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Homeostatic niche specification among naïve and activated B cells: A growing role for the BLyS family of receptors and ligands

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Abstract

B lymphocyte homeostasis encompasses the establishment and maintenance of independently regulated niches, within which cells compete for viability promoting resources. The BLyS/BLyS receptor family controls the size and composition of these niches, by governing the selection and survival of most peripheral B cells. Moreover, different receptor-ligand sets from this family dominate the regulation of various B cell subsets. These observations suggest a model whereby the regulation of BLyS receptors by differentiative and stimulatory cues yield characteristic BLyS receptor signatures, thus specifying homeostatic niche and competitive advantage.

Keywords: B lymphocyte; Homeostasis; BLyS

1. Introduction

The mechanisms governing lymphocyte homeostasis must calibrate cell numbers to levels that impart protection yet lie within plausible resource consumption limits. This mandate yields a problem in steady-state cellular dynamics that must accommodate multiple, seemingly conflicting factors. First, the random genetic processes that generate antigen receptors impose a need for specificity-based selection to minimize potential self-reactivity and maximize protective utility. This implies that homeostatic regulation must be integrated with the mechanisms underlying such selection. Second, the co-existence of discrete B cell subsets whose sizes, dynamics, and repertoires differ suggests that related but independent homeostatic systems regulate these pools. Finally, alternative activation outcomes, notably those that yield short-lived antibody forming cells (AFCs) versus long-lived progenitors of memory responses, indicate that the process of activation includes cues that direct cells to alternative, independently controlled homeostatic niches.

The BLyS/BLyS receptor family plays a central role in the integrated homeostatic regulation of peripheral B cells. As characterization of this TNF subfamily has unfolded, a paradigm for niche-specific regulation has emerged [1], based on the coupling of BLyS receptor expression to exogenous stimuli that specify differentiation into the various pre- and post-immune B cell pools. Herein we overview the nature and dynamics of naïve and activated peripheral B cell subsets, and discuss the BLyS/BLyS receptor family's role in their homoeostatic control. Finally, we propose a model whereby alternative activation signals differentially alter expression of the three BLyS receptors, thereby specifying the occupation of independently regulated homeostatic niches.

2. Nature and dynamics of pre-immune B lymphocyte subsets

Naïve B cells and their progenitors can be divided into several phenotypically, functionally, and anatomically distinct subsets. The sizes, lineage relationships, and dynamics of these subsets have undergone intense investigation during the last decade, and are summarized in Table 1. In normal adults, pre-immune B cell populations are derived from

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Table 1
Properties of marrow and peripheral B cell subsets

Subset		Pool size (millions)	Turnover rate (%/day)	Production rate (10^6/day)	BLyS receptors expressed	Primary BLyS ligand dependence
Marrow	pro-B	5	30	1.5	None	None
	pre-B	50	30	15	None	None
	Immature	35	30	10–15	BR3?	?
Transitional	T1	1.5	30		BCMA?	?
	T2	2.0	30	∼1.5 overall	TACI BR3	BLyS
	T3	1.0	30		TACI BR3	BLyS
Mature primary	FO	∼45	<2	0.5	TACI BR3	BLyS
	MZ	5–7	∼4	Varies	BR3?	BLyS
	B1	1.5	?	?	?	Not via BR3, if any
Post-Ag	GC	Varies	?	Varies	?	BLyS, APRIL?
	Marrow PCs	?	<1?	?	BCMA	BLyS or APRIL

marrow progenitors that, following lineage commitment and rearrangement of immunoglobulin genes, express surface IgM and enter the immature marrow pool (see [2,3] for reviews). These newly formed B cells leave the marrow to complete maturation in the periphery, where they pass through several transitional stages (T1, T2, T3) before entering one of the resting primary B cell subsets [4–8]. Under normal steady-state conditions, the majority of cells that complete transitional maturation join the follicular (FO) pool, which comprises about 80% of adult peripheral B cells. Alternatively, some newly formed cells may differentiate to join the marginal zone (MZ) pool, either directly or after acquiring FO characteristics [9].

