



Review

B Cell Development and Primary Immunodeficiencies with Hypogammaglobulinemia

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Abstract. The differentiation of B cells along the pathway of B cell development has been well characterized. In the bone marrow, the differentiation from pro-B cells to immature B cells can be defined by several surface antigens, such as a surrogate light chain. Immature B cells become mature B cells and then circulate in the peripheral blood as naive B cells. In the peripheral lymphoid tissues, naive B cells differentiate into memory B cells, which express the CD27 molecule, or plasma cells. Primary immunodeficiencies with hypogammaglobulinemia are caused by defects of the specific molecules which are needed for the B cell differentiation. Recent studies of the genes responsible for such immunodeficiencies have clarified B cell development as well as their pathogenesis. We discuss here the molecules affecting the B cell development and primary immunodeficiencies with hypogammaglobulinemia.

Key words: B cell development; primary immunodeficiency; hypogammaglobulinemia; CD27; memory B cells.

Introduction

The developmental pathway of early B cells has been well investigated in humans and mice^{8, 14, 18}. Discrete subpopulations of B lineage committed cells can easily be identified based on the expression of several molecules on the cell membrane and within the cytoplasm and on the status of immunoglobulin (Ig) rearrangement. In the bone marrow, stem cells differentiate into pro-B cells, pre-B cells and immature B cells. In the peripheral blood (PB), naive B cells differentiate into memory B cells or plasma cells.

Analyses of the genes responsible for primary immunodeficiencies have served in understanding the

B cell development in humans. Recently, several genes responsible for primary immunodeficiencies with hypogammaglobulinemia were identified. Patients with mutations in the $\lambda 5$ and μ chains were found to have normal numbers of pro-B cells and few pre-B cells^{15, 22}. In addition, the arrest of the B cell development in an early stage was suggested in X-linked agammaglobulinemia (XLA)⁵.

Various B cell subsets have been identified in the PB, spleen and tonsils, and are believed to represent cells at different stages of development from naive B cells to memory B cells. On the basis of research recently accumulated, it has been demonstrated that CD27 antigen represents a key marker for memory

Abbreviations used: Ig – immunoglobulin; PB – peripheral blood; XLA – X-linked agammaglobulinemia; XHIM – X-linked hyper-IgM syndrome; SL – surrogate light chain; TdT – deoxynucleotidyl transferase; cH μ – cytoplasmic μ heavy chain; pre-BCR – pre-B cell receptor; V – variable; Btk – Bruton's tyrosine kinase; B⁻SCID – B cell negative severe combined immunodeficiency; CVID – common variable immunodeficiency.

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B cells³. X-linked hyper-IgM syndrome (XHIM) has been shown to result from mutations in the CD40 ligand (CD154) gene. CD40/CD154 interactions may promote the differentiation into memory B cells in germinal centers⁴. We have demonstrated that a CD27⁺ B cell population, memory B cells, is absent in patients with XHIM². We discuss here the molecules affecting B cell development and primary immunodeficiency with hypogammaglobulinemia.

B Cell Development

In the bone marrow, hematopoietic stem cells differentiate into pro-B cells, already committed to the B cell lineage. Pro-B cells coexpress CD19, CD10, CD34 and surrogate light chain (SL), which is composed of VpreB and $\lambda 5$, on their surface and terminal deoxynucleotidyl transferase (TdT), but not cytoplasmic μ heavy chain (c μ), within the cytoplasm (Fig. 1).

Pro-B cells differentiate into more mature forms of B cell lineage cells, large pre-B cells, and these down-regulate the expression of TdT and CD34, but do express high levels of c μ . At this stage, B cells carry

a productive VDJ rearrangement at least in one allele. SL is important for pro-B cells to differentiate into pre-B cells. Soon after a productive VDJ rearrangement has occurred, SL forms a so-called pre-B cell receptor (pre-BCR). Pre-BCR is involved in the selection and expansion of large pre-B cells. Large pre-B cells differentiate into small pre-B cells which do not express SL on the surface. Light chain VJ rearrangements are detectable in small pre-B cells. Immature B cells are characterized by the appearance of surface IgM in the absence of IgD.

When IgD receptors are expressed on the surface, immature B cells become mature B cells and down-regulate the expression of CD10. After they succeed in generating a functional antigen receptor, they are released into the B cell pool as naive B cells. The differentiation of naive B cells into memory B cells occurs within germinal centers in secondary lymphoid organs, where activated naive B cells undergo vigorous proliferation, somatic hypermutation of Ig variable (V) region genes, isotype switching, interaction with antigens, antigen-driven selection, and differentiation into memory B cells and plasma cells^{10, 13}.

