B Cell Development and Maturation

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Abstract

Since the identification of B cells in 1965 (Cooper et al. 1965), three has been tremendous progress in our understanding of B cell development, maturation and function. A number of B cell subpopulations, including B-1, B-2 and regulatory B cells, have been identified. B-1 cells mainly originate from the fetal liver and contain B-1a and B-1b subsets. B-2 cells are derived from the bone marrow (BM) and can be further classified into follicular B (FOB) and marginal zone B (MZB) cells. Regulatory B cells (Bregs) function to suppress immune responses, primarily by production of the anti-inflammatory cytokine IL-10. B cell tolerance is established at several checkpoints, during B cell development in the BM (central tolerance) as well as during B cell maturation and activation in the periphery (peripheral tolerance). This chapter will focus on the regulation of important processes during the development and maturation of B-1 and B-2 cells.

Keywords

Ig gene · V(D)J recombination · Follicular B · Marginal zone B · B-1

1.1 Introduction

B cell development proceeds in an orderly fashion and is regulated by intrinsic genetic programs and by external cues such as cytokines that are present in the specialized microenvironments of fetal liver and BM. One intriguing feature of B cell development is that it is accompanied by immunoglobulin (Ig) gene rearrangements. Progenitor B cells rearrange their Ig heavy chain (HC) genes to differentiate into precursor B (pre-B) cells that express μ HCs. Pre-B cells then rearrange their Ig light chain (LC) genes to differentiate into IgM^+ immature B cells and then become IgM^+IgD^+ mature, resting B cells. Defects in each stage of the B cell development and maturation pathway can lead to primary immunodeficiencies, autoimmune diseases and even B cell malignancies. In this chapter, we will discuss the mechanism of Ig gene rearrangement, regulation of B-2 (FOB and MZB) cell development, the elimination/inactivation of autoreactive B cells

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(central and peripheral tolerance), regulation of B-1 cell development, fate decision of B-1a vs. B-1b subsets, and the function of B-1 cells.

1.2 Immunoglobulin (Ig) Gene Rearrangement

Antigen receptor gene rearrangement, which is a defining feature of the adaptive immune system, is a unique mechanism to generate diversity in both T and B cells from limited numbers of variable (V) gene segments through genetic recombination. We will focus here on Ig gene rearrangement, which occurs during the early stages of B cell development to generate a diverse repertoire of antibodies.

1.2.1 Structure of Ig Genes

The genome structure of the mouse Ig heavy (H) and light (L) [kappa (*Igκ*) and lambda (*Igλ*)] loci is shown in Fig. 1.1. An antibody is composed of two identical HCs and two identical LCs (either κ or λ), consisting of variable (V) and constant (C) regions linked by disulfide bonds. *Igh*, *Igκ* and *Igλ* genes in mice are located on chromosomes 12, 6 and 16 and in humans on chromosomes 14, 2 and 22, respectively. The V exons of the Ig heavy chains are generated by somatic recombination (rearrangement) of variable (V), diversity (D) and joining (J) gene segments, whereas the V exons of the Ig light chains are generated by rearrangement of V and J but no D segments. During the early stages of B cell development, somatic recombination, known as V(D)J recombination, mediates a physical and permanent juxtaposition of the Ig gene segments at the DNA level that results in a mature V exon and generation of a functional μ HC gene. V(D)J recombination gives rise to a large, diverse repertoire of Ig proteins. In mice, there are 97 V, 14 D and 4 J segments located in the *Igh* locus, 94–96 V and 4 J segments located in the *Igκ* locus, and 3 (laboratory mice) or 8 (wild mice) V and 3 J segments located in the *Igλ* locus.

Downstream of these rearranging gene segments are exons to encode the constant (C) regions of the antibody heavy and light chains. The C exons are not formed by the rearrangement of smaller gene segments and in the *Igh* locus encode several antibody classes and subclasses. Although the *Igκ* locus contains a single C_κ exon, the mouse *Igλ* locus contains four C_λ exons. Moreover, the *Igh* locus contains eight C_H exons, namely Cμ, Cδ, Cγ3, Cγ1, Cγ2b, Cγ2a (BALB/c)/Cγ2c (C57BL/6), Cε and Cα. Each C_H exon encodes a particular Ig isotype. For H and L chains, the most V-proximal C exon is joined to the mature V exon at the RNA level by conventional splicing, which is then translated to generate the H or L protein.

Because of this specific gene structure and mechanism, B cells can generate about 10^{11} different BCR or antibodies by V(D)J

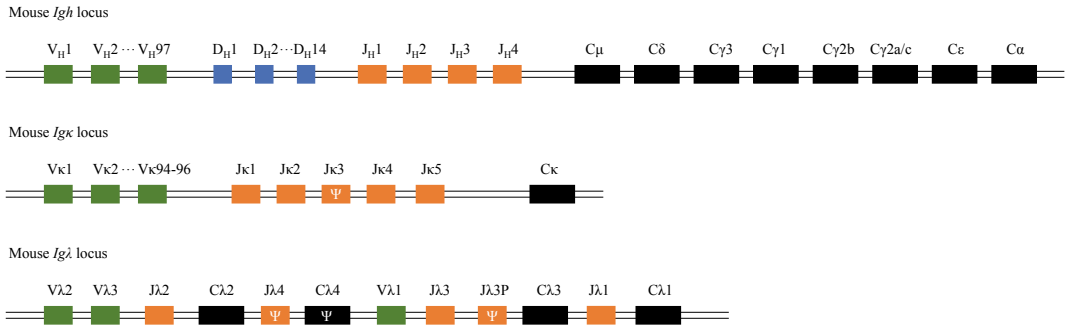

Fig. 1.1 Immunoglobulin loci of mouse (*Notes* The organization of mouse *Igh* locus, *Igκ* locus and *Igλ* locus. Ψ, pseudogene. Not all gene segments and pseudogenes are shown)

recombination (Nussenzweig and Alt 2004). Ig V genes also undergo somatic hypermutation during the germinal center reaction, which further increases the diversity and can change the affinity and sometimes the specificity of antibodies. Such a vast number of different antibodies, the "repertoire," are essential for neutralizing a universe of pathogenic bacteria and viruses.

1.2.2 The Mechanism of V(D)J Recombination

V(D)J recombination can be divided into two processes, i.e., DNA cleavage and DNA repair. The DNA cleavage is a site-specific reaction initiated by the lymphoid-specific proteins recombination-activating gene (RAG) 1 and RAG2 and the ubiquitously expressed DNA-binding protein high-mobility group box protein 1 or 2 (HMGB1 or HMGB2) (van Gent et al. 1997). These proteins bind to the recombination signal sequences (RSSs) that flank each gene segment and introduce a double-strand break (DSB) between the RSS and the flanking coding DNA. Then, joining of the DSB is mediated by the non-homologous end-joining (NHEJ) DNA repair pathway (reviewed by Lieber 2010; Chang et al. 2017).

