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Permalink

<https://escholarship.org/uc/item/0ts1j4v2>

Journal

The Journal of Immunology, 208(2)

ISSN

0022-1767

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Publication Date

2022-01-15

DOI

10.4049/jimmunol.2100988

Peer reviewed



HHS Public Access

Author manuscript

J Immunol. Author manuscript; available in PMC 2023 March 29.

Published in final edited form as:

J Immunol. 2022 January 15; 208(2): 257–266. doi:10.4049/jimmunol.2100988.

Features of B cell responses relevant to allergic disease

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Abstract

This review delves into B cell responses in the context of allergy. The primary contribution of B cells to allergy is the production of IgE, the antibody isotype that triggers immediate hypersensitivity reactions through the release of mediators from mast cells and basophils. B cells may also have protective roles in allergy, such as through the production of IgG or as regulatory B cells. Here we focus on the basic principles of B cell differentiation and discuss features relevant to allergic immune responses. In particular, we discuss 1) class switch recombination, 2) plasma cell differentiation, 3) germinal centers and affinity maturation, and 4) memory B cells and recall responses, with an emphasis on IgE, IgG1, and IgG4. We also consider how B cells may contribute to allergic responses independent of antibody production, for example, by serving as antigen presenting cells.

Introduction

The major well-established contribution of B cells to allergy is through the production of IgE antibodies specific for components of allergens. Secreted IgE is captured by a high affinity Fc receptor, FcεRI, that is abundant on the surface of two major classes of effector cells: mast cells and basophils. These cells are pre-loaded with IgE, and binding of antigens derived from allergens to specific IgE results in cross-linking of FcεRI and signal transduction. This may result in a rapid response in which pre-formed granules are released, termed degranulation. The mediators contained in these granules, such as histamine, are responsible for the key features of immediate hypersensitivity (1). Mast cells and basophils also produce various cytokines, chemokines, and proteases that contribute to allergic inflammation and modify the cellular environment. Local activation of mast cells and basophils in tissues contributes to the symptoms associated with allergic responses

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Conflict of interest statement

C.D.C.A. is a member of the scientific advisory board for Walking Fish Therapeutics. C.D.C.A.'s spouse is an employee and shareholder of Bristol Myers Squibb. These companies had no involvement in this work, and we declare no other competing financial interests.

—for example, degranulation of mast cells under the skin causes erythema, edema, and pruritis. Widespread degranulation of mast cells and/or basophils in the body may result in a dangerous life-threatening condition known as systemic anaphylaxis. FcεRI is also expressed on some antigen presenting cells in humans, including some subsets of dendritic cells. With the importance of IgE to allergy, the development of new methodologies to detect IgE-producing B cells and plasma cells has enabled significant progress in the past decade in understanding the factors that regulate these responses (2).

It is important to note that other antibody isotypes derived from B cells also play important roles in allergy. In humans, IgG4 has been implicated in immunological tolerance to allergens and the amount of IgG4 increases during allergen immunotherapy (3). Interestingly, it has been reported that IgG4 has the unusual ability for the heavy chain dimers to dissociate and reassociate with other heavy chains, resulting in some antibodies with a single binding site rather than two binding sites for a given antigen, thereby reducing the likelihood of cross-linking and immune complex formation (4). Despite its roles in tolerance, however, excessive production of IgG4, as occurs in IgG4-related disease, may also be pathological (5). Other antibody isotypes, such as IgG1 or IgA, could also potentially help neutralize allergens and reduce the likelihood of their binding to IgE. Immune complexes formed by IgG bound to allergens may also ligate inhibitory FcγRIIb receptors on B cells, basophils, and some subsets of mast cells, which can suppress the responses of these cells (6). Overall, it is thus important to consider that B cells may play a critical role both in inducing allergic responses through IgE and also in suppressing allergic responses through IgG and possibly IgA.

Here we will first discuss the stages of B cell differentiation and consider features relevant to allergic disease. We will also briefly discuss some other potential roles of B cells independent of antibody production.

Class switch recombination

Naïve B cells express B cell receptors (BCRs) of the IgM and IgD isotypes through alternative splicing of the IgM and IgD constant regions. The genes encoding the constant regions of IgG, IgE, and IgA isotypes are located downstream. In order to express these other isotypes, B cells must undergo a class switch recombination (CSR) event through a DNA rearrangement at switch regions that precede the constant regions. The DNA containing the previously expressed constant region, and any intervening constant regions, is excised and permanently removed from the chromosome. For example, a B cell can ‘switch’ from IgM/IgD to IgG1, resulting in the loss of the constant regions encoding IgM, IgD, and IgG3. The CSR process can be repeated to a downstream isotype, in a process known as sequential switching. For example, a B cell that has ‘switched’ to IgG1 can then further ‘switch’ to IgE, resulting in the loss of the constant regions encoding IgG1, IgA1, IgG2, and IgG4 (note that mice do not have IgA1 or IgG4 constant regions). Direct switching from IgM/IgD to any of these isotypes can also occur; for example, B cells can switch from IgM/IgD to IgE resulting in IgE expression and the loss of all IgG constant regions (7).

This carefully controlled process of CSR results in changes in 1) the signaling properties of the BCR and 2) secreted antibody function. The way in which CSR occurs is also

important to consider in terms of the differentiation path of the B cell. A B cell expressing the IgE constant region could have been derived by direct switching from IgM/IgD, or by sequential switching through an IgG or IgA1 isotype (Figure 1A). In contrast, however, a B cell expressing IgG could never have switched to IgE. A B cell that expresses IgE could only further switch to the last constant region encoding IgA2 in humans (IgA in mice). The process of sequential switching often leaves a 'footprint' in the switch region enabling detection of the constant region(s) that were previously expressed, such that in some B cells one can definitively detect when the process of sequential switching has occurred (7). As discussed below, this may have important implications for the origin and fate of B cells expressing IgE.

A prerequisite to CSR is the induction of transcription of the downstream constant region to which the B cell will switch (7). This so-called germline transcription is thought to provide increased accessibility to the DNA of the constant region enabling the recombination event to occur. Preceding each constant region is a unique promoter element, enabling selective control of germline transcription by signals from various receptors including the B cell receptor, innate pattern recognition receptors, cytokine receptors, and CD40 (8). In the case of the T-cell dependent responses that will be discussed here, T cells contribute to CSR through cytokine production and the expression of CD40L. Most studies indicate that IgE responses are T-cell dependent (9).

Classical studies highlighted the critical role of the cytokine IL-4 in CSR to IgE (9). In contrast, the cytokine interferon gamma (IFN- γ) inhibited CSR to IgE and promoted CSR to IgG2 isotypes (9). The original identification of stable populations of T cells that produced IL-4 (Th2 cells) versus IFN- γ (Th1 cells) led to the hypothesis that the Th1/Th2 dichotomy was a critical factor in determining whether CSR to IgE occurred (10). This Th1/Th2 balance has formed the basis of understanding how CSR to IgE is regulated in numerous textbooks and reviews. This Th1/Th2 dichotomy was also foundational for some forms of the hygiene hypothesis, with the notion that exposure to viral or bacterial infections that promote Th1 responses would inhibit CSR to IgE. A lack of these infections in early life due to increased hygiene has been proposed to promote a Th2-biased response favoring IgE production and allergy (11, 12).

However, some key aspects of CSR to IgE were never explained by the Th1/Th2 dichotomy. CSR to IgG1 and IgG4 can also occur in the presence of IL-4 (9, 13, 14), thus CSR to IgE and allergic sensitization are not necessarily consequences of IL-4 production. Indeed, CSR to IgE appears to be a remarkably rare event in vivo, whereas B cells can readily be induced to switch to IgE in cell culture, suggesting other mechanisms negatively regulate CSR to IgE in vivo (14). In addition, rather than effector Th2 cells, the cells that produce IL-4 in lymphoid tissues are primarily follicular helper T cells (Tfh) (15–17). Recent studies have highlighted that Tfh cells play a critical role in IgE CSR in models of allergic immune responses and helminth infection (18–22).

One of the major cytokines produced by Tfh cells is IL-21. Elevated IgE responses in mice lacking the IL-21 receptor were first noted nearly two decades ago (23, 24). IL-21 was proposed in separate studies to either inhibit IgE germline transcription, thereby suppressing

IgE CSR (25), or to induce the apoptosis of B cells expressing IgE (26). IL-21 was also reported to inhibit sequential switching from IgG1 to IgE in cultures of mouse B cells (27). However, paradoxically, in some cell culture studies of purified human B cells, IL-21 seemed to promote IgE production (28, 29). It was proposed that IL-21 suppresses IgE production indirectly through the action of other cytokine(s), such as by inducing IFN- γ expression in T cells (28).

While IFN- γ can inhibit IgE CSR in cell culture (9), IFN- γ was largely dispensable in mice for IgE regulation, as IFN- γ -deficient mice showed normal frequencies of IgE-producing cells in the context of adjuvants that promoted type 1 and/or type 2 immune responses (14). It seems likely that in most immune responses, the abundance of IFN- γ is not sufficient to have a significant impact on IgE CSR. In contrast, lower amounts of IFN- γ can induce CSR to IgG2 isotypes (9).

Recent work has clarified that IL-21 is the critical cytokine for the negative regulation of CSR to IgE in both mouse and human B cells. In mice lacking IL-21 or its receptor (IL-21R), the vast majority of plasma cells produced IgE, whereas in normal mice most plasma cells produced IgG isotypes (14). Similarly, elevated IgE was observed in human patients with IL-21R mutations (30). The IL-21R signals primarily through the adapter STAT3, and dominant negative mutations in STAT3 cause hyper-IgE syndrome (also known as Job's syndrome) (31, 32). Dramatically increased IgE responses were observed in chimeric mice in which B cells selectively lacked expression of the IL-21 receptor (IL-21R), demonstrating that IL-21R signaling in B cells is critical for IgE regulation (14). Indeed, selective deficiency of STAT3 in B cells, but not in T cells, also resulted in greatly elevated IgE responses in mice (14, 33, 34). This finding is also supported by a report of somatic mutations in STAT3 in B cells in a human patient leading to high serum IgE (35). Taken together, these studies have established that IL-21, signaling through the IL-21R and STAT3 in B cells, is a major negative regulator of IgE responses in vivo.

