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REVIEW

Autoreactive IgE in Chronic Spontaneous/Idiopathic Urticaria and Basophil/Mastocyte Priming Phenomenon, as a Feature of Autoimmune Nature of the Syndrome

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Abstract Recent years of research have shed a new light on the role of IgE in immune reactions. It seems to be more than just a contribution to immediate type of allergic response. It appears that monomeric IgE may enhance mast cell activity without cross-linking of FcεRI by IgE specific allergen or autoreactive IgG anti-IgE antibodies. Monomeric IgE molecules are heterogeneous concerning their ability to induce survival and activation of mast cells only by binding the IgE to FcεRI, but not affecting degranulation of cells. It also turned out that IgE may react to autoantigens occurring in the blood not only in chronic spontaneous urticaria (CSU) but also in other autoimmune diseases. The aforementioned phenomena may promote the activity of mast cells/basophils in CSU that easily degranulate when influenced by various inner (autoreactive IgG against IgE and FcεRI, autoreactive IgE for self-antigens) and outer factors (cold, heat, pressure) or allergens. These findings forced the new approach to the role of autoimmunity, self-antigens and IgE autoantibodies in the pathology of CSU. CSU put in the scheme of autoreactive IgG and autoreactive IgE seems to be either a kind of an autoimmune disease or a clinical manifestation of some other defined autoimmune diseases or both.

Keywords Autoreactive IgE · Chronic urticaria · Self-antigens · Mastocyte priming · Autoimmune reactivity

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Introduction

For many years, autoimmunity in chronic urticaria was manifested by the presence of both IgG anti-IgE and anti-FceRI (Maurer et al. 2004; Zuberbier et al. 2000). Recently, high efficiency of omalizumab, the monoclonal antibody against immunoglobulin E (anti-IgE), in skin diseases, particularly in chronic spontaneous urticaria (CSU)/angioedema and chronic inducible urticaria (CINDU)/angioedema has been observed, initiating different approach to understanding the pathomechanism of this complex syndrome (Chang et al. 2015) (Fig. 1). Randomized multicenter clinical trial conducted by Maurer et al. (2011), which revealed the alleviation of symptoms in 70 % of patients suffering from CSU and having autoreactive IgE against thyroid peroxidase (TPO) after omalizumab was introduced to the therapy, appeared to have crucial meaning in this field. To begin with, this observation suggests the autoimmune nature of the CSU/CINDU and histaminergic angioedema. However, equally interesting and important is the role of IgE and FcεRI in immune reactions, as it exceeds the immediate type of allergic response (Maurer et al. 2011; Zuberbier et al. 2000). Among others, monomeric IgE may enhance mast cell survival and activity without cross-linking of FcεRI binding IgE to its surface by an allergen, or autoreactive IgG (Asai et al. 2001). It also turned out that IgE may react to autoantigens present in the body, not only in CSU but also in other autoimmune diseases (Hatada et al. 2013; Maurer et al. 2004).

In some patients suffering from CSU, autoreactive IgE against TPO can be found in serum (Altrichter et al. 2011). The publication by Hatada et al. (2013) revealed, that anti-double stranded deoxyribonucleic acid (anti-dsDNA) IgE levels were significantly higher in patients with chronic

