

Perspective

Food allergy as a biological food quality control system

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Summary

Food is simultaneously a source of essential nutrients and a potential source of lethal toxins and pathogens. Consequently, multiple sensory mechanisms evolved to monitor the quality of food based on the presence and relative abundance of beneficial and harmful food substances. These include the olfactory, gustatory, and gut chemosensory systems. Here we argue that, in addition to these systems, allergic immunity plays a role in food quality control by mounting allergic defenses against food antigens associated with noxious substances. Exaggeration of these defenses can result in pathological food allergy.

Introduction

Food allergy is in many ways a mysterious problem. It is a potentially life-threatening condition that afflicts millions of people in industrialized countries, including 8% of children in the United States (Gupta et al., 2011). Alarming, the prevalence of food allergies has been growing steadily, particularly in the past two decades, implicating modern environmental factors in disease susceptibility. The usual suspects of the modern environment include changes in diet, reduced exposure to micro- and macro-parasites, and the associated changes in the gut-resident microbiota and intestinal immune system (Iweala and Nagler, 2019). Additional environmental risk factors may include chemical additives in processed foods, detergents, textiles, and other household products (Robinson and Miller, 2015). Because food allergy is on the rise in many industrialized countries with diverse medical, cultural, and culinary traditions, it is likely that more than one environmental factor is responsible for the disease epidemiology. All of these considerations make understanding the role of the environment in food allergy a formidable task.

Food allergy is an adverse reaction to food mediated by the immune system. Specifically, it is dependent on type 2 immunity (Box 1). Symptoms of food allergy include vomiting, diarrhea, stomach cramps, swelling of the tongue, hives, as well as potentially lethal anaphylaxis, characterized by a dramatic drop in blood pressure, circulatory collapse, and bronchospasm (Reber et al., 2017). Why does the immune system react so violently to something essential for survival?

Allergic reactions to food are elicited by dietary proteins. Although allergies have been documented to over 100 different foods, eight food groups account for the majority of cases: milk, egg, peanut, tree nuts (cashew, almond, pecan, walnut, and hazelnut), soy, fish, and shellfish (Sampson, 2016). In addition, allergy to sesame seeds and oil is becoming increasingly common (Adatia et al., 2017). Dozens of protein allergens have

been identified in these food sources (Sathe et al., 2016; Tordesillas et al., 2017). What is so special about these proteins that prompts the immune system's reaction against them? Allergic reactions are widely assumed to be mistargeted responses to innocuous antigens present in the environment, including in food; it appears that some antigens are more innocuous than others. If the allergy is indeed an erroneous response, then the immune system seems to be very precise in repeating the same errors.

Here we will discuss food allergy from a broader physiological perspective. The main premise of this perspective is that a physiological counterpart of food allergy is what we would call a "food quality control system." This system operates by monitoring food composition, computing its quality, and controlling consumption, digestion, and absorption of nutrients or expulsion of noxious substances. Defense from harmful substances is mediated by neuronal and immune mechanisms, and exaggerated execution of these defense mechanisms manifests as food allergy symptoms.

The immunological mechanisms of food allergy are summarized in Box 2 and have been expertly reviewed recently (Berin and Shreffler, 2016; Iweala and Nagler, 2019; Wesemann and Nagler, 2016).

Food composition

Natural foods are typically composed of hundreds to thousands of individual chemical components (Barabási et al., 2020). Different foods vary in the composition and relative abundance of these substances. As a first approximation, food components can be divided into nutrients and non-nutrients. Nutrients include macronutrients (carbohydrates, proteins, and lipids) and micronutrients (vitamins and minerals). Non-nutrients include food components the animal cannot digest or absorb as well as noxious substances. In terms of their effect on animal fitness, nutrients are generally beneficial, noxious substances are

Box 1. Two types of immune responses

Immune responses can be broadly divided into two categories (type 1 and type 2) depending on the T helper cells and effector mechanisms involved (Stetson et al., 2004). Type 1 immunity is mediated by interferon γ (IFN- γ)—producing Th1 and ILC1 cells, IL-17- and IL-22-producing Th17 and ILC3 cells, antibodies of the IgG2 and IgG3 isotypes, and macrophages and neutrophils as the effector cells. Type 2 immunity is orchestrated by Th2, Th9, and ILC2 cells that produce IL-4, IL-5, IL-9, and IL-13; antibodies of the IgE isotype; and macrophages, mast cells, basophils and eosinophils, smooth muscle, and epithelial cells as the effector cells (for a review, see Iwasaki and Medzhitov, 2015). The two types of immune responses differ in the predominant defense strategy; type 1 immunity employs a “seek and destroy” strategy and targets pathogens directly, whereas type 2 immunity is primarily based on barrier defenses and expulsion of macroparasites from the digestive and respiratory tracts and the skin. Accordingly, the main targets of type 2 immunity are epithelial, intestinal, bronchial, and vascular smooth muscle cells and sensory neurons that operate reflexes promoting expulsion of harmful substances from the body, such as sneezing, coughing, itching, vomiting, and diarrhea. Thus, type 2 immunity can be used for expulsion of macroparasites and noxious environmental substances (Palm et al., 2012).

detrimental, and the indigestible components can be neutral or beneficial (indigestible fibers, for example, promote peristalsis). This classification, however, requires additional qualifications. First, the beneficial or detrimental effects of most food components are dependent on their absolute quantity; consuming too much or too little of these components leads to poor health (e.g., nutrient deficiency versus excess leading to toxicity; Figure 1A). For nutrients, this dependence is known as Bertrand’s rule (Mertz, 1981; Raubenheimer et al., 2005), and for noxious substances, it is known as hormesis (preconditioning by small doses of noxious stimuli; Figure 1B; Simpson and Raubenheimer, 2012). In the extreme case of highly toxic substances, the dose-response curve has a convex shape, reflecting increasingly detrimental effects with the toxin dose (Figure 1C). Additionally, the positive or negative values of different nutrients and noxious substances depend on their relative abundance (Simpson and Raubenheimer, 2012). Finally, positive or negative values of nutrients or toxins can be conditional on the organism’s status and microbiota composition. Thus, many xenobiotics can be modified by the animal’s detoxification systems (Bernhardt, 2006) or by the intestinal microbiota, rendering them “neutral” (and in some cases, making them more toxic) (Iason, 2005; Koppel et al., 2017).

Collectively, the sum of food components with positive and negative values weighed by their relative abundances define the overall biological quality of food, which, in turn, is evaluated by multiple sensory mechanisms, as we discuss next.

Sensing and responding to food components

Given the complexity of food composition, it should come as no surprise that animals evolved sophisticated mechanisms to monitor and evaluate food substances and their relative abundance. Multiple chemosensory pathways have evolved to evaluate food quality before, during, and after ingestion and are based, respectively, on the olfactory, gustatory, and gut chemosensory systems. These sensory pathways elicit the appropriate behavioral and physiological responses aimed at optimizing the quality of the consumed food. In particular, these food quality control systems maximize ingestion, digestion, and absorption of components with positive values and minimize ingestion and absorption of components with negative values. Sensing food quality has innate (hard-wired) and acquired (learned) components.

Food evaluation begins with the visual and olfactory systems, which detect cues correlated with the quality of food (Li and Lib-

erles, 2015). For example, primates detect ethanol and ethyl-esters as proxies for sugar content in fruits (Nevo and Valenta, 2018), whereas skatol, methane thiol, putrescine, and cadaverine serve as proxies for contaminated and decaying foods (Kavaliers et al., 2004). Perception of these odorants induces food consumption or avoidance, respectively.