IL-21 was confirmed to inhibit IgE CSR by suppressing IgE germline transcription, but did not selectively promote the apoptosis of IgE-expressing lymphocytes (14). The molecular mechanism by which the IL-21-IL-21R-STAT3 axis suppresses IgE germline transcription remains unknown. The effect of IL-21 on IgE CSR was found to depend on the strength of CD40 signaling; strong CD40 signaling enabled IgE CSR to occur even in the presence of IL-21 (2, 14). This finding, together with the potent ability of IL-21 to promote proliferation of human B cells, may explain why some earlier studies of human B cells had found that IL-21 could promote IgE production. In the context of weaker signals through CD40, IL-21 clearly inhibited the IgE CSR of human B cells (14).

The effects of IL-21 on IgE CSR likely depend on the balance of IL-21 and IL-4 signals (2, 36). Recent studies have shown a variation in the timing and relative amounts of IL-21 and IL-4 produced by Tfh during immune responses (37, 38). Mice with haploinsufficiency in the genes encoding IL-4 or IL-4R α had greatly reduced IgE responses but normal IgG1 responses to immunization or infection (39, 40). IL-4R α signals through the adapter STAT6, and haploinsufficiency in the gene encoding STAT6 also nearly abrogated IgE production in mice and B cell cultures (41). In the context of limited amounts of IL-4, IL-21 strongly

promoted IgG1 but not IgE CSR in cultures of both mouse and human B cells (14). These findings may explain why in typical immune responses, most B cells undergo CSR to IgG1 rather than to IgE.

For human B cells, the control of CSR to IgE versus IgG4 is an important component of allergen sensitization versus tolerance. Surprisingly, the molecular mechanisms regulating CSR to IgE versus IgG4 are not well understood. Of cytokines, IL-10 has been most clearly implicated in inhibiting IgE and promoting IgG4 responses of human B cells (42–45). IL-10 does not seem to be a direct switch factor for IgG4, but may potentiate CSR to IgG4 in the context of IL-4. IL-10 has also been reported to inhibit IgE CSR of human B cells, although this finding is not consistent and may be due to indirect activity of IL-10 on other cell types (42, 45–48). The interpretation of some studies may also be complicated by effects of IL-10 on cell proliferation, plasma cell differentiation and antibody production (42, 48–50). While some studies suggested IL-10 may also inhibit IgE responses in mice, a direct analysis of mouse IgE B cells showed that IL-10 had no measurable effect on the differentiation of IgE B cells from purified naïve B cells in cell culture, and normal frequencies of IgE B cells and PCs were observed in IL-10-deficient mice (14). More studies are needed to determine the physiological relevance and cellular source(s) of IL-10 and other factors that may regulate CSR to IgE versus IgG4 in human B cells in vivo.

While IL-4 is critical for IgE CSR, the role of the related cytokine IL-13 is less clear. IL-13 is primarily secreted by Th2 and ILC2 cells, and some recent studies in mice have described a subpopulation of Tfh cells that express IL-13, denoted as Tfh2 or Tfh13 cells (51–53). In mice, naïve B cells do not express the IL-13RA1 subunit of the type II IL-4 receptor needed for responses to IL-13 (54, 55), and genetic deficiency in IL-4 or antibody blockade of IL-4 abrogate the primary IgE response to immunization (9, 17, 56), making it unlikely that IL-13 plays a significant role in the initial CSR to IgE. Interestingly, Tfh2/Tfh13 cells also express IL-4 yet have reduced expression of IL-21, making them potentially important candidates for promoting IgE CSR independent of their IL-13 production. One group has reported IL-13RA1 is upregulated by mouse GC B cells, with the highest expression on IgE GC B cells, after immunization with allergen (51). Whether IL-13 enhances IgE CSR of IgG1 GC B cells, or directly affects IgE GC B cells such as by promoting proliferation, differentiation, and/or survival, has not yet been tested. It is important to note that unlike naïve mouse B cells, human naïve B cells express IL-13RA1 (57, 58), and IL-13 has indeed been reported to directly promote IgE CSR in human B cell cultures (59–61). The expression patterns of IL-4 and IL-13 in human Tfh in tissues, and relevance of these cytokines to IgE CSR, needs further exploration.

Plasma Cells

B cells that have received appropriate signals through their BCR, CD40, cytokine receptors, and/or innate pattern recognition receptors may terminally differentiate into antibody-secreting cells. In the first stage of this differentiation, these antibody-secreting cells are referred to as plasmablasts due to ongoing cell proliferation (62). The plasmablasts then continue differentiation into plasma cells that exit the cell cycle. For the purposes of this review, we will not distinguish between plasmablasts and plasma cells, thus we will refer

to all antibody-secreting cells as plasma cells (PCs). We do note two major categories of PCs: short-lived PCs that undergo apoptosis within the first few days, versus long-lived PCs that continue to secrete antibody for months or years. Short-lived PCs accumulate in extrafollicular foci in lymphoid tissues such as the spleen and lymph nodes, whereas most long-lived PCs migrate to the bone marrow. Both short-lived and long-lived PCs have also been found to accumulate in the lamina propria of mucosal tissues (63–65).

Interestingly, IgE B cells have an increased preponderance to undergo PC differentiation compared with B cells expressing other isotypes, such as IgG1 (27, 66–68). While antigen ligation of the BCR is typically part of the PC differentiation process, multiple groups have reported that the IgE BCR promotes PC differentiation even in the absence of antigen (66, 68). The IgE BCR was found to exhibit constitutive, weak signaling that differs from other isotype BCRs. Ectopic expression of the IgE BCR in primary B cells demonstrated that the IgE BCR promotes PC differentiation in the context of T cell help signals.

In primary immune responses in lymphoid tissues, activated B cells ultimately migrate to two major areas: extrafollicular foci where they undergo PC differentiation, or the center of B cell follicles where they form germinal centers (GCs) (69). At later stages of the primary immune response, PCs may differentiate from GC B cells and exit these structures. As a result, there are essentially two initial waves of PC responses, the first in extrafollicular foci and the second derived from GCs. A key difference in these responses is that most of the PCs in extrafollicular foci are short-lived, whereas a subset of PCs derived from the GC are long-lived and often migrate to other sites such as the bone marrow. In addition, in the extrafollicular foci, most PCs express antibodies encoded by their original germline sequences, with minimal numbers of somatic mutations, and these antibodies typically have low to moderate affinity for antigen. In contrast, PCs derived from GCs are often extensively somatically mutated and selected for particular characteristics of antibody-antigen binding, such as increased affinity, as discussed below. These distinctions between the extrafollicular and GC-derived PCs are not absolute; for example, somatic mutations can occur in extrafollicular foci (70). In addition, some immune responses seem to favor extrafollicular responses and others seem to favor GC responses. This has not yet been thoroughly evaluated in the context of allergens. In addition, as described below, many allergy models and some types of human allergy involve repetitive allergen exposure, in which the characteristics of the initial primary response to the allergens is unknown.

Interestingly, data available thus far from primary immune responses suggests that a large fraction of the initial IgE produced is derived from the extrafollicular foci, and accordingly, most of the initial IgE PCs generated are short-lived and secrete antibodies encoded by germline sequences with low to moderate affinity for antigen (71) (Figure 1B). Studies of *Bcl2* transgenic mice further suggest that the vast majority of IgE PCs undergo apoptosis (67). Nevertheless, a smaller proportion of IgE PCs are derived from GCs, which may give rise to a limited number of long-lived IgE PCs (Figure 1B). Some studies in rodents have reported the persistence of a small number of IgE PCs in the bone marrow or in lymph nodes long after primary immunization (72). It has been reported that the IgE BCR hinders migration to the chemokine CXCL12, which is important for PC migration to the bone marrow (73). Consequently, the IgE BCR may disfavor the ability of IgE PCs to

reach niches for long term survival. Interestingly, in mice deficient in *Blnk*, an adapter involved in BCR signaling, it was observed that IgE B cells were more abundant in GCs and that long-term production of antigen-specific IgE could be detected in serum (66), though whether these findings are directly linked needs further investigation.

Upon subsequent exposures to antigen, memory B cells (described further below) undergo a recall response, in which they may undergo rapid differentiation to PCs and/or GC B cells (74, 75). Most PCs derived from memory B cells produce somatically mutated antibodies, often with high affinity for antigen. Some of these PCs may be short-lived and others are long-lived, the latter of which tend to migrate to the bone marrow. Many allergy models in rodents involve repetitive dosing with allergens over an extended period, such that one may presume the majority of IgE PCs are derived from memory B cells. There have been limited direct spatiotemporal studies of the IgE PC response in these settings, although there are certainly some reports of finding IgE PCs that may be long-lived in the bone marrow in some of these models at their endpoints (76, 77). It remains unclear, however, how the magnitude of these IgE responses to repetitive dosing with allergens compares to the predominant generation of short-lived IgE PCs in primary immune responses. There is also evidence in humans that IgE PCs may differentiate and/or reside in the lamina propria of mucosal tissues (7, 78, 79), though the life span of these cells has again not been thoroughly evaluated.