The absolute and relative sizes of the transitional, FO, and MZ subsets remain relatively constant throughout life, suggesting stringent homeostatic controls over the generation and maintenance of these pre-immune pools. Since the two primary determinants of a population's size are the rate at which cells enter the population and the residence time of cells within the population, in vivo labeling strategies have been employed to investigate the dynamics of bone marrow and peripheral B cell pools [4,6,10–12]. These studies have revealed two fundamental properties of these populations that must be accommodated by models forwarded to explain their homeostatic regulation. First, residence times in the immature marrow and transitional pools are relatively short, as evidenced by the 3-day turnover times in both cases [4,6]. In contrast, residency times in the FO and MZ pools are substantially longer, with average turnover times of ∼80–100 and ∼30 days, respectively. Second, based on the differences in production rates (Table 1), fewer than 5% of the immature B cells generated in the marrow can be accounted for among the cells entering naïve mature peripheral pools. Together, these findings suggest that most newly formed B cells die during the differentiation stages spanning BCR expression in the marrow and entrance to the mature pre-immune pools.

Pronounced cell losses at the marrow-periphery interface reflect a composite of specificity-based negative and positive selection imposed upon emerging B cells. These processes include the elimination or editing of potentially autoreactive clonotypes [13–24], as well as the differentiative failure of cells whose BCR fails to meet a minimum level of signaling strength ([25–27], reviewed in [28,29]). In addition to mediating the successful differentiation of newly formed B cells, BCR signaling is also critical to the survival of mature B cells. This is evidenced by the rapid death of mature B cells within established FO pools following conditional BCR ablation [30], as well as the perturbed lifespan of FO and MZ B cells in various transgenic or BCR signaling defective strains [30–33].

An increasingly appreciated aspect of BCR-mediated selection within transitional and mature primary pools is that the propensity for survival conferred by BCR specificity is *relative*, rather than absolute. Thus, the degree of differentiative success and longevity within these pools is ultimately determined by the competing cohort. This principle has been amply demonstrated by experiments in which clonotypes that can successfully mature in an oligoclonal environment fail when differentiating in a competing milieu of normal BCR diversity [31,34–37]. These observations indicate that naïve B cells compete for limited, viability promoting resources. Moreover, they suggest that the level of these resources defines a set-point for pre-immune pool size. Finally, subsets with differing capacities and requisites for resource capture exist within the overall pre-immune pool, as evidenced by the selective preservation, expansion, or loss of MZ versus FO B cells under lymphopenic or cytokine deprivation conditions ([38]; Srivastava et al., this volume).

3. Activation induces divergence into homeostatically independent niches

The contrasting lifespan characteristics of naïve versus antigen-experienced cells suggests that activation releases cells from homeostatic constraints operative in pre-immune populations and fosters divergence into niches under alternative homeostatic control. Further, both the mode of activation and the origin of the responding clones determines the homeostatic niche targeted for occupation and hence the competing

cohort. For example, among FO B cells, BCR engagement in conjunction with CD40 ligation leads to the initiation of germinal center (GC) reaction, affinity maturation, isotype-switching, and the formation of relatively long-lived memory populations. In contrast, stimulation of MZ cells, or stimulation of FO B cells in a manner characteristic of T-independent responses, generally yields rapid expansion and differentiation to relatively short-lived AFC clones.

The independent regulation of pre-immune versus activated and/or antigen-experienced B cell subsets is evidenced by the constancy of naïve pool sizes despite expansion of the responding, antigen-specific clonotypes during primary responses. Conversely, depleting memory plasma cells through ablation of a receptor crucial for their survival has little influence on the size of the FO pool, providing further evidence that the pre- and post-immune pools are controlled independently [39]. Accordingly, the mediators of peripheral B cell homeostasis must not only allow coordinated control over the size and composition of pre- and post-immune pools, but must also afford a means whereby the differentiative events associated with activation can channel responding cells into independent homeostatic niches.