The gustatory system operates during ingestion and monitors nutrients and potentially noxious compounds present in food (Breslin, 2013). The five major tastes—sweet, umami, salty, sour, and bitter—report food quality by detecting the relative concentrations of sugars, amino acids, salts, simple acids, and potentially toxic compounds, respectively (Yarmolinsky et al., 2009). Activation of the sweet, umami, salty, and sour receptors, within specific ranges, leads to hedonistic behavioral responses and food acceptance (Breslin, 2013). Conversely, activation of bitter taste receptors generates innate aversive behavior and food rejection (although small concentrations of some bitter compounds can be tolerated and learned to be enjoyed) (Breslin, 2013).

If the food passes the olfactory and gustatory checkpoints, it enters the gastrointestinal (GI) system and is evaluated by the chemosensory mechanisms of the gut. These mechanisms primarily rely on specialized intestinal epithelial cells, including entero-endocrine cells (EECs), entero-chromaffin cells (ECCs), and tuft cells (Gribble and Reimann, 2016). These cells are equipped with a variety of nutrient and xenobiotic sensors, including taste receptors, and upon detection of their cognate stimuli, they produce signals (neuropeptides, neurotransmitters, eicosanoids, and cytokines) that act on sensory neurons and various resident cells of the immune system, including myeloid cells (macrophages, dendritic cells [DCs], and mast cells) and lymphoid cells (innate lymphoid cells [ILCs] and T cells).

EECs play a critical role in coordinating food digestion, absorption, and metabolism. These cells are positioned along the GI tract and sense luminal contents, including nutrients, microbial metabolites, bile acids, and non-nutrient ingested compounds (Gribble and Reimann, 2016, 2019). In response to luminal stimuli, EECs secrete cell-specific gut hormones to communicate with resident cells of the gut mucosa, afferent neurons, as well as distal organs of the GI system (Furness et al., 2013; Gribble and Reimann, 2016, 2019).

Importantly, the distribution of specific EECs varies along the proximal to distal axis of the GI tract, which allows them to report the composition of the intestinal content within each region along this axis (Gribble and Reimann, 2016). This integration of

Box 2. Immune response to allergens

It is currently unknown how the immune response to food allergens is initiated. Specifically, it is not known how intestinal classical DCs (cDCs), which control the balance between oral tolerance and food allergy, acquire luminal antigen or how the intestinal innate immune system senses allergens to elicit allergic inflammation and the adaptive immune response. Recent studies suggest that macrophages, which extend transepithelial dendrites into the lumen, and goblet cells acquire luminal antigens at steady state (Mazzini et al., 2014; McDole et al., 2012) and are required for induction of oral tolerance (Kulkarni et al., 2020; Mazzini et al., 2014). Interestingly, under inflammatory conditions, antigen uptake and oral tolerance-inducing mechanisms are suppressed (Esterházy et al., 2019; Kulkarni et al., 2018). In the most extreme cases, viral infection drives proinflammatory T cell responses to innocuous food proteins, resulting in food intolerance (Bouziat et al., 2017, 2018). Coupled with antigen uptake, epithelial sensing of allergens induces production of IL-25, IL-33, and TSLP, which promote allergic inflammation (Hammad and Lambrecht, 2015). These cytokines activate ILC2 cells to produce IL-5, which induces recruitment of eosinophils and promotes their growth (Hogan et al., 2001), and IL-13, which promotes goblet cell differentiation and mucus production, as well as enterochromaffin cell hyperplasia (Cheng and Locksley, 2014; Manocha et al., 2013).

To initiate the adaptive immune response, intestinal cDCs migrate to the draining lymph nodes, where they activate CD4 T cells and induce their differentiation into Th2 cells or T follicular helper (Tfh) cells. Th2 cells migrate to the affected tissue, where they terminally differentiate in response to locally produced IL-25, IL-33, and TSLP (Van Dyken et al., 2016) and, in turn, produce IL-4, IL-5, and IL-13 to orchestrate local responses upon antigen encounter. In the draining lymph nodes, Tfh cells produce IL-4 and IL-13 to activate B cells for IgE production (Gowthaman et al., 2019; Reinhardt et al., 2009). IgE is then secreted into the bloodstream and binds to the high-affinity FcεRI receptor expressed on basophils (in the blood) and mast cells (in tissues). Upon IgE binding to its cognate antigen, signaling through the FcεRI receptor leads to basophil and mast cell degranulation and release of histamine and other inflammatory mediators, such as leukotrienes and platelet-activating factors (Oettgen and Burton, 2015; Johnston et al., 2014). Histamine acts on smooth muscle cells, epithelial and endothelial cells, and sensory neurons to induce the hallmarks of allergic vasodilation and vascular permeability, leading to tissue swelling, itching, rhinitis, bronchospasm, peristalsis, and nasal and bronchial mucus production (Galli et al., 2008).

Repeated exposure to allergens can result in a state of hypersensitivity in susceptible individuals. Hypersensitivity is characterized by high reactivity to even minute amounts of allergens. Although IgE and mast cells are required for most types of allergic hypersensitivity, they are not sufficient because allergic and non-allergic people have mast cells and, presumably, allergen-specific IgE. The physiological parameters that define the hypersensitive state are presently unknown. However, recent evidence suggests that IgE glycosylation patterns play an important role (Shade et al., 2020).

positional and chemical information represents the progression of the digestive process as well as the relative abundance of nutritive versus noxious substances along the intestinal tract. Signaling to local and distal cells that control digestion, motility, metabolism, and immunity allows regionally defined responses to this information. For example, lipid sensing in the duodenum and jejunum promotes lipid digestion, whereas lipid sensing in the ileum inhibits gastric emptying and peristalsis (a phenomenon known as the ileal brake) (Van Citters and Lin, 2006). Thus, sensing of the same substance in proximal and distal parts of the intestine has different meanings and promotes different responses.

Glucagon-like peptide 1 (GLP-1) and cholecystokinin (CCK) are examples of EEC-derived signals produced in response to macronutrient sensing. GLP-1 is produced by L cells (a subtype of EECs) in response to glucose (Drucker, 2018; Drucker and Nauck, 2006) and acts on pancreatic β cells to promote insulin secretion to prevent a surge of blood glucose concentration after a meal (Scrocchi et al., 1996). CCK is produced by I cells (another subtype of EECs) in response to dietary lipids and acts on the gallbladder and pancreas to trigger release of bile acids and lipases required for digestion and absorption of lipids (Gribble and Reimann, 2016). GLP-1 and CCK also signal to the central nervous system via sensory afferents of the vagus nerve, activating neural satiety circuits (Dockray, 2009; Figure 2). Thus, GLP-1 and CCK produced by EECs in response to dietary macronutrients coordinate digestive and behavioral responses to macronutrients, two of many gut hormones types that operate in this manner. The full complement of gut hormones and their

respective cell types, mechanisms of action, and inductive cues have been reviewed extensively elsewhere (Furness et al., 2013; Gribble and Reimann, 2016, 2019).

Although EECs are primarily focused on sensing macronutrients, ECCs and tuft cells appear to be more specialized to monitor noxious components of the luminal contents (Bellono et al., 2017; Luo et al., 2019; Nadsombati et al., 2018; Figure 2). ECCs detect chemical irritants and bacterial metabolites, resulting in release of serotonin and histamine, which act on vagal and enteric sensory neurons to induce defensive reactions. Serotonin and histamine produced by ECCs, enteric neurons, and mast cells induce peristalsis and mucus production by goblet cells (Alcaino et al., 2018; Bellono et al., 2017; Heredia et al., 2009; Prinz et al., 2013). These effects can also be induced by acetylcholine produced by parasympathetic neurons (Specian and Neutra, 1980). In addition, serotonin activation of vagal afferents promotes nausea (Andrews et al., 1990). Although nausea reduces food intake and, thus, ingestion of potentially toxic substances, increased peristalsis (and at the extreme, vomiting and diarrhea) helps to expel the ingested harmful substances, limiting their absorption.