Overall, limited information is available about the relevance of short-lived IgE PCs or long-lived IgE PCs to serum IgE production at a given snapshot in time, such as at the endpoint of an allergy model or in a sample collected from a human patient. It is important to note that even when IgE PCs are short-lived, IgE-mediated allergen reactivity may persist for some time, as IgE was found to be retained on mast cells in mice for months in the absence of detectable IgE production (80, 81). Upon allergen re-exposure, memory B cells may differentiate into IgE PCs to maintain allergic sensitization. While allergen re-exposure regularly occurs in the respiratory tract, not all allergic responses involve highly repetitive exposures. For example, patients who become allergic to bee venom or food allergens and develop anaphylaxis may do everything they can to avoid these exposures. In patients with allergic rhinitis, there is substantial evidence for seasonal variation in serum IgE that correlates with exposure to pollen, suggesting that some of this IgE is produced by short-lived IgE PCs that differentiate during each pollen season (82–86). Interestingly, blocking the IL-4 receptor with the monoclonal antibody dupilumab in patients results in a substantial drop in serum IgE over time (87, 88), suggesting a large fraction of IgE production may be derived from recent IgE CSR and the generation of short-lived IgE PCs. Some fraction of IgE production, however, seems persistent, which may be derived from long-lived PCs (89). It seems plausible that the relative proportions of IgE production that derive from short-lived PCs versus long-lived PCs may vary depending on the allergen properties and other characteristics, such as the frequency and route of exposure. More studies are needed to determine the factors that lead to the generation of short-lived versus long-lived IgE PCs specific for allergen components and their relative contributions to allergic diseases.

GCs and Antibody Affinity

During immune responses, GCs form within B cell follicles in secondary lymphoid organs, such as the tonsils and lymph nodes, as well as in some ectopic lymphoid structures (78, 90). In GCs, B cells undergo a remarkable process of somatic hypermutation of their antibody variable genes. These mutations may alter the characteristics of the binding of the antibody to its cognate antigen (e.g., a component of an allergen). In some B cells, these mutations may lead to higher affinity binding of antibody to cognate antigen, and this confers an advantage to those B cells for antigen uptake and presentation to T cells, leading to selection. Selected GC B cells may then differentiate into PCs or memory B cells, both of which may be long-lived. This process results in a gradual increase over time in the affinity of encoded antibodies for antigens that can encompass several orders of magnitude, known as affinity maturation.

It is important to note, however, that increases in affinity are not the only changes in antibodies that are selected for in GCs (90). Somatic mutations can also reduce antibody binding to self antigens, thereby increasing selectivity for foreign antigens (91–93). Remarkably, studies with similar foreign and self antigens have shown selection for somatic mutations that allow selective binding to particular conformational properties, such as whether antigens are polyvalent versus monovalent, or differ in flexibility (91, 94). Over time as selected GC B cells differentiate into PCs, the secreted antibody begins to compete with the ability of GC B cells to bind to antigen (95). This may favor the selection of B cells that encode antibodies that bind a different region (epitope) of the antigen or to different antigens, ultimately leading to diversification of the antibody response. In the context of immune responses to allergens, GCs may thus have several important impacts on the antibody response, including 1) an increase in affinity to particular antigen components of allergens, 2) an increase in selectivity for binding to antigens derived from allergens rather than self antigens, 3) a change in the conformational properties of antibody binding and 4) an increase in the diversity of allergen epitopes bound by antibodies.

Interestingly, several studies have shown that B cells that have undergone CSR to IgE are greatly disfavored within the GC compared to B cells that have switched to other isotypes (27, 67, 96–99) (Figure 1B), due to properties of the IgE BCR (66, 68). In IgE GC B cells, the surface expression of the IgE BCR is very low (68, 96), resulting in decreased antigen uptake and presentation (68). As a result, IgE GC B cells likely compete poorly for T cell help in GCs, consistent with the observation of prolonged cell cycle times in IgE GC B cells compared with IgG1 GC B cells (68). The low surface expression of the IgE BCR on IgE GC B cells also hinders antigen-induced BCR signaling (96), whereas the constitutive activity of the IgE BCR on IgE B cells in the absence of antigen binding promotes PC differentiation (66, 68). Some studies, but not others, have reported increased rates of apoptosis among IgE GC B cells (66, 68, 96). Taken together, IgE B cells are at a competitive disadvantage within GCs, consistent with the finding that IgE B cells only appear transiently in the early phase of GCs and rapidly disappear from these structures. This loss of IgE B cells over time from GCs was also observed in IL-21-deficient mice with enhanced IgE CSR (14), suggesting that most IgE CSR occurs outside of GCs, consistent with recent evidence for CSR to IgG isotypes (100). We have proposed that the

transient presence of IgE B cells in GCs is a regulatory mechanism to reduce the likelihood of generating long-lived IgE cells encoding high affinity antibodies to allergens, thereby reducing the risk of developing anaphylaxis (71). It is important to note, however, that the transient presence of IgE B cells in GCs could still be significant, as this may contribute to the generation of a small number of IgE PCs encoding moderate to high affinity antibodies. Overall, the generation of affinity matured IgE PCs derived from GCs is proposed to be miniscule compared with the generation of IgG PCs (71). In mucosal lymphoid tissues, GCs also play a significant role in the generation of IgA PCs (63).

Given the limited participation of IgE B cells in the GC response, other mechanisms have been proposed to account for the generation of high affinity IgE antibodies to allergens. A model that has been extensively evaluated involves sequential switching of B cells to IgE through an IgG1 intermediate stage (7). In this model, IgG1 B cells undergo extensive somatic hypermutation and selection in GCs, potentially acquiring mutations that increase antibody affinity for antigen, followed by subsequent CSR to IgE and PC differentiation, providing a path to the production of high affinity IgE specific for allergens. Evidence supporting this model has been derived from 1) a temporal analysis of the IgE B cell response including the detection of high affinity somatic mutations and the detection of 'footprints' revealing past CSR to IgG1 and 2) decreased high affinity IgE production in mice with a targeted disruption of the IgG1 locus (27, 96, 101). Further supporting this sequential switching model, studies of human IgE PCs have also revealed evidence of IgG1 'footprints' in some cells as well as the presence of somatic mutations in the antibody variable regions (102).

The sequential switching model provides a solid mechanistic basis for the generation of somatically mutated, high affinity IgE antibodies, yet we also draw attention to some features of the IgE responses studied that are often overlooked. In studies of a mouse model in which all B cells started out expressing the same BCR, after repeated immunization, a higher proportion of sequences derived from IgG1-switched B cells contained high affinity somatic mutations than from IgE-switched B cells (27, 96). In studies of the adoptive transfer of IgG1 memory B cells, high affinity somatic mutations were detected in a greater proportion of IgG1 PCs than IgE PCs derived from these memory B cells (103). These findings would suggest that greater selection for high affinity mutations occurs in the IgG1 response than in the IgE response, even in the context of sequential switching from IgG1 to IgE. This could be due to the ability of the IgE BCR to autonomously promote PC differentiation even without antigen binding (66, 68), whereas antigen binding to the IgG1 BCR promotes PC differentiation, thereby enabling greater selective pressure for high affinity mutations in the generation of IgG1 PCs. Thus, although sequential switching contributes to the acquisition of numerous somatic mutations in IgE PCs, the degree to which these mutations confer high affinity binding is more limited than in IgG1 PCs. Greater selection for high affinity mutations in IgG1 PCs than in IgE PCs was also observed at later stages of primary immune responses, in which these cells are likely derived from GC B cells (67). Notably, human studies showing significant numbers of somatic mutations in IgE-producing cells have not determined whether these mutations increase the affinity of the encoded antibodies for allergens. As we noted above, somatic mutations in the GC not only increase affinity, but could also have other effects such as decreasing binding to self antigens

and altering the selectivity of antibody binding to particular conformations of antigens. We propose that sequential switching through IgG1 could therefore also play a role in refining the selectivity and diversity of the IgE antibody response.

The degree to which high affinity IgE production occurs in different allergic diseases remains unknown. Studies of mast cell responses in cell culture and in mice have shown that high affinity IgE binding to antigen can be sensed through FcεRI by a kinetic proofreading mechanism, resulting in enhanced degranulation and release of mediators (104). However, high-affinity IgE did not seem to be essential for anaphylaxis in a mouse model of peanut allergy, perhaps due to challenge with a large dose of antigen and/or the generation of a polyclonal IgE antibody response targeting different antigen epitopes that allows FcεRI cross-linking on mast cells (81). From basic principles, it would seem that IgE antibody affinity should determine the relative amount of allergen needed to elicit a response. It is thus tempting to speculate that high affinity IgE may be relatively abundant in patients that are susceptible to anaphylaxis upon consuming minute amounts of foods to which they are allergic. In contrast, although many individuals produce IgE specific for antigens derived from aeroallergens, these responses almost never elicit anaphylaxis, and thus these aeroallergen-specific IgE antibodies could primarily be of low to moderate affinity.

GC responses could also be protective against the development of allergic responses. IgG B cells that undergo numerous rounds of somatic hypermutation and selection in GCs are thought to ultimately differentiate into IgG memory B cells and IgG PCs that are long-lived (90). If GCs are induced in response to encounter with allergens, this would result in the sustained production of high affinity IgG for antigens derived from allergens. This IgG could neutralize the allergens preventing them from reaching mast cells and basophils loaded with IgE. Alternatively, IgG bound to allergens could form immune complexes that ligate inhibitory FcγRIIb receptors on B cells, basophils, and some subsets of mast cells. We propose that strong or prolonged GC responses would also result in the sustained maintenance of a larger population of Tfh expressing IL-21, which as described above is inhibitory toward IgE CSR, thereby decreasing the likelihood of generating allergen-specific IgE.

Eliciting allergic responses, therefore, may actually be difficult in the context of strong GC responses. Indeed, it was proposed that allergic sensitization may actually be favored in the context of weak GC responses (105, 106). This hypothesis is supported by evidence that in aeroallergen sensitization, IgE is made to allergen components that elicit weak IgG responses. In rodent allergy models, immunization with low doses of antigen or without adjuvant have been reported to favor IgE rather than IgG production (105). There is also substantial evidence that IgE CSR and production may occur in some peripheral tissues, as has been discussed in depth in other reviews (7, 78). While some of these tissues may develop ectopic lymphoid structures containing GCs, in many cases GCs may not be present in peripheral tissues, which may support the generation of local IgE responses. We highlight new work showing that in peanut allergy, IgE-switched cells were detected in the stomach and duodenum that were clonally related to IgG and IgA-switched cells, suggesting the possibility of local CSR to IgE and local IgE production in the stomach and duodenum in food allergy (79).