4. Members of the BLyS/BLyS receptor family are the molecular mediators of naïve and activated peripheral B cell homeostasis

During the last 5 years, the BLyS family of TNF homologues has emerged as a pivotal determinant of peripheral B cell survival and homeostasis, prompting extensive review and commentary [40–48]. The BLyS family includes two ligands, BLyS and APRIL, as well as three receptors, BR3, TACI, and BCMA. Mounting evidence indicates that this family of ligands and receptors influences virtually all B lineage subsets subsequent to the immature marrow stage. Further, BLyS and APRIL influence the various B cell pools differently, based in part on disparate expression of the three receptors within each subset. The ligands, BLyS and APRIL, share 50% homology at the protein level and exhibit several other similarities. Both are synthesized as type II transmembrane proteins, secreted as homotrimers after proteolytic cleavage, and are thought to be active only in their soluble forms. An important distinction is that BLyS and APRIL differ in their binding capacity for the various BLyS family receptors (see below).

BLyS was simultaneously described by several laboratories, and therefore, appears under several names in the literature, including BLyS [49], BAFF [50], TALL-1 [51], and THANK [52]. Many of the biological effects mediated by BLyS reflect the modulation of survival. Initial studies showed dramatic increases in FO and MZ B cell numbers following either exogenous BLyS administration or BLyS overexpression [49,50,53]. Additionally, in vivo BrdU labeling studies of transitional cells showed that exogenous BLyS administration promotes survival in the late transitional pools, increasing the proportion of cells completing differentiation and joining the mature FO cell compartment [54]. Finally, the deletion of BLyS or the administration of competing soluble receptors in vivo yielded profound but reversible reductions in the number of resting mature B cells [55]. Together, these observations clearly established a role for BLyS in the homeostatic regulation of naïve peripheral B cells [49,50,56].

The role of APRIL in B cell homeostasis remains less clearly delineated, probably due to the receptor binding redundancy of BLyS, as well as the lack of any known receptors uniquely reactive with APRIL. Thus, when APRIL is either deleted or overexpressed, neither the differentiation of transitional B cells nor the magnitude of the FO and MZ compartments is altered. However, APRIL transgenic mice exhibit enhanced TI-2 responses [57], and APRIL knockout mice produce increased antibody titers to T-dependent (TD) and T-independent-type 1 (TI-1) stimuli [58,59]. Together these data suggest that while APRIL's influence on pre-immune B cells is largely ancillary to those of the BLyS-BR3 axis, it likely plays a role in the control of activated B cells.

Further evidence supporting different roles for the two ligands comes from analyses of the three BLyS family receptors. Perhaps most importantly, BLyS is the only known ligand for BR3, whereas TACI and BCMA are bound by both BLyS and APRIL. Accordingly, B cells that express BR3 are disposed to unique effects of BLyS, and ample evidence indicates that BLyS-BR3 interactions are key to the survival of naïve peripheral B cells. Whereas TACI is also expressed on pre-immune B cells, its exact role remains obscure. A negative regulatory role for TACI has been inferred from observations with TACI knockout mice, which show increased peripheral B cell numbers, enhanced antibody responses to TD and TI-1 responses, and hallmarks of humoral autoimmunity. However, the production of antibodies resulting from TI-2 stimuli appears impaired in these mice [60,61], suggesting the role of TACI may be more complex. BCMA does not seem to be expressed at high levels on cells within pre-immune pools and its deletion has little effect on these populations. In contrast, BCMA is necessary for the survival of at least some post-immune compartments, as evidenced by the loss of long-lived bone marrow plasma cells in the BCMA knockout mouse [39,62].

