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Can IgE-mediated allergic diseases be prevented by using allergen-specific IgG antibodies?

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SUMMARY

The prevalence of allergic disease has increased significantly over the past few decades, especially in children. Prenatal period may represent an ideal time for the implementation of interventions to prevent allergy and allergic diseases. In this hypothesis, allergen-specific immunoglobulin G (IgG) antibodies may combine with maternal allergens as blocking antibodies with immunoglobulin E (IgE) or mask antigenic determinants in their binding to prevent the sensitization of the fetus. It may also modify fetal immune response to prevent the production of allergen-specific IgE antibodies and the further development of allergic diseases. Recent epidemiological, immunological and intervention studies supporting the hypothesis were summarized. Anti-mite human IgG Fabs (antigen binding fragments) were prepared from two immunoglobulin genes libraries and they were confirmed to have a specific binding blocking property by an in vitro mastocyte degranulation inhibition test. Allergen-specific human IgG antibodies may have a potential use in the prenatal immunoprophylaxis or the prevention of allergic diseases after birth.

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Background

The prevalence of allergic diseases such as asthma dramatically increased in the second half of the 20th century, especially in children. Such diseases represent a serious burden to human health. The increase in the prevalence of asthma has been associated with an increase in atopic sensitization. It is estimated that around 300 million people in the world currently have asthma and among those more than 50% of adults and at least 80% of affected children are allergic [1,2]. In view of the recent high prevalence of allergic asthma, the development of effective preventive and therapeutic approaches have become increasingly important. With the rapid advance in theoretical immunology and therapeutic antibody, immunotherapy has become one of the most popular methods in the prevention and treatment of allergic asthma. Humanized anti-IgE antibody rhuMab-E25 (recombinant humanized monoclonal antibody) named Omalizumab was successfully approved by the Food and Drug Administration (FDA, US) and it went into clinical application in 2003 [3]. As anti-IgE antibody could only bind to serum free IgE, it therefore could not totally abolish target cell responsiveness.

As a result, Omalizumab is now mainly used only as a tertiary preventive strategy to relieve clinical symptoms especially for severe asthma patients. Recently, evidence has demonstrated that allergy sensitization may occur in fetal life and prenatal aeroallergen exposure was related with a significant nonlinear increase in cord blood IgE [4]. As the fetal immune system may be primed for the development of allergic disease before birth and prenatal exposures may influence the future development of allergic disease, early prevention was increasingly important and strongly recommended by WAO (World Allergy Organization) and WHO (World Health Organization) as early as the prenatal stage for primary prevention and after birth for secondary prevention [5].

Hypothesis

It was known that cross-linking of IgE occurs after binding to a specific allergen, triggering an intracellular biochemical chain reaction which results in subsequent clinical symptoms of allergic disease. Therefore, blocking or interfering with the cross-linking of IgE may have the potential for use in immunoprophylaxis and treatment of allergic diseases. Allergen-specific IgG antibodies may combine with specific maternal allergens as blocking antibodies with IgE or mask antigenic determinants in their binding to decrease the maternal allergens level. Meanwhile, IgG antibodies could pass through placenta, modulating fetal immune response. These two mechanisms occurring alone or in combination may

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prevent the sensitization of the fetus and the production of allergen-specific IgE antibodies. The use of IgG antibodies may prove an ideal method for the prevention of the development of allergic diseases. Therefore we theorize that allergen-specific IgG (or Fab fragment) antibodies may be administered to pregnant women to increase the maternal and fetal specific IgG levels as a supplement in order to achieve early prevention of allergy and allergic diseases. Human allergen-specific IgG antibodies may be produced in vitro through various methods including antibody engineering technique. It is practical and cost-efficient to produce in large quantities using standard procedures.

Are maternal allergen-specific IgG important in the prevention of infant allergic disease?

A prospective study in humans recently found that high levels of maternally transferred aeroallergen-specific IgG in cord blood may inhibit IgE production and reduce subsequent sensitization rate and atopic symptoms in the offspring [6]. This study accords with epidemiological studies showing that those born just before the birch and grass pollen seasons (likely to have low levels of maternally transferred pollen-specific IgG) are at higher risk of developing pollen sensitization [7]. Evidence from children whose mother received allergen-specific immunotherapy during pregnancy (likely to induce IgG4 blocking antibodies) also indicates protection against allergic sensitization. More recently, maternal immunization with ovalbumin showed a marked inhibition of antigen-specific IgE antibody production and lowered Th2/Th1 (T helper cell) cytokine levels and only postnatal IgG injection was able to inhibit offspring IgE antibody response [8]. Maternal IgG antibody in the offspring may diminish allergen processing and presentation to T cells, consequently preventing neonatal sensitization [9].

As more and more evidence indicates that maternal allergen-specific IgG does protect offspring from allergic sensitization, the mechanisms are still not clear. Furthermore, recent studies are still not perfectly designed or robust enough to draw firm conclusions regarding the effects of maternal allergen-specific IgG antibodies. Conflicting data has yielded that early exposure may in some individuals results in immunologic tolerance rather than sensitize the infant [5] and that passive IgG transference during pregnancy induced an increased percentage of interleukin-10 (IL-10) secreting CD4⁺ (cluster of differentiation 4) T cells which may help limit Th1 cytokine production [10].

