Diagnosis and prevention of IgE- and IgG-mediated anaphylaxis
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The classical IgE-, mast cell- and basophil-, FcεRI-, histamine-dependent pathway of anaphylaxis is well established in both humans and mice. This reaction, which requires very little antigen and antibody, probably accounts for all anaphylaxis that is triggered in both species by small quantities of parenterally-inoculated antigen (e.g.; insect stings). In contrast, while IgG can mediate murine anaphylaxis, it is not clear that IgG anaphylaxis occurs in humans. In mice, all three IgG isotypes that can bind to Fcγ receptors (IgG1, IgG2a and IgG2b) can mediate an anaphylactic response that is clinically very similar to that mediated by IgE; however, murine IgG-mediated anaphylaxis requires approximately 100-fold more antigen and antibody than murine IgE-mediated anaphylaxis. As a result, IgG antibodies can block IgE-mediated anaphylaxis (by binding allergen before it can reach mast cell IgE and by activating an inhibitory Fcγ receptor) when allergen quantities are small, but mediate anaphylaxis when allergen is present in a relatively large quantity. Murine IgG-dependent anaphylaxis has a considerably different pathogenesis than IgE anaphylaxis, in that it is mediated by activating Fcγ receptors (FcγRI, FcγRII and FcγRIII) on macrophages, neutrophils and basophils, which produce platelet activating factor that, like histamine, increases vascular permeability and smooth muscle contractility. The induction of diarrhea and shock within minutes after oral antigen inoculation in murine models of food allergy appears to be entirely IgE-mediated, with IgG antibody having a potential disease blocking role. This is consistent with requirements for systemic absorption of ingested antigens to induce anaphylaxis and with the small amounts of ingested antigen that are systemically absorbed in a sufficiently intact form to induce this disease.

Based on the murine observations, IgG-mediated anaphylaxis might be most likely to occur in humans who have been repeatedly injected with large quantities of a foreign immunogenic molecule. Consistent with this, anaphylactic responses have been reported to occur in people who have antigen-specific IgG antibodies but no detectable antigen-specific IgE antibodies and no evidence of increased mast cell degranulation (i.e.; increased serum tryptase), after repeated injection of a large quantity of foreign antigen (e.g.; chimeric IgG monoclonal antibodies, dextran, aprotinin, IgA-containing plasma (in IgA-deficient individuals) or purified von Willibrand’s factor (in patients who lack that clotting factor)).

The different pathogenic mechanisms involved in IgE- vs. IgG-mediated anaphylaxis leave different “footprints” in blood cells and serum, at least in the mouse. Because IgE-, but not IgG-mediated anaphylaxis induces considerable mast cell degranulation and basophil IL-4 production, it is accompanied by increased serum tryptase levels (in humans) or mouse mast cell protease 1 levels (in mice) and IL-4-induced increases in soluble IL-4Rα levels in serum and CD8+ T cell membrane IL-4Rα expression (so far, only demonstrated in mice). In contrast, because the IgG/allergen complexes that cause IgG-mediated anaphylaxis modulate FcγRIII, IgG-, but not IgE-mediated anaphylaxis is associated (in mice) with decreased neutrophil expression of FcγRIII. We are currently studying Crohn’s disease patients who are repeatedly inoculated with the therapeutic chimeric anti-TNF monoclonal antibody, infliximab, to determine whether the reactions that occur with ~5% of infusions show the footprint of IgG-mediated anaphylaxis that we have observed in mice.

Recently, we have applied a rapid desensitization approach, by injecting sequentially doubling doses of anti-FcεRIα mAb or FcγRII/RIII mAb every hour into mice, starting with a dose too small to induce perceptible disease and finishing with a dose that would normally induce IgE- or IgG-mediated anaphylaxis, respectively. Our results indicate that this procedure can be administered without inducing perceptible illness and respectively blocks IgE- or IgG-mediated anaphylaxis. Indeed, these procedures were less likely than rapid desensitization with an allergen to induce hypothermia in mice that had previously been sensitized to that allergen by active immunization; furthermore, the anaphylaxis-blocking effect of rapid desensitization with an anti-FcR monoclonal antibody was longer lasting than that of rapid desensitization with the specific antigen and could be safely sustained by repeated injection of the anti-FcR monoclonal antibody. We are currently using humanized mice to develop ways to apply this approach to humans, to make it more rapid and to provide an extra layer of safety by suppressing the ability of even large doses of anti-FcR monoclonal antibody to induce anaphylaxis. Success in this endeavor would provide a way to rapidly and safely suppress all IgE-mediated and much IgG-mediated disease.