Autoimmune chronic spontaneous urticaria: What we know and what we do not know

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Chronic spontaneous urticaria (CSU) is a mast cell–driven skin disease characterized by the recurrence of transient wheals, angioedema, or both for more than 6 weeks. Autoimmunity is thought to be one of the most frequent causes of CSU. Type I and II autoimmunity (ie, IgE to autoallergens and IgG autoantibodies to IgE or its receptor, respectively) have been implicated in the etiology and pathogenesis of CSU. We analyzed the relevant literature and assessed the existing evidence in support of a role for type I and II autoimmunity in CSU with the help of Hill's criteria of causality. For each of these criteria (ie, strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy), we categorized the strength of evidence as "insufficient," "low," "moderate," or "high" and then assigned levels of causality for type I and II autoimmunity in patients with CSU from level 1 (causal relationship) to level 5 (causality not likely). Based on the evidence in support of Hill's criteria, type I autoimmunity in patients with CSU has level 3 causality (causal relationship suggested), and type II autoimmunity has level 2 causality (causal relationship likely). There are still many aspects of the pathologic mechanisms of CSU that need to be resolved, but it is becoming clear that there are at least 2 distinct pathways, type I and type II autoimmunity, that contribute to the pathogenesis of this complex disease. (J Allergy Clin Immunol 2017;139:1772-81.)

Key words: *Chronic spontaneous urticaria, autoimmunity, IgE–anti-self, IgG–anti-FcεRI/IgE, causality, Hill's criteria of causality*

Abbreviations used
AAb: Autoantibody
ASST: Autologous serum skin test
BAT: Basophil activation test
BP: Bullous pemphigoid
CSU: Chronic spontaneous urticaria
dsDNA: Double-stranded DNA
SLE: Systemic lupus erythematosus
TPO: Thyroperoxidase

Chronic spontaneous urticaria (CSU) is a mast cell–driven skin disease characterized by the recurrence of transient wheals (hives), angioedema, or both for more than 6 weeks.[1] Several mechanisms have been investigated as possibly contributing to the pathogenesis of CSU, including infections, food intolerance, coagulation cascade, genetic factors, and autoimmunity.[1] Autoimmunity (ie, autoimmune mechanisms of skin mast cell activation) is held to be a frequent underlying cause of CSU. Two types of Gell and Coombs hypersensitivity reactions[2] have been postulated to be relevant in patients with autoimmune CSU.

A type I hypersensitivity to self, also called autoallergy, in which antigens crosslink the IgE on mast cells and basophils to cause release of vasoactive mediators (Fig 1), was first suggested by Rorsman[3] in 1962 to explain urticaria-associated basopenia. A role of autoallergy in urticaria was also postulated from the finding in 1999 of IgE autoantibodies (AAbs) against the thyroid microsomal antigen in the serum of a female patient with CSU.[4] This work has been confirmed and extended to propose autoallergy in the pathogenesis of both CSU and chronic inducible urticaria.[5-10]

A Type II hypersensitivity reaction in which antibodies, usually IgG or IgM, bind to antigen on a target cell (Fig 1) was originally postulated after the identification of IgG-AAbs against IgE in 3 of 6 patients with CSU.[11] The presence of these AAbs was confirmed by Grattan et al[12] in 1991 in patients whose sera induced a wheal-and-flare response when injected intradermally: the autologous serum skin test (ASST). The presence of AAbs to the high-affinity receptor for IgE on mast cells and basophils (IgG–anti-FcεRI) in a subset of patients with CSU was reported by the same group 2 years later.[13] In theory, IgG–anti-FcεRII/CD23 AAbs that were identified in sera of patients with CSU can also elicit mast cell degranulation through activation of eosinophils, with the consequent release of major basic protein and other mast cell secretagogues (Fig 1).[14]

We assessed the evidence for a role of these 2 forms of autoimmunity in patients with CSU using Hill's 9 criteria of

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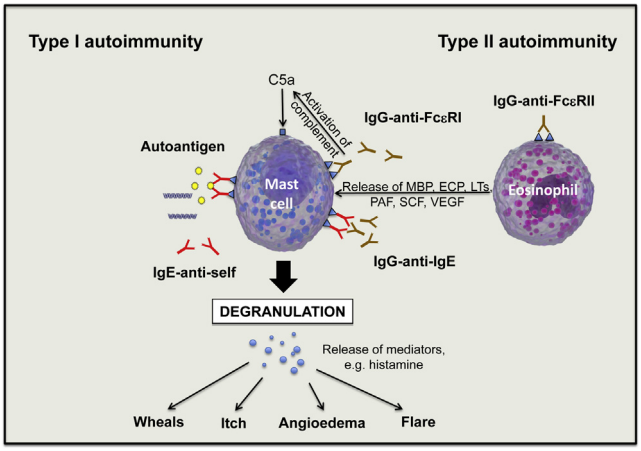

FIG 1. Mechanisms of mast cell activation in patients with chronic spontaneous autoimmune urticaria. *Type I autoimmunity*: Type I autoantigens ("autoallergens") can activate mast cells and basophils by crosslinking IgE-AAbs. *Type II autoimmunity*: IgG-AAbs can do the same by binding to IgE or to FcεRI, which might involve complement C5a and the CD88/C5aR receptor. IgG-AAbs against the low-affinity IgE receptor (FcεRII) might activate eosinophils and induce subsequent mast cell degranulation. *ECP*, Eosinophil cationic protein; *LTs*, leukotrienes; *MBP*, major basic protein; *PAF*, platelet-activating factor; *SCF*, stem cell factor; *VEGF*, vascular endothelial growth factor.

