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*J Immunol* 2016; 197:4187-4192; ;

doi: 10.4049/jimmunol.1601476

<http://www.jimmunol.org/content/197/11/4187>

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## From IgE to Omalizumab

Toshiaki Kawakami<sup>\*,†</sup> and Ulrich Blank<sup>‡,§,¶,||</sup>

IgE is the least abundant Ig isotype, yet it plays a critical role in allergic reactions and host protection from helminth infection. Although IgE was discovered 50 years ago, the ultimate evidence for its role in human allergic diseases was obtained by the efficacy of anti-IgE therapy in many clinical trials on asthma and other allergic diseases. Beginning from the discovery of IgE 50 y ago, followed by studies of IgE receptors and activation mechanisms, this review provides a historic perspective of allergy research that has led to the development of anti-IgE therapy and other strategies targeting IgE and its receptors. Current IgE studies toward future precision medicine are also reviewed. *The Journal of Immunology*, 2016, 197: 4187–4192.

The year 2016 is special in the history of immunology (Fig. 1). It marks the 50th anniversary of the discovery of IgE and the 100th anniversary of the inauguration of *The Journal of Immunology*. The discovery of IgE has been celebrated by special sessions and symposia organized by several research societies around the theme of IgE and allergy. Indeed, the realization that IgE was the “long-sought” reagenic Ab that causes allergic reactions sparked an exciting time of research that also led to the identification of its culprit target cells, mast cells and basophils, which express high-affinity receptors for IgE (FcεRI). A low-affinity IgE receptor (FcεRII or CD23) was found to be expressed on mature B cells and other immune cells. Along with the development of molecular biological and hybridoma techniques in subsequent years, recombinant anti-IgE Abs were generated and tested in human asthmatics and other allergy patients. Numerous clinical trials of the humanized monoclonal anti-IgE omalizumab clearly demonstrated its effectiveness in treating these diseases. Currently, omalizumab is a U.S. Food and Drug Administration–approved medicine to treat moderate-to-severe asthma and chronic idiopathic urticaria. This review places the successful translational research into historic and future perspectives, eventually leading toward precision medicine.

### Discovery of IgE

Readers who are interested in details recalling the story of the discovery of IgE are referred to two recent papers by Ishizaka

and Ishizaka (1) and by Johansson (2), with the latter describing an atypical myeloma protein that turned out to be physicochemically identical to the Ab the Ishizakas discovered. At the time when the Ishizakas and other scientists were trying to identify the agent that causes allergic reactions, the only assay available for this purpose was the so-called Prausnitz–Küstner (PK) reaction. Prausnitz and Küstner described this reaction in 1921 showing that an intracutaneous injection of the serum of Küstner, who was allergic to fish allergen, to Prausnitz (who was not allergic to fish), followed by injection of the allergen into the same skin site the next day resulted in the induction of a wheal and erythema reaction. The Ab-like substance in the patient serum responsible for erythema-wheal reactions was called “reagin.” In the beginning of the 1960s reagin was thought to belong to a newly discovered Ig isotype, IgA (3), as a serum fraction, largely composed of IgA, isolated from hay fever patients was shown to have such skin-sensitizing activity. However, further studies by Ishizaka et al. (4) showed that their IgA Abs lacked the ability to sensitize human skin in PK reactions. Because he thought that biological activities of an Ab are decided by the structure of the Fc portion of the Ab, K. Ishizaka surmised that the reagenic activity in the IgA fraction in hay fever patients might be due to an impurity in the IgA preparation, an idea supported experimentally. This observation created a big hurdle, as it suggested that the concentration of reagenic activity in the original serum was <1 μg/ml. Such low levels of a substance made it extremely difficult, if not impossible, to purify it in amounts substantial enough for further physicochemical analyses, which at that time were the accepted approach to identify a novel protein. He then changed strategy, focusing on the preparation of rabbit Abs specific for reagin for identification. Ishizaka et al. (5) immunized rabbits with a reagin-rich fraction of the serum of hay fever patients and adsorbed the obtained serum with human IgG, IgA, and IgD. Using this antiserum in PK tests, they demonstrated that, even after extensive adsorption, the rabbit serum contained Abs specific for human reagin. Using this antiserum, reagin-rich fractions were identified after ion-exchange column chromatography of the serum from ragweed-sensitive patients and the reagenic activity, as quantified by PK reactions, was well correlated with their reactivity to the antiserum

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Received for publication August 24, 2016. Accepted for publication October 3, 2016.

This work was supported by National Institutes of Health Grants HL124283, AR064418, and AI115534 (to T.K.) and by funding from the Nipponham Foundation for the Future of Food (to T.K.).

