

Mimotope and Anti-Idiotypic Vaccines to Induce an Anti-IgE Response

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Abstract

We have defined epitopes on human IgE by screening different phage display random peptide libraries with a monoclonal anti-IgE antibody termed BSW17. The selected mimotopes and epitopes within the Cε3 and Cε4 region of IgE induced antibodies that were nonanaphylactogenic and had biological activity similar to BSW17. The chemically synthesized and KLH-coupled IgE epitopes or mimotopes were used to induce an anti-IgE response in rhesus monkeys. The immunized rhesus monkeys were subsequently protected in a PCA test when sensitized with human IgE and triggered with the corresponding allergen. Furthermore, using the same monoclonal anti-IgE antibody, we also generated an anti-idiotypic antibody that showed sequence homology with the IgE epitope in the Cε3 domain. This anti-idiotypic antibody as well as the mimotopes were then used in a mouse model to induce orally an anti-IgE immune response. For this purpose mice were fed by intragastric gavages with bacteriophages displaying the small IgE-homologous structures. Orally immunized mice produced serum anti-IgE antibodies that were inhibited by BSW17 suggesting that it may be possible to induce a systemic anti-IgE response orally.

Introduction

At present different approaches are pursued to treat allergic patients independent of their immune response against specific allergens. The most advanced approach is the passive administration of anti-IgE antibodies that are not anaphylactogenic because they recognize structures close to the binding site of IgE for the high affinity receptor of IgE (FcεRI) [1, 2]. This treatment is now in phase 3 of clinical evaluation and is described in this volume by Jardieux et al. The passive administration of anti-IgE antibodies aims at neutralizing IgE and preventing its binding to the high affinity receptor. Preclinical studies are presently also performed using a soluble α-chain of FcεRI [3]. Basically, this approach represents a strategy similar to using monoclonal antibodies against IgE.

Administration of anti-IgE antibody has already been shown to effectively eliminate IgE from the circulation and phase 2 trials already document a beneficial effect for the patients [2]. This treatment, and similarly a treatment with soluble α-chain may have the disadvantage that anti-IgE antibodies or soluble α-chains must be given in excess of the existing IgE in the body. Thus, atopic individuals may need constant and repeated treatments with relatively high amounts of monoclonal antibodies. Until today such antibodies are still costly in their production. Due to their genetical backgrounds some individuals may be capable of forming anti-idiotypic antibodies, possibly belonging to a rare group of nonresponders for this kind of treatment.

Either as a stand-alone treatment or to complement passive administration of antibody one may therefore think that active immunization with defined epitopes from IgE may lead to the generation of autoantibodies in humans that may have the same effect as the anti-IgE treatment [1, 2]. We therefore developed an experimental vaccine that eventually may be used in humans to induce a temporary autoimmune response. However, more preclinical experimentation is needed to further understand the induction of such a possibly harmful autoimmune response and to better control it.

Selection of Suitable IgE Epitopes

There are reports that the complete IgE molecule can be used to neonatally abrogate an IgE response [4]. Attempts have also been undertaken to use IgE constant domain to induce an anti-IgE response. From our previous mapping studies on the biological activity of anti-IgE it became clear that there are only few antibodies against IgE that are nonanaphylactogenic [5, 6]. Thus, it is mandatory to select epitopes that would only induce nonanaphylactogenic antibodies. As a template we have, therefore, used a murine monoclonal antibody termed BSW17 [7], which in addition to being nonanaphylactogenic also inhibits human IgE synthesis [8] binds to surface IgE [9], and is capable of removing this IgE after prolonged incubation [9]. As previously shown, it was possible to select mimotopes from large libraries of bacteriophages expressing random peptides. Interestingly, we found peptides that were finally mapped either to a region within the Cε4 domain or a region within the Cε3 domain. The mimotope that maps within the Cε3 domain partially overlaps the possible IgE binding site to the high affinity IgE receptor [10]. In rodents both types of mimotopes induced an anti-IgE response that was inhibited by the monoclonal antibody that had been used to select them from random peptide libraries [11].

Inhibition of PCA in Rhesus Monkeys by Active Immunization

The immunization models in rodents do, of course, not represent a useful test system, because human IgE does not bind to their effector cells. However, human IgE can bind to cells from rhesus monkeys. Thus, such monkeys were immunized with either the IgE mimotopes or the linear sequences representing the corresponding epitopes on IgE. After boosting and documenting an existing anti-IgE titer in

the monkeys, they were passively sensitized with a human chimeric antibody directed against NIP-BSA. Skin reactions were made manifest by intravenously injecting the antigen NIP-BSA. Control monkeys were immunized with carrier protein. All four types of monkeys either immunized with the Cε3 mimotope or epitope, or the Cε4 mimotope or epitope did no longer show a skin reaction. This documents that the immunized monkeys had formed anti-IgE antibodies that were capable of neutralizing IgE to prevent binding to the effector cells. It can therefore be assumed that a similar vaccination approach in humans might lead to the formation of the same type of blocking antibodies.

Mimicking a Mimotope by an Anti-Idiotypic

Our isolated mimotopes and epitopes represent minimal structures as they were recognized by the monoclonal antibody BSW17. However, according to the network hypothesis and anti-idiotypic antibody recognizing the monoclonal antibody BSW17 may finally represent a similar structure or epitope as present on IgE. Furthermore, anti-idiotypic antibodies do not need a carrier protein to induce an immune response and may be perfectly suitable to act as an immunoregulatory agent for inducing an anti-IgE response.

Rather than using bacteriophages, expressing random peptides, we used a pool of libraries expressing human variable immunoglobulin genes. Screening of these libraries with the monoclonal antibody BSW17 resulted in the isolation of an anti-idiotypic antibody recognizing BSW17 by its variable site. The light chain of this antibody showed sequence homology with the Cε3 mimotope. In addition, when this antibody was used to immunize rabbits, an anti-IgE response was induced that was inhibited by BSW17. These data document that it is possible to generate similar structures by anti-idiotypic antibodies as with the peptide approach.

Oral Immunization to Induce an Anti-IgE Response

As we had now three active principles at our disposal that were immunogenic and induced an immune response against IgE, we intended to test whether they may be applied orally. The utilization of a gastric simulation test (pepsin treatment at pH 1.2 [12]) demonstrated that phage displayed Cε3 mimotopes and the Fab fragments were susceptible to digestion with pepsin. As bacteriophages retain their infectivity during digestion in the stomach (as

demonstrated in the gastric simulation test), we fed mice by intragastric gavages with bacteriophages, in order to transport these peptides, albeit through the stomach. This treatment indeed induced an anti-IgE response, suggesting that the bacteriophages infected resident *Escherichia coli* that subsequently generated fresh phage particles expressing our desired antigens.

However, it was not possible, so far, to prove the replication of the bacteriophages either by direct isolation of phage

particles or phage DNA from mouse feces. At present it is not known what mechanism is responsible for the induction of the anti-IgE response. Based on our controls, namely oral feeding with the mimotopes fused to a phage protein alone, which did not lead to the induction of an anti-IgE response, one must assume that the complete phage is nevertheless necessary. Our results show that it may be possible to induce a systemic anti-IgE response by delivering the vaccine by the oral route.

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