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Commentary Article

Are Intestinal Leukotrienes the Directors of Food Allergy?

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Abstract

Oxidative stress in the intestine, if not counteracted by an antioxidant-rich diet, can generate new substances called pseudoleukotrienes (ØLTs).

These ØLTs appear to activate inflammatory signals and immune cells (like mast cells and type 2 helper T cells), potentially increasing the risk of an allergic reaction in sensitized individuals.

Recent research highlighted the role of an intestinal enzyme, Dipeptidase 1 (DPEP1), which can protect against severe anaphylaxis by degrading leukotrienes, key mediators of allergic reactions.

Enriching the modern diet with polyphenols could be an effective strategy to counteract oxidative stress and prevent or mitigate food allergies. Developing drugs that prevent the free radical process at intestine level as well drugs which block the generation of LTs by intestinal mast cells may represent new pharmacological approach to the treatment of food allergy.

Keywords: Pseudoleukotriene; Immune Cells; Food Allergies

Introduction

Epidemiological studies report an increase in food allergy cases even in developing countries [1-3]. Among the hypothesized causes for the increase in food allergies is the rapid dietary changes that have occurred in recent decades [4]. In particular, the depletion of antioxidants (polyphenols) in the foods consumed by most people in industrialized countries is highlighted [5,6]. Recently, Si-Yang Liu, et al., have demonstrated that oxidative stress causes the generation of a family of sulfidopeptides derived from octanoic acid similar to cysteinyl leukotrienes, named by the authors pseudoleukotriene (øLT)C, øLTD and øLTE, as they are structurally analogous to LTC4, LTD4 and LTE4 [7].

Pseudoleukotrienes may have activities similar to CysLTs, e.g., triggering inflammatory signals within epithelial cells of the airways and likely the intestine. They activate type 2 helper T cells and type 2 innate lymphoid cells, with consequent expansion of goblet cells, which facilitate allergen passage and expansion of tissue mast cells.

Leukotrienes are known to be among the mediators of anaphylaxis released by mast cells and basophils, which are the primary effector cells of IgE-mediated allergic reactions. In food induced anaphylaxis Bachtel and Coll, showed, in a murine model, that intestinal mast cell-derived leukotrienes mediate anaphylactic response to ingested antigens [8].

Reinforcing the role of leukotrienes in food-induced anaphylaxis is Hoyt's observation that the resistance to food anaphylaxis in sensitized mice depends on the reduced availability of LTD4, the LT with the highest affinity for CysLT receptor 1, due to dipeptidase 1 (Dpep1) variants. DPEP1 is expressed in intestinal epithelium and catabolizes leukotriene D4 (LTD4) [9]. Authors found that mice with a more active isoform of DPEP1 could break down LTD4 more effectively protecting them from severe food anaphylaxis, while mice with less active isoform of DPEP1 had higher levels of LTD4 and more severe food anaphylaxis.

Hypothesis

If not counteracted by a diet rich in antioxidants (particularly polyphenols), oxidative stress in the intestine may increase the generation of pseudoleukotrienes. The increased concentration of pseudoleukotrienes in the intestine may promote the activation of mast cells, type 2 innate lymphocytes and dendritic cells.

Hyperactivation of mast cells, dendritic cells and type 2 lymphocytes might explain the increased risk of food allergy in food-sensitized individuals. It is well known that the presence of food-specific IgE is a necessary but not sufficient condition to trigger an allergic reaction. Indeed, some individuals with food-specific IgE are asymptomatic despite consuming the allergen for which they have specific IgE.

Proposal to reduce the incidence of food allergies in the population. To counteract oxidative stress, it is desirable that the modern diet followed in developed countries be particularly enriched with polyphenols. Polyphenols have all the characteristics of a promising product useful for preventing and alleviating food allergies. They are natural products widely present in the plant kingdom, safe and possess immunomodulatory and anti-inflammatory properties (Fig. 1) [10].

