IMMUNOLOGY

Opening the gateway to food-induced anaphylaxis

Cysteinyl leukotrienes are important drivers of the anaphylactic response to ingested food antigens

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Allergy to peanuts is the deadliest food allergy and affects 1 to 2% of people worldwide.

Food allergy is an incurable chronic condition that affects more than half a billion people worldwide. Allergies to food arise when the immune system mounts an adaptive response to food antigens, and subsequent exposure results in the cross-linking of allergen-specific immunoglobulin E (IgE)–high-affinity IgE receptor (FcεRI) complexes on mast cells. Cross-linking triggers these immune cells to release factors that cause allergic symptoms ranging from mild local reactions to life-threatening anaphylaxis. Puzzlingly, the quantity of food-specific IgE does not accurately predict allergic symptoms upon exposure and some "sensitized-but-resistant" individuals have measurable food-specific IgE but can ingest the food without symptomatic reactions (*1*). On pages 614 and 613 of this issue, Hoyt *et al.* (*2*) and Bachtel *et al.* (*3*), respectively, report that cysteinyl leukotrienes (CysLTs) are important drivers of oral, IgE-mediated anaphylaxis, offering hope of a potential therapeutic approach for treating food allergy.

Hoyt *et al.* sought to understand why some strains of mice are susceptible to oral food-induced anaphylaxis, whereas others are resistant despite equal IgE-producing capabilities. This led to the identification of genetic variants in the gene encoding dipeptidase 1 (DPEP1), an enzyme that catabolizes cysteinyl leukotriene D4 (LTD4) into cysteinyl leukotriene E4 (LTE4). Both leukotrienes are lipids involved in inflammation. Resistant strains expressed a DPEP1 variant with higher catabolic activity in the jejunal microvillar membrane and the lamina propria of the small intestine, whereas susceptible strains had DPEP1 variants with lower catabolic activity and expression limited to the jejunal microvillar membrane. The authors further demonstrated that LTD4 promoted allergen transport across the gut epithelium into the tissue and circulation. Mouse strains with more LTD4, because of its reduced catabolism by DPEP1, had increased allergen transport and peripheral blood allergen concentrations and developed anaphylaxis.

Bachtel *et al.* examined the differences between oral (mucosal) and systemic (parenteral) exposure of allergen in murine models of anaphylaxis. This approach also led to the identification of a critical role for CysLTs in oral anaphylaxis. Notably, in both studies, the CysLT synthesis inhibitor, zileuton, attenuated orally induced anaphylaxis but had no effect on anaphylaxis when the allergen was parenterally administered through intravenous or intraperitoneal routes. In the study of Bachtel *et al.*, this result was associated with CysLTs produced by a specific subset of intestinal mast cells. Mast cells can be divided into subsets on the basis of anatomical and tissue location and by protease content. These characteristics are also tied to differences in histological staining patterns (*4*, *5*). In humans, the presently accepted subgroups are based on the type of protease that is released upon degranulation: chymase, tryptase, or both. Tryptase-producing mast cells are usually found in mucosal surfaces, although they are not yet well-defined in humans. In mice, mast cells located in connective tissues and organs such as the lungs, trachea, skin, peritoneal cavity, and submucosa of the intestines are collectively considered connective tissue mast cells. These usually express mast cell proteases 4 to 7 (MCPT4 to MCPT7). By contrast, mucosal mast cells are found in mucosal linings of the

gastrointestinal tract and lungs and express MCPT1 and MCPT2. In the lung, mucosal mast cells are generated in response to type 2 inflammation, which is characteristic of chronic inflammatory conditions such as asthma. By contrast, connective tissue mast cells are constitutively present (*6*). Mucosal mast cells can also be distinguished from their connective tissue counterparts by the expression of Mas-related G protein–coupled receptor member X2 (Mrgprx2), which triggers IgE-independent degranulation (*7*). Bachtel *et al.* determined that in response to allergens, mucosal mast cells primarily produce leukotrienes, whereas connective tissue mast cells primarily produce histamine.

Before the studies by Hoyt *et al.* and Bachtel *et al.*, evidence of a clear division of labor between mast cell subsets was lacking, beyond that dictated by their location. By defining subsets according to the mRNA molecules present in each subset (using the method single-cell RNA sequencing), Bachtel *et al.* found that mucosal mast cells expressing the protease MCPT1 in the lining of the intestine produced less histamine but more CysLTs than connective tissue mast cells. CysLTs released from the mucosal subset were critical for orally induced anaphylaxis but not anaphylaxis after peritoneal exposure, which was dependent on histamine released from connective tissue mast cells.

