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

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Background: The Maillard reaction occurs between reducing sugars and proteins during thermal processing of foods. It produces chemically glycated proteins termed advanced glycation end products (AGEs). The glycation structures of AGEs are suggested to function as pathogenesis-related immune epitopes in food allergy.
Objective: This study aimed at defining the T-cell immunogenicity of food AGEs by using ovalbumin (OVA) as a model allergen.
Methods: AGE-OVA was prepared by means of thermal processing of OVA in the presence of glucose. Activation of OVA-specific $CD4^+$ T cells by AGE-OVA was evaluated in cocultures with bone marrow–derived murine myeloid dendritic cells (mDCs) as antigen-presenting cells. The uptake mechanisms of mDCs for AGE-OVA were investigated by using inhibitors of putative cell-surface receptors for AGEs, as well as mDCs deficient for these receptors.
Results: Compared with the controls (native OVA and OVA thermally processed without glucose), AGE-OVA enhanced the activation of OVA-specific $CD4^+$ T cells on coculture with mDCs, indicating that the glycation of OVA enhanced the T-cell immunogenicity of the allergen. The mDC uptake of AGE-OVA was significantly higher than that of the controls. We identified scavenger receptor class A type I and II (SR-AI/II) as a mediator of the AGE-OVA uptake, whereas the receptor for AGEs and galectin-3 were not responsible. Importantly, the activation of OVA-specific $CD4^+$ T cells by AGE-OVA was attenuated on coculture with SR-AI/II–deficient mDCs.
Conclusion: SR-AI/II targets AGE-OVA to the MHC class II loading pathway in mDCs, leading to an enhanced $CD4^+$ T-cell activation. The Maillard reaction might thus play an important role in the T-cell immunogenicity of food allergens. (J Allergy Clin Immunol 2010;125:175-83.)

Key words: *Food allergy, food allergen, Maillard reaction, T-cell immunogenicity, dendritic cells, macrophage scavenger receptor*

The Maillard reaction is a chemical reaction between reducing sugars and proteins and generates the so-called advanced glycation end products (AGEs; ie, protein derivatives with glycation structures, such as Nϵ-carboxyethyl-lysine [CEL], Nϵ-carboxymethyl-lysine [CML], pyrralin, and GA-pyridine).[1] Because the Maillard reaction occurs during storage and thermal processing of foods, a possible involvement of AGEs in the pathology of food allergy is of great concern. This assumption is corroborated by the fact that some patients with food allergy show anaphylactic reactions only against stored or heated foods.[2,3] Moreover, the presence of AGEs in food allergens could be linked to an increased binding ability of IgEs from patients allergic to the respective allergen.[4-7] These observations suggest that the Maillard reaction creates new pathogenesis-related immune epitopes in patients with food allergy.

Several studies have shown diverse effects of AGEs on dendritic cells (DCs). For instance, AGEs derived from BSA augmented maturation of human DCs and increased their capacity to stimulate allogeneic T-cell activation.[8] In contrast, adrenocorticotropic hormone–derived AGEs were shown to inhibit the

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Abbreviations used
AGE: Advanced glycation end product
APC: Antigen-presenting cell
CEL: Nϵ-carboxyethyl-lysine
CFSE: Carboxyfluorescein succinimidyl ester
CML: Nϵ-carboxymethyl-lysine
DC: Dendritic cell
FITC: Fluorescein isothiocyanate
GA: Glycolaldehyde
mDC: Myeloid dendritic cell
MR: Mannose receptor
OVA: Ovalbumin
RAGE: Receptor for AGEs
SR-AI/II: Scavenger receptor class A type I and II

maturation and T-cell stimulatory capacity of the human DCs.[9] Together, these observations suggest that T-cell immunogenicity of antigens could be influenced by the Maillard reaction. However, the effect of AGEs derived from food allergens on DC function, the subsequent activation of allergen-specific T cells, or both is poorly understood.

Antigen-specific T-cell activation is preceded by the uptake of antigens by DCs. Receptors expressed on the cell surface mediate the majority of antigen uptake by DCs.[10,11] Importantly, antigen-presenting cells (APCs), such as DCs and macrophages, express several receptors known to bind AGEs, such as the so-called receptor for AGEs (RAGE),[12,13] galectin-3,[14] macrophage scavenger receptor class A type I and II (SR-AI/II),[15,16] scavenger receptor class B type I,[17] and CD36.[18] These receptors have been identified by investigating endothelial cells,[12,13] macrophages,[15,16] or Chinese hamster ovary cells transfected with putative receptors for AGEs.[14,17,18] However, the receptors that mediate the uptake of AGEs by DCs remain to be identified.

The aim of this study was to define the influence of the Maillard reaction on the T-cell immunogenicity of food allergens. We used AGE-ovalbumin (OVA; ie, the Maillard reaction products of glucose and the egg white allergen OVA) as a food allergen model of AGEs. We found that AGE-OVA does not trigger the maturation of bone marrow–derived murine myeloid dendritic cells (mDCs) but enhances the activation of allergen-specific $CD4^+$ T cells. Moreover, we demonstrated that the enhanced T-cell immunogenicity of AGE-OVA depends on a SR-AI/II–mediated uptake of AGE-OVA by mDCs. Our findings support the significance of AGEs as pathogenesis-related factors in food allergy.

METHODS

Mice

C57BL/6 J (B6) mice and SR-AI/II–deficient mice on a B6 background were purchased from Jackson Laboratories (Bar Harbor, Me).[19] RAGE-deficient mice on a B6 background were kindly provided by Dr T. Shoji (Osaka Medical College, Osaka, Japan).[20] OT-II mice expressing a T-cell receptor specific for the peptide $OVA_{323–339}$ were kindly provided by Professor H. Schild and Dr S. Sudowe (Johannes-Gutenberg-University, Mainz, Germany).[21] Mice were housed under pathogen-free conditions, and animal experiments were performed in compliance with German legislation.

Preparation of AGE-OVA and AGE-BSA

AGE-OVA and AGE-BSA (ie, the Maillard reaction products) were prepared as described previously.[22] Briefly, 1 mmol/L OVA or BSA (Sigma-Aldrich, Steinheim, Germany) was incubated with 1 mol/L glucose in 100 mmol/L sodium phosphate buffer (pH 7.4) at 50°C for 6 weeks. OVA incubated under the same conditions but without glucose and native OVA were used as controls. Protein concentrations of the final samples were measured by using a bicinchoninic acid assay kit (Pierce, Rockford, Ill). The protein concentration was further verified by analyzing valin concentrations using ion-exchange chromatography with Ninhydrin postcolumn derivatization after acid and enyzmatic hydrolysis because valin is not modified by the Maillard reaction.[23]

Verification of glycation structures in AGE-OVA

A protocol is described in the Methods section of this article's Online Repository at www.jacionline.org.

Preparation of recombinant OVA

A protocol is described in the Methods section of this article's Online Repository.

Fluorescein isothiocyanate labeling of OVAs

A protocol is described in the Methods section of this article's Online Repository.

Generation of bone marrow–derived mDCs

A protocol is described in the Methods section of this article's Online Repository.

Assessment of mDC maturation

A protocol is described in the Methods section of this article's Online Repository.

Assessment of T-cell activation and proliferation

Splenic $CD4^+$ T cells were isolated from OT-II mice using an isolation kit from Miltenyi Biotec (Bergisch Gladbach, Germany). $CD4^+$ T cells (8.0×10^5 cells/mL) were cocultured with mDCs (1.6×10^5 cells/mL) and stimulated with either form of OVA for 24 hours to evaluate T-cell activation. In the experiment with SR-AI/II–deficient mDCs the APCs (2.5×10^6 cells/mL) were first incubated with either form of OVA for 3 hours and then fixed with 0.008% glutaraldehyde before 21 hours of coculturing with $CD4^+$ T cells (5.0×10^6 cells/ml). After coculturing, the concentration of IL-2 in the supernatants was measured by means of ELISA (eBioscience, San Diego, Calif). $CD4^+$ T cells were first stained for 15 minutes with 10 μmol/L carboxyfluorescein succinimidyl ester (CFSE; Invitrogen, Karlsruhe, Germany) and then cocultured with mDCs stimulated with either form of OVA to evaluate T-cell proliferation. Cell proliferation was evaluated by measuring the intensity of CFSE in the $CD4^+$ T cells with a flow cytometer, LSR II (BD Bioscience, Heidelberg, Germany). Data were analyzed with FlowJo version 7 software (Treestar, Inc, Ashland, Ore).

Assessment of the uptake of AGE-OVA by mDCs

mDCs (1.0×10^6 cells/mL) were incubated for 15 minutes with fluorescein isothiocyanate (FITC) conjugates of AGE-OVA or of native OVA and OVA thermally processed without glucose as controls. Lactose (150 mmol/L; Sigma-Aldrich) was added to the mDCs 30 minutes before the addition of AGE-OVA or the controls to inhibit a possible galectin-3–mediated uptake.[24] Only samples with a comparable FITC/protein molar ratio were used to evaluate the uptake level of AGE-OVA and the controls. After incubation with FITC conjugates of AGE-OVA or the controls, mDCs were stained with both phycoerythrin-conjugated anti-mouse CD11b and allophycocyanin-conjugated anti-mouse CD11c mAbs. The FITC intensity of $CD11b^+CD11c^+$ cells was then analyzed by using flow cytometry. mDCs were first fixed with 4% paraformaldehyde solution (Pierce) after incubation of

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