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Influence of the Maillard Reaction on the Allergenicity of Food Proteins and the Development of Allergic Inflammation

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Abstract

Purpose of Review The Maillard reaction (MR) is a non-enzymatic reaction between reducing sugars and compounds with free amino groups such as proteins and takes place during thermal processing and storage of foods. This review aims to discuss potential effects of dietary MR products on the pathological mechanisms of allergic diseases.

Recent Findings Since the MR leads to modification of proteins with various types of glycation structures, the impact of the MR on the immunogenicity and potential allergenicity of food proteins in many allergenic foods has been assessed. In addition, recent studies have suggested that the MR products, in particular "advanced glycation end products (AGEs)," contained in the diet may be involved in the development of chronic inflammation by acting as inflammatory components and affecting the gut microbiome.

Summary This review found that the biological, immunological, and allergic properties of dietary MR products are diverse due to the complexity of the MR.

Keywords Maillard reaction · Food allergens · Advanced glycation end products (AGEs) · Pattern recognition receptors · Gut microbiome

Abbreviations

AGEs	Advanced glycation end product
CML	Nε-Carboxymethyl-lysine
CKD	Chronic kidney disease
DAMP	Damage-associated molecular pattern
DCs	Dendritic cells
MR	Maillard reaction
PRR	Pattern recognition receptor
RAGE	The receptor for the advanced glycation end products
SCFA	Short chain fatty acid
SR	Scavenger receptor
TDM1	Type 1 diabetes
TDM2	Type 2 diabetes

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Introduction

The Maillard reaction (MR, also referred to as "non-enzymatic browning" or "glycation") represents a complex series of chemical reactions between carbonyl and amino compounds. This reaction occurs during thermal processing and storage of foods, as well as in vivo, particularly in the diabetic milieu, producing high glucose concentration in the blood, and in the course of aging [1]. The MR cascade usually is subdivided into three stages (Fig. 1). In the early stage of the reaction, a nucleophilic addition of the amino group of amino acids, peptides, or proteins to the carbonyl group of a reducing sugar is followed by dehydration and rearrangement to result in Amadori compounds (aminoketoses). The "intermediate stage" of the reaction may be summarized as the formation of highly reactive α-dicarbonyl compounds from Amadori compounds via enolization and dehydration. In the final stage, the dicarbonyl compounds react with the amino groups (e.g., primary amine group, or the free side chain amine and guanidino groups of lysine and arginine) of amino acids, peptides, and proteins and

