

Regulation of the IgE response

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Abstract

IgE was the last of the five immunoglobulin classes to be discovered and is the antibody that is responsible for much of human type I allergic disease. This review summarizes recent developments with respect to control of IgE synthesis with an emphasis on Th2 (T helper 2) control and regulation using IgE Fc receptors.

Introduction and context

The primary biological function of IgE is to provide immunity against multicellular parasitic pathogens such as helminths. Large IgE responses are seen in both humans and other mammals as a result of such infections. In developed countries, where such diseases are rare, IgE responses directed against innocuous allergens result in type I allergic disease. Since IgE is the only immunoglobulin class thought to be involved in human type I allergy, methods to control IgE synthesis represent a clear way to control this disease. This remains a significant challenge. Indeed, the closest approach is immunotherapy, which was initiated in the early 1900s. Immunotherapy involves administering increasing doses of allergen to achieve desensitization and/or tolerance. Significant improvements in allergen purity have greatly enhanced its effectiveness, especially when treating patients with responses to only these well-characterized allergens [1]. While the mechanism remains controversial, neutralizing antibodies (IgG in nature) to the allergen as well as tolerance induction are potentially both involved.

Major recent advances

The development of therapies that would specifically inhibit class switching to IgE would have a dramatic impact on allergic disease. However, mechanisms for isotype switching are usually common to other Ig classes (see [2,3] for review). The discovery of the role of activation-induced deaminase (AID) by the Honjo

laboratory [4] was a key event. Additionally, T-cell help, long known to be critical for isotype switching, comes from CD40-CD40L (CD40-CD40 ligand) interaction and specific cytokines. Patients who lack either AID or CD40L are limited primarily to an IgM response [5,6]. While other cytokines such as BAFF (B-cell activating factor belonging to the tumor necrosis factor family) and APRIL (a proliferation-inducing ligand) can induce both T cell-independent and T cell-dependent class switching to IgE (at least *in vitro*), current thought is that CD40-CD40L and AID are required for significant *in vivo* IgE production. B-cell activation via Toll-like receptor 4 (TLR4) also effectively induces IgE class switching. However, at least in mice [7], TLR4 stimulation attenuates the mouse asthma model. One unique feature of IgE class switching is the general necessity for T helper 2 (Th2) differentiation. Since interleukin-4 (IL-4) production is important not only for Th2 development but also for isotype switching, blocking its activity represents a clear strategy for IgE control. Clinical trials were performed using a soluble form of the IL-4 receptor; however, modest efficacy was achieved in asthma treatment (discussed in [8]). Potential new directions in cytokine therapy for allergic disease come from recent studies with IL-21, IL-25, and IL-33 and thymic stromal lymphopoietin (TSLP). Over 10 years ago, the Hodgkin laboratory reported that isotype switching to IgG and IgE required multiple cell divisions [9]. Up to five divisions were required for IgG, and eight were required for optimal IgE production. While the IgG data from this

mouse study were later replicated in humans [10], human IgE production required additional signals. Adding IL-21 to the culture allowed our group to extend the multiple division requirement for IgE production to humans [11]. IL-21 is known to signal through STAT3 (signal transducer and activator of transcription 3), and Avery *et al.* [12] demonstrated that B cells from patients with loss-of-function mutations in STAT3 did not respond to IL-21. Interestingly, mutations in STAT3 are also associated with the autosomal dominant form of HIES (hyper IgE syndrome) [13], a condition in which patients have extremely elevated serum IgE levels, recurrent eczema, and an increased risk for skin and lung infections. IL-25 (also called IL-17E) has emerged as another key regulator of the Th2 response. Overexpression of IL-25 results in enhanced IgE responses [14]. Recent evidence suggests that IL-33, a member of the IL-1 family, has a role in Th2-mediated disease (reviewed in [15]). Blockade of the mouse IL-33 receptor results in inhibition of antigen-specific IgE production, at least in response to low antigen doses [16]. TSLP has been shown to upregulate OX40L on dendritic cells. Blocking the interaction with OX40 by neutralizing antibodies resulted in decreased Th2 development and IgE production [17]. Finally, γ , δ T cells can have both IgE-enhancing and IgE-suppressing properties and recent evidence indicates that the suppressing γ , δ T cells are important in controlling the airway allergen response [18]. Because these later studies were completed in rodent models, current studies are needed to determine whether human IgE production is regulated by similar mechanisms. Data suggesting some involvement of IL-25 and IL-33 with human Th2 development have already been reported [19,20].

