

B cells: The many facets of B cells in allergic diseases



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B cells play a key role in our immune system through their ability to produce antibodies, suppress a proinflammatory state, and contribute to central immune tolerance. We aim to provide an in-depth knowledge of the molecular biology of B cells, including their origin, developmental process, types and subsets, and functions. In allergic diseases, B cells are well known to induce and maintain immune tolerance through the production of suppressor cytokines such as IL-10. Similarly, B cells protect against viral infections such as severe acute respiratory syndrome coronavirus 2 that caused the recent coronavirus disease 2019 pandemic. Considering the unique and multifaceted functions of B cells, we hereby provide a comprehensive overview of the current knowledge of B-cell biology and its clinical applications in allergic diseases, organ transplantation, and cancer. (J Allergy Clin Immunol 2023;152:567-81.)

Key words: Allergen-specific immunotherapy (AIT), B cells, antibody-secreting cells, regulatory B (Breg) cells, IL-10

The classical function of B cells in the immune system involves their unique capacity to differentiate into antibody-secreting plasma cells. Although antibodies play a key role in the immunologic protection of the host against invading pathogens, they can also contribute to chronic inflammatory responses to allergens and autoantigens. In addition to their role in antibody production, B cells can regulate immune responses through immunosuppressive cytokine production and antigen presentation.

The first report demonstrating the existence of B cells stems from 1890, when von Behring and Kitasato published their seminal article on “circulating antitoxins,” which were yet to

Abbreviations used

AD:	Atopic dermatitis
AIT:	Allergen-specific immunotherapy
AR:	Allergic rhinitis
BCR:	B-cell receptor
BM:	Bone marrow
Breg:	Regulatory B
CD:	Cluster of differentiation
COVID-19:	Coronavirus disease 2019
CSR:	Class-switch recombination
DC:	Dendritic cell
DH:	Diversity heavy chain
DOCK8:	Dedicator of cytokinesis 8
GC:	Germinal center
HSC:	Hematopoietic stem cell
JH:	Joining heavy chain
JL:	Joining light chain
MZ:	Marginal zone
MBC:	Memory B cell
SARS-CoV-2:	Severe acute respiratory syndrome coronavirus 2
SHM:	Somatic hypermutation
Treg:	Regulatory T
VH:	Variable heavy chain
VL:	Variable light chain

be defined as “antibodies.”¹ They found that these antitoxins were important for protection against diphtheria and tetanus. Later, Paul Ehrlich proposed that the source of these circulating antitoxins was cells with specific antigen receptors, known as B-cell receptors (BCRs).²

The human immune system can be broadly categorized into the innate and adaptive arms, both of which are composed of humoral and cellular components. In this context, B cells are indispensable antibody-secreting cells, critical for humoral immunity. Although technological developments have considerably advanced our understanding of B cells, the underlying mechanisms of B-cell biology remain to be fully elucidated. We hereby present a comprehensive review of our current knowledge of B cells from their origin to their development, maturation, subsets, and role in allergic inflammation and other diseases.

ORIGINS OF B CELLS

Mammalian B-cell ontogeny begins around 6 weeks post-conception in the fetal liver, and the production of B cells occurs simultaneously in both the fetal liver and the fetal bone marrow (BM) from the second trimester.³ The precursor cells that B cells are differentiated from are termed “hematopoietic stem cells

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(HSCs).^{4,5} Initially, B-cell development begins when HSCs differentiate into multipotent progenitor cells that subsequently generate common myeloid progenitors and common lymphoid precursors.⁶ Different B-cell populations are generated as pro-B cells and later appear as pre-B cells approximately 7 to 8 weeks postconception and as mature B cells after 9 weeks postconception. However, not all B-cell subsets descend from the same progenitor. For example, 2 major B-cell subsets including B1 and B2 subsets both are developed from different pathways during embryonic hematopoiesis in humans. Even though the cell surface phenotype can change contingent on the microenvironment, the interactions in the microniche might determine the development of the B1/B2 axes.⁷ In the fetal liver, B-cell progenitors appear to differentiate into B1 cells⁸⁻¹⁰ whereas B2 cells are located in the adult spleen and BM. Accordingly, B1 cells in the fetal liver are considered to be of HSC origin. In adults, B1 cells mainly reside in pleural and peritoneal cavities,¹¹ whereas B2 cells undergo further development in the BM and constantly recirculate between lymphoid tissues and blood. Indeed, both B1 and B2 cells play a crucial role in affinity maturation and long-lasting antibody responses.¹² Moreover, B1- and B2-cell subsets are precursors of 4 different B-cell subtypes: B1-a, B1-b, marginal zone (MZ), and B2/follicular.¹³

B1 cells

B1 cells were first identified in mice and are typically subdivided into B1-a and B1-b cells by their expression of cluster of differentiation (CD) 5 in the former and the lack thereof in the latter.¹⁴⁻¹⁶ However, there are no clear functional differences between them. B1 cells in mice mainly originate from fetal liver HSCs,¹⁷ but originate from the BM HSCs in adult humans.⁹ Mouse B1 cells reside in pleural and peritoneal cavities,⁷ whereas human B1 cells are mainly located in the umbilical cord blood and peripheral blood.¹⁸ Moreover, B1 cells are able to secrete natural antibodies and are responsible for most of the natural IgM.¹⁵ They secrete cytokines as well as capture antigens and present them to T cells.^{19,20}

B2 cells (follicular and MZ B cells)

B2 cells develop in the BM from multipotent HSCs as the conventional B cells. The B2 cells leave the bloodstream and differentiate into follicular and MZ B cells when they migrate into the lymph nodes and spleen, respectively.^{4,21} Mature follicular B cells recirculate in the blood and lymphatics through secondary lymphoid structures. They begin to form in the germinal center (GC) on activation by T_H cells.²² Follicular B cells make up the main contingent of the T-cell-dependent B-cell response of the adaptive immunity and develop into plasma cells, producing high-affinity antibodies.^{4,22}

MZ B cells are found in the MZ of the spleen, express polyreactive antibodies, and are sensitive to Toll-like receptor (TLR) stimulation.^{4,22} The MZ B cells carry B-cell receptors (BCRs), which preferentially bind to the antigens of blood-borne pathogens, such as the cell wall components of bacteria. The combination of BCR activation and signals from TLRs trigger the transitional B cells into the MZ to rapidly develop into IgM-secreting plasma cells. As such, they form the first line of defense to protect from pathogens that reach the spleen.^{4,23}

B-CELL DEVELOPMENT AND MATURATION

A schematic representation of processes involved in B-cell development is shown in Fig 1. The earliest precursor cells restricted to the B-cell lineage are termed pro-B cells, and these initiate immunoglobulin heavy chain gene rearrangement. This process is initiated by rearranging the diversity heavy chain (DH) and joining heavy chain (JH) segments on the immunoglobulin heavy chain and then combining DHJH with the rearranged variable heavy chain (VH) segment. After joining the VHDHJH segment, pro-B cells initiate the expression of the pre-BCR and mature into pre-B cells.⁴ The pre-BCR is composed of a μ -H chain with the surrogate light chain (composed of V pre-B and $\lambda 5$), and signal-transducing components Ig- α and Ig- β .^{4,5,23,24} Because B cells can express immunoglobulin heavy and light chains, the expression of pre-BCR undergoes allelic exclusion, a process that halts recombination of the heavy chain on the other chromosomes, ensuring the expression of only one type of heavy chain gene.^{4,5,24} During the pre-B-cell stage, the light chain is synthesized by recombination of the variable light chain (VL) and joining light chain (JL) arrangement,²⁵ producing 2 types of light chains, namely kappa and lambda. The light chain rearrangement is determined by the gene order and often begins with kappa locus in mice and humans.²⁶ When the heavy chain and light chain are present, the cell that expresses IgM transitions into an immature B cell, which then develops in the spleen to mature into naive, follicular, or MZ B cells. Before leaving the BM, the immature B cells undergo negative selection for autoreactivity. If BCRs on immature B cells recognize a self-antigen with high affinity, they will undergo clonal deletion or receptor editing.²³ In receptor editing, the light-chain gene goes through another round of VLJL recombination. The light-chain gene continues to generate new light chains by VLJL recombination until an immunoglobulin molecule is generated that has low or no measurable affinity for the self-antigens encountered.²³