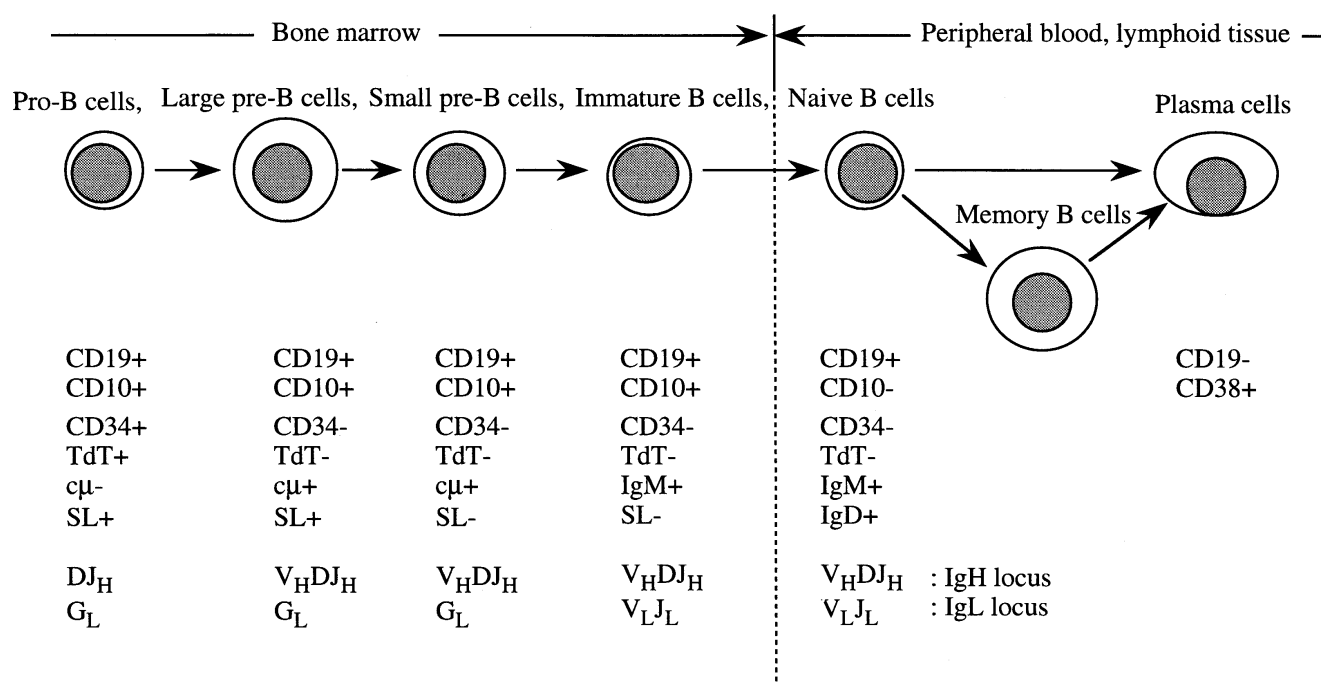


Fig. 1. B cell development expression of molecules on the surface and inside the cytoplasm and gene rearrangement of IgH and IgL loci. CD19 is expressed on the surface of all B cell lineage cells except plasma cells. CD10 is expressed on pro-B to immature B cells. CD34 and TdT are only expressed on pro-B cells. C μ appears from large pre-B cells and when IgM is expressed on the surface, pre-B cells become immature B cells. Expression of SL is found at pro-B and large pre-B cells. V_H to DJ_H rearrangements occur at the transition from pro-B to large pre-B cells. At the transition from large to small pre-B cells, V_L to J_L rearrangements take place. Abbreviations: TdT – terminal deoxynucleotidyl transferase; c μ – cytoplasmic μ ; SL – surrogate light chain; IgH – immunoglobulin heavy chain; IgL – immunoglobulin light chain

Memory B Cells and B Cell Differentiation into Plasma Cells

We have recently proposed that the CD27 molecule is a memory B cell marker³. Morphologically, two subpopulations of PB CD27⁺ and CD27⁻ B cells differentiated: CD27⁺ B cells are larger cells with abundant cytoplasm and CD27⁻ B cells are smaller with scant cytoplasm³. Functional differences between the two populations have also been identified. Upon stimulation *in vitro* assay, CD27⁺ B cells, in contrast to CD27⁻ B cells, are quickly activated and can produce larger amounts of IgA, IgM, IgG and IgG subclasses^{3, 17}. With regard to IgE secretion, CD27⁺ B cells produce higher levels of IgE than do CD27⁻ B cells with IL-4 and CD40 signaling¹⁶. Single cell studies demonstrated that the majority of IgD⁺ CD27⁺ PB B cells, unlike IgD⁺ CD27⁻ B cells, carry mutated V region genes^{11, 12}. This finding also supports the view that CD27 is a memory B cell marker.

Triggering via CD27 on B cells by the CD27 ligand (CD70) yielded an increase in the number of plasma cells in the presence of such stimuli as IL-10^{2, 9, 16}, and the prompt differentiation into plasma cells occurred in CD27⁺ B cells, but not in CD27⁻ B cells^{1, 19}. Actually, CD40/CD154 interactions may promote the differentiation into memory B cells in germinal centers⁴. Two of the major cell-to-cell signaling mechanisms may thus regulate the mature B cell differentiation. Since CD154 was expressed on T cells soon after their activation and CD70 was expressed later², the CD40/CD154 interaction acts in the early phase, inducing the expansion of

a memory B cell pool, and memory B cells appear to differentiate into plasma cells via the CD27/CD70 interaction.

