

Allergic Manifestations as the Results of a Conditional Autoimmune Response

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Abstract

By means of repertoire cloning we have isolated human anti-IgE antibodies as well as human anti-FcεRI antibodies. Whether the naturally occurring anti-IgE autoantibodies play a pathophysiological role may be disputed, but the beneficial role of recombinant anti-IgE antibodies as a therapeutic agent has been shown. On the other hand, the natural antibodies isolated from an antibody library of a nonallergic individual against the FcεRI α-chain are anaphylactogenic, if FcεRI was not occupied. Thus, anti-FcεRI autoantibodies may be part of a conditional autoimmune reaction, leading to urticaria if local IgE is consumed, e.g. after an immediate reaction. Thus, anti-FcεRI antibodies may represent an amplification arm of the late reaction. The normal occurrence of anti-IgE and anti-IgE receptor autoantibodies may suggest that it might also be feasible to induce such autoantibodies by vaccination. In a monkey model using a mimotope of human IgE it was possible to induce a beneficial anti-

IgE autoimmune response. The actual epitope of the IgE molecule was then also molecularly reconstructed by generating recombinant anti-idiotypic antibodies. These antibodies also induced effectively an anti-IgE response in monkeys, suggesting that not only mimotopes but also anti-idiotypic antibodies may be used to generate an autoimmune response. Both of our projects suggest that active immunization may be a new form of immunomodulation for the treatment of allergic disease.

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Introduction

Autoantibodies against IgE and the high affinity receptor of IgE have been described [1–4]. Their physical existence has also been proven by the isolation of both types of autoantibodies by repertoire cloning. Thus, while the natural occurrence of such autoantibodies is beyond doubt, the question remains whether these autoantibodies may have a pathophysiological role.

A putative role of such autoantibodies can be deduced from the fact that either chimeric or humanized anti-IgE antibodies have been used in clinical trials, documenting that anti-IgE antibodies may indeed have an immunoregulatory role in vivo. Their possible role seems to be simi-

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lar to the biological properties that had been defined in vitro. Namely, anti-IgE antibodies that are useful for treatments, must not be anaphylactogenic and must be capable of neutralizing IgE in the sense that binding of IgE to effector cells of allergy is prevented. In vitro the inhibition of IgE synthesis has also been well documented [5, 6].

A second line of evidence for the existence of immunoregulatory autoantibodies may be the fact that it was possible to isolate small fragments of IgE, called mimotopes, that are recognized by antibodies having this kind of activity. We have recently shown that such IgE mimotopes can be used to actively immunize animals documenting their specific immunogenicity. In the case of a rhesus monkey model, where human IgE binds to monkey IgE receptors, it could also be claimed that the anti-IgE immune response was actually an autoimmune response.

The third line of evidence for a possible biological role of autoantibodies lays in the fact that we have been able to isolate anti-idiotypic antibodies against antibodies that have an immune regulatory role, again implying that such autoantibodies may have a biological role.

In vitro experiments have shown that murine anti-FcεRI antibodies have distinct biological properties. Monoclonal antibodies against FcεRI have been described that are either anaphylactogenic or not and antibodies that can inhibit the binding of IgE to the α-chain of the IgE receptor or not [7–9].

The biological activity of the anti-FcεRI autoantibody was also indirectly suggested by sera from patients with such autoantibodies in mediator release assays in vitro [10], or by reinjecting the sera into the skin of the patients, resulting in a wheal and flare reaction [11]. Thus, there is ample evidence from novel therapeutic strategies using anti-IgE antibodies and from diverse biological in vitro systems that autoantibodies may indeed have also a biological function [12]. Nevertheless, the existence of autoantibodies with a biological function is still indirect and final proof for a pathophysiological role has not yet been given.

Results and Discussion

In the case of anti-IgE autoantibodies we have previously not been successful in isolating autoantibodies that would have a similar biological function as those humanized antibodies that are now successfully used in clinical trials for treating allergy [12]. In fact the antibodies that have been isolated previously were directed

against epitopes that would render the autoantibodies anaphylactogenic [13]. Thus, in order to document whether in the human genome anti-IgE autoantibodies would be present we panned a human antibody library first on the previously described IgE mimotopes, second on the anti-idiotypic antibodies that are molecularly similar to the IgE mimotopes and finally on human IgE. This resulted indeed in antibodies that seem to have a similar specificity as the antibody BSW17 that has all the biological characteristics that would be useful for a passive vaccination approach. These human recombinant autoantibodies now have to be further analyzed with respect to their biological function. But their isolation makes a strong point, namely that we do have the potential of making human antibodies with a beneficial physiological role.

In the case of autoantibodies against FcεRI we used a human naive IgM antibody library expressed on the filamentous phage M13. As reported previously, we were again capable of isolating human anti-α-chain antibodies [14]. Interestingly these libraries contained, as expected, antibodies specific for the FcεRI α-chain with heavy chains that were still in germline configuration and with light chains that were only minimally mutated. To our own astonishment these autoantibodies were of high affinities (1.4×10^{-8} and 7.2×10^{-9} M), but when tested on normal human basophils they did not induce histamine release albeit both studied anti-FcεRI antibodies clearly recognized surface FcεRI expressed on a transfectoma cell line. These, at the first view contradicting results, were resolved by demonstrating that both recombinant human autoantibodies were inhibited by IgE for their recognition on solid phase FcεRI α-chain. Furthermore, stripping of human normal basophils with lactic acid to remove cell-bound IgE resulted in an increase in histamine release whereas readdition of human IgE prevented mediator release.

Thus, the isolated anti-α-chain autoantibodies perfectly recognized surface IgE receptors if the receptor was not occupied. The autoantibodies were, therefore, termed conditional autoantibodies as they would not qualify as actual autoantibodies as long as most IgE receptors of the effector cells are occupied by IgE. Namely, the occupied FcεRI would fulfill the criteria, like many other autoantigens, of an immunologically hidden antigen for normally not being recognized by B cells.

Our findings provide also a new role of these anti-FcεRI autoantibodies in certain diseases such as urticaria and deliver at the same time a possible explanation why such antibodies could actually be isolated from normal

individuals. In order to illustrate a possible pathophysiological role of these antibodies *in vivo*, a small amount of human recombinant monoclonal anti-FcεRI autoantibody was injected into the arm of a volunteer together with an allergen. As expected the antibody by itself had no anaphylactogenic activity but was nevertheless capable of enhancing the late phase reaction. During the late phase reaction it is well known that increased expression of FcεRI can be observed and based on the foregoing immediate reaction it is also understandable that IgE may have been 'consumed'. Thus, locally in the tissue a new 'condition' may arise where there may now be more anti-FcεRI autoantibodies than IgE to occupy the receptor.

Therefore, we proposed a model of a conditional autoimmunity that may lead in normal individuals to pseudoallergic reactions in case stimuli are present that either decrease surface IgE levels or increase the expression of FcεRI. It can be speculated that in many instances the late reaction may be magnified by the presence of such autoantibodies and that in the case of patients with urticaria a relatively fine imbalance between IgE receptor occupancy and the presence of such autoantibodies may result in the typical symptoms of urticaria patients. One may even continue to speculate that nonimmunological triggers resulting in an enhanced expression of FcεRI may lead to urticaria symptoms.

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