RSSs flank germ line V_H segments on their 3′ sides, J_H segments on their 5′ sides and D_H segments on both sides. Similarly, the V_L and J_L segments of both the *Igκ* and *Igλ* loci are flanked by RSSs on their 3′ sides and 5′ sides, respectively. The RSS is a short DNA sequence containing a conserved heptamer (consensus sequence 5′-CACAGTG-3′) and nonamer (consensus sequence 5′-ACAAAAACC-3′) separated by either 12 or 23 base pairs (±1 bp), namely the 12 RSSs and 23 RSSs, respectively (Ramsden et al. 1994). The first three positions in the heptamer are the most conserved and are necessary for guiding the RAGs to the correct site of cleavage at the border between the heptamer and the coding segment. Similarly, the tract of adenines is the most invariant portion of the nonamer and is known to guide RAG1 binding at the RSS (Yin et al. 2009). While the sequence of the spacer is less well conserved, the length of the spacer is important as the 12 and 23 RSSs differ by one turn of the DNA helix, placing the heptamers and nonamers of the two RSSs in the same rotational phase and ensuring mutually complementary binding (Ciubotaru et al. 2015). Therefore, only when one gene segment is flanked on one side by a 12 RSSs and the other gene segment is flanked by a 23 RSSs can the pair interact and be recognized by the RAG complex and undergo V(D)J recombination. Such a mechanism has been called the 12/23 rule. The V(D)J recombinases first assemble on a single 12 or 23 RSSs, creating a signal complex (SC) in which nicking can occur (Fig. 1.2). Synapsis with a partner leads to the formation of the paired complex (PC) in which cleavage can occur. Several lines of evidence suggest that the PC is formed by the "capture model," in which one SC captures the appropriate partner RSS to form the PC, maintaining the same protein content in both the SC and the PC (Curry et al. 2005; Jones and Gellert 2002; Mundy et al. 2002; Swanson 2002). However, the capture model is not universally accepted. Some studies support the "association mode," in which two preformed SCs associate to form the PC (Shlyakhtenko et al. 2009; Landree et al. 2001). Under physiological conditions, the DSB is generated only by "coupled cleavage" in the PC. In a two-step transesterification reaction of "coupled cleavage," the free 3′ hydroxyl attacks the phosphate on the bottom strand of the DNA directly (McBlane et al. 1995). Then, hairpin formation in the PC generates two DNA DSBs and yields a pair of blunt DNA ends and two sealed DNA hairpins, all of which are held together by the RAGs (Hiom and Gellert 1998). Both the blunt ends, termed the signal ends, and the DNA hairpins, termed coding ends, are then handed over to the NHEJ DNA repair pathway. After repair, the blunt ends are joined to form the discarded product, a DNA deletion circle. Once opened, the hairpin ends are processed and ligated, yielding the coding joint that contains the newly joined antigen receptor gene segments. In the *Igh* locus, the recombination of D_H and J_H segments occurs first, and then the D_HJ_H recombines with V_H segment to form the complete $V_HD_HJ_H$ exon. In both the *Igκ* and *Igλ* loci, there is only one

recombination step between a V_L and a J_L gene segment. Importantly, the fusion of V, D and J segments is not always precise, which leads to junctional diversity at the site of rearrangement, including the deletion of nucleotides in the joint region and the addition of the so-called P- or N-nucleotides. In the last steps of V(D)J recombination, if the DNA ends of the rearranging gene segments are digested by an exonuclease prior to ligation, there will be deletion of a few nucleotides in the D to J and/or V to D junctions. If the hairpin is not opened symmetrically, a single-stranded extension is created, resulting in palindromic insertions (P-nucleotides). Extra nucleotides can also be created by the terminal dideoxynucleotidyl transferase (TdT), which can randomly add "non-templated" N-nucleotides onto the ends of these strands before their final ligation. N-nucleotide addition occurs almost exclusively in the *Igh* locus because TdT is preferentially expressed in pro-B cells undergoing VDJ_H rearrangement. Although this imprecision can introduce diversity in the CDR3 regions of the antibody heavy and light chains, it can also lead to frameshift mutations if deleted or added nucleotides are not in multiples of three (one codon). As a result, 2/3 V(D)J rearrangements are non-functional, aka nonproductive.

The rearrangement of the Ig loci occurs at particular developmental stages in a temporally ordered and allele-exclusive manner. The *Igh* locus is rearranged first, followed by *Igκ* and *Igλ*. After a productive VDJ_H rearrangement is completed on chromosome 12 in a developing mouse B cell, the now functional VDJ-Cμ gene is transcribed and translated. Expression of this μ chain marks an important checkpoint in Ig gene rearrangement and B cell development. Any further V(D)J recombination in the *Igh* locus on the other chromosome 12 is blocked. This outcome is called allelic exclusion, because only one chromosome contributes the H chain gene product (Schatz and Ji 2011; Vettermann and Schlissel 2010). Similarly, only one of the L chain genes, κ or λ, is expressed during normal B cell

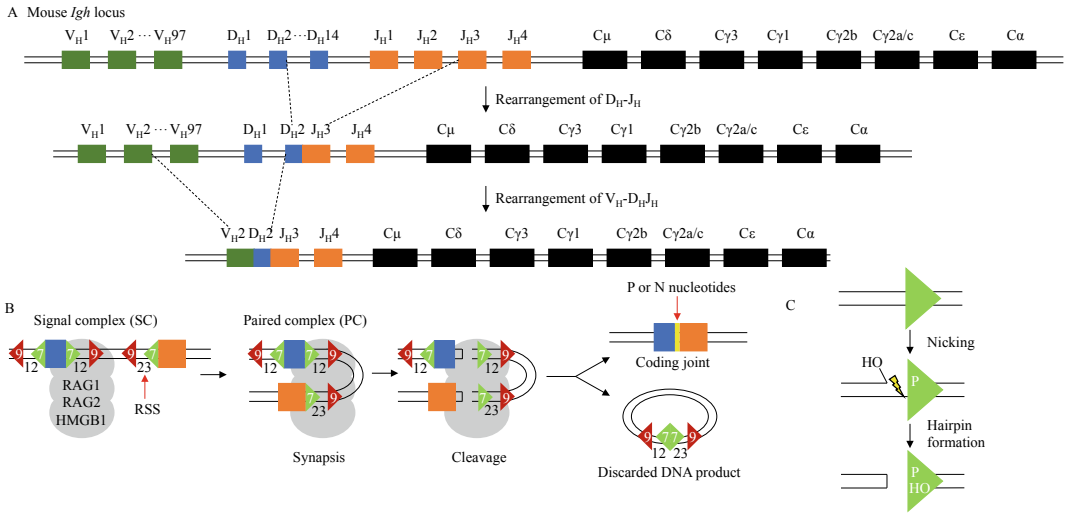

Fig. 1.2 Schematic representation of V(D)J recombination in the mouse *lgh* locus. **a**. In this hypothetical example, D_H2 has joined to J_H3, and then V_H2 has joined to D_H2J_H3. **b**. A single recombination signal sequence (RSS) can be recognized by a RAG1/RAG2/HMGB1 complex and form a signal complex (SC), which then captures another RSS to form the paired complex (PC). Nicking can occur in the SC or PC, but hairpin formation can occur only in the context of the PC. After cleavage, hairpin coding ends and blunt signal ends are processed by the non-homologous end-joining pathway, creating an imperfectly joined coding joint (imperfect joining contains P- or N-nucleotides indicated by the yellow section between coding gene segments) and a discarded DNA product. **c**. Two steps of RAG-mediated DNA cleavage including nicking and hairpin formation. The triangle depicts RSS, and the flanking coding gene segment is omitted for clarity. HO, hydroxyl group

development. (Some exceptional situations will be discussed in the section on B cell central tolerance.)