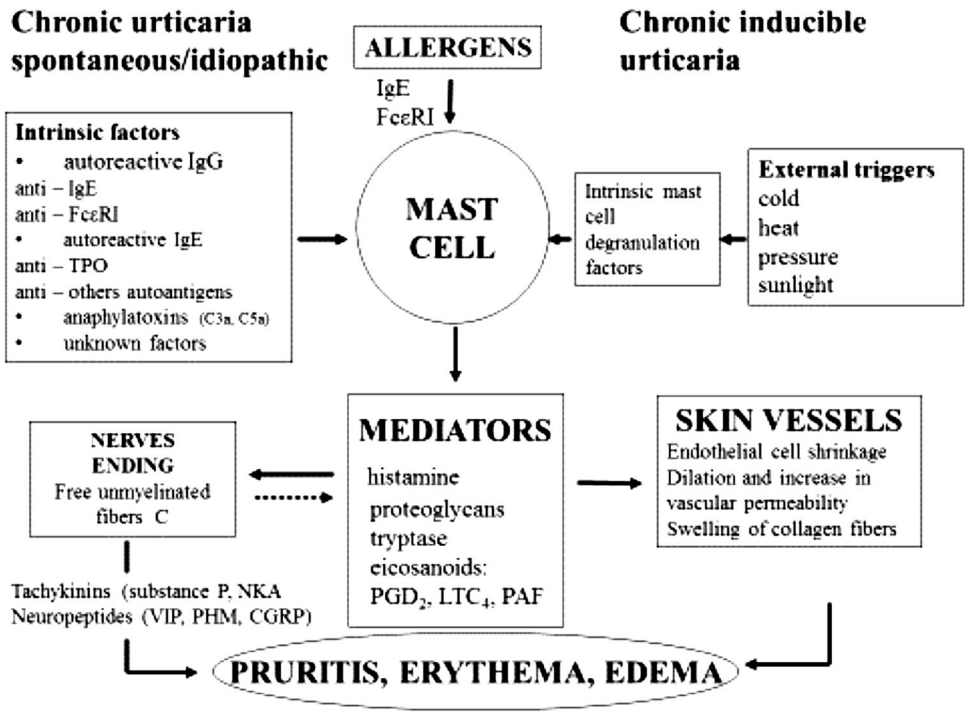

Fig. 1 Final common pathway in various types of chronic urticaria with pivotal role of mast cell stimulated by internal and external inflammatory triggers. *NKA* Neurokinin A, *VIP* vasoactive intestinal peptide, *PHM* peptide histamine methionine, *CGRP* calcitonin gene-related peptide, PGD_2 prostaglandin D2, LTC_4 leukotriene C4, *PAF* platelets activating factors

urticaria and atopic dermatitis than in healthy subjects, but no differences in the anti-dsDNA IgG levels were observed. The aforementioned phenomena may promote (priming) the activity of mast cells/basophils in CSU that easily degranulate when influenced by various inner (autoreactive IgG against IgE and FcεRI, autoreactive IgE for self-antigens) and outer factors (cold, heat, pressure) or allergens (Confino-Cohen et al. 2012; Lourenço et al. 2008). Our knowledge about the role of allergens and specific IgE in pathogenesis of CSU is rather obscure, usually allergens are considered to induce acute urticaria. Despite the fact that CSU is not an allergic disease, IgE sensitization is higher in chronic urticaria patients than in the global adult population, suggesting that it is one, even exceptional, important etiopathogenic factor in chronic urticaria (Augey et al. 2011). Thus allergens, as external factors may participate in chronic urticaria pathology like one from multiple factors, causing mastocyte/basophil priming in CSU-CINDU (Fig. 2).

New insight into the pathogenesis of chronic urticaria forced a change in viewpoint on topics concerning the classification of this complex syndrome. Acknowledged external trigger factors, for example, heat, cold, pressure, sunlight are responsible for developing CINDU, whereas internal trigger factors causing CSU sometimes may not be identified (Zuberbier et al. 2014). Thus, according to current knowledge about the etiopathogenesis of chronic urticaria, in the CSU, the subtypes with the identified internal factors indicating the autoimmune disease and subtypes with unknown internal factors, which define the illness as the idiopathic form (CIU: chronic idiopathic urticaria) can be distinguished (Confino-Cohen et al. 2012).

The complexity of pathophysiological mechanism of CSU is reflected in an interesting study conducted by Bossi et al. (2011), which revealed the increase of skin vascular permeability due to histamine and other mediators released from patient's serum samples stimulated mastocytes devoid high affinity IgE receptors. As in many other works concerning the CSU, the above mentioned authors have not shown any factor of patient's sera which could be responsible for degranulation of mastocytes, but undoubtedly mast cells activating factors were other than anti-FcεRI, anti-IgE autoantibodies or autoreactive IgE.

