

# Immune system over-reactivity – Are allergens the real aggressors? Who is to blame?

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The majority of allergic disease pathologies are caused by immunoglobulin E (IgE)-mediated mechanisms that are initiated by allergens. Although a number of different allergic diseases exist, we will focus on allergic asthma (AA), allergic rhinitis (AR), and food allergies, given their increasing global prevalence over the last 50 years (1). Worldwide, approximately 40-50% of children are sensitized to one or more common food or aeroallergens (1). Table 1 provides prevalence statistics in North America for common allergic diseases in both adults and children (1-4). One possible theory to explain the rising trend of allergic pathologies is the hygiene hypothesis. This theory was originally proposed by Strachan in 1989 and suggests that the increase in allergic conditions throughout the 20th century may be attributed to lower rates of infection and allergen exposure among children (5). Strachan believed that infections and unhygienic contact could promote protection against allergic diseases. Although his theory oversimplifies the observed phenomena and does not consider the importance of the timing of allergen exposure, disease phenotypes, the environment, and the individual's genotype, the hygiene hypothesis holds some truth in explaining the upswing in allergic diseases (5). This theory has still not gained widespread acceptance, largely due to contradicting evidence over the years. For example, one study indicated that low socioeconomic status in children was a strong predictor of the development of asthma, which indirectly demonstrates that unhygienic exposure may not be protective (6). More recent evidence has supported the hygiene hypothesis, suggesting that avoidance of common allergens in early childhood can predispose children to the development of allergies (7,8).

In 2000 the American Academy of Pediatrics (AAP) encouraged parents to delay the introduction of common food allergens, particularly peanuts, to infants considered

Type of Allergy	Prevalence in Children	Prevalence in Adults	Reference
Allergic rhinitis	40%	20%	1
Food Allergy	6%	4%	2
Allergic asthma	13.5%	8.5%	3,4

at high risk of developing atopy (9). However, in 2015, the Learning Early about Peanut Allergy (LEAP) study found that children who regularly consumed a peanut snack had a lower risk of developing peanut allergy than children who avoided all peanut products (7). The study randomly assigned 640 infants between the ages of 4-11 months with risk factors for developing food allergies (severe eczema, egg allergy, or both) to either consume or avoid peanuts until 60 months of age. Prior to randomization, all participants underwent a skin prick test against peanut allergen to stratify participants based on their initial peanut allergy status. Infants that developed wheals greater than 4mm in diameter were excluded on the basis of having preexisting peanut allergy. Those with wheals less than 4mm in diameter were stratified into either a negative cohort (wheals <1mm) or a positive cohort (wheal 1-4mm) and then randomized to peanut consumption or avoidance. Infants in the consumption group were given at least 6 grams of peanut protein per week in the form of Bamba, a peanut butter and puffed maize snack (7). Among those in the negative cohort (n=530), the ratio of peanut allergy at 60 months in the avoidance group compared to the consumption group was over 7:1 (p<0.001). The ratio was lower in the positive cohort (n=98), but still over 3:1 (p=0.004), which further highlights the benefits of early peanut consumption (7). This groundbreaking LEAP study