1.2.3 B Cell Receptor Expression and Tonic Signaling

After $V_HD_HJ_H$ recombination of the *Igh* locus is successfully completed, an intact μ HC protein can be synthesized. Such a free μ HC would usually be retained in the endoplasmic reticulum (ER) as part of the ER quality control system. However, the μ HC in pre-B cells can be expressed at low levels on the cell surface because it associates with a surrogate light chain (SLC), which is composed of two proteins, VpreB and λ5. Two μ HCs and two SLCs plus the Igα/Igβ signaling heterodimer form the pre-BCR, which is expressed transiently to test the functionality of this particular $V_HD_HJ_H$-Cμ combination. The pre-BCR triggers an intracellular signal to inform the cell that the μ HC protein is successfully expressed and associated with the SLCs. If the Ig HC gene rearrangement is unsuccessful or the μ HC fails to associate with the SLC, $V_HD_HJ_H$ recombination will ensue on the other *Igh* allele. This newly generated μ HC protein undergoes the same process of quality testing through the pre-BCR. Failure of Ig HC rearrangement on both chromosomes occurs in about half of the pre-B cells, which will be eliminated by apoptotic death. If the pre-B cell generates a functional pre-BCR, it will promote proliferation and *Igκ* or *Igλ* rearrangement; typically, the *Igκ* locus rearranges first. Only B cells with fully functional H and L chains can survive to become immature B cells. A BCR complex on the B cell surface, which contains two functional H and L chains plus the Igα/Igβ signaling heterodimer, delivers an intracellular signal that terminates all Ig locus rearrangements and mediates central tolerance at the same time. Moreover, both pre-BCR and mature BCR can also generate low-level tonic survival signals through a ligand-independent pathway, termed tonic (pre-)BCR signaling, to support (pre-)B cell survival and further development. Furthermore, the tonic (pre-)BCR signal also plays an important role in B cell carcinogenesis. However, the mechanisms for the initiation of tonic (pre-)BCR signaling are still not fully understood. Based on the existing data, three models have been suggested, namely the homotypic pre-BCR-binding model, lipid raft compartmentalization model and equilibrium model (reviewed in Monroe 2004).

1.3 B-2 Cell Development and Maturation

The majority of B-2 cells originate from the multipotent hematopoietic stem cells (HSCs) in the BM; therefore, the BM microenvironment has a major influence on their development. When an immature B cell starts migrating into the periphery via the bloodstream, it first becomes a transitional B cell and finally differentiates into a FOB or MZB. Only a fraction of BM transitional B cells differentiate into B-1 cells.

1.3.1 BM Microenvironment

BM stromal cells create distinct microenvironments, known as niches, which provide support for self-renewal and differentiation of HSCs into mature blood cells. Although B cell development is known to occur in the niches, their functional organization remains unclear. Some important environmental factors supplied by the cellular niches maintain B cell development.

The adult BM niches contain several cell types associated with HSC development. Osteoblasts generate bone and control the differentiation of HSCs, endothelial cells line the blood vessels and also regulate HSC differentiation, reticular cells mediate processes connecting cells to bone and blood vessels, and sympathetic neurons control the release of hematopoietic cells from the BM. The BM is densely packed with stromal cells and hematopoietic cells of every BM lineage and at every stage of differentiation. With age, however, fat cells gradually replace

50% or more of the BM compartment, and the efficiency of hematopoiesis decreases. The lineage choices that an HSC makes depend largely on the environmental signals it receives. Several microenvironmental components that act on B cell precursors have been identified. CXC chemokine ligand 12 (CXCL12), FLT3 ligand (FLT3L), interleukin-7 (IL-7), stem cell factor (SCF) and receptor activator of nuclear factor-κB ligand (RANKL) have each been shown to be essential for B cell development in vivo.

The main physiological receptor for CXCL12 is CXC chemokine receptor 4 (CXCR4). The CXCL12–CXCR4 axis is essential for the earliest stages of B cell development in the fetus and adult (Nagasawa 2006; Nagasawa et al. 1996; Tokoyoda et al. 2004). FLT3L is a ligand for FTL3, which is essential for the development of pre-pro-B cells (Sitnicka et al. 2002; Sitnicka et al. 2003; Hunte et al. 1996). The receptor for IL-7 is comprised of two chains: IL-7Rα and the cytokine receptor common γ-chain. IL-7 can induce the expression of MCL1 to mediate the survival of B cell precursors (Opferman et al. 2003). IL-7Rα has been shown to deliver a signal that specifically induces VDJ recombination at the *Igh* locus (Corcoran et al. 1998). SCF is a ligand for the class III receptor tyrosine kinase KIT and is encoded by a gene that maps to the steel locus of mice. Cells expressing membrane-bound SCF might function as a niche for pro-B and pre-B cells (Driessen et al. 2003). The transmembrane protein RANKL is a tumor necrosis factor (TNF) family member that is essential for the development of osteoclasts and for bone remodeling. The receptor for RANKL is RANK, which belongs to TNF receptor (TNFR) family and is expressed by DCs, T cells and osteoclast precursors. RANKL expression by lymphoid cells is important for the development of pre-B cells and immature B cells (Kong et al. 1999; Anderson et al. 1997).

It is worth noting that most of the preceding information about the BM microenvironment is derived from studies done in mice. Although its general features are likely also true for humans, the requirements for B cell development are not completely identical in the two species. For example, IL-7 is essential for both T and B cell developments in mice, but only for T cell development in humans (Prieyl and LeBien 1996).

1.3.2 Stages of B Cell Development and Important Transcription Factors

The major stages of B cell development in the BM include the HSC, the multipotent progenitor (MPP), the common lymphoid progenitor (CLP), and then the progenitor B cell (pro-B cell), the precursor B cell (pre-B cell) and the immature B cell. Hardy et al. have elegantly shown that B cell developmental stages can be divided into fractions A, B, C, C′, D and E. Ig gene

Cell stage		Status of Ig genes	Surface Ig	AA4.1	B220	CD43	HSA	BP-1	C-Kit	IL-7Ra	CD19	CD25
Pre-pro B	Fraction A	Germ line arrangement	None	+	+	+	+	-	+	+	-	-
Early pro B	Fraction B	D_HJ_H	None	+	+	+	++	-	++	++	+	-
Late pro B	Fraction C	Some $V_HD_HJ_H$	None	+	+	+	++	-	++	++	+	-
Large pre B	Fraction C'	$V_HD_HJ_H$	Pre-BCR	+	+	+	+++	+	++	++	+	+
Small pre B	Fraction D	$V_HD_HJ_H$ & V_LJ_L arrangement	Decreased Pre-BCR	+	+	-	+++	+	-	++	+	+
Immature B	Fraction E	$V_HD_HJ_H$ & V_LJ_L	IgM-BCR	+	+	-	+++	-	-	-	+	-
Mature B	Fraction F	$V_HD_HJ_H$ & V_LJ_L	IgM-BCR IgD-BCR	-	+	-	+	-	-	-	+	-

Fig. 1.3 Ig gene rearrangements and expression of marker proteins during B cell development

rearrangement status and the expression of several defining cell surface proteins during these stages of B cell development are shown in Fig. 1.3.