Immature B cells that migrate out of the BM become transitional B cells and express IgD once they enter the spleen. As demonstrated in a mouse model study, the expression of IgD is vital to B-cell development because it has a higher activation threshold than IgM. This enables B cells to ignore autoantigens with a weak affinity to self-antigen and yet remain responsive to foreign antigens.²⁷ Other essential role of IgD expression is to help limit the affinity of autoreactive B-cell memory responses.²⁸ The maturity of follicular or MZ B cells is mainly dependent on the specificity of their BCRs. MZ B cells act as the first line of defense against blood-borne pathogens and differentiate into short-lived IgM-secreting plasma cells. They respond preferentially to T-cell-independent antigens and undergo class-switch recombination (CSR). CD40 is a costimulatory protein and is expressed on antigen-presenting cells such as DCs and B cells. CD40 binds to its ligand CD40L, which is transiently expressed on T cells and can trigger activation and differentiation of T cells.²⁹ The CD40/CD40L costimulatory pathway induces differentiation of B cells into immunoglobulin-secreting plasma cells. CD40 promotes secretion of IgM, IgG, and IgE in the presence of IL-4 and IL-13, and IgA in the presence of IL-10 and TGF- β . Therefore, the generation of cellular and humoral immune responses is mainly regulated by the engagement of CD40. In addition, the B-cell and T-cell interaction activates the follicular B cell to further evolve in the GC, consisting of T follicular helper cells, follicular dendritic cells (DCs), and dark zone stromal cells.³⁰ Furthermore,

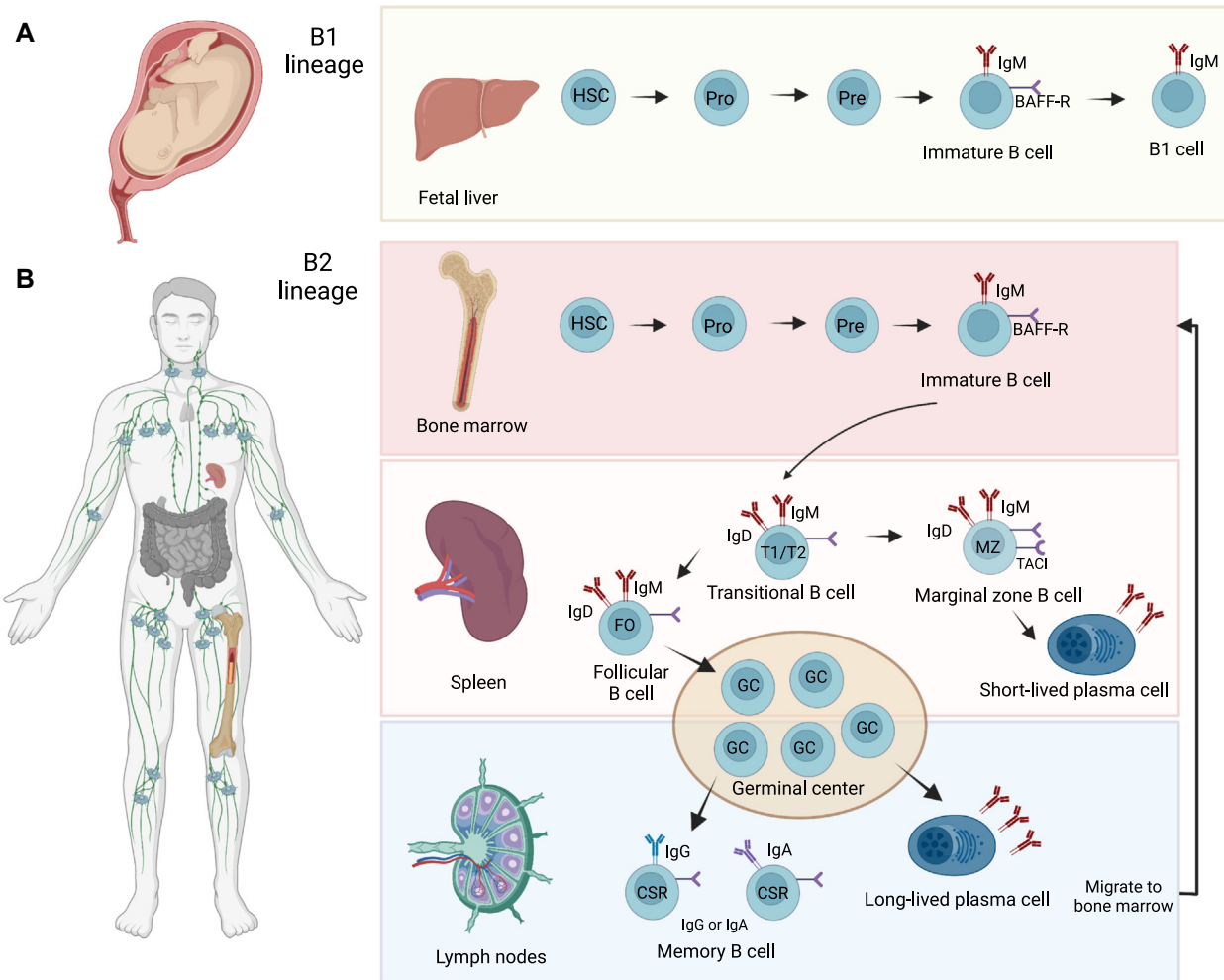


FIG 1. B-cell development. **A**, Before birth, B cells that develop from fetal liver-derived stem cells differentiate into the B1-cell lineage. **B**, After birth, B cells originating from HSCs in the BM differentiate into the B2-cell lineage. They further differentiate into pro-B cells, pre-B cells, and immature B cells, respectively. These immature B cells express IgM and subsequently enter the spleen as transitional B cells. With survival signals through B-cell-activating factor receptor (BAFF-R), these transitional B cells further develop into follicular B cells or MZ B cells. This differentiation is controlled by the specificity of their BCRs. Once MZ B cells encounter an antigen, they subsequently develop into short-lived plasma cells. In parallel, follicular B cells bind to the antigen and enter the GC. These GC B cells further develop into MBCs or long-lived plasma cells. SHM and CSR occur in MBCs and alter the BCR affinity and the isotype (IgM to IgG, IgA, or IgE). Both MBCs and long-lived plasma cells continue to migrate to the BM. *TACI*, Transmembrane activator and cytophilin ligand interactor.

follicular B cells interact with T_H cells as part of the adaptive immune response through CSR and somatic hypermutation (SHM). Both processes continue and result in the differentiation into memory B cells (MBCs) or plasma cells.

