

The perfectly potent peanut

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To understand the pathogenesis of allergic inflammation, we must answer a fundamental question: what makes an allergen an allergen?

The molecular dissection of the interaction between host and allergen is providing key insights to answer this elusive question. Conceptually, a complete allergen has properties that facilitate both the induction of an IgE response and the triggering of an IgE-mediated reaction on re-exposure. Proteins that have these features are uncommon,¹ and the structural characteristics that favor induction of IgE may be distinct in some cases from those that favor triggering. For example, in the case of milk allergy, particulate allergens preferentially taken up by Peyer patch M cells are more potent for inducing an IgE response, whereas more soluble allergens, which can be rapidly absorbed across the intestinal epithelium, play a larger role triggering reactions once IgE sensitization is present.²

A growing body of research in the past several years has documented a relationship between inductive allergenicity and activation of the innate immune system.³ Many allergens are now known to behave as adjuvants by a variety of mechanisms. For example, we have previously reported that peanut allergen directly activates human dendritic cells in a manner that favors the induction of T_H2 differentiation.⁴ In this issue of the Journal, investigators from the laboratory of Fred Finkelman at Cincinnati Children's hospital now present data supporting a novel hypothesis that direct allergen activation of the innate immune system could also contribute to triggering a reaction as well (see the article by Khodoun et al in this issue).

In an animal model using mice preconditioned for responsiveness to vasoactive mediators, Khodoun et al demonstrate that intravenous administration of soluble peanut extract (PE) can directly induce anaphylactoid shock by a predominantly complement and platelet activating factor (PAF)-dependent but IgE-independent mechanism. In an elegant series of experiments to explore the mechanisms of shock in this model, they demonstrate that although mast cells are activated, symptoms are dependent on PAF release from macrophages and basophils that have been activated by complement. LPS contamination was excluded as a factor in this model.

How might we extrapolate the findings from this model to generate hypotheses about allergic responses in humans? These animals after all are susceptible only to very high doses of intravenously administered PE, and only after they have been preconditioned with sustained exposure to IL-4 or helminth infection. They are then in addition pretreated with the β -blocker propranolol to enhance reaction severity. Normal healthy animals are not susceptible to direct PE-induced shock and, so far, no cases of anaphylactoid reactions to peanut have been reported in the medical literature.

Although translation of these observations to the human condition initially appears remote, the data that a specific biological pathway is being activated in these animals are very convincing, and the investigators show that this activity is present in other nut extracts, but not present in other common food allergen extracts such as from milk or egg. Further, they demonstrate that PE activates complement in human serum. Interestingly, *in vitro* complement activation has also been reported for at least 1 other allergen extract, *Hymenoptera* venom,⁵ and it is well known that the anaphylatoxins C3a and C5a can activate human basophils and mast cells.

The authors attempt to address the question of clinical relevance in an additional series of experiments. Intravenous administration of PE to healthy mice, although ineffectual by itself, was able to exacerbate anaphylaxis induced by anti-IgE treatment, and this effect was completely abolished in a C3 knockout. Of the most potential relevance, intragastric administration of PE was also shown to be capable of inducing weak complement activation *in vivo* as well as exacerbating systemic anti-IgE-induced anaphylaxis. The authors do not address whether this effect is also mediated by macrophage activation and PAF.

As with any animal model, there are fundamental questions of relevance to human pathophysiology that must be tested. In addition, the presented findings are limited by the uncharacterized nature of the complement-activating component present in PE. Nevertheless, it is intriguing that allergens that have been frequently associated with severe clinical reactivity (peanuts, tree nuts, *Hymenoptera*) share the capacity to activate complement directly. The role of PAF in this model is also intriguing given the attention recently brought to bear on the relationship between PAF and its degradation to severe anaphylaxis in humans.⁶

There is 1 report investigating complement activation during controlled food challenges. Sampson⁷ measured C3a and C5a levels pre and post oral food challenges in 18 patients with objective symptoms and reported no statistically significant change; however, these were neither severe reactions nor were the challenge foods specified. In the case of *Hymenoptera* sting, there is a report of 8 subjects undergoing sting challenges in which 7 of 7 of the individuals who reacted had elevated C3a levels that peaked at 15 minutes.⁸ Larger follow-up studies from the same group make no mention of complement measurements, however.⁹

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Understanding the mechanisms that predispose individuals toward more severe allergic reactivity is an important public health goal because currently there are no validated means for targeting interventions toward those at greatest risk. Potential biological risk factors in addition to PAF degradation that have been implicated by a range of experimental approaches include coexisting allergic disease¹⁰ and features of the specific IgE response.¹¹ If certain allergens, such as those from peanuts and tree nuts, do in fact exacerbate reactions by additional innate immune activating mechanisms in humans, this would reinforce the need to focus clinical intervention and may have implications for research into additional treatment strategies. It is also tempting to speculate on the possibility that the poor tolerance of injection immunotherapy to peanut¹² could be related to this activity.

The other potentially relevant question that is not experimentally addressed in the current study, although it is raised in the discussion, is what role a complement-activating component of PE may play as an adjuvant to enhance the inductive allergenicity of peanut. This seems likely to prove to be the more biologically significant role, because even small amounts of activated complement may be very important for initiating immune responses. Anaphylatoxins and other complement split products (eg, C3d) have been shown to influence adaptive immunity in myriad ways through direct interaction with B and T cells as well as dendritic cells and other innate cells.^{13,14} A particularly relevant example may be the attenuation of *Aspergillus*-induced allergic asthma in mice that are deficient in C3 or C3a receptor.¹⁵ This potential mechanism of allergenicity also has clinical implications. For example, if a complement-activating factor in allergens is relevant to the human immune response, should PE used for immunotherapy be treated to remove or inactivate this activity? Alternatively, might this activity actually be beneficial for immunotherapy? There is much research to look forward to that will be stimulated by this novel and intriguing report that serves as an excellent example of how basic model organism science can open new potential avenues for both basic and clinical research and understanding.

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