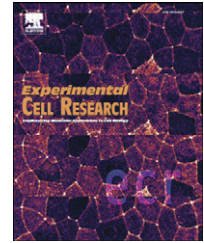


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Review

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

modified by NPSR1 polymorphisms [20]. NPSR1-A was found to be regulated by LPS-stimulation, offering a possible mechanism for risk modification [20]. Gene–environment interactions may also induce altered actions of gene activity persisting during life, so called epigenetic modifications. Whether environmental factors might influence the epigenetic inheritance of epigenetic ‘allergy genes’ or epigenetic mechanisms play a role in the development of allergic diseases is an open area of research [18,21]. Further epidemiologic studies in combination with research on gene–environment, gene–gene interactions and epigenetic regulation are required to identify risk from protective factors.

Intrauterine environment

There are several indications that the intrauterine environment could be important for later allergy development. Allergies often develop early in life and allergy development in the child has in some studies been demonstrated to be more strongly associated with allergy in the mother than with paternal allergy [22,23]. Evident differences in the immune response in cord blood of allergic and non-allergic mothers indicate that maternal allergy in fact can have intrauterine effects on the fetal immune system [24,25]. Environmental exposures of the mother during pregnancy have been demonstrated to affect the risk of allergy development in the child. For example, maternal exposure to pets, endotoxin in house dust and a farming environment have been connected to a protection against allergic sensitization in the children [26–28]. Dietary exposure during pregnancy has also been investigated in relation to allergy development and extensive studies have been performed of the gut microbial flora but conclusive data are still lacking.

A few years ago, we detected IgE antibodies within the fetal part of the placenta bound to Hofbauer cells (placental macrophages) irrespective of maternal allergy status (Fig. 1) [29]. This finding is intriguing, since the prevailing conception is that only IgG antibodies

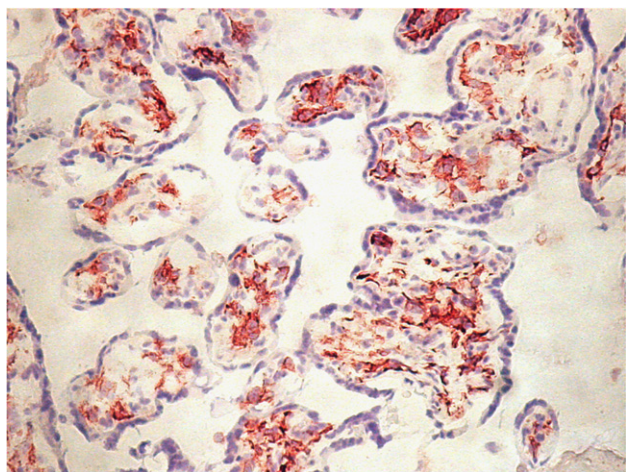


Fig. 1 – Immunohistochemical staining of IgE in human full term placenta. The section is counterstained with hematoxylin (blue). Positive staining is seen as red inside the villous stroma. Magnification 200×.

can cross the placental barrier from mother to child and raises several questions regarding origin and function of IgE in the placenta. The placental IgE antibodies have been shown to be of maternal origin and can be allergen specific when the mother is allergic [29]. Allergens have been demonstrated to be able to cross the placental barrier from mother to child in an *ex vivo* placental perfusion model and by direct measurement in cord blood and amniotic fluid. The simultaneous presence of maternal IgE and low concentrations of allergens may lead to IgE-mediated antigen focusing via high affinity IgE receptor (FcεRI) on fetal antigen presenting cells. IgE bound to FcεRI on antigen presenting cells serves as allergen-focusing structures and increases the antigen presenting capacity of a low concentration of allergen to allergen-specific T cells [30]. This could represent a route of priming of the fetal immune system to allergens. Binding of allergens and IgE on placental cells might also lead to a local production of cytokines, which affects the development of the fetal immune system. Depending on the amount of IgE and allergen present, some fetuses might be primed for allergy development later in life.

We have recently investigated gene expression in the placenta in relation to lifestyle and allergic sensitization of the parents [31]. We found that expression of CD14 was higher in placentas of families living on a farm and IL-12(p40) was lower expressed when families were living on a farm compared to not living on a farm. We also found higher expression of STAT4 and lower expression of GATA3 in placentas of families with sensitized compared to non-sensitized mothers. These results show that lifestyle and parental sensitization can affect the intrauterine environment at the level of gene and protein expression.

