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Invited Review

Memory B cells and CD27

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Summary. Following antigen activation in germinal centers, B cells develop into memory B cells or plasma cells. Triggering via B-cell immunoglobulin receptors by antigens, cytokines and direct cell-to-cell contact by B and T cells plays an important role in the B cell differentiation into memory or plasma cells. Adult human peripheral blood B cells are separated into three subtypes by the expression of IgD and CD27, which belong to the tumor necrosis factor receptor (TNFR) family: IgD+ CD27- naive B cells, IgD+ CD27+ and IgD- CD27+ B cells. CD27+ B cells are larger cells with abundant cytoplasm carrying somatic hypermutation, and have an ability to produce immunoglobulin, indicating that CD27 is a memory marker of B cells. The ligation of CD27 yields crucial signals that positively control the entry of B cells into the pathway to plasma cells. We review observations on subpopulations and differentiation of mature B-cells by T/B cell interaction via CD27/CD70 as compared with CD40/CD154 interaction, and discuss about memory B cells.

Key words: Memory B cells, CD27, CD70, Plasma cells

Introduction

Accumulated research and clinical data over the past several years have demonstrated convincingly that T-B cell interactions in germinal centers (GCs) or the periarteriolar lymphoid sheath (PALS) play key roles in somatic hypermutation, B cell activation, proliferation and differentiation into memory B cells or plasma cells (Kelso, 1995). The differentiation of precursors along the pathway of B-cell development has been well characterized in bone marrow: stem cells differentiate into pro-R cells, large pre-B cells, small pre-B cells and immature B cells (Ghia et al., 1998). The pre-B cells contain μ in the cytoplasm and immature B cells express IgM receptor on the surface. When the IgD receptor is expressed on the surface, immature B cells become mature B cells. The mature B cells become activated in the T cell zones of PALS and then migrate into B cell zones to form germinal centers.

To produce antibodies, the differentiation of B cells into specific antibody-secreting cells (plasma cells) is required. Triggering via B cell immunoglobulin receptors by antigens, cytokines such as IL-2, IL-6 and IL-10, and direct cell-to-cell contact between T and B cells plays an important role in the differentiation of mature B cells. However, the mechanism of differentiation toward memory B cells or plasma cells from mature B cells has been unclear until now. Recently, we have found that CD27 on B cells is memory marker of B cells and CD27+ B cells differentiate toward plasma cells by contact with CD27 ligand (CD70) transfectants in cooperation with stimuli such as IL-10 (Agematsu et al., 1997, 1998a,b). Here, we discuss the function of CD27 molecule in B cells as a memory marker.

TNFR/TNF family in B cell function

With regard to the T-cell help by direct T/B cell interaction, the members of a new superfamily, tumor necrosis factor receptor (TNFR) superfamily (Mallet and Barclay, 1991), such as TNFR-I, TNFR-II, nerve growth factor receptor (NGFR), CD27, CD30, CD40, CD95 (Fas), CD134 (OX-40), CD137 (4-1BB), play an important role in the activation, proliferation, differentiation and cell death of B cells.

As for the effects of NGF on immune systems, it has recently been demonstrated that NGF is constitutively produced by B cells and maintains viability of cells with the surface phenotype of memory B cells, indicating that NGF is an autocrine survival factor for memory B lymphocytes (Torcia et al., 1996).

CD40/CD40 ligand (CD154) interaction is important for the B cell proliferation and immunoglobulin production. However, recent reports demonstrated that the CD40-mediated signal induced B cell proliferation and differentiation into memory B cells, but suppressed their capacity to differentiate along the plasma cell pathway (Arpin et al., 1995; Silvy et al., 1996),

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Table 1. Characteristics of peripheral blood B cells separated by the expression of IgD and CD27.

	IgD+ CD27-	IgD+ CD27+	IgD- CD27+
Percentages in adult B cells	60%	10%	30%
Percentages in cord blood B cells	>95%	<5%	<5%
Morphology	small scant cytoplasm	large abundant cytoplasm	large abundant cytoplasm
Immunoglobulin production			
SAC+IL-2 stimulation			
IgA	-	-	+++
IgM	-	+++	+++
IgG	-	++	+++
IL-4+anti-CD40 stimulation			
IgE	++	ND	+++
Somatic hypermutation	-	+	+

indicating that CD40 signaling pathway is instrumental for the clonal expansion of memory B cell pool, but does not operate in the late of the response.