Memory B cells

Long-term allergen sensitization or tolerance may be maintained by long-lived PCs (discussed above) or by memory B cells. Antigen-specific memory B cells persist in a relatively quiescent state, ready to be rapidly reactivated upon de novo antigen exposure. Upon reactivation, memory B cells may differentiate into PCs or GC B cells, or further expand the pool of memory B cells. The tendency to undergo these differentiation paths depends on the isotype of BCR expressed and the transcriptional state of the cell. Particular subsets of memory B cells have been identified that preferentially undergo these differentiation paths. For more information, we refer the reader to other reviews that discuss these topics in depth (74, 75, 107)

Some memory B cells recirculate throughout the body whereas others seem to become resident in tissues, referred to as resident memory B cells. For example, resident memory B cells have been identified in the lung after viral infection (108, 109). Within lymphoid tissues, memory B cells may also alter their migration patterns, such as to a subcapsular niche in lymph nodes, which is thought to enable rapid encounter with incoming antigen and cognate Tfh cells (110). The relevant niches in which memory B cells reside in the context of allergic disease have not yet been investigated.

Given the importance of IgE in allergy, there has been considerable interest in whether a population of IgE memory B cells contributes to long-term allergic sensitization. Answering this question has been challenging because such cells are likely exceedingly rare, and numerous technical artifacts can obscure the detection of bona-fide IgE B cells (71, 111). Sporadic reports have appeared in the literature regarding the detection of IgE memory B cells in patient samples, yet one has to approach these data with extreme caution as to the methodology used, especially when these cells seem to be unusually abundant. As a case in point, one study has highlighted how most putative IgE memory B cells detected in human blood samples were false positives (111). Most rigorous studies in mice and humans would seem to suggest that the frequency of IgE memory B cells in circulation is almost negligible (96, 111), which would make these cells likely of minimal significance in the context of the recall response to allergen re-exposure. We do not exclude the possibility of exceptions to this finding in particular patients, for example those with mutations in genes important for regulation of the IgE response (2). In addition, these findings do not exclude the possibility of resident IgE memory B cells in tissues. Overall, what has been learned in recent years about the IgE BCR suggests that its expression may be incompatible with the generation of a stable population of memory B cells, because the IgE BCR exhibits antigen-independent signaling that promotes PC differentiation and/or apoptosis (66, 68).

It seems much more likely based on existing evidence that upon allergen re-exposure, new IgE PCs are derived from memory B cells expressing other isotypes. In these recall responses, these memory B cells would first need to undergo CSR to IgE. This is supported by classical studies showing a requirement for IL-4 in the production of IgE in secondary immune responses to helminth parasite infection, suggesting de novo CSR to IgE was essential (112). Most studies thus far have focused on the role of IgG1 memory B cells in the production of IgE after antigen re-exposure (7) (Figure 1C). Immunization of mice in which the extracellular domains of IgG1 were swapped with IgE, thereby altering the IgG1

BCR, resulted in diminished IgE secondary responses (113). As discussed above in regard to sequential switching, it has been reported in mice that the production of high affinity IgE after antigen re-exposure depends on IgG1 memory B cells, particularly the CD73⁺ CD80⁺ subset (103). Taken together, these findings implicate IgG1 memory B cells as significant contributors to IgE production relevant to allergic disease, and this may be particularly important for high affinity IgE production. It remains unclear, however, whether memory B cells expressing other isotypes, such as IgM, may also contribute to IgE production after allergen re-exposure.

Other potential roles of B cells in allergy

In addition to their role in the production of antibodies, B cells may also make other significant contributions to allergic immune responses. These include, but are not necessarily limited to, their role as antigen presenting cells, their contributions to lymphoid tissue organization, and as regulatory B cells. B cells are known to be critical antigen presenting cells for Tfh cells and are required for the maintenance of Tfh (114). These Tfh cells in secondary lymphoid tissues may subsequently develop into central memory T cells that recirculate, and may thereby contribute to the pool of effector Th2 cells involved in eliciting local tissue inflammation, such as in the lung in mouse models of allergic airway disease (115, 116). Conversely, by promoting Tfh responses, B cells may reduce the likelihood of generating effector Th2 cells that home to the lung (117). In cell culture, it has been established in numerous studies that B cells may serve as antigen presenting cells for Th2 cells, such as in cultures of lymphocytes derived from the lung in mouse models of allergic airway disease (118). However, it remains unclear whether B cells serve as antigen presenting cells for Th2 cells in vivo. Interestingly, B cells readily accumulate in the lung in mouse models of house dust mite immunization (116). B cells are also known to produce molecules, such as lymphotoxin- α 1 β 2, that act on other cells in the local tissue environment, with impacts on chemokine production and the organization of lymphoid tissues (119). Whether this function of B cells is relevant to allergic inflammation in peripheral tissues, such as in the lung, remains unknown. Conversely, regulatory B cells express cell surface molecules and produce various cytokines, such as IL-10, which dampen the allergic response (120). Interestingly, one study has reported a subset of regulatory B cells that produces both IL-10 and IgG4, which may be important for allergen tolerance (121).

Conclusions

In this review, we provided a detailed discussion of the fundamental stages of B cell differentiation in the context of allergy. Given the critical importance of IgE for allergic sensitization and pathogenesis, we focused primarily on the unique features of IgE responses. CSR to IgE is tightly regulated by cytokines, and once IgE B cells are generated, the distinct features of the IgE BCR determine cell fate. We compared IgE responses to IgG1 and IgG4 responses, which may be protective in allergy. Our discussion of B cell differentiation highlights key 'decision points' that may ultimately determine allergic sensitization versus tolerance. For example, CSR to IgE, IgG1, and IgG4 are all promoted by IL-4, yet these are differentially regulated by the relative amounts of IL-21 and IL-10, as

well as the strength of CD40 signaling. Germinal center responses may also both suppress and promote allergy. Within the germinal center, selection occurs for IgG and IgA B cells at the expense of IgE B cells, ultimately leading to the production of high affinity IgG and IgA that may suppress responses to allergens. Conversely, sequential switching of IgG cells to IgE contributes to the production of high affinity IgE antibodies and may also affect antibody selectivity and diversity. Throughout the review, we have provided insights into which conclusions can be robustly drawn from published data, as well as the many unknowns regarding B cells in the context of allergic diseases. Future studies may greatly benefit from high resolution studies of single cells in relevant tissue sites through recent innovations in RNA sequencing, flow cytometry, and microscopy.

Acknowledgments

We thank current and former members of the Allen laboratory and the Sandler Asthma Basic Research Center for helpful discussions forming the basis of the principles discussed in this review. C.D.C.A. was a Pew Scholar in the Biomedical Sciences, supported by The Pew Charitable Trusts. Research related to this review was supported in part by the National Institute of Allergy and Infectious Diseases of the NIH (R01AI130470 and R21AI154335), the Weston Havens Foundation, the Program for Breakthrough Biomedical Research, which is partially funded by the Sandler Foundation, and the Cardiovascular Research Institute and the Sandler Asthma Basic Research Center at UCSF. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.

Biography



Christopher Allen, Ph.D.

Institutional History

- Assistant Director for Diversity, Equity, and Inclusion in the Cardiovascular Research Institute, University of California, San Francisco, 2021–present
- Associate Professor, University of California, San Francisco, 2018-current
- Assistant Professor, University of California, San Francisco, 2012–2018
- Sandler-Newman Foundation UCSF Fellow in Asthma Research, University of California, San Francisco, 2007–2012
- Ph.D., University of California, San Francisco, 2007
- B.S., Massachusetts Institute of Technology, 2001

Research Interests:

- Allergy

- Asthma
- B cells
- Basophils
- IgE
- Lung biology

My research career has been profoundly shaped by my family, mentors, and experiences. I am fortunate to have two remarkable, supportive parents who have been trailblazers in their families and in their careers in education. They had some key parallels in their upbringing, as their primary caretakers were their grandmothers who were originally from Puerto Rico and Mexico. When I was young, we moved from the foothills of Los Angeles, which had relatively good air quality, to the San Gabriel Valley, which had some of the poorest air quality. Consequently, I developed persistent asthma, such that we were forced to relocate again to San Diego County. Although I had relatively mild asthma for the rest of my childhood, in my first year as an undergraduate at MIT, my asthma got out of control, and I realized how little had changed in treatment since I was a young child, driving my ambition to do research in this area. At MIT, I also had the opportunity to do research with Professor Herman Eisen, a historic figure in immunology. I then came to UCSF for my Ph.D. and had excellent mentorship from Professor Jason Cyster in studies of germinal center B cells. Returning to my interests in asthma, I was then selected for a faculty fellow position in the Sandler Asthma Basic Research Center at UCSF, in which I started my laboratory focusing on studies of IgE. I was subsequently recruited to a faculty position at UCSF, where I have continued to build my research program in allergy.

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References

1. Galli SJ, and Tsai M. 2012. IgE and mast cells in allergic disease. *Nat Med* 18: 693–704. [PubMed: 22561833]
2. Wade-Vallance AK, and Allen CDC. 2021. Intrinsic and extrinsic regulation of IgE B cell responses. *Curr Opin Immunol* 72: 221–229. [PubMed: 34216934]
3. Akdis M, and Akdis CA. 2014. Mechanisms of allergen-specific immunotherapy: multiple suppressor factors at work in immune tolerance to allergens. *J Allergy Clin Immunol* 133: 621–631. [PubMed: 24581429]
4. Aalberse RC, and Schuurman J. 2002. IgG4 breaking the rules. *Immunology* 105: 9–19. [PubMed: 11849310]
5. Aalberse RC, Platts-Mills TA, and Rispens T. 2016. The Developmental History of IgE and IgG4 Antibodies in Relation to Atopy, Eosinophilic Esophagitis, and the Modified TH2 Response. *Curr Allergy Asthma Rep* 16: 45. [PubMed: 27221343]
6. Kanagaratham C, El Ansari YS, Lewis OL, and Oettgen HC. 2020. IgE and IgG Antibodies as Regulators of Mast Cell and Basophil Functions in Food Allergy. *Front Immunol* 11: 3000.