With the expression of the B cell lineage-specific marker B220 (CD45R) and the increased expression of the transcription factor EBF1, the developing cell enters pre-pro-B cell stage or fraction A. EBF1, along with E2A, binds to the *Igh* locus, promoting D_HJ_H recombination. Moreover, EBF1 is also essential for the expression of many B cell-associated proteins, including Igα (CD79a), Igβ (CD79b), and the genes encoding the pre-BCR. Pre-pro-B cells remain in contact with CXCL12-secreting stromal cells in the BM. But, after the successful D_HJ_H recombination, which means the cell enters the early pro-B cell stage or fraction B, the developing cell moves within the BM in search of IL-7-secreting stromal cells. Meanwhile, the expression of PAX5, which is one of the EBF1 transcriptional targets, blocks the expression of non-B lineage genes. In addition, many important B cell genes are turned on at this stage, under the control of PAX5 and other transcription factors. During this stage, one of the defining markers of B lineage cells and an important component of the (pre-)B cell co-receptor, CD19, is expressed. In addition, PAX5 promotes V_H to D_H recombination by contracting the *Igh* locus, bringing the V_H gene segments and the D_HJ_H region into closer proximity. Then, the developing B cell enters the late pro-B cell stage or fraction C and most cells have initiated V_H to D_HJ_H Ig gene segment recombination, which is completed by the onset of the early pre-B cell stage. During the pro-B-cell stage or fractions A-C, Igα and Igβ, which are signaling components of the BCR, begin to be expressed, and the expression of c-Kit enables the cell to receive signals from stem cell factor. However, by the beginning of the pre-B cell stage, the expression of c-Kit is irreversibly turned off.

After successful $V_HD_HJ_H$ recombination, the cell expresses a pre-BCR, which is composed of the rearranged μ heavy chain, complexed with VpreB and λ5 plus Igα and Igβ. The developing B cell enters the large proliferating pre-B cell stage or fraction C′. This is an important checkpoint, and only cells with a productively rearranged heavy chain can be selected into the next stage. The pre-BCR is then lost from the surface, and this signals entry into the small/late pre-B cell stage or fraction D. At this stage, light chain rearrangement is initiated with the re-expression of the *Rag1/2* genes. In the mouse, light chain rearrangement begins on one of the κ chain chromosomes, followed by the other. If neither κ chain rearrangement is successful, rearrangement is then attempted on each of the λ chain chromosomes. At the same time, there is very little expression of TdT and therefore N region addition occurs less frequently in light chains than in heavy chains. After successful light chain gene rearrangement and expression, the integrated IgM receptor (BCR) is expressed on the cell surface, which means the developing B cell enters the immature B cell stage or fraction E.

Throughout B cell development, PU.1 sets the stage for lymphoid and myeloid development, and lineage priming in lymphoid progenitors is mediated by Ikaros. In addition, E2A regulates the chromatin landscape to promote gene expression during B cell development and EBF1 plays an important role as a central coordinator of B cell development, collaborating with FOXO1.

1.3.3 B Cell Central Tolerance

There are three mechanisms of central B cell tolerance, clonal deletion, receptor editing and anergy. If an immature B cell recognizes a self-antigen that is present at high concentration in the BM, its BCRs are cross-linked, delivering a strong signal to the cell. In this case, the B cell may undergo apoptosis, a process called clonal deletion. Alternatively, such a B cell may reactivate RAG1 and RAG2 expression and initiate a new round of V_LJ_L recombination. A Vκ segment upstream of the originally rearranged VκJκ unit is joined to a downstream Jκ. As a result, the former rearranged VκJκ exon in the self-reactive immature B cell is deleted and a new Ig light chain is expressed, thus creating a B cell receptor

with a new, potentially no longer autoreactive, specificity. This process is called receptor editing. If the edited light chain rearrangement is nonproductive, rearrangement may proceed at the other κ locus, and if that is also nonproductive, rearrangements at the λ light chain loci may follow. Finally, if the receptors on the developing B cell recognize self-antigens with low affinity, the cells may become functionally unresponsive or anergic, due to downregulation of BCR expression and BCR signaling. In principle, receptor editing at the *Igh* locus is not possible, since there are no germ line D_H gene segments available for further VDJ rearrangement; all were deleted during the original V→DJ rearrangement step. However, a "cryptic" RSS heptamer is present in many V_H genes and can be used in a process called V_H gene replacement, in which an upstream V_H gene segment recombines with the cryptic heptamer, replacing most of the V region in a preexisting VDJ exon. Whether this process is more important for diversification than for central B cell tolerance is somewhat controversial, since it appears to occur mainly in pre-B cells that have not yet undergone light chain gene rearrangement and thus their antigen specificity has not yet been defined (Kumar et al. 2015; Sun et al. 2015; Kelsoe 2015).

David Nemazee and colleagues generated mice transgenic for both a heavy and a light chain specific for the H-2K^k MHC molecule. In mice with H-2K^d but no H-2K^k MHC molecules, the transgenic BCR was expressed on B cells and a high concentration of transgenic antibody could be measured in the serum. However, in mice with H-2K^k but no H-2K^d MHC molecule, no anti-H-2K^k B cells or secreted antibodies could be detected, suggesting that all immature B cells bearing the potentially autoimmune BCR had been deleted in the BM. Interestingly, in mice with both H-2K^d and H-2K^k MHC, not all B cells bearing the autoimmune transgenes were deleted, and some of them underwent light chain receptor editing and no longer bound the H-2K^k antigen (Nemazee and Bürki 1989; Tiegs et al. 1993).

Goodnow and colleagues developed double-transgenic mice carrying transgenes encoding membrane hen egg white lysozyme (mHEL) driven by a class I MHC promoter and anti-HEL BCR, which mimics the situation of a self-antigen and a corresponding autoreactive BCR. B cells in double-transgenic mice were arrested at the pre-B stage and underwent efficient clonal deletion, with few B cells reaching the periphery (Hartley et al. 1993). However, when the mHEL transgene in double-transgenic mice was replaced by a soluble HEL (sHEL) transgene linked to a metallothionein promoter and sHEL was expressed in the periphery, but not in the BM, the double-transgenic mice were able to generate mature, peripheral B cells bearing the anti-HEL BCR. However, these B cells were functionally nonresponsive, or anergic, a mechanism called B cell peripheral tolerance (Cyster et al. 1994). Based on these results, it appears that in normal animals, not all self-reactive B cells are deleted in the BM. Some are released to the periphery but are inactivated. It has been suggested that such cells could be abnormally reactivated by non-BCR-mediated signals, resulting in their differentiation into plasma cells and resultant antibody-mediated autoimmune diseases.