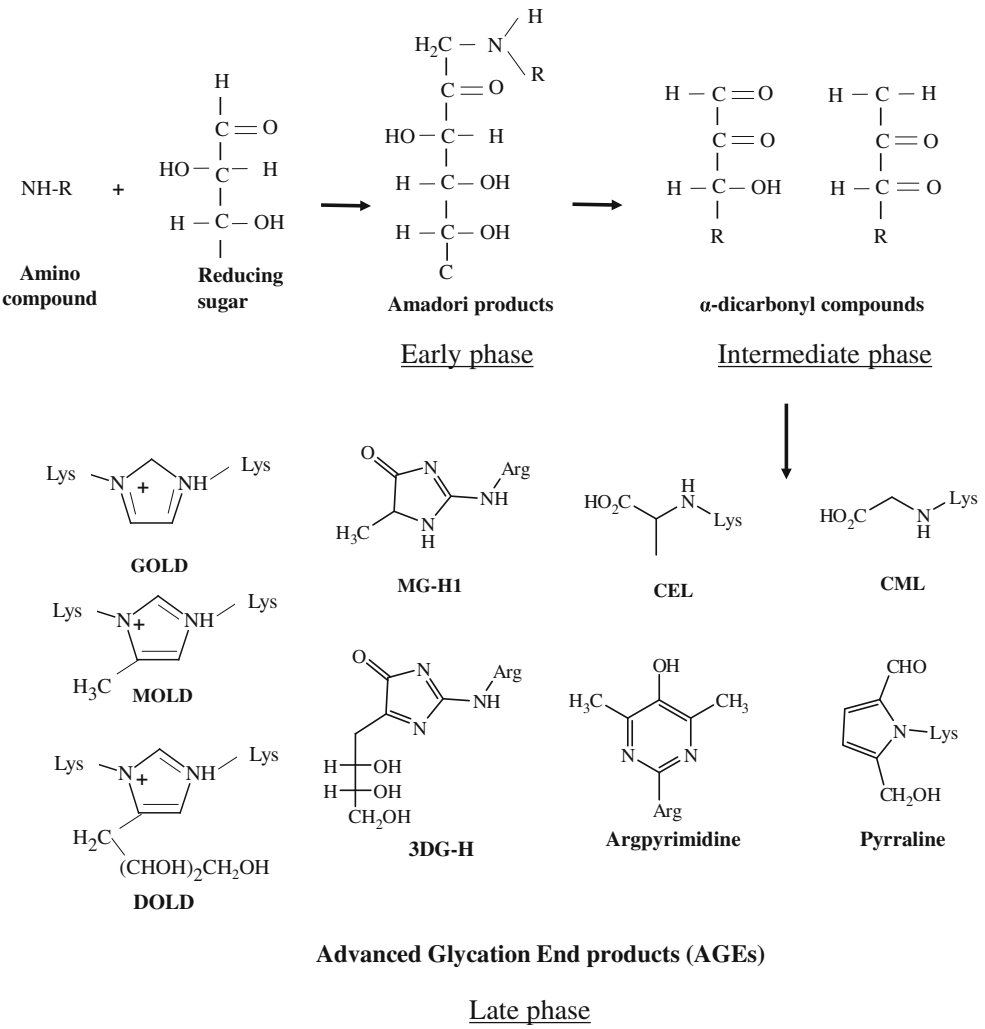

Fig. 1 A scheme of the Maillard reaction. The reaction is divided into three (early, inter, and late) phases. Chemical formulas of compounds representative for each phase are indicated. CML, Nε-carboxymethyl-lysine; CEL, Nε-carboxyethyl-lysine; MGO, hydroimidazolones (derived from methylglyoxal); 3-DG, 3-deoxyglucosone; GOLD, bis(lysyl)imidazolium derivatives (1,3-bis-(5-amino-5-carboxypentyl)-1H-imidazolium); MOLD, 1,3-bis(5-amino-5-carboxypentyl)-4-methyl-1H-imidazolium; DOLD, 3-deoxy-glucosone-derived lysine dimer. Adapted from reference [1]

induce the formation of the so-called advanced glycation end products (AGEs). Representative AGEs include Nε-carboxymethyl-lysine (CML), Nε-carboxyethyl-lysine (CEL), pyrraline, hydroimidazolones (derived from methylglyoxal (MG), argpyrimidine, glyoxal (GO), and 3-deoxyglucosone (3-DG)), and bis(lysyl)imidazolium salts such as 1,3-bis-(5-amino-5-carboxypentyl)-1H-imidazolium (GOLD), 1,3-bis(5-amino-5-carboxypentyl)-4-methyl-1H-imidazolium (MOLD), and 3-deoxyglucosone-derived lysine dimer (DOLD) (Fig. 1). Furthermore, the majority of the sensory-active compounds (responsible for aroma, taste, color, etc.) in thermally processed foods are generated by the MR in the final stage.

The major concern regarding the MR in allergy research is the possible effect of glycation on the potential allergenicity of food proteins, since many allergenic foods are subjected to thermal processing before consumption. Evidence collected so far suggests that dietary MR products may promote the development of chronic inflammation via engagement with pattern recognition receptors (PRRs). Additionally, dietary MR products have the potential to affect gut microbiota, which may have an influence on the inflammatory status in chronic disorders including allergy. This review introduces such biological, immunological, and allergenic properties of the MR products by referring to recent scientific findings.

