The Role of Lymphocytes in Eosinophilic Gastrointestinal Disorders

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KEYWORDS

• Eosinophilic esophagitis • Eosinophilic gastroenteritis
• Lymphocyte • helper T cell • Food allergy

Eosinophilic gastrointestinal disorders (EGIDs) encompass a variety of disorders named after the organ of involvement with inflammation and eosinophilia and its resultant symptoms. EGIDs include specific entities such as eosinophilic esophagitis (EoE), eosinophilic gastroenteritis (EG), and eosinophilic colitis.[1] Although the pathogenesis of EGIDs is still poorly understood, dietary food antigens have been shown to cause EGIDs through several short-term clinical studies. Various clinical trials of food elimination resulted in various degrees of clinical response and histologic improvement. These trials included amino acid–based formula therapy[2–4] and elimination of suspected allergens based on testing[5] or elimination of six major allergens.[6] Reintroduction of the foods resulted in reoccurrence of symptoms,[2] proving a causative relationship of EGIDs to food antigens. This relationship of EGIDs with food allergy points to a potential breach of oral tolerance in EGIDs and to a potentially important role played by lymphocytes in responding to the oral food antigens. In this article, the concept of oral tolerance is discussed briefly, focusing on the role of regulatory T lymphocytes in the process. Discussion then centers on the available evidence for the role that lymphocytes play in the induction and pathogenesis of EGIDs, focusing specifically on T lymphocytes carrying the type 2 helper T-cell phenotype (T_H2), which is important in mediating allergic phenomena. The authors also summarize available evidence for a potential breach in oral tolerance in EGIDs. Among the EGIDs, EoE

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and EG are particularly discussed because they have been the most extensively studied and the most challenging subsets of EGIDs to clinicians and researchers alike.

ORAL TOLERANCE

The gastrointestinal tract is the largest immunologic organ in the body. Despite the large extent of dietary antigenic exposure, only a small percentage of individuals develop food allergy, which is due to the development of oral tolerance to dietary proteins. Oral tolerance refers to a state of active inhibition of immune responses to an antigen by means of prior exposure to that antigen through the oral route.[7]

Normally, dietary proteins that escape gastrointestinal luminal digestion and processing come in contact with the intestinal epithelium and the underlying mucosal immune system in various ways. Dietary antigens can be sampled by intestinal dendritic cells that extend processes into the lumen.[8] Particulate antigens can be taken up by microfold cells overlying Peyer's patches and delivered to dendritic cells in the subepithelial dome region and then to underlying B-cell follicles of the Peyer's patches.[9,10] Immunoglobulin (Ig)A switching occurs in these cells, mediated by transforming growth factor (TGF)-β–secreting T cells, hence contributing to oral tolerance.[11] Soluble dietary antigens may cross the intestinal epithelium through transcellular or paracellular routes to encounter T lymphocytes or macrophages in the lamina propria.[12,13] In addition to dendritic cell–presenting antigens, intestinal epithelial cells are thought to act as nonprofessional antigen-presenting cells given that they constitutively express major histocompatibility complex class II molecules on their basolateral membranes[14,15] and present antigen to primed T cells.

After the dietary antigen is in contact with immune cells, oral tolerance can be induced by two mechanisms, depending on the quantity of antigen (**Fig. 1**). High-dose oral tolerance is mediated by lymphocyte anergy,[16] which occurs through T-cell receptor ligation in the absence of costimulatory signals[17] or by lymphocyte deletion, which occurs by means of Fas-mediated apoptosis (see **Fig. 1**B).[18] Low-dose tolerance is mediated by regulatory T cells. In addition to $CD8^+$ T cells[19,20] and natural killer T cells,[21] various types of regulatory $CD4^+$ T cells play a role in low-dose tolerance.[22–24] These cells include T_H3 cells, which mediate suppression through secreted TGF-β,[25,26] T regulatory cells 1 that mediate suppression through secreted interleukin (IL)-10,[27] and $CD4^+CD25^+$ cells that mediate suppression possibly through surface-bound TGF-β (see **Fig. 1**C).[28,29] A breach in any of these mechanisms has been demonstrated to result in loss of oral tolerance to an antigen in animal models and is hypothesized to lead to food allergies in humans.[30]

EOSINOPHILIC ESOPHAGITIS

Lymphocytes are Increased in Number in Eosinophilic Esophagitis

Rare intraepithelial lymphocytes are normally found in the esophagus of healthy individuals.[31–33] These cells were historically referred to as squiggle cells by histopathologists because of their irregular nuclear contours resulting from their intermingling with esophageal epithelial cells, as seen by microscopic examination of hematoxylin and eosin–stained sections of the esophageal mucosa.[33] Squiggle cells were found to be T lymphocytes.[32,33] In the esophageal epithelial layer, suppressor T cells ($CD8^+$) are more frequent than helper T cells ($CD4^+$);[31,34] whereas in the esophageal lamina propria, lymphocytes are comprised mainly of helper T cells.[34]

The number of esophageal intraepithelial T lymphocytes is increased in patients who have EoE compared with healthy control subjects, as demonstrated by immunohistochemical staining for $CD3^+$ cells.[31,35,36] Both CD4 and CD8 subsets of the T lymphocytes were found to be increased in EoE, with maintenance of CD8

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