1.3.4 B-2 Cell Maturation in the Periphery

1.3.4.1 Transitional B Cells

Immature B cells have a short half-life and are ready for export to the peripheral lymphoid organs, usually the spleen, where they complete their developmental program. During B-2 cell maturation in the periphery, transitional B cells play an important role in linking BM immature and peripheral mature B cells. Moreover, transitional B cells express similar defining cell surface markers, such as AA4.1, HSA and IgM, as immature B cells, and are still susceptible to negative selection.

Newly generated immature B cells that have yet to acquire the ability to recirculate throughout the body are known as T1 B cells. They are found in the BM and the periarteriolar lymphoid sheath (PALS) of spleen and are AA4.1$^+$ IgM^{high} IgD$^-$ CD21$^-$ CD23$^-$. After entering spleen

follicles, they acquire cell surface IgD, CD21 and CD23 and the ability to recirculate, but still carry markers of immaturity and are known as T2 B cells. T3 is a third non-proliferating transitional population, which resembles T2 with the exception of a lower level of surface IgM. Recent experiments have suggested that the T3 population may represent B cells that have been rendered anergic by contact with soluble self-antigen but have not yet been eliminated from the B cell repertoire. These transitional B cells can be distinguished by different combinations of surface markers (Allman and Pillai 2008). Studies of the signal transduction pathways in the transitional B cells compared to mature B cells after BCR ligation have identified significant functional differences. T1 and T2 B cells do not proliferate or upregulate the co-stimulatory molecule CD86 in response to BCR stimulation and are susceptible to apoptosis. Thus, the early transitional stages comprise an important peripheral tolerance checkpoint. Despite their muted response to BCR stimulation, gene knockout studies, such as in mice lacking BLNK, PLCγ or BAFF, provide convincing evidence for the importance of intact BCR-mediated signals to drive progression from the transitional B cell stages to the mature B cell stage (Chung et al. 2003).

1.3.4.2 Follicular and Marginal Zone B Cells

The different BCR signaling pathways integrated with BAFFR and Notch2 signaling, as well as signals that mediate their migration and retention, determine the commitment of B cells from the transitional B cell to the mature FOB or MZB cell fate (Pillai and Cariappa 2009; Cerutti et al. 2013). The phenotype and function of FOB and MZB are summarized in Fig. 1.4.

Tonic or even strong BCR signaling, a BAFF survival signal and NF-κB signaling are necessary for the transitional B cell to develop into FOB, which are located in primary follicles and also recirculate via blood and lymphatics into secondary lymphoid organs and back into the BM. FOB tend to have more diversity of Ig V(D)J genes than do MZB. In addition, the main function of FOB is to mediate adaptive Ab production. FOB interact with helper T cells to form germinal centers, undergo class switch recombination (CSR) and somatic hypermutation (SHM) and eventually produce high-affinity antibodies to eliminate pathogens or give rise to memory B cells that function to prevent the reinfection with the same pathogen.

Weak BCR signaling (above and beyond tonic signaling), NF-κB signals and Notch2 signaling are important for the transitional B cell to develop into the MZB, which reside in the outer white pulp of the spleen between the marginal sinus and the red pulp. In the spleen, the Notch2 ligand delta-like 1 (DL1), which is present at high concentrations in venules but is not found in the BM, is a key activator accounting for MZB development. In addition, migration and retention of MZB to the follicles are mediated by the sphingosine 1-phosphate receptor (S1PR1) and CXC chemokine ligand 13 (CXCL13). Although MZB cells seem to primarily express nonmutated Ig V(D)J genes, some other cells, such as DCs, macrophages and iNKT cells, can trigger CSR in MZB. Unlike FOB, MZB constitutively express elevated levels of MHC class

Subsets	Surface markers	Location	Functions
Follicular B	$CD19^+$ $B220^+$ IgM^{dull} IgD^{hi} $CD21^{mid}$ $CD23^+$	Recirculating cell, which can be found in spleen, lymph node and bone marrow and other tissues	1. Main component of the T cell-dependent B cell adaptive immune response 2. Give rise to high affinity antibody-producing PC
Marginal zone B	$CD19^+$ $B220^+$ IgM^{hi} IgD^{dull} $CD1d^{hi}$ $CD21^{hi}$ $CD23^-$	Lining outside the marginal sinus and bordering the red pulp	1. Natural Ab secretion 2. T cell-dependent and -independent responses to blood-borne pathogens

Fig. 1.4 Phenotypes and function of follicular B and marginal zone B cells

II and CD80 and CD86 molecules and display a robust antigen-presenting activity, which is required for the activation of T follicular helper (TFH) cells. Moreover, MZB can also rapidly respond to blood-borne antigens and differentiate into short-lived plasmablasts that produce large amounts of IgM. Therefore, the MZB is considered as a gatekeeper to perform surveillance between the conventional boundaries of innate and adaptive immunity.

1.3.5 B Cell Peripheral Tolerance

In peripheral tissues, mature B lymphocytes that recognize self-antigens in the absence of specific helper T cells may become anergic and/or die by apoptosis. However, most of the mechanisms of peripheral tolerance are reversible because of the potential need for mature B cells to respond to viruses and microorganisms that may carry similar epitopes to self-antigens.

If a self-reactive B cell is repeatedly stimulated by self-antigens, it becomes anergic to further activation. Such cells require high levels of the growth factor BAFF for survival and thus cannot compete efficiently with less BAFF-dependent normal naive B cells for survival in lymphoid follicles. Therefore, these B cells that have encountered self-antigens have a shortened life span and are rapidly eliminated. B cells that bind with high avidity to self-antigens in the periphery may also undergo apoptotic death by the mitochondrial pathway independent of growth factor dependence. The risk of generating peripheral self-reactivity is higher for B cells than T cells because B cells, uniquely, can undergo a high rate of somatic mutation of Ig V genes in germinal centers. These B cells may be actively eliminated via the interaction of Fas on the activated B cells with FasL on helper T cells. Failure of peripheral B cell tolerance may lead to autoimmunity, as observed in Fas- and FasL-deficient mice. On the other hand, B cells that recognize self-antigens with low affinity may be prevented from activation by the engagement of various inhibitory receptors. These inhibitory receptors act to set a threshold for B cell activation, which allows responses to foreign antigens with T cell help or innate immune responses but does not allow responses to self-antigens. This mechanism of peripheral tolerance was revealed by studies showing that mice with defects in the SHP-1 tyrosine phosphatase or the CD22 inhibitory receptor develop autoimmunity. Immunoreceptor tyrosine-based inhibitory motifs (ITIM) in the cytoplasmic tail of CD22 are phosphorylated by LYN, and this inhibitory receptor then recruits SHP-1, thus attenuating B cell receptor signaling. Moreover, foreign antigens systemically administered at high doses also preferentially induce tolerance rather than immune responses (Klinman 1996).

