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IgE, what is it good for?

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Introduction

Fifty years ago the first report of Immunoglobulin E (IgE) was published, and since then this antibody has revolutionized the diagnosis and management of allergic disease. Kimishige and Teruko Ishizaka, *et al*, initially described IgE after an extensive investigation of a substance that Coca and Cooke had called “reagin” as early as 1923.¹ Little work occurred on “reagin” from the 1920’s until the 1960’s, when newer techniques had been developed that aided in the detection and identification of proteins. It was at this point that the Ishizakas described an anti-serum that was able to block the body’s allergic response, and called this molecule γE-globulin in their 1966 seminal paper.² Interestingly, this molecule did not fix complement or induce a precipitin reaction like other immunoglobulins. Simultaneously, Hans Bennich and S.G.O. Johansson discovered a paraprotein in a leukemia patient that did not appear to be any of the known immunoglobulins at that time. They termed this paraprotein IgND and found that it had similar properties to reagin.³ Utilizing IgND antibodies and γE-globulin, both of which inhibited the Prausnitz-Kustner test (i.e., passive transfer of cutaneous anaphylaxis), Bennich, Johansson, and the Ishizakas, respectively, were able to demonstrate that the antibody isotype was in fact reagin.⁴ In 1968, the World Health Organization International Reference Center for Immunoglobulins officially named γE-globulin and IgND as Immunoglobulin E.⁵ The discovery of this new immunoglobulin opened the door to research and better understanding of the allergic response, as well as detection and diagnosis of specific allergic triggers. While these advancements in technology and understanding of allergic disease have developed over the last 50 years, there still remains a paucity of information on why IgE is produced and what

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its role is beyond allergic disease. Or, to paraphrase a popular rock song, “IgE, what is it good for?”

IgE

IgE, like other immunoglobulins, is produced by B cells and plasma cells (usually) in response to an antigenic stimulus. The presence of IL-4 and IL-13 induce immunoglobulin class switching from other isotypes to IgE.^{6,7} These two cytokines interact with receptors on the surface of B-cells to initiate a signaling cascade mediated by Janus kinase 3 (JAK3) and signal transducer and activator of transcription 6 (STAT6).⁸ A second signal is required in order for class switching to IgE to occur, and this involves CD40 on the B-cell interacting with CD40-ligand on the T-cell.⁹ Once IgE is produced by allergen specific B-cells, it is released into the circulation.

The discovery of IgE has resulted in the development of highly sensitive and specific immunoassays to detect its presence in serum. The most commonly used detection assay today is the fluorescent enzyme immunoassay (e.g., ImmunoCAP), which has replaced the better-known radioallergosorbent test (RAST). These tests detect IgE specific to particular antigens, and can be extremely helpful in the diagnosis and management of many allergic diseases.¹⁰

There is a form of IgE, known as “natural IgE” that is produced without the need for antigen presentation and T cell co-stimulation (although it may still require IL-4).¹¹ This natural IgE does not appear to undergo somatic hypermutation and is directed against self-antigens. The amount of this IgE appears to increase with age, although its function is not known. There is some evidence that this IgE may cross-react with antigens found in the environment, and may be important in the toxin hypothesis described below.¹²

Regardless of whether it is produced with or without T cell help, IgE is present in very small concentrations in the serum. In fact, it is present in the lowest concentration of all the immunoglobulins, with normal human serum concentrations being approximately 50 ng/mL (compare this to IgG, which is around 10 mg/mL). The half-life of free IgE is also much shorter than IgG (approximately 2 versus 21 days, respectively).¹³ The IgE molecule is about 190 kDa in size and structurally similar to other immunoglobulins with two heavy and two light chains. The heavy chains are made up of 4 constant domains (Cε1–4), as opposed to IgG, which has only 3 constant domains in its heavy chain. The Cε2 region of IgE actually replaces the hinge region found on IgG, resulting in an asymmetrically folded molecule. IgE is commonly found circulating in the blood and attached to many different cell types through one of its receptors. The Cε2–3 region binds to these receptors anchoring it in place on the cell surface. IgE can remain bound to its high affinity receptor (FcεRI) for several weeks.^{14,15}

Receptors for IgE

There are two known receptors for IgE, FcεRI and CD23 (FcεRII). FcεRI, the high affinity receptor for IgE, is composed of a tetramer, αβγ₂, on mast cells and basophils, and as a trimer, αγ₂, on other cells such as monocytes, dendritic cells, eosinophils, and platelets.^{16–19}

