

Correspondence

Reply

To the Editor:

In his correspondence, Turner¹ argues that factors other than increased intestinal permeability contribute to heightened food allergen absorption in humans prone to severe allergic reactions and anaphylaxis. He notes that there is a lack of evidence supporting the role of heightened intestinal permeability in mediating symptomatic food allergy in humans, and that gut-barrier dysfunction may be a result of allergic inflammation, rather than a cause. These critiques highlight both the challenges of studying food allergy in humans and the need to understand differences that may exist in food allergy pathogenesis between humans and mice.

Human enterocytes have been shown to express CD23a, the low-affinity IgE receptor, and to participate in IgE-mediated endocytosis of luminal food allergens *in vitro*.² Similarly, allergic sensitization was shown to increase antigen uptake by enterocytes in CD23^{+/+} but not CD23^{-/-} mice. Thus, evidence in humans and mice suggests that upon sensitization, IgE-mediated allergen-specific uptake likely contributes to allergen absorption.³ We posit that both IgE-dependent and IgE-independent mechanisms of allergen absorption contribute to enhanced allergen absorption in those with food allergy. Indeed, Turner¹ provides compelling evidence that peanut-allergic patients display augmented systemic absorption of the peanut allergen Ara h 6, relative to nonallergic controls following consumption. The kinetics of allergen presence in the blood are remarkably similar between these data and our own results using egg protein in mice.⁴ Although we readily detect food-specific IgA in the stool of allergic mice, we have not observed food-specific IgE by ELISA; however, it is possible that our assays are not sensitive enough to detect gut IgE. The role of specific-allergen absorption mediated by IgE is compelling and merits further study. In particular, it would be interesting to test whether peanut-allergic patients display increased systemic absorption of innocuous food proteins, or only with allergens that they are sensitized to, because this would help differentiate increased intestinal permeability from antibody-mediated uptake.

Another factor that could contribute to enhanced systemic allergen absorption in those with food allergy (Fig 1 Turner)¹ is altered gut epithelial permeability. Although our data indicate heightened intestinal permeability at baseline in C3H/HeJ mice, this strain is food allergy-prone, and we are actively studying whether genetic susceptibility loci dictate this allergen absorption

phenotype. Because this phenotype exists before sensitization occurs, it is unlikely to be due to damage arising from allergic inflammation or IgE-mediated uptake. Rather, it correlates with the number of goblet cells present in the proximal small intestine, cells that mediate uptake of luminal antigens via goblet cell-associated antigen passages. Our results parallel findings in humans that cofactors that transiently increase intestinal permeability can render a normally resistant patient susceptible to food allergy symptoms.⁵ This suggests that inherent differences in intestinal permeability, or transient perturbations in the gut barrier to proteins, may predict whether a patient will absorb an allergen on ingestion. Although compelling, this hypothesis is difficult to test in humans due to the challenges of measuring gut permeability noninvasively. However, more work is needed in humans and mice to test the roles of both IgE-mediated allergen absorption and goblet cell-associated antigen passages in mediating susceptibility to anaphylaxis, because this has the potential to identify new therapeutic targets and diagnostic markers to stratify anaphylaxis risk for patients with food allergy.

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