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VIEWPOINT

T-Independent Immune Response: New Aspects of B Cell Biology

Sidonia Fagarasan and Tasuku Honjo*

Recent results emphasize the roles of T-independent antibody response in humoral defenses, for which B1 cells and marginal zone B cells are mostly responsible. We discuss how these cells are activated, migrate, and differentiate into antibody-producing cells in various lymphoid tissues. Based on recent findings in each of these areas of B cell biology, we propose a possible mechanism for peripheral tolerance of autoreactive B cells at target organs.

T and B lymphocytes are two principal players in the immune response, with T cells controlling much of the activity of B cells. B cell activation by protein antigens requires binding of the antigen to the B cell surface immunoglobulin (Ig) and also requires costimulation by antigen-specific T cells through CD40-CD40 ligand interaction and the secretion of cytokines. Appropriately activated B cells proliferate and differentiate to plasma cells or to long-lived memory cells, and it is during this process of differentiation that B cells manifest unique strategies for further diversifying the repertoire of antigen-specific B cell receptors (BCR). They achieve this by altering the genetic information that encodes the BCR through somatic hypermutation and class-switch recombination. Yet another mechanism for genetic alteration, RNA editing, can now be added to the list of remarkable strategies of the B cell for this amplification of genetic information. Activation-induced cytidine deaminase (AID) is a potential RNA-editing enzyme, and AID deficiency in mice and humans causes a complete defect in class switching and hypermutation (*1*, *2*). One may wonder why B cells use such sophisticated genetic strategies for diversification of their antigen receptor molecules, whereas T cells use only VDJ recombination to achieve the same ends. The use of additional strategies for increasing repertoire formation in B cells seems somewhat at odds with the ability of T cells to control all the activities of B cells. In fact, recent development in B cell biology indicates that B cell activities can be regulated in a T-independent manner. In this Viewpoint, we summarize the recent progress in this field and propose a possible mechanism for T-independent regulation of autoreactive B cells.

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Activation and Migration of B1 Cells and Their Physiological Role in Antibody Production

T cell–dependent immune responses generally involve conventional (B2) B cells. By contrast, the other subset of B cells, B1 cells, appears to produce antibodies in a T-independent manner. These cells, originally defined by the surface expression of CD5 and high levels of IgM, arise early during ontogeny, home predominantly to the peritoneal and pleural cavities, have a capacity for self-renewal, and display different receptor specificities (*3*, *4*). B1 cells recognize common bacterial antigens such as phosphorylcholine as well as self-antigens, such as phosphatidylcholine, Ig, DNA, and membrane proteins on erythrocytes and thymocytes (*4*). Production of autoantibodies by B1 cells is supported by the fact that the neoplastic expansion of B1 cells such as in chronic lymphocytic leukemia (B-CLL) is often associated with autoimmune symptoms (*4*, *5*). B1 cells play an important role in innate immunity by secreting large amounts of natural antibodies of the IgM class, which can be produced without exposure to any environmental antigens or immunization.

B1 cells also make a unique contribution to the mucosal immune response. Many IgA plasma cells of the intestine are derived from peritoneal B1 cells, suggesting that frequent migration of lymphocytes takes place between the peritoneal cavity and the gut-associated lymphatic tissues (GALT) (*6*). This has been confirmed in studies with alymphoplasia (*aly/aly*) mice, which have a mutation in the nuclear factor kappa B (NF-κB)–inducing kinase gene (NIK, a mediator of activation of NF-κB by the tumor necrosis factor receptor family) (*7*). In these mice, which lack lymph nodes, Peyer's patches, and a splenic marginal zone (MZ), it was revealed that peritoneal B1 cells must migrate out to GALT to produce antibodies (*8*). Transfer of *aly/aly* peritoneal B cells into RAG-$2^{-/-}$ mice revealed that the B cells could not generate plasma cells in mesenteric lymph nodes (MLN) and lamina propria of intestine, nor could they secrete Ig of any isotype. The defective chemotactic responses and chemokine-induced activation of NF-κB in *aly/aly* peritoneal B cells suggests a close involvement of NIK in signal transduction of the chemokine receptors. Therefore, the complete absence of B cell populations ($B220^+IgM^+$ small lymphocytes and $B220^-IgA^+$ plasma cells) in the lamina propria of *aly/aly* mice (*8*, *9*) is not simply due to the lack of Peyer's patches, but must also result from a migration defect of peritoneal B cells (Fig. 1).

