Mechanisms of allergic diseases

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B-cell biology and development

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B cells develop from hematopoietic precursor cells in an ordered maturation and selection process. Extensive studies with many different mouse mutants provided fundamental insights into this process. However, the characterization of genetic defects causing primary immunodeficiencies was essential in understanding human B-cell biology. Defects in pre–B-cell receptor components or in downstream signaling proteins, such as Bruton tyrosine kinase and B-cell linker protein, arrest development at the pre–B-cell stage. Defects in survival-regulating proteins, such as B-cell activator of the TNF-α family receptor (BAFF-R) or caspase recruitment domain–containing protein 11 (CARD11), interrupt maturation and prevent differentiation of transitional B cells into marginal zone and follicular B cells. Mature B-cell subsets, immune responses, and memory B-cell and plasma cell development are disturbed by mutations affecting Toll-like receptor signaling, B-cell antigen receptor coreceptors (eg, CD19), or enzymes responsible for immunoglobulin class-switch recombination. Transgenic mouse models helped to identify key regulatory mechanisms, such as receptor editing and clonal anergy, preventing the activation of B cells expressing antibodies recognizing autoantigens. Nevertheless, the combination of susceptible genetic backgrounds with the rescue of self-reactive B cells by T cells allows the generation of autoreactive clones found in patients with many autoimmune diseases and even in those with primary immunodeficiencies. The rapid progress of functional genomic research is expected to foster the development of new tools that specifically target dysfunctional B lymphocytes to treat autoimmunity, B-cell malignancies, and immunodeficiency.
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Key words: *B cell, B lymphocyte, immunodeficiency, development, humoral immunity, autoimmunity, tolerance*

Abbreviations used

AID:	Activation-induced cytidine deaminase
APRIL:	A proliferation-inducing ligand
BAFF:	B-cell activator of the TNF-α family (aka BLYS)
BAFF-R:	BAFF receptor
BCMA:	B-cell maturation factor
BCR:	B-cell antigen receptor
Blimp-1:	B lymphocyte–induced maturation protein 1
BLNK:	B-cell linker protein (aka Sark homology 2 domain–containing leukocyte protein of 65 kDa [SLP65])
BM:	Bone marrow
BTK:	Bruton tyrosine kinase
CARD11:	Caspase recruitment domain–containing protein 11 (aka CARMA1)
CNR2:	Cannabinoid receptor 2
CSR:	Class-switch recombination
CVID:	Common variable immunodeficiency
DOCK8:	Dedicator of cytokinesis 8
GC:	Germinal center
GFP:	Green fluorescent protein
H-chain:	Heavy chain
HEL:	Hen's egg lysozyme
L-chain:	Light chain
MyD88:	Myeloid differentiation primary response gene–88
MZ:	Marginal zone
N_{BH}:	B-cell helper neutrophil
NF-κB:	Nuclear factor κ light chain enhancer of activated B cells
nur77:	Nuclear receptor 77
S1P:	Sphingosine-1-phosphate
SHM:	Somatic hypermutation
TACI:	Transmembrane activator, calcium modulator, and cyclophilin ligand interactor
TLR:	Toll-like receptor
WAS:	Wiskott-Aldrich syndrome

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Terms in boldface and italics are defined in the glossary on page ■■■.

B cells and their antibodies are the central elements of humoral immunity and protect, as part of the adaptive immune system, against an almost unlimited variety of pathogens. Defects in B-cell development, selection, and function lead to autoimmunity, malignancy, immunodeficiencies, and allergy. Combined with the enormous increase in knowledge about gene function and the genetic diversity of human subjects that has developed since the human genome was deciphered, primary immunodeficiencies are a still-growing source of mutations, providing unique opportunities to study the function of the human immune system. In addition, each newly discovered immunodeficiency represents a new challenge to develop the most optimal and personalized forms of treatment.

In this review we discuss human B-cell development (Fig 1) in light of genetic defects discovered by studying primary

immunodeficiencies. By pointing out differences and common features with corresponding mouse models, we provide an overview on mechanisms regulating the maturation, survival, and selection of B lymphocytes in protective and autoimmune responses.

EARLY B-CELL DEVELOPMENT IN THE BONE MARROW

In adult human subjects, as in all mammals, B lymphocytes develop in the bone marrow (BM) from hematopoietic precursor cells. During embryonic life, the BM is seeded by hematopoietic stem cells developing in the fetal liver. Their precursor cells originate from the aorta-gonad-mesonephros,[1,2] which is formed by descendants of the ***mesoderm***. Early BM-dependent stages of B-cell development are structured along the functional rearrangement process of the immunoglobulin gene segments.[3] V_H, D_H, and J_H, rearrangements of the ***heavy chain (H-chain)*** together with the V_L-J_L rearrangements of the ***light chain (L-chain)*** gene segments generate a B-cell repertoire expressing antibodies capable of recognizing more than 5×10^{13} different antigens. According to the rearrangement of the H-chain and L-chain gene segments, 3 developmental stages are defined. In the first stage, pro–B cells rearrange the D and J segments of the H-chain, followed by a second rearrangement joining an upstream V region to the rearranged DJ segment.