Autoantigens Reacting with IgE, as Potential Internal Trigger Factors in Chronic Urticaria

Self-antigens are a hallmark of any autoimmune disease and play a key role in induction of the autoimmune response. Altered immune tolerance leads to autoantibody production and triggers the autoimmune inflammation. Autoimmune diseases are associated mostly with IgG autoantibodies, however, the role of other classes of immunoglobulins, especially IgE, in autoimmune pathology has recently been discussed (Charles and Rivera 2011). Dema et al. (2014) presented the broad spectrum of IgE autoantibodies and their possible association with systemic lupus erythematosus (SLE), especially lupus nephritis. Autoreactive IgE are also present, coexisting with

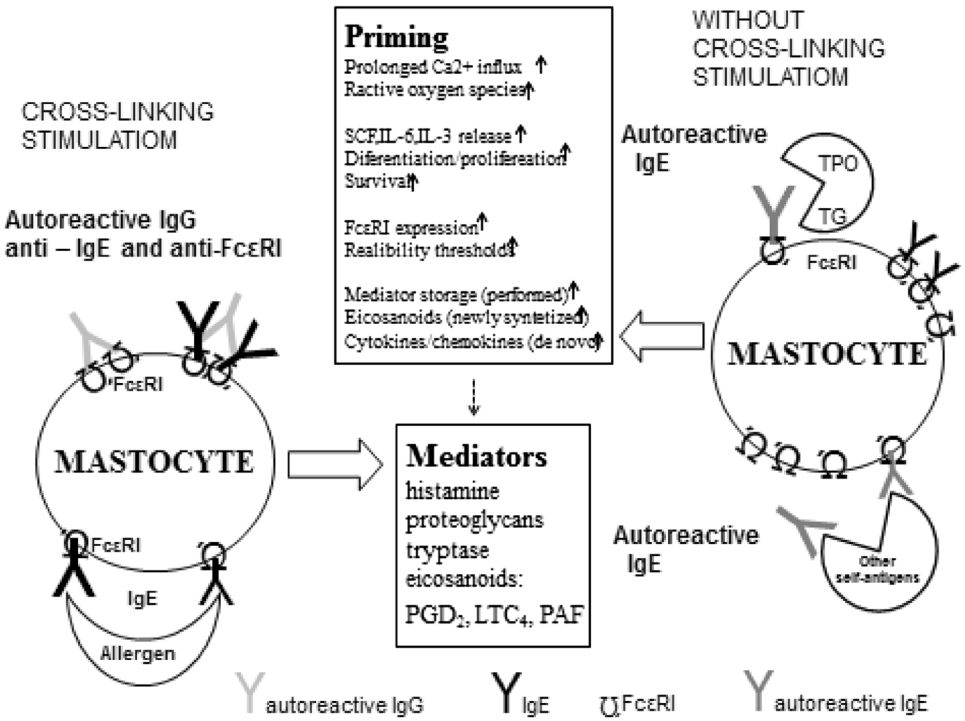

Fig. 2 Possible mast cell priming pathway including heterogeneous effects of monomeric IgE due to cross-linking and without cross-linking stimulation of FcεR1 on mastocytes in CSU/CINDU. *TPO* thyreoperoxidase, *TG* thyroglobuline, PGD_2 prostaglandin D2, LTC_4 leukotriene C4, *PAF* platelets activating factors

autoantibody IgG, in many autoimmune diseases in which they enhance inflammatory processes, and by their immunoregulatory capacities, facilitate the amplification of autoimmune inflammation, contributing to the progression of organ damage (Altrichter et al. 2011). The presence of IgE autoantibodies was also revealed in rheumatoid arthritis (Permin and Wiik 1978). The list of self-antigens capable of stimulating IgE autoantibodies production is still growing and includes: antinuclear antigens (ANA), dsDNA in SLE, single stranded DNA in SLE (Dema et al. 2014), Smith antigen in SLE, soluble nuclear antigens of the SS-B type in Sjögren syndrome, soluble nuclear antigens of the SS-A type in Sjögren syndrome, anti-BP180 and anti-BP230 in bullous pemphigoid (Ishiura et al. 2008), anti-TPO and anti-thyroglobulin in Hashimoto thyroiditis (Ishiura et al. 2008; Maurer et al. 2011). Thus, the connection between autoreactive IgE and self-antigens suggests the correlation of CSU and other autoimmune diseases (Confino-Cohen et al. 2012). CSU put in the scheme of autoreactive IgG and autoreactive IgE seems to be either a kind of autoimmune disease or a clinical manifestation of some other defined autoimmune diseases or both, in which self-antigens reacting with IgE may be internal trigger factors, activating or degranulating mastocytes/basophils (Hatada et al. 2013).