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Abbreviations used in this article: HRF, histamine-releasing factor; PK, Prausnitz–Küstner.

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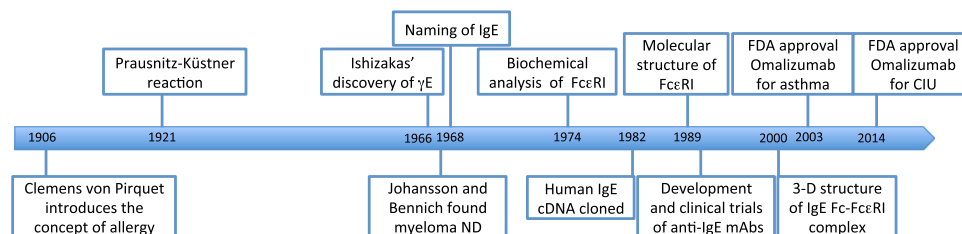


**FIGURE 1.** Timeline of IgE-related research. The major discoveries related to IgE research that led to the development of IgE-targeting therapeutics are highlighted.

(5, 6). Radioimmuno-electrophoresis and sucrose density gradient ultracentrifugation showed that the reagin belongs to the fast  $\gamma$ -globulin fraction with a molecular mass of 190,000 Da, which differed from the properties of the other Ig isotypes. Perfect correlation between Ag-binding activity of this Ab, initially termed  $\gamma$ E (with “E” meaning erythema) (5), and its reaginic activity convinced them to think that  $\gamma$ E is associated with reaginic activity. They subsequently purified  $\gamma$ E from ragweed-sensitive patients. Their rabbit anti- $\gamma$ E Abs were also used to confirm that the atypical myeloma protein IgND isolated by Johansson and colleagues (7) was identical to  $\gamma$ E. IgND was shown to block the PK reaction (8). An immunoassay for IgND was developed to show increased levels of IgND in allergic asthma (9), followed by the development of a radioallergosorbent test, to detect and quantify allergen-specific IgE Abs (10). IgE myeloma protein from the second patient was used for purification of anti-IgE Ab and labeling IgE-bound cells, leading to the description of basophils and mast cells as major cell types that bind IgE via the Fc portion of the molecule (11, 12) among others.

#### *IgE receptors, FcεRI, and CD23*

Using rat basophilic leukemia cells, the binding properties of IgE and its FcεRI were characterized by Metzger and colleagues (13, 14). They showed that IgE binds as a monomer to a single univalent receptor with very high affinity ( $\approx 10^{10} \text{ M}^{-1}$ ) and slow off-rate, explaining the long persistence of reaginic activity in the skin. Furthermore, using crosslinking agents and conditions of solubilization in mild detergents, they found that the receptor is a multisubunit structure containing besides one IgE-binding  $\alpha$  subunit, one  $\beta$  subunit (15) and a dimer of disulfide-linked  $\gamma$  subunits (16). The cDNA cloning of all components of the rodent receptor (17–19) by Kinet and colleagues (20, 21) confirmed that the receptor contained the three subunits. Successful expression of a functional receptor (in terms of IgE binding) on the surface of COS-7 cells was, however, only achieved when the cDNAs for all three subunits were cotransfected in the case of rodent receptors, whereas human receptors could also be expressed as trimers in the absence of  $\beta$ -chains (21). Later, Kinet and colleagues (22, 23) showed that the  $\beta$  subunit plays a critical role in receptor stabilization/maturation and signal amplification. The cloning and expression of the receptor subunits also contributed to advancing the study of signal transduction of the receptor. Important steps in the understanding constituted the discovery by Reth (24) that the signal-transducing  $\beta$  and  $\gamma$  subunits share a signaling motif, called ITAM, with T and B cell receptor signaling chains. Early studies also showed that crosslinking of IgE receptors induced tyrosine phosphorylation events (25), in-

cluding phosphorylation of  $\beta$  and  $\gamma$  subunits (26). Several tyrosine kinases were shown to be involved in the early steps of FcεRI signaling, including Src (27), Syk (28), and Tec (29) family kinases. The availability of cDNAs of the  $\alpha$ -chain also allowed large-scale production for studies of the three-dimensional structure with the first complex between an Ig and its receptor being published in the year 2000 (30).