The OX40-OX40 ligand pair promotes B-cell proliferation and differentiation, and increases immunoglobulin secretion in mice (Stuber et al., 1995; Stuber and Strober, 1996). OX40 ligand cross-linking results in the down-regulation of the transcription factor B cell-specific activator protein (BSAP). They also showed that blocking of OX40-OX40 ligand interaction in vivo results in a profound decrease of the anti-hapten IgG response and inhibition of the development of the periarteriolar lymphoid sheath-associated B cell foci, indicating that OX40-OX40 ligand interaction in vivo is necessary for the differentiation of activated B cells into Ig-producing cells. However, in our experiments in human system, OX40-transfectants did not enhance IgA, IgM and IgG secretion in the presence of stimuli (unpublished data).

CD27 and immunoglobulin production

Recently, we have demonstrated that the interaction between CD27 and CD27 ligand (CD70), which is expressed not only on activated B cells but also on T cells, especially activated CD4+ CD45RO T cells (Agematsu et al., 1995a), can enhance immunoglobulin production by B cells (Agematsu et al., 1995b; Kobata et al., 1995). CD27/CD70 interaction can induce the production of IgA, IgG, IgM, IgE and IgG subclass (Nagumo and Agematsu, 1998; Nagumo et al., 1998). Adult peripheral blood B cells are separated into at least two subtypes: IgD+ CD27- B cells and IgD- CD27+ B cells. CD27+ B cells produce large amounts of immunoglobulins in the presence of stimuli, but CD27- B cells do not (Maurer et al., 1992). The immunoglobulin synthesis from CD27+ B cells is greatly enhanced by the contact with its ligand, CD70 (Nagumo and Agematsu, 1998; Nagumo et al., 1998). CD27+ B cells are furthermore separated into IgD+ and IgD- cells (Fig. 1). IgD- CD27+ B cells produce IgG, IgM and IgA, whereas IgD+ CD27+ B cells predominantly produce IgM (Table 1) (Agematsu et al., 1997).

CD27 as marker of memory B cells.

CD27+ B cells are significantly larger than CD27- B cells and have abundant cytoplasm (Fig. 2). In addition, CD27+ B cells produce IgA, IgM and IgG by SAC+ IL-2, and IgE by IL-4 + CD40 signaling, whereas CD27- B cells do not produce IgA, IgM and IgG by SAC+ IL-2 (Table 1). Cord blood B cells do not express CD27 and CD27 expression on B cells increases with age (Fig. 1). On the basis of these findings we advanced that CD27+ B cells are memory ones and CD27- B cells are naive (Agematsu et al., 1997).

Antigen-specific differentiation of naive to memory

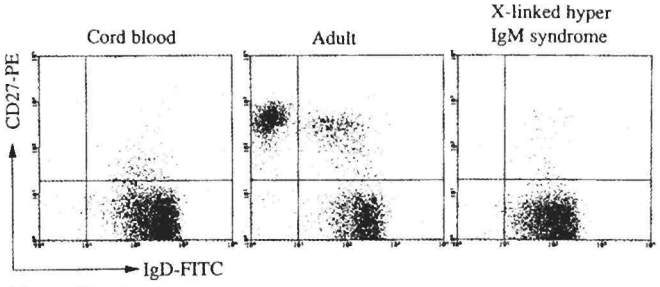

Fig. 1. B cell subpopulations separated by IgD and CD27. Three color analysis was carried out by gating CD20-PerCP positive B cells.

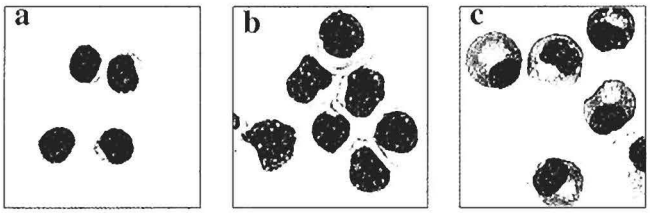

Fig. 2. B cell subpopulations and plasma cells. **a.** CD27- naive B cells. **b.** CD27+ memory B cells. **c.** plasma cells induced by CD70 transfectants in the presence of IL-10.