Autoreactive IgE in chronic urticaria and its role in mastocyte/basophil priming IgE mediated response to the allergen is based on the binding of the allergen to the Fab fragments of IgE which is linked to high affinity receptor for IgE (FceRI), that is located on the surface of basophil or mast cell (Wang and Clement 2000). This leads to degranulation of mast cells/basophils and in consequence to the release of histamine, sulphidoleukotrienes and interleukins (ILs), which are responsible for the immediate allergic reaction (Twaroch et al. 2015).

To activate mast cells for secretion of inflammatory mediators, the binding of two or more IgE molecules by allergen is necessary (cross-linking) (Kitaura et al. 2003). Clustering intracellular domains of Fc receptors which are associated with cross linked IgE molecules results in a complex sequence of reactions within the mast cell which lead to its activation (Lee et al. 2012). Transduction of the signal from FcεRI is mediated and regulated via kinases and phosphatases which in consequence impact the presence of IP-3 in cells and Ca^{2+} mobilization from endoplasmic reticulum (Kopeć et al. 2006).

Recently accumulated evidence has shown that IgE, by binding to FcεRI on mastocytes without FcεRI cross-linking, can promote activity of mast cells (priming), which is demonstrated by such markers of priming, as proliferation and survival of these cells, decreasing the release ability of mediator threshold, increasing the level of their sensitivity to various stimuli and ability to synthesize *de novo* inflammatory mediators and cytokines (Asai et al. 2001; Kitaura et al. 2003) (Fig. 2). Basophils and mast cells are the main target cells in CSU/CINDU and they may present higher susceptibility to degranulation, which is the essence of priming phenomenon, and production of pro-inflammatory factors without degranulation in active phase of the disease (Chang et al. 2015) (Fig. 2). Recent data emphasize

the role of blood basophils in CSU manifestation, because in active stage of the disease, reduction of cells number in blood (basopenia) is observed, due to autoantibody mediated sequestration and elimination of basophils coexisting with the recruitment of blood basophils to skin urticarial lesions (Saini 2009). Until now, no external factor which could activate basophils in this way has been revealed, therefore, it can be assumed that trigger factor may be a self-antigen linking with the autoreactive IgE and affecting basophil/mastocyte priming phenomenon (Chang et al. 2015). Changes in IgE receptor-signaling molecule expression levels together with the altered degranulation ability of blood basophils are a manifestation of this phenomenon in active CSU patients. This situation may arise from the heterogeneity of IgE or up regulation of certain genes controlling the production of many pro-inflammatory cytokines, chemokines and adhesion molecules (Jayapal et al. 2006; Kitaura et al. 2003).

For many years it seemed interesting that, in general, basophils from CSU patients poorly responded to stimulation with a variety of factors (FLMP, PAF, bradykinin, MCP-1, C5a) including the anti-IgE (Greaves 2003). Luquin et al. (2005) confirmed hypo-responsiveness of these cells to many stimuli, but surprisingly enough they also observed the increased responsiveness of basophils of patients with chronic urticaria to different sera regardless of their origin, i.e., patient's sera and even healthy subject's sera. The serum factor was not identified then, but from contemporary point of view in these sera such factors as self-antigens for autoreactive IgE or other pro-inflammatory factors including cytokines, that comprise abnormal regulation of signaling pathways of basophils could occur. Above all, an extraordinary therapeutic effect of anti-IgE therapy by means of omalizumab in CSU/CINDU, irrespective of its etiology, speaks for such a scenario (Chang et al. 2015).