Host–microbe interactions

Microorganisms can trigger allergic symptoms by acting as allergens. One such microorganism is the yeast *Malassezia*, part of the normal human cutaneous microbial flora. There is evidence that this yeast is involved in the pathogenesis of atopic eczema/dermatitis, a chronic relapsing inflammatory skin disease. We and others have shown that approximately 50% of adult patients with atopic eczema have specific IgE- and T-cell reactivity and/or positive atopy patch test (APT) reaction to *Malassezia sympodialis* (*M. sympodialis*), reactions rarely found in other allergic diseases indicating a specific link between atopic eczema and *M. sympodialis* [32]. Another piece of evidence is that the global gene-signature in skin biopsy specimens from positive APT reactions to *M. sympodialis* is similar to the global gene-expression program observed in lesional atopic eczema skin supporting that *M. sympodialis* has a pathogenic role in atopic eczema [33]. Furthermore, we have found that the elevated pH of atopic eczema skin can induce an increased allergen release from *M. sympodialis* [32], leading to enhanced host–microbe interactions.

So far we have successfully cloned, sequenced and characterized 10 *M. sympodialis*-derived allergens and determined the 3D crystal structures of Mala s 1 and Mala s 6 [32]. Interestingly, some of the identified *M. sympodialis* allergens lack homology to known proteins whereas others have potential cross-reactivity to human homologues like cyclophilin, thioredoxin, and MnSOD, all three stress-inducible enzymes. By molecular mimicry leading to cross-reactivity, sensitization might be induced primarily by exposure to *Malassezia*, likely in conjunction with a damaged skin barrier. We have recent

data supporting this concept for MnSOD and for cyclophilin [32]. These results provide an explanation at the molecular level for the autoreactivity to hMnSOD observed in a subgroup of atopic eczema patients sensitized to *M. sympodialis* [32]. The uniqueness of some of the allergens identified from *M. sympodialis* makes them highly interesting as diagnostic tools. The allergens with homology to human structures render a unique opportunity to dissect pathogenic mechanisms in atopic eczema in relation to co-recognition with endogenous structures. With our *M. sympodialis* allergens, we have created tools that have improved the diagnosis of atopic eczema and revealed a previously overlooked impact of *M. sympodialis* hypersensitivity [32]. Based on our research [32], it is now possible worldwide to diagnose allergen-specific IgE in serum to *Malassezia* with ImmunoCAP (Phadia Diagnostics AB).

Molecular mechanisms in host–microbe recognition

By characterizing different molecular structures of *Malassezia*, it is possible to gain more information about the yeast itself and specific host–microbe interactions that might be suitable targets for interventions. When we had obtained the crystal structure of Mala s 1, a major *M. sympodialis* allergen, it showed a 6-fold β -propeller structure representing a new fold among allergens [34]. Furthermore, the putative active site of Mala s 1 overlaps structurally to the putative active sites of the hypothetical fungal proteins Q4P4P8 and Tri 14, from the maize parasite *Ustilago maydis* and the wheat parasite *Gibberella zeae* [34], suggesting that Mala s 1 and the parasite proteins may exhibit similar functions. Tri14 is a protein of the mycotoxin (trichothecene) synthesis gene cluster largely responsible for the pathogenicity of *G. zeae* and suggested to be involved in host-cell recognition or in cell-wall processes involved in plant cell invasion by the parasite. Interestingly, Mala s 1 is localized in the cell wall and exposed to the yeast cell surface. The genomes of the *Malassezia* species *Malassezia globosa* and *Malassezia restricta* were recently sequenced [35] and we are in the process to obtain the full genome of *M. sympodialis* which will give valuable information on host–microbe interactions. Knowing the full genome will also facilitate the production of yeast knockouts for functional studies and indicate therapeutic targets.

