

Multi-faceted regulation of IgE production and humoral memory formation

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Abstract

IgE antibodies play a protective role against parasites and environmental toxins by its strong effector functions. However, aberrant IgE production can contribute to the development of allergic disorders, and thus is tightly regulated. Beside its very short half-life, IgE is normally produced only transiently and its affinity maturation is limited under physiological immune responses. Although such distinct characteristics of IgE among Ig classes are well-known, the underlying molecular mechanisms have not been understood until recently. Somatic or genetic defects of such mechanisms can lead to pathogenesis of allergic diseases. In this review, we summarize recent advances in our understanding of the mechanisms that control the production of IgE and formation of IgE-type humoral memory, focusing on the B cell immune responses.

Keywords

B cell

B-cell receptor

Germinal center

Humoral memory

IgE

Introduction

IgE antibody (Ab) is produced by plasma cells (PCs) derived from B cells having undergone class-switching (CS) to IgE isotype during type 2 immune responses. IgE plays a pivotal role in protection against parasite infection and environmental toxins by activating mast cells and basophils through binding FcεRI, a high-affinity Fc receptor for IgE. On the other hand, IgE is best known as a mediator of allergic responses through the same mechanism.^{1,2} Cross-linking of IgE bound to FcεRI by cognate antigen (Ag) induces rapid degranulation and release of inflammatory mediators, leading to an immediate hypersensitivity response.¹ Due to the strong biological effects of this response, systemic triggering by IgE can cause a life-threatening reaction called

anaphylaxis. Besides, misdirected IgE production against non-infectious environmental Ags such as food components or pollen can cause allergic disorders. IgE is the least abundant isotype among five Ab classes (IgM, IgD, IgG, IgA and IgE) in the sera of healthy individuals: the serum concentration of IgE is 10,000 to 50,000-fold less than that of IgG.³ This is primarily due to the extremely short half-life of IgE protein in the circulation (about 1 day). Even after immunization in animal experiments, the serum level of IgE increases only transiently and swiftly return to a baseline, indicating that IgE production is tightly regulated. In this review, we summarize the mechanisms that regulate IgE production, focusing on the B cell immune responses and humoral memory formation.

The function of IgE

IgE has strong effector functions through binding to FcεRI. Upon crosslinking of IgE–FcεRI complex by specific Ag, mast cells and basophils release various mediators such as histamine, prostaglandins, heparin and proteases, which give rise to immediate allergic reactions through stimulation of endothelial cells, smooth muscle cells and C-fibres.^{1,2,4} These immediate allergic reactions induce coughing, vomiting and diarrhea, contributing to the expulsion of parasites and environmental toxins.² It has been reported that Ag-specific IgE, FcεRI and mast cells are required to avoid mortality caused by phospholipase A₂, a bee venom cytolytic enzyme.^{5,6} A recent study showed that the IgE–FcεRI axis in mast cells is necessary for the protection against secondary infection with *Staphylococcus aureus*, a pathogenic bacteria expressing various toxins, through detoxification and antibacterial activity exerted by IgE-activated mast cells.⁷ Thus, IgE has important roles in the host defense against parasite infection and noxious substances.

IgE production during T cell dependent type 2 immune responses

IgE production is one of the hallmarks of type 2 immune responses and, in most cases, strictly dependent on IL-4 secreted by CD4⁺ T helper (T_H) cells. Parasite infection induces strong type 2 responses, which is known to occur after tissue damage.⁸ Viral infection can trigger not only type 1 but also type 2 responses by inducing tissue damage likely through death of infected cells.⁹ Infection with toxin-producing bacterial species was also reported to trigger type 2 responses.¹⁰ Alum, a widely used adjuvant for human vaccines and immunization of experimental animals, is known to mediate the type 2 responses through induction of cell death.¹¹ Such infections and immunizations induce