What makes B1 cells leave the peritoneal cavity? Where do they proliferate and differentiate into plasma cells? And what is the immunological significance of their antibody production? LPS stimulation of peritoneal B cells but not splenic cells up-regulates expression of the chemokine receptors and enhances their chemotactic response. Migration of peritoneal B cells appears to require some as-yet-unknown stimuli distinct from those necessary for self-renewal because *aly/aly* mice have an increased number of peritoneal B1 cells. Two different mouse models suggest that proliferation and differentiation to plasma cells may take place in the MLN. One model is represented by HL Tg mice, in which almost all B cells express the autoantibody to red blood cells (anti-RBC) and develop autoimmune hemolytic anemia (*10*). In these mice, only B1 cells escape from clonal deletion and proliferate in the peritoneal cavity. However, in the presence of activated autoreactive transgenic γδT cells, the number of peritoneal B1 cells drastically decreases in parallel with the appearance of abundant IgM plasma cells in the MLN (*11*). Thus, noncognate help from activated γδT cells appears to induce migration of autoreactive B1 cells from the peritoneal cavity to MLN, where they differentiate into plasma cells. The other model, represented by the transfer of normal peritoneal B cells into immunodeficient mice, has demonstrated abundant IgA plasma cells in MLN, the majority of which are actively dividing (*8*, *12*). Moreover, IgA-producing B1 hybridomas from MLN have somatically mutated heavy chain (V_H) genes and bind to intact commensal bacteria (*12*).

A role of B1-derived IgA plasma cells in humoral defense at the mucosal surface was recently revealed by studies of Zinkernagel's group (*13*). They demonstrated that IgA produced against cell wall protein antigens of commensal bacteria is principally secreted by B1 cells. Secretory IgA from the intestine of germ-free mice does not bind bacterial antigens [neither proteins nor lipopolysaccharides (LPS)], whereas intestinal washings from specific pathogen-free mice contain IgA antibodies reacting specifically with bacterial wall components. These data offer clear evidence that these IgAs are not simply natural antibodies, but are specifically induced in response to bacterial antigens present in the intestine (Fig. 1). More importantly, they are produced without T cell help. Thus, mice deficient in T cells harbor IgA plasma cells in the lamina propria of the intestine, and their secretory IgAs show binding of commensal bacteria, identical to that seen in mice with T cells. In contrast, the sera of normal mice show neither IgA nor IgG antibodies specific to commensal bacteria, except in cases where the microorganisms are present in systemic circulation. In this case, the antibodies are derived from a T-dependent response by B2 cells. These observations demonstrate that B1 cell-derived IgA antibodies play an important role in host defenses at the mucosal surface, preventing systemic penetration of