7. He JS, Narayanan S, Subramaniam S, Ho WQ, Lafaille JJ, and Curotto de Lafaille MA. 2015. Biology of IgE production: IgE cell differentiation and the memory of IgE responses. *Curr Top Microbiol Immunol* 388: 1–19. [PubMed: 25553792]
8. Geha RS, Jabara HH, and Brodeur SR. 2003. The regulation of immunoglobulin E class-switch recombination. *Nat Rev Immunol* 3: 721–732. [PubMed: 12949496]
9. Finkelman FD, Holmes J, Katona IM, Urban JF Jr., Beckmann MP, Park LS, Schooley KA, Coffman RL, Mosmann TR, and Paul WE. 1990. Lymphokine control of in vivo immunoglobulin isotype selection. *Annu Rev Immunol* 8: 303–333. [PubMed: 1693082]
10. Coffman RL. 2006. Origins of the T(H)1-T(H)2 model: a personal perspective. *Nat Immunol* 7: 539–541. [PubMed: 16715060]
11. Renz H, and Herz U. 2002. The bidirectional capacity of bacterial antigens to modulate allergy and asthma. *Eur Respir J* 19: 158–171. [PubMed: 11843315]
12. Romagnani S. 2004. Immunologic influences on allergy and the TH1/TH2 balance. *J Allergy Clin Immunol* 113: 395–400. [PubMed: 14758340]
13. Avery DT, Bryant VL, Ma CS, Malefyt RD, and Tangye SG. 2008. IL-21-induced isotype switching to IgG and IgA by human naive B cells is differentially regulated by IL-4. *J Immunol* 181: 1767–1779. [PubMed: 18641314]
14. Yang Z, Wu CM, Targ S, and Allen CDC. 2020. IL-21 is a broad negative regulator of IgE class switch recombination in mouse and human B cells. *J Exp Med* 217: e20190472.
15. Reinhardt RL, Liang HE, and Locksley RM. 2009. Cytokine-secreting follicular T cells shape the antibody repertoire. *Nat Immunol* 10: 385–393. [PubMed: 19252490]
16. King IL, and Mohrs M. 2009. IL-4-producing CD4+ T cells in reactive lymph nodes during helminth infection are T follicular helper cells. *J Exp Med* 206: 1001–1007. [PubMed: 19380638]
17. Liang HE, Reinhardt RL, Bando JK, Sullivan BM, Ho IC, and Locksley RM. 2011. Divergent expression patterns of IL-4 and IL-13 define unique functions in allergic immunity. *Nat Immunol* 13: 58–66. [PubMed: 22138715]
18. Kobayashi T, Iijima K, Dent AL, and Kita H. 2017. Follicular helper T cells mediate IgE antibody response to airborne allergens. *J Allergy Clin Immunol* 139: 300–313 e307.
19. Meli AP, Fontes G, Leung Soo C, and King IL. 2017. T Follicular Helper Cell-Derived IL-4 Is Required for IgE Production during Intestinal Helminth Infection. *J Immunol* 199: 244–252. [PubMed: 28533444]
20. Noble A, and Zhao J. 2016. Follicular helper T cells are responsible for IgE responses to Der p 1 following house dust mite sensitization in mice. *Clin Exp Allergy* 46: 1075–1082. [PubMed: 27138589]
21. Vijayanand P, Seumois G, Simpson LJ, Abdul-Wajid S, Baumjohann D, Panduro M, Huang X, Interlandi J, Djuretic IM, Brown DR, Sharpe AH, Rao A, and Ansel KM. 2012. Interleukin-4 production by follicular helper T cells requires the conserved Il4 enhancer hypersensitivity site V. *Immunity* 36: 175–187. [PubMed: 22326582]
22. Harada Y, Tanaka S, Motomura Y, Harada Y, Ohno S, Ohno S, Yanagi Y, Inoue H, and Kubo M. 2012. The 3' enhancer CNS2 is a critical regulator of interleukin-4-mediated humoral immunity in follicular helper T cells. *Immunity* 36: 188–200. [PubMed: 22365664]
23. Ozaki K, Spolski R, Feng CG, Qi CF, Cheng J, Sher A, Morse HC 3rd, Liu C, Schwartzberg PL, and Leonard WJ. 2002. A critical role for IL-21 in regulating immunoglobulin production. *Science* 298: 1630–1634. [PubMed: 12446913]
24. Kasaian MT, Whitters MJ, Carter LL, Lowe LD, Jussif JM, Deng B, Johnson KA, Witek JS, Senices M, Konz RF, Wurster AL, Donaldson DD, Collins M, Young DA, and Grusby MJ. 2002. IL-21 limits NK cell responses and promotes antigen-specific T cell activation: a mediator of the transition from innate to adaptive immunity. *Immunity* 16: 559–569. [PubMed: 11970879]
25. Suto A, Nakajima H, Hirose K, Suzuki K, Kagami S, Seto Y, Hoshimoto A, Saito Y, Foster DC, and Iwamoto I. 2002. Interleukin 21 prevents antigen-induced IgE production by inhibiting germ line C(epsilon) transcription of IL-4-stimulated B cells. *Blood* 100: 4565–4573. [PubMed: 12393685]
26. Harada M, Magara-Koyanagi K, Watarai H, Nagata Y, Ishii Y, Kojo S, Horiguchi S, Okamoto Y, Nakayama T, Suzuki N, Yeh WC, Akira S, Kitamura H, Ohara O, Seino K, and Taniguchi

- M. 2006. IL-21-induced Bepsilon cell apoptosis mediated by natural killer T cells suppresses IgE responses. *J Exp Med* 203: 2929–2937. [PubMed: 17178921]
27. Erazo A, Kutchukhidze N, Leung M, Christ AP, Urban JF Jr., Curotto de Lafaille MA, and Lafaille JJ. 2007. Unique maturation program of the IgE response in vivo. *Immunity* 26: 191–203. [PubMed: 17292640]
28. Pene J, Guglielmi L, Gauchat JF, Harrer N, Woisetschlager M, Boulay V, Fabre JM, Demoly P, and Yssel H. 2006. IFN-gamma-mediated inhibition of human IgE synthesis by IL-21 is associated with a polymorphism in the IL-21R gene. *J Immunol* 177: 5006–5013. [PubMed: 17015683]
29. Wood N, Bourque K, Donaldson DD, Collins M, Vercelli D, Goldman SJ, and Kasaian MT. 2004. IL-21 effects on human IgE production in response to IL-4 or IL-13. *Cell Immunol* 231: 133–145. [PubMed: 15919378]
30. Kotlarz D, Zietara N, Milner JD, and Klein C. 2014. Human IL-21 and IL-21R deficiencies: two novel entities of primary immunodeficiency. *Curr Opin Pediatr* 26: 704–712. [PubMed: 25321844]
31. Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, Freeman AF, Demidowich A, Davis J, Turner ML, Anderson VL, Darnell DN, Welch PA, Kuhns DB, Frucht DM, Malech HL, Gallin JI, Kobayashi SD, Whitney AR, Voyich JM, Musser JM, Woellner C, Schaffer AA, Puck JM, and Grimbacher B. 2007. STAT3 mutations in the hyper-IgE syndrome. *N Engl J Med* 357: 1608–1619. [PubMed: 17881745]
32. Minegishi Y, Saito M, Tsuchiya S, Tsuge I, Takada H, Hara T, Kawamura N, Ariga T, Pasic S, Stojkovic O, Metin A, and Karasuyama H. 2007. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. *Nature* 448: 1058–1062. [PubMed: 17676033]
33. Dascani P, Ding C, Kong X, Tieri D, Hu X, Zhang HG, Kitamura D, Bolli R, Rouchka EC, and Yan J. 2018. Transcription Factor STAT3 Serves as a Negative Regulator Controlling IgE Class Switching in Mice. *ImmunoHorizons* 2: 349–362. [PubMed: 31026806]
34. Kane A, Lau A, Brink R, Tangye SG, and Deenick EK. 2016. B-cell-specific STAT3 deficiency: Insight into the molecular basis of autosomal-dominant hyper-IgE syndrome. *J Allergy Clin Immunol* 138: 1455–1458 e1453.
35. Alcantara-Montiel JC, Staines-Boone T, Lopez-Herrera G, Berron-Ruiz L, Borrego-Montoya CR, and Santos-Argumedo L. 2016. Somatic mosaicism in B cells of a patient with autosomal dominant hyper IgE syndrome. *Eur J Immunol* 46: 2438–2443. [PubMed: 27488252]
36. Crotty S. 2015. A brief history of T cell help to B cells. *Nat Rev Immunol* 15: 185–189. [PubMed: 25677493]
37. Gonzalez DG, Cote CM, Patel JR, Smith CB, Zhang Y, Nickerson KM, Zhang T, Kerfoot SM, and Haberman AM. 2018. Nonredundant Roles of IL-21 and IL-4 in the Phased Initiation of Germinal Center B Cells and Subsequent Self-Renewal Transitions. *J Immunol* 201: 3569–3579. [PubMed: 30446568]
38. Weinstein JS, Herman EI, Lainez B, Licona-Limon P, Esplugues E, Flavell R, and Craft J. 2016. TFH cells progressively differentiate to regulate the germinal center response. *Nat Immunol* 17: 1197–1205. [PubMed: 27573866]
39. Muller U, Stenzel W, Kohler G, Polte T, Blessing M, Mann A, Piehler D, Brombacher F, and Alber G. 2008. A gene-dosage effect for interleukin-4 receptor alpha-chain expression has an impact on Th2-mediated allergic inflammation during bronchopulmonary mycosis. *J Infect Dis* 198: 1714–1721. [PubMed: 18954266]
40. Robinson MJ, Prout M, Mearns H, Kyle R, Camberis M, Forbes-Blom EE, Paul WE, Allen CD, and Le Gros G. 2017. IL-4 Haploinsufficiency Specifically Impairs IgE Responses against Allergens in Mice. *J Immunol* 198: 1815–1822. [PubMed: 28115531]
41. Burgis S, and Gessner A. 2007. Unexpected phenotype of STAT6 heterozygous mice implies distinct STAT6 dosage requirements for different IL-4 functions. *Int Arch Allergy Immunol* 143: 263–268. [PubMed: 17347574]
42. Jeannin P, Lecoanet S, Delneste Y, Gauchat JF, and Bonnefoy JY. 1998. IgE versus IgG4 production can be differentially regulated by IL-10. *J Immunol* 160: 3555–3561. [PubMed: 9531318]

