

Conditional Autoantibodies in Urticaria Patients: A Unifying Hypothesis

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Chronic urticaria may be characterized by conditional autoantibodies against the α -chain of the high-affinity receptor for IgE (Fc ϵ RI). These autoantibodies are termed conditional as they only recognize unoccupied Fc ϵ RI. The same conditional reactivity pattern has also been found in sera of atopic and normal healthy donors. Any condition resulting in accessibility of Fc ϵ RI will render these autoantibodies anaphylactogenic. This finding offers a unifying

hypothesis for the manifestation of different forms of urticaria. Non-immunologic triggers may thereby influence directly or indirectly the number of accessible Fc ϵ RI allowing the conditional autoantibodies to induce urticaria symptoms. Key words: allergy/high affinity IgE receptor (Fc ϵ RI)/histamine release/IgE/phage display/recombinant antibodies. *Journal of Investigative Dermatology Symposium Proceedings* 6:150–152, 2001

Allergic urticaria as the least common form of this disease is assumed to be IgE mediated; however, nonallergic urticaria may also be indirectly IgE mediated, if we assume that autoantibodies against the α -chain of the high-affinity IgE receptor (Fc ϵ RI α -chain) play the pathophysiologic role (Fiebiger *et al*, 1996; Greaves, 2000).

The presence of such autoantibodies has been shown by immunologic means, but their physical demonstration has been complicated by the presence of anti-IgE antibodies that would interfere in diagnostic and cellular immuno assays (Horn *et al*, 1999; Marone *et al*, 1999; Sabroe *et al*, 1999; Zuberbier *et al*, 2000). In order to understand the pathophysiologic mechanisms and to aid in the future therapy of urticaria, it would therefore be very important to document the molecular existence of anti-Fc ϵ RI antibodies.

In the past the same situation prevailed with anti-IgE antibodies that were believed to be an *in vitro* artifact. After we had cloned anti-IgE antibodies from the human rearranged immunoglobulin repertoire, it became obvious that such antibodies may even play a pathophysiologic role (Vogel *et al*, 1993; Stämpfli *et al*, 1994; Rudolf *et al*, 1996). We used the technique of phage display to perform an immunoglobulin variable chain repertoire cloning in order to find human anti-IgE antibodies. The present utilization of humanized anti-IgE antibodies for the therapy of allergies has also elucidated the potential role of natural anti-IgE antibodies (Barnes, 2000; Fahy, 2000; Fick *et al*, 2000).

ANTI- Fc ϵ RI AUTOANTIBODIES IN NORMALS

As we had previously described anti-Fc ϵ RI autoantibodies in normals (Horn *et al*, 1999), our first interest was to clone such autoantibodies and to compare these with antibodies occurring in urticaria patients. The interest in these natural autoantibodies also lies in the fact that one would have to assume that such

autoantibodies would not have a pathophysiologic role and would clearly be different from autoantibodies that may occur in urticaria patients.

The anti-Fc ϵ RI antibodies we cloned from normal blood donors had extremely interesting properties. First, their heavy chains were in germline configuration, but were still of high affinity for the α -chain of Fc ϵ RI. When tested on normal basophils, these antibodies expressed in an eucaryotic cell line as full-length antibodies, were not anaphylactogenic; however, if normal basophils were stripped of their surface IgE by a lactic acid treatment, the anti-Fc ϵ RI autoantibodies became anaphylactogenic. As we found that the antibodies perfectly stained a transfectoma cell line expressing the α -chain of the IgE receptor, we had to conclude that these autoantibodies only recognized IgE receptor expressing cells if the IgE receptor was not occupied. We could confirm this finding by re-sensitizing normal basophils with IgE and thereby preventing the anaphylactogenic activity of the autoantibodies.

Based on these data we termed the autoantibodies conditional autoantibodies. They partly fulfilled the principle of recognizing a hidden antigen, but the antigen was not hidden by compartmentalization or through its location within the cell, but only by the condition that the receptor had to be occupied or not.

CHARACTERIZATION OF AUTOANTIBODIES FROM URTICARIA PATIENTS

Using the same technique of antibody phage display, we cloned autoantibodies from a pool of B cells from four urticaria patients. The unexpected finding was that from 12 randomly selected antibodies we found only one identical immunoglobulin heavy chain. Most surprisingly this heavy chain was identical to the heavy chain previously found in the most frequently isolated antibody from a normal blood donor. At present it is not known whether antibodies of other specificities do exist in urticaria patients, but taking into account our isolation and selection principles it was most likely no coincidence that we ended up with the same heavy chain antibodies as the ones found in normal donors.