The tetrameric form is responsible for immediate hypersensitivity reactions; however, in a mouse model of viral induced atopic disease, we found the trimeric form expressed on dendritic cells, and expression of FcεRI by dendritic cells was critical for development of post-viral atopic disease.²⁰

FcεRI is found in high numbers on the membranes of mast cells and basophils. IgE binds to FcεRIα with high affinity ($K_d \sim 1\text{nm}$), which at physiologic concentrations of IgE, results in fully saturated receptors.²¹ This high affinity and avidity allows IgE to persist for weeks to months when bound to FcεRI.^{14,15} Cross-linking IgE bound to FcεRI aggregates the receptors, and induces signaling. Once aggregated, immunoreceptor tyrosine-based activation motifs (ITAMs) on FcεRIβ and FcεRIγ stimulate a phosphorylation cascade resulting in the exocytosis of preformed mediators as well as induction of transcription factors that begin to produce further mediators propagating the IgE-FcεRI mediated response.¹⁶

CD23 is quite different in structure and function compared to FcεRI.²² CD23 is a type II integral membrane protein with a C-type lectin domain at the c-terminal end of the extracellular component of the receptor. It is the globular head at the c-terminal end where IgE binds.²³ There are two isoforms of CD23, CD23a and CD23b. CD23a is exclusively found on B cells whereas CD23b is found on many cells including T cells, monocytes, dendritic cells, neutrophils and others. In contrast to the very high affinity binding of IgE to FcεRI, CD23 binds to IgE with much lower affinity (K_d 0.1–1μM), suggesting the IgE may not be the primary ligand for this receptor.²⁴ Interestingly, binding of IgE to CD23 acts as a negative feedback loop on B cells, suppressing IgE synthesis.^{24,25} When CD23 interacts with MHC class II it can facilitate antigen processing.^{24,26} CD23 also has a co receptor, CD21, which stimulates IgE synthesis when binding a trimeric form of CD23, and inhibits IgE synthesis when binding monomeric CD23.^{27,28} In the gastrointestinal tract CD23 also aides in transport of IgE-antigen complexes across intestinal epithelium to underlying tissues.²⁹

Functional consequence of IgE

IgE is most commonly associated with allergic disease and thought to mediate an exaggerated and/or maladaptive immune response to antigens. Once antigen specific IgE has been produced, re-exposure of the host to that particular antigen results in the typical immediate hypersensitivity reaction. This reaction occurs within minutes of exposure to the offending agent; these immediate effects include: hypotension, bronchospasm, urticaria, vomiting, diarrhea, and others.³⁰ While preformed chemicals mediate the immediate hypersensitivity reaction, *de novo* production of other mediators, instigated by cross-linking of IgE-FcεRI, result in a late phase allergic response. This late phase response is thought to represent the inflammation in chronic allergic diseases; as a result, both the immediate and late phase responses are mediated by downstream effects of IgE.^{19,31}

To understand the role of IgE in immune responses, it is best to determine what happens in its absence. Anti-IgE (omalizumab) targets and binds to the Cε3 domain of free IgE and effectively removes it from the circulation. Because omalizumab binds to the Cε3 domain of

IgE it prevents free IgE from binding to FcεRI (it is also unable to cross-link FcεRI bound IgE).³² Omalizumab is FDA approved for two allergic disorders, severe persistent asthma and chronic idiopathic urticaria, and clearly has clinical efficacy in these diseases. Busse, *et al*, looked at the effect of omalizumab in inner city children who had moderate to severe persistent asthma. What they found supported a central role for IgE in asthma exacerbations, as omalizumab reduced exacerbations not just during pollen seasons but throughout the year.³³ In fact, the reduction in viral induced asthma exacerbations suggested that IgE might be important in the anti-viral immune response. As mentioned above, in our mouse model of viral induced atopic disease, IgE against the virus is crucial for development of disease.²⁰ In fact, others and we have demonstrated that humans make IgE against respiratory viruses.^{34–36} Therefore, IgE is part of the antiviral immune response, and is plausible that viral induced asthma exacerbations are simply a result of crosslinking of this antiviral IgE during a respiratory viral infection.