the release of damage-associated molecular patterns (DAMPs), alarmins and cytokines from epithelial cells and innate immune cells, leading to the generation of IL-4-producing T_H cells, for which underlying mechanism is not fully elucidated. Early studies demonstrated that IgE production was reduced in mice deficient for T_H2-lineage determining factors such as STAT6 or GATA3.[12](#), [13](#), [14](#) Thus, IgE production was proposed to be dependent on T_H2 cells. However, a recent study has demonstrated that follicular helper T (T_{FH}) cells, a T_H cell subset localizing in the B cell follicle and highly expressing B cell stimulating molecules such as CD40 ligand (CD40L),[15](#) are the major source of IL-4 in the lymphoid tissues.[16](#), [17](#), [18](#) Analyses of mice lacking the CNS2, an *Il4* cis-regulatory element required for IL-4 expression specifically in T_{FH} cells, revealed that IL-4 produced by T_{FH} cells was vital for IgE production after immunization with ovalbumin in alum or *Leishmania* infection.[19,20](#)

IL-4 was originally identified as a B cell-stimulating factor^{[21,22](#)} and has been widely accepted as a crucial factor to induce B cell CS to IgE.^{[23,24](#)} Together with the NF-κB signaling activated through CD40 on B cells, IL-4 signaling through STAT6 strongly induces Cε germline transcripts and expression of activation-induced cytidine deaminase (AID), both of which are essential for class-switch recombination (CSR) from IgM (direct CSR) or IgG (sequential CSR) to IgE.^{[3](#)} B cells class-switched to IgE express membrane-bound IgE as a B cell receptor (IgE-BCR) and differentiate into PC to secrete IgE. Thus, it is presumable that IgE production is controlled at multiple stages during the type 2 immune responses.

Characteristics of IgE production

Limited production

Serum IgE concentration is normally very low, being less than 200 ng per mL in healthy humans and mice.^{[25](#)} This is attributed to the shortest serum half-life of IgE among all Ab classes and also to a limited IgE production. Normally, IgE production is very transient and short-lived in experimental animals after immunization with T-dependent Ags that induce long-lasting production of IgG classes,^{[26,27](#)} suggesting an active suppression mechanism for IgE production ([Fig. 1](#)).

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Fig. 1. Characteristics of IgE production during type 2 immune responses. Parasite infection causes tissue damage and leads to the generation of IL-4 producing T_{FH} cells, which induces IgE-CSR of Ag-specific B cells. IgE⁺ B cells differentiate into short-lived PCs without participating the GC reaction. Thus, IgE produced after parasite infection is low-affinity and its production is transient. The produced IgE is captured by mast cells or basophils and maintained for a long period, which exerts host defense against reinfection. On the other hand, repetitive allergen exposure induces affinity maturation of IgE⁺ cells, likely through driving their participation in the GC reaction, and persistent production of IgE. The resultant high-affinity IgE Abs are captured by mast cells or basophils at high level, thereby giving rise to detrimental reactions after allergen re-exposure.

Unlike circulating IgE, it has been reported that IgE captured on mast cells or basophils can be maintained for at least 56 days after its single injection into B-cell deficient mice.²⁸ The transfer of Ag-specific IgE produced in the primary response against bee venom or *S. aureus* was sufficient for protection against challenge with the same antigen.^{5,7} These studies suggest that IgE captured on mast cells or basophils can play a long-lasting immunological memory to exert immediate protective responses upon secondary challenge. Thus, long-lasting Ab production, one of the hallmarks of humoral memory, may not be necessary for IgE-mediated host protection. Instead, as evident by the example that repeated exposure of individuals to venoms often results in severe anaphylaxis,^{29,30} IgE production at high level can be detrimental. Therefore, the quantitative regulation of IgE production must be needed for the prevention of allergic disorders.

In contrast to the transient IgE production in physiological settings, persistent IgE production has been observed in some allergic patients without allergen re-exposure.³¹ A recent study reported that extraordinarily chronic (15 weeks) allergen challenges of

normal mice induced IgE-secreting long-lived PCs in the bone marrow, giving rise to persistent IgE production.³² These studies indicate that long-lasting humoral IgE memory can be developed in some allergic conditions ([Fig. 1](#)).

