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IgE receptor signaling in food allergy pathogenesis

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Abstract

The pathogenesis of food allergy remains poorly understood. Recent advances in the use of murine models have led to discoveries that mast cells and IgE receptor signaling not only drive immediate hypersensitivity reactions but also exert an immunoregulatory function, promoting the development of allergic sensitivity to foods. We review the evidence that IgE, IgE receptors, key signaling kinases and mast cells impair oral tolerance to ingested foods, preventing the induction of regulatory T cells (Treg) and promoting the acquisition of pro-allergic T helper (Th) 2 responses. We discuss innovative strategies that could be implemented to counteract these immunoregulatory effects of IgE-mediated mast cell activation, and potentially reverse established sensitization, curing food allergy.

Introduction

Food allergy is an immunological disorder characterized by dysregulated responses and the development of immediate hypersensitivity reactions to ingested foods. Rates of occurrence have soared over the last two decades in developed nations, affecting children disproportionately. The current standard of practice is to advise allergen avoidance, and a lack of mechanistic understanding of the processes underlying the induction of tolerance vs. sensitization to food allergens frustrates our ability to develop actual treatments. In this review, we discuss recent advances in our understanding of the pathology of this disorder stemming largely from novel approaches with animal models of disease. These studies have elucidated a previously unappreciated role for IgE receptor signaling in mast cells as an amplifier of immune sensitization and a disrupter of immunological tolerance to ingested foods.

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IgE, its receptors and their signaling pathways

IgE binds to two main receptors, the high affinity FcεRI ($K_d \sim 1\text{nm}$) and the low affinity FcεRII or CD23 (K_d 0.1–1μm). A handful of other receptors, including galectin-3, FcγRIIb, FcγRIV, have been documented to interact with IgE, but these will not be discussed here [1]. These receptors have set expression patterns, with FcεRI primarily on mast cells, basophils and dendritic cells and CD23 on B cells, a variety of innate cell types and epithelial cells. Crosslinking of FcεRI by IgE and allergen results in initiation of signaling via the immunoreceptor tyrosine-based activation motifs (ITAMs) in the cytoplasmic tail of the receptor, triggering the recruitment and activation of several key kinases including Syk, Lyn and Fyn. Activation of Syk is essential for propagation of signaling as Syk phosphorylates LAT, which serves as a scaffold for the assembly of the signaling complex that leads to both degranulation and cytokine gene transcription (Figure 1). FcεRI signaling has recently been reviewed in depth by Sibilano and colleagues [2]*. CD23 signaling is less well elucidated, and cytoplasmic signaling is thought to be inessential for some of this molecule's functions. It is known that binding of IgE and antigen to CD23 results in the formation of nucleotide messengers (cAMP) and nuclear translocation of the transcription factor NFκB [3]. Differences in splicing and expression patterns for CD23 may alter signaling between cell types, with B cells but not monocytes reported to activate Fyn and Akt [4].

Facilitated antigen binding and presentation

IgE interacting with its receptors is considered to have a significant role in maintaining a sensitized state in food allergic patients by focusing and stimulating memory T and B cell responses. Specific IgE binds to allergens with high affinity, creating IgE:allergen complexes that can then be endocytosed through cellular receptors much more efficiently than might normally occur via random sampling by phagocytes. The effect of the IgE in this setting is to target the allergen to antigen-presenting cells, facilitating binding and presentation of the allergen to adaptive immune cells. This effect can occur through both CD23 and FcεRI. Facilitated antigen presentation by IgE has been shown to enhance T cell proliferative responses in peanut-allergic subjects [5].

FcεRI: The hair-trigger response

FcεRI-bearing cells, predominantly mast cells but also basophils to a lesser extent, are responsible for the immediate hypersensitivity reactions in allergy. IgE can trigger FcεRI signaling and degranulatory release of vasoactive mediators in response to minute concentrations of antigen, creating a highly amplified system for allergen detection and response. Studies in murine models have established obligate roles for IgE, FcεRI, Syk, and mast cells in the onset of immediate hypersensitivity reactions and anaphylaxis following acute food allergen challenge in sensitized animals [6–13]6**, 7**, 10*.