Tuft cells detect helminths and *Tritrichomona* protozoa infections and release interleukin-25 (IL-25) and leukotriene C4, which act on ILC2s to induce production of IL-5 and IL-13, which drive the type 2 immune response (Box 2; Gerbe and Jay, 2016; Howitt et al., 2016; McGinty et al., 2020; von Moltke et al., 2016). Although the ligands that activate tuft cells are still an active area of research, recent studies have demonstrated that succinate activates tuft cells and the type 2 immune response via

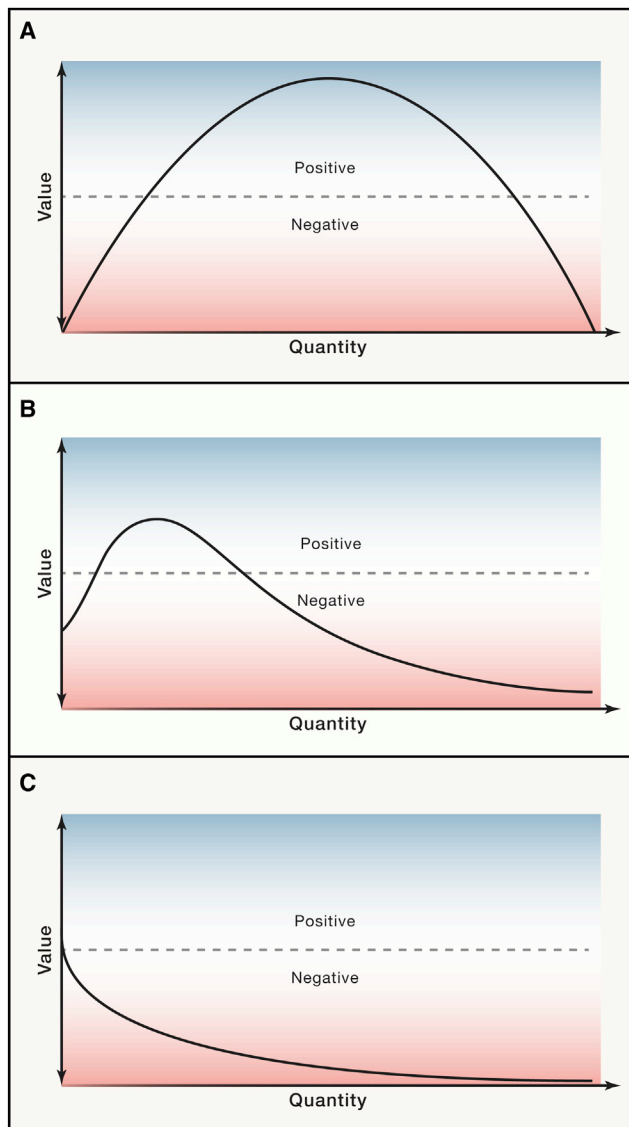


Figure 1. Dose-response curves for different classes of food substances

(A) Bertrand's rule: the value of nutrients is a function of their quantity, with intermediate quantities having positive value and low and high quantities having negative value.

(B) Hormesis: high quantities of toxic substances have negative value, but low quantities can have positive value because of "preconditioning" of the organism (e.g., induction of detoxification genes). Very low quantities of toxic substances can have negative value because of lack of preconditioning.

(C) In the extreme case, highly toxic substances have negative value at all quantities. This could be due to the lack of any defenses against such toxins (and, thus, lack of hormesis).

the succinate receptor SUCNR1 (Lei et al., 2018; Luo et al., 2019; McGinty et al., 2020; Nadjisombati et al., 2018; Schneider et al., 2018). Tuft cells also express genes involved in the taste-sensing pathway (Howitt et al., 2016), including TAS1R3, which senses umami and sweet tastants (Howitt et al., 2020) and members of the TAS2R family, which sense bitter tastants (Luo et al., 2019). Although these receptors have been shown to be impor-

tant in sensing and responding to intestinal protozoan infections, whether and how tuft cells contribute to the defense against noxious compounds in food has not yet been examined.

Food sensing by the olfactory, gustatory, and gut chemosensory systems is integrated by the central nervous system (CNS), which computes the absolute and relative values of different food components. This information is relayed to the CNS through several afferent fibers, including the cranial nerves I (olfactory), V (trigeminal), VII (facial), IX (glossopharyngeal), and X (vagus) as well as the visceral spinal afferents of the dorsal root ganglia (DRG) (Spencer et al., 2016). Vagal afferents transmit sensory information from the proximal gut, where they can be activated by mechanical stimuli (e.g., gastric distention) and by GLP-1, CCK, and other mediators produced by EECs (Kaelinberger et al., 2018; Williams et al., 2016). Following food ingestion, information about nutrient composition and quantity from vagal inputs is relayed to the *nucleus tractus solitarius* (NTS) in the hindbrain. From there, NTS neurons project to the parabrachial nucleus (PBN) and to the forebrain to promote satiety and reward responses to foods with positive valence (Campos et al., 2016; Han et al., 2018; Tan et al., 2020). A major neuronal circuit that influences appetite and controls food intake involves agouti-related peptide (AgRP)- and proopiomelanocortin (POMC)-expressing neurons in the arcuate nucleus of the hypothalamus (Waterson and Horvath, 2015). These neurons are activated during fasting and feeding, respectively, and, accordingly, AgRP neurons promote food consumption and related behaviors, whereas POMC neurons control satiety and anorexic behavior (Andermann and Lowell, 2017; Chen and Knight, 2016). In addition, behavioral responses to foods with different valences are controlled by the amygdala (Wang et al., 2018).

In summary, food-sensing modalities can be broadly divided into detection of nutrients and detection of noxious substances. As a general rule, the sensory pathways for noxious substances have lower thresholds (higher sensitivity) compared with the pathways that detect nutrients (Inagaki et al., 2014; LeDue et al., 2016). The biological rationale for this difference is that the high threshold (and strong desensitization) of nutrient sensors promotes selection of high-quality foods, whereas the low threshold (and low desensitization) for noxious substances minimizes consumption of low-quality foods.

Although these sensing pathways are primarily understood in terms of processing of individual stimuli, as alluded to before, the gut-brain axis evaluates the relative quantities of nutrients and toxins and normalizes them by the energy budget to translate into the decision of food consumption versus avoidance (Karasov and Martinez del Rio, 2007). Furthermore, the state of the organism may influence food selection by tuning the sensitivities of different pathways for specific macronutrients and noxious substances. Thus, individual tastes can elicit attractive or aversive behavior, but the relative abundances of nutrients and toxins and the metabolic needs of the animal ultimately dictate whether a food is accepted or rejected (Breslin, 2013). For example, a deficit in essential amino acids promotes increased consumption of foods containing them, whereas an energy deficit promotes consumption of high-calorie foods (Simpson and Raubenheimer, 2012). This phenomenon is generally known as "specific cravings" (for salty, savory, fatty, or sweet foods),