CSR and affinity maturation

CSR affects the heavy-chain C regions of IgM by exchanging it with a different isotype, thus altering the effector function of the immunoglobulin while maintaining its antigen specificity.^{25,31} By undergoing CSR, B cells can express IgA, IgG, or IgE.³⁰ In a mouse study, IgG^+ B cells were demonstrated to undergo a stricter positive selection than IgM in the GC. Even with a lower CSR, there were more IgG^+ GC B cells than IgM^+ GC B cells, and the former

preferentially differentiate into memory and plasma cells compared with IgM^+ GC B cells.³² SHM introduces mutations in the V region of the heavy and light chain, altering the affinity of the immunoglobulin for its cognate antigen. CSR and SHM both depend on the same DNA-modifying enzyme, activation-induced cytidine deaminase, and the interaction of CD40/CD40L.³² Moreover, the process of CSR is controlled by TRAF3, which helps restrict BCR signal strength. Without TRAF3, BCR signal strength would increase and disrupt B-cell tolerance to autoreactivity and B-cell homeostasis.³³ CSR occurs in the GC in the B-cell follicles of the secondary lymphoid organs.^{23,31} Although it is believed that CSR occurs within the GC, studies on mouse models and single-cell analysis of human tonsils suggest that CSR takes place during the B-cell and T-cell

TABLE I. Murine and human B-cell subsets

B-cell type		Human markers (CD19 ⁺ , CD20 ⁺ B cells ⁴³)	B-cell type	Murine markers (CD19 ⁺ , B220 ⁺ B cells ⁴³)
Transitional B cells ⁴⁴⁻⁴⁷		CD10 ⁺ , CD21 ⁺ , CD24 ⁺⁺ , CD27 ⁻ , CD38 ⁺⁺ , IgD ⁺	Transitional B cells ⁴⁸	CD21 ⁺ , CD24 ⁺ , CD93 ⁺ , IgD ⁺ , IgM ⁺⁺
Naive B cells ^{46,47}	Resting	CD21 ⁺ , CD24 ⁺ , CD27 ⁻ , CD38 ⁺ , IgD ⁺	Naive B cells ⁴⁹	CD5 ⁺ , CD21 ⁺ , CD23 ⁺ , CD27 ⁻ , B220 ⁺⁺ , IgD ⁺⁺
	Activated	CD21 ⁻ , CD24 ⁻ , CD27 ⁻ , CD38 ⁻ , IgD ⁺		
Follicular B cells ⁴		CD23 ⁺ , B220 ⁺ , IgD ⁺⁺ , IgM ⁺	Follicular B cells ^{21,50}	CD1d ⁺ , CD5 ⁻ , CD21 ⁺ , CD23 ⁺ , Cd43 ⁻ , IgD ⁺⁺ , IgM ⁺
MZ B cells ^{4,45}		CD1c ⁺⁺ , CD21 ⁺⁺ , CD23 ⁻ , CD24 ⁺ , CD27 ⁺ , B220 ⁺ , IgD ⁺ , IgM ⁺⁺	MZ B cells ^{21,50}	CD1d ⁺⁺ , CD5 ⁻ , CD21 ⁺⁺ , CD23 ⁻ , Cd43 ⁻ , IgD ⁻ , IgM ⁺⁺
B1a ⁵¹		CD5 ⁺ , CD11b ⁺ , CD23 ⁻ , CD43 ⁺ , IgD ⁻ , IgM ⁺	B1a ^{21,50}	CD1d ⁺ , CD5 ⁺ , CD9 ⁺ , CD23 ⁻ , CD43 ⁺ , IgM ⁺⁺
B1b ⁵¹		CD5 ⁻ , CD23 ⁻ , CD43 ⁺ , B220 ⁻ , IgD ⁻ , IgM ⁺	B1b ^{21,50,51}	CD1d ⁺ , CD5 ⁻ , Cd9 ⁺ , CD23 ⁻ , CD43 ⁺ , IgM ⁺⁺
Plasma cells ^{46,47,52}	Plasma cell	CD20 ⁻ , CD24 ⁻ , CD27 ⁺⁺ , CD38 ⁺⁺ , CD138 ⁺ , IgD ⁻	Plasma cells ⁵⁰	CD9 ⁺⁺ , CD19 ⁻ , CD21 ⁻ , CD38 ⁻ , CD138 ⁺⁺ , B220 ⁻ , CXCR4 ⁺ , IgD ⁻ , IgM ⁻
	Plasmablasts	CD19 ⁻ , CD20 ⁻ , CD24 ⁻ , CD27 ⁺⁺ , CD38 ⁺⁺ , CD138 ⁻ , IgD ⁻		
MBCs ^{46,47,52}	Double-negative	CD21 ⁻ , CD24 ⁺ , CD27 ⁻ , CD38 ⁺ , IgD ⁻	MBCs ⁴⁹	CD5 ⁻ , CD9 ⁺ , CD37 ⁺ , CD38 ⁺ , CD47 ⁺ , CD80 ⁺
	Nonswitched	CD21 ⁺ , CD24 ⁺ , CD27 ⁺ , IgD ⁺		
	IgM only	CD27 ⁺ , IgD ⁻ , IgM ⁺		
	Switched	CD27 ⁺ , IgD ⁻ , IgM ⁻		
Breg cells ^{47,53,54}		CD5 ⁺ , CD27 ⁻ , CD38 ⁺⁺ , CD43 ⁺ , PD ⁻ L1 ⁺	Breg cells ^{21,48}	CD1d ⁺⁺ , CD5 ⁺ , CD21 ⁺ , CD24 ⁺ , IgM ⁺⁺

interaction outside the GC and SHM occurs inside the GC.^{34,35} IgA CSR is regulated by IL-10 and TGF- β that is produced by T_H cells in mucosal and other tissues. In addition, 2 cytokines of the TNF family, B-cell-activating factor (BAFF) and proliferation-inducing ligand (APRIL), are involved in class switching to IgA. Interestingly, mutations in the *TACI* gene also affect IgA CSR and can cause IgA deficiency.³⁶ In the GC, the proliferation of B cells is regulated by transcription factor BCL-6, reducing the expression of decay-accelerating factor (DAF/CD55).³⁷

Somatic hypermutation

Inside the GC, the dark zone contains activated B cells that proliferate and undergo SHM, and in the light zone, GC B cells are selected in an antigen- and T-cell-dependent manner. These B cells retrieve antigen on follicular DCs that can uniquely retain and display antigen in the form of immune complex. If the affinity to the antigen is high, the GC B cell can proliferate back into the dark zone for another round of SHM or mature into a memory or plasma cell. This process is called affinity maturation whereby SHM antibodies increase their affinity.³⁸ This generates highly antigen-specific antibodies and MBCs. The remaining GC B cells that were not selected undergo apoptosis.^{30,31} In a mouse study, GC B cells expressing Bcl6^{lo}CD69^{hi}IRF4⁺ were found to elicit a more stable interaction with T follicular helper cells and were more likely to differentiate into plasma cells, whereas cells with Bcl6^{hi}CD69^{hi} expression were recycled back into the GC dark

zone.³⁹ PHF14, a PHD finger transcription factor, regulates the proliferation of GC B cells by reducing the expression of p21.⁴⁰ The chemokine CCL22, upregulated in GC B cells, is essential for affinity maturation because it assists in promoting positive selection by attracting T follicular helper cells.⁴¹ The follicular DCs in the light zone reduce IL-4 availability by expressing IL4Ra and thus induce the production of MBCs.⁴²

Types of B cells and their subsets

Several subsets of B cells have been well characterized in numerous studies including in mice and humans. The B-cell subsets differ in their phenotypic characteristics and expression of suppressive molecules, with some subsets having shared features. Here, we discuss the main types of B cells including transitional, naive, B1, B2 (follicular and MZ B cells), memory, effector, plasma, and regulatory B (Breg) cells (Table I). In addition, the surface markers of different B-cell subsets are shown in Fig 2.