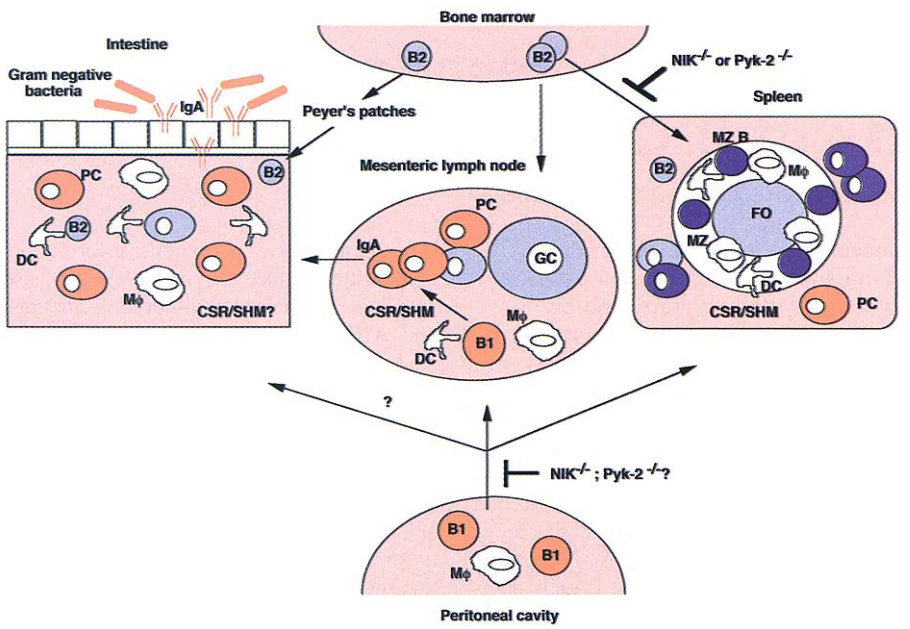

Fig. 1. Migration, differentiation, and antibody production of B1 cells and MZ B cells. Peritoneal B1 cells migrate to the GALT system and spleen, where they differentiate into plasma cells. NIK is essential for B1 cell migration and MZ formation. Homing of B cells to the MZ is dependent on Pyk-2. Differentiation of B1 cells does not require T cell help or the presence of germinal centers. CSR/SHM, class switch recombination/somatic hypermutation; DC, dendritic cells; FO, follicular B cells; GC, germinal centers; Mϕ, macrophages; PC, plasma cells. B1 cells and B1 cell–derived PCs are in orange. B2 cells, follicular structures containing B2 cells, and PCs derived from B2 cells are in blue. MZ B cells and PCs derived from MZ B cells are in purple. Activated B1 and MZB cells are shown larger than B2 cells.

commensal bacteria, for which T cell help and follicular organized structures (like Peyer's patches and germinal centers) are not necessary.

Marginal Zone B Cells

Another strategic site of defense is represented by the splenic MZ. Located at the junction of white and red pulp, the MZ contains macrophages, dendritic cells, and B cells and provides a first line of defense against blood-borne pathogens. B cells residing here have a surface phenotype distinct from other spleen B cells, including higher expression of complement receptors and IgM (*14*). In some respects, MZ B cells resemble peritoneal B1 cells, and like B1 cells, they are very sensitive to LPS stimulation, which induces their rapid differentiation into plasma cells (*14*, *15*). That MZ B cells play an important role in T-independent antibody responses, particularly to T-independent type II antigens, was demonstrated by the recent studies in mice deficient for Pyk-2 tyrosine kinase (*16*). Pyk-2–deficient mice have no MZ B cells, probably due to the impaired response of these cells to chemokines and a resulting homing defect to the spleen MZ. Pyk-2–deficient mice exhibit a severe diminution of IgM, IgG3, and IgG2a in response to Ficoll, a typical T-independent type II antigen. Similar to B1 cells, antibody production by MZ B cells is closely related to their capacity to home to a proper environment (Fig. 1). Recent studies of Ravetch and colleagues (*16*) demonstrate the important role of complement and its receptors (CR) for specific targeting of the antigen to MZ B cells. In the absence of C3 or CD21/CD35 (CR1/2), MZ B cells no longer bind the antigen, which is reflected by the severe reduction of antibody response to polysaccharide antigens. Furthermore, association of CD21 with CD19 and B cell receptor lowers the activation threshold of naïve B cells that have encountered low-affinity antigens (*17*). This would explain, at least in part, how MZ B cells can be activated in the absence of T cell help (*16*). Thus, MZ B cells represent one example of how innate immunity mediated by complement is coupled to the adaptive immune response.

Positive and Negative Regulation of T-Independent Antibody Response

What T-independent signals might induce proliferation and rapid differentiation of B1 and MZ B cells into Ig-secreting cells? One candidate for transmitting such signals is B lymphocyte stimulator–(BlyS) (Fig. 2). Direct evidence for this comes from studies in which the overexpression or injection of BLyS significantly increased the number of MZ B cells and serum levels of Ig (*18*–*20*). BLyS is expressed by macrophages, monocytes, and probably by dendritic cells and T cells (*18*, *20*, *21*), whereas its receptors (TACI and BCMA) are constitutively expressed on mature B cells (*19*). The expression pattern of both the receptors and ligand, an increased expression of BLyS by interferon-γ (IFN-γ) stimulation (*18*), and its correlation with the expansion of MZ B cells in BLyS-Tg models, strongly suggest that BLyS may function as a positive regulator in T-independent and a T-dependent immune response. Furthermore, overexpression of BLyS is accompanied by other important and impressive modifications, like the appearance of pathogenic antibodies and lupus-like autoimmune disease (*19*, *20*). Thus, BLyS is an example of a strong B cell stimulator, the disregulation of which drives B-cell differentiation toward a pathogenic state.