In addition to eliciting immediate hypersensitivity, mast cell activation by IgE and FcεRI leads to a secondary, late-phase reaction fueled by cytokine production and leukocyte recruitment and a recurrence of symptoms 8–12 hours after initial allergen exposure. Mast cell-derived cytokines, acting on both innate and adaptive immune cell types, favor Th2 responses that incite chronic allergic inflammation, and have demonstrated roles in the

development of pathology in models of allergic disease [14–16]. Most notably with respect to the polarization of the T cell response, mast cell activation by IgE drives the synthesis of the Th2-inducing cytokine interleukin (IL)-4 in quantities that are capable of increasing systemic levels of this cytokine approximately ten-fold (Oettgen and Burton, *Advances in Immunology*, in press). The relatively high frequency of mast cells at environmental interfaces where allergens are first encountered, including the skin, airways and gastrointestinal tract, suggests that these cells may promote the development of allergic sensitization.

IgE receptor signaling promotes sensitization

We recently set out to test the hypothesis that IgE receptor signaling in mast cells contributed to the development of allergic sensitization and pathology in food allergy. A previous study by Wang *et al.* had shown a contribution of mast cells, FcεRI and mast cell-derived IL-13 to the development of intestinal inflammation using an adjuvant driven-system [13]. Other studies investigating the effects of mast cells and IgE in sensitization to antigens applied to the skin or airways indicated that the mast cell effect was most evident in the absence of adjuvant [17,18]. Testing the roles of mast cells and IgE in food allergy required the use of an animal model of the disease. The prevailing murine models have relied on the use of parenteral immunization and/or adjuvant to break oral tolerance, and elicit rather weak responses to allergen challenge unless the allergen is injected systemically. Because they circumvent the normal pathways of enteral sensitization, such models are not well suited to providing accurate information regarding the mechanisms of immune sensitization to food allergens. In collaboration with Dr. Talal Chatila, we used associations between susceptibility to allergic disease and IL-4 receptor alpha chain (IL-4Rα) polymorphisms in the human population to inform the development of a new genetic atopic mouse model of food allergy based upon an IL-4Rα F709 mutation [8,19]. In this model, repeated feedings of allergen (peanut or the model allergen OVA) in the absence of adjuvant evoke Th2 responses, IgE production, mast cell expansion and IgE-dependent anaphylaxis upon enteral allergen challenge [6,8]6**. Anaphylactic shock was abrogated in mice lacking FcεRIα, mast cells (either Cre-driven deletion or Kit-deficiency-mediated absence), the FcεRI-proximal kinase Syk specifically in mast cells, or in mice treated with anti-IgE or a small molecule antagonist of Syk [6]**.

Interestingly, we found that F709 mice lacking IgE, FcεRI or mast cells not only failed to manifest allergic reactions, but developed radically different adaptive immune responses to the allergen. Unlike their wild-type counterparts, atopic F709 mice exhibited strong Th2-biased immune responses to allergen and failed to generate effective, stable regulatory T cell (Treg) that could control the allergy [7]**. In the absence of mast cells or IgE signaling, however, F709 mice regained the ability to induce Treg, resulting in reduced Th2 responses in allergen-specific CD4⁺ T cells and a lack of specific IgE production [6,7]**. Studies employing selective reconstitution of the mast cell compartment in mast cell-deficient mice with normal or cytokine-deficient bone marrow cultured mast cells demonstrated that mast cell-derived IL-4 was central to this process [6]**. While mast cell activation may directly promote Th2 induction, B cell switching to IgE and other aspects of the allergic response, our studies suggest that the ability to disrupt Treg induction and function may be the most

critical mast cell effect (Figure 2) [7]**. Treg control of inappropriate Th2 responses to ingested foods is impaired in many food allergic patients, and reappears in individuals who outgrow their allergies [20–22]. In both F709 mice and allergic humans, allergen-specific Treg exhibit reprogramming into Th2-like effector cells, and actively contribute to the worsening of allergic pathology in the mice. In the absence of FcεRI, F709 mice developed stable, effective Treg that suppressed Th2 responses [7]**.