Transitional B cells

These B cells are at an immature, transitional stage and have just completed the generation of a functional BCR (IgM/IgD isotype). They migrate as immature cells from the BM to the peripheral lymphoid organs (spleen and lymph nodes) where they settle as naive cells in either the follicular zone or the MZ.⁴

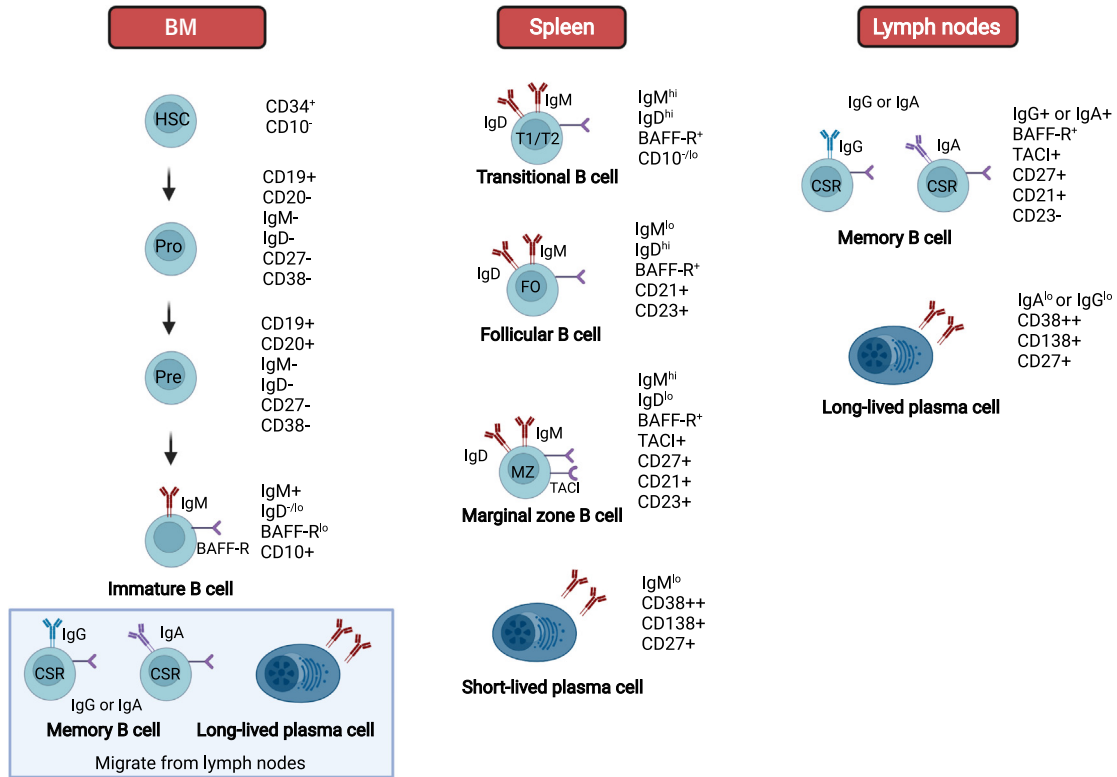


FIG 2. B-cell subsets and their surface markers. B-cell differentiation occurs in the BM, spleen, and lymph nodes. Each B-cell subset is characterized by different surface markers. HSCs express CD34⁺ and CD10⁻, and progressively develop into pro-B cells (CD19⁺, CD20⁻, IgM⁻, IgD⁻, CD27⁻, CD38⁻), pre-B cells (CD19⁺, CD20⁺, IgM⁻, IgD⁻, CD27⁻, CD38⁻), and immature B cells (IgM⁺, IgD^{lo}, BAFF-R⁺, CD10⁺). In the spleen, there are transitional B cells (IgM^{hi}, IgD^{hi}, BAFF-R⁺, CD10^{-/lo}), follicular B cells (IgM^{lo}, IgD^{hi}, BAFF-R⁺, CD21⁺, CD23⁺), MZ B cells (IgM^{hi}, IgD^{lo}, BAFF-R⁺, TACI⁺, CD27⁺, CD21⁺, CD23⁺), and short-lived plasma cells (IgM^{lo}, CD38⁺⁺, CD138⁺, CD27⁺). In addition, MBCs (IgG⁺ or IgA⁺, BAFF-R⁺, TACI⁺, CD27⁺, CD21⁺, CD23⁻) and long-lived plasma cells (IgA^{lo} or IgG^{lo}, CD38⁺⁺, CD138⁺, CD27⁺) are mainly produced in the lymph nodes and later migrate to the BM. BAFF-R, B-cell-activating factor receptor; TACI, transmembrane activator and calcium-modulator and cytophilin ligand interactor.

Naive B cells

B cells in general are referred to as naive when they express a functional BCR but have not yet encountered their specific antigen.⁴ When speaking in more specific terms, there are 3 subsets of naive B cells, namely B1 cells, follicular cells, and MZ B cells.¹⁴ Follicular B cells and MZ B cells are also referred to as B2 cells.⁴

Plasmablasts and plasma cells

Plasmablasts are the rapidly produced and short-lived effector cells that leave GC and terminally differentiate into nondividing plasma cells. They do not play a role in contributing to the long-lasting humoral immunity like plasma cells. The plasma cells are the final differentiation stage of mature B lymphocytes. After affinity maturation in the GC, B cells develop into either short-lived or long-lived plasma cells. Both are well known for their ability to secrete vast quantities of antibodies during an immune response, and long-lived plasma cells have an extended lifespan in both humans^{55,56} and mice.^{57,58} They possess a large Golgi network to uphold the production of antibodies. Long-lived plasma cells reside mainly in the gut⁵⁹ and BM⁶⁰ where they continuously release antibodies into the bloodstream. Different types of plasma cells also contribute to additional functions,⁵⁹ such as in gut

homeostasis with IgA production,⁶¹ regulatory T (Treg)-cell induction in mice,⁶² or immunosuppressive roles in autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and Sjögren syndrome.^{63,64}

Memory B cells

MBCs are constituents of the adaptive arm of the immune system and develop in the GC of secondary lymphoid organs during infections. They retain the BCR characteristics for the antigen that activated their parent B cell to trigger a faster and stronger response on reexposure. MBCs mainly express class-switched isotypes, with subgroups expressing IgM and IgD.^{43,65} IgM MBCs have the tendency to generate new GC, while class-switched MBCs differentiate into plasma cells on antigen challenge.⁶⁶ The spleen is the major reservoir of memory B cells in humans^{67,68} and mice,^{69,70} with additional reservoirs in the tonsils and the BM.⁸ Tissue-resident MBCs maintain their localization by altering their expression of chemokines and homing receptors.⁷¹

Effector B cells

B cells are well known to secrete cytokines such as IL-2, IL-4, TNF- α , and IL-6 (B effector 2 cells) or IFN- γ , IL-12, and TNF- α (B effector 1 cells) that influence the differentiation of effector

TABLE II. The role of B cells in allergic inflammation, nonallergic disorders, and infections

Disease	Role of B cells
AD	<ul style="list-style-type: none"> ● Production of (allergen-specific) IgE¹⁰⁸ ● Suppression of skin inflammation by controlling T follicular helper–cell maturation by Breg cells¹⁰⁹
AR	<ul style="list-style-type: none"> ● Production of antigen-specific IgE in the nasal mucosa^{110,111} ● Expansion of IgE repertoire¹¹² ● T-cell activation¹¹³ ● Production of IL-6 by CD38⁺ B cells¹¹⁴
Allergic asthma	<ul style="list-style-type: none"> ● Production of IgE¹¹⁵ ● Impaired IL-10 production by DOCK8-deficient Breg cells¹¹⁶
Food allergy	<ul style="list-style-type: none"> ● Production of food antigen-specific IgE ● Maintenance of IgE memory^{117,118}
Autoimmune disorders	<ul style="list-style-type: none"> ● Production of autoantibodies¹¹⁹⁻¹²³ ● Cytokine production¹²⁴⁻¹²⁷ ● Antigen presentation to autoreactive T cells¹²⁸⁻¹³¹
Cancer	<ul style="list-style-type: none"> ● Secretion of protumorigenic factors^{132,133} ● T-cell suppression through suppressive cytokine secretion^{134,135} ● Generation of circulating immune complexes¹³⁶ ● Production of antibodies against tumor antigens^{137,138} ● Antigen presentation^{139,140}
Transplantation	<ul style="list-style-type: none"> ● Induction of Treg cells through multiple mediators^{141,142}
Infections	<ul style="list-style-type: none"> ● Production of virus-specific neutralizing antibodies¹⁴³⁻¹⁴⁵

subsets.⁷² Two populations of effector B cells, namely B effector 1 cells and B effector 2 cells, generate distinct patterns of cytokines depending on the environment in which the cells were triggered during their primary encounter with antigen and T cells.⁷³ These effector B-cell subsets consequently control the differentiation of naive CD4⁺ T cells to T_H1 and T_H2 cells through the production of polarizing cytokines such as IL-4 and IFN- γ .