Effect of the MR on the Potential Allergenicity of Food Proteins

The first hypothesis linking the MR to allergy was that the reaction enhances the potential allergenicity of food allergens by creating novel IgE epitopes. The hypothesis was based on observations that some allergic patients reacted only to thermally processed foods and displayed no allergic reactions to the raw counterparts [2]. However, so far, there is no scientific evidence showing the presence of IgE antibodies specific to the glycated forms of proteins or glycated structures. Several studies have investigated the influence of the MR on the

potential allergenicity of food allergens in chicken egg, cow milk, peanuts, tree nuts, sea foods, and other allergenic foods. The results of such studies have been listed and discussed in several review articles [3–5]. These studies revealed that the effects of the MR are diverse, depending on the thermal stability of the allergens, the number of lysine/arginine residues in allergens, types and concentrations of reducing sugars, composition of the food matrix, and treatment conditions (e.g., temperature, pH, duration, and moisture). Glycation may influence the affinity and/or accessibility of allergens for specific IgE antibodies owing to change(s) in the electric charge and hydrophobicity of proteins. Glycation may also impart structural changes in proteins, since the MR induces aggregation of proteins by intra- or inter-molecular cross-linking between lysine and arginine residues, or two lysine(s) or arginine(s) in the formation of shared AGEs (Fig. 1) [1]. However, in many cases, heat treatment rather than glycation acts as the primary factor in altering the allergenicity of food allergens during thermal processing.

High-temperature treatments often alter the protein structure of allergens, i.e., by heat-induced denaturation, subsequent renaturation, oligomerization, and aggregation by cooling [3]. Heat labile food allergens (e.g., Bet v 1 homologues such as Pru av 1, a major cherry allergen [6]) lose their potential allergenicity by heat treatment owing to the loss of conformational epitopes. Alternatively, the IgE reactivity of some allergens may be enhanced if sequential epitopes for IgE antibodies are exposed by heat treatment. It appears that glycation influences such effects of heat on some allergens. For instance, glycation protected the loss of allergenicity by heat, when Ara h 2/6, the major peanut allergen, was incubated with glucose at 145 °C for 20 min under dry condition [7]. Heat under the same dry condition enhanced the allergenicity of Ara h 1, another peanut allergen, and the MR did not alter the effect of heating [7]. Cucu et al. showed that the capacity of crude hazelnut proteins to induce mediator release by basophils was reduced by incubation in phosphate-buffered saline with glucose at 70 °C for 48 h [8]. It has been suggested that the reduction was promoted by glycation of hazelnut allergens Cor a 1 and Cor a 2. These studies suggest the difficulty in predicting the effect of MR on the potential allergenicity of allergenic foods.

Effect of the MR on T Cell Immunogenicity of Food Allergens

Glycation by the MR does not seem to create novel IgE epitopes. However, accumulated evidence suggests that the MR products, in particular AGEs, are recognized by several PRR expressed on the surface of antigen presenting cells such as dendritic cells (DCs) and macrophages. PRRs are host sensors, which detect molecules typical for the pathogens in immune systems, but also react to food components that are not observed in mammals. PRRs recognizing AGE structures include macrophage scavenger receptors, e.g., SR-A1 (SCARA1), SR-A1.1 (SR-AII), SR-B1 (SR-BI) and SR-B2 (CD36), SR-E1 (lectin-like oxidized low-density lipoprotein receptor-1: LOX-1), SR-H1 (fasciclin EGF-like, laminin-type EGF-like, and link domain-containing scavenger receptor-1: FEEL-1) and SR-H2 (FEEL-2), galectin-3, TLR-4, and the receptor for the advanced glycation end products (RAGE) [9–11]. Among them, the scavenger receptors are endocytic receptors described as candidates for antigen-specific targeting to the MHC class II loading pathway. It means that scavenger receptors efficiently transfer their antigenic ligands to cellular compartments, where the ligands are processed and loaded onto the MHC class II molecules in the form of antigenic peptides for $CD4^+$ T cell activation. We found that glycation of ovalbumin (OVA, egg white allergen) by the MR, in particular modification with pyrraline, promotes the uptake of the allergen by DCs via binding to SR-AI/II; this in turn significantly enhances OVA-specific $CD4^+$ T cell activation and IgE production [12••, 13]. A similar observation, i.e., enhanced uptake of the MR product by DCs via SR-A engagement, was also reported for β-lactoglobulin, a major cow's milk allergen [14]. Our results suggest that glycated food allergens may be processed for enhanced T cell immunogenicity and, therefore, reduce the threshold for allergen sensitization, when compared with the native forms of the allergens.