Vaccines/novel treatment strategies

At present, the tools for both allergy diagnosis and treatment of allergic disease with immunotherapy are mainly based on crude allergen extracts prepared from natural sources, such as whole mites or cat dander. It is difficult to standardize these extracts, since different batches of extracts from one allergen source may vary in allergen composition and content [36,37]. Defined single allergens are preferable for both diagnosis and therapy. The introduction of DNA technology into the field of allergen characterization has made it possible to clone genes for specific allergens and produce them as highly pure recombinant proteins. Hundreds of single allergens from different sources have been identified, cloned and expressed as highly pure and well-defined recombinant allergens. They can be produced in large amounts and are gradually replacing allergen extracts in allergy diagnosis and allergen-specific immunotherapy (SIT).

While the symptoms of different allergic diseases can be reduced by allergen avoidance and pharmacological treatment, SIT is the only treatment in use which may affect the natural course of allergy and give long-lasting reduction of allergic symptoms. SIT is based on repeated controlled administration of increasing doses of allergen extracts, usually of 30–50 subcutaneous injections scattered over a period of 3–5 years [38]. The intention is to reduce allergic reactions, or cause unresponsiveness, to the specific allergens that are recognized by the patient's immune system. Since the treatment is time consuming, this leads to low patient compliance and the treatment is also associated with local and even systemic side effects why the treatment must be given under the close supervision of trained physicians. SIT may be further improved by genetically modifying recombinant allergens into hypoallergens, which have a reduced allergenic capacity, but a retained T cell reactivity. Another approach is to modify recombinant allergens to target the MHC class II pathway of antigen presentation to enhance immunogenicity [39]. The application of these techniques to modify allergens in SIT could improve therapeutic efficacy and safety while reducing allergic side-effects.

Sub-lingual immunotherapy (SLIT) has been introduced to overcome the invasive injection procedure, and its clinical efficacy and safety are becoming more and more accepted but SLIT requires, as SIT, a high self discipline to complete the 3–5 year long treatment period [38]. Another administrative route which recently has been tried is intralymphatic allergen administration which in a study was found to drastically reduce the number of injections needed and treatment time down to 8 weeks to achieve protection [40]. However, this preliminary study needs to be verified and a drawback is the necessity of ultrasound guidance for injection into the lymph nodes. Still another attractive route for allergen SIT is epicutaneous needle-free administration using patches that can even be applied at home [41]. This strategy seems promising with an aim to target the antigen presenting DCs in the skin such as the Langerhan's cells and merits further investigations since it is vital to understand how different DCs exert their control over the quality and magnitude of the immune response to be able to design efficient immunotherapy vaccines. Another tool which might be useful for allergy vaccine development is exosomes. Exosomes are small membrane vesicles, 30–100 nm in diameter of endocytic origin that are released extracellularly by most cell types, including DCs, upon fusion of multivesicular bodies with the cell membrane [42]. Exosomes have been found in body fluids like bronchial alveolar lavage fluid, breast milk and serum. They have the capacity to stimulate or suppress immune responses largely depending on their cell type and origin and thereby their phenotype and cargo. Exosomes have the potential to function as transporters of allergen and we have found that B cell derived exosomes can present Bet v 1 peptides and stimulate Bet v 1-specific T cell lines to proliferate and to produce the Th2-like cytokines IL-5 and IL-13 [42], suggesting that exosomes could be an immuno-stimulatory factor in an allergic immune response. In contrast, exosomes isolated from intestinal epithelial cells (tolerosomes) have been shown in mice to induce antigen (ovalbumin)-specific tolerance and exosomes isolated from human breast milk can inhibit anti-CD3-induced cytokine production and increase the number of regulatory T cells suggesting a role to prevent allergy development [42].

Another focus of research is the utilization of nanotechnology for specific immunotherapy. Nanoparticles can be constructed to carry a vaccine or a therapeutic drug to organs or cells for delivery of the

cargo thereby enhancing efficacy while reducing side effects. We have found that nanosized mesoporous silica particles are non-toxic and do not induce activation of human DCs [43], thus making them suitable as carriers for biomedical applications. Additionally, experiments in mice have demonstrated that allergen-coupled carbohydrate-based microparticles can act as an adjuvant for allergy vaccination, both in a prophylactic [44] and therapeutic setting [45]. The development of SIT using nanotechnology, either engineered nanomaterials or endogenous exosomes, in combination with tailor-made allergy vaccines and optimizing the route for administration is a promising strategy for prevention or treatment of allergic diseases which have become a global health problem.

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