Regulatory B cells

Breg cells encompass a range of B-cell subsets that can suppress or regulate immune responses. The ability to exhibit regulatory functions appears to be inducible in different B-cell subsets rather than as a separate lineage of cells (Box 1).⁷⁴ Breg cells can develop from naive, memory, or plasma cells depending on the stimuli that they are exposed to, such as CpG, IL-2, IL-6, or IFN- α .^{75,76} Different Breg cells act on different parts of the immune system; they may induce Treg cells,⁷⁷ prevent differentiation of naive T cells into T_H1 or T_H17 cells,⁷⁸ suppress the production of inflammatory responses, and induce IgG₄ production.⁷⁹ Breg cells suppress inflammatory responses via the production of immune-modulatory cytokines such as IL-10,^{11,78,80-83} IL-35,⁸⁴⁻⁸⁶ and TGF- β .^{87,88} Different subsets of Breg cells bear unique phenotypes and functions. In mice, B-1a cells are innate immune-like B cells that predominantly inhabit the peritoneal and pleural cavities.⁷ These CD19⁺CD5⁺B1a cells mainly produce the immunosuppressive cytokine, IL-10. Similarly, this regulatory function was also observed in murine CD5⁺CD1d^{hi} B10 cells.⁸⁹ Several studies on the immune regulatory role of B10 cells have been shown in other disease models including allergic inflammation, intestinal inflammation, arthritis, and lupus.^{90,91} Another type of murine Breg cells is referred to as “immature” or “transitional” B cells. These transitional 2-MZ precursor B cells display immune-mediated functions in several diseases including allergy, autoimmunity,

cancer, and skin allograft. IL-10–producing CD138⁺ plasmablasts are decisive in reducing autoimmune inflammation by suppression of DC function for the generation of pathogenic T cells in the draining lymph nodes.⁹² Furthermore, T-cell immunoglobulin and mucin domain-1, a type I transmembrane glycoprotein, contains an IgV domain and a mucin domain that facilitates the trafficking of T_H cells, T_H1 and T_H17, during inflammation and autoimmunity.⁹³ Human Breg cells display different subsets and phenotypes. The first Breg cells were identified in the CD19⁺CD24^{hi}CD38^{hi} immature B-cell fraction in the peripheral blood of healthy individuals.⁷⁸ These CD19⁺CD24^{hi}CD38^{hi} Breg cells inhibited naive T-cell generation into T_H1 and T_H17 cells and converted CD4⁺CD25[−] T cells into Treg cells via IL-10 production. In addition, Breg cells suppressed the T_H1 response in a partly IL-10–dependent manner and through a CD80-CD86 interaction with T cells. In patients with systemic lupus erythematosus, B cells present lipid antigen to CD1d-restricted invariant natural killer T cells that maintain tolerance in autoimmunity.⁹⁴ Discovered in 2013, CD19⁺CD25⁺CD71⁺CD73[−]-inducible Breg cells (Br1 cells) play an important role in allergen-specific immune tolerance.⁷⁹ Br1 cells are suppressive B cells that ameliorate inflammation by the release of IL-10, induce the generation of Treg cells, and enhance IgG₄ production. Improved clinical inflammation in house dust mite allergy was positively correlated with increased frequency of Der p 1–specific IgG₄⁺ B cells, plasmablasts, and IL-10⁺ and dual-positive IL-10⁺IL-1RA⁺ Breg cells throughout immunotherapy.⁹⁵ CD24^{hi}CD27⁺ (B10) B10 cells are well known to produce a large amount of IL-10 and suppress TNF- α production by monocytes in peripheral blood.⁹⁰ Moreover, CD27^{int}CD38^{hi} plasmablasts from peripheral blood of healthy individuals were found to secrete IL-10 when stimulated with CpG (a TLR9 agonist) and/or cytokines IL-2, IL-6, and IFN- α .⁹² Future studies on generating IL-10 B cells will provide valuable information for the development of tailored medical treatments. Other Breg-cell–suppressive mechanisms include

Box 1. Summary of the characterization and function of Breg cells

- Main source of IL-10, TGF- β , and IL-35 cytokines secretion¹⁰²
- The activation of macrophage and DCs is inhibited by Breg cells via the secretion of IL-10¹⁰³
- Breg cells regulate effector T cell (T_H1 and T_H17) and induce Treg-cell expansion through the secretion of IL-10, TGF- β , and IL-35 cytokines¹⁰⁴
- Several surface molecules on Breg cells including BCR, CD80, CD86, PD-L1, CD40, Fas ligand, inducible costimulator ligand, MHC, TLR4, and aryl-hydrocarbon receptor are well expressed and suppress the inflammatory responses¹⁰³
- Breg-cell surface molecule, CD1d, activates natural killer T cells with suppressive function⁹⁴
- Breg-cell surface molecules, CD39 and CD73, are essential enzymatic molecules in the adenosine pathway suppressing allergic responses^{13,97}

FasL- and granzyme-B-mediated killing of effector T cells,⁹⁶ and the formation of free adenosine through enzymatic conversion of ATP to adenosine by CD39 and CD73.⁹⁷ Furthermore, ligand for inhibitory checkpoint molecule PD1 is expressed on several types of Breg cells.^{79,98} In addition, T-cell immunoglobulin and mucin domain-1^{93,99,100} and aryl-hydrocarbon receptor are associated with controlling different immune cells including T_H17, Treg cells, and DCs, as expressed on certain Breg cells.¹⁰¹ In an IL-10-producing Breg-cell study, elevated IgG₄ levels were found, suggesting that Breg cells regulate immune responses both directly by secreting IL-10 and indirectly by generating IgG₄ antibodies.⁷⁹

THE ROLE OF B CELLS IN ALLERGIC INFLAMMATION AND OTHER DISEASES

In the past decades, the prevalence of allergic diseases has increased dramatically, impacting around 30% of the population worldwide.¹⁰⁵ These allergic diseases negatively affect the quality of life and have a major socioeconomic impact, representing a serious global concern. Allergic inflammation is generally characterized by a type 2 immune response attributed to both the innate and adaptive arms of the immune system. This type of immune response involves the engagement of epithelial cells, antigen-presenting cells, innate lymphoid cells, T_H2 cells, B cells, eosinophils, and mast cells.¹⁰⁶ T_H2 cells and antigen-specific IgE are the main mediators in allergic diseases such as allergic rhinitis, allergic asthma, and food allergy.¹⁰⁷ The functions of B cells in allergic diseases and other diseases in humans are summarized in [Table II](#).