43. Akdis CA, Blesken T, Akdis M, Wuthrich B, and Blaser K. 1998. Role of interleukin 10 in specific immunotherapy. *J Clin Invest* 102: 98–106. [PubMed: 9649562]
44. Meiler F, Klunker S, Zimmermann M, Akdis CA, and Akdis M. 2008. Distinct regulation of IgE, IgG4 and IgA by T regulatory cells and toll-like receptors. *Allergy* 63: 1455–1463. [PubMed: 18925882]
45. Lin AA, Freeman AF, and Nutman TB. 2018. IL-10 Indirectly Downregulates IL-4-Induced IgE Production by Human B Cells. *ImmunoHorizons* 2: 398–406. [PubMed: 31026808]
46. Punnonen J, de Waal Malefyt R, van Vlasselaer P, Gauchat JF, and de Vries JE. 1993. IL-10 and viral IL-10 prevent IL-4-induced IgE synthesis by inhibiting the accessory cell function of monocytes. *J Immunol* 151: 1280–1289. [PubMed: 8393044]
47. Caven TH, Shelburne A, Sato J, Chan-Li Y, Becker S, and Conrad DH. 2005. IL-21 dependent IgE production in human and mouse in vitro culture systems is cell density and cell division dependent and is augmented by IL-10. *Cell Immunol* 238: 123–134. [PubMed: 16600195]
48. Armitage RJ, Macduff BM, Spriggs MK, and Fanslow WC. 1993. Human B cell proliferation and Ig secretion induced by recombinant CD40 ligand are modulated by soluble cytokines. *J Immunol* 150: 3671–3680. [PubMed: 8097223]
49. Kobayashi N, Nagumo H, and Agematsu K. 2002. IL-10 enhances B-cell IgE synthesis by promoting differentiation into plasma cells, a process that is inhibited by CD27/CD70 interaction. *Clin Exp Immunol* 129: 446–452. [PubMed: 12197885]
50. Rousset F, Garcia E, Defrance T, Peronne C, Vezzio N, Hsu DH, Kastelein R, Moore KW, and Banchereau J. 1992. Interleukin 10 is a potent growth and differentiation factor for activated human B lymphocytes. *Proc Natl Acad Sci U S A* 89: 1890–1893. [PubMed: 1371884]
51. Gowthaman U, Chen JS, Zhang B, Flynn WF, Lu Y, Song W, Joseph J, Gertie JA, Xu L, Collet MA, Grassmann JDS, Simoneau T, Chiang D, Berin MC, Craft JE, Weinstein JS, Williams A, and Eisenbarth SC. 2019. Identification of a T follicular helper cell subset that drives anaphylactic IgE. *Science* 365: eaaw6433.
52. Clement RL, Daccache J, Mohammed MT, Diallo A, Blazar BR, Kuchroo VK, Lovitch SB, Sharpe AH, and Sage PT. 2019. Follicular regulatory T cells control humoral and allergic immunity by restraining early B cell responses. *Nat Immunol* 20: 1360–1371. [PubMed: 31477921]
53. Kim CJ, Lee CG, Jung JY, Ghosh A, Hasan SN, Hwang SM, Kang H, Lee C, Kim GC, Rudra D, Suh CH, and Im SH. 2018. The Transcription Factor Ets1 Suppresses T Follicular Helper Type 2 Cell Differentiation to Halt the Onset of Systemic Lupus Erythematosus. *Immunity* 49: 1034–1048 e1038.
54. Andrews R, Rosa L, Daines M, and Khurana Hershey G. 2001. Reconstitution of a functional human type II IL-4/IL-13 receptor in mouse B cells: demonstration of species specificity. *J Immunol* 166: 1716–1722. [PubMed: 11160216]
55. Heng TS, Painter MW, and Immunological Genome Project C. 2008. The Immunological Genome Project: networks of gene expression in immune cells. *Nat Immunol* 9: 1091–1094. [PubMed: 18800157]
56. Kuhn R, Rajewsky K, and Muller W. 1991. Generation and analysis of interleukin-4 deficient mice. *Science* 254: 707–710. [PubMed: 1948049]
57. Graber P, Gretener D, Herren S, Aubry JP, Elson G, Poudrier J, Lecoanet-Henchoz S, Alouani S, Losberger C, Bonnefoy JY, Kosco-Vilbois MH, and Gauchat JF. 1998. The distribution of IL-13 receptor alpha1 expression on B cells, T cells and monocytes and its regulation by IL-13 and IL-4. *Eur J Immunol* 28: 4286–4298. [PubMed: 9862366]
58. Ogata H, Ford D, Kouttab N, King TC, Vita N, Minty A, Stoeckler J, Morgan D, Girasole C, Morgan JW, and Maizel AL. 1998. Regulation of interleukin-13 receptor constituents on mature human B lymphocytes. *J Biol Chem* 273: 9864–9871. [PubMed: 9545327]
59. Punnonen J, Aversa G, Cocks BG, McKenzie AN, Menon S, Zurawski G, de Waal Malefyt R, and de Vries JE. 1993. Interleukin 13 induces interleukin 4-independent IgG4 and IgE synthesis and CD23 expression by human B cells. *Proc Natl Acad Sci U S A* 90: 3730–3734. [PubMed: 8097323]

60. Cocks BG, de Waal Malefyt R, Galizzi JP, de Vries JE, and Aversa G. 1993. IL-13 induces proliferation and differentiation of human B cells activated by the CD40 ligand. *Int Immunol* 5: 657–663. [PubMed: 7688562]
61. Defrance T, Carayon P, Billian G, Guillemot JC, Minty A, Caput D, and Ferrara P. 1994. Interleukin 13 is a B cell stimulating factor. *J Exp Med* 179: 135–143. [PubMed: 7903680]
62. Nutt SL, Hodgkin PD, Tarlinton DM, and Corcoran LM. 2015. The generation of antibody-secreting plasma cells. *Nat Rev Immunol* 15: 160–171. [PubMed: 25698678]
63. Pabst O. 2012. New concepts in the generation and functions of IgA. *Nat Rev Immunol* 12: 821–832. [PubMed: 23103985]
64. Lemke A, Kraft M, Roth K, Riedel R, Lammerding D, and Hauser AE. 2016. Long-lived plasma cells are generated in mucosal immune responses and contribute to the bone marrow plasma cell pool in mice. *Mucosal Immunol* 9: 83–97. [PubMed: 25943272]
65. Bemark M, Hazanov H, Stromberg A, Komban R, Holmqvist J, Koster S, Mattsson J, Sikora P, Mehr R, and Lycke NY. 2016. Limited clonal relatedness between gut IgA plasma cells and memory B cells after oral immunization. *Nat Commun* 7: 12698.
66. Haniuda K, Fukao S, Kodama T, Hasegawa H, and Kitamura D. 2016. Autonomous membrane IgE signaling prevents IgE-memory formation. *Nat Immunol* 17: 1109–1117. [PubMed: 27428827]
67. Yang Z, Sullivan BM, and Allen CD. 2012. Fluorescent in vivo detection reveals that IgE(+) B cells are restrained by an intrinsic cell fate predisposition. *Immunity* 36: 857–872. [PubMed: 22406270]
68. Yang Z, Robinson MJ, Chen X, Smith GA, Taunton J, Liu W, and Allen CD. 2016. Regulation of B cell fate by chronic activity of the IgE B cell receptor. *Elife* 5: e21238.
69. MacLennan IC, Toellner KM, Cunningham AF, Serre K, Sze DM, Zuniga E, Cook MC, and Vinuesa CG. 2003. Extrafollicular antibody responses. *Immunol Rev* 194: 8–18. [PubMed: 12846803]
70. Elsner RA, and Shlomchik MJ. 2020. Germinal Center and Extrafollicular B Cell Responses in Vaccination, Immunity, and Autoimmunity. *Immunity* 53: 1136–1150. [PubMed: 33326765]
71. Yang Z, Robinson MJ, and Allen CD. 2014. Regulatory constraints in the generation and differentiation of IgE-expressing B cells. *Curr Opin Immunol* 28: 64–70. [PubMed: 24632082]
72. Holt PG, Sedgwick JD, O’Leary C, Krska K, and Leivers S. 1984. Long-lived IgE- and IgG-secreting cells in rodents manifesting persistent antibody responses. *Cell Immunol* 89: 281–289. [PubMed: 6542454]
73. Achatz-Straussberger G, Zaborsky N, Konigsberger S, Luger EO, Lamers M, Crameri R, and Achatz G. 2008. Migration of antibody secreting cells towards CXCL12 depends on the isotype that forms the BCR. *Eur J Immunol* 38: 3167–3177. [PubMed: 18925577]
74. Kurosaki T, Kometani K, and Ise W. 2015. Memory B cells. *Nat Rev Immunol* 15: 149–159. [PubMed: 25677494]
75. Weisel F, and Shlomchik M. 2017. Memory B Cells of Mice and Humans. *Annu Rev Immunol* 35: 255–284. [PubMed: 28142324]
76. Luger EO, Fokuhl V, Wegmann M, Abram M, Tillack K, Achatz G, Manz RA, Worm M, Radbruch A, and Renz H. 2009. Induction of long-lived allergen-specific plasma cells by mucosal allergen challenge. *J Allergy Clin Immunol* 124: 819–826 e814.
77. Asrat S, Kaur N, Liu X, Ben LH, Kajimura D, Murphy AJ, Sleeman MA, Limnander A, and Orengo JM. 2020. Chronic allergen exposure drives accumulation of long-lived IgE plasma cells in the bone marrow, giving rise to serological memory. *Sci Immunol* 5: eaav8402.
78. Gould HJ, Takhar P, Harries HE, Durham SR, and Corrigan CJ. 2006. Germinal-centre reactions in allergic inflammation. *Trends Immunol* 27: 446–452. [PubMed: 16949872]
79. Hoh RA, Joshi SA, Lee JY, Martin BA, Varma S, Kwok S, Nielsen SCA, Nejad P, Haraguchi E, Dixit PS, Shutthanandan SV, Roskin KM, Zhang W, Tupa D, Bunning BJ, Manohar M, Tibshirani R, Fernandez-Becker NQ, Kambham N, West RB, Hamilton RG, Tsai M, Galli SJ, Chinthrajah RS, Nadeau KC, and Boyd SD. 2020. Origins and clonal convergence of gastrointestinal IgE(+) B cells in human peanut allergy. *Sci Immunol* 5: eaay4209.