Limited affinity maturation

It has been reported that increasing affinity of IgE elevates a sensitivity of mast cells and basophils for degranulation.^{33,34} Thus, another important parameter affecting the magnitude of IgE-mediated allergic response is the affinity of IgE against specific Ag. During T-cell-dependent immune responses, some activated B cells form germinal centers (GCs) where they proliferate extensively and acquire somatic hypermutation (SHM) that is randomly introduced in the variable regions of the immunoglobulin heavy (IgH) and light chain (IgL) genes. Then, GC B cells undergo affinity maturation through positive selection mediated by T cell help and finally differentiate into memory B cells or PCs. Thus, Abs produced from GC-derived clones are typically of high affinity for Ag.

On the contrary, the affinity maturation of IgE is very limited. It was shown that, during the primary *Nippostrongylus brasiliensis* (Nb) infection in mice, amount of total IgE produced is large but IgE that can bind to Nb is almost undetectable by the enzyme-linked immunosorbent assay and that IgE Abs cloned from the infected mice lacked SHM.³⁵ Thus, such IgE Abs are nonspecific or have too low affinities to be detected. However, an acute cutaneous anaphylaxis assay by injecting Nb–Ag into the skin of the infected mice was able to confirm the existence of Ag-specific IgE.³⁵ Furthermore, another study showed that Nb infection in quasi-monoclonal mice that express monoclonal IgH and IgL against an irrelevant hapten Ag did not result in the optimal IgE production.³⁶ These results indicate that the IgE Abs induced by parasite infection are indeed Ag-specific and may have extremely low affinities for Ag, partly because of the lack of affinity maturation in the GC or of GC altogether ([Fig. 1](#)). Such unique characteristics of IgE are similar to those of IgM and IgG produced upon *Salmonella* infection that induces a robust PC response but not GC formation.³⁷ Compared with the IgE Abs produced upon parasite infection, those from children with allergic asthma were reported to have accumulation of SHMs and to show evidence of affinity maturation.³⁸ A recent study using Ab-cloning from single peripheral blood B cells of patients with peanuts allergy reported that allergen-specific IgE gained high affinity by acquiring SHMs. Moreover, these SHMs also allowed IgE to gain a cross-reactivity to the clinically important peanut allergens Ara h2 and Ara h3, belonging to two distinct protein families.³⁹ These data suggest that, in the development of allergic

diseases, cellular events distinct from what happens during the protective response against parasite or noxious substances occur in B cell responses, leading to abnormal affinity maturation of IgE ([Fig. 1](#)). Taken together, not only quantitative but also qualitative regulation of IgE production is important for the prevention of allergic disorders.

Regulatory mechanisms for IgE production

Regulation of class switching to IgE

Class switching of B cells to IgE (IgE-CS) is a critical factor that regulates the magnitude of IgE production. A prototypic T_H1 cytokine interferon- γ (IFN- γ) was found to directly inhibit CSR to IgE by suppressing C ϵ germline transcription in cultured B cells.⁴⁰ IL-10, a cytokine produced by regulatory T cells and B cells, was also reported to inhibit IgE-CS of human B cells *in vitro*.^{41, 42, 43} However, a recent *in vivo* study reported that the frequencies of IgE⁺ B cells were normal in IFN- γ ⁻ or IL-10-deficient mice after immunization with protein Ag in alum adjuvant, questioning a dominant *in vivo* role of IFN- γ or IL-10 in the suppression of IgE-CS.⁴⁴ IL-21, a cytokine produced by T_{FH} cells, has been reported to have a great impact on the regulation of IgE production. An early study revealed that IgE production after immunization was greatly elevated in IL-21 receptor-deficient mice.⁴⁵ The action of IL-21 on IgE suppression was direct on B cells and likely through inhibition of C ϵ germline transcription induced by IL-4.⁴⁴ The major source of IL-21 for IgE suppression was T_{FH} cells.⁴⁴ Considering that the major source of IL-4 in the lymphoid tissues is T_{FH} cells,^{16, 17, 18} it seems plausible that, during cognate interaction between GC B cells and T_{FH} cells, IL-4-signaling drives B cell proliferation,^{21,22} while IL-21 suppresses IgE-CSR induced by IL-4 ([Fig. 2](#)).