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These observations agree with a previous report that mucosal mast cells expressing MCPT1 were specifically activated in orally challenged mice and that connective tissue mast cells expressing MCPT7 were primarily activated by parenteral exposure of allergen (*8*). Similarly, another study investigated the role of basophils, mast cells, and connective tissue mast cells in mouse models of anaphylaxis to peanut (*9*). That work used mouse strains engineered to lack all mast cells and basophils, connective tissue mast cells alone, or basophils alone and demonstrated that anaphylaxis triggered by parenteral exposure to peanut was partially reliant on mast cells and/or basophils. The anaphylaxis observed in mast cell–deficient animals appeared to be driven by platelet-activating factor, which is most likely induced by IgG-mediated activation of neutrophils as well as macrophages (*10*). This is consistent with the findings by Bachtel *et al.* and others who verified that oral exposure to an allergen is largely dependent on IgE, whereas exposure through parenteral routes is not. This is also reminiscent of the impact of interleukin 9 in orally induced anaphylaxis and airway hyperresponsiveness (such as constriction) to an allergen but not in parenteral allergen-induced anaphylaxis (*11*–*13*).

Notably, by studying mice lacking both CysLT receptors 1 and 2 (CysLTR1 and CysLTR2), Bachtel *et al.* demonstrated that the receptors nonredundantly promote mucosal mast cell expansion, with a larger contribution from CysLTR1. Acute administration of montelukast, a small-molecule inhibitor of CysLTR1, did not protect against orally induced anaphylaxis. Similarly, oral allergen exposure was not affected by inhibition of either CysLTR1 or CysLTR2 but was partially blocked by inhibition of both receptors. These observations further support a role for CysLTs in orally Induced anaphylaxis, potentially by promoting expansion and effector functions of mucosal mast cells. Taken together, these results indicate a potential redundancy in the acute function for both CysLT receptors in orally induced anaphylaxis but nonredundancy in mucosal mast cell expansion.

There are some differences in the studies of Hoyt *et al.* and Bachtel *et al.* that could be associated with the models used, such as the agents used to sensitize animals to allergens. Another important distinction is the effect of CysLTs on allergen transfer into the circulation and the extent of systemic mast cell activation. Also, the source of LTD4 was nonhematopoietic cells in Hoyt *et al.* and hematopoietic cells in Bachtel *et al.* These observations suggest that in patients, there could be multiple sources of CysLTs, depending on conditions and potentially on variations in the synthesis and responsiveness of cells. Because altered microbiome and sustained signaling by interleukin 4 (a cytokine produced by various immune cells that promotes allergic inflammation) can overcome some of the differences observed in these strains, it is possible that microbial metabolites or immune signals can modify the activity of these pathways.

Zileuton is a small-molecule inhibitor of CysLT synthesis that is being used now to treat asthma. Because Hoyt *et al.* and Bachtel *et al.* show that zileuton can inhibit orally induced anaphylaxis, future translational studies are warranted that examine the effectiveness of zileuton in preventing anaphylactic food allergic reactions in humans. The mechanism proposed by both studies seems plausible in patients, as Hoyt *et al.* provide some data to support a CysLT-dependent pathway in humans. Although little is known about the role of CysLTs in human intestinal mast cell development and anaphylaxis, their production increases in humans after anaphylaxis (*14*).

Predicting which patients will have severe allergic reactions remains a major clinical challenge. CysLTs were primarily thought to be involved in late-phase anaphylaxis symptomology. The identification of LTD4 as a modifier of food-induced anaphylaxis in mouse models where sensitization and IgE production did not differ provides a target for understanding why there are sensitized-but-resistant patients. Polymorphisms in the generation and metabolism of CysLTs could provide an approach for identifying patients most at risk. Moreover, there are likely additional mechanisms for the sensitized-resistant phenomenon because some patients can be sensitized to multiple food antigens and be symptomatic to some but resistant to others. It remains to be determined whether the mechanisms proposed by Bachtel *et al*. and Hoyt *et al*. are antigen specific. □

REFERENCES AND NOTES

1. C. A. Keet, R. A. Wood, E. C. Matsui, *J. Allergy Clin. Immunol.* **130**, 1207 (2012).
2. L. R. Hoyt *et al*., *Science* **389**, eadp0240 (2025).
3. N. D. Bachtel *et al*., *Science* **389**, eadp0246 (2025).
4. A. A. Irani, N. M. Schechter, S. S. Craig, G. DeBlois, L. B. Schwartz, *Proc. Natl. Acad. Sci. U.S.A.* **83**, 4464 (1986).
5. H. R. Katz, R. L. Stevens, K. F. Austen, *J. Allergy Clin. Immunol.* **76**, 250 (1985).
6. T. Derakhshan *et al*., *J. Exp. Med.* **218**, e20200321 (2021).
7. M. Tauber *et al*., *J. Exp. Med.* **220**, e20230570 (2023).
8. S. Benedé, M. C. Berin, *PLOS ONE* **13**, e0190453 (2018).
9. L. L. Reber *et al*., *J. Allergy Clin. Immunol.* **132**, 881, 11 (2013).
10. F. D. Finkelman, *J. Allergy Clin. Immunol.* **120**, 506, quiz 516 (2007).
11. A. Pajulas *et al*., *Mucosal Immunol.* **16**, 432 (2023).
12. E. E. Forbes *et al*., *J. Exp. Med.* **205**, 897 (2008).
13. H. Osterfeld *et al*., *J. Allergy Clin. Immunol.* **125**, 469 (2010).
14. M. Nassiri, O. Eckermann, M. Babina, G. Edenharter, M. Worm, *J. Allergy Clin. Immunol.* **137**, 312 (2016).

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