2001).

	Synonymous	Immune response	Effector mechanism	Clinical expression
Type I	Reaginic	IgE	mast cell/basophil degranulation	Anaphylaxis, urticaria, rhinitis, asthma
Type II	Cytotoxic	IgG	cytotoxicity	Blood dyscrasia
Type III	Immune complex disease	IgG and/or complement	deposits of immune complexes	Vasculitis, allergic alveolitis
Type IV	Delayed Type IVa	Th1	macrophages	Eczema, allergic alveolitis
	Type IVb	Th2	eosinophils	Rhinitis, asthma, exanthema
	Type IVc	Tc	cytotoxicity	Eczema, exanthema
	Type IVd	Th17	neutrophils	Exanthema

Modified from Gell-Coombs and Pichler.
Different mechanisms may underlie one clinical disorder (e.g. in asthma or exanthema)

II. The atopic phenotype

A particular inherited tendency to develop allergy has for a long time been recognized as a predisposing condition to type I allergy. Referred to as *atopy*, it was originally coined to differentiate the familial syndrome of asthma and hay fever from 'allergy'. Atopy is defined by a familial and/or personal predisposition to develop IgE antibodies to environmental (e.g. inhaled) antigens (Johansson et al, 2001), which has a genetic

(oligogenic) background. Results of ongoing cohort studies indicate that the clinical evolution of atopic subjects is highly variable and can not be predicted in a given subject, despite the efforts of some authors to extrapolate from the results of epidemiological studies describing the *allergic march* of atopic individuals.

The sensitization process, i.e. the generation of allergen specific IgE antibodies, is driven by cognate interactions between antigen presenting cells (APC, particularly dendritic cells) and T-lymphocytes. It involves multiple mechanisms that are influenced by the genetic background, allergen exposure and co-factors. In genetically susceptible individuals, dendritic cells activated by the allergen in a pro-inflammatory milieu in the airway or digestive mucosa or in the skin instruct T cells to polarize into Th2 cells, which produce a specific set of cytokines, including IL-4, IL-5, IL-9 and IL-13. These cytokines drive B cell switching to IgE production (IL-4, IL-13), basophil/mast cell development (IL-4, IL-9), eosinophil accumulation (IL-5, IL-9) as well as epithelial mucus production (IL-9, IL-13), all of which are hallmarks of allergic inflammation.

The *Th2 bias* in allergy could either relate to a defective stimulation of Th1 and/or T regulatory (Treg) immunity. The number and/or function of Treg cells that control immune tolerance to allergens (and self-antigens), might be deficient in allergic individuals (Ling et al, 2004; Hawrylowicz et al, 2005). This regulatory T-cell subset includes natural Foxp3+ Treg cells, which exert their suppressive effects on effector T cells probably through TGF- β signalling and membrane mechanisms, and IL-10 producing CD4+CD25+ Tr1 cells. Tissue macrophages could also play an important suppressive role, notably in the lung (Holt, 1986), while the role of other cells in allergy, including the recently described Th17 cells still need to be investigated.

The epithelium could also play a key primary role during sensitization. Functional dysregulation of the so-called *epithelial-mesenchymal trophic unit* has been suggested to play an important role in asthma (Holgate 2007) as well as atopic dermatitis,. Resulting from a deficient barrier function, these changes would favour Th2-type allergic inflammation towards allergens and lead to abnormal repair processes. The epithelium can release various mediators regulating the induction and fate of the immune response, such as chemokines, cytokines and proteins such as thymic stromal lymphopoietin (TSLP). Several cofactors probably influence the sensitization processes, including products of commensal (and pathogenic) microbes that may act by activating APC and epithelial receptors of innate immunity (e.g. *Toll-like* receptors), and the involvement of the environment is increasingly recognized with a complex role of combined exposure to allergens, pollutants and microbes. The *hygiene hypothesis* suggests that reduced exposure to Th1-promoting factors during childhood is behind the increase in allergic diseases in western countries (von Mutius, 2007).

The atopic phenotype has nevertheless a strong inheritance –component; the risk of transmission of atopy from an affected mother being four times higher than from an affected father, probably as a result of genomic imprinting (Cookson, 2002). This genetic predisposition has been linked to several gene loci related to the immune system, including genes encoding (or nearby) TCR α/δ , MHC, Fc-epsilonRI β (chromosome 11q13) and cytokine clusters, e.g. IL-4, IL-2, IFN- γ (e.g. 5q34).

III. Immediate and late phase allergic responses

Following sensitization, the effector phase underlying the clinical manifestations of allergy can occur upon further allergen exposure. The *immediate phase* occurs within minutes after exposure to the sensitizing allergen and is mediated by mast cells or basophils. These cells bear high-affinity receptors for IgE (called Fc ϵ RI) on their surface, which can be cross-linked by the appropriate allergen. After activation, mast cells and basophils de-granulate, releasing biologically active preformed mediators (histamine, tryptase, lipid mediators). These mediators in turn induce a range of reactions which may involve different parts of the body including wheal-and-flare response due to local vasodilation and tissue edema (skin); sneezes and mucosal itchiness (eyes, nose); bronchoconstriction and cough (bronchi); itchy mouth and lip/tongue swelling (oral mucosa), or generalized pruritus and vasodilation (urticaria/angioedema, anaphylaxis).