Effect of MR on T Cell Differentiation

It is an important question as to whether the MR products possess a capacity to induce Th2 cell differentiation, which in turn promotes induction and development of type I allergy. Buttari et al. showed that the AGEs of plasma β2 glycoprotein I (β2 GPI) triggered maturation of monocyte-derived human DCs, and polarized allogenic naïve $CD4^+$ T cells into Th2 cells in a co-culture with mature human DCs [15]. AGEs of β2GPI appear to bind RAGE in human DCs, which might confer a T cell stimulatory capacity that promotes Th2 cell differentiation. The early research on RAGE was in the context of diabetic microvasculopathy and focused on the role of RAGE as a receptor for endogenous AGEs (in vivo MR products) [16]. Through these studies, RAGE is now well known as an inflammatory receptor that is involved in the initiation of inflammatory cycles that perpetuate oxidative stress and pro-inflammatory cytokines via nuclear factor-kB (NF-kB) upregulation [17]. RAGE is expressed in multiple cell types at very low levels in the absence of a disease condition, with increased expression noted in a range of cell types and tissues in inflammatory states [18]. Besides, RAGE is expressed in T cells. Using a murine model of allergic asthma, Akirav et al. showed that RAGE expression in T cells is crucial in the

development of Th1 responses, and RAGE deficiency promotes the development of Th2 response [19]. Notably, RAGE was intracellularly expressed in T cells from healthy subjects only after TCR activation, but constitutively expressed in T cells from patients with diabetes [20]. The levels of RAGE expression in T cells of allergic patients are not known and need to be investigated to assess the effect of dietary AGEs, including AGEs of food allergens, on the activation and function of allergen-specific T cells.

Potential Effects of Dietary MR Products on Allergic Inflammation

Depending on food preparation methods, modern Western diets may contain large amounts of dietary AGEs. The estimated daily intake of dietary AGEs ranges from 25 to 75 mg [21]. Many AGEs (e.g., CML and pyrraline) found in the foods have been detected in endogenous AGEs accumulated in the tissues [22]. Tessier et al. showed that feeding mice with CML-BSA resulted in its accumulation in murine organs, in particular the kidneys, intestines, and lungs [23]. This suggests that a similar accumulation of dietary AGEs may occur in the human organs, although the result cannot be directly interpolated to explain the condition in humans. Notably, several studies have shown that expression of RAGE is upregulated in chronic inflammation including allergic asthma [10, 24••]. Given the role for RAGE as an AGE-binding inflammatory receptor, there is a postulation that dietary AGEs are involved in the development of inflammatory disorders including allergic diseases [25, 26]. However, the involvement of dietary AGEs in the development of allergic disease has not been investigated. Moreover, the ability of RAGE to recognize dietary AGEs has been challenged in recent years.

In diabetes mellitus research, a number of randomized controlled trials have been performed to assess the effect of dietary AGEs on overweight individuals, patients with type 1 and type 2 diabetes (TDM1 and TDM2) or chronic kidney disease (CKD), and healthy subjects [27, 28]. Several reviews suggest that low-AGE intake may be beneficial in reducing biomarkers of inflammation and oxidative stress levels in healthy adults and patients with CKD [27, 28]. In addition, several studies showed that the consumption of a high-AGE diet for periods greater than 2 weeks increases the expression of pro-inflammatory biomarkers, specifically TNF-α, and the circulating levels of AGEs in healthy and overweight individuals and patients with TDM1, TDM2, and CKD, although the levels of a pro-inflammatory cytokine, i.e., IL-6, was not associated with the consumption. The observation is only partly consistent with the role of RAGE, as stimulation of the receptor leads to the production of IL-6 and TNF-α [27, 28]. There are studies with contradictory results as well, showing that a high- or low-AGE diet had no significant effect on any inflammatory mediator after 6 weeks of dietary intervention [29, 30]. The discrepancy in the outcome of the clinical studies has been explained by the high heterogeneity between the studies (e.g., ages of recruited patients, recipe for high-AGE diets leading to different calorie densities, the presence of other inflammatory components, oxidized lipids in the diets, and in particular the method used to "quantify" the amount of glycation compounds [1]). Notably, only high molecular weight serum fractions (> 50 kDa) isolated from diabetics with nephropathy were able to stimulate RAGE but not low molecular weight serum fractions [31]. Dietary glycated proteins undergo the normal digestion process after intake, and therefore, free glycated amino acids or peptides may be absorbed. Further work is necessary to show whether the small fraction of glycated proteins escaping intestinal digestion may enter the circulation in intact form and may effectively interact with RAGE.