ALLERGIC INFLAMMATION

Allergic diseases including atopic dermatitis (AD), allergic rhinitis (AR), allergic asthma, food allergy, and anaphylaxis commonly emerge from an inflammatory response to allergens. These foreign allergens can derive from naturally occurring plants or animal proteins.¹⁴⁶ Sensitization to allergens occurs during allergen exposure to damaged skin and to gut epithelial cells. It is well known that some of these allergens with diverse structures and immune epitopes can be cleaved by enzymes in the gut. When allergens encounter damaged skin, the epithelial cells react by producing alarmins such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP). These alarmins act on DCs, which migrate to draining lymph nodes where they present allergen-derived peptides on the MHC class II molecules to naive T cells. Then, antigen-specific T_H cells differentiate into effector T_H2 cells in the presence of IL-4. A set of interleukins, such as IL-4 and IL-13, is produced by T_H2 cells and induce B cells to differentiate

into IgE-producing plasma cells. On allergen uptake, allergen interacts with IgE antibodies that directly bind to the high-affinity IgE receptor on mast cells and basophils and induce degranulation and release of mediators including cytokines, histamine, and proteases, which result in allergic symptoms and life-threatening anaphylaxis.¹⁴⁷ Anaphylaxis can proceed through an immunologic IgE-dependent pathway or the combination of IgG antibody and activation of the complement system.¹⁴⁸

Atopic dermatitis

AD is the most common skin disease characterized by severe itching and eczema-like lesions.¹⁰⁸ It is mainly caused by an imbalance in T_H1/T_H2 mechanisms and is found to be closely related to food allergy.¹⁴⁹ Initially, AD is thought to mainly occur in an IgE-independent manner, and high level of IgE often correlates with *Staphylococcus* colonization.^{107,150} But evidently, elevated levels of serum total or allergen-specific IgE due to polysensitization to various allergens are often observed in AD. A study showed that patients with severe AD are characterized by lower numbers of Breg cells when compared with healthy individuals.¹⁵¹ Supporting these results, another study also demonstrated a decreased frequency of CD24^{hi}CD38^{hi} Breg cells in patients with severe AD. This study further demonstrated that IL-6 significantly increased IL-10 production in B10 cells *in vitro* from healthy donors but not B10 cells from donors with severe AD.^{107,152} *In vitro* stimulation with CpG in patients with AD did not elicit a significant response in CpG-induced IL-10 compared with healthy individuals.¹⁵³ In addition, B-cell depletion therapy with the anti-CD20 mAb (rituximab) showed amelioration of skin inflammation in AD.¹⁵⁴

Allergic rhinitis

AR is an allergic reaction to respiratory allergens such as pollen, dust, mold, and animal epithelia, resulting in inflammation of the nasal mucosa. The number of IgE⁺ B cells and IgE⁺ plasma cells was elevated in the nasal mucosa of patients with AR compared with nonallergic controls.¹¹⁰ Allergen-specific IgE is locally produced at the nasal mucosa,^{110,111} and it is well known as the key driver of disease in AR.¹⁵⁵ These IgE antibodies bound to high-affinity IgE receptors on basophils and mast cells induce the release of histamine, leukotrienes, and proinflammatory cytokines. Wu et al¹¹² provided a first glance into an expanding IgE repertoire on allergen exposure in the pollen season, albeit in a limited number of samples. Individuals with AR are characterized by a higher proportion of CD23⁺ B cells and elevated CD23 expression on B cells compared with individuals without

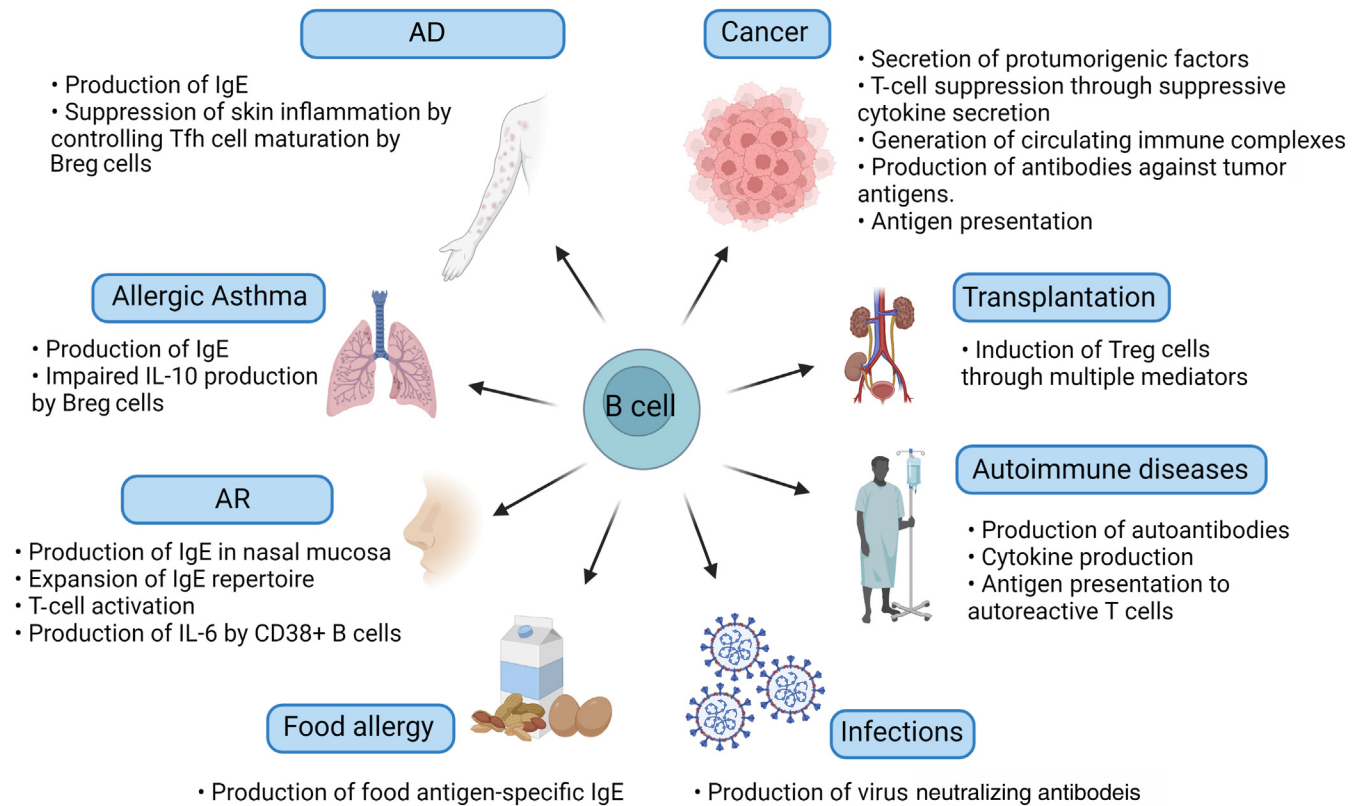


FIG 3. Overview of B-cell functions in allergic inflammation and other diseases. B cells play a pivotal role in the secretion of antibodies that protect the host immune system, particularly against various inflammatory conditions such as AD, allergic asthma, AR, food allergies, cancer, allograft injury after transplantation, autoimmune diseases, and infections.

allergy.^{156,157} CD23 is the low-affinity receptor for IgE, and the surface density on B cells correlates with allergen uptake, possibly enhancing antigen presentation and subsequent T-cell activation.¹¹³ In a recent study, the role of another B-cell subset was examined and antigen-specific CD38⁺ B-cell frequency was found to be elevated in patients with AR.¹¹⁴ On allergen exposure, these CD38⁺ cells produce IL-6 and convert Treg cells into T_H17 cells, compromising the therapeutic effects of immunotherapy.