During the *late phase response*, occurring more than 4 hours afterwards, eosinophils and T cells are recruited and release pro-inflammatory mediators (TNF- α , IL-1, CC chemokines, proteases, cysteinyl-leucotrienes (sometimes known as *slow reacting substance of anaphylaxis*) (Varner, 2000) that drive persistent tissue inflammation. IgE antibodies are also involved during late-phase reactions, probably by facilitating the recognition by APC (dendritic or B cells) of the allergen 'focalized' to cell-surface IgE-receptors (*IgE-mediated facilitated antigen presentation*; Maurer et al, 1995). Late-phase clinical symptoms include local redness and edema (skin) and bronchoconstriction (airways).

IV. Clinical expression of allergy

Allergic rhinitis (and *rhinoconjunctivitis*) represents the archetypal manifestation of allergy, with typical episodes of sneezing, itchy nose (and eyes), runny and/or blocked nose triggered on exposure to tree and/or grass pollens (spring and summertime *hayfever*, respectively), animal danders (cat, dog, horse), moulds or house dust (mite) as the most common antigens. The latter can be sometimes less clearly identified by the

patient, and this is probably due to chronic exposure rather than an intermittent trigger which can be more readily identified.

Allergic asthma is characterized by episodes of respiratory symptoms, such as chest tightness, breathlessness, cough, wheezing, with evidence of lower-airway obstruction and non-specific bronchial hyperresponsiveness to irritants (such as cold, smoke, exercise, or indirect pharmacological stimuli, e.g. adenosine). Allergic rhinitis and asthma are very frequently associated and involve type I (mast cell) and type IV (eosinophilic) reactions.

Food allergy may present as oral allergy symptoms (contact urticaria of the oral and upper respiratory mucosae), acute urticaria with/without angioedema, or anaphylaxis (sometimes only following exercise), rapidly (usually within 2 hours) after the ingestion of foods such as cow's milk, egg or (pea)nut; or nuts, fish, seafood, fruits as most common allergens in children and adults, respectively.

Venom and *drug allergy* are not part of atopic manifestations *per se* (i.e. atopy does not seem to represent a risk factor for these allergies) and may reactions may range from skin rash to severe anaphylaxis. Delayed type IV reactions frequently underly drug allergy (Pichler, 2003).

V. Chronic disease of target organs

Structural components play a driving role in chronic allergic disease, particularly in the lower airways (chronic asthma) and the skin (atopic dermatitis). The atopic phenotype can be associated with intrinsic abnormalities of the structure of target organs, particularly the lung and/or the skin, probably largely related to genetic determinants. Other factors that could contribute to chronicity of allergic inflammation in the target organ include superantigens from commensal microbes such as *Staphylococcus aureus* (Gould 2007) and persistent exposure to a range of environmental stimuli such as viruses, tobacco smoke and ambient air pollution.

In chronic *asthma*, functional changes in the epithelium and connective tissue (myofibroblasts) of the lung airways, referred to on a morphological basis as *remodelling*, may lead to vicious circles of impaired frontline defence mechanisms (physical barrier, mucociliary clearance, antimicrobial proteins) and exaggerated immune cell recruitment. These abnormalities of the target organ of allergic inflammation include in asthma epithelial shedding and deficient production of epithelial cytokines such as TGF- α and type I interferons (IFN- β ; Wark 2005) in responses to viral infection, subepithelial fibrosis, and smooth muscle hyperplasia and hypertrophy. The resulting hyperresponsiveness of the bronchial smooth muscle to direct stimuli (e.g. histamine, methacholine) can be measured during lung function testing in the clinic. Interestingly, non-atopic subjects may

also develop so-called *intrinsic*, non-atopic asthma which is clinically and immunologically very similar to its atopic variant, typically affecting older female subjects (more frequently with aspirin intolerance, and nasal polyposis). Although unproven, this particular asthma phenotype might result from purely local allergic responses to unidentified antigens, without systemic atopic features.

In *atopic dermatitis* (or *atopic eczema*), the skin also displays several structural abnormalities, interfering with host defence mechanisms. These include increased epidermal permeability, potentially following disruption of the barrier function by irritants and/or allergens as a primary event, increased epidermal proliferation and changes in cell differentiation. The course of the disease may become at least partly independent of allergen exposure, as observed in asthma. Presumably this is in relation to intrinsic skin abnormalities.

Genetic and genomic studies have identified skin-related genes, e.g. the epidermal differentiation complex (1q21), encoding proteins regulating the physical (barrier) and/or immunological (chemotaxis of leukocytes) functions of keratinocytes. Altered function of EDC is not documented in asthma and defective barrier function in the airway mucosae might relate to impaired production of protective proteins including immunoglobulins such as IgA and mucus. Also, in asthma heritability is due to a few genes. *ADAM-33* (20p) has emerged as an interesting predisposing gene, not only for asthma but also for chronic obstructive lung disease (Holgate 2007), illustrating a gene that could set, at least in part, the susceptibility to develop lung function decline following cigarette smoking or allergen sensitization. Figure 1 illustrates the complex relationship between atopy, asthma and atopic dermatitis, as well as related candidate genes.

