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Allergic mechanisms of Eosinophilic oesophagitis

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A B S T R A C T

Eosinophilic oesophagitis (EoE) is characterized by oesophageal dysfunction and oesophageal eosinophilia refractory to proton-pump-inhibitor treatment. EoE is a food allergy, as elimination of food trigger(s) abrogates the disease, while trigger reintroduction causes recurrence. The allergic mechanism of EoE involves both IgE and non-IgE processes. There is a break in oral tolerance, the immune mechanism allowing enteric exposure to food and micro-organisms without causing deleterious immune responses. Changes in life-style, alterations in gut flora and use of antibiotics may be increasing disease prevalence. Mouse models of EoE and human studies revealed the role of regulatory T-cells and iNKT-cells in the pathogenesis. Th2-cytokines like IL-4, IL-5 and IL-13, and other cytokines like TGFβ and TSLP are involved, but perhaps no one cytokine is critically important for driving the disease. Control of EoE may require a pharmaceutical approach that blocks more than one target in the Th2-inflammatory pathway.

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Introduction

The concept of eosinophilic oesophagitis (EoE) as a food allergy seems foreign to many patients, and even physicians, since EoE does not exhibit the typical symptoms associated with allergic reactions, like hives, swelling, pruritus, wheezing or anaphylaxis. Instead, it causes symptoms of oesophageal dysfunction, such as dysphagia, food impaction, vomiting and pain. The National Institute of Allergy and Infectious Disease expert panel defines food allergy as "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food" [1]. According to this definition, EoE is unambiguously a food allergy since elimination of the food trigger abrogates the disease, while reintroduction causes disease recurrence [2,3]. Histologically, EoE is characterized by significant oesophageal eosinophilia (>15 eos/HPF) refractory to treatment with proton-pump-inhibitors (PPIs) [4].

Oesophageal eosinophilia was first described by Dobbins and colleagues in 1977 in a patient with concurrent eosinophilic gastroenteritis and a normal pH study [5]. Landres and co-workers, in 1978, reported the first case of eosinophilic infiltration isolated to the oesophagus with associated oesophageal dysfunction [6]. The absence of acid reflux, based on a negative pH study, suggested factors other than gastroesophageal reflux disease (GERD) were operative. Two case series, published in 1982 and 1985, concluded GERD was the underlying cause of EoE [7,8].

However this paradigm of oesophageal eosinophilia as a result of GERD shifted in 1993 when Attwood and colleagues retrospectively compared patients with oesophageal eosinophilia who had normal and abnormal 24-hour pH studies [9]. They concluded that patients with significant oesophageal eosinophilia, dysphagia, and a normal pH study represented a distinct clinical group caused by factors other than GERD. In 1995, Kelly and colleagues published convincing evidence that food proteins were the cause of this non-GERD trigger of oesophageal eosinophilia [2]. They showed elimination of food proteins from the diet by administrating amino-acid based elemental diets significantly reduced PPI-refractory oesophageal eosinophilia and improved clinical symptoms. Moreover, reintroduction of the food proteins caused recurrence of the symptoms. Markowitz and colleagues replicated these observations in 2003 with a larger cohort [10]. Recent clinical trials with empirical elimination diet [11] and skin testing-directed elimination diet [3] further support EoE as a food allergen-driven disease. Although there is overwhelming evidence that food allergens drive EoE, not all patients achieve histological and/or symptomatic remission with elimination diets. This discrepancy may result from non-compliance to treatment or other allergic triggers (e.g. aeroallergens).

This review discusses our current understanding of the allergic mechanisms involved in EoE. Also delineated are potential therapeutic targets and opportunities for future research.

IgE or non-IgE mediated?

Food allergy is classified based on the mechanism of antigen recognition: IgE-mediated (immediate type) or non-IgE-mediated (delayed type). Food allergy is usually caused by IgE-mediated reactions. IgE-mediated food allergy is characterized by a reproducible, rapid onset of symptoms after ingesting the offending food. The classic example is the immediate development of hives, swelling, and wheezing after consuming peanuts in an individual with IgE-mediated peanut allergy. To trigger an IgE-mediated food allergic reaction, an individual must first be exposed to the food antigen and become sensitized by producing antigen-specific IgE antibodies. During sensitization, activated antigen-presenting cells (APCs) prime the native T-cells to differentiate into Th2-cells, which provide the signals necessary to induce B-cell class-switching to generate IgE. These antigen-specific IgE molecules attach to the surface of mast cells. Upon re-exposure to the offending substance, the allergen crosslinks the IgE molecules on the mast cells, causing rapid release of their preformed inflammatory mediators. This response is followed by subsequent *de novo* synthesis and release of lipid mediators, cytokines and chemokines that orchestrate a late phase immune response during which inflammatory cells such as eosinophils infiltrate tissue.

Although EoE patients do not exhibit the typical IgE-mediated food allergic reactions, their oesophageal lining, and only their oesophageal lining, acquires the characteristic elements of an IgE-mediated response, such as dendritic cells (DCs), antigen-specific IgE, class-switched B-cells [12],