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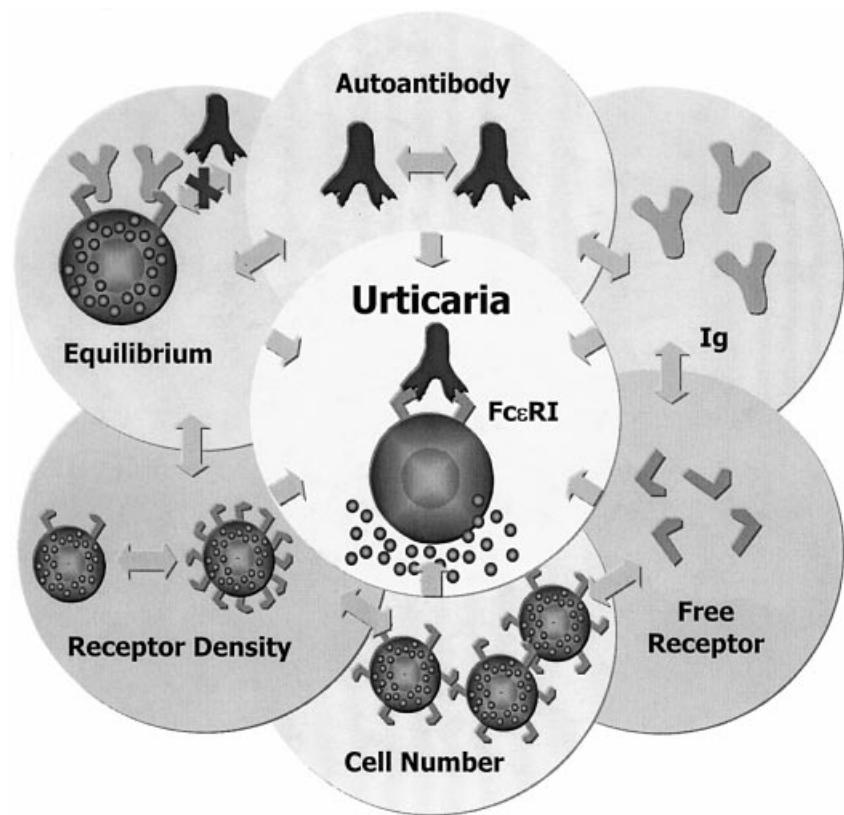


Figure 1. Proposed mechanism of anti-FcεRI conditional autoantibodies

CONDITIONAL AUTOANTIBODIES AS A UNIFYING HYPOTHESIS IN URTICARIA

Figure 1 depicts a hypothesis that we propose for the role of anti-FcεRI antibodies in urticaria. The presence of autoantibodies against the α -chain of the IgE receptor has been described by others (Fiebiger *et al*, 1996; Greaves, 2000). In this hypothesis, we would like to propose the model that any disturbance in a given homeostasis or equilibrium between the number of IgE receptors, the degree of occupancy of IgE receptors, the level of free *versus* receptor bound IgE, and the level of conditional autoantibodies may be responsible for the manifestation of urticaria.

Non-specific and non-IgE mediated mechanisms may lead to an increased expression of IgE receptors on basophils and mast cells (Stallman *et al*, 1977; Chen *et al*, 1999). If IgE levels are unaltered during the same period, then a large number of surface receptors may now become available for the conditional anti-FcεRI autoantibody and the induction of symptoms by these antibodies. A similar phenomenon may be achieved if the number of cells expressing IgE receptors is increased locally, either through local proliferation or through an extravasation of chemotactically attracted cells with free receptors.

As the conditional autoantibodies can also bind to the recombinant α -chain of FcεRI in *in vitro* assays (Pachlopnik *et al*, 1998), it may be assumed that the secreted form of the α -chain as it occurs in serum (Saban *et al*, 1994) may actually become an agonist or antagonist for the autoantibodies and interfere with the postulated equilibrium of the involved reaction partners to induce urticaria symptoms.

The IgE level by itself, of course, will determine the extent of free IgE receptors. Recently, during clinical evaluation of therapeutic anti-IgE antibodies it has been shown that they down-regulated the IgE receptor density on basophils and mast cells (Saini *et al*, 1999). Thus, IgE alone may be responsible for the regulation of the IgE receptor expression, which might link autoimmune forms of urticaria to the IgE-mediated triggerings of allergic urticaria.

The proposed hypothesis would also allow for triggering mechanisms in urticaria that have so far not been associated with immune mechanisms, e.g., cold, sun exposure, alcohol excess, endocrine disorders, and emotional stress. All these triggers may lead to an altered local blood supply or affect IgE receptor gene expression. Our hypothesis would also offer an explanation why many people suffer only occasionally from mild forms of urticaria, as the antibodies in normals and urticaria patients are in germline configuration and would not need to be produced by an autoimmune response. If the so-called conditional autoantibodies belong to the pool of natural antibodies, then it can be envisaged that many people may undergo a short period of acute urticaria symptoms without recognizing the symptoms as a quasi normal conditional autoimmune state.

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