Although allergy and diseases such as asthma and atopic dermatitis are often used interchangeably, it is important to realize that whereas up to 50% of the western population is atopic, only 10% have either asthma or atopic dermatitis (Pearce, 1999). A challenging issue is to identify the factors implicated in the translation of the atopic phenotype into a particular disease (and/or its chronicity), which probably relates both to environmental factors and organ-related genes in a complex and interactive relationship.

VI. Conclusions

A much better understanding of the pathophysiology of allergy - an increasing health disorder in western countries - has been gained over the 2 past decades, with a resurgence of interest in the role of IgE along tissue components. Our view of the allergic reaction has extended from the initiation of IgE-sensitization to maintenance of allergic inflammation. Further identification of susceptibility genes within the target organs (e.g.

epithelium) will help to understand the development of allergic diseases in atopic individuals, i.e. with an IgE/Th2-prone immune system, as well as the role of allergens and the environment.

Figure 1. Pathophysiology of allergy: relationship between atopy, asthma and atopic dermatitis, and related candidate genes.

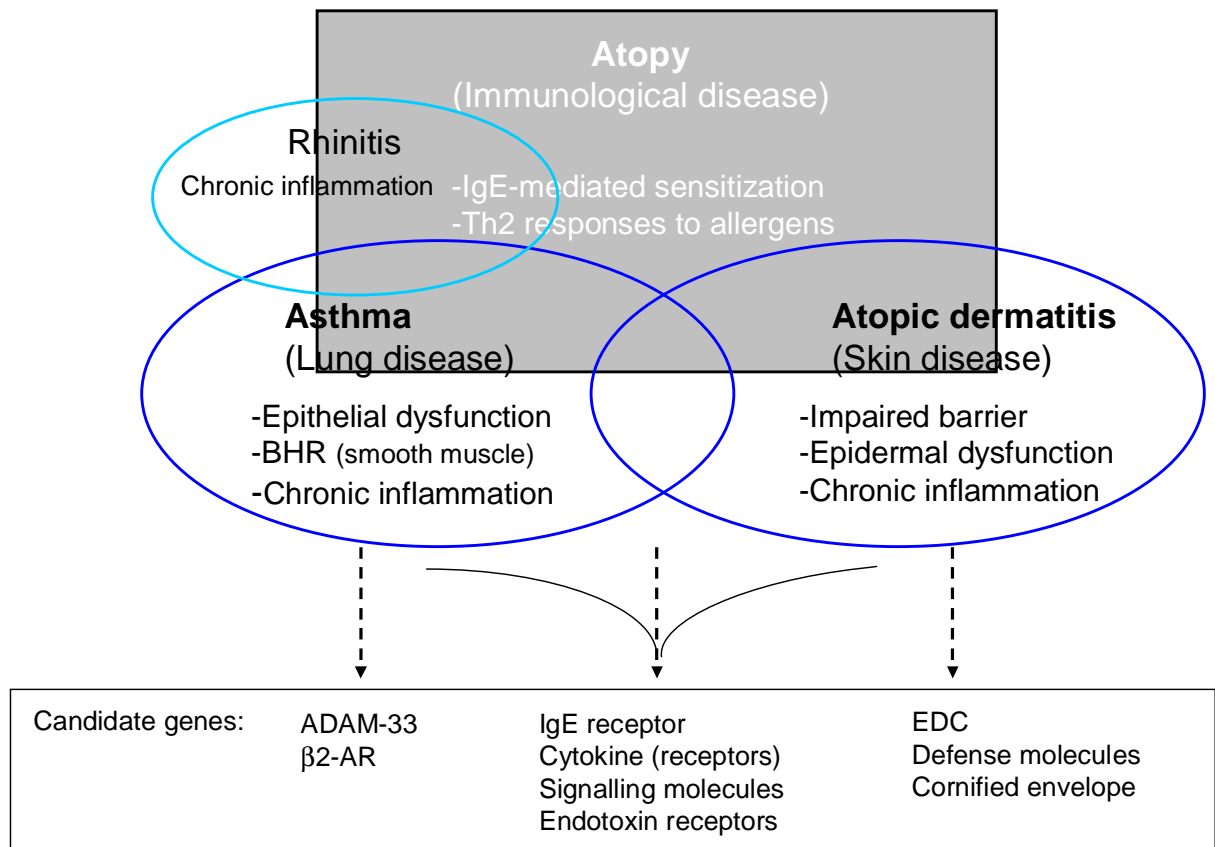


Figure 1 legend. Both genetic and functional studies in asthma and atopic dermatitis indicate that these manifestations, closely linked to atopy, are also 'local' organ diseases including impaired function of the epithelium (asthma, dermatitis) and smooth muscle (asthma).

Abbreviations: ADAM: a disintegrin and metalloprotease; BHR: bronchial hyperresponsiveness; EDC: epidermal differentiation complex; β2-AR: β2-adrenergic receptor; Th2: T-helper 2.

VII. References

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