1.4 Development of B-1 Cells

B-1 cells, which are considered to be an innate-like B cell population, have distinct developmental process, unique phenotype, anatomic location, self-renewing capacity and functional characteristics from conventional B-2 cells (Hoffmann et al. 2007; Witt et al. 2003; Berland and Wortis 2002). It has been nearly 40 years since B-1 cells were first identified in mouse spleen in the early 1980s; these cells expressed Ly-1 (now known as CD5), a pan T cell surface glycoprotein (Hayakawa et al. 1983). Later studies found a second subset of B-1 cells, now termed B-1b cells, which did not express CD5 but showed similar phenotypic and histologic features as the $CD5^+$ B-1a cells (Stall et al. 1992; Kantor et al. 1992). B-1 cells mainly reside in pleural and peritoneal cavities, whereas there are few B-1 cells in peripheral lymph nodes (LNs), and the frequency of B-1 cells in spleen is low (Hayakawa et al. 1985; Hardy et al. 1984). We can now use a combination of different cell surface markers to distinguish B-1a and B-1b: $CD5^+$ $CD11b^{+/-}B220^{lo}$ IgM^{hi} IgD^{lo} $CD23^-$ $CD43^+$ for B-1a cells and $CD5^-$ $B220^{lo}$ IgM^{hi} IgD^{lo} $CD23^-$ $CD43^+$ for B-1b cells (reviewed in Prieto and Felippe 2017).

1.4.1 B-1 Cell Developmental Model

B-1 cells function in natural antibody secretion, cytokine production and maintenance of tissue homeostasis, and therefore it is important and essential to understand their development during ontogeny. Yolk sac is the first site of hematopoiesis at day 7 in mouse embryo, while HSCs first emerge in the aorta-gonado-mesonephros (AGM) region at embryonic day 10.5 (Weissman et al. 1977; Moore and Metcalf 1970; Müller et al. 1994; Yoshimoto et al. 2011). HSCs migrate to the fetal liver, where they dramatically expand, and finally they settle in spleen and BM before birth (Morrison et al. 1995; Ikuta and Weissman 1992). It is well known that HSCs in BM are able to differentiate into the common myeloid progenitors (CMPs) and CLPs. The CMPs give rise to neutrophils, basophils, eosinophils, monocyte/macrophages, erythrocytes and myeloid dendritic cells. The CLPs further develop into B lymphocytes, T lymphocytes, innate lymphoid cells and lymphoid dendritic cells (Seita and Weissman 2010; Kondo et al. 1997; Akashi et al. 2000). An increasing number of studies have revealed that there are several waves of hematopoietic cell emergence during embryogenesis including primitive hematopoietic progenitors and HSCs (Yoshimoto 2015). The first wave is termed primitive hematopoiesis, during which red blood cells are produced to provide oxygen for embryonic growth. However, the primitive hematopoietic system is transient and is rapidly replaced upon HSC emergence (Yoshimoto 2015; Orkin and Zon 2008). In essence, the origin of B-1 cells has been a controversy for decades and has centered on two hypotheses regarding their origin and their developmental relationship with B-2 cells: lineage model and selection model.

1.4.2 Lineage Model

In 1989, Herzenberg et al. put forward the lineage model, in which distinct progenitors generate B-2 and B-1 cells, respectively, at different times during development (Herzenberg and Herzenberg 1989). Many experiments support this conjecture. Studies have suggested that an "ontological switch" occurs during B cell development, and a similar process has been described for the development of erythrocytes and γδT cells (Hardy and Hayakawa 1991; Ikuta et al. 1990).

Transfer experiments demonstrated that B cell progenitors in fetal liver were able to give rise to both B-1 and B-2 cells while adult BM transplant failed to repopulate the B-1a cell compartment of lethally irradiated mice (Hayakawa et al. 1985; Ghosn et al. 2012). Similarly, in chimeric mice made by reconstitution with a mix of adult BM and fetal liver, B-1 cells were almost exclusively derived from fetal liver, while B-2 cells were derived from either BM or fetal liver (Herzenberg 2000). Subsequent studies indicated that B-1a progenitors were found mainly in fetal liver, while B-1b progenitors were found principally in adult BM (Kantor et al. 1992; Montecino-Rodriguez et al. 2006; Hardy and Hayakawa 1991). Moreover, in B cell depletion chimeras, endogenous progenitor cells were able to develop into B-2 cells but only a small number of B-1 cells (mainly B-1b) (Hamilton and Kearney 1994; Lalor et al. 1989a, b). Solvason and Godin et al. have shown that embryonic para-aortic splanchnopleura and fetal omentum contained progenitors that could give rise to B-1a and B-1b cells but not conventional B cells (Godin et al. 1993; Solvason et al. 1991, 1992). However, further research made clear that some B-1 progenitor cells originated from primitive B-2 progenitor cells in adult BM (Esplin et al. 2009).

While these results indirectly suggested the independent origin of B-1 and B-2 cells, the most direct evidence supporting the lineage hypothesis was the discovery of B-1 cell precursors. In 2006, abundant B-1 B cell progenitors phenotypically distinct from progenitors for B-2 cells were identified in fetal BM. These Lin^{-} $CD45R^{lo-neg}$ $CD19^{+}$ cells emerged during the late stage of embryonic development (Montecino-Rodriguez et al. 2006). Further study demonstrated that B-1a precursors with the

phenotype $CD5^+$ $CD45R^{lo}$ IgM^{hi} were found at day 8.5–9.0 in the mouse embryo, but not B-1b or B-2 cell precursors (Godin et al. 1993).

Additional evidence supporting the lineage model is that B-1 cells display much more limited diversity than B-2 cells. In contrast to B-2 cells, Ig repertoires of B-1 cells tend to be more restricted and autoreactive (Tornberg and Holmberg 1995). Studies showed that B-1 cells preferred to use certain V(D)J genes in their Igs (Mercolino et al. 1989; Kantor et al. 1997). About 50% of B-1 cells derived from fetal liver progenitors had no N-nucleotide insertions at either the D_H or J_H junction because of low expression of TdT, whereas N-nucleotide insertions increased in B-1a and B-1b cells derived from B cell progenitors in adult BM (Holodick et al. 2014; Prieto and Felippe 2017). The biological consequences of these differences in N addition were shown in studies where TdT expression in fetal liver was forced by transgenesis. Compared to WT mice, the TdT transgenic mice with more N-nucleotide insertions in fetal B cells were more sensitive to pneumococcal infection (Benedict and Kearney 1999). This study indicated that B-1 cells with lower Ig diversity in fetal life are essential for the normal adult immune response to infection.

1.4.3 Selection Model

Unlike the lineage model, which postulates that B-1 cells and B-2 cells are derived from distinct progenitors, the selection model proposes that all B cells originate from the same progenitor cells but that the antigen specificity of the B cell receptor determines the B cell differentiation fate (Baumgarth 2011; Ratcliffe 2016).