Production of human IgG antibodies specific to allergens

The rapid evolvement of antibody engineering has led to more powerful methods and more efficiency system capable of producing recombinant antibodies of desired specificity. Concerning its wide range application in modern medicine, therapeutic antibodies could be a valuable method in dealing with allergy and allergic diseases [11,12]. In our present study, a human IgG Fab genes library was constructed from the lymphocytes of several allergic asthma patients who received a long period of immunotherapy with house dust mites' extracts. Theoretically there is a higher probability of obtaining anti-mite IgG Fab antibodies from this library. Another human IgG genes library was prepared from 300 healthy volunteers making it theoretically possible to obtain IgG Fab specific to any antigen including mite allergen. Mite allergen represents one of the most important allergen sources worldwide which is an independent risk factor for the development of asthma in children [13,14]. IgG Fab antibody specific to mite allergen was successfully screened from these two libraries. Fab is a small fragment with one antigen binding domain formed by variable region of heavy and light chain. While binding to specific allergen, this small aller-

gen-Fab complex could be easily cleared or destroyed without harmful effects on human body. In addition, lacking Fc region (the fragment crystallizable region), there is no risk to activate the complement system.

Gene modification of human IgG antibodies

Antibody engineering technique makes it possible for gene modification in vitro to meet the varied need in bioscience and clinical medicine. As in our study, one of the mite-specific IgG Fabs we obtained from the library belongs to VH3 (variable heavy chain gene, VH) family which is the largest of the seven families and comprises about 50% of the expressed VH repertoire in mature B cells (<http://imgt.cines.fr/>). It was indicated that there was a highly significant decrease in the use of VH3 by IgE-positive B cells in the allergic nasal mucosa compared with that expected on the basis of the normal repertoire in PBMCs (peripheral blood mononuclear cells) observed by previous researchers [15]. Chain shuffling of cloned genes may be a useful shortcut to find genes of immunoglobulins which recognize similar epitope. As for the heavy chain's germline, it was interesting to find that VH5 bias may be a good choice for gene modification as it was always related to IgE associated diseases [16]. IgA VH sequences also exhibited a significant but less extreme bias toward VH5 compared with that seen in IgE sequences. The observation of VH5 bias in both IgE and IgA, their colocalization in the nasal mucosa, and the fact that allergen might bind to the subset of B cells expressing VH5, leads to selective proliferation or rescue from apoptosis [17]. If the gene usage of our IgG Fab fragments could belong to VH5 family, this mutation might increase the affinity of the IgG Fab fragments to bind allergens and block the cross-linking of IgE and the degranulation of mast cells.

It is known that the affinity is one of the most important characteristics for antibodies. The affinity of IgG fragment to specific allergens could be analyzed by a surface plasmon resonance assay [18]. The association and dissociation constants indicate specific binding affinity between the antibody and the allergen. It is both necessary and important to improve the affinity for further study in vivo and possible application for clinical immunophylaxis of allergic diseases. In antibody molecules, the complementarity-determining regions (CDRs) especially CDR3 of the heavy- and light-chains, are responsible for high-affinity binding with antigens. It is possible to mature affinity by chain shuffling or site-directed mutagenesis in recombinant antibody technology to improve affinity of the original antibody [19,20]. The strength of antibody binding to its antigen is not only determined by affinity but also by the valency of interaction, with multivalent interactions leading to an increase in functional affinity. Several strategies have been developed to generate di- or multivalent assembly of Fv domains, or to yield fusions of antibody fragment to constant domains which are able to dimerise or apply heterologous peptide or protein domains to scFv or Fab fragments with the potential to di- or multimerise.

Extending functions and future considerations

It is possible to determine the tendencies of mite allergens to bind with human IgG Fab through the examination of mediator release. In the present study, the results of in vitro mastocyte degranulation inhibition test showed that mite allergen-specific IgG Fab could significantly inhibit mast cell degranulation indicating that it could block or interfere with the specific binding of mite allergen to IgE on mast cells. Nevertheless, the mechanisms involved in the regulation of allergic responses are still unclear, it is necessary to introduce the antibodies into a primate animal model which holds

high homology with human beings to achieve similar convincing inhibition results. Another important issue urgently needs to be addressed before clinical trial is to prolong the short half-life of Fab fragment without provoking harmful reactions.

In general, IgE-mediated allergic asthma continues to increase especially in children. To the present, this trend has still not been completely stopped or reversed. It is increasingly important for mankind to search for better methods of prevention and treatment especially for early prevention which is emphasized by WAO and WHO. From all the evidences accumulated above, it is logical to hypothesize that human IgG antibodies specific to allergens may have a potential use in the early prevention of allergy and allergic diseases. We hope this along with other strategies recommended by WAO will contribute greatly to the prevention of allergy and allergic diseases.

Conflict of interest statement

We have no conflicts of interest.

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