5. Competition for BLyS signaling via BR3 modulates the survival and selection of naïve peripheral B cells

Signaling via BR3 is the primary determinant of BLyS-mediated positive regulatory effects in pre-immune peripheral pools. The expression of BLyS receptors shifts as newly formed B cells pass through the transitional stages and enter the FO B cell pool in a manner consistent with increasing reliance on BR3 (Table 1; [54]). The critical role of BR3 is evident from the compromised transitional differentiation,

decreased FO B cell lifespan, and lack of MZ cells observed in the BR3 mutant A/WySnJ mouse, as well as in BLyS and BR3 knockouts [55,63–66]. The lack of perturbed pre-immune compartments in BCMA or APRIL knockouts [61] further attests to the dominant role of BLyS-BR3 signaling in these compartments.

Further experiments using the A/WySnJ strain revealed that mature B lymphocytes continuously compete for BLyS signaling through BR3 [67]. These experiments showed that in (A/WySnJ X BALB/c)F1 individuals, the FO B cell turnover rate is intermediate between normal and A/WySnJ, indicating that continuous capture of BLyS-BR3 signals mediates FO B cell lifespan. Moreover, mature A/WySnJ-derived FO B cells competed poorly with BR3-sufficient cells in mixed marrow chimeras, indicating that the relative levels of functional BR3 establish competitive fitness. Subsequent studies using BR3 knockout mice have confirmed the dominant role of BLyS-BR3 signaling for the maintenance of FO and MZ B cells [68].

The thresholds for both positive and negative selection within transitional subsets are linked to BLyS availability. Early evidence for this included the observations that exogenous BLyS administration enhanced the success of transitional differentiation and that BLyS transgenic mice displayed B cell hyperplasia and humoral autoimmune manifestations. More recent studies using the HEL/anti-HEL transgenic model, where B cells reactive with soluble self antigen escape deletion until the late transitional stages [23], have directly demonstrated that excess available BLyS can rescue the differentiation of autoreactive cells [69,70]. Moreover, under excess BLyS conditions, the absence of interclonal competition allowed MZ differentiation of autoreactive cells, whereas intermediate levels of competition afforded only FO differentiation.

The molecular processes through which BR3 signaling promotes viability among naïve B cells are the subject of intense investigation. Accumulating evidence suggests a link between BLyS signaling and Bcl-2 family member expression via NFκ-B signaling pathways [71–79]. Thus, ectopic expression of BLyS leads to increased levels of several anti-apoptotic Bcl-2 family members among peripheral B cells [53], and the addition of BLyS to FO B cells in vitro upregulates Bcl-2 family members including Bcl-xl, A-1, and others [54,72,80]. Further, some but not all of the defects in the BR3 mutant A/WySnJ or TACI-Ig transgenic mice are repaired through introduction of Bcl-2 or Bcl-xL [78,81,82]. Finally, the expression of pro-apoptotic genes may be lessened or attenuated by BLyS signaling via BR3 [83] and recent analyses have suggested that BLyS signaling may prevent the pro-apoptotic activities of molecules such as nuclear PKC-δ [84]. More recently, a connection between cell cycle control and BLyS-mediated signaling has emerged, suggesting a potential relationship between cell cycle control systems and the homeostatic maintenance of peripheral pools ([85]; Woodland and Schmidt, this volume).

6. The mediators of BLyS family signaling shift during B cell activation and memory

In addition to their profound influence on the selection, formation, and longevity of primary B cells, members of the BLyS-BLyS receptor family also play an important role in the antigen-driven activation of mature B cells, as well as the generation and maintenance of memory populations. Early studies in the A/WySnJ mouse revealed normal primary IgM responses for both TI and TD antigens, but poor secondary humoral responses and low IgG levels [86]. Moreover, while rudimentary germinal centers form following immunization in these mice, they fail to evolve normally; consistent with more recent reports indicating compromised germinal center formation when BLyