Potential role of advanced glycation end products in the T_H2 adjuvant effect of peanut protein

To the Editor:

Ruiter et al showed that peanut protein induces a T_H2 response by eliciting retinaldehyde dehydrogenase production in myeloid antigen-presenting cells.[1] Noting that such an effect can also be produced by pathogen-associated molecular patterns, Ruiter et al[1] excluded the possibility that the effect was produced by endotoxin or aflatoxin. However, they did not exclude the possible role of advanced glycation end products (AGEs).

AGEs are created during the browning of foods, including during the roasting of peanuts, and they contribute to peanuts' allergenicity.[2] AGEs activate the same receptor (receptor for advanced glycation end products [RAGE]) as does the damage-associated molecular pattern HMGB1.[3] Although some of the experiments reported by Ruiter et al[1] used raw peanut extract, key studies showing gene expression and enzyme production used an extract made from roasted peanuts.

In addition to their deleterious effects in conditions ranging from asthma, atherosclerosis, and diabetes to aging and Parkinson disease,[4,5] AGEs have been hypothesized to be a root cause of food allergy.[3]

An argument against the role of AGEs here is that they work via the stimulation of Toll-like receptor (TLR) 4, whereas in the study by Ruiter et al[1] signaling of the antigen-presenting cells occurred largely via TLR1 and TLR2. However, Ruiter et al[1] found that blocking TLR1/TLR2 reduced enzyme expression by 70%. Was the other 30% due to AGEs?

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Disclosure of potential conflict of interest: J. D. Miller is the owner and President of Mission: Allergy, Inc.

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https://doi.org/10.1016/j.jaci.2021.08.033

Reply

To the Editor:

We thank Miller[1] for his interest in our article "Peanut protein acts as a T_H2 adjuvant by inducing RALDH2 in human antigen-presenting cells,"[2] which appeared in the July 2021 issue of the *Journal of Allergy and Clinical Immunology*. Miller[1] raised the interesting point of a potential role of advanced glycation end products (AGEs) in the T_H2 adjuvant effect of peanut protein. AGEs are present in raw peanuts, and their levels are increased during the process of roasting, which is known to contribute to peanuts' allergenicity.[3] These components activate the receptor for advanced glycation end products (RAGE), and AGEs have been shown to stimulate human dendritic cells and promote T_H2 responses.[4]

In the experiments that we performed for our article,[2] we did not specifically study the role of AGEs or RAGE in the induction of RALDH2 in human antigen-presenting cells by peanut protein. Miller[1] pointed out correctly that most of the data were generated by using protein extracts from roasted peanuts. Nevertheless, for some experiments we used a highly potent fraction (labeled PN Fr in our article[2]) from a protein extract made from raw peanuts, which we described in the Methods section of our article. This fraction strongly induced expression of RALDH2 in myeloid dendritic cells (mDCs) as well as monocytes, and we used PN Fr to elucidate the role of the Toll-like receptor 1 (TLR1)/TLR2 heterodimer in the induction of RALDH2 by peanut protein. Furthermore, we found that a protein extract from raw peanuts was twice as potent as an extract from roasted peanuts of the same cultivar (Jumbo Virginia) in inducing expression of RALDH2 in mDCs (data not shown in the article). Together, these observations indicate that raw peanut protein strongly induces RALDH2 in mDCs and that this capacity is not increased by roasting. This would argue against the involvement of AGEs, but we cannot rule it out with certainty. To definitively prove that AGEs are not involved in the induction of RALDH2 by peanut protein in human mDCs, it will be necessary to block or inhibit signaling through RAGE.

Although AGEs seem unlikely to play a major role in the induction of RALDH2 in human antigen-presenting cells, this does not exclude their involvement in the T_H2 adjuvant effect of peanut protein. In this regard, it is interesting to note that we observed a T_H2-skewing effect of peanut protein even in the mDC–T-cell cocultures without the RALDH2 substrate retinaldehyde (Fig 5 *D* and *F* in our article[2]). These data suggest that in addition to the induction of RALDH2 in antigen-presenting cells, there are other mechanisms by which peanut protein acts as a T_H2 adjuvant. Previously, our group has shown that the peanut glycoprotein allergen *Arachis hypogaea* 1 binds to the C-type lectin receptor DC-SIGN and activates human dendritic cells to induce T_H2 differentiation of naive T cells.[5] It is tempting to speculate that the activation of RAGE on human antigen-presenting cells by peanut-derived AGEs also contributes to the T_H2-skewing properties of peanut protein, and this will be an interesting subject of further study.

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Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

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