The idea that IgE exists for allergic disease and asthma does not seem to make evolutionary sense. Why would a system that makes a person ill be advantageous? There are several hypotheses as to why we have IgE, and why it might be beneficial. One hypothesis is that IgE is a host defense mechanism against parasitic infection. During a helminthic infection there are strong Th2 responses mediated by anti-parasite IgE similar to that seen with an allergic response to a particular antigen.³⁷ In fact, it has been shown that platelets and eosinophils kill parasites via IgE and FcεRI.^{38,39} For example, *Schistosoma mansoni*, a blood fluke, infection is not cleared well in mice that are deficient in IgE.⁴⁰ However, unlike the situation with FcεRI expression on platelets and eosinophils, this process is likely mediated through CD23, since mice deficient in FcεRI were able to clear the infection at a rate similar to mice sufficient in FcεRI.⁴¹ Clearance of other parasites like *Trichinella spiralis* requires removal from the gastrointestinal system. IgE has been found to accelerate this process by inducing intestinal smooth muscle contractility. Additionally, larvae must be killed, and IgE has been found in high concentrations in necrotic larval cysts, suggesting that IgE helps mediate killing through release of toxic granules from effector cells (e.g. eosinophil).⁴²

There is also some evidence that Th2 immune responses to helminthes can participate in acute wound healing. IL-4 receptor signaling, which is part of Th2 response, resulted in reduced IL-17 mRNA levels and increased the production of insulin-like growth factor 1 (IGF-1), IL-10 and M2 macrophages resulting in the rapid resolution of tissue damage in a *Nippostrongylus brasiliensis* infection model.⁴³ Arginase I (Arg I), which is a product of alternatively activated (i.e., IL-4 and IL-13) macrophages, suppresses intestinal inflammation in mice infected by *S. mansoni*. To reduce inflammation, Arg I promotes TGF-β production and Foxp3 expression while suppressing *S. mansoni* specific T cell proliferation and limiting Th17 differentiation.⁴⁴ Since IgE can help drive Th2 responses (via mast cells and basophils), it stands to reason that it might play a role in wound healing. However, this is speculative and to date no clear role for IgE in the wound healing process has been documented.

IgE has long been associated with detecting very miniscule amounts of specific protein. Several investigators have hypothesized that IgE acts, therefore, as a surveillance

mechanism for the immune system. Heyman suggested that IgE is produced to act as an enhancer for other antibody responses such as IgG.⁴⁵ Mice who have been immunized with bovine serum albumin (BSA) – trinitrophenyl (TNP) and given TNP specific IgE exhibited significant enhancement of the production of BSA specific IgG -- up to 100 fold higher compared to mice in whom no TNP specific IgE was given.⁴⁶ BSA specific IgG secreting B cell numbers also increased rapidly in the mice given IgE, as well.⁴⁷ Other studies have suggested that this response is dependent upon CD23 and not FcεRI. CD23 has been demonstrated to participate in allowing B cells to pick up small amounts of antigen through IgE and target the antigen for degradation and subsequent presentation to T cells (so called “antigen focusing”).^{48,49} Whether these roles of CD23 are important in the immune response is less clear, since infection with *N. brasiliensis* in CD23 deficient mice led to a normal immune response, including normal production of IgE.⁵⁰

Another hypothesis for IgE being a sensor for low levels of protein is the “toxin hypothesis” published by Profet in 1991.⁵¹ In her manuscript, she hypothesized that allergic reactions (precipitated by IgE) evolved from a defense mechanism allowing the body to react immediately to small amounts of noxious substances. The toxin hypothesis posits that the body evolved to produce IgE to expel these harmful substances quickly and effectively. Symptoms such as sneezing, vomiting, diarrhea, and cough help to achieve this goal. Hypotension, a common symptom in severe allergic reactions, reduces the rate at which toxins circulate through the blood to target organs, and could be thought of as a means to lessen the systemic effect of these toxins.⁵¹

Evidence for the “toxin hypothesis” comes from a study in which Marichal, *et al*, described a beneficial effect for IgE-FcεRI in the immune response to repeat bee stings. In this model, mice were injected with enough honeybee venom to simulate 1–2 stings, with subsequent development of a typical Th2 response with production of bee venom specific IgE. Three weeks after the initial stings, mice were challenged with what were usually fatal amounts of honeybee venom; however, in mice that had previously been sensitized to honey bee venom, there was a significant reduction in mortality. This reduced mortality was shown to depend upon IgE and FcεRI (and mast cells). Therefore, in this mouse model it did appear that IgE played a protective role preventing death from an overwhelming toxin exposure. Similar IgE dependent protective effects were found with Russel’s viper venom exposure, strongly supporting the toxin hypothesis as a *raison d’être* for the evolution of IgE.⁵²

Conclusion

The discovery of IgE 50 years ago ushered in a very productive and exciting time in allergy and immunology. Much has been learned about the structure and function of IgE, as well as its receptors. While the role of IgE in allergic disease has been well studied, it is less clear why this immunoglobulin isotype has been retained evolutionarily. More recent studies have begun to shed light on its potential beneficial role to the host (see Figure 1). While more research into IgE in the immune response is needed, it is clear that this antibody, which is most closely aligned to our specialty, has multifaceted functions well beyond just making us wheeze and sneeze!