80. Kubo S, Nakayama T, Matsuoka K, Yonekawa H, and Karasuyama H. 2003. Long term maintenance of IgE-mediated memory in mast cells in the absence of detectable serum IgE. *J Immunol* 170: 775–780. [PubMed: 12517940]
81. Jimenez-Saiz R, Chu DK, Mandur TS, Walker TD, Gordon ME, Chaudhary R, Koenig J, Saliba S, Galipeau HJ, Utley A, King IL, Lee K, Ettinger R, Wasserman S, Kolbeck R, and Jordana M. 2017. Lifelong memory responses perpetuate humoral TH2 immunity and anaphylaxis in food allergy. *J Allergy Clin Immunol* 140: 1604–1615 e1605.
82. Berg T, and Johansson SG. 1971. In vitro diagnosis of atopic allergy. IV. Seasonal variations of IgE antibodies in children allergic to pollens. *Int Arch Allergy Appl Immunol* 41: 452–462. [PubMed: 5000356]
83. Levy DA, and Osler AG. 1967. Studies on the mechanisms of hypersensitivity phenomena. XVI. In vitro assays of reaginic activity in human sera: effect of therapeutic immunization on seasonal titer changes. *J Immunol* 99: 1068–1077. [PubMed: 4168658]
84. Gleich GJ, Jacob GL, Yunginger JW, and Henderson LL. 1977. Measurement of the absolute levels of IgE antibodies in patients with ragweed hay fever. *J Allergy Clin Immunol* 60: 188–198. [PubMed: 893877]
85. Sato K, Nakazawa T, Sahashi N, and Kochibe N. 1997. Yearly and seasonal changes of specific IgE to Japanese cedar pollen in a young population. *Ann Allergy Asthma Immunol* 79: 57–61. [PubMed: 9236501]
86. Henderson LL, Larson JB, and Gleich GJ. 1975. Maximal rise in IgE antibody following ragweed pollination season. *J Allergy Clin Immunol* 55: 10–15. [PubMed: 45925]
87. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, Wang L, Kirkesseli S, Rocklin R, Bock B, Hamilton J, Ming JE, Radin A, Stahl N, Yancopoulos GD, Graham N, and Pirozzi G. 2013. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med* 368: 2455–2466. [PubMed: 23688323]
88. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, Busse WW, Ford L, Sher L, FitzGerald JM, Katelaris C, Tohda Y, Zhang B, Staudinger H, Pirozzi G, Amin N, Ruddy M, Akinlade B, Khan A, Chao J, Martincova R, Graham NMH, Hamilton JD, Swanson BN, Stahl N, Yancopoulos GD, and Teper A. 2018. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. *N Engl J Med* 378: 2486–2496. [PubMed: 29782217]
89. Luger EO, Wegmann M, Achatz G, Worm M, Renz H, and Radbruch A. 2010. Allergy for a lifetime? *Allergol Int* 59: 1–8. [PubMed: 20186004]
90. Cyster JG, and Allen CDC. 2019. B Cell Responses: Cell Interaction Dynamics and Decisions. *Cell* 177: 524–540. [PubMed: 31002794]
91. Sabouri Z, Schofield P, Horikawa K, Spierings E, Kipling D, Randall KL, Langley D, Roome B, Vazquez-Lombardi R, Rouet R, Hermes J, Chan TD, Brink R, Dunn-Walters DK, Christ D, and Goodnow CC. 2014. Redemption of autoantibodies on anergic B cells by variable-region glycosylation and mutation away from self-reactivity. *Proc Natl Acad Sci U S A* 111: E2567–2575.
92. Burnett DL, Langley DB, Schofield P, Hermes JR, Chan TD, Jackson J, Bourne K, Reed JH, Patterson K, Porebski BT, Brink R, Christ D, and Goodnow CC. 2018. Germinal center antibody mutation trajectories are determined by rapid self/foreign discrimination. *Science* 360: 223–226. [PubMed: 29650674]
93. Reed JH, Jackson J, Christ D, and Goodnow CC. 2016. Clonal redemption of autoantibodies by somatic hypermutation away from self-reactivity during human immunization. *J Exp Med* 213: 1255–1265. [PubMed: 27298445]
94. Burnett DL, Schofield P, Langley DB, Jackson J, Bourne K, Wilson E, Porebski BT, Buckle AM, Brink R, Goodnow CC, and Christ D. 2020. Conformational diversity facilitates antibody mutation trajectories and discrimination between foreign and self-antigens. *Proc Natl Acad Sci U S A* 117: 22341–22350.
95. Toellner KM, Sze DM, and Zhang Y. 2018. What Are the Primary Limitations in B-Cell Affinity Maturation, and How Much Affinity Maturation Can We Drive with Vaccination? A Role for Antibody Feedback. *Cold Spring Harb Perspect Biol* 10.

96. He JS, Meyer-Hermann M, Xiangying D, Zuan LY, Jones LA, Ramakrishna L, de Vries VC, Dolpady J, Aina H, Joseph S, Narayanan S, Subramaniam S, Puthia M, Wong G, Xiong H, Poidinger M, Urban JF, Lafaille JJ, and Curotto de Lafaille MA. 2013. The distinctive germinal center phase of IgE+ B lymphocytes limits their contribution to the classical memory response. *J Exp Med* 210: 2755–2771. [PubMed: 24218137]
97. Talay O, Yan D, Brightbill HD, Straney EE, Zhou M, Ladi E, Lee WP, Egen JG, Austin CD, Xu M, and Wu LC. 2012. IgE(+) memory B cells and plasma cells generated through a germinal-center pathway. *Nat Immunol* 13: 396–404. [PubMed: 22366892]
98. Talay O, Yan D, Brightbill HD, Straney EEM, Zhou M, Ladi E, Lee WP, Egen JG, Austin CD, Xu M, and Wu LC. 2012. Reply to “On the differentiation of mouse IgE+ cells”. *Nat Immunol* 13: 623–624. [PubMed: 22713817]
99. Talay O, Yan D, Brightbill HD, Straney EEM, Zhou M, Ladi E, Lee WP, Egen JG, Austin CD, Xu M, and Wu LC. 2013. Addendum: IgE+ memory B cells and plasma cells generated through a germinal-center pathway. *Nat Immunol* 14: 1302–1304. [PubMed: 24240161]
100. Roco JA, Mesin L, Binder SC, Nefzger C, Gonzalez-Figueroa P, Canete PF, Ellyard J, Shen Q, Robert PA, Cappello J, Vohra H, Zhang Y, Nowosad CR, Schiepers A, Corcoran LM, Toellner KM, Polo JM, Meyer-Hermann M, Victoria GD, and Vinuesa CG. 2019. Class-Switch Recombination Occurs Infrequently in Germinal Centers. *Immunity* 51: 337–350 e337.
101. Xiong H, Dolpady J, Wabl M, Curotto de Lafaille MA, and Lafaille JJ. 2012. Sequential class switching is required for the generation of high affinity IgE antibodies. *J Exp Med* 209: 353–364. [PubMed: 22249450]
102. Satitsuksanoa P, Daanje M, Akdis M, Boyd SD, and van de Veen W. 2021. Biology and dynamics of B cells in the context of IgE-mediated food allergy. *Allergy* 76: 1707–1717. [PubMed: 33274454]
103. He JS, Subramaniam S, Narang V, Srinivasan K, Saunders SP, Carbajo D, Wen-Shan T, Hidayah Hamadee N, Lum J, Lee A, Chen J, Poidinger M, Zolezzi F, Lafaille JJ, and Curotto de Lafaille MA. 2017. IgG1 memory B cells keep the memory of IgE responses. *Nat Commun* 8: 641. [PubMed: 28935935]
104. Torigoe C, Inman JK, and Metzger H. 1998. An unusual mechanism for ligand antagonism. *Science* 281: 568–572. [PubMed: 9677201]
105. Aalberse RC, and Platts-Mills TA. 2004. How do we avoid developing allergy: modifications of the TH2 response from a B-cell perspective. *J Allergy Clin Immunol* 113: 983–986. [PubMed: 15131584]
106. Aalberse RC, Hoekzema R, and Grayson MH. 2021. Do germinal centers protect most of us from becoming allergic? *Ann Allergy Asthma Immunol* 127: 301–305. [PubMed: 34102303]
107. Harms Pritchard G, and Pepper M. 2018. Memory B cell heterogeneity: Remembrance of things past. *J Leukoc Biol* 103: 269–274. [PubMed: 29345369]
108. Allie SR, Bradley JE, Mudunuru U, Schultz MD, Graf BA, Lund FE, and Randall TD. 2019. The establishment of resident memory B cells in the lung requires local antigen encounter. *Nat Immunol* 20: 97–108. [PubMed: 30510223]
109. Onodera T, Takahashi Y, Yokoi Y, Ato M, Kodama Y, Hachimura S, Kurosaki T, and Kobayashi K. 2012. Memory B cells in the lung participate in protective humoral immune responses to pulmonary influenza virus reinfection. *Proc Natl Acad Sci U S A* 109: 2485–2490. [PubMed: 22308386]
110. Moran I, Nguyen A, Khoo WH, Butt D, Bourne K, Young C, Hermes JR, Biro M, Gracie G, Ma CS, Munier CML, Luciani F, Zaunders J, Parker A, Kelleher AD, Tangye SG, Croucher PI, Brink R, Read MN, and Phan TG. 2018. Memory B cells are reactivated in subcapsular proliferative foci of lymph nodes. *Nat Commun* 9: 3372. [PubMed: 30135429]
111. Jimenez-Saiz R, Ellenbogen Y, Bruton K, Spill P, Sommer DD, Lima H, Wasserman S, Patil SU, Shreffler WG, and Jordana M. 2019. Human BCR analysis of single-sorted, putative IgE(+) memory B cells in food allergy. *J Allergy Clin Immunol* 144: 336–339 e336.
112. Katona IM, Urban JF Jr., Kang SS, Paul WE, and Finkelman FD. 1991. IL-4 requirements for the generation of secondary in vivo IgE responses. *J Immunol* 146: 4215–4221. [PubMed: 1674956]