It is well known that the Ig repertoires of B-1 and B-2 cells are clearly different (Lalor and Morahan 1990). B-1a cells are known to produce autoantibodies, such as antibodies against single-stranded DNA, Thy-1, red blood cells, oxidized lipids including phosphatidyl choline (PtC) and rheumatoid factor, whereas such autoantibodies are rarely produced by B-2 cells (Casali et al. 1987; Hardy et al. 1987; Mercolino et al. 1988). These lines of evidence suggest that autoantigens might be the major driving force for repertoire selection of B-1 cells. In addition, B-1 cells that specifically recognize PtC account for a large proportion of B-1 cells in the peritoneal cavity of adult mice (Mercolino et al. 1986, 1988; Arnold and Haughton 1992). Further studies showed that these cells utilize a restricted set of Ig variable genes (in C57BL/6 mice, B-1 cells mainly use V_H12 paired with $V_\kappa4$ or V_H11 with $V_\kappa9$) (Mercolino et al. 1988; Arnold and Haughton 1992; Hardy et al. 1989; Arnold et al. 1994). Moreover, Hayakawa et al. showed that there were no Thy-1-specific B-1 cells or anti-Thy-1 antibodies in Thy-1 knockout mice (Hayakawa et al. 1999, 2003). These observations provided very strong evidence that B-1 cells were selected for self-reactivity.

As discussed above, the strength of the BCR signal can affect the development of B-1 cells. The number of B-1 cells is significantly reduced in mice with impaired BCR signaling. On the other hand, mutations of negative regulators such as CD22 or CD72, which lead to increased BCR signaling, in general promote B-1 cell development and inhibit the development of B-2 cells (reviewed in Berland and Wortis 2002).

Mice transgenic for B-1-derived BCR (V_H12 alone or in combination with Vκ4) developed mostly B-1 cells, which is consistent with the hypothesis that BCR specificity plays an important role in the development of B-1 cells (Arnold et al. 1994). In addition, Lam and Rajewsky reported that BCR specificity and surface density influenced differentiation into these subsets (Lam and Rajewsky 1999). Very recently, by using an inducible mouse model, Graf et al. were able to change BCR specificity in transgenic mice in vivo and elegantly demonstrated that B-2 cells were able to differentiate into B-1 cells upon switching of their BCR to one typical of a self-reactive BCR from B-1 cells (Graf et al. 2019). These induced B-1 cells not only expressed typical surface markers but also obtained the

functional characteristics of B-1 cells. However, in their system, B-1 cells could scarcely be transformed into B-2 cells. These results provide concrete evidence that BCR specificity determines the B-1 versus B-2 cell lineage choice.

1.4.4 Two-Pathway Model

Despite accumulating evidence, the origin and development of B-1 cells are still controversial. Studies have shown that there is feedback inhibition of B-1 development. Peripheral B-1 cell pools are generated during late embryonic life and a few weeks after birth, then they are maintained by self-renewal, and further de novo B-1 cell development is inhibited (reviewed in Berland and Wortis 2002, Herzenberg 2000). Furthermore, recent studies revealed that Lin28b is a master regulator of B-1 cell development in fetal but not in adult hematopoiesis. Lin28b, first identified in *Caenorhabditis elegans*, acts to block the maturation of let-7 family microRNAs and the emergence of their active forms (Shyh-Chang and Daley 2013). The data in mice showed that in neonates Lin28b functioned to promote positive selection of self-reactive B-1 cells, similarly in adult mice that overexpress Lin28b (Chung et al. 2012; Poe et al. 2012; Benhamou et al. 2016; Vanhee et al. 2019). BM stem cells overexpressing Lin28b were able to give rise to B-1a cells, but their BCR repertoire was different from that found in conventional B-1a cells (Yuan et al. 2012; Zhou et al. 2015). These results suggested that the reciprocal expression of Lin28b and let-7 (the Lin28b levels are high in fetal and low in adult HSCs) controls the timing of developmental events. Recent studies proposed that the lineage model and selection model both occur to ensure the generation and maintenance of B-1 cells throughout life (Hardy and Hayakawa 2015; Baumgarth 2011). Revealing the origin of B-1 cells is a very interesting area of research that can also help us better understand the role of these cells.

1.4.5 Regulation of B-1a vs B-1b Cell Development

B-1a cells are the main producer of poly-reactive and autoreactive natural IgM antibodies, which are involved in the clearance of apoptotic cells and their nuclear and cytoplasmic components (Jellusova et al. 2010). Failure to eliminate apoptotic cells can lead to autoantibody production (Hanayama et al. 2004). Paradoxically, expansion of B-1a cells was found to be associated with autoimmunity (Duan and Morel 2006; Binder and Silverman 2005). On the other hand, B-1b cells were shown to respond specifically to T-independent antigens. Adoptive transfer experiments showed that B-1b cells mediated long-lasting IgM memory to infection (Cunningham et al. 2014). Both peritoneal B-1a and B-1b cells are important for host defense against pathogens that enter the peritoneum through the gut epithelium (Roy et al. 2013). Despite the functional differences between B-1a and B-1b cells, little is known about the developmental relationship between these two subsets. Hoffmann et al. have demonstrated that Siglec-G is a B-1 cell inhibitory receptor that controls expansion of the B-1a cells (Hoffmann et al. 2007). We have recently found that Kelch-like 14 (KLHL14) promotes B-1a development in mice (Li et al. 2018).

A model has been proposed for the regulation of B-1a and B-1b development (Hardy 2006). In this model, the B-1 progenitor may develop into either a B-1a or a B-1b cell, depending on the strength of BCR signal triggered by self-antigen. B-1 precursors expressing BCR that bind to self-antigen strongly and thus trigger strong BCR signals become B-1a cells, whereas B-1 precursors expressing BCR that bind to self-antigen with intermediate strength develop into B-1b cells. In support of this model, mice overexpressing CD19 generated primarily B-1a cells whereas CD19-deficient mice generated mainly B-1b cells (Haas et al. 2005). In addition, mice lacking NCK, an adaptor protein that recruits

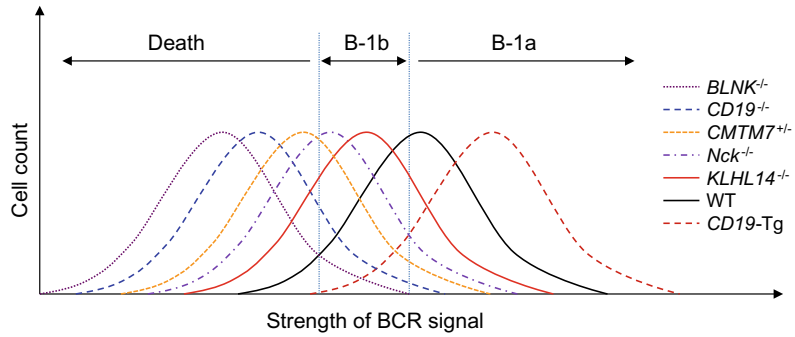

Fig. 1.5 Relationship between the strength of BCR signaling and the development of B-1a and B-1b cells. The graph is based on a previously suggested model for B-1a/B-1b development (Hardy 2006), along with the results of mice deficient for or overexpressing CD19 (Haas et al. 2005), mice deficient for BLNK (Pappu et al. 1999) or NCK (Castello et al. 2013), mice heterozygous for CMTM7 (Zhang et al. 2014) and *KLHL14*$^{-/-}$ mice (Li et al. 2018). *Source* Adapted from Li et al. (2018)

BCAP to the BCR, or mice heterozygous for CMTM7, had reduced B-1a but increased B-1b cells (Castello et al. 2013; Zhang et al. 2014; Liu et al. 2019). Furthermore, mice lacking the B cell linker protein (BLNK) had a severe reduction of both B-1a and B-1b cells (Pappu et al. 1999), suggesting that very weak BCR signal inhibits the development of both B-1a and B-1b cells. Figure 1.5 illustrates the relationship between the strength of BCR signaling and the development of B-1a and B-1b cells (Li et al. 2018).