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Abbreviations

IgE Immunoglobulin E

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Learning Objectives

At the conclusion of this activity, participants should be able to:

- Understand the biology of IgE.
- Discuss the competing theories behind the production of IgE.

Q1: In what year did the Ishizaka's first describe IgE?

- A. 1956
- B. 1966
- C. 1967
- D. 1968
- E. 2006

Q1 ANS: B. 1966.

Rationale: 2016 marks the 50 year anniversary of the discovery of IgE. The Ishizaka group in Denver, Colorado discovered what they described as γ E-globulin and reported their findings in the *Journal of Immunology* in 1966.

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Q2: Where does Omalizumab bind to IgE?

- A. C ϵ 1
- B. C ϵ 2
- C. C ϵ 3
- D. C ϵ 4
- E. C γ 3

Q2 ANS: C. C ϵ 3.

Rationale: Omalizumab, anti-IgE, is a monoclonal antibody that is used to treat asthma and chronic idiopathic urticaria. It functions to bind to the C ϵ 3 region of IgE. This results in the removal of all freely circulating IgE molecules. This removal has been shown to markedly reduce asthma exacerbations in inner city youth with allergic asthma.

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Q3: In which cell type is the $\alpha\beta\gamma 2$ tetrameric form of Fc ϵ RI found?

- A. mast cell
- B. monocyte
- C. platelets
- D. dendritic cells
- E. T cells

Q3 ANS: A. Mast cell

Rationale: The tetrameric form of Fc ϵ RI is found on the mast cell and basophil, the two cell types most associated with the allergic response. The trimeric form of Fc ϵ RI, which consists of $\alpha\gamma 2$, is found on monocytes, platelets, and dendritic cells. The trimeric form of Fc ϵ RI has been found to play a role in the development of mucous cell metaplasia in mice.

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Q4: The toxin hypothesis suggests that IgE is produced to help the body perform what task?

- A. augment cellular recruitment
- B. enhance the effect of toxins on the body
- C. induce immunologic memory
- D. increase reaction time to foreign substances
- E. expel offending substances

Q4 ANS: E. expel offending substances

Rationale: The toxin hypothesis was suggested in 1991 that allergies evolved as a defense mechanism to quickly expel and neutralize toxins. IgE mediated reactions usually cause symptoms of sneezing, cough, vomiting, diarrhea and hypotension that are suggested help expel the noxious substance from the body.

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Q5: Which of the following is a characteristic of FcεRI?

- A.** acts as a negative feedback when IgE is bound to it inhibiting IgE synthesis.
- B.** interacts with MHC Class II to stimulate processing of IgE bound antigens to peptides
- C.** has a co-receptor, CD21, that can augment or inhibit IgE synthesis
- D.** initiates signaling cascade resulting in the immediate hypersensitivity reaction.
- E.** transports IgE-antigen complexes across intestinal lumen

Q5 ANS: D. initiates signaling cascade resulting in the immediate hypersensitivity reaction.

Rationale: FcεRI, or the high affinity receptor for IgE, is found on many cells including mast cells and basophils. These cells produce allergic mediators and initiate the immediate hypersensitivity reaction when IgE crosslinks antigen when bound to FcεRI. All of the other answers are proposed functional properties of CD23, IgE's other receptor.

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Figure 1. The many roles of IgE

IgE can bind to either FcεRI (the high-affinity receptor for IgE, composed of either an α, β, and 2 γ chains or simply an α and 2 γ chains) or CD23 (the low-affinity receptor, here shown as a trimer, although it also occurs as a monomer), with the resulting functions for each receptor shown. Shown with the “crown”, IgE is most known for its role in allergic disease. However, as discussed in the text, via FcεRI, IgE has been shown to play a role in antiviral immune responses to respiratory viruses, protection from toxin exposure, as a sensor for small quantities, and as part of the immune response against parasites. Through

CD23, IgE has been demonstrated to operate as a sensor for small quantities, play a role in the immune response against parasites, and regulate IgE synthesis by B cells.

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