

Journal Pre-proof

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PII: S0091-6749(21)00898-8

DOI: <https://doi.org/10.1016/j.jaci.2021.06.002>

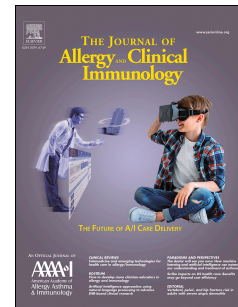
Reference: YMAI 15149

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 3 May 2021

Revised Date: 1 June 2021

Accepted Date: 3 June 2021



Please cite this article as: Berin MC, New Ideas: Food allergy stems from food quality sensing, *Journal of Allergy and Clinical Immunology* (2021), doi: <https://doi.org/10.1016/j.jaci.2021.06.002>.

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New Ideas: Food allergy stems from food quality sensing

Comment on: Food allergy as a biological food quality control system, Florsheim et al, Cell, 2021.

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Conflict of Interest: Dr. Berin reports that her institution receives grants on her behalf from the National Institutes of Health.

Key Words: Neuronal, noxious, toxin, food, sensory epithelium, nutrient sensing, allergy, sensitization

In a recent issue of Cell, Esther Florsheim, Ruslan Medzhitov and colleagues propose a new paradigm for food allergy ¹.

"We suggest that the immune system (specifically, type 2 or allergic immunity) participates in food quality control by monitoring food composition and using dietary proteins as cues associated with food quality. Net positive quality results in immune tolerance toward dietary antigens, whereas net negative value results in allergic sensitization via induction of antigen- specific IgE antibodies."

This is based in part on an idea that allergy is a system for expulsion of toxins. The authors argue that net negative value of food allergens stems from allergens being inherently noxious or being physically associated with noxious substances. Allergens can physically associate with a variety of molecules from lipopolysaccharide to metals, and these associated molecules can promote either allergy or tolerance. Roth-Walter et al recently demonstrated that iron bound to the milk protein beta-lactoglobulin promoted tolerance through activation of the aryl hydrocarbon receptor while the allergen without iron as cargo drove allergy ². Food proteins may also directly activate the innate immune system, as Ruiter et al recently demonstrate with peanut which activated human dendritic cells via TLR1/2 heterodimers to drive Type 2 immunity ³. Florsheim et al propose that allergens that are protease inhibitors, and therefore may interfere with digestive enzymes, would be net negative proteins due to detrimental effects on the host. Medzhitov and colleagues have recently shown that nutrient sensing, specifically carbohydrate sensing, can alter epithelial cell phenotype and function through the action of gd T cells ⁴. This interesting work directly ties nutrient content to the status of the mucosal immune system. We are starting to understand that there is a complex interaction between foods, specialized epithelial cells and the innate immune system, although the net cost or benefit to the host from each food is not always clear. Foods themselves are complex and contain many components beyond the major proteins that could be sensed by a variety of mechanisms.

The theory that food allergy is a spectrum of food quality control is difficult to reconcile with food allergy that develops early in life before the food has been incorporated into the diet. As shown by the LEAP study, dietary avoidance of peanut in early life is detrimental

and promotes peanut allergy, while oral exposure is protective ⁵. Most children with a peanut or tree nut allergy react to peanut or tree nut on their first known ingestion. Thirty-six percent of infants enrolled in a trial of early egg ingestion had egg-specific IgE at 4 months of age, before any known ingestion of egg, and 31% of infants had allergic reactions when they started to ingest egg⁶. Keet et al recently reported on 321 infants (4-11 months) with no known exposure or history of reaction to peanut, but with elevated risk of peanut allergy (family history, eczema, and/or personal history of other food allergy) ⁷. 21% of the cohort had evidence of sensitization to peanut prior to any ingestion of peanut, and 18% of infants with eczema had clinical peanut allergy. Eczema and age were the largest risk factors for peanut allergy. It is difficult to reconcile the proposed food quality control system with immune reactions that occur on the first known ingestion of the food and where the major risk factors originate from the skin and environmental exposures. A quality control system that breaks tolerance in response to associated noxious stimuli such as toxins is more likely to underlie the phenomenon of late-onset food allergy.

A topic reviewed extensively in the manuscript by Florsheim et al is the sensing system found throughout the oral and gastrointestinal tract that integrates with the central nervous system. Smell receptors, taste receptors, and nutrient and noxious sensing by specialized epithelial cells such as enteroendocrine, enterochromaffin, or tuft cells communicate with the nervous system through a range of mediators. Activation of these pathways can lead to behavioral changes such as food aversion, and physiologic reactions such as vomiting, which protects the host from continued exposure to noxious agents. Food aversion has been shown to be a feature of food allergy in mice, and mediated through IgE, mast cells, and sensory nerves feeding into the central nervous system ⁸. Bienenstock and colleagues demonstrated mast cell-nerve cross-talk, including the phenomenon of mast cell activation in response to a conditioned stimulus ⁹. Crosson et al recently reported in this journal ¹⁰ that sensory nerves express the high-affinity IgE receptor and can be activated by allergen-IgE complexes. The potential role of epithelial sensors in responding to luminal contents, whether through IgE or other mechanisms, and triggering allergic reactions has not yet been explored but may help to explain reactivity to trace amounts of food allergens.

Another way to interpret the food quality-control hypothesis is to think about the sensory-immune-neuronal axis in the process of sensitization and during allergic reactions (Figure 1). While we commonly think of innate immune cells such as dendritic cells being the main sensors of allergenic potential, sensory epithelial cells are placed at the interface between the external and internal environment and are in the best position to patrol the quality of the intestinal contents. Metabolites such as succinate that are naturally found in seafood and also used as food additives can activate Tuft cells. This paradigm expands the type of stimulus driving sensitization beyond binding to pattern recognition receptors. When considering acute allergic reactions to foods, it is clear that the IgE-mast cell-neuronal axis is involved as symptoms are likely spread through the nervous system. Here again there is room to consider the role of the sensory epithelium and whether it is necessary for antigens to physically cross the epithelial barrier in order to drive hypersensitivity reactions, or whether the sensory epithelium could respond to antigens and activate nerves without the need for mast cell intermediaries.

The food quality control hypothesis is a proposal rather than a review of literature and therefore should not be critiqued for lack of evidence. The lack of acknowledgement of reactions to foods on the first known oral exposure is a limitation of this hypothesis. The emphasis on the role of sensory epithelial cells upstream of the immune system, and the nervous system downstream of the immune system is a novel and whole-organism view of food allergy. Appropriate investigation of these neuro-immune mechanisms will require collaborative efforts between multi-disciplinary teams but will likely open exciting new approaches to therapeutic interventions that limit neuronal spread of symptoms.

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Figure Legend

Figure 1: The figure depicts the hypothesized role of the sensory-immune-neuronal axis in sensitization and allergic reactions to foods. Sensory epithelial cells including enteroendocrine cells (purple) and tuft cells (blue) react to luminal foods and respond to the net impact of nutrients, danger signals, toxins, etc in the food. Tuft cells can release cytokines that impact the downstream immune response. During reactions, mast cell-nerve interactions drive behavioral and physiological changes. It is possible that sensory epithelial cells can be triggered to initiate reactions without antigens having to cross the epithelial barrier. Figure prepared with BioRender.com.