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Review

The role of epigenetic mediation and the future of food allergy research

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ABSTRACT

IgE-mediated food allergy is a developing global health problem with prevalence rising at alarmingly fast rates. In this review, we discuss the interplay between genetics, epigenetics, and environmental exposures in the pathogenesis of food allergies. We aim to highlight the most recent evidence that suggests how epigenetic control may mediate genetic susceptibility of food allergies. We also examine how epigenetic modifications may be the key in explaining how environmental factors modulate and modify gene expression, leading to the dysregulation of immune tolerance and consequently, the development of food allergies. The emerging epigenetic paradigm in food allergies is likely to provide new mechanistic insight into food allergy risk and development as well as shape our therapeutic and preventive strategies.

Contents

1. Introduction

IgE-mediated food allergy (FA) is defined as "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food" [1]. FA is a complex, multifactorial disease and is quickly becoming a global health problem as it is estimated to affect 1–10% of the population worldwide [2]. Furthermore, FA prevalence has increased by a staggering rate of more than 18% between 1997 and 2007 in the United States [3]. Today it is estimated that FA likely affects nearly 5% of all adults and 8% of children [4].

Despite the rising increase in FA prevalence, there is still no cure. Standardized care is complete avoidance of eliciting food, with epinephrine delivered in the event of accidental ingestion. In today's society, with modern processed foods containing traces of allergens, complete avoidance is very difficult, and accidental exposures are commonplace. Consequently, there are an estimated 90,000 emergency room visits related to food allergies every year

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in the U.S. [5], and more than $25 billion is spent on FA care [6]. Studies reveal that avoidance and fear of accidental ingestion significantly decreases quality of life for both affected individuals and their caretakers [7]. Due to this immense disease burden, there is an ever-growing need for an effective FA therapy and/or preventative strategy. However, both the development of therapies and preventative strategies are dependent upon a deeper understanding of FA mechanisms and causes.

Our understanding of FA mechanisms is incomplete. In this review, we discuss the interplay between genetics, epigenetics, and environmental exposures in the pathogenesis of FA. We examine current evidence that suggests that epigenetics may explain how environmental factors modulate and modify gene expression, leading to the dysregulation of immune tolerance and consequently, the development of FA. Furthermore, we examine how the emerging epigenetic paradigm in FA is likely to provide a better understanding of FA risk and development, which provides promise of improving experimental therapies as well as elucidating potential prevention and treatment approaches.

1.1. Understanding biological mechanisms of FA

Unfortunately, FA is a complex disease. Thus, there is still much that remains unknown in regards to the causes and underlying biological mechanisms. Currently, FA is understood to be the dysregulation of normal immune tolerance where tolerance is the mechanism in which the adaptive immune system does not elicit an inflammatory response to self-antigens or innocuous antigens like food proteins [3,8,9]. The mechanisms of immune tolerance remain largely unknown, but it is believed that several antigen-presenting immune cells including dendritic cells [10], macrophages [11], and T regulatory cells (Treg) [12] mediate the suppression of an inappropriate immune response. In non-allergic individuals, food antigens promote the generation of antigen specific Treg cells. In allergic individuals, exposure to specific food-antigens promotes a TH2-skewed T-cell response and generates food-specific IgE antibodies from B cells that lead to an inflammatory immune response [8]. Considering that the dysregulation of immune tolerance is the basis of FA, gaining a better understanding of immune tolerance mechanisms will provide great insight into the etiology of FA.

Like many other complex diseases, it is known that the cause of FA is multifactorial and is the result of the interplay between genetics and environmental factors. Evidence supports that genetics play a role in FA development as revealed through familial aggregation studies, heritability estimates, and candidate gene studies over the past 10 years [13–16]. Moreover, a review written by Hong et al. discusses over 10 genes that have been associated with FA or food sensitivities [13]. Interestingly, several of these genes are involved in antigen presentation and/or a shift of the immune system towards a Th2 response [13]. Such association provides a possible link in how genetic predisposition impacts the dysregulation of the immune system leading to FA phenotype. However, it also evident that genetics alone cannot explain the increasing prevalence of FA nor can it explain why only some predisposed individuals develop FA. Consequently, research has turned to studying gene-environment interactions, particularly during critical stages of development in effort to understand FA etiology and the rise of the epidemic.