A second area of investigation regarding IgE control involves the interaction of IgE with its two Fc receptors. Studies focusing on high-affinity IgE receptor (Fc ϵ RI) are directed primarily toward blocking the Fc ϵ RI/IgE interaction. The crystal structure of the Fc ϵ RI/IgE complex is known [21] and may ultimately lead to the development of compounds that can block this interaction. At present, such agents are not available, but a current treatment approved by the US Food and Drug Administration for severe asthma involves injecting a monoclonal anti-IgE antibody (Xolair[®], or omalizumab) that binds the identical or closely associated region of IgE that interacts with the Fc ϵ RI [22,23]. This monoclonal antibody effectively blocks IgE binding to the Fc ϵ RI. Additionally, extended therapy (due to the protection from degradation that IgE binding gives the Fc ϵ RI) results in low Fc ϵ RI expression levels [24]. This treatment has shown good efficacy. However, the primary disadvantages are the expense and the form of administration. Since IgE

synthesis is not inhibited, the antibody injections need to be repeated approximately every three weeks.

The second IgE receptor (Fc ϵ RII or CD23) is expressed primarily on B lymphocytes in mice and, since its discovery, has been proposed to be a natural regulator of IgE synthesis [25]. CD23 is upregulated by IL-4 and stabilized on the cell surface by IgE binding. This stabilization prevents cleavage from the cell surface by the CD23 sheddase(s) [25]. Indeed, mice that lack CD23 exhibit some augmentation in their IgE response to allergens but not helminth infection [26]. CD23 transgenic mice that overexpress the receptor on lymphocytes have greatly reduced IgE responses [27]. A clinical trial using anti-CD23 (lumiliximab) directed against the lectin part of the molecule resulted in a reduction in serum IgE levels by approximately two-thirds, but this was not sufficient to significantly influence disease symptomology [28]. This anti-CD23 is thought to mimic IgE binding and stabilize CD23, resulting in less cleavage by ADAM10 (a disintegrin and metalloprotease 10). Use of this anti-CD23 in conjunction with the anti-IgE mentioned above remains to be tested. Antibodies directed against the stalk region of the molecule result in CD23 instability, significantly enhanced CD23 cleavage, and enhanced IgE production [29]. In addition, soluble CD23 trimer has been shown to increase IgE production in the human *in vitro* culture model [30]. These studies stimulated interest in identifying the CD23 sheddase. In collaboration with the Blobel laboratory, we recently identified the primary sheddase as the metalloprotease ADAM10 [31]. This result was confirmed by Lemieux *et al.* [32]. Recently, Jackson *et al.* [33] reported that matrix metalloprotease 9 (MMP9) can also act as a CD23 sheddase following TLR4 activation with lipopolysaccharide. However, MMP9 deficiency is associated with high IgE levels in mice [34], potentially due to excess IL-4 production. We are currently investigating whether ADAM10 may be a potential target for controlling IgE production.

Future directions

New therapies that harness the natural regulator capacity of CD23 (discussed above) or T-regulatory cells (reviewed in [35]) are promising areas for future investigation. Agents that influence the nervous system have recently been shown to influence the mouse IgE response [36,37], so this is also an area of future investigation. Finally, the investigation of the innate and adaptive immunity-associated cytokines discussed above (IL-25, IL-33, and TSLP) for control of human IgE responses will certainly be of interest. The goal of IgE synthesis inhibition should give broad-spectrum type I allergy control and thus remains a very worthy objective.

Abbreviations

ADAM10, a disintegrin and metalloprotease 10; AID, activation-induced deaminase; CD40L, CD40 ligand; FcεRI, high-affinity IgE receptor; IL, interleukin; MMP9, matrix metalloprotease 9; STAT3, signal transducer and activator of transcription 3; Th2, T helper 2; TLR4, Toll-like receptor 4; TSLP, thymic stromal lymphopoietin.

Competing interests

The authors declare that they have no competing interests.

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