An important question is whether any negative regulator controlling B cell responses exists that can be activated without T cell involvement. If it does not, it becomes difficult to visualize how T-independent immune responses could be regulated. There are several down-modulators of BCR signaling, including CD22, Fcγ receptor type II (FcγR II), and CD5, which are discussed in the accompanying Review (*22*). PD-1, a member of the Ig superfamily containing an immunoreceptor tyrosine-based inhibitory motif (ITIM) in the cytoplasmic region, is expressed on activated T cells and B cells (*23*, *24*). This molecule emerged as another candidate for the negative regulation of antigen receptor signaling because PD-1–deficient mice exhibit splenomegaly, selective augmentation of the IgG3 antibody response to a T-independent type II antigen, and enhanced proliferative response of B cells by stimulation with antibody to IgM (*24*). PD-1–deficient C57BL/6 mice develop spontaneous lupus-like proliferative arthritis and glomerulonephritis with IgG3 deposition as they age. Presence of the deficiency of PD-1 in BALB/c mice results in a dilated cardiomyopathy and production of autoantibodies specific to heart tissue (*25*). The ligand for PD-1 (PDL-1) was recently identified and shown to inhibit proliferation of T cells stimulated with antibody to CD3 (*26*). In B cells the co-ligation of PD-1 with BCR caused inhibition of proliferation, Ca^{2+} influx, and tyrosine phosphorylation (*27*). A particularly interesting feature of this ligand is its constitutive expression on peripheral organs, including kidney, heart, and lung, in addition to its induced expression on dendritic cells after IFN-γ stimulation (*26*).

Taking these findings into account, it is possible to construct a model for PD-1 involvement in the regulation of autoreactive B cell responses. Autoreactive B cells can be accidentally activated by T-independent as well as T-dependent mechanisms, and such activation signal may be often suboptimal because of weak cross-reactivity or limiting amounts of stimulants. Although B cells that have been hypoactivated in this way could not differentiate into plasma cells, they could survive due to induction of antiapoptotic proteins, like bcl-2. In this state, they could probably enter into the circulation. When such hypoactivated B cells encounter self antigens, they could be easily restimulated, which would induce them to express PD-1. Engagement of PD-1 with its ligand ex-

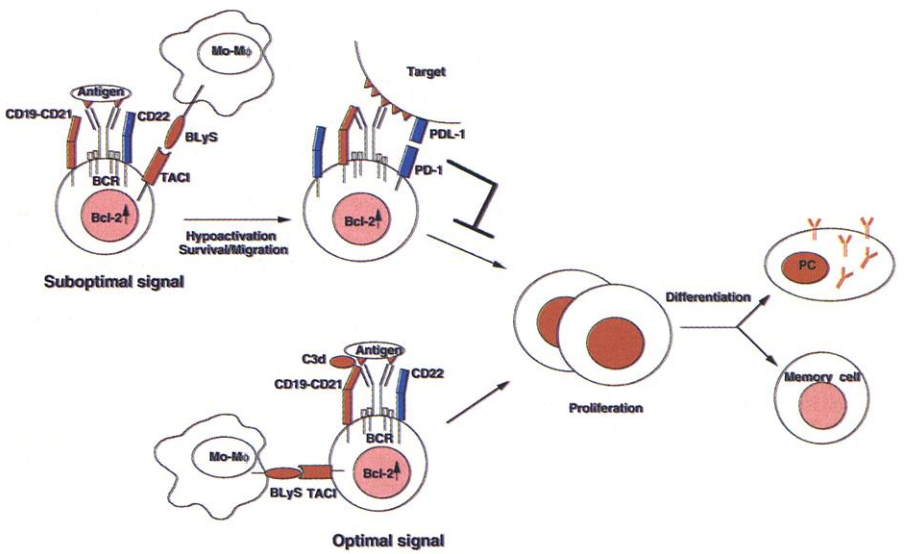

Fig. 2. Possible roles for BLyS/TACI and PD-1/PDL-1 in the regulation of autoreactive B cells. Antigen recognition by BCR and CD19-CD21 engagement in conjunction with BLyS/TACI interaction promotes activation, proliferation, and differentiation of B cells. Under conditions at which the antigen receptor signal is suboptimal, BLyS/TACI interaction would allow survival of B cells and migration into circulation, without differentiation into PCs. Among these circulating hypoactivated B cells, some are autoreactive. PD-1/PDL-1 interactions suppress the activation of autoreactive B cells at the target site and maintain peripheral tolerance. Optimal signaling pathways that lead to effector cell differentiation is also depicted. Mo-Mϕ, monocyte-macrophages.

pressed on various organs would allow the suppression of activated autoreactive B cells at the target site without the need for T cell involvement. This would be sufficient to prevent the subsequent differentiation of these B cells into plasma cells (Fig. 2).