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Fig. 2. Regulations of IgE production. In the primary response, activated IgM⁺ or IgG⁺ B cells undergo class-switching to IgE by receiving IL-4 from T_{FH} cells. IL-21 secreted by T_{FH} cells negatively regulates IgE-CSR, thereby suppressing the magnitude of IgE response. Some of activated IgM⁺ and IgG⁺ B cells massively proliferate to form GC, where they undergo SHM and affinity-based selection. GC B cells having gained high affinity for Ag may differentiate into memory B cells or long-lived PCs, which maintain high-affinity Ab in the serum. On the contrary, the participation of IgE⁺ B cells in the GC is very transient. They rapidly differentiate into short-lived PCs, undergo apoptosis and barely form memory B cells or long-lived PCs under physiological immune responses. Thus, affinity maturation and long-lasting production of IgE is restrained.

It has been reported that Bcl6, a transcriptional repressor expressed in GC B cells, negatively regulates the C ϵ germline transcription induced by IL-4 stimulation, thereby inhibiting IgE-CSR.⁴⁶ Consistent with this, Bcl6-deficient mice showed elevated serum IgE after immunization.⁴⁷ Thus, IgE-CSR is normally suppressed in GC B cells.

A recent study reported that a subfraction of T_{FH} cells called “T_{FH}13” cells produces IL-13 in addition to IL-4 but low amounts of IL-21, and that IL-13 derived from those cells were required for the production of high- but not low-affinity IgE.⁴⁸ Importantly, these T_{FH}13 cells were induced by repetitive allergen inhalation but not by Nb infection,⁴⁸ for which the underlying mechanisms remain elusive. The mechanism of how IL-13 promotes the production of high-affinity IgE is also currently unclear. However, considering that IL-13 activates STAT6 through the type II IL-4 receptor,⁴⁹ it would be possible that IL-13 induces sequential IgE-CS from high-affinity GC B cells. In addition to this, the lower expression of IL-21 by T_{FH}13 cells might contribute to the promotion of IgE-CS. Collectively, under the physiological conditions, inhibition of IgE-CS contributes to restraining the IgE production, which can be abrogated by allergic sensitization.

Regulation of IgE⁺ B cell development

GC is the site for affinity maturation, and thus required for the generation of high-affinity memory B cells and long-lived PCs, both of which are vital for humoral immunity.⁵⁰ A pioneer study revealing the unique propensity of IgE⁺ B cells described that IgE⁺ cells were predominantly PCs but not GC B cells.⁵¹ Later studies, using reporter mouse strains tracking the membrane-type IgE expression, have revealed that a few IgE⁺ GC B cells certainly exist after immunization^{52, 53, 54} but their participation in GC is very transient and their number rapidly declines, which is in striking contrast with

that of IgG⁺ GC B cells.^{53,54} These studies revealed that IgE⁺ B cells are restrained from developing as GC B cells under the physiological conditions (Fig. 2).

It has been reported that IgE⁺ B cells have several characteristics that may restrain their development in the GC. The ratio of PCs to GC B cells in IgE⁺ cells was higher than IgG1⁺ cells during primary responses.⁵³ The deletion in B cells of Blimp1, a master transcriptional regulator for PC differentiation, increased the frequency of IgE⁺ GC B cells. These data indicated that IgE⁺ cells are predisposed to PCs.^{53,55} Furthermore, compared to IgG1⁺ GC B cells, IgE⁺ GC B cells contained a higher frequency of apoptotic cells⁵⁴ and expressed a lower level of surface BCR^{53,54} as well as costimulatory molecules for T cells such as OX40L and ICOSL.⁵⁴ Some of these characteristics were also observed in IgE⁺ B cells derived from *in vitro* cultures: IgE⁺ cells expressed Blimp1 at a higher level and contained more PCs^{53,56} and contained more apoptotic cell⁵⁷ than IgG1⁺ cells. These results suggested that such characteristics of IgE⁺ B cells are determined by a B cell-intrinsic manner.