The functional rearrangement of the μ–H-chain gene segments opens the entry into the next phase, the pre–B-cell stage. In human subjects pre–B cells undergo 1 or 2 cell divisions and rearrange the gene segments encoding the κ and λ chains.[4] Combined with the μ chain, an IgM molecule is formed and expressed on the cell surface. These cells are termed immature B cells. Immature B cells leave the BM and migrate to the spleen, where they finalize early development by differentiating into naive, follicular, or ***marginal zone*** (MZ) B cells.

Considering the enormous diversity of antibody specificities, the first challenge of the immune system is to find a balance between variable specificities against pathogens while avoiding autoreactivity. Therefore B cells are screened at several checkpoints during development for their degree of autoreactivity. The first screen takes place after differentiation of pro-B into pre-B cells.[5] Expression of the productively rearranged μ–H-chain, of the surrogate L-chains (in human subjects composed of λ-like and V-preB), and of the signal-transducing components Ig-α and Ig-β allows the formation of the so-called pre–B-cell antigen receptor (BCR) complex. The pre-BCR has 2 tasks. The first task is to shut down the activities and expression of the enzyme machinery catalyzing the rearrangements of the H-chain gene segments, a process termed allelic exclusion.[6] This prevents the expression of 2 H-chains with 2 different specificities by the same cell. The second task is to initiate the rearrangement of the L-chain genes.

Several genetic defects affecting components of the pre-BCR or downstream signaling proteins have brought to light human B-cell development and uncovered fundamental differences in B-cell lymphopoiesis between mice and human subjects. In human subjects, for example, mutations in genes encoding components of the ***IL-7*** signaling cascade, such as IL-2 receptor common γ,[7] the IL-7 receptor α chain,[8] or the associated kinase Janus kinase 3,[9] do not affect the B-cell compartment, but they do interrupt T-cell development, leading to severe combined immunodeficiency (B^+T^- severe combined immunodeficiency).

GLOSSARY

ACTIN: A protein found in microfilaments and active in muscular contraction, cellular movement, and maintenance of cell shape.

ACTIVATION-INDUCED CYTIDINE DEAMINASE (AID): An enzyme that catalyzes mutation of deoxycytidine to deoxyuracil in single-stranded DNA. AID is critical for somatic hypermutation. Mutations in AID result in autosomal recessive hyper-IgM syndrome.

AFFINITY MATURATION: As a consequence of somatic hypermutation, B cells increase their average affinity for antigen as the humoral immune response progresses. Such cells are preferentially activated and therefore have selective survival. Affinity maturation occurs in germinal centers.

5×10^{13}: For comparison purposes, there are roughly 10^{14} cells in the human body, of which only 10^{13} are human. 5×10^{13} is roughly 40 billion more than the number of stars in the Milky Way Galaxy. There are 5×10^{12} known digits in π. One million years is approximately 3.2×10^{13} seconds.

GERMINAL CENTER: A central proliferative area of a lymphoid follicle. It forms during T cell–dependent humoral immune responses.

HEAVY CHAIN (H-CHAIN): Part of the core structure of an antibody molecule. Antibodies contain 2 identical H-chains that consist of variable and constant regions. The constant regions of the H-chain mediate effector functions of the antibody.

IL-7: A hematopoietic cytokine binding to cytokine receptors of the common γ chain family. In addition to being vital to the survival and expansion of both precursor T lymphocytes, IL-7 stimulates the proliferation and differentiation of cytotoxic T and natural killer cells and stimulates the antitumor properties of monocytes and macrophages.

LIGHT CHAIN (L-CHAIN): An antibody molecule also contains 2 identical L-chains that contain 1 variable domain and 1 constant domain. The variable region of 1 H-chain is juxtaposed with the variable region of 1 L-chain to form the antigen-binding site of the antibody molecule.

MARGINAL ZONE: A splenic zone located next to the marginal sinuses, the site of entry into the spleen for lymphocytes, macrophages, and dendritic cells in human subjects. The marginal sinus separates the white pulp from the red pulp.

MESODERM: The 3 primary germ layers of an embryo are the mesoderm, ectoderm, and endoderm. The mesoderm develops from the ectoderm on the 15th day of life. The mesoderm is the source of bone, muscle, connective tissue, and dermis.

NUCLEAR FACTOR κB (NF-κB): A family of transcription factors that promote the expression of a variety of survival and differentiation factors, as well as inflammatory mediators. NF-κB is present in an unstimulated state in the cytoplasm, where it is bound by IκB, an inhibitory protein.

PEYER PATCHES: Aggregates of lymphoid follicles that are a component of gut-associated lymphoid tissue. Antigen-driven priming and maturation of naive T and B lymphocytes occurs here. They are located primarily in the ileum.

SOMATIC HYPERMUTATION: High-frequency point mutations that occur in a mature B cell at the hypervariable sites of both the V_H and V_L genes. The amino acid products of these sites, particularly at V, D, and J junctions, are the specific points of contact with antigen within the binding groove.

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