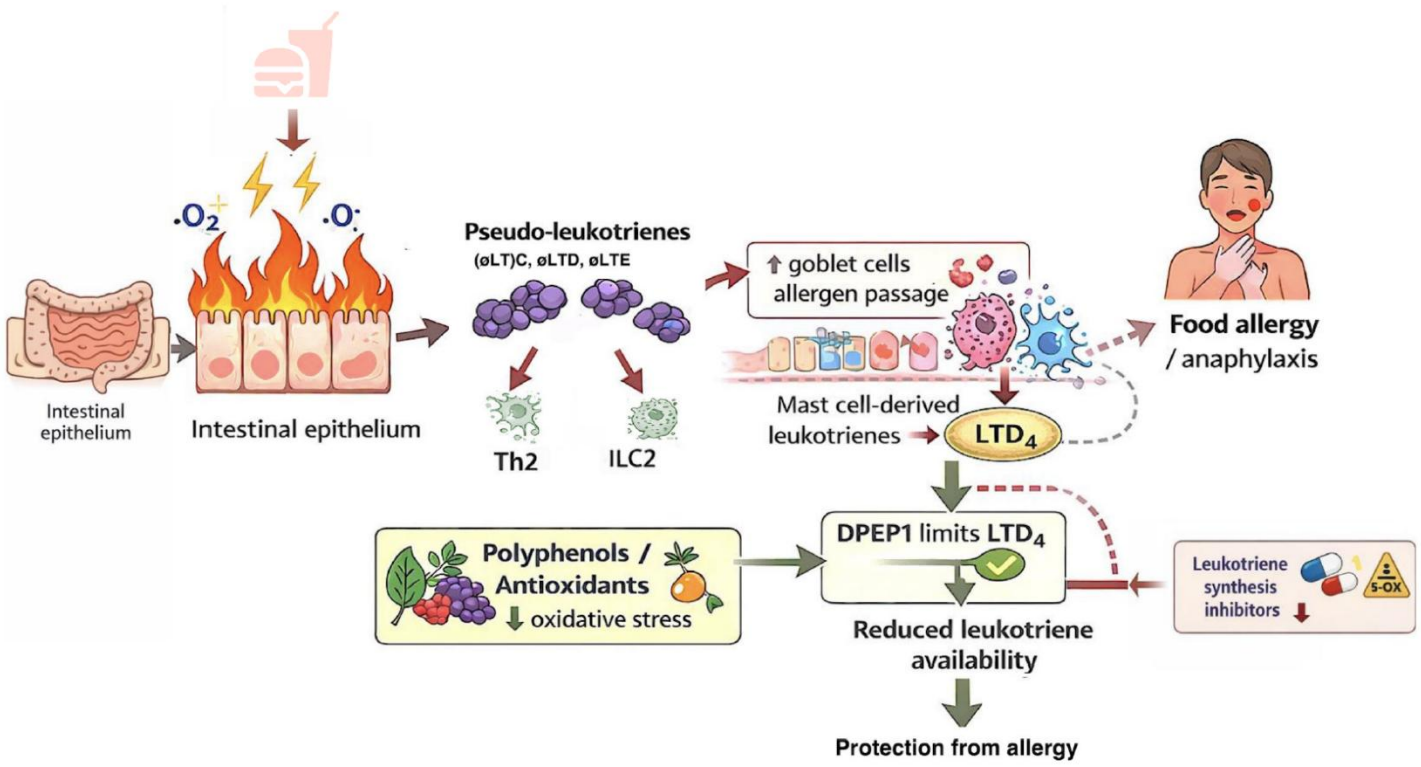

Figure 1: Oxydative stress of intestinal epithelium leads to generation of pseudoleukotrienes which activate type 2 helper T cells and type 2 innate lymphoid cells, with consequent expansion of goblet cells, which facilitate allergen passage and expansion of tissue mast cells. Antioxydant products found in some food, drugs that inhibit the generation of leukotrienes and high activity of DPEP1 counteract the manifestation of food allergy even in subjects sensitized to foods.

Development of New Drugs Targeting Leukotrienes

In light of recent observations attributing an important role to leukotrienes in the manifestations of food allergy, it is desirable that clinical pharmacological research develops new drugs that target leukotrienes. By considering the importance of the discovery of pseudoleukotrienes it could be useful to develop drugs that prevent the free radical process particularly at intestine level [11]. It is interesting that in ulcerative colitis, a chronic inflammatory condition characterized by increased Reactive Oxygen Species (ROS), Cai, et al., designed a negatively charged ROS-responsive nanocarrier using diselenide-bond-modified Carboxymethyl Cellulose (CMC) for the targeted delivery of curcumin, a natural ROS-scavenging antioxidant. The nanoparticles scavenge excessive ROS, restore intestinal barrier function and modulate the gut microbiota [12].

Many natural compounds with anti oxydant properties have anti-allergic effects and have been investigated in animal models and *in-vitro* studies [13]. Polyphenols and flavonoids would appear to be interesting candidates for clinical studies on food allergy [14-16]. We believe that molecules capable of reducing the intestinal production of pseudoleukotrienes may prove to be effective drugs against food allergy.

Zileuton by blocking 5-lipoxogenase (aLOX5) prevent leukotrienes synthesis, including LTD4 and it has been shown to protect sensitized mice from oral allergen-induced anaphylaxis, but not from intravenous administartion of allergen [8]. Zileuton, an old drug licensed for treating asthma or other leukotrienes synthesis inhibitors may find a new indication in the treatment of food allergy.

Conclusion

Recent research has shifted attention to leukotrienes formed in the intestine as the primary triggers of food allergy. This discovery may change the approach to the treatment of food allergy, developing strategies that reduce intestinal oxidative stress and/or block the generation of leukotrienes by intestinal mast cells.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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None.

Data Availability Statement

Not applicable.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore, was exempt.

Informed Consent Statement

Informed consent was taken for this study.

Authors' Contributions

All authors contributed equally to this paper.

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