Memory B cells with low-affinity BCR can be developed in the absence of GC^{58,59}; however, there is no direct evidence showing the existence of IgE⁺ memory B cells in normal immune responses. Indeed, depletion of IgE-expressing cells had no impact on the secondary IgE response in a transfer model, suggesting the negligible contribution of IgE⁺ B cells for the memory recall responses.⁵⁴ IgG1⁺ memory B cells appeared to contribute to the secondary IgE responses.⁶⁰ This is also supported by an earlier report showing that IgE, but not IgG1, production required IL-4 during the secondary responses,⁶¹ suggesting a requirement of *de novo* CSR to IgE in the secondary responses. Consistent with these observations, culture-derived IgG1⁺, but never IgE⁺, B cells differentiated into memory-phenotype cells after transferring into recipient mice.⁵⁶ Therefore, IgE-expressing B cells are restrained from differentiating into memory B cells and thus no functional IgE⁺ memory B cells normally exist (Fig. 2).⁶²

Autonomous signaling of IgE-BCR

It has long been considered that class-switched BCRs, especially IgG-BCR and IgE-BCR, have specific functions, as they have long cytoplasmic tails containing a highly conserved motif.^{63, 64, 65} Laffleur *et al.* firstly reported that IgE-expression itself renders B cells highly short-lived by using knockin mice that allow an enforced expression of human IgE heavy chain in B cells after tamoxifen administration.⁵⁷ This report also showed that the expression of human IgE heavy chain in B cell lines resulted in a relocation of IgE-BCR to the lipid rafts and increased apoptosis.⁵⁷

More recent two reports have described a unique autonomous signaling activity of IgE-BCR that does not need antigen recognition and restrains the GC development of IgE⁺ B cells.^{66,67} Intriguingly, both reports have shown that extracellular domains of IgE-BCR are responsible for such activity.^{66,67} Considering that IgE Ab has a unique asymmetric bent conformation in which CH2 folds back onto the CH3–CH4 domains,⁶⁸ it seems possible that the unique structure of IgE extracellular domains mimics the conformational change of BCR that is induced upon antigen binding, thereby leading to the activation of BCR signaling ([Fig. 3](#)). Furthermore, the extracellular membrane-proximal domain (EMPD) of IgE, which is located between CH4 and the transmembrane domains, constitutively recruits CD19, a co-stimulating receptor of BCR required for the PI3K pathway activation.⁶⁶

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Fig. 3. A model of autonomous signaling of IgE-BCR. After class-switching to IgE, B cells express IgE-BCR on their surface. The IgE-BCR autonomously activates BCR-signaling components such as Syk and BLNK, likely due to its unique bent structure of extracellular domains. In the signaling pathways downstream of BLNK, p38 and JNK promote apoptosis. In parallel, a co-stimulating molecule CD19 constitutively binds to EMPD of IgE-BCR, drives IRF4 expression and PC differentiation. By these mechanisms, IgE⁺ B cells rapidly differentiate into short-lived PCs and are barely maintained as GC B cells, which prevents long-lasting IgE-memory formation.

The autonomous IgE-signaling activates BCR-signaling components Syk and BLNK as well as CD19, leading to an increase of expression of IRF4, a transcription factor required for PC differentiation ([Fig. 3](#)).⁶⁶ Thus, the expression of IgE-BCR induced PC differentiation in the absence of Ag,^{66,67} which may cause premature termination of the