Allergic asthma

Allergic asthma is triggered by inhalation of an aeroallergen, promoting a type 2 inflammatory response in the lower respiratory tract of susceptible individuals. Consequently, the airway becomes obstructed and limits the expiratory airflow.¹⁵⁸ In patients with asthma, the number of Breg cells was reported to be downregulated and its IL-10–producing capacity was significantly lower in response to LPSs compared with healthy individuals.¹⁵⁹ In asthmatic mice, IL-10–secreting Breg cells were decreased in a CD9⁺ B-cell subset, suggesting CD9 as a marker of IL-10–competent Breg cells.^{160,161} This CD9⁺ B-cell subset could suppress T_H2- and T_H17-driven inflammation, increase the ratio of Treg/effector T-cell in the lung,¹⁶² and generate CD3⁺CD4⁺CD25⁻ effector T-cell apoptosis through the mitogen-activated protein kinase signaling pathway.¹⁶¹ The protective role of CD9⁺ Breg cells in the development of asthma and immunologic tolerance was

reported in a house dust mite–induced mouse model of asthma. Recently, elevated serum IgE levels were detected in patients with a mutation in the dedicator of cytokinesis 8 (DOCK8), making them more susceptible to developing allergic diseases.¹¹⁵ A DOCK8 knockout murine asthma model was generated to study the effect of DOCK8 deficiency on Breg cells.¹¹⁶ DOCK8-deficient Breg cells elicited a reduced response to TLR9 signaling, suggesting a possible defect in producing IL-10 and thus suppressing their immunoregulatory function, which could be restored by IL-21 by inducing normal signal transducer and activator of transcription 3 phosphorylation and reducing inflammatory infiltration as demonstrated in a mouse model of allergic asthma.^{116,163} Supportive treatment based on management of asthma is often by anti-IgE therapy with biologicals such as omalizumab, benralizumab, and dupilumab.¹⁶⁴ The omalizumab is an anti-IgE antibody that is used to treat moderate to severe allergic asthma.¹⁶⁵ For eosinophilic asthma, benralizumab is a widely used antibody that binds the α subunit of the receptor to IL-5.¹⁶⁶ Lastly, dupilumab directly inhibits IL-4 and IL-13 signaling in allergic individuals by blocking the IL-4R α chain.¹⁶⁷

Food allergy

Food allergy has been defined as an adverse immune response to food proteins and can be divided into IgE-mediated, non-IgE-mediated, and mixed-type.¹⁶⁸ The development of food allergy has been suggested to be closely associated with AD and often

occurs after the allergens encounter the damaged skin. B cells play a prominent role in IgE-mediated food allergies due to their ability to produce food antigen-specific IgE antibodies. Most specific IgE antibodies primarily arise from previously class-switched, antigen-experienced cells.¹⁶⁹ CSR typically takes place near or in the GC of lymphoid organs, but recent evidence suggests that local class-switching to IgE can also occur in tissues of the gastrointestinal tract.¹⁷⁰ Allergen-specific IgE can persist for years even after extended periods without allergen exposure, implying the existence of a circulating pool of allergen-specific IgE-producing long-lived plasma cells.¹⁷¹ There is increasing evidence suggesting that patients with allergy have allergen-specific IgE memory that when activated can contribute to the replenishment of this IgE plasma cell pool.^{117,118} On the basis of murine studies, we can say that IgG₁ MBCs maintain IgE memory by sequential switching to IgE-producing cells.¹⁷²⁻¹⁷⁵ Whether IgE MBCs exist and form the basis of IgE memory in humans or whether IgE memory in humans also resides in IgG- or IgA₁-switched MBCs remains a topic of debate. However, a recent study showed the coexistence of clonally related IgE plasmablasts and IgG MBCs, supporting the concept of IgG MBCs as provenance of IgE memory.¹⁷⁶ Patients with a late eczematous reaction after milk challenge were characterized by a lower level of IL-10-producing CD19⁺CD5⁺ Breg cells compared with the milk-tolerant group.¹⁷⁷ Supporting these results, a lower frequency of CD19⁺CD5⁺Foxp3⁺ B-cell fraction in CD5⁺ B cells was demonstrated in patients with milk allergy compared with milk-tolerant individuals.¹⁷⁸ Correspondingly, on allergen stimulation, TGF-β1⁺ CD19⁺CD5⁺ Breg-cell numbers increased in milk-tolerant individuals.¹⁷⁹

ALLERGEN TOLERANCE

In addition to playing a pivotal role in the pathogenesis of allergies through the production of antigen-specific IgE, B cells are involved in the development of allergen tolerance. Mainly, B cells contribute to allergen tolerance through immunosuppressive cytokines such as IL-10, TGF-β, and IL-35, which induce Breg cells and the production of protective IgG₄ isotypes.¹⁸⁰ IL-21 is a broad negative regulator of IgE CSR in mouse and human B cells. Mixed results have been reported on IL-21, such as the inhibition of IgE was observed in PBMC cultures, whereas IgE was promoted in pure B-cell cultures.¹⁶³ In contrast, IL-10 mainly suppresses IL-4-induced IgE and helps to stimulate the secretion of IgG₄.¹⁸¹ In addition, IgG₄ antibodies can first capture the allergen before binding to high-affinity IgE receptor, thereby preventing the activation of mast cells and basophils.¹⁸²⁻¹⁸⁴ Recent evidence suggests that IgA antibodies possess similar neutralizing capabilities.^{185,186}

There are extensive studies on allergen tolerance from models of natural exposure to high doses of allergens such as in beekeepers, cat owners, and helminth infections. Beekeepers receive multiple stings during the beekeeping season, but almost none during autumn and winter months, outside of the beekeeping season. Numerous studies on bee venom allergen-specific T and B cells in healthy beekeepers greatly contribute to our understanding of the underlying mechanisms that induce allergen tolerance.^{102,187,188} High-dose exposure in beekeepers was associated with amelioration of T-cell-related cutaneous late-phase swelling, increased IL-10-producing Tr1 cells, and increased antigen-specific IgG₄ production.¹⁸⁹ Certain molecules derived from Breg cells such as IL-10, PD-L1, and CTLA4 can also

suppress allergen-specific T cells. Cat owners are directly exposed to cat allergens and are known to develop long-term immune tolerance.¹⁹⁰ Recent evidence suggests that monoclonal Fel d 1-specific IgG₄ antibody administration in patients with cat allergy is very effective and can significantly ameliorate the allergic response.¹⁹¹ During infection by parasitic helminths, studies suggest that the frequency of IL-10-producing CD19⁺CD1d^{hi} B cells increased with a concomitant reduction in T-cell proliferation, and subsequently with low IFN-γ production.¹⁹² *Schistosoma mansoni* is the best-described helminth for the study of the immunoregulatory functions of Breg cells.¹⁹³ Furthermore, allergen-specific immunotherapy (AIT) is considered an insightful model to investigate allergen tolerance.^{194,195} During the course of AIT, several studies have demonstrated an increased frequency of Breg cells together and allergen-specific IgG₄ antibodies.^{196,197}

AIT is a very effective medical treatment for patients with allergy, usually performed under the supervision of highly experienced clinicians. The repetitive gradually increased specific-allergen doses can be administered to patients orally, sublingually, or subcutaneously. Successful AIT is the only curative treatment for allergic diseases because it repairs allergen tolerance.¹⁹⁸⁻²⁰⁰ A study by Heeringa et al²⁰¹ investigated the effect of sublingual immunotherapy on the IgE and IgG subclass-expressing MBCs before, during, and after therapy. Participants having moderate to severe seasonal AR were recruited for sublingual immunotherapy. Their findings demonstrated that sublingual immunotherapy suppressed allergic responses by increasing the anti-inflammatory allergen-specific IgG₂ and IgG₄ isotypes.²⁰¹ In subcutaneous immunotherapy, responder patients with AIT against house dust mite allergy were found to have a higher frequency of IL-10⁺ and/or IL-1RA⁺ Breg cells.⁹⁵ In grass-pollen allergy, the ratio of IL-10-producing Breg cells over T_H17 cells is increased after the initial treatment of subcutaneous immunotherapy against grass-pollen allergoid. This ratio of IL-10-producing Breg/T_H17 cells emerges as potential early prediction of AIT efficacy.²⁰² Similar results were found in a study performed on beekeepers and venom immunotherapy. A higher frequency of CD73⁻CD25⁺CD71⁺IL-10⁺ Br1 cells was found in beekeepers and patients receiving venom immunotherapy.¹⁰² Other studies also indicated elevated IL-10⁺ B cells in bee venom allergen-specific compared with non-specific B cells and induced IgG₄ production compared with non-IL-10-secreting B cells.⁷⁹ In addition, a recent study on subcutaneous immunotherapy against fungi *Alternaria alternata* in asthmatic mice showed a higher frequency of Breg cells.²⁰³

NONALLERGIC DISORDERS

In addition to the protective role of B cells against allergic diseases, its immunoregulatory function extends to the regulation of nonallergic disorders by suppressing excessive inflammation contributing to disease, such as in autoimmune disorders, cancer, transplantation, and infections (Fig 3).

