The false alarm hypothesis: Food allergy is associated with high dietary advanced glycation end-products and proglycating dietary sugars that mimic alarmins

Peter K. Smith, BMedSci, MBBS, FRACP, PhD,[a] Madhan Masilamani, PhD,[b] Xiu-Min Li, MD,[b] and Hugh A. Sampson, MD[b] *Southport, Australia, and New York, NY*

The incidence of food allergy has increased dramatically in the last few decades in westernized developed countries. We propose that the Western lifestyle and diet promote innate danger signals and immune responses through production of "alarmins." Alarmins are endogenous molecules secreted from cells undergoing nonprogrammed cell death that signal tissue and cell damage. High molecular group S (HMGB1) is a major alarmin that binds to the receptor for advanced glycation end-products (RAGE). Advanced glycation end-products (AGEs) are also present in foods. We propose the "false alarm" hypothesis, in which AGEs that are present in or formed from the food in our diet are predisposing to food allergy. The Western diet is high in AGEs, which are derived from cooked meat, oils, and cheese. AGEs are also formed in the presence of a high concentration of sugars. We propose that a diet high in AGEs and AGE-forming sugars results in misinterpretation of a threat from dietary allergens, promoting the development of food allergy. AGEs and other alarmins inadvertently prime innate signaling through multiple mechanisms, resulting in the development of allergic phenotypes. Current hypotheses and models of food allergy do not adequately explain the dramatic increase in food allergy in Western countries. Dietary AGEs and AGE-forming sugars might be the missing link, a hypothesis supported by a number of convincing epidemiologic and experimental observations, as discussed in this article. (J Allergy Clin Immunol 2017;139:429-37.)

Key words: *Food allergy, alarmins, glycation, advanced glycated end-products, receptor for advanced glycated end-products*

Food allergies have increased dramatically in the last 30 years, particularly in westernized developed countries. More recently, developing countries are observing a similar trend. Food allergy and its common comorbidity eczema represent "gateway" diseases, seemingly opening the door for the chronic inhalant diseases of allergic asthma, rhinitis, and conjunctivitis. Establishing the important factors in the development of food allergy has been a focus of research in many centers; however, there has not been a conclusive answer to firmly clarify the mechanisms by which food allergy occurs. The major explanations behind the increase in food allergy currently include a combination of the following:

1. Hygiene/microbiota type and microbial diversity. This theory developed from animal studies in which rearing in sterile environments resulted in allergic features including dermatitis, T_H2 responses, and anaphylaxis.[1,2] In 1989, Strachan[3] proposed the hygiene hypothesis, and studies demonstrating the influence of microbiota type, timing, diversity, farm exposure, and intervention studies with probiotics and prebiotics add credence to this line of thought.[4-6] Bach[7] convincingly correlated an increase in both allergic and autoimmune disease with a reduction in severe infections
2. The timing of complementary food introduction appears to be important in the development of tolerance. Recently, the concept of giving peanut in the first year of life has been shown to reduce peanut allergy in a high-risk cohort in the United Kingdom.[8,9]
3. Low vitamin D levels in infancy appear to be a risk factor for the development of peanut and egg allergy, and the distance one lives from the equator in the United States and Australia has been correlated with epinephrine autoinjector prescriptions used as a surrogate for food allergy.[10-12]
4. Other cofactors include antibiotics, diversity of feeding, use of antacids, and types of fatty acids (lower levels of omega 3 and linoleic acid) in the diet, and phylates in plastics appear to promote allergic responses.[13,14]

Food allergy involving IgE is a maladaptive and learned immunologic threat response to an innocent allergen (usually common foods) that should normally provide nutrition and health benefits. Something is likely to have changed dramatically in the Western lifestyle in the last half-century that is promoting this

From [a]the School of Medicine, Griffith University, Southport, and [b]the Jaffe Food Allergy Institute, Division of Allergy & Immunology, Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York.

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Corresponding author: Peter K. Smith, BMedSci, MBBS, FRACP, PhD, School of Medicine, Griffith University, 17/123 Nerang St, Southport 4215, Australia. E-mail: pksm@mac.com.

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Abbreviations used
AGE: Advanced glycated end-products
CML: N(ε)-carboxymethyllysine
DC: Dendritic cell
HMGB1: High molecular group box 1
OVA: Ovalbumin
RAGE: Receptor for advanced glycated end-products
TLR: Toll-like receptor

immunologic misdirection. IgE-mediated milk allergy is reported to currently affect between 2% and 7.5% of children[15]; however, the first case of allergy to milk (fatal anaphylaxis) was reported in the German literature in 1905.[16]