causality, which were developed by Sir Austin Bradford Hill, an English epidemiologist and statistician, as a research tool for the medical field (Table I).[15,16] These criteria should be viewed as guidelines rather than a checklist of definite causes. Furthermore, Hill did not indicate how many of the 9 criteria need to be fulfilled to define the relationship as causal. When we reviewed the data on autoimmunity and CSU, we categorized the strength of evidence for each criterion as "insufficient," "low," "moderate," or "high" (Tables II and III), as previously described.[17,18] Finally, we assigned established levels of causality based on Hill's criteria (Table IV, see the "Systematic review methodology" in this article's Online Repository at www.jacionline.org).[19]

1: STRENGTH OF ASSOCIATION AND 2: CONSISTENCY

Type I autoimmunity

The strength of association between IgE-AAbs and CSU is currently unknown, and the relative risks have not been assessed. Six independent studies from different teams evaluated the link between CSU and IgE-AAbs, such as IgE–anti-double-stranded DNA (dsDNA)[9] and IgE–anti-thyroperoxidase (TPO; Table V).[5,6,10,20,21] Three of these studies show that serum levels of IgE-AAbs (anti-dsDNA or anti-TPO) are significantly higher in patients with CSU than in healthy subjects.[6,9,10]

Three studies failed to reproduce an association between IgE-AAbs and CSU.[5,9,20] In the first of these studies, all of 23 patients with CSU showed serum IgG–anti-TPO, but no patient had positive results for IgE–anti-TPO.[20] In the second study only 2 of 20 patients with CSU with IgG–anti-thyroid antibodies had detectable IgE–anti-thyroid antibodies.[5] In the third study Hatada et al[9] did not find differences in levels of IgE against thioredoxin, peroxiredoxin, or thyroglobulin between patients with CSU and healthy subjects. A radioimmunoassay or direct ELISA[5,9,20] approach was used in all 3 studies, where IgG-AAbs to the antigen can mask the presence of IgE-AAbs because competition.[22] In contrast, Altrichter et al,[6] who showed a high prevalence of IgE–anti-TPO in patients with CSU, used a site-directed human IgE capture ELISA in which IgE–anti-TPO does not compete with IgG–anti-TPO antibodies.

Strength of evidence: Low

Type II autoimmunity

Although the presence of IgG-AAbs to IgE and FcεRI has been repeatedly observed in patients with CSU (Table VI),[11,23-40] the strength of association and relative risks have not been formally assessed. However, many independent studies have reported higher rates of IgG–anti-IgE, IgG–anti-FcεRI, or both in immunoassays in patients with CSU in comparison with healthy control subjects,[23-26] atopic patients,[27,28] patients with inducible urticaria,[24] and patients with psoriasis.[28] This was not the case in all studies.[29-33]

The rates of IgG–anti-FcεRI positivity in patients with CSU were investigated by 14 studies, and the prevalence of these AAbs ranged from 4% to 64%. In healthy control subjects the prevalence of IgG–anti-FcεRI ranged from 0% to 57%, as reported by 10 studies (Table VI). Rates of IgG–anti-IgE positivity in patients with CSU ranged from 0% to 69% (7 studies) compared with 0% to 30% in healthy control subjects (6 studies, Table VI). In all studies IgG-AAbs were detected by means of Western blotting, ELISA, or both or immunoenzymetric assays.

Strength of evidence: Moderate

3: BIOLOGICAL PLAUSIBILITY AND 4: COHERENCE

Type I autoimmunity

Several independent findings support the plausibility and coherence of type I autoimmunity as a relevant cause of CSU (Table VII).[6,9,10,41-44] IgE-AAbs in the blood of patients with CSU, such as IgE–anti-TPO and IgE–anti-dsDNA, have been shown to bind to basophils and to induce degranulation after interaction with their specific antigen.[9,10]

A second reason why it is plausible that IgE–anti-self can induce the signs and symptoms of CSU is the analogy with acute urticaria caused by IgE-mediated immediate hypersensitivity. IgE against a wide range of environmental allergens is known to cause acute urticaria.[63] Also, IgE-AAbs in some patients with CSU might contribute to higher levels of total IgE,[10] which was proposed to be a potential marker for severe CSU.[64] One study reported significantly higher levels of total IgE in patients with urticaria with IgE–anti-TPO compared with those without AAbs.[10] Additional evidence-based arguments for the coherence of type I autoimmunity as a cause of CSU are that other autoimmune diseases are common comorbidities of patients with CSU[6,41] and that wheals in patients with CSU show features of IgE/allergen-induced late-phase cutaneous reactions, including T-cell infiltrates (Table VII).[42-44]

Strength of evidence: Moderate for biological plausibility and high for coherence

Type II autoimmunity

Direct evidence that type II autoimmune CSU, according to the revisited Witebsky's postulates,[65] is plausible comes from studies that show that IgG-AAbs from the serum of patients with CSU are