B cells is generally believed to occur within the germinal center, in which activated naive B cells undergo vigorous proliferation and somatic hypermutation of immunoglobulin variable (V) region genes. Therefore, naive B cells are expressing V region genes without somatic hypermutations, whereas memory B cells carry mutated V genes. Recently, it has been demonstrated that human B cells expressing CD27 in peripheral blood (Klein et al., 1998) and spleen (Tangye et al., 1998) carry somatically mutated V region genes. In lymphoid tissue, memory B cells are believed to reside in marginal zone. Immunohistology by using anti-CD27 mAb revealed that marginal zone B cells in human spleen (Tangye et al., 1998) and human tonsil (our unpublished data) were positive for CD27. These findings indicate that CD27 cell surface antigen represents a general marker of memory B cells.

X-linked hyper-IgM syndrome (XHIM) has been shown to result from mutations in the CD40 ligand (CD154) gene, resulting in impaired CD40/CD154 interactions and germinal center formation. We demonstrated that IgD- CD27+ B cell population was absent in patients with XHIM (Agematsu et al., 1998a). Since CD40/CD40L interactions may promote the differentiation into memory B cells in germinal centers (Arpin et al., 1995), these findings also support a view that CD27+ B cells are memory cells.

Generation of plasma cells by CD27 signaling

Plasma cells are finally differentiated cells of the B-cell lineage, but the exact pathway and regulation of their differentiation have not been clarified in detail until now. The striking function of CD27 in B cells is its great promotion to plasma cells (Fig. 2). We demonstrated that the CD27 signal resulted in the terminal differentiation of peripheral blood memory B cells into plasma cells in B cell activation systems using IL-10, augmented by the addition of IL-2. In contrast, the CD40 signal increased the number of B cells, but not of plasma cells (Jacquot et al., 1997; Agematsu et al., 1998b; Nagumo et al., 1998b). Thus, CD27 is crucial in controlling the differentiation of memory or activated B cells into plasma cells and the expression of CD27 on memory B cells is important for prompt differentiation into plasma cells.

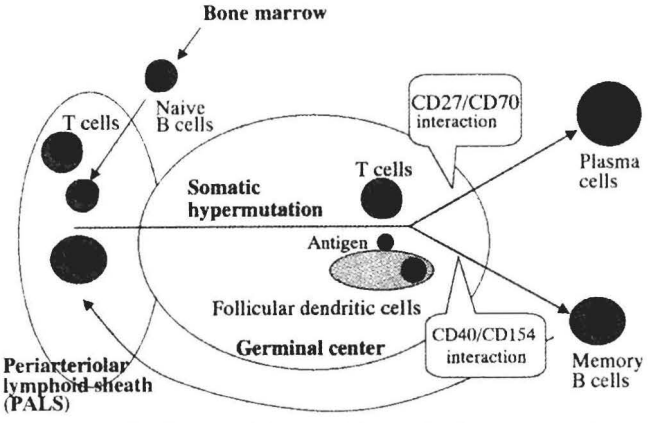

Fig. 3. B cell development in lymphoid tissue. B cells become activated in the T-cell zones (called periarteriolar lymphoid sheath) and migrate into B-cell zone to form germinal center. After germinal center B cells undergo somatic hypermutation and pick up antigen from follicular dendritic cells, the B cells are directed toward memory B cells by CD40 ligand (CD154) or toward plasma cells by CD27 ligand (CD70).

Concluding comments

In conclusion, by virtue of their morphology, increased expression with age, immunoglobulin production, localization within the marginal zone, the presence of mutations in Ig V region genes, and their enhanced ability to differentiate to plasma cells, CD27+ B cells are memory B cells.

In the immune response, activated helper T cells not only secrete cytokines but also express molecules on the surface, such as CD154 and CD70. The cell-to-cell interaction between T and B cells via two signalings, CD40/CD154 and CD27/CD70, strictly regulates the B cell activation, proliferation, differentiation and cell death. CD40/CD154 interaction acts on an early phase of B cell activation and induces the expansion of a memory B cell, and then the memory B cells differentiate into plasma cells via CD27/CD70 (Fig. 3).

We finally comment on the difference in B cell response to CD27/CD70 interaction between human and mice. Our findings presented here should be testified in the murine system including CD27-/- mutant mice (Gravestein et al., 1996) and blocking antibody injection, whereas effect of CD27/CD70 interaction on B cell immunoglobulin synthesis between the murine and human systems are somewhat different (J. Borst and T Kobata, personal communication). In human, since memory B cells and naive B cells can be clearly separated by CD27 surface expression, CD27 will become a powerful tool for analyzing the immune system and diseases such as immunodeficiency, autoimmune diseases and allergy.

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