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Non-IgE Mediated Mechanisms in Food Allergy and Clinical Relevance

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Introduction

Food allergies have traditionally been defined and studied through the lens of IgE-mediated hypersensitivity, in which allergen-specific IgE antibodies bind to mast cells and basophils, leading to rapid release of histamine and other inflammatory mediators. This paradigm explains classic allergic reactions such as urticaria, anaphylaxis, and immediate gastrointestinal symptoms. However, it has become increasingly evident that not all food allergies conform to IgE-mediated mechanisms. A significant subset of food-related hypersensitivities occur without detectable IgE antibodies and instead involve cellular immune pathways, primarily mediated by T cells, eosinophils, macrophages, and epithelial immune signaling. These non-IgE mediated food allergies manifest with delayed-onset symptoms, often localized to the gastrointestinal tract or skin, and are notoriously challenging to diagnose due to the lack of specific biomarkers. This article explores the mechanisms, clinical syndromes, diagnostic challenges, and therapeutic implications of non-IgE mediated food allergies, emphasizing their growing relevance in modern clinical immunology [1].

Description

The immunopathogenesis of non-IgE mediated food allergies is complex and multifactorial. Instead of rapid mast cell activation, the dominant process involves antigen-specific T cells that recognize food-derived peptides and drive pro-inflammatory cytokine release. Th1 and Th17 cells secrete interferon-gamma, IL-17, and TNF-alpha, promoting mucosal inflammation, while defective regulatory T cell responses impair the induction of tolerance to dietary antigens. Epithelial-derived cytokines such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 amplify innate immune activation, while recruitment of eosinophils and macrophages leads to chronic tissue remodeling and barrier dysfunction. Recent work has also highlighted the influence of genetic variants in barrier-related genes such as filaggrin and desmoglein, as well as the role of dysbiosis in disrupting immune homeostasis. Taken together, these findings illustrate that non-IgE mediated food allergies arise at the intersection of adaptive and innate immunity, in which the epithelial barrier plays a pivotal role [2].

Clinically, several distinct syndromes exemplify the relevance of these mechanisms. Food protein-induced enterocolitis syndrome (FPIES) is a severe gastrointestinal allergy typically seen in infants, presenting with repetitive vomiting, diarrhea, and lethargy one to four hours after ingestion of a triggering food such as cow's milk, soy, rice, or oats. Food protein-induced enteropathy (FPE) presents with chronic diarrhea, malabsorption, and failure to thrive, resembling celiac disease but triggered by other food proteins. Villous atrophy and intraepithelial lymphocytosis are characteristic findings, and the process is driven by cytotoxic T cells rather than IgE antibodies. Finally, eosinophilic gastrointestinal disorders (EGIDs), including eosinophilic esophagitis (EoE), gastritis, and colitis, represent chronic antigen-driven inflammation characterized by dense eosinophilic infiltration of the gastrointestinal mucosa. EoE in particular has emerged as a major non-IgE mediated food allergy in both children and adults, often associated with milk, wheat, soy, or egg, and is driven by Th2 cytokines such as IL-5 and IL-13 acting in concert with epithelial barrier dysfunction [3,4].

Despite increasing recognition, diagnosing non-IgE mediated food allergies remains difficult. The delayed onset of symptoms complicates food-symptom correlation, and conventional allergy tests are usually negative. Oral food challenge remains the gold standard but carries risks of severe reactions in conditions like FPIES, while endoscopy and biopsy can reveal tissue inflammation, eosinophilia, or villous atrophy in enteropathies and EGIDs. Current research is investigating T cell-based assays, cytokine signatures, and other immunological biomarkers to improve diagnostic precision. The cornerstone is strict dietary elimination of the offending antigen, which often requires avoidance of common triggers such as cow's milk, soy, egg, and wheat. Infants with severe conditions may require extensively hydrolyzed or amino acid-based formulas. Emerging biologics targeting IL-5, IL-13, and the IL-33/ST2 axis are under investigation, reflecting a shift towards precision immunotherapy. Oral immunotherapy, which has shown benefit in IgE-mediated food allergies, has an uncertain and potentially risky role in non-IgE mediated conditions, given their T cell-driven pathology. Nutritional monitoring is essential, especially in children, to prevent growth failure and micronutrient deficiencies during elimination diets [5].

Conclusion

Non-IgE mediated food allergies represent a heterogeneous but clinically significant group of disorders characterized by delayed hypersensitivity reactions to dietary proteins. Their pathogenesis involves T cell-driven immune responses, epithelial barrier dysfunction, and eosinophilic inflammation rather than IgE-mediated mast cell activation. Syndromes such as FPIES, FPIAP, FPE, and eosinophilic gastrointestinal diseases illustrate the spectrum of clinical manifestations, from transient infantile conditions to chronic lifelong disorders. Continued research into the molecular mechanisms, the microbiome, and the development of novel immunotherapies holds promise for improved diagnosis, safer treatments, and more effective long-term management. As our understanding expands, non-IgE mediated food allergies are increasingly recognized not as rare exceptions but as integral components of the broader field of food allergy and clinical immunology.

Acknowledgement

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Conflict of Interest

None.

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