1.4.6 The Functions of B-1 Cells

1.4.6.1 Natural Antibody Secretion

Antibodies that spontaneously appear without any external antigenic stimulation, such as in antigen-free mice, are referred to as natural antibodies (Tlaskalová-Hogenová et al. 1992; Coutinho et al. 1995). B-1 cells are able to produce natural antibodies, mainly IgM, IgA and IgG3. Actually, B-1 cells produce about 80% of natural IgM, which forms a pentamer and has low affinity but high poly-reactivity and complement activation ability. Several studies revealed that sIgM$^{-/-}$mice (mice that lack secretory IgM) were more sensitive to pathogen infection (Baumgarth et al. 2000; Boes et al. 1998b; Subramaniam et al. 2010). These results demonstrated that IgM, as the first and crucial barrier, plays an important role in protection against pathogen invasion prior to the establishment of adaptive responses (Fearon and Locksley 1996; Baumgarth et al. 1999). Moreover, sIgM$^{-/-}$mice were reported to have low levels of B-2-dependent IgG responses to antigens, consistent with the results reported in FcμR knockout mice (Baumgarth et al. 2000; Boes et al. 1998a; Ouchida et al. 2012). These data suggested that an IgM-FcμR signal might participate in enhancing IgG responses. B-1 cells could be induced to undergo CSR in vitro, preferentially generating IgA and Ig subclasses (Kaminski and Stavnezer 2006; Tarlinton et al. 1995). Natural poly-reactive IgA is abundant in the intestinal mucosa, where it acts to maintain a homeostatic environment between host and microbiota (Smith and Baumgarth 2019). Until now, we know less about the function of natural IgG3, although one study showed that it was able to protect individuals from *P. aeruginosa* infection (Panda et al. 2013).

1.4.6.2 Pathogen Defense

We are surrounded by a variety of pathogens including bacteria, viruses, fungi and parasites. As discussed in 1.4.6.1, B-1 cells are capable of secreting natural antibodies to protect from infection. Upon pathogen invasion, B-1 cells migrate to the secondary lymphoid tissues and then differentiate into antibody-secreting cells (Choi et al. 2012; Kawahara et al. 2003).

However, B-1 cells might have opposite function. For example, during nematode parasite infection, B-1 cell-derived IgE downregulated the degranulation of mast cells, thereby impeding parasite expulsion, which results in part from smooth muscle contraction induced by mediators contained in the mast cell granules (Martin et al. 2018). B-1 cells may have other functions. Recent studies revealed that B-1 cells were able to secrete several kinds of cytokines. Natural or induced IL-10 produced by B-1 cells contributes to control the extent of inflammation (Mosser and Zhang 2008; Gonzaga et al. 2015), and B-1 cells can secrete IL-3 and GM-CSF, which promote inflammatory responses (Weber et al. 2015). Similar to B-2 cells, B-1 cells have the ability to present antigens. For example, B-1 cells could present OVA peptide to OVA-specific $CD4^+$ T cells in vivo (Margry et al. 2013). Furthermore, B-1a cells can promote $CD4^+$ T cells to differentiate into Th17 cells (Zhong et al. 2007). In conclusion, in addition to their ability to secrete natural antibodies, B-1 cells are able to secrete cytokines, as well as uptake and present antigens to T cells during pathogen invasion (Novaes E Brito et al. 2019; Smith and Baumgarth 2019).

1.4.6.3 Tissue Homeostasis Maintenance and Autoimmunity

During the process of apoptosis, dead cells release self-antigens such as single-stranded DNA, which B-1 cells can recognize via their BCR. Antibodies secreted by the plasma cell progeny of these B-1 cells are thought to promote phagocytosis, leading to the removal of self-antigens (Chen et al. 2009). Several features of B-1 cells are considered anti-inflammatory; e.g., they are a major source of IL-10, which can suppress inflammatory responses, and they can secrete IgA, which does not activate complement. Thus, IgA-mediated immune responses could avoid complement-mediated tissue damage in the intestinal mucosa (Smith and Baumgarth 2019). B-1 cells and the IgM antibodies they produce play an important role in immune homeostasis. Compared to control mice, lpr mice without secreted IgM showed elevated levels of IgG autoantibodies and severe symptoms of glomerulonephritis along with increased mortality rates (Boes et al. 2000). In contrast, B-1 cells may instead contribute to the development of autoimmune diseases. Following studies indicating that B-1 cells accumulated in the thymus during the developmental of lupus nephritis, Sato and colleagues speculated that these autoreactive B-1 cells, which expressed high levels of co-stimulatory molecules, activate cognate autoreactive T cells, resulting in the production of autoantibodies (Sato et al. 2004). Moreover, studies found that the number of B-1 cells is increased in patients with Sjogren's syndrome and rheumatoid arthritis (Dauphinée et al. 1988; Youinou et al. 1990). Together, these observations suggest a link between B-1 cells and the development of autoimmune diseases.

1.4.7 Human B-1 Cells

Following the discovery of mouse B-1 cells, several studies also found $CD5^+$ B cells in rheumatoid arthritis patients (Casali et al. 1987; Hardy et al. 1987). However, researchers suspected that CD5 cannot be used as a marker to identify human B-1 cells for two major reasons: (1) CD5 can be detected on almost all types of human B cells from immature to memory B cell, especially on activated, transitional and pre-naive B cells (Lee et al. 2009; Sims et al. 2005; Freedman et al. 1989); (2) it was found that $CD5^-$ human B cells could produce natural antibodies like $CD5^+$ cells (Kasaian et al. 1992). Subsequently, Griffin et al. identified a population of B cells in human umbilical cord and peripheral blood with a phenotype of $CD20^+$ $CD27^+$ $CD43^+$ $CD70^-$, which had similar characteristics and functions to mouse B-1 cells (Griffin et al. 2011). However, there are some differences between human and mouse B-1 cells. For example, antibodies produced by human B-1 cells had N-nucleotide insertions and substantial somatic mutations (Rothstein and Quach 2015). There are studies showing that human B-1 cells might develop from Lin^- $CD34^+$ $CD38^{lo}$ stem

cells (Quách et al. 2016). However, the origin and tissue distribution of human B-1 cells are not fully understood.

1.5 Conclusion

Although there has been tremendous progress in our understanding of B cell development, maturation and function, many questions still remain to be answered. It is not fully understood how the function of different B cell subsets, including FOB, MZB, B-1a and B-1b cells, is regulated and coordinated during bacterial and viral infections. It is also less clear what B cell subsets contribute to the production of IgA in the gut. An additional intriguing issue is that impaired B cell development not only results in reduced B cell numbers and immunodeficiencies, but frequently causes autoantibody production. Furthermore, less is known about the regulation of human B cell development and maturation. Further studies are needed to fully understand the regulatory mechanisms of B cell development and function in mice and humans.

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