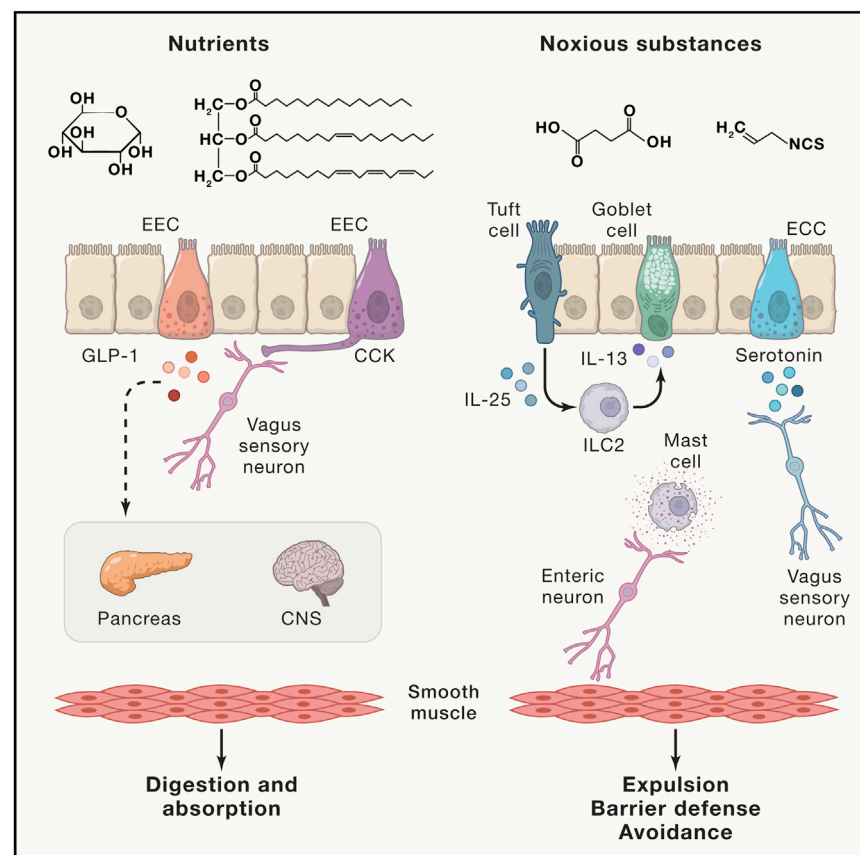


Figure 2. Intestinal sensory pathways for nutrients and noxious substances

Nutrient sensing by EECs leads to production of gut hormones that coordinate behavioral and physiological responses that maximize the absorption of ingested nutrients (left panel). Sensing of noxious substances (for example, by tuft cells and ECCs) may lead to intestinal, physiological, and behavioral responses to minimize exposure to these noxious substances (right panel). These include barrier reinforcement via IL-13-induced goblet cell hyperplasia and mucus secretion in response to IL-25 signaling in ILC2s, mast cell degranulation and release of inflammatory mediators, and release of serotonin and histamine by ECCs, which influences intestinal motility and signals to the CNS. In contrast to the noxious substance-sensing pathways depicted on the right, the nutrient-sensing pathways on the left have lower sensitivity and higher adaptation (desensitization).

acids within dietary proteins. Likewise, sodium is directly sensed by the gustatory system but other minerals and vitamins are not because other essential micronutrients are required in much smaller amounts than what would normally be present in the consumed foods (Simpson and Raubenheimer, 2012).

Similar to many macro- and micronutrients, most toxins and noxious substances cannot be detected directly by the olfactory, gustatory, or gut chemo-

where loss of metabolic balance promotes consumption of foods that can restore the balance. This food selection strategy works well in natural environments with diverse food sources. In a modern environment with unbalanced food choices, it can lead to overeating to compensate for nutritional deficits, resulting in positive energy balance and obesity.

The flip side of specific cravings is selective avoidance of potentially noxious substances, which is achieved by reducing the sensitivity thresholds for sensors that detect them. This is best illustrated during pregnancy, when olfactory and gustatory sensitivity for and avoidance of foods with potentially noxious components (e.g., soft cheeses rich in bacteria) is increased to minimize the potential harmful effect on the fetus (Sherman and Flaxman, 2002). Tuning the sensitivity of the sensory pathways as a function of the organismal state allows for optimal food selection. The relationship between sensory inputs and the organismal state is illustrated schematically in Figure 3.

Learned behavior in food selection

If we consider the entire universe of chemical compounds that can be present in food, it is clear that only a fraction of them can be detected directly by the receptors of the sensory pathways. For example, mammals have a dedicated taste receptor for glutamate (TAS1R1/TAS1R3) but apparently not for other amino acids. The reason why sensing of glutamate is sufficient is likely because it would normally be found with other amino

sensory systems (i.e., they “don’t smell or taste”). However, when left undetected, they can cause adverse effects on the organism. So how is their consumption avoided? The mechanisms involved rely on learned avoidance; the adverse effects of noxious substances are associated with cues that are detectable by the special senses (i.e., olfaction, taste, and vision). The best-known example of this strategy is the phenomenon of conditioned flavor (or taste) avoidance (or aversion). Because the differences between flavor and taste and between avoidance and aversion (for a discussion, see Schier and Spector, 2019) are not relevant to this discussion, we will refer to these phenomena as conditioned taste aversion (CTA) for simplicity.

CTA is a defensive behavior that associates the flavor or taste of consumed food with adverse consequences, such as visceral malaise and nausea (Domjan, 1980; Garcia et al., 1955; Schier and Spector, 2019). A number of noxious substances, including lithium chloride, bacterial toxins, and chemotherapy drugs, can induce these flavor- or taste-specific aversive responses (Arthurs et al., 2012). The neuronal circuits underlying CTA involve the NTS, PBN, amygdala, and insular cortex (Campos et al., 2018; Yamamoto et al., 1994). Interestingly, immune responses can also promote development of CTA (Ader and Cohen, 1975; Cara et al., 1994).

CTA is an example of classical (Pavlovian) or operant associative learning (Schier and Spector, 2019). Toxins present in the food are unconditioned stimuli (UCSs) that cannot be detected

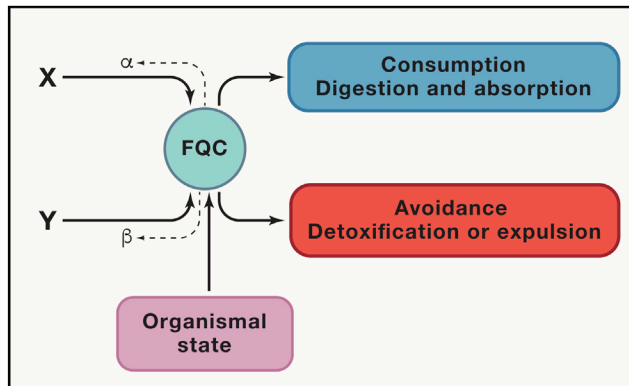


Figure 3. A model of the food quality control system

Sensory inputs (x and y) with positive or negative values have sensitivity parameters (α and β). The sensory inputs are integrated by the food quality control center (FQC), which also receives input from the “organismal state” (for example, energy budget and metabolic balance). Food selection is adjusted by tuning the sensitivity parameters (dashed arrows) to optimize consumption of high-quality foods; i.e., foods that correct the metabolic and energy balance and minimize exposure to toxins. The FQC integrates the input from sensory pathways and the organismal state to elicit appropriate responses, such as consumption versus avoidance and digestion and absorption versus expulsion and detoxification. In a simple scenario, x and y may have intrinsic positive and negative values (nutrient versus toxin). In more complex scenarios, the positive or negative value of a sensory input is determined by the organismal state through parameter tuning.

by the special senses but do elicit an unconditioned response (UR), the visceral malaise, or, in some cases, a perception of bad taste (when the chemical can be detected by bitter taste receptors, for example). The food components that can be detected by olfactory and gustatory pathways are the conditioned stimuli (CSs). Combination of the two stimuli results in the CTA so that any foods with a flavor linked to the malaise caused by the toxin are avoided in the future (Figure 4A).

This “guilty by association” strategy is beneficial because it reduces the chances of consuming a toxin that is not detectable otherwise. However, it comes at the cost of avoiding consumption of toxin-free foods containing the flavor that happened to be associated with toxins. CTA is not only necessary to avoid toxins that cannot be directly detected by any sensory systems but also for toxins that are only detectable after ingestion (by the gut chemosensory pathways). The advantage of learned avoidance is that it anticipates the effects of toxins before they are consumed. This benefit offsets the cost of avoidance of toxin-free foods. Thus, when it comes to dietary toxins, “better safe than sorry” seems to be a dominant strategy.

In summary, the food quality control systems discussed so far integrate sensory inputs about the substances present in foods and their intrinsic values, abundance, and relative proportions. The outputs of this control system are behavioral responses (avoidance versus attraction), barrier responses (absorption versus barrier fortification through mucus production), and tuning of the transit rate (peristalsis). Food aversion, mucus overproduction, and increased peristalsis are defensive responses triggered by detection of harmful substances. At the extremes, these defenses manifest as nausea, vomiting, diarrhea, and malabsorption. Notably, these reactions are also common

symptoms of food allergy, raising the possibility that food allergy is a pathological manifestation of a food quality control system.

Allergic defenses: protective versus pathological

Most diseases can be thought of as aberrant versions of normal biological functions. This implies that, for a given pathological state, process, or function, there is a normal physiological counterpart. For example, the normal counterpart to fibrosis is tissue repair, and the normal counterpart to sepsis is immune defense from infection. The pathology can be an altered or exaggerated version of the normal function. In addition, some normal functions, particularly defenses, often operate at a cost to fitness and are often mislabeled as pathological. For example, most symptoms of acute infections are caused by the inflammatory response. Some of these symptoms can be due to unavoidable side effects (collateral damage), whereas other symptoms are actually manifestations of defense mechanisms at work (Stearns and Medzhitov 2016). Similarly, vomiting and diarrhea in food poisoning are not pathological processes per se—they are defenses that aim to remove the pathogens and their toxins. Blocking these defenses with medications would exacerbate the disease, although suppression of excessive forms of these reactions is, in most cases, desirable. It is, therefore, important to understand whether any given symptom is reflective of pathology or an expression of defenses. And in the cases of “true pathology,” it is important to define the normal physiological counterpart to the pathological process.

Allergies have long been assumed to be mistargeted responses to innocuous environmental antigens, with the normal counterpart being the defense against parasitic worms. This assumption is largely based on the fact that anti-parasitic and allergic responses are mediated by the same effector arm of the immune system; namely, by the type 2 immune response. An alternative view, originally proposed by Profet (1991), is that allergy is a defense against environmental toxins. Indeed, all symptoms of allergic reactions, including rhinitis, sneezing, coughing, vomiting, diarrhea, and itching, have one thing in common: they are defense mechanisms designed to remove harmful environmental substances from the skin and the respiratory and GI tracts (Palm et al., 2012). Here we extend and reconcile these views by suggesting that allergic responses are a form of defense that normally protects from noxious substances but becomes pathological when exaggerated or mistargeted. Examples of exaggerated allergic responses include anaphylaxis, edema, and hives. Examples of mistargeted allergic responses include many instances of reactivity toward innocuous antigens that are targeted because of prior association with noxious substances (see below). Thus, we suggest that the physiological counterpart of food allergies is the food quality control system that limits exposure to harmful substances in foods. Normal operation of this system does not result in clinical symptoms and, therefore, is not recognized as a distinct mode of function of “allergic immunity.” Pathological food allergies, on the other hand, are exaggerated versions of this defense system that result in clinical symptoms.

The immune system and food quality control

Given the existence of olfactory, gustatory, and gut chemosensory pathways, why would the immune system evolve to

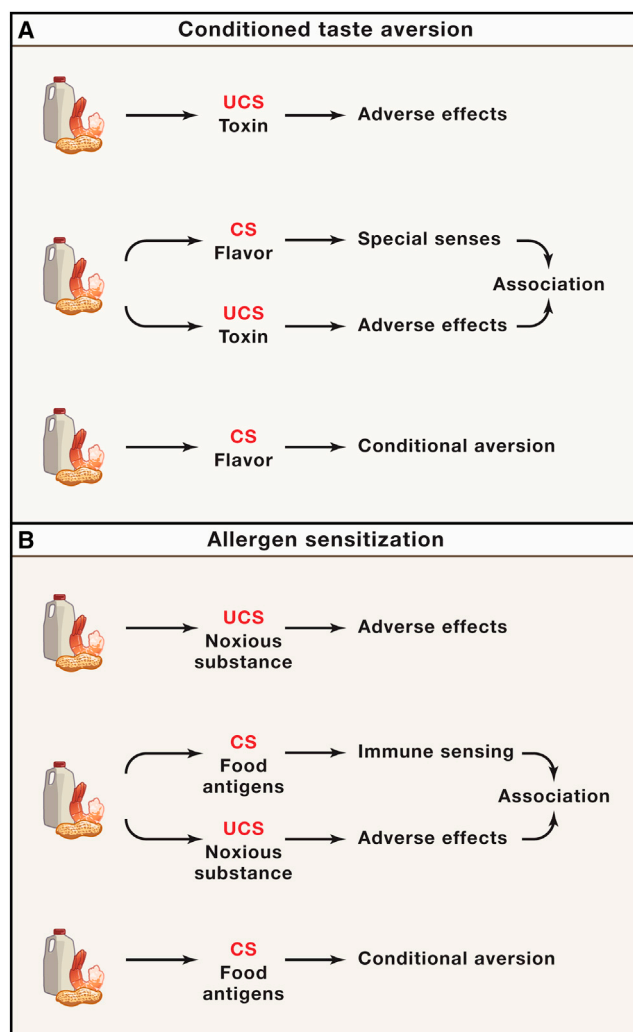


Figure 4. Parallels between CTA and allergic sensitization

(A and B) CTA and allergic sensitization rely on association of a conditioned stimulus (CS) with an unconditioned stimulus (UCS). UCSs (toxins or noxious substances) elicit adverse effects, which are the unconditioned responses (URs). Flavors (smell and taste) play the role of CSs in CTA (A), whereas dietary protein antigens play the role of CSs in allergic sensitization (B). Following association, CSs (flavor or food antigens) elicit a conditioned aversion response (CR), which, in the case of allergic sensitization, includes an allergic response to food.

participate in food quality control as well? The reason here is likely the same that explains the involvement of learned behaviors in CTA. In CTA, neutral cues that are detectable by the olfactory and gustatory sensory pathways (CSs) are associated with malaise caused by exposure to noxious substances (UR). This associative learning helps to avoid future consumption of foods containing harmful substances that cannot themselves be directly detected by the special senses. What if the food containing noxious substances has no associated taste or flavor or any other specific cues detectable by the sensory systems? We suggest that the sensing mechanisms involved in these cases are based on detection of antigens by the immune system. The role of dietary antigens in this scenario is analogous to the role

of olfactory and gustatory cues detected by the nervous system. The UCSs in both cases are the noxious substances present in food, and the UR is their adverse effect on the organism (Figure 4B).

From this perspective, dietary antigens present in foods are used by the immune system to “tag” foods that contain harmful substances, much like taste and smell are used to tag harmful foods in CTA. Specifically, the antigens serve as CSs that are assigned a positive or negative value depending on the presence or absence of noxious substances in the food containing the antigens. In the absence of noxious substances, a positive value is assigned, with the outcome of immune recognition being immune tolerance. If harmful substances are present, then the antigens in the same food are assigned a negative value, and the outcome of their recognition is allergic sensitization (Figure 4). The antigens in the latter case would be operationally defined as “allergens.”

Cooperative functions of immune and neuronal defenses in allergy

Defense responses to noxious substances can be triggered directly through specialized neuronal reflexes (for example, via vagus nerve afferents that monitor the intestinal and respiratory tracts) and through DRG neurons in the skin specialized for itch sensation (Bautista et al., 2014; Coleridge and Coleridge, 1994; Mawe and Hoffman, 2013). Activation of these sensory neurons by noxious stimuli, such as dust particles in the airways, toxic substances in the gut, or irritants on the skin, trigger defensive reflexes, such as sneezing, vomiting, and scratching. These defensive reflexes operate in all healthy people regardless of whether they have allergies. Interestingly, at least in some cases, activation of the neuronal reflexes is initiated by cytokines that are known for their role in allergic responses. For example, irritants induce skin keratinocytes to produce thymic stromal lymphopoietin (TSLP), which stimulates DRG neurons via the transient receptor potential cation channel, subfamily A, member 1 (TRPA1) to trigger the itch response (Bautista et al., 2014; Wilson et al., 2011).

These same defensive reflexes can also be activated downstream of immune recognition of noxious chemicals and allergens by mast cells. Mast cells reside in barrier tissues, including skin, gut, and lung, in close proximity to sensory neurons (Forsthe, 2019). Mast cells can be activated directly by certain classes of noxious chemicals detected by the mas-related G protein-coupled receptor (Mrgpr) family of pruritogen receptors (Green and Dong, 2016; McNeil et al., 2015) as well as by neuropeptides such as substance P, released by nociceptive neurons (Green et al., 2019; Serhan et al., 2019). More commonly, mast cells are activated upon detection of allergens by immunoglobulin E (IgE) antibodies. These antibodies are bound to FcεRI receptors on mast cells (and basophils), leading to their activation upon allergen recognition by IgE (Galli and Tsai, 2012). Activated mast cells release histamine, proteases, and lipid mediators. Histamine acts on H1 histamine receptors on the adjacent sensory neuron terminals, triggering (via the TRPV1 channel) their firing and activation of defensive neuronal reflexes (Bautista et al., 2014; van Diest et al., 2012; Wouters et al., 2016). This allergen-IgE-mast cell-dependent input into neuronal afferents

dramatically expands the sensory capacity of neuronal reflexes because IgE can detect an almost limitless universe of antigens. In addition, antibodies can undergo affinity maturation, resulting in very-high-affinity IgE antibodies (Erazo et al., 2007). Finally, involvement of the adaptive immune system affords memory of past encounters with antigens recognized by IgE antibodies. These features also create a vulnerability in the system: high-affinity IgE antibodies deposited on mast cells at the body's barriers enable extreme sensitivity to trace amounts of antigens, a hallmark of allergic hypersensitivity.

The involvement of vagal reflexes in IgE-dependent and IgE-independent responses highlights the prominent role of the parasympathetic system in allergic defenses, which often has an antagonistic relationship with the sympathetic system. The most familiar example of this dichotomy is the effect of epinephrine on the anaphylactic response. In the course of a systemic allergic reaction, histamine released by airway mast cells causes bronchoconstriction, leading to a life-threatening blockade of respiration. Presumably, the normal counterpart of this response is to reduce exposure to harmful airborne substances. A widely used countermeasure to bronchospasm is injection of high doses of epinephrine, a neurotransmitter of the sympathetic nervous system, to cause relaxation of bronchial smooth muscles. Likewise, parasympathetic neurons promote and sympathetic neurons suppress secretion and peristalsis in the GI tract (Furness et al., 2013). Additional examples of parasympathetic (cholinergic) stimulation promoting and sympathetic (adrenergic) stimulation suppressing allergic reactions include stimulation of ILC2 cells by neuromedin U (produced by cholinergic neurons) and inhibition of ILC2 cells by calcitonin gene-related peptide (CGRP) and norepinephrine (produced by adrenergic neurons) (Cardoso et al., 2017; Klose et al., 2017; Moriyama et al., 2018; Nagashima et al., 2019; Wallrapp et al., 2017). Although skin irritants are detected by the somatosensory rather than the autonomic nervous system, a similar dichotomy exists in the sense that the pain sensation that triggers a sympathetic response is also known to suppress the itch sensation (Wang and Kim, 2020). Thus, the parasympathetic arm of the autonomic nervous system is generally synergistic and the sympathetic arm is antagonistic to allergic defenses. Finally, although the enteric nervous system is not traditionally divided into sympathetic and parasympathetic arms, it does have motor activities (e.g., control of peristalsis and secretion) that act "in the same direction" with either arm of the sympathetic or parasympathetic division (Furness, 2012). Based on the reasoning outlined above, one could predict that the neuronal circuits of the enteric division that complement parasympathetic activity would also be engaged in allergic defenses in the gut, whereas the ones that complement sympathetic activity would be suppressive to allergic reactions. Although, under normal conditions, the autonomic nervous system is primarily involved in regulation of visceral functions and systemic homeostasis, hyperactive autonomic responses are involved in defenses. The extreme state of sympathetic activity—the fight or flight response—aims to protect from injury or predation. The extreme state of parasympathetic activity, nausea, aims to protect from toxic substances. This is consistent with the notion that defenses often evolve as extensions of homeostatic systems (Stearns and Medzhitov, 2016).

It should be noted here that the IgE-dependent responses are not limited to activation of neuronal reflexes. In addition to sensory neurons, mast cell-derived mediators (histamine, prostaglandins, leukotrienes, platelet-activating factors, and cytokines) act on smooth muscle, vascular endothelium, and mucosal epithelium to activate a variety of responses associated with allergic inflammation, such as edema, mucus production, peristalsis, and bronchoconstriction (Galli et al., 2020). Like the neuronal reflexes discussed above, all of these responses operate to promote barrier function, restriction of access, and expulsion of harmful substances. They operate at a cost to other physiological functions, including respiration and digestion. Thus, even when appropriately controlled, these defenses can result in common symptoms of allergy. When excessive, these responses qualify as allergic disease (Palm et al., 2012).

In summary, IgE-mediated recognition of dietary antigens complements and dramatically expands the sensory capacity of the chemosensory pathways involved in food quality control. IgE antibody production is CD4 T cell-dependent, and T cells require protein antigens for activation. Therefore, IgE-mediated food surveillance has to rely on detection of dietary proteins. The dietary proteins that are detected by IgE antibodies and capable of eliciting allergic reactions are referred to as "food allergens." Because the main premise of our thesis is that allergic defenses protect from noxious substances, does that mean that allergens are necessarily noxious? We address this question in the next section.

What makes an allergen an allergen?

We postulate that, to be able to elicit allergic sensitization, dietary proteins have to be associated with some noxious cues present in the food. This is clearly illustrated in experimental models of food allergy, where a protein antigen administered alone causes oral tolerance (Rezende and Weiner, 2017) but when co-administered with cholera toxin or some other noxious agent, the same antigen elicits allergic sensitization (Marinaro et al., 1995; Snider et al., 1994). The association between an antigen and a noxious stimulus can be purely temporal, such as when a toxic substance happens to be present in the gut lumen along with a protein antigen (the toxin and the protein may even come from different food sources consumed around the same time). Protein antigen and toxic substances can also co-occur in the same food sources, resulting in a better correlation between the two. A dietary protein could also be physically associated with a toxic substance. Finally, a dietary protein can itself possess a noxious activity. In all four cases, the antigen can become a target of IgE antibodies, and, therefore, by definition, would become an allergen. However, in the first two cases, the allergens are intrinsically innocuous and are just being used by the immune system as a proxy for foods that contain noxious substances (much like flavor and taste are used as proxies for toxins in CTA). In the latter two cases, the allergens are intrinsically noxious because they are physically associated with harmful molecules or have enzymatic or physio-chemical properties that are detected as harmful.