Autoimmune disorders

The presence of autoantibodies is one of the hallmarks of autoimmune disorders, such as in multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and Sjögren syndrome.¹¹⁹⁻¹²³ Increased levels of SHM transform nonautoreactive B cells into autoreactive B cells.²⁰⁴⁻²⁰⁷ The autoantibodies can also form circulating immune complexes that activate the complement pathway and Fc-receptor-dependent effector

function.^{206,208-211} In addition to the production of autoantibodies, several other B-cell abnormalities have been identified, such as atypical cytokine production or defective B-cell regulation.¹²⁴⁻¹²⁷ Furthermore, B cells can execute their role as antigen-presenting cells, which is crucial for activating autoreactive T cells, contributing to the disease pathogenesis.¹²⁸⁻¹³¹ B cells from good-responding patients to rheumatoid arthritis drug therapy exhibited an increased CD39, an inhibitor that significantly restores proliferation and TNF-producing capacity in CD4⁺ T cells.²¹² In autoimmune uveitis, mice treated with IL-35-producing Breg cells developed mild experimental autoimmune uveitis and the disease protection correlated with expansion of IL-10- and IL-35-secreting Treg cells.⁷⁴

Cancer

B cells represent a substantial component of tumor-infiltrating lymphocytes, suggesting a prominent role in the regulation of tumor responses.^{134,213} Since the 1970s, there is growing evidence suggesting that B cells can promote tumor development because they are known to secrete protumorigenic factors,^{132,133} suppress T cells through cytokine secretion by Breg cells,^{134,135} and generate circulating immune complexes that induce inflammation.¹³⁶ This may occur by interfering with antitumor immune responses via the production of angiokine^{133,214} or IgG₄ antibodies.²¹⁵⁻²¹⁷ However, B cells can also inhibit tumor development by producing antibodies against tumor antigens^{137,138} and through antigen presentation to T cells in tumor-adjacent tertiary lymphoid structures.^{139,140} In human papilloma virus-associated cancer patients, B-cell markers including CD19 and IGJ (referred as *JCHAIN* and encodes the J-chain) are considered as novel B-cell prognostic biomarkers for 3-year overall survival. Their single-cell RNA sequencing showed that radiotherapy and PD-1 blockade enhance B-cell clonality, decrease CDR3 length, and induce B-cell SHM.²¹⁸ Moreover, B-cell-deficient mice showed reduced tumor growth compared with wild-type mice.^{219,220} Using B-cell-specific deletion mice, inducible costimulator ligand (ICOSL) in B cells boosts antitumor immunity by increasing the effector to regulatory T-cell ratio. The study also suggests that CD55, a complement-inhibitory protein, displays an opposite effect in chemotherapy.¹⁶⁴

Transplantation

The role of B cells in the development of allograft tolerance has been investigated in both human and murine models.²²¹⁻²²³ After renal transplantation, B cells secrete antibodies that mediate graft rejection. Hyperacute, acute, and chronic rejection in patients is often controlled by donor-specific antibodies.²²⁴ However, Breg cells promote allograft tolerance through multiple mediators that induce Treg cells, such as IL-10 and TGF- β .^{141,142} There are several studies suggesting the potential for adoptive transfer of Breg cells to prolong skin allograft survival.^{225,226} A supporting study by Li et al²²⁷ demonstrated that adoptive transfer of transplanted Breg cells into heart transplanted mice effectively induced tolerance by blocking the CD40-TRAF6 signaling pathway. Evidence from kidney transplant recipients pointed to a B-cell signature associated with tolerance consisting of upregulation of B-cell-related genes and their molecular pathways.²²⁸ In agreement with these results, Pallier et al²²⁹ and Schuller et al²³⁰ demonstrated that patients tolerant to transplantation without an immunosuppressive

treatment have a more regulatory B-cell phenotype compared with patients with a stable graft having immunosuppression. In murine model of heart transplantation, the tolerant alloreactive B cells retained the ability to recognize alloantigen via T-cell maturation into CXCR5⁺PD-1⁺ T follicular helper cells. They contribute to transplantation tolerance of previous GC responses, while keeping their antigen-presenting cell capacity and by suppressing *de novo* alloreactive B-cell responses.²³¹

Infections

Although B cells play a key role in regulating disease inflammation, they can also weaken immune responses during viral, bacterial, and helminth infections. For example, Breg cells suppress hepatitis B virus-specific CD8⁺ T cells and HIV virus-specific CD8⁺ T cells and increase the frequency of IL-10-producing B cells.^{232,233} In HIV-induced murine model, B cells that were isolated and *in vivo*-engineered with 2 adeno-associated viral vectors secreted high titers of neutralizing anti-HIV antibodies. These data suggested that *in vivo* B-cell engineering to express therapeutic antibodies is a safe, potent, and scalable method for infectious disease treatments.²³⁴

Moreover, Breg cells produce IL-10 to block the secretion of type-I interferon after respiratory syncytial viral infection.²³⁵ In experimentally rhinovirus-infected subjects, B cells were characterized by an antiviral gene profile driven by IFN- α and on rhinovirus stimulation the B cells rapidly differentiated into plasmablasts.²³⁶ Similarly, in a separate study, Treg cells from patients with asthma were found to mount a stronger antiviral response in response to rhinovirus infection compared with healthy controls. Moreover, the Treg-cell-suppressive capacity was compromised in individuals with asthma.²³⁷ In the recent global pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),²³⁸ mRNA vaccines encoding the SARS-CoV-2 spike protein were developed to induce a robust SARS-CoV-2-specific antibody response.¹⁴³⁻¹⁴⁵ A recent study compared the immune response mounted after natural infection compared with mRNA vaccination. Primary MBCs induced after natural infection exhibited a higher degree of affinity maturation compared with those induced in response to mRNA vaccination and so have a stronger antigen-binding capacity and are more efficient at producing plasmablasts and MBCs.²³⁹ Furthermore, the severity of the disease seems to correlate with certain B-cell subset frequencies, suggesting that B cells could be used as potential biomarkers to assess disease severity.²⁴⁰ Single-cell B-cell repertoire analysis of patients with mild and severe COVID-19 infections exhibited the expansion of a naive-derived, low-mutation IgG₁ population of antibody-secreting cells demonstrating features of a low selective compartment. These cells show a high frequency of clonotypes specific for both SARS-CoV-2 and autoantigens, including pathogenic autoantibodies against the glomerular basement membrane.²⁴¹ These B cells represent the origins and resolution of autoreactivity in severe COVID-19.

CONCLUSION

B cells are classically known for their inflammatory and immunoregulatory role through antibody production and secretion of immunosuppressive molecules, respectively. Over the past 50 years, technological advances have revolutionized our

understanding of B cells and we can now explore this dual functionality in further detail. In allergic conditions, B cells promote inflammation by presenting the antigen-derived peptide to T cells, activating allergen-specific T cells, and producing high-affinity IgE antibodies that lead to type I hypersensitivity. In contrast, B cells also suppress inflammation and induce immune protection by secreting immunosuppressive cytokines IL-10 and anti-inflammatory IgG₄ antibodies. In allergen tolerance, allergen-specific antibody subclasses such as IgG₁, IgG₂, IgG₄, and IgA appear to have crucial roles against allergies. The induction and maintenance of Breg cells are essential for achieving allergen tolerance through AIT. It should be noted that overactivation of Breg cells could inhibit beneficial immune responses in infection and cancer, thereby contributing to a worse disease outcome. Given our current understanding of B cells as key regulators of inflammatory responses, future studies should consider B cells as potential targets for novel treatments and clinical biomarkers.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

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