GC B cell program. The autonomous IgE-BCR signaling also promoted apoptosis, consistent with the earlier *in vivo*⁵⁴ and *in vitro*⁵⁷ findings, through p38- and JNK-mediated pathway dependent on the BLNK-signaling, thereby driving short-lived PC fate (Fig. 3).⁶⁶ However, this apoptosis induction could not be confirmed by the other report showing that IgE-BCR did not induce apoptosis *in vitro* and that IgE⁺ GC B cells exhibited no sign of cell death *ex vivo*.⁶⁷ Although the reason for this discrepancy is currently unclear, it would be possible that culture conditions affect the rate of apoptosis event of IgE-expressing cells, and the frequency of apoptotic IgE⁺ GC B cells might be affected by experimental procedures. An additional model has also been proposed: the autonomous IgE-BCR signaling leads to downmodulation of surface BCR expression, reducing Ag uptake and presentation, thereby making it less likely for IgE⁺ B cells to receive T cell help.⁶⁷ This model may not be mutually exclusive with the others. In *BLNK*-homozygous or *CD19*-heterozygous mutant mice, the number of IgE⁺ GC B cells were significantly increased after immunization.^{66,67} *Syk* heterozygous mice, *IRF4* heterozygous mice, or mice treated with a pharmacological inhibitor of BTK, a protein kinase downstream of BLNK, also exhibited increase of IgE⁺ GC B cells.⁶⁷ In immunized *BLNK*-homozygous or *CD19*-heterozygous mutant mice, serum IgE titer was maintained at high level for a long period. These results indicated that abrogation of the autonomous IgE-BCR signaling resulted in a heightened magnitude of IgE responses *in vivo*. Moreover, *BLNK*-deficient mice generated IgE⁺ long-lived PCs carrying affinity-enhancing SHMs and unusual IgE⁺ memory B cells after immunization.⁶⁶ Secondary Ag challenge in *BLNK*-deficient mice resulted in severer active anaphylaxis.⁶⁶ Collectively, these studies clearly indicated that the autonomous IgE-BCR signaling strongly inhibits the development of IgE⁺ B cells, memory B cell formation and affinity maturation of IgE, thereby restraining the magnitude and duration of IgE production to prevent excessive allergic reactions in mice. In human B cells, whether IgE-BCR autonomously signals and promotes short-lived PC fate has not been tested. Nevertheless, in a few cases of severe atopic patients with elevated IgE, loss-of-function germline mutations in *CARD11*, which encodes a scaffold protein downstream of the BLNK-dependent signaling pathway, have been found and speculated to be associated with dampening the autonomous IgE-BCR signaling.⁶⁹ Thus, in this field, it would be important to analyze autonomous activity of IgE-BCR signaling in human B cells and to elucidate whether such signaling defects can be found in patients with allergic diseases.

Conclusions

The production of IgE is tightly controlled in quantitative and qualitative ways, which is mainly achieved by following two mechanisms: 1) Inhibition of IgE-CS and 2) Suppression of IgE⁺ B cell development by autonomous IgE-BCR signaling. As shown by the animal models, disruptions of the molecular machinery underlying such regulations may lead to abnormal IgE production and the development of allergic disorders in humans. In fact, it has been reported that polymorphisms in the IL-21 or IL-21 receptor genes were associated with elevated serum IgE^{70, 71, 72} and that circulating T_{FH} cells in allergic patients with elevated IgE serum titer express a high level of IL-13.⁴⁸ The elevated IgE production in both cases may be the result of enhanced IgE-CS events. As for the BCR-signaling defect, congenital loss of key BCR-signaling molecules such as BLNK or CD19 might be a less frequent event, since it causes developmental arrest of human B cells.⁷³ Thus, somatic loss or modification of such molecules in activated B cells may cause abnormal IgE production. A recent study revealed that the acquisition of somatic mutations is a key step for the development of self-reactive clones in human autoimmune diseases, similar to the somatic evolution of cancer cells.⁷⁴ This might be the case for IgE-mediated allergic diseases. Thus, investigations of somatic defects in BCR-signaling molecules in IgE⁺ B cells of human allergic patients are awaited. Elucidation of such defects could lead to the development of new strategies to prevent allergic disorders.

Conflict of interest

The authors have no conflict of interest to declare.

Acknowledgments

We thank S. Fukao for discussion and critical comments. This work was supported by the Astellas Foundation for Research on Metabolic Disorders and the Takeda Science Foundation (to K.H.), the Naito Foundation and the Uehara Memorial Foundation (to D.K.).

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