In immunology jargon, antigens are distinguished from immunogens (also known as adjuvants). Immunogens/adjuvants are detected by the innate immune system, which is necessary to

induce the immune response, whereas antigens are detected by the adaptive immune system and confer fine specificity of the response (Iwasaki and Medzhitov, 2010). Antigens are generally not sufficient to induce a response by themselves (without immunogen/adjuvant) unless they are intrinsically immunogenic (i.e., they combine antigen and immunogen activities). In anti-microbial (or type 1) immunity, immunogenicity is the consequence of pattern recognition of conserved microbial structures, typically found in bacterial cell walls or viral nucleic acids (Medzhitov, 2007). In allergic (type 2) immunity, the nature of the immunogenic signal is not defined, but we suggest that immunogenicity is conferred by noxious stimuli that elicit allergic defenses. Examples of allergens with intrinsically noxious activities include venoms and proteases. Accordingly, venoms and protease allergens are intrinsically immunogenic; they have adjuvant activity and can elicit the allergic immune response by themselves (Florsheim et al., 2015; Palm et al., 2013; Sokol et al., 2008). Moreover, at least in the case of venoms, the allergic response they elicit has been shown to be protective (Marichal et al., 2013; Palm et al., 2013).

The current definition of allergens (as any antigen that can be detected by IgE antibodies) thus conflates two distinct classes of entities: allergens that are intrinsically noxious (and therefore immunogenic) and allergens that are intrinsically innocuous but are used by the immune system as a proxy for noxious stimuli. The reason the latter category exists is because some noxious stimuli are not “visible” by the immune system; that is, they are not antigenic. For example, many small molecules cannot be used by the immune system as antigens because T cell-mediated immune responses require protein antigens. Conflation of distinct classes of allergens into a single definition can be a source of confusion, and we therefore suggest a modified terminology that distinguishes immunogenic allergens (type A) from non-immunogenic ones (type B). Type A allergens (e.g., papain, venoms, the house dust mite allergen Der p 2, etc.) are intrinsically immunogenic and can elicit sensitization without additional adjuvants (Florsheim et al., 2015; Sokol et al., 2008). In contrast, type B allergens are not intrinsically immunogenic; therefore, to elicit allergic sensitization in experimental models, they have to be co-administered with adjuvants (e.g., alum or cholera toxin). The type B category also includes allergens that can elicit allergic reactions because of antigen mimicry and cross-reactivity, as observed for parasite antigens (Fitzsimmons et al., 2014).

Although, in experimental settings, almost any protein antigen can be turned into a type B allergen, in natural settings, antigens must have certain properties that are conducive to immune recognition at barrier tissues. For example, antigens have to be airborne to elicit respiratory allergies. In the case of food allergies, antigens have to be resistant to gastric pH and enzymatic digestion to be detectable by the immune system (Sathé et al., 2016; Tordesillas et al., 2017).

Food allergens and food quality control

Let us now return to the question posed in the introduction: why do certain dietary proteins tend to be the targets of allergic responses? As we argue above, the normal function of allergic reactions in the gut is protection from noxious substances present in food. Further, allergens can differ in their degree of association

with noxious substances; at one extreme, the allergens are themselves noxious (type A allergens), and at the other extreme, their association is purely coincidental (type B allergens). Everything else falls somewhere in between; some allergens may be physically bound to noxious compounds, whereas other allergens could be always present in the same food sources that contain harmful chemicals. To understand why certain dietary proteins are common targets of allergic responses, we need to define their relation to noxious substances present in different food sources. We also need a better understanding of what constitutes a noxious activity.

From an evolutionary perspective, “noxious” or “harmful” is not necessarily something that makes you feel sick. Rather, what makes a substance noxious is its ability to interfere with some biological function. Depending on how vital a particular function is, there can be different outcomes, from “upset stomach” to cardiac arrest and death. For example, chemicals that suppress the activity of digestive enzymes may not cause any feeling of malaise, but from a biological perspective, they are noxious because they interfere with digestive function.

With this broader definition in mind, what are the common noxious substances found in foods? One large class of compounds are plant secondary metabolites (PSMs), including alkaloids, terpenoids, phenolics, and glycosides. These compounds have numerous functions in plant biology, including defense from herbivores (Iason, 2005). The defense functions of PSMs range from making food unpalatable to suppression of digestion and overt toxic effects on the animal (Howe and Westley, 1988). The interplay between expression of defensive compounds in different plant organs and the animal’s ability to detect and mitigate them dictate whether a plant is edible. Here we will discuss several examples of edible and inedible plants, the defensive compounds that dictate this distinction, and how this might inform our understanding of food allergies.

Throughout the Anacardiaceae plant family, of which cashews and pistachios are common targets of allergic responses, phenols are widely used as antimicrobials and deterrents to herbivores (Schulze-Kaysers et al., 2015). Curiously, the inedible members of Anacardiaceae rely on potent phenolic alkylcatechols (e.g., urushiol produced by poison ivy) to deter herbivores (Schulze-Kaysers et al., 2015), whereas edible members, such as cashews, mangoes, and Brazilian peppers, produce a class of less irritating phenolics known as alkylresorcinols (Carlos and Sosa, 2004). These mild irritants are also abundant in the edible portions of wheat and rye (Ross, 2012), which are also commonly targeted by allergic responses.

Members of the Juglandaceae (walnut) family, another common source of food allergens, produce a variety of phenolic defensive compounds, some of which are toxic. For example, juglone, in addition to allelopathic effects on neighboring plants, is cytotoxic and a skin irritant (Bonamonte et al., 2001). Moreover, juglone has been found to promote parasite expulsion in mice (Maki and Yanagisawa, 1985), suggesting that this and related compounds may stimulate intestinal allergic defense programs.

In contrast to the phenolic compounds commonly utilized by members of Anacardiaceae, members of the nitrogen-fixing family Fabaceae (legumes) tend to rely on alkaloids. Here again, the PSMs produced dictate whether a species is edible or

inedible. The inedible family members produce alkaloids that induce neuromuscular arrest, liver damage, or cytotoxicity and are therefore toxic to humans (Wink, 2013). Related Fabaceae species that lack these toxins are cultivated as some of the most important staple crops in the world, such as soy, peanuts, beans, lentils, and peas. These edible species favor non-protein amino acids, which induce protein misfolding, and terpenoids, which are antimicrobial and herbivore deterrents because of their bitter taste (Wink, 2003). Mild irritants, such as alkylresorcinols, or defensive compounds that disrupt the host's metabolic machinery, such as non-protein amino acids, might be sensed directly via specific receptors or indirectly via their harmful effects on animal tissues. These and many other PSMs would be interesting candidates as noxious substances that may contribute to protective type 2 responses or, at the extremes, allergic sensitization.

Animal products can also contain PSMs that are derived from the host's diet or microbiota. For example, dairy milk is a unique source of compounds not found elsewhere in the human diet, given that its fat content solubilizes phenolic metabolites produced by the bovine microbiota (Foroutan et al., 2019; O'Connell and Fox, 2001). One such example is equol, which is the product of rumen bacterial biotransformation of the Fabaceae-derived isoflavone daidzein (O'Connell and Fox, 2001). The Fabaceae family members red clover and soybeans are common components of commercialized dairy cow feed (Hoikkala et al., 2007). The potentially noxious activity of phenols in milk would be due to their anti-nutritive properties that alter normal digestion and barrier function. For example, phenolic compounds in the gut bind to and inhibit digestive enzymes (O'Connell and Fox, 2001) or their substrates (Kardum and Glibetic, 2018), increasing the amount of undigested protein and antigen.