A low-affinity receptor for IgE, FcεRII, was found to be expressed on lymphocytes and monocytes (31, 32). Kishimoto and colleagues (33) demonstrated that this receptor is identical to the B cell-specific differentiation Ag CD23. They showed that immature B cells do not express CD23/FcεRII but that IL-4 induces CD23/FcεRII expression. They also showed that B cells lose CD23/FcεRII expression after they undergo isotype switching, and increased soluble CD23/FcεRII as a complex with IgE was observed in the serum of atopic patients. Several groups, including those of Yodoi, Kishimoto, and Delespesse (34–36), independently cloned the cDNA of the CD23/FcεRII molecule. CD23/FcεRII expressed on B cells binds IgE, and upon allergen binding gets internalized and digested in the lysosomes, allowing allergen presentation to T cells along with MHC class II molecules. This Ag presentation pathway is efficient in taking up low-concentration allergens. CD23/FcεRII is also involved in feedback regulation of IgE production after crosslinking of membrane IgE receptors and CD23-bound IgE with a specific allergen (37, 38). Anti-CD23 mAbs were shown to reduce blood IgE levels by  $\sim 50\%$  in human clinical studies (39, 40). However, it is not clear whether CD23 contributes to human diseases (41).

#### *Properties and clinical application of anti-IgE Abs*

Allergic diseases such as allergic asthma, allergic rhinitis, atopic dermatitis, and food allergy are caused by IgE-mediated type I hypersensitivity reactions. However, this dogma, that is, that IgE and their target cells are essential for these diseases, has not been rigorously proven in some of these diseases even today. This was particularly troubling when observations were made that IgE (42) and mast cells (43, 44) are dispensable in multiple asthma models. Later, it was shown that sensitization of animals with allergen in the presence of aluminum hydroxide or large doses of allergen obliterates the necessity of mast cells and IgE in airway inflammation induced by allergen challenge of sensitized mice (45, 46). Regardless of this controversy, anti-IgE mAbs were developed to target both membrane-bound and soluble IgE as potential therapeutics (47–49). Omalizumab is a humanized monoclonal anti-IgE Ab with a  $K_d$  of 6–8 nM for IgE. It inhibits allergic responses by binding to serum IgE molecules, thereby preventing their interactions with IgE receptors. It can also be used in allergen-specific immunotherapy to reduce signs

of anaphylaxis associated with allergy shots and to accelerate immunization schedule and dosing. Numerous excellent reviews on omalizumab have been published (50–57).

Unlike many anti-IgE Abs that can crosslink FcεRI-bound IgE, thus causing activation of mast cells and basophils, omalizumab is not anaphylactogenic. It binds the Cε3 domain of free IgE, preventing it from binding to FcεRI (58, 59), but it does not bind IgE already bound by FcεRI or CD23 on the cell surface (48). By depleting IgE, omalizumab downregulates the expression of FcεRI on mast cells and basophils as well as APCs. The positive correlation between the basophil FcεRI surface expression levels and serum IgE concentrations was known for a long time (60). Later it was shown that IgE-free FcεRI is unstable and internalized for degradation (61, 62), thus limiting activation of mast cells and basophils. The structural basis for the ability of omalizumab to block IgE from binding to both CD23 and FcεRI was recently revealed by x-ray crystallography of the IgE/omalizumab complex (63). Omalizumab inhibition of FcεRI binding involves substantial steric conflict with the receptor at site 2, whereas its inhibition of CD23 binding is due to a greater steric overlap of omalizumab with CD23 than that for FcεRIα and a more extensive overlap between IgE residues that engage omalizumab and CD23 as compared with FcεRIα (Fig. 2). In addition to the depletion of free IgE and downregulation of FcεRI, anti-IgE effects might be related to accumulated soluble immune complexes of anti-IgE/IgE 5- to 10-fold higher than the basal levels of IgE (64–67), inhibition of IgE-committed B cells (68, 69), and neutralization of the cytokinergic activity of IgE (70).

Omalizumab is indicated for moderate to severe asthma with serum IgE levels of 30–700 IU/ml. It is ineffective for asthmatics who have very high IgE levels. Omalizumab's effects on allergic asthma are shown by improvements in the quality of life, as well as marked reduction of asthma exacerbations, emergency room visits, and use of systemic corticosteroids and rescue bronchodilators (71–73). However, it has fewer effects on lung function (51, 56, 57). As noted above, the primary outcome of omali-

zumab is the prevention of asthma exacerbations, which has been noted also with other mAbs that affect type 2 inflammation (74–76). This suggests the existence of feed-forward pathways that involve Th2 cytokines, IgE, and mast cells as the main mechanisms for allergic asthma. The major cause of asthma exacerbations is viral respiratory infections (77, 78). The Inner City Asthma Study demonstrated that omalizumab treatment reduces the frequency of asthma flares associated with seasonal virus exposure (79). Long-term effects of omalizumab in some studies include a reduced airway wall area, reduced sputum eosinophilia, increased baseline lung function, and reduced epithelial reticular basement membrane thickening (80, 81). Moreover, potential benefits of omalizumab were also shown in nonallergic phenotypes of severe asthma (82, 83).