Targeting IgE signaling to reverse sensitization

Current treatment strategies for food allergy are limited. Clinical trials have demonstrated that regulated incrementally increasing ingestion of allergen, called oral immunotherapy (OIT) can lead to a desensitized state in many patients and in some instances, long-term tolerance [23–26]. The process, however, is slow, only partially effective and fraught with side effects due to allergic reactions. Recently, a humanized monoclonal anti-IgE, omalizumab, has been employed as adjunct therapy to OIT, and has permitted rapid allergen dose escalation while reducing untoward reactions [27,28]. We reasoned that neutralization of IgE or inhibition of mast cells might have the added, unanticipated benefit of favoring the restoration of tolerance and Treg-dominated immune responses. We modeled this in F709 mice, placing them on a program of daily allergen ingestion mimicking human OIT, and additionally treated some of the mice with a neutralizing anti-IgE antibody. Mice treated with anti-IgE during desensitization therapy regained Treg-dominated responses to allergen and showed reductions in Th2 cells [6]**. Unlike available anti-mouse IgE antibodies, omalizumab has been engineered such that it does not interact with FcεRI-bound IgE; thus it cannot activate mast cells by crosslinking IgE, but also fails to remove receptor-bound IgE and so leaves cells still able to activate upon exposure to allergen. In the interest of developing a therapeutic approach that could block IgE receptor signaling in food allergy, we employed a novel, highly specific Syk inhibitor developed by Merck. This small molecule kinase inhibitor abrogated anaphylaxis when given prophylactically to mice 15 minutes prior to allergen challenge. When administered during the oral desensitization regimen, Syk inhibitor led to the reversal of sensitization in allergic F709 mice, reducing IgE levels, mast cell burden and Th2 bias while favoring the generation of new Treg-dominated responses, none of which was seen in vehicle control-treated mice. Importantly, anaphylactic responses to allergen challenge were greatly reduced in mice that received OIT with Syk inhibitor long after the therapy was discontinued, indicating that immunological tolerance was restored [6]**. Treg taken from Syk inhibitor-treated mice were able to suppress the development of allergic pathology, an ability that is critically lacking in Treg taken from mice with severe food allergy (Figure 2) [6,7]**.

Conclusions

Clinical studies on the effects of omalizumab during OIT for peanut allergy are underway. Initial studies on the effects of OIT or omalizumab-assisted OIT on the induction of Treg have been inconsistent [21,29–31], but with improved techniques for identifying and analyzing allergen-specific Treg, Syed and colleagues demonstrated that Treg populations are clearly enhanced in peanut-allergic patients undergoing OIT [32]**. While omalizumab cannot neutralize receptor-bound IgE and may be insufficient to block even all soluble IgE

in severely allergic individuals, we anticipate it will have a beneficial effect. Omalizumab treatment has been shown to completely inhibit IgE:CD23-mediated facilitated allergen binding to B cells [33], and decrease FcεRI⁺ DC-driven proliferation of allergen specific Th2 cells [34]. Furthermore, long-term neutralization of IgE by omalizumab leads to reduced expression of FcεRI and loss of receptor-bound IgE on mast cells, basophils and dendritic cells [35–37]. This effect may be instrumental in facilitating successful tolerance induction. Incrementally increasing exposure to allergen within a short time frame (rush desensitization) is an effective means of internalizing IgE and FcεRI, and renders mast cells unresponsive to that allergen [38,39]*. It is our hope that omalizumab is simply the first of many rational approaches to targeting the IgE:mast cell axis, and that the development of other drugs (e.g., quilizumab, Syk inhibitor, anti-FcεRI) [40]* will accelerate our acquisition of knowledge regarding the functions of IgE receptor signaling in allergic pathology and permit effective treatment of these intractable diseases.

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Highlights

- IgE, IgE receptor signaling and mast cells promote sensitization to food allergens
- IgE and mast cells disrupt Treg induction, favoring Th2 responses
- Treg that are generated exhibit Th2 reprogramming and are defective
- Silencing the IgE:mast cell axis reverses allergic sensitization

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Figure 1.

IgE receptor signaling pathways. A) CD23 ligation promotes activation of the src kinase Fyn and cytosolic nucleotide intermediates, resulting in MAP kinase cascades and nuclear translocation of NFκB. B) Crosslinking of the high affinity IgE receptor, FcεRI, by IgE and allergen causes Syk-dependent formation of the LAT/SLP76 signaling complex. This scaffold facilitates the activation of multiple kinase pathways, leading to degranulation and cytokine transcription.

Figure 2.

Immunoregulatory effects of IgE and mast cells, and potential therapeutic interventions. Activation of mast cells through FcεRI and Syk drives the synthesis of IL-4, favoring Th2 polarization in T cells and IgE switching in B cells. Mast cell-derived IL-4 acts via STAT6 in Foxp3⁺ Treg to induce the expression of GATA3, reprogramming the Treg into a Th2-like pathogenic cell. Molecules that target Syk (Syki), IgE (anti-IgE omalizumab or anti-IgE M1' quilizumab) or IL-4 (dupilumab, pitrakinra) may have the ability to counteract these effects.