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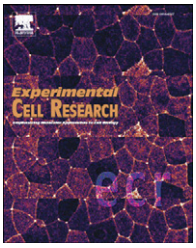

Review

Mechanisms of IgE-mediated allergy

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ABSTRACT

Allergic diseases are a global health problem today. Knowledge is still lacking about what causes some people to develop allergies while others remain tolerant to environmental antigens. The recent increase in prevalence suggests an involvement of gene–environment interactions and epigenetic mechanisms. Since allergies often develop early in life, the intrauterine environment has been proposed to play a role in predisposing some individuals to become allergic. The development of techniques to produce allergens as highly pure recombinant proteins has improved the tools for allergy diagnosis and treatment. Novel strategies for allergen-specific immunotherapy include tailor-made vaccines and alternative routes for administration.

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Introduction

Allergies are today a major health problem. The prevalence of allergic diseases, such as allergic asthma, allergic rhinitis and atopic eczema has been increasing world-wide during recent decades, particularly in the western industrialized countries [1]. There have been some reports that the prevalence rates may be declining or plateauing, however, a recent systematic review of asthma prevalence shows that there is no overall global downward trend in the prevalence [2]. The allergic reaction can be antibody- or cell mediated [3]. In the majority of cases, the allergic symptoms are initiated by IgE antibodies that are produced in response to otherwise harmless

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environmental antigens, i.e. allergens. This type of allergy is the focus of this review.

IgE and the allergic response

The discovery of the IgE antibody was made in the 1960s by two independent research groups [4,5]. This discovery was a major breakthrough in understanding the mechanisms of allergy and has had major effects on the diagnosis and treatment of patients with allergy. One immediate benefit of the availability of IgE and the development of tests for allergen-specific IgE antibodies is the ability to analyze and standardize allergen preparations. Advances in these areas have opened up new ways to develop diagnostic and therapeutic agents. Anti-IgE (omalizumab) is for example used today in the treatment of severe allergic asthma [6].

The initial phase in the development of IgE-mediated allergy is termed sensitization. During this reaction, an allergen enters the body through the epithelial barrier of the skin, airway or gut and is taken up by antigen-presenting cells (APCs). A diminished barrier function due to genetic or environmental factors can enhance this process [7]. For example, loss-of-function mutations in the gene for filaggrin (a protein that is important for maintaining the skin barrier function) are associated with an increased risk for development of atopic eczema/dermatitis [3]. The most potent APCs in the body are the dendritic cells (DCs). DCs can respond to foreign pathogens and also sample self antigens and harmless environmental proteins continuously to create immune tolerance. This dual capacity gives them power to dictate immune responses and has evoked hope that DCs can be manipulated *in vitro* or *in vivo* for use in immunotherapy. During the initial contact between foreign antigens and our immune system, the APCs will decide whether the naïve $CD4^+$ antigen-specific T cells will develop into Th1, Th2 or Th17 effector cells or regulatory T cells (Treg). In individuals where signals from the APC will cause differentiation of Th2 cells, production of IL-4 and IL-13 from these cells will drive B cell class-switch to IgE production and secretion of allergen-specific IgE. The secreted allergen-specific IgE will subsequently bind to mast cells in the tissue. Upon second encounter with the same allergen, the mast cells will be activated and release potent inflammatory mediators, such as histamine and proteases.

Natural killer (NK) or NKT cells and DCs can mutually influence each other's respective activity, shaping the ensuing adaptive immune response. We provided the first evidence that NK cells and DCs do interact *in vivo* [8]. Thus, NK cells and DCs seem to cooperate in regulating immune responses. There are subtypes of NKT cells and both self and foreign ligands can activate NKT cells through binding to CD1d, suggesting that they can act as pro-inflammatory as well as tolerogenic cells in immune responses. We recently proposed a novel disease mechanism in atopic eczema where induction of IL-18 skews the invariant NKT cell population in a CD1d-dependent manner [9]. This imbalance affecting the invariant NKT cell population could be partly responsible for setting the stage for the subsequent chronic phase of atopic eczema.

It is not known why some individuals start producing IgE when encountering allergens while others do not. Probably there are several factors involved, like the host genotype, type of allergen, allergen concentration in the environment, route of exposure and whether exposure occurs together with agents that can either enhance or down-regulate the sensitization process. Individuals that have a genetic predisposition to produce IgE directed to allergens, i.e. become sensitized, are termed atopic [1]. Properties of the allergens themselves can also be part of promoting the production of IgE and development of allergic disease. Many allergens are proteases. Der p 1, present in the house dust mite *Dermatophagoides pteronyssinus*, for example, has proteolytic activity and can increase the permeability of the bronchial epithelium [7].

The presence of allergen-specific IgE or elevated total IgE levels is not equal to presence of symptoms of allergic disease [10]. In studies made in South America and Africa, >30% of the studied subjects carried substantial levels of IgE to house dust mite. Considering that the people worldwide suffering from helminth infections are rarely affected by allergic symptoms, it is clear that a strong Th2 response is not the sole factor behind allergy. Chronic helminth infections might result in IgE responses that are cross-reactive to allergens. For example, parasitic antigens, such as tropomyosins and glutathione S-transferases, have their allergenic homologues in house dust mite [11].

Gene–environment interaction

The recent increase in allergic disease most likely reflects changes in the interactions between the external environment and genes. Epidemiological studies have shown striking regional differences in the prevalence of allergic diseases world-wide and this has given rise to several hypothesis related to environmental exposure including microbes and parasites. A reduction in childhood infections was suggested as a risk factor in the late 1980s when Strachan reported an inverse association between family size and hay fever [12]. This was the basis for the 'hygiene hypothesis', which since then has evolved and been modified, but is still considered a potential explanatory factor behind allergy development [13]. Not only infections, but also environmental exposures to non-viable microbial products may pertain to the hygiene hypothesis. We and others have previously found that lifestyle factors related to the anthroposophic way of life and living on a farm lessen the risk of allergic diseases in childhood [14,15]. The protective effect of farm environment has been connected to exposure to diverse microbial environments and also to consumption of unpasteurized farm milk [16]. Relating to these environmental exposures and to the hygiene hypothesis, it has been proposed that allergy develops because of an impaired maturation of the neonatal immune system from the immature Th2 response at birth to the more balanced Th1/Th2 immune function which should normally develop upon exposure to pathogenic and non-pathogenic microbes [17].

Most of the genes that have been investigated in relation to allergy risk are connected to innate immunity. CD14 is perhaps the most extensively studied gene and it has been reported to be involved in modulating allergy risk [18]. Gene–environment studies in the European PARSIFAL study demonstrated that the protective effect of farm milk consumption was associated with polymorphisms in the CD14 gene [19] and that the protective effects of farm animal exposure, which includes high levels of bacterial components such as lipopolysaccharides (LPS), are