Although not approved by the U.S. Food and Drug Administration at the time, the efficacy of omalizumab or another anti-IgE TNX-901 was shown by decreased nasal and ocular symptoms, reduced antihistamine use, and improved quality of life scores in allergic rhinitis (84–88), as well as by an increased threshold dose of allergenic food required to trigger hypersensitivity reactions in food allergy (89–92). However, clinical improvements by omalizumab were not seen in two double-blind, placebo-controlled trials on atopic dermatitis (93, 94), despite ample evidence for the involvement of IgE in murine models of atopic dermatitis (95, 96). Use of omalizumab was approved for the treatment of chronic idiopathic urticaria, although little is understood regarding the pathogenesis of this syndrome with multiple phenotypes (97–99). In case IgG autoantibodies against IgE or FcεRIα or IgE autoantibodies against thyroperoxidase (100) are involved, the effect of omalizumab might be understood by reduced levels of IgE. Interestingly, many omalizumab-responding patients had low or undetectable levels of IgE, and therefore how anti-IgE works in these patients is unclear.

As with other humanized Abs, omalizumab occasionally causes anaphylactic reactions (101). Related to this adverse

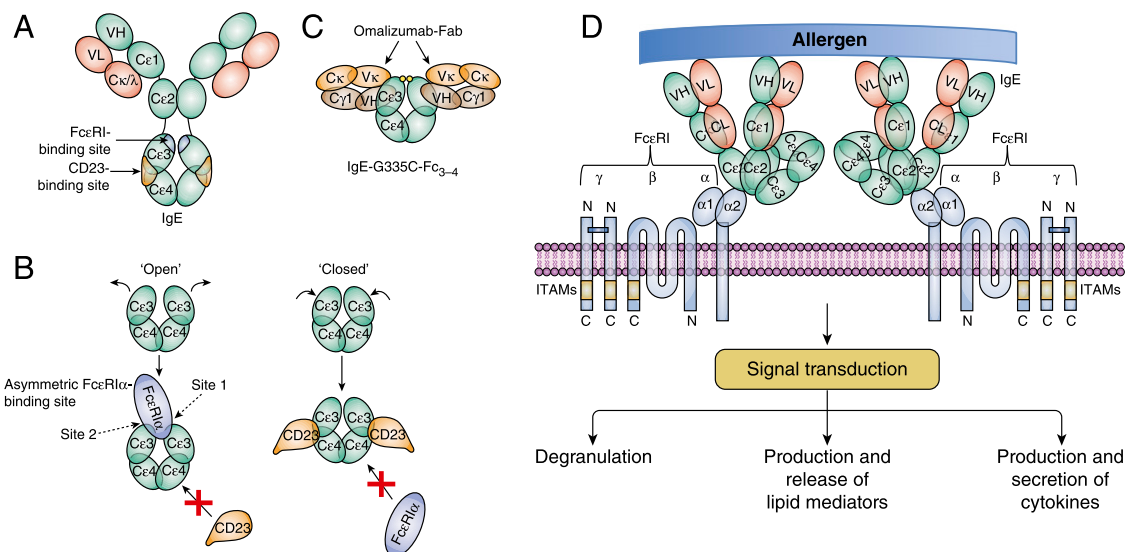


**FIGURE 2.** IgE, its interaction with omalizumab, and FcεRI-mediated mast cell activation. (A) IgE and the relative locations of the FcεRIα- and CD23-binding sites. (B) Open and closed conformations of the IgE/Fcε3–4 domains interacting with FcεRIα and CD23, respectively. (C) Symmetric interaction of two omalizumab Fabs with IgE/Fcε3–4. Modified from Pennington et al. (63). (D) Crosslinking of IgE-bound FcεRI with a multivalent allergen leads to activation of mast cells. The activated cells degranulate and produce/release lipid mediators and cytokines. Signal transduction via the FcεRI was recently reviewed (124–127). Domains of IgE and omalizumab are represented by ovals.

effect, the recently demonstrated ability of omalizumab to promote the dissociation of IgE/FcεRIα complexes (102) implies that omalizumab might have some ability to bind to IgE that has bound to FcεRI. Fortunately, a concern of increased risk of malignancy was refuted (103).