Furthermore, IgE-FcεRI connection potentiates the ability of mast cells to store and synthesize *de novo* inflammatory mediators and cytokines, which could change the relation between anti-IgE, IgE and FcεRI (Matsuda et al. 2005). Indeed, Lourenço et al. (2008) have shown that basophils of patients with CSU pretreated with IL-3 and then stimulated with anti-IgE, demonstrated a functionally activated profile, possibly due to in vivo priming. The authors proved that blood basophils of patients with CSU were reduced in number and displayed increased surface expression of FcεRIα, which was positively correlated with the IgE serum levels. Moreover, high expression of IL-3 receptor on basophils was detected only in positive autologous serum skin test ($ASST^{+}$) of patients with CSU but pretreatment with IL-3 upregulated histamine excreting function of blood basophils and induced a quick hyper-responsiveness to anti-IgE cross-linking on basophils of all patients with CSU as compared to healthy controls. Thus, skin mast cells in patients with CSU become more sensitive and unstable or activated as the result of certain abnormal factors in their milieu. In other words, mastocyte/basophils are standing by to response to some stimuli regardless of their immunological (CSU) or physical (CINDU) proveniences.

Autoimmune Nature of Chronic Urticaria

The autoimmune nature of CIU/CSU has been recognized by many researchers for over 40 years. Rorsman (1962) was the first who noticed that particular feature, but the most important works on the subject were published in the 80s and the 90s of the twentieth century.

Early developed studies concerned mainly occurrence of self-antigen IgG autoantibodies with absence or observed in the minority autoreactive IgE in chronic urticaria (Bar-Sela et al. 1999; Concha et al. 2004; Tedeschi et al. 2001). Decade later, Altrichter et al. (2011) have found in 54 % cases with CSU enhance of IgE anti-TPO and such discrepancy of results may be due to progress in laboratory technics but also reflects the scale of the problems concerning etiopathogenesis of the disease.

The main finding, which supports the hypothesis of autoimmune disorders, as important pathogenic aspect in CIU/CSU, was detection of serum IgG antibodies anti-IgE by Gruber et al. (1988) and anti-FcεR1α by Hide et al. (1993). The process of cross-linking adjacent FcεR1 receptors by these autoantibodies induces their dimerization and cell activation. Anti-IgE autoantibodies work in a similar way, namely they cross-link two IgE located nearby on mast cells or basophil surface, and subsequently activate the effector cells (Yalcin 2014).

Autoantibodies activating mast cells and basophils, which release histamine and other pro-inflammatory factors are called functional. These autoantibodies may bind FcεR1α and activate basophils or mast cells even when IgE has been removed from its natural receptor-FcεR1 (Horn et al. 2001). According to some hypothesis, the change in the receptor occupancy by IgE, may be triggered by cold, heat, pressure and result in urticaria appearance (Miescher et al. 2001). The prevalence of different types of autoantibodies in patients with CIU/CSU was evaluated by Sabroe et al. (2002). They have found that 26 % of patients had immunoreactive histamine-releasing anti-FceRI autoantibodies and 9 % of them had anti-IgE autoantibodies. The other possible mechanism of autoimmune disorders in chronic urticaria was presented by Puccetti et al. (2005), who have reported that antibodies against FcεRII/CD23 induce indirect basophil degranulation via eosinophil activation, and by Grattan et al. (1995), who showed the presence of endothelial autoantibodies in CSU patients.

The most commonly used diagnostic tool in clinical practice in CIU/CSU is ASST. ASST, according to EAACI/GA2LEN task force consensus report (Konstantinou et al. 2009, 2013) is defined as an in vivo test, which assesses autoreactivity to intradermally injected factors of autologous serum, acting either indirectly through the release of mediators from cutaneous mast cells or other cells or directly on the microvasculature of skin. Autoreactivity does not define autoimmune urticaria, but may point to the occurrence of mast cell activating autoantibodies in $ASST^+$ CSU patients (Staubach et al. 2006). Occurrence of functional autoantibodies should be confirmed by the basophil histamine release assay, and their specificity is evaluated with the use of either Western blot, ELISA, or immunoenzymetric assays (Caproni et al. 2004). In addition to the basophil histamine release assay, the flow cytometric basophil activation test is a valuable tool to assess the expression of basophil activation markers (CD63, CD203) after stimulation by autoreactive serum factors which occur in CSU (Frezzolini et al. 2010; Kang et al. 2014).