Numerous studies associate many environmental factors with FA development including timing of food introduction and feeding pattern [18–25], diet and nutrition [26–28], exposure to environmental pollutants and tobacco smoke [29–32], prematurity and low birth weight [33,34], microbial exposure [35–39], and race/ethnicity [72–74]. Hong and Wang thoroughly reviewed these environmental factors and their relationship with the development of FA [17]. Many of these environmental exposures are thought to impact the regulation of the immune system either directly or indirectly. However, there is limited understanding of how these factors affect the development of FA. It is suspected that epigenetic paradigms may be the key to understanding genetics, environmental exposures, and the rise of FA.

1.2. Why study the epigenetics of FA

We currently know very little about the role of epigenetics in FA, and only three studies provide direct evidence linking epigenetics and the disease [40–42]. Martino et al. investigated whether variation in DNA methylation (DNAm) underscores the suboptimal neonatal CD4+ T-cell gene expression associated with the development of FA [40], including impaired T-cell expansion and reduced IFN-γ production [43–46]. Martino et al. previously found that the immature neonatal CD4+ T-cell response involves altered expression of T-cell activation genes that signal through the NF-κB pathway [46]. In their follow-up study, the authors examined genome-wide DNAm profiles in CD4+ T-cells from 12 children with FA and from 12 non-allergic controls at birth and again at 12 months. They found that the dysregulation of DNAm at MAPK signaling-associated genes during early CD4+ T-cell development may contribute to suboptimal T-lymphocyte responses in early childhood associated with the development of FA [40]. Another study by Syed et al. discovered the role of DNAm in sustained unresponsiveness in patients who underwent oral immunotherapy (OIT) [41]. We will discuss this study later in this review during our therapy discussion. Both of these studies were very small in sample size but provide evidential support that epigenetic control indeed does contribute to FA development. Further linking epigenetics and FA, the first genome-wide association study (GWAS) of FA in 2759 US participants revealed the important role of differential DNAm in mediating identified genetic risk factors for peanut allergies. [42]. Considering this direct evidential support and our current understanding of epigenetics, the study of epigenetics in FA is a promising avenue that may lead to a better understanding of the mechanisms underlying FA etiology. Today there is growing recognition that epigenetic mechanisms are essential for normal development and that epigenetic regulation mediates T cell differentiation and maintains TH1/TH2 balance [47,48]. Thus, altering epigenetic mechanisms may disrupt normal human development and may lead to the dysregulation of the immune system associated with complex, allergic disease phenotype. It has been shown that both genetics and environmental factors can alter epigenetic profile [49,50]. Thus, epigenetics may be the missing piece to understanding environmental–genetic interactions and FA risk. Furthermore, numerous recent studies have explored DNAm in allergic disease such as asthma, eczema, and allergic rhinitis. Hong and Wang have recently reviewed these studies in depth [47]. Considering the clinical similarity between FA and other allergic disease, these studies provide evidence that it is likely that epigenetics changes are involved in the development of FA.

1.3. Epigenetic mediation of genetic susceptibility

To our knowledge, only one study thus far has used GWAS to discover genes that may contribute to the risk of developing FA. The first GWAS of a well-defined FA was performed in a US cohort of children and their biological parents [42]. The authors performed a three-stage GWAS looking for genetic associations with any FA particularly focused on milk, egg, and peanut allergies (PA). The study found that genetic variants in the HLA-DR and HLA-DQ gene region were significantly associated with PA in children of European ancestry. The GWAS revealed that this gene region accounted for approximately 20% of PA in the study population [42]. Previous studies that associated mutations in HLA genes with PA and

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