#### *Other therapies targeting IgE and IgE receptors*

New strategies targeting IgE have been explored (51), including anti-IgE mAb QGE031, with higher affinity ( $K_d$  of 139 pM) to the Cε3 domain of IgE than omalizumab (104, 105), and designed ankyrin repeat protein E2\_79, which can accelerate the dissociation of IgE/FcεRI complexes (102, 106). An interesting strategy is to disrupt IgE production by targeting a segment (the M1' domain or CεmX) (107) of membrane IgE on human IgE-switched B cells that is not present in serum IgE (108). FcεRI could also be targeted to desensitize allergy patients. Khodoun et al. (109) showed that rapid desensitization with anti-FcεRI mAb suppresses both active and passive IgE-mediated anaphylaxis without inducing disease: the procedure starts with an mAb too small to induce disease, which is doubled hourly until a saturating dose is reached. Desensitization was accomplished by decreasing mast cell signaling through FcεRI and slow, but eventual removal of nearly all IgE from the mast cell surface. Importantly, however, we note that the clinical relevance of the potential therapeutics discussed in this section has not been established.

#### *IgE heterogeneity and personalized precision medicine*

Asthma and allergic diseases are syndromes presenting with a set of signs and symptoms (110). Efforts are currently directed toward defining endotypes of these diseases (71). The measurement of an increasing number of clinical parameters and biomarkers will allow stratification of patients along specific pathophysiologic pathways. IgE has not been a good biomarker, whereas eosinophils or exhaled NO levels correlate to greater responsiveness to omalizumab (111).

Similar to IgG, IgE consists of variable and constant regions in both H and L chains. Given that biologic activities reside in the constant Fc portion of the molecule, all IgE molecules are thought to behave in the same way except for their unique ability to recognize specific Ags. However, the Ag recognition ability of the variable Fab portion might not be simply one Fab to one Ag. A well-characterized DNP-specific IgE molecule SPE-7 can recognize several haptens as well as a protein thioredoxin (112). Thus, this observation raises the possibility that an IgE molecule on mast cells or basophils might fortuitously recognize multiple Ags and activate these cells. Interestingly, SPE-7 IgE was recognized as the most potent cytokinergic IgE molecule. Originally, two groups found that monomeric IgE molecules promote mast cell survival in the absence of growth factors, but two studies differed in the cytokine-producing abilities of IgE molecules (113, 114). Subsequently, this difference was shown to be due to the ability of IgE molecules used, resulting in the proposal of the existence of two types of IgE, that is, highly cytokinergic versus poorly cytokinergic IgEs (115). Highly cytokinergic IgEs can induce large aggregates of FcεRI, whereas poorly cytokinergic IgEs induce much smaller FcεRI aggregates (115). Therefore, highly cytokinergic IgEs can activate mast cells almost as strongly as can IgE plus Ag. A recent study reported the Fv–Fv interacting ability of SPE-7 IgE as a mechanism for high

cytokinergic activity (116). In contrast, poorly cytokinergic IgEs can only promote cell survival weakly.

Another known heterogeneity among IgE molecules is their reactivity to histamine-releasing factor (HRF). HRF can activate mast cells and basophils primed with a certain type (so-called IgE<sup>+</sup>) of IgE molecules, leading to the release of histamine, IL-4, and IL-13 (117). IgE<sup>+</sup> can be derived from some, but not all, atopic patients. HRF is found in body fluids of patients with allergic reactions and is thus implicated in the pathogenesis of allergic diseases (118, 119). Interestingly, ~25% of the tested IgE molecules directly bind HRF via IgE Fab interactions of two IgE-binding sites within the HRF molecule (120). Because HRF can be present as a disulfide-linked dimer, dimeric HRF-bound IgE can crosslink FcεRI molecules to activate mast cells and basophils. HRF inhibitors that block interactions between IgE and HRF inhibit IgE plus HRF-induced activation of mast cells in vitro and airway inflammation in IgE-dependent in vivo models of asthma (120). Because HRF, also known as translationally controlled tumor protein or fortilin (121, 122), is one of the most abundantly expressed proteins in all tested cell types, secreted HRF works as a kind of autoantigen to induce allergic reactions (123).

## Conclusions

It was a long journey of 36 years from the discovery of IgE before omalizumab was first approved for the treatment of asthma. The research from the identification of IgE as the reaginic Ab to successful translation to omalizumab is a triumphant example of how immunologic research can bring a benefit to patients. As richly illustrated in this case, one cannot overemphasize the importance of basic science to further enrich therapeutic options to treat allergic diseases.

## Disclosures

The authors have no financial conflicts of interest.

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