Patient suffering from CSU with positive ASST usually experience more severe course of the disease (Nettis et al. 2002). The developed studies have documented more weals, systemic symptoms, higher itch scores, greater frequency of urticarial episodes and antihistamines consumption in these patients (Sabroe et al. 1999).

The prevalence of autoimmune diseases is higher among chronic urticaria $ASST^+$ patients (Asero et al. 2003, 2005; Caminiti et al. 2005; Permin and Wiik 1978; Sabroe et al. 1999). In addition $ASST^+$ patients have more often augmented levels of autoimmune markers like rheumatoid factor and antinuclear antibodies (De Swerdt et al. 2005; Ryhal et al. 2001).

In addition, patients with CIU/CSU, especially $ASST^+$, have distinctive genetic features. Greater prevalence of HLA-B*50, together with significant positive association between the presence of anti-TPO and ANA was found in these patients, that suggests the possibility of an autoimmune mechanism being the triggering factor for CSU (Calamita and Pelá Calamita 2013). HLA allele DRB1*04 and DQB1*0302 are more frequently present in these patients, than in healthy population (Aydogan et al. 2006; Oztas et al. 2004). What is more, DRB1*04 and DQB1*0301/4 are significantly more common in $ASST^+$ CSU patients than in ASST-negative ones (O'Donnell et al. 1999).

Therapeutic Implications and Final Remarks

The most important arguments supporting autoimmune nature of CSU include the presence of functional IgG and IgE autoantibodies and their correlation with disease severity (Konstantinou et al. 2009, 2013) and reproducibility of ASST through passive transfer of serum of affected patients into the skin of healthy ASST-negative individuals (Grattan and Francis 2000). To a certain extent, the association of particular HLA haplotypes and other autoimmune diseases with CSU (Aydogan et al. 2006) and symptoms improvement after immunosuppressive treatment (Boguniewicz 2008) may suggest autoimmune context of pathogenesis of CSU.

The gold standard in CSU/CINDU treatment are non sedative second generation antihistamines, but even used at fourfold increasing dose they ensure a therapeutic efficacy in about 60 % of patients only (Zuberbier et al. 2014). For patients unresponsive to antihistamines and added anti-leukotrienes, immunosuppressive agents have long been used including systemic steroids and cyclosporine (Panaszek and Basińska 2006). These drugs, however, have some adverse effects. Therefore, biological agents provided in the form of monoclonal antibodies, which have anti-inflammatory effects, interfering with pathway characteristic for chronic urticaria are still being sought (Makris et al. 2014).

Case reports published in recent years, have suggested high efficacy of omalizumab in chronic urticaria refractory to conventional therapy. Casuistic observations led to the development of well planned multicenter and multiphase randomized placebo controlled clinical trials. The first one conducted by Maurer et al. (2011), which was critical for developing consecutive clinical trials, revealed high effectiveness and safety of omalizumab in treatment of this disease (Kaplan et al. 2013; Maurer et al. 2013; Saini et al. 2015). Administration of omalizumab, due to its ability to reduce free monomeric IgE with FcεRI downregulation, diminishes the various effects of IgE, being able to maintain and enhance mast cell activities and hereafter reduces the ability of mast cells to manifest inflammatory mechanisms in patients with CSU (Savage et al. 2012). Furthermore, omalizumab may neutralize autoantigens which are captured by omalizumab–IgE complexes (Saini et al. 2015). Other biologicals applied in chronic urticaria, such as TNF-α-antagonists and rituximab are tested in small clinical studies and described in some case reports (Makris et al. 2014).

There are still at least two problems which should be solved in reference to the common final pathway in CSU/CINDU that is inflammatory activity of mast cells in affected skin in different types of urticaria. Although for the CINDU subtypes, there are identifiable external triggers, the intrinsic pathologic factors that transduce external signals to activate mast cell have not been identified yet. The second issue in CSU, if considered at least 20–30 % of cases of CSU as autoimmune syndrome dependent on the presence of intrinsic autoantigens with autoreactive IgE and IgG, is the fact that in some cases the internal triggers

may not be recognized. These subtypes of chronic urticaria still remain idiopathic.

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