113. Turqueti-Neves A, Otte M, Schwartz C, Schmitt ME, Lindner C, Pabst O, Yu P, and Voehringer D. 2015. The Extracellular Domains of IgG1 and T Cell-Derived IL-4/IL-13 Are Critical for the Polyclonal Memory IgE Response In Vivo. *PLoS Biol* 13: e1002290.
114. Crotty S. 2019. T Follicular Helper Cell Biology: A Decade of Discovery and Diseases. *Immunity* 50: 1132–1148. [PubMed: 31117010]
115. Ballesteros-Tato A, Randall TD, Lund FE, Spolski R, Leonard WJ, and Leon B. 2016. T Follicular Helper Cell Plasticity Shapes Pathogenic T Helper 2 Cell-Mediated Immunity to Inhaled House Dust Mite. *Immunity* 44: 259–273. [PubMed: 26825674]
116. Dullaers M, Schuijjs MJ, Willart M, Fierens K, Van Moorleghem J, Hammad H, and Lambrecht BN. 2017. House dust mite-driven asthma and allergen-specific T cells depend on B cells when the amount of inhaled allergen is limiting. *J Allergy Clin Immunol* 140: 76–88 e77.
117. Hondowicz BD, An D, Schenkel JM, Kim KS, Steach HR, Krishnamurthy AT, Keitany GJ, Garza EN, Fraser KA, Moon JJ, Altemeier WA, Masopust D, and Pepper M. 2016. Interleukin-2-Dependent Allergen-Specific Tissue-Resident Memory Cells Drive Asthma. *Immunity* 44: 155–166. [PubMed: 26750312]
118. Lindell DM, Berlin AA, Schaller MA, and Lukacs NW. 2008. B cell antigen presentation promotes Th2 responses and immunopathology during chronic allergic lung disease. *PLoS One* 3: e3129.
119. Shen P, and Fillatreau S. 2015. Antibody-independent functions of B cells: a focus on cytokines. *Nat Rev Immunol* 15: 441–451. [PubMed: 26065586]
120. Jansen K, Cevhertas L, Ma S, Satitsuksanoa P, Akdis M, and van de Veen W. 2021. Regulatory B cells, A to Z. *Allergy* 76: 2699–2715. [PubMed: 33544905]
121. van de Veen W, Stanic B, Yaman G, Wawrzyniak M, Sollner S, Akdis DG, Ruckert B, Akdis CA, and Akdis M. 2013. IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses. *J Allergy Clin Immunol* 131: 1204–1212. [PubMed: 23453135]

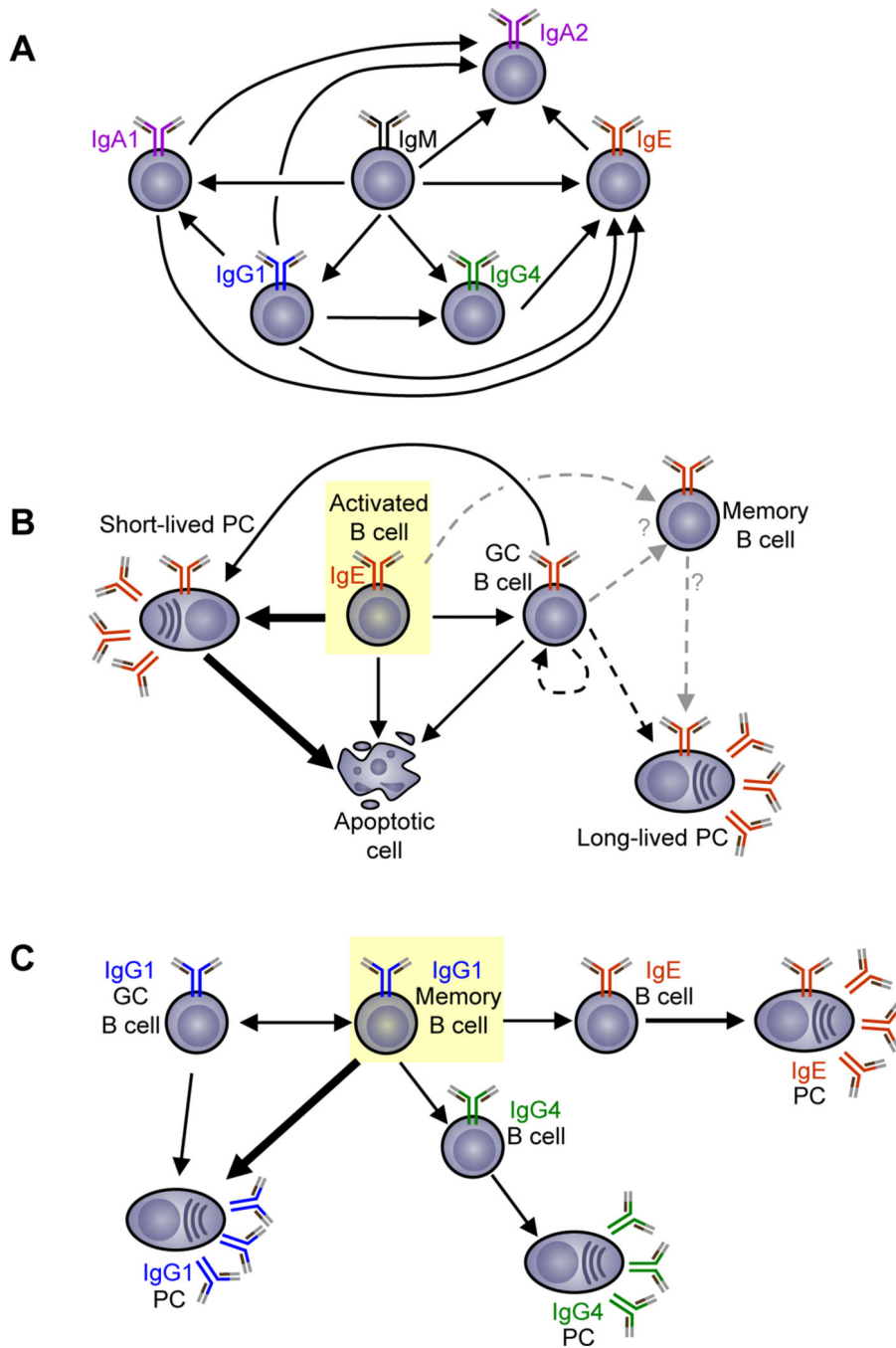


Figure 1: Key decision points in B cell responses affecting IgE production

A) CSR showing potential for direct and sequential switching of isotypes relevant to allergic immune responses (human isotypes are shown). All B cells start out expressing IgM and/or IgD by alternative splicing. Current data suggest CSR occurs in activated B cells prior to GC formation. Once B cells are activated (as shown in figure), IgD expression is downregulated and B cells express IgM on their surface. CSR is initiated by the transcription of downstream Ig heavy chain constant region(s) followed by DNA rearrangement at switch regions. This leads to the expression of the constant region of a new isotype (such as the switch from

IgM to IgG1) and the loss of intervening constant region DNA. The constant regions are illustrated in different colors. This process can be repeated resulting in sequential switching (such as IgM to IgG1 to IgE). As the upstream constant region DNA has been excised, the B cell cannot 'go back' to a previous isotype.

B) The potential fates of an activated IgE B cell are shown, which are important for determining the magnitude, duration, and affinity of IgE production in allergic diseases. IgE B cells are predominantly observed to differentiate into short-lived PCs, which then undergo apoptosis. A smaller proportion of activated IgE B cells differentiate into GC B cells; however, IgE B cells are not maintained in GCs due to PC differentiation, reduced proliferation, and/or increased apoptosis. Nevertheless, IgE GC B cells may contribute to the generation of a small number of long-lived IgE PCs. Such long-lived IgE PCs may also be derived from sequential switching (see panel C). Theoretically, activated IgE B cells may differentiate into memory IgE B cells in a GC-independent or -dependent manner, however there is little conclusive evidence that this occurs. Some studies, but not others, have also provided evidence for increased rates of apoptosis among activated IgE B cells.

C) The potential differentiation programs of IgG1 memory B cells are shown, which are critical for determining whether allergic sensitization occurs upon allergen re-exposure. Most IgG1 memory B cells are thought to differentiate into IgG1 PCs upon antigen re-exposure, and this may protect against allergy. IgG1 memory B cells may also enter into GC responses for further maturation/diversification, ultimately generating additional IgG1 memory B cells and IgG1 PCs. Memory IgG1 B cells may also undergo CSR to other isotypes such as IgG4 and IgE, and then these switched B cells may become PCs. After allergen re-exposure, IgG1 memory B cells thus have the potential to contribute to IgG1/IgG4 production that may promote allergen tolerance, versus IgE production resulting in exacerbation of allergic disease.