Editorial

IgG4 is closely associated with eosinophilic esophagitis

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What this study means

Rosenberg *et al.*'s study (1) confirms the presence of abundant IgG4 in eosinophilic esophagitis (EoE) and has added important novel findings: that the abundant IgG4 is also present in pediatric EoE patients, that IgG4 content correlates with the degree of disease activity as measured by both eosinophil counts and by other histologic findings, and that IgG4 content also correlates with many, but not all, of the EoE mRNA markers. Of particular note is the correlation with IL-10, which induces expression of IgG4 rather than IgE (2). Together, these findings show that IgG4 is closely associated with EoE. This is an important confirmation and extension of the prior work. In contrast, relatively modest and variable IgG4 associations are seen in many other allergic and inflammatory diseases.

What IgG4 means in the context of EoE

Unlike classical IgE-mediated allergies like asthma, EoE does not respond to omalizumab, an anti-IgE monoclonal antibody (3). The lack of an IgE effect could be because IgG4 and other non-IgE antibodies function as blocking antibodies inhibiting IgE mast cell or basophil activation (4), as well as by binding mast cell FcGRIIb receptors (5). There is no evidence for IgG4 in the direct pathogenesis of EoE. There is instead compelling evidence in a mouse model (6) and some evidence in humans (7) that Th2 lymphocytes might be crucial in the development of EoE.

Future directions

While we (3) and others (8) have demonstrated IgG4 specific to the usual EoE trigger foods, we have found that the food specificity of serum IgG4 antibodies is a relatively poor predictor of which food(s) trigger EoE in a particular patient (unpublished observations). It remains unclear whether the food specificity of local/locally produced IgG4 will better predict the trigger foods.

The authors, correctly in my view, favor that the IgG4 is largely made locally. A detailed understanding of the immune response in the subepithelial stroma, where nearly all the local IgG4 plasma cells reside (3), will be needed to fully understand this disease. While this site is relatively inaccessible, new biopsy techniques allow biopsy of deeper tissue; and early studies have been done (9). I agree with the authors that the IgG4 and the associated IL-10 noted here, as well as the occasional induction of EoE by oral immunotherapy (10), suggest that EoE is not solely an allergy, but also, in part, an immunoregulatory immune response. The presence of regulatory B cells as well as TGF-beta-related induced regulatory T cells are both highly likely to be present in this tissue site.

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