Given their chemical structures and small size, PSMs cannot be detected by the immune system directly and may instead require physical or temporal association with dietary plant proteins to render them allergenic. In addition, protein allergens may have properties that make them intrinsically noxious. As is the case with PSMs, plant proteins may have noxious activities that evolved as herbivore deterrents. Notably in this regard, the majority of plant allergens are proteins involved in storage or defense (Breiteneder and Clare Mills, 2005). Many allergenic storage proteins belong to the prolamin or cupin superfamily. The prolamin superfamily is characterized by high proline and glutamine content and represents the major storage proteins of cereal grains and other grasses (Breiteneder and Clare Mills, 2005). This superfamily also contains 2S albumins, which are storage proteins found in dicotyledonous plants. Allergens in this family include Ara h 2 in peanuts, Ses i 2 a in sesame, Ber e 1 found in Brazil nuts, and Tri a 19 in wheat, among others (Breiteneder and Radauer, 2004). Proteins of the prolamin superfamily are highly resistant to heat and proteolysis (Radauer and Breiteneder, 2007), which may facilitate persistence in the GI tract following ingestion. The cupin superfamily is highly diverse, and allergenic proteins within this large superfamily are found in the vicilin and legumin families (Breiteneder and Radauer, 2004). These globular storage proteins are found in legumes, including peanuts, soybeans, and lentils, and nuts, including walnuts and hazelnuts (Breiteneder and Clare Mills, 2005; Breite-

neder and Radauer, 2004). Allergens in this family include Ara h 1, Jug r 2, and Cor a 9, found in peanuts, walnuts, and hazelnuts, respectively.

In addition to storage proteins, pathogenesis-related (PR) proteins are a major source of plant allergens (Sinha et al., 2014). PR proteins are involved in host defense and can be induced by infection, stress, or injury and are characterized by stability at low pH, low molecular weight, and resistance to proteolytic degradation (Sinha et al., 2014). PR proteins have diverse functional properties, including antimicrobial, antifungal, and insecticidal activity; membrane permeabilization; as well as roles in development and stress tolerance (Sinha et al., 2014). The PR family proteases Act c 1, Gly m Bd 30K, and Cuc m1 are allergens found in kiwis, soybeans, and melons, respectively (Breiteneder and Radauer, 2004). In addition to acting as allergens themselves, PR proteins also underlie a number of cross-reactive allergic responses because of their high sequence similarity with other plant proteins not known to be involved in defense (Breiteneder and Clare Mills, 2005; Sinha et al., 2014). For example, allergic responses to PR proteins found in latex are associated with hypersensitivity to certain fruits, a phenomenon known as latex-fruit syndrome (Breiteneder and Clare Mills, 2005; Sinha et al., 2014). Other PR proteins include non-specific lipid transport proteins (nsLTPs), members of the prolamin family that possess antifungal and antimicrobial activity and are also highly resistant to proteolytic degradation (Breiteneder and Radauer, 2004; Sinha et al., 2014). Allergenic nsLTPs include Pru p 3, found in peaches, and Cor a 8, found in hazelnuts (Breiteneder and Radauer, 2004).

The overrepresentation of proteins involved in storage or defense among plant allergens suggests that these functional categories may be intrinsically noxious and, therefore, inherently allergenic. A characteristic particularly common among food allergens is their interaction with lipids. This property enables the allergens to destabilize phospholipid membranes and participate in lipid transfer reactions that may exert membrane-damaging effects on animal cells. In addition, lipid binding properties may enable food allergens to physically associate with hydrophobic PSMs that may have noxious activity. Similarly, some food proteins may be allergenic because they chelate heavy metals (Profet, 1991). Finally, the noxious activity of some food allergens is due to their interference with digestive enzymes. Examples include hen egg ovomucoid, a trypsin inhibitor (Lineweaver and Murray, 1947), and trypsin and chymotrypsin inhibitors expressed by edible members of the Fabaceae family (Wink, 2003).

Non-plant food allergens, such as shellfish and fish, can also contain noxious substances that are likely targeted by the immune system. Major allergens in shellfish and fish—tropomyosin and parvalbumin, respectively—exhibit thermal stability and resistance to digestion (Faber et al., 2017). Shellfish and fish are often contaminated by toxins produced by algae or plankton (Ruethers et al., 2018) and with noroviruses that infect tuft cells and cause gastroenteritis (Wilen et al., 2018). Enteric viral infections can induce inflammatory responses to dietary antigens (Bouziat et al., 2018; Bouziat et al., 2017), which may also contribute to allergic sensitization.

PSMs and common food allergens, together or in isolation, have multiple noxious activities toward animals, which may

account for their allergenicity. There appear to be three common threads of noxious activities of these food components: anti-digestive effects that interfere with digestive and absorptive processes (e.g., phenolic compounds), anti-metabolic effects (e.g., non-protein amino acids) that interfere with metabolic utilization of nutrients, and membrane-destabilizing (irritant) activity (e.g., saponins and lipid-binding allergens).

Finally, food allergies are known to follow certain patterns of co-reactivity within plant families; for example, individuals allergic to walnuts are also very likely to be allergic to pecans (both belong to Juglandaceae), whereas cashew allergy is strongly associated with pistachio allergy (both belong to Anacardiaceae) (Brough et al., 2020). Because these patterns follow the plant family relations, one possible explanation is that allergens derived from related plants may have higher degrees of similarity and cross-reactivity. An additional possibility, however, is that members of the same family share noxious PSMs that promote allergic sensitization toward related plant foods. For example, walnuts and pecans (Juglandaceae family) share naphthoquinones like juglone, whereas cashews and pistachios (Anacardiaceae family) share alkylresorcinols. This possibility may be particularly relevant for allergic “preferences” that run in families (when different family members are allergic to foods from the same plant family) because it may indicate genetic variation in PSM-specific detoxification pathways. Future research into these relations between PSMs and allergies could shed light on the underlying mechanisms of allergic sensitization.

Conclusions and perspectives

Here we discussed food allergy within a broader framework of food quality control. Like any control system, food quality control consists of sensors, integration centers, and effector pathways. The sensors evaluate the values of food composition based on the presence of individual food components (nutrients, toxins, etc.) and their relative ratios. Integration centers process sensory inputs and tune sensitivity thresholds based on the internal state of the organism. Net positive value of sensory inputs promotes food ingestion, digestion, and absorption as well as metabolic utilization of the nutrients. Net negative value promotes food avoidance and suppresses absorption by increasing intestinal barrier function and peristalsis rate. These are defensive responses that, at the extreme, result in nausea, vomiting, and diarrhea. 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. Detection of dietary proteins associated with noxious substances promotes the same responses that are induced by defensive neuronal reflexes; that is, avoidance and expulsion of noxious substances. Thus, we suggest that the normal function of allergic immunity in the gut is to protect from harmful food components. In a subset of people, this function becomes exaggerated, resulting in a state of allergic hypersensitivity. This hypersensitive state is characterized by a very low threshold of activation of the defensive responses, which can be a life-threatening condition. What makes some people

hypersensitive is unclear, but given the effect of environmental factors, the ultimate reason for allergies to be on the rise has likely to do with a mismatch between the modern environment and our evolutionary history. One such factor could be the increasing reliance on processed foods depleted from natural compounds that can promote hormesis effects. Another factor is the increasing consumption of artificial chemicals (food preservatives, dishwasher detergents, etc.) that we have not evolved to handle with natural defenses and that do not promote hormetic preconditioning and, therefore, may result in dysregulated allergic reactions.

Regardless of specific mechanisms, what makes this particular defense system so vulnerable to dysregulation? One reason is that allergic sensitization can occur through a “guilty by association” mechanism, which is inherently error prone. Specifically, allergic immunity is prone to making false-positive errors. In the trade-off between sensitivity and specificity, the benefit of detection of potentially harmful substances outweigh the costs of rejecting harmless foods, provided other food sources are available. This rationale may have contributed to the evolution of a highly sensitive, if less specific, system for monitoring food quality. Dramatic changes in the modern environment have rendered allergic defenses ill suited to deal with the challenges of the increasingly “unnatural” world. However, a better understanding of the natural defense mechanisms and their tuning by the environment may help prevent allergic diseases and would lead to rational approaches to effective therapies.

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