In summary, there are two types of B cells that appear to be regulated in a T-independent manner. B1 cells, well known for their unique surface markers, have distinct pathways for their activation and migration. The physiological importance of B1 cells in maintenance of the homeostasis at the mucosal surface is clearly demonstrated. The other T-independent B cells, MZ B cells, also appear to have distinct activation and migration pathways. In addition, studies on BLyS, PD-1, and several other molecules have started to elucidate the molecular mechanisms of positive and negative regulation of T-independent immune response. Thus, B cells appear to "have their own kingdom"; they are not always subordinate to T cells. These new aspects of B cell biology will not only affect strategies of immune therapy but also the conceptual framework of evolutional immunology.

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REVIEW

Dynamics of T Lymphocyte Responses: Intermediates, Effectors, and Memory Cells

Antonio Lanzavecchia and Federica Sallusto

The immune response is initiated in organized lymphoid tissues where antigen-loaded dendritic cells (DCs) encounter antigen-specific T cells. DCs function as packets of information that must be decoded by the T cell before an appropriate immune response can be mounted. We discuss how the dynamics of DC–T cell encounter and the mechanism of T cell differentiation make the decoding of this information stochastic rather than determinate. This results in the generation of both terminally differentiated effector cells and intermediates that play distinctive roles in protection, immunoregulation, and immunological memory.

T lymphocytes recognize antigens by engaging the T cell receptor (TCR) with peptide-MHC (major histocompatibility complex) displayed on the surface of antigen-presenting cells (APCs) (*1*, *2*). Triggering of TCRs results in T cell proliferation and differentiation into a variety of cell fates that determine the class of immune response. $CD4^+$ T lymphocytes can polarize toward T helper 1 (T_H1) or T_H2 cells, which produce different sets of cytokines [interferon-γ (IFN-γ) or interleukin-4 (IL-4), IL-5, and IL-13, respectively] and mediate protection from intracellular or extracellular pathogens (*3*, *4*). $CD8^+$ T lymphocytes differentiate into cytotoxic T cells capable of killing virus-infected cells (*5*). T lymphocytes can also differentiate into regulatory cells, for example, helper cells that migrate to the B cell areas to initiate T cell–dependent antibody responses or suppressor T cells that down-regulate immune responses by secreting inhibitory cytokines (*6*). Some T cells generated during the primary response survive for years as memory cells, which can confer immediate protection and generate more rapid and effective responses upon reencounter with antigen (*7–9*).

T cell responses are initiated in the T cell areas of secondary lymphoid organs where naïve T cells encounter antigen-loaded dendritic cells (DCs), a professional type of APC (*10*). There is growing evidence that the information needed to generate different classes of immune response is carried by DCs. Here we focus on the dynamics of DC–T cell interaction. First, we discuss how DCs classify pathogens and assemble packets of information that are delivered to T cells. Then, we consider how T cells decode this information—generating, along a linear differentiation pathway, different types of T cell fates (intermediates as well as effectors). In conclusion, we propose a unified model for DC control of T cell responses.

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Dendritic Cells: Packets of Information for T Lymphocytes

DCs are scattered throughout all nonlymphoid tissues where they reside in a resting, so-called immature, state. In response to "danger" signals such as pathogens, inflammatory cytokines, or necrotic cells, DCs migrate to the T cell areas of secondary lymphoid organs and switch from an antigen-capturing to an antigen-presenting and T cell–stimulating mode (*10*, *11*). During this process, defined as DC maturation, the cells assemble peptide–MHC complexes, up-regulate costimulatory molecules, and elaborate cytokines. This results in the formation of packets of information that are delivered to T cells in the draining lymph node (Fig. 1).

Immature DCs efficiently capture exogenous antigens (*12*) and, upon maturation, load the antigenic peptides on preformed empty, as well as newly synthesized, MHC class II molecules (*13–16*). While maturing DCs shut off antigen capture and class II synthesis, the newly formed complexes accumulate on the cell surface and acquire extremely long half-lives, exceeding 100 hours. This mechanism allows DCs to retain peptide–class II complexes for several days once they have been assembled, thereby maximizing presentation of those antigens associated with the infec-