

Correspondence

Autoimmune chronic spontaneous urticaria*To the Editor:*

Kolkhir et al¹ provide a welcome and comprehensive review of the literature on IgE and IgG autoantibodies in patients with chronic spontaneous urticaria (CSU) and the evidence for their relevance to disease pathogenesis. I would like to clarify 3 points arising in their article.

First, they propose a model of urticaria pathogenesis based on Gell and Coombs types I (anaphylactic) and type II (cytotoxic/cytolytic) hypersensitivity.² Through this model, they propose that specific IgE to soluble autoantigens, including thyroid peroxidase, can initiate mast cell degranulation, resulting in release of histamine and other proinflammatory mediators in patients with CSU (a type I response). They also examine the evidence for IgG autoantibodies causing degranulation by binding IgE or the high-affinity IgE receptor FcεRI on mast cells and basophils and refer to this as type II hypersensitivity. However, Gell and Coombs defined a type II reaction as being initiated by antibody reacting to either an antigenic component of the tissue cell or an antigen that has become intimately associated with tissue cells in which complement is usually, but not always, necessary to effect cellular damage rather than stimulation. Kay³ proposed a modification of the Gell and Coombs classification in 2008 to distinguish receptor-mediated stimulation of mast cells and basophils by anti-FcεRIα autoantibodies (type 2b), as seen in patients with chronic urticaria, Graves disease, and myasthenia gravis from cytotoxic/cytolytic hypersensitivity (type 2a) involving complement-induced lysis, seen in some drug and transfusion reactions. The term type V hypersensitivity reaction has also been proposed to account for stimulation of a target cell population by autoantibodies, notably Graves disease, in which antibodies bind to and stimulate the thyroid-stimulating hormone receptor, but Weetman⁴ also cites chronic urticaria as an example.

Second, the authors observe that antibodies involved in type II reactions are usually IgG or IgM but do not find direct evidence for IgM autoantibodies in patients with CSU, even though there is indirect evidence that they might be relevant. Gruber et al⁵ described IgM anti-IgE autoantibodies using an enzyme immunoassay in sera of 2 patients with cold urticaria, one of which released histamine, but not from patients with chronic (spontaneous) urticaria or urticarial vasculitis. Immunoabsorption of IgM from the serum fractions of 3 patients with CSU from which IgG had been removed already almost abolished residual histamine release from healthy donor basophils, although the eluted IgM fraction had minimal functional activity.⁶ Therefore it is possible that IgM autoantibodies to IgE or FcεRIα can occur in patients with CSU, and more research is needed.

Third, Kolkhir et al¹ describe testing IgG autoantibodies in patients with CSU for functional activity through use of a basophil activation test but do not distinguish between the basophil histamine release assay (BHRA) and detection of basophil membrane activation marker expression by using flow cytometry (basophil activation test [BAT]). These tests have different methodologies with different outcomes and might carry different interpretations. In the BHRA serum from the patient is incubated with basophils from a healthy donor. Any resulting histamine release is expressed as a percentage of total histamine. By contrast, the BAT is most commonly used in the context of food allergy when autologous IgE-primed basophils are activated by allergens; it has been used as a test for activation marker upregulation in heterologous basophils after incubation with sera from patients with chronic urticaria. Because the principle of using an indirect measure of basophil activation (histamine) in the BHRA is different from looking for direct evidence of activation marker upregulation in the BAT, it is preferable to keep these terms distinct. The correlation coefficient between CD63 expression on healthy donor basophils induced by serum from patients with chronic urticaria and the BHRA result in one study was low, but concordance between the 2 tests was higher; the BHRA showed higher sensitivity for a positive autologous serum skin test result.⁷

Clive Grattan, MA, MD, FRCP

From Guy's Hospital, London, United Kingdom. E-mail: clive.e.grattan@gstt.nhs.uk.
Disclosure of potential conflict of interest: C. Grattan declares that he has no relevant conflicts of interest.

REFERENCES

1. Kolkhir P, Church MK, Weller K, Metz M, Schmetzer O, Maurer M. Autoimmune chronic spontaneous urticaria: what we know and what we do not know. *J Allergy Clin Immunol* 2017;139:1772-81.
2. Gell PGH, Coombs RRA. The classification of allergic reactions underlying disease. In: Coombs RRA, Gell PGH, eds. *Clinical aspects of immunology*. London: Blackwell; 1963:317-37.
3. Kay AB. Allergy and hypersensitivity: history and concepts. In: Kay AB, Kaplan AP, Bousquet J, Holt P, eds. *Allergy and allergic diseases*. 2nd ed. Oxford (United Kingdom): Wiley-Blackwell; 2008:19.
4. Weetman AP. Hypersensitivity: stimulatory (type V). Wiley (NY): *Encyclopedia of Life Sciences*; 2001; pp 1-6.
5. Gruber BL, Baeza ML, Marchese MJ, Agnello V, Kaplan AP. Prevalence and functional role of anti-IgE autoantibodies in urticarial syndromes. *J Invest Dermatol* 1988;90:213-7.
6. Grattan CEH, Francis DM, Hide M, Greaves MW. Detection of circulating histamine releasing autoantibodies with functional properties of anti-IgE in chronic urticaria. *Clin Exp Allergy* 1991;91:695-704.
7. Altrich ML, Helsey JF, Altman LC. Comparison of the in vivo autologous skin test with in vitro diagnostic tests for diagnosis of chronic autoimmune urticaria. *Allergy Asthma Proc* 2009;30:28-34.

<https://doi.org/10.1016/j.jaci.2017.09.014>