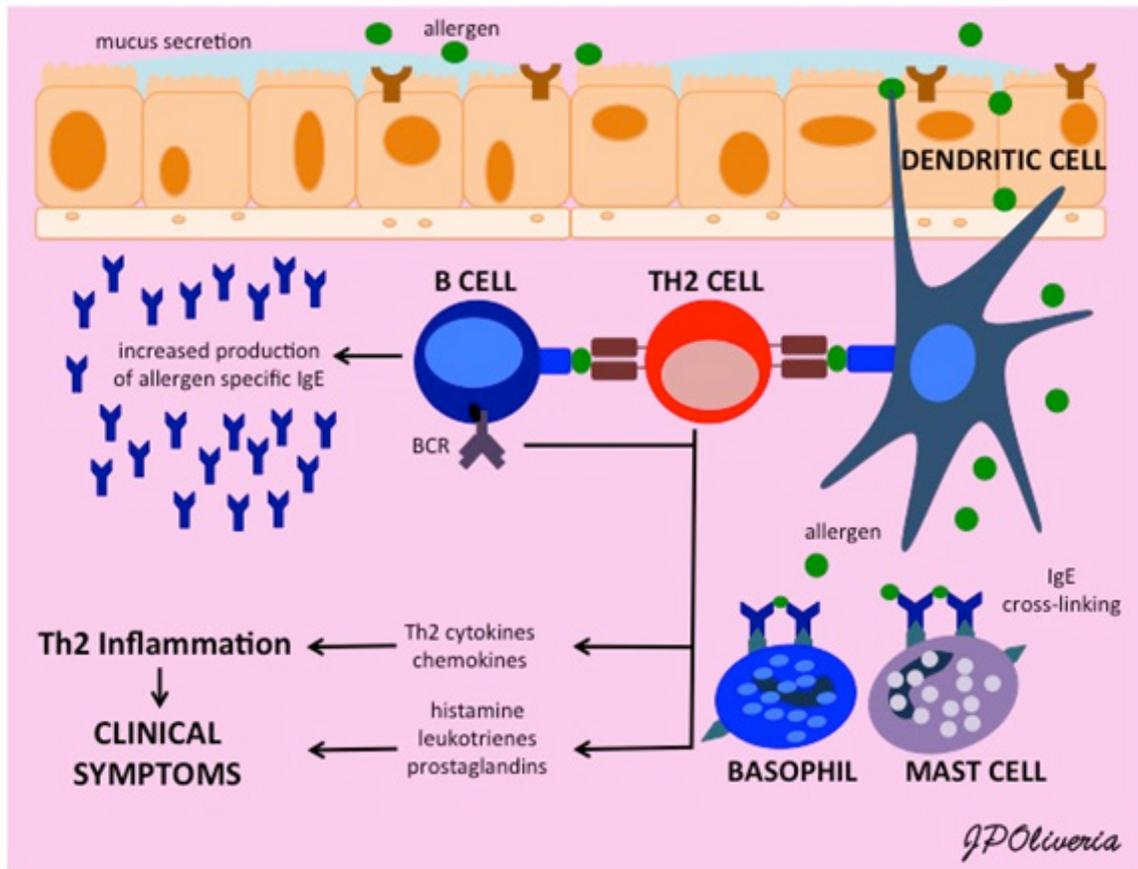


Figure 1. Pathogenesis of the allergic inflammatory cascade in asthma.

has a variety of implications, most significantly, starting a shift towards early exposure of potentially allergenic foods among children considered high risk for allergy (10).

In addition to the LEAP study, which specifically focused on peanut allergy, other studies have investigated the effects of early life exposure to other allergens. One such study investigated an inner-city birth cohort considered at high risk of developing asthma (n=560) (8). Within this cohort, a nested case-controlled study of 104 infants was completed to determine associations between environmental factors, aeroallergen sensitization, and recurrent wheezing at age three. In this study, children with the highest exposure to cockroach, mouse, and cat allergens during their first year of life were the least likely to have recurrent wheeze and allergic sensitization (odds ratios of 0.60, 0.65, and 0.75, respectively;  $p \leq 0.01$ ) (8). This study suggests that early exposure to aeroallergens among children may also act as a protective factor against the development of early wheeze, a frequent precursor to asthma. Congruent with Strachan's hygiene hypothesis, the findings in this study strengthen his initial notion that exposure to allergens is critical for building tolerance at a

young age to prevent the onset of allergic diseases (5).

Early exposure to common allergens seems to reduce the risk for developing allergies, but once an allergy does develop, allergen avoidance is highly suggested (yet sometimes unfeasible). The inability to avoid environmental allergens has resulted in vast research in drug development for the treatment of allergies. At the forefront of this exciting field is allergy immunotherapy, whereby increasing doses of allergen are administered to a patient to develop immune tolerance (11). Allergen-specific immunotherapy (AIT) is a desensitizing therapy that has the potential to decrease allergic symptoms if tolerated by the individual. The therapy modulates important cells in IgE-mediated inflammation, including T-cells, B-cells, basophils, eosinophils, and mast cells (11). In the pathogenesis of allergic diseases, T-helper type 2 cells are important cells in propagating allergic responses and inflammatory processes driven by type 2 cytokines (e.g., IL-4, IL-5, IL-13); however, by inducing a tolerant state in these peripheral T-cells, allergic inflammation can be dampened (refer to Figure 1 for an outline of the pathogenesis of the allergic inflammatory cascade). AIT promotes the generation

of allergen-specific regulatory T-cells, which effectively suppresses T-cell proliferation and the accompanying type 2 cytokine release (11). Several types of AIT exist, varying in routes of allergen administration, including oral immunotherapy (OIT), subcutaneous immunotherapy (SCIT), and sublingual immunotherapy (SLIT) (12). OIT has shown promising results among individuals with peanut, egg, and milk allergies, yet it remains unclear whether a permanent state of tolerance can be achieved using OIT (12). SLIT and SCIT are considered more effective than OIT because the allergen is directly absorbed into the blood stream with avoidance of first-pass metabolism in the liver (12). However, in order to achieve the desired clinical effects of these treatments, compliance is of critical importance. A recent retrospective analysis found that only 23% of SCIT users and 7% of SLIT users complete the recommended 3-year treatment duration, which may prevent the desired clinical effects of immunotherapy (13). Fortunately, alternative therapeutics are being developed to attenuate allergen-induced responses. Although these therapies are not curative, they are effective in reducing allergic symptoms. Two of the most promising therapies include omalizumab, a humanized antibody that selectively binds to the heavy chain of free IgE in the serum, and mepolizumab, a humanized monoclonal antibody against IL-5 (14). One study found that targeting thymic stromal lymphopoietin (TSLP), an upstream cytokine that promotes allergic inflammation, with an anti-TSLP antibody could also effectively attenuate allergen-induced airway responses in patients with mild AA (15). Another potential therapy is an antibody against the alarmin cytokine IL-33, another upstream cytokine in the allergic cascade (15,16).

Although allergens are the aggressors when it comes to initiating an allergic response, early life exposure may confer protection against their development. Furthermore, after allergic sensitization, AIT can be used to desensitize an individual to certain allergens. Thus, allergens cannot always be perceived as the enemy; in some cases, they serve as valuable assets in protecting against and treating allergies. Due to the increasing prevalence of allergic diseases continued investigation into novel therapies for allergy treatment is imperative. ■

#### List of Abbreviations

AA - allergic asthma, AR - allergic rhinitis, AIT - allergen specific immunotherapy, IgE – immunoglobulin E, LEAP - Learning Early about Peanut Allergy, OIT - oral immunotherapy, SCIT - subcutaneous immunotherapy,

SLIT - sublingual immunotherapy, TSLP - thymic stromal lymphopoietin

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