

Letter to the editor

Relevance of (IgG anti-IgE)-IgE complexes, IgG subclass and modern IgG antibody autoanalyzers in the dying IgG reagin story

The authors of the position paper on food-specific IgG4 and its lack of diagnostic utility are to be commended for their excellent 2008 report (1). Laboratory testing for reagenic IgG antibodies to foods in the serum of patients, when IgE-mediated food allergy cannot be established using validated assays, is a world-wide problem. In the position paper (1), Stapel et al. summarize the commonly held rationale for IgG reagenic antibodies that involves basophil histamine release (BHR) following incubation with monoclonal anti-human IgG4. It is worth extending this mechanistic discussion to include the 1992 work of Lichtenstein et al. (2). In contrast to the previous studies (e.g. 3) that used basophils almost exclusively from non-atopic donors, Lichtenstein used basophils from atopic and nonatopic donors. No histamine release (<10%) was detected from any of 13 nonatopic donor cells following incubation with a panel of highly specific IUIS-documented human IgG subclass-specific monoclonal antibodies (4), while 85% of the same cells released to anti-IgE. In contrast, 75% of atopic donor cells released >10% histamine to one or more human anti-IgG subclass-specific monoclonal antibodies.

Fluid phase inhibition, lactic acid treatment and passive sensitization were performed to confirm specificity of anti-IgG induced BHR (2). Fluid phase IgE inhibited anti-IgE but not anti-IgG induced histamine release. Lactic acid treatment ablated anti-IgG induced BHR. Passive

sensitization with purified IgG myeloma proteins could not restore BHR, indicating IgG interactions with low affinity IgG Fc receptors on basophils are not the major mechanism for anti-IgG induced BHR. These results indicated that IgG antibodies were complexed to IgE and resident on the basophil surface by means of IgE Fc receptors.

When all IgE (and presumably IgG anti-IgE complexes) were removed from an IgG responder's serum, the adsorbed serum was no longer able to passively sensitize basophils for subsequent anti-IgG induced BHR (2). In contrast, the same serum sham-adsorbed effectively sensitized basophils for release by anti-IgG monoclonal antibodies. These data implicated (IgG anti-IgE) IgE complexes in the sera and on the cells of donors that release to anti-IgG monoclonal antibodies.

Serum from 'anti-IgG releaser' donors passively resensitized basophils for anti-IgG induced BHR with the same IgG subclass pattern seen with anti-IgG releaser donor's cells. BHR was most commonly induced with two human IgG3 specific monoclonal antibodies that bound hinge region epitopes on all allotypic forms of IgG3 (2). The relative frequency of IgG subclass specificity was IgG3 > IgG2 > IgG1 > IgG4, suggesting that IgG3 antibodies are most often bound to IgE on the basophil surface and/or most readily accessible for cross-linking by monoclonal antibodies, possibly because of their extended rigid hinge region. These

data also emphasize extending this discussion from IgG4 to antibodies of all IgG subclasses.

Circulating IgG anti-IgE autoantibodies and IgG anti-IgE complexes have been detected directly in the serum of the (anti-IgG releasing) donors. The Lichtenstein data have led to a reinterpretation of the findings of IgG-induced mediator release and a further weakening of the argument for the existence of human IgG reagins. It appears that either only atopic individuals possess basophil IgE receptor bound IgG anti-IgE-IgE complexes or only cells from these individuals can be triggered by anti-IgG antibodies that cross-link the IgE receptors through this complex.

Finally, the published IgG4 anti-food data (5) in the position paper (1) are presented as relative percentage binding and arbitrary units. Possibly, it is time to revisit the quantitative aspects of food allergen-specific IgE and IgG antibodies in atopic (food/nonfood allergic) and nonatopic populations using modern quantitative autoanalysers and chip-based technologies (6, 7) that allow both isotypes of food-specific antibodies to be more precisely determined by investigators using the same technology in different parts of the world.

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