It should also be noticed that "the interaction of endogenous AGEs with RAGE" is not the only mechanism for the onset and development of diabetic complications and aging diseases. Endogenous AGEs damage tissues and trigger inflammation mainly by three mechanisms: (i) inducing structural deformation or high cross-linking of proteins, in particular long-lived extracellular matrix proteins [16, 18], (ii) acting as a component in signal transduction cascades in the cells [32], and (iii) interacting with AGE receptors. AGE cross-linked proteins accumulate in a variety of organs, which leads to tissue damage and dysfunction, including those of the kidneys, retina, and nerves, as well as the formation of atherosclerotic plaques in hyperglycemia [16, 18]. In the damaged cells and tissues, damage-associated molecular pattern (DAMP) proteins such as the high-mobility group box (HMGB)-1, adenosine triphosphate proteins, S100 calcium-binding proteins, amyloid fibrils, and nucleic acid backbones are released [33, 34••]. DAMP binds RAGE, Toll-like receptors 2 and 4, and triggers the release of pro-inflammatory cytokines, as well as the upregulation of RAGE expression [35]. Recent studies have suggested that the interaction of DAMP with RAGE takes the major role in development of diabetic complications [33, 34••]. Dietary AGEs may enhance inflammatory responses by binding to RAGE in such chronic inflammatory milieu. However, evidence for the effect of dietary AGEs in chronic inflammation is only suggestive and should be elucidated with caution through further investigation. In this context, it will be important to carefully control the experimental conditions to generate individual AGEs for model studies in order to reflect the physiological conditions. Moreover, the extent of the MR in experimental diets must be comprehensibly described based on the chromatographic analysis of individual glycation compounds (Fig. 1), and not by sum parameters such as "AGE content" originating from immunological methods or merely calculation based on questionable databases.

Potential Effects of Dietary MR Products on Gut Microbiota

There is growing evidence that dysbiosis, a qualitative and quantitative change in the intestinal flora, is associated with the pathogenesis of multiple diseases including allergic reactions [36, 37]. Therefore, the adverse or positive effects of the MR products including AGEs on gut microbiome are of interest. Dietary MR products alter the microbiological profile in humans. A pilot randomized open-label controlled trial recruited patients with end-stage renal disease (ESRD) undergoing peritoneal dialysis (PD) ($n = 20$) and investigated the effect of dietary AGE restriction on their microbiome [38]. The trial attempted to evaluate an association between the levels of AGEs and inflammation markers and oxidative stress in patients with ESRD. The trial showed that dietary AGE restriction altered the bacterial gut microbiota, with a significant reduction in *Prevotella copri*, a bacterial strain enhancing susceptibility to arthritis [39]. The results suggest that AGEs maintain an unfavorable bacterial strain potentially involved in inflammation. Seiquer et al. showed negative correlations between (i) lactobacilli count and intake of dietary AGEs (hydroxymethylfurfural and CML) and (ii) bifidobacteria count and intake of Amadori compounds, the products of the early stage of the MR, in adult healthy subjects [40]. The MR products appeared to have specific effects on the composition of intestinal microbiota, depending on the chemical structures. Contrarily, a bifidogenic effect on human microbiota was described for milk protein glycated with galactose [41]. Interestingly, Nam Bui et al. found that a bacterium, i.e., *Intestinimonas* strain AF211, can convert lysine and the Amadori product, i.e., fructoselysine, stoichiometrically into butyrate and acetate [42]. This was the first evidence showing that a certain type of bacteria uses an MR product as their energy source. AGEs such as CML and pyrraline were shown to be metabolized by the human microbiota to different extents [43].

The short chain fatty acids (SCFAs) such as acetate, propionate, and butyrate are the end products of gut bacterial digestion of food-derived components. It is now well known that SCFAs regulate innate and adaptive immune cell generation, trafficking, and function [44, 45]. In particular, the effect of SCFAs on regulatory T cells (Treg) is of importance in the modulation of allergic inflammation. The interaction between butyrate and GPR109a, which binds multiple SCFAs, promotes the production of IL-10 and retinol dehydrogenases (enzymes producing retinoic acid) from macrophages and DCs, thereby inducing Treg generation [46]. SCFAs also regulate Treg differentiation through epigenetic modifications by histone deacetylase inhibition, which leads to increased Foxp3 expression [47]. The severity of atopic disease correlated inversely with gut microbial diversity and with the abundance of butyrate-producing bacteria [48, 49]. So far, the effect of Amadori compounds in the gut microbiome has not been well identified, and it needs to be assessed whether these compounds can really increase the concentration of SCFAs by affecting the digestion of a particular gut bacterial species in humans.

Conclusion

The effect of the MR on allergic diseases is complex. The MR changes structures and/or electrostatic properties of certain proteins including allergens by glycation. It may reduce, enhance, or not alter the immunogenicity and allergenicity of food proteins. So far, studies indicate that there is no generic way to predict the effect of the MR on the immunogenicity and allergenicity of food proteins. Dietary AGEs may promote allergic inflammation by amplifying inflammatory cascades via RAGE engagement. In addition, dietary MR products might act as a double-edged sword by affecting the gut microbiota through negative selection (through inducing unfavorable bacterial species) or positive selection (inducing favorable bacterial species that can utilize the MR products for immune modulation). Further investigation in the biological and immunological properties of MR products is needed to elucidate the role of the MR in the pathogenesis of allergic diseases and to establish dietary strategies for the prevention and treatment of such diseases.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

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References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Hellwig M, Henle T. Baking, ageing, diabetes: a short history of the Maillard reaction. Angew Chem Int Ed Engl. 2014;53(39):10316–29.
2. Berrens L. Neoallergens in heated pecan nut: products of Maillard-type degradation? Allergy. 1996;51:277–8.

3. Toda M, Heilmann M, Ilchmann A, et al. The Maillard reaction and food allergies: is there a link? Clin Chem Lab Med. 2014;52(1):61–7.
4. Gupta RK, Gupta K, Sharma A, Das M, Ansari IA, Dwivedi PD. Maillard reaction in food allergy: pros and cons. Crit Rev Food Sci Nutr. 2018;58(2):208–26.
5. Teodorowicz M, van Neerven J, Savelkoul H. Food processing: the influence of the Maillard reaction on immunogenicity and allergenicity of food proteins. Nutrients. 2017;9(8):835
6. Scheurer S, Lauer I, Foetisch K, Moncin MSM, Retzek M, Hartz C, et al. Strong allergenicity of Pru av 3, the lipid transfer protein from cherry, is related to high stability against thermal processing and digestion. J Allergy Clin Immunol. 2004;114(4):900–7.
7. Vissers YM, Iwan M, Adel-Patient K, Stahl Skov P, Rigby NM, Johnson PE, et al. Effect of roasting on the allergenicity of major peanut allergens Ara h 1 and Ara h 2/6: the necessity of degranulation assays. Clin Exp Allergy. 2011;41(11):1631–42.
8. Cucu T, De Meulenaer B, Bridts C, et al. Impact of thermal processing and the Maillard reaction on the basophil activation of hazelnut allergic patients. Food Chem Toxicol. 2012;50(5):1722–8.
9. Zani IA, Stephen SL, Mughal NA, Russell D, Homer-Vanniasinkam S, Wheatcroft S, et al. Scavenger receptor structure and function in health and disease. Cell. 2015;4(2):178–201.
10. Ramasamy R, Yan SF, Schmidt AM. Advanced glycation endproducts: from precursors to RAGE: round and round we go. Amino Acids. 2012;42(4):1151–61.
11. Sakaguchi M, Kinoshita R, Putranto EW, et al. Signal diversity of receptor for advanced glycation end products. Acta Med Okayama. 2017;71(6):459–65.
12.•• Ilchmann A, Burgdorf S, Scheurer S, et al. Glycation of a food allergen by the Maillard reaction enhances its T-cell immunogenicity: role of macrophage scavenger receptor class A type I and II. J Allergy Clin Immunol. 2010;125(1):175–83 **This study was the first to show that AGEs of a food allergen possess higher T cell immunogenicity than native form of molecule due to binding to SR-A expressed on the cell surface of DCs.**
13. Heilmann M, Wellner A, Gadermaier G, Ilchmann A, Briza P, Krause M, et al. Ovalbumin modified with pyrraline, a Maillard reaction product, shows enhanced T-cell immunogenicity. J Biol Chem. 2014;289(11):7919–28.
14. Perusko M, van Roest M, Stanic-Vucinic D, et al. Glycation of the major milk allergen β-lactoglobulin changes its allergenicity by alterations in cellular uptake and degradation. Mol Nutr Food Res. 2018;62(17):e1800341.
15. Buttari B, Profumo E, Capozzi A, Facchiano F, Saso L, Sorice M, et al. Advanced glycation end products of human β-glycoprotein I modulate the maturation and function of DCs. Blood. 2011;117(23):6152–61.
16. Rowan S, Bejarano E, Taylor A. Mechanistic targeting of advanced glycation end-products in age-related diseases. Biochim Biophys Acta Mol basis Dis. 2018;1864(12):3631–43.
17. Rojas A, Morales M, Gonzalez I, Araya P. Inhibition of RAGE axis signaling: a pharmacological challenge. Curr Drug Targets. 2018;19.
18. Ramasamy R, Shekhtman A, Schmidt AM. The multiple faces of RAGE-opportunities for therapeutic intervention in aging and chronic disease. Expert Opin Ther Targets. 2016;20(4):431–46.
19. Akirav EM, Henegariu O, Preston-Hurlburt P, Schmidt AM, Clynes R, Herold KC. The receptor for advanced glycation end products (RAGE) affects T cell differentiation in OVA induced asthma. PLoS One. 2014;9(4):e95678.
20. Durning SP, Preston-Hurlburt P, Clark PR, Xu D, Herold KC, Type 1 Diabetes TrialNet Study Group. The receptor for advanced glycation endproducts drives T cell survival and inflammation in type 1 diabetes mellitus. J Immunol. 2016;197(8):3076–85.
21. Henle T. AGEs in foods: do they play a role in uremia? Kidney Int Suppl. 2003;84:S145–7.
22. Poulsen MW, Hedegaard RV, Andersen JM, de Courten B, Bügel S, Nielsen J, et al. Advanced glycation endproducts in food and their effects on health. Food Chem Toxicol. 2013;60:10–37.
23. Tessier FJ, Niquet-Léridon C, Jacolot P, Jouquand C, Genin M, Schmidt AM, et al. Quantitative assessment of organ distribution of dietary protein-bound 13C-labeled Nε-carboxymethyllysine after a chronic oral exposure in mice. Mol Nutr Food Res. 2016;60(11):2446–56.
24.•• Oczypok EA, Perkins TN, Oury TD. All the "RAGE" in lung disease: the receptor for advanced glycation endproducts (RAGE) is a major mediator of pulmonary inflammatory responses. Paediatr Respir Rev. 2017;23:40–9 **This review article discusses the role of RAGE in the development of pulmonary inflammation including asthma.**
25. Smith PK. Do advanced glycation end-products cause food allergy? Curr Opin Allergy Clin Immunol. 2017;17(5):325–31.
26. Smith PK, Masilamani M, Li XM, Sampson HA. The false alarm hypothesis: food allergy is associated with high dietary advanced glycation end-products and proglycating dietary sugars that mimic alarmins. J Allergy Clin Immunol. 2017;139(2):429–37.
27. Clarke RE, Dordevic AL, Tan SM, Ryan L, Coughlan M. Dietary advanced glycation end products and risk factors for chronic disease: a systematic review of randomised controlled trials. Nutrients. 2016;8(3):125.
28. Van Puyvelde K, Mets T, Njemini R, et al. Effect of advanced glycation end product intake on inflammation and aging: a systematic review. Nutr Rev. 2014;72:638–50.
29. Semba RD, Gebauer SK, Baer DJ, Sun K, Turner R, Silber HA, et al. Dietary intake of advanced glycation end products did not affect endothelial function and inflammation in healthy adults in a randomized controlled trial. J Nutr. 2014;144(7):1037–42.
30. Baye E, de Courten MP, Walker K, et al. Effect of dietary advanced glycation end products on inflammation and cardiovascular risks in healthy overweight adults: a randomised crossover trial. Sci Rep. 2017;7(1):4123.
31. Calder CL, Ortega G, Vij A, Chawla K, Nnamdi-Emetarom C, Stephanie S, et al. Morbid obesity is an independent risk factor for postoperative renal dysfunction in young adults: a review of the American College of Surgeons National Surgical Quality Improvement Program database. Am J Surg. 2016;211(4):772–7.
32. Ott C, Jacobs K, Haucke E, Navarrete Santos A, Grune T, Simm A. Role of advanced glycation end products in cellular signaling. Redox Biol. 2014;2:411–29.
33. Nogueira-Machado JA, Volpe CM, Veloso CA, et al. HMGB1, TLR and RAGE: a functional tripod that leads to diabetic inflammation. Expert Opin Ther Targets. 2011;15(8):1023–35.
34.•• Hudson BI, Lippman ME. Targeting RAGE Signaling in inflammatory disease. Annu Rev Med. 2018;69:349–64 **This review article discusses the role of RAGE and DAMP in the development of inflammation.**
35. Ibrahim ZA, Armour CL, Phipps S, Sukkar MB. RAGE and TLRs: relatives, friends or neighbours? Mol Immunol. 2013;56(4):739–44.
36. Huang YJ, Marsland BJ, Bunyavanich S, O'Mahony L, Leung DYM, Muraro A, et al. The microbiome in allergic disease: current understanding and future opportunities-2017 PRACTALL document of the American Academy of Allergy, Asthma & Immunology and the European Academy of Allergy and Clinical Immunology. J Allergy Clin Immunol. 2017;139(4):1099–110.
37. Gilbert JA, Quinn RA, Debelius J, Xu ZZ, Morton J, Garg N, et al. Microbiome-wide association studies link dynamic microbial consortia to disease. Nature. 2016;535(7610):94–103.
38. Yacoub R, Nugent M, Cai W, Nadkarni GN, Chaves LD, Abyad S, et al. Advanced glycation end products dietary restriction effects on bacterial gut microbiota in peritoneal dialysis patients; a randomized open label controlled trial. PLoS One. 2017;12(9):e0184789.

39. Rosenbaum JT, Asquith MJ. The microbiome: a revolution in treatment for rheumatic diseases? Curr Rheumatol Rep. 2016;18(10):62.
40. Seiquer I, Rubio LA, Peinado MJ, Delgado-Andrade C, Navarro MP. Maillard reaction products modulate gut microbiota composition in adolescents. Mol Nutr Food Res. 2014;58(7):1552–60.
41. Corzo-Martínez M, García-Campos G, Montilla A, Moreno FJ. Tofu whey permeate is an efficient source to enzymatically produce prebiotic fructooligosaccharides and novel fructosylated α-galactosides. J Agric Food Chem. 2016;64(21):4346–52.
42. Bui TP, Ritari J, Boeren S, et al. Production of butyrate from lysine and the Amadori product fructoselysine by a human gut commensal. Nat Commun. 2015;6:10062.
43. Hellwig M, Bunzel D, Huch M, Franz CMAP, Kulling SE, Henle T. Stability of individual Maillard reaction products in the presence of the human colonic microbiota. J Agric Food Chem. 2015;63(30):6723–30.
44. Koh A, De Vadder F, Kovatcheva-Datchary P, et al. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. Cell. 2016;165(6):1332–45.
45. McKenzie C, Tan J, Macia L, Mackay CR. The nutrition-gut microbiome-physiology axis and allergic diseases. Immunol Rev. 2017;278(1):277–95.
46. Sivaprakasam S, Prasad PD, Singh N. Benefits of short-chain fatty acids and their receptors in inflammation and carcinogenesis. Pharmacol Ther. 2016;164:144–51.
47. Zeng H, Chi H. Metabolic control of regulatory T cell development and function. Trends Immunol. 2015;36(1):3–12.
48. Nylund L, Nermes M, Isolauri E, Salminen S, de Vos WM, Satokari R. Severity of atopic disease inversely correlates with intestinal microbiota diversity and butyrate-producing bacteria. Allergy. 2015;70(2):241–4.
49. Wopereis H, Sim K, Shaw A, Warner JO, Knol J, Kroll JS. Intestinal microbiota in infants at high risk for allergy: effects of prebiotics and role in eczema development. J Allergy Clin Immunol. 2018;141(4):1334–42.