Primary Immunodeficiencies with Hypogammaglobulinemia

Recently, several genes responsible for primary immunodeficiencies with hypogammaglobulinemia were identified. It was found that disorders with defects of such genes inhibit B cell development at certain stages. In a patient with mutation of $\lambda 5$, pro-B cells could not differentiate into pre-B cells¹⁵ (Fig. 2). There were normal numbers of pro-B cells and few large pre-B cells in this patient¹⁵. The Bruton's tyrosine kinase (Btk) gene is responsible for XLA^{20, 21}. Btk gene analysis has facilitated the identification of various mutations in XLA cases⁷. It is also an autonomous B-lineage defect caused by a block in the early B cell development of pro-B to pre-B cells. YEL et al.²² reported impaired B cell development in a patient who had a mutation in the μ heavy-chain. The patient had normal percentages of the earliest precursors, pro-B cells. However, there was a marked decrease in the number of cells at the next stage in the B cell differentiation²². The B-lineage defect caused by a block in the early B cell development of pro-B to pre-B cells is shown in some patients with B cell negative severe combined immunodeficiency (B⁻ SCID).

In several immunodeficiencies with hypogammaglobulinemia, this may be caused by a defect occurring

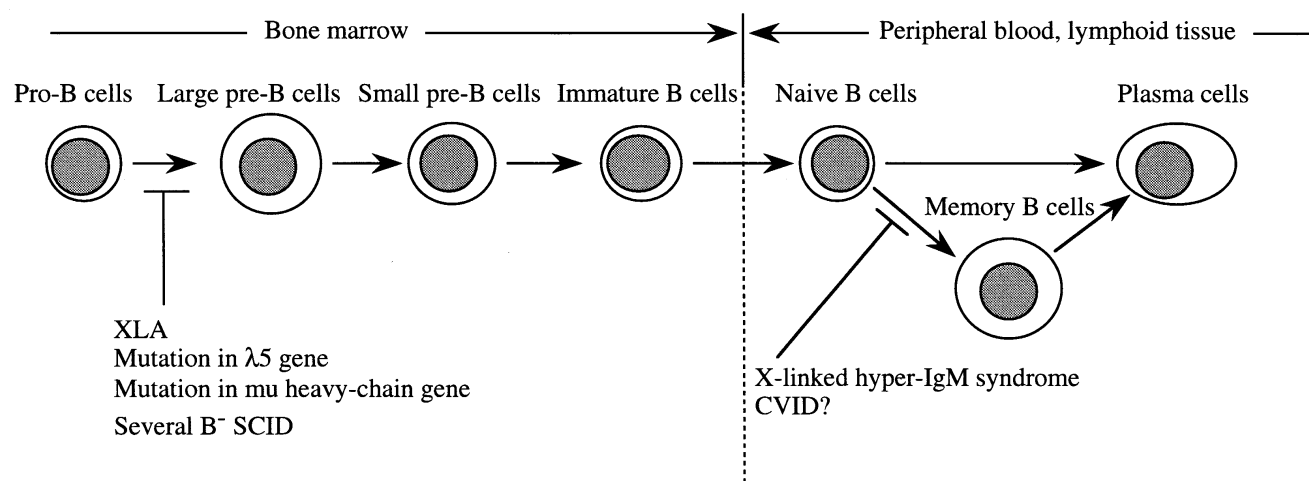


Fig. 2. B cell development and blocked site by primary immunodeficiency with hypogammaglobulinemia. B cell development is blocked at pro-B to large pre-B cells in the patients with XLA, mutation in $\lambda 5$ gene, mutation in μ heavy-chain and some B⁻ SCID. It is blocked at naive to memory B cells in the patients with X-linked hyper-IgM syndrome. Several CVID are suspected B cell development stopped at the stage of naive B cell. Abbreviations: XLA – X-linked agammaglobulinemia; B⁻ SCID – B cell negative severe combined immunodeficiency; CVID – common variable immunodeficiency

at various steps in the mutation pathway of naive B cells into antibody-secreting cells, i.e. plasma cells. CD27⁺ B cells, i.e. memory B cells, are absent in adult patients suffering from XHIM with mutations in CD154, which as the impaired CD40/CD154 interactions and germinal center formation². Some patients with common variable immunodeficiency (CVID) probably have a defect of the differentiation from naive B cells to memory B cells, resulting in hypogammaglobulinemia⁶.

Conclusions

Analyses of the mutation in genes responsible for primary immunodeficiencies with hypogammaglobulinemia have helped in the understanding of B cell development in humans. There is increasing knowledge about the B cell differentiation pathway, but molecular mechanisms of some immunodeficiencies remain to be determined. In particular, the B cell differentiation in CVID should be analyzed further which is expected the B cell development in more detail. Further characterization of the B cell development in patients with hypogammaglobulinemia will eventually lead to the elucidation of the immunodeficiencies, yield additional diagnostic and therapeutic interventions for the patients, and contribute to our better understanding of the immune system.

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