Only recently, it has become apparent that allergic reactions are not solely based on IgE antibodies and T_H2 cells. Many other cell types, including innate lymphoid cells and epithelial barrier functions, for example, play a crucial role in the allergic response.[17-22] However, much of the research focus has attempted to link adaptive immune responses, such as IgE levels and cytokine patterns, to allergic phenotypes. Similarly, there have been risk associations made with a variety of genes involving barriers, IgE, cytokines, antiproteases, pattern recognition and response molecules, and food allergy. Human genetics could not have changed dramatically in the last 20 to 30 years in westernized countries; however, the way the genes function can be altered by environmental factors (eg, methylation, ubiquitination, and histone acetylation), and this is another direction of research. It appears that the extent and pattern of gene methylation can predict the likelihood of food allergy.[23] The parameters for the majority of epigenetic research remain focused at the level of allergic phenotypes and adaptive immune responses. Adaptive immune responses are largely guided by messages and signaling from the innate immune system; however, there has been minimal focus on innate immunity in terms of the mechanism of food allergy.

ALARMINS, ADVANCED GLYCATED END-PRODUCTS, AND RECEPTOR FOR ADVANCED GLYCATED END-PRODUCTS

High mobility group box 1 is a major alarmin that promotes T_H2 responses

Alarmins are normally released from all cells that undergo nonprogrammed cell death.[24] This is an innate mechanism by which dying cells signal danger and recruit elements of the adaptive immune response. The high mobility group box 1 (HMGB1) is a key alarmin released with tissue damage. Activated dendritic cells (DCs) secrete HMBG1, and this appears to be critical in the activation and proliferation of T lymphocytes.[25] HMGB1 can be released from cells during inflammation or through stimulation from pathogen-associated molecular patterns, such as Toll-like receptors (TLRs).[24]

HMGB1 binds to receptor for advanced glycated end-products

HMBG1 binds to its receptor, receptor for advanced glycation end-products (RAGE; an immunoglobulin family member only present in mammals), to induce maturation of DCs, neurite growth, and activation and migration of monocytes, macrophages, neutrophils, and DCs and to induce inflammation and oxidative pathways.[24,26-28] HMGB1 can signal through both RAGE and TLRs, such as TLR2 and TLR4.[29,30] Although TLR2/4 stimulation has been reported to be protective against food allergy,[31] an airway model of allergy has shown that TLR4 agonism in conjunction with HMBG1 amplifies the allergic response[32] and blocks the TLR4-attenuated allergic response to fungal proteinase.[33] RAGE also binds to and is activated by other alarmins, such as S100 proteins and amyloid β-peptide.[34]

HMGB1/RAGE alarmin signaling is critical for allergic responses

Activation of RAGE receptors is proinflammatory and promotes adaptive (and maladaptive in the cases of diabetes, atherosclerosis, and Alzheimer disease) immune responses.[35,36] RAGE knockout mice have attenuated responses to inhalant allergens.[37] Ullah et al[32] have recently demonstrated a role for the HMGB1-RAGE axis in airway sensitization and airway inflammation. The attenuated response to inhalant allergens in *Rage*$^{-/-}$ mice[37] might be due to significantly reduced numbers of DCs in the lung and draining lymph nodes. Recently, Oczypok et al[38] have shown that RAGE drives allergic airway inflammation by promoting IL-33 expression and accumulation of type 2 innate lymphoid cells in the airways. Thus far, there is no direct evidence suggesting advanced glycation end-products (AGEs) trigger food allergy through interaction with RAGE.

Western diet high in AGEs can induce alarmin signaling

The RAGE receptor also binds to and is activated by glycated proteins. High blood sugar levels (eg, in patients with diabetes) are associated with increased glycation of endogenous proteins and a proinflammatory state.[39] The Western diet can contribute significantly to the AGE pool, with up to 10% of dietary consumed AGEs being absorbed systemically and only an estimated one third being excreted.[35,40] Dietary AGEs are produced in high amounts, particularly with animal proteins and fats that are cooked at high temperatures (eg, fast foods and cooked meats are particularly high in AGEs), to expose amino acid chains to which sugars bind. There are several intermediate products in the formation of AGEs, such as Amadori, and Schiff base during the Maillard reaction. The Maillard reaction (also referred to as "glycation") describes a complex series of chemical reactions between carbonyl compounds, such as reducing sugar, and amino compounds, such as amino acids and protein. AGEs are a heterogeneous group of compounds that are produced at the late phase of the Maillard reaction.[41] We see glycation in many foods as the crispiness and browning of foods with cooking; however, AGEs are also readily formed with super-high heating, such as microwave cooking and frying.[40] Sugar moieties are bound to proteins or lipids, leading to formation of AGEs (also called glycotoxins). The most well-characterized glycotoxins are methylglyoxal[42] and N(ε)-carboxymethyllysine (CML).[43] Methylglyoxal is a carcinogen capable of cleaving DNA and inducing damage to nucleic acids.[42,44,45] Fructose is a key substrate in the formation of methylglyoxal.

As highlighted previously, RAGE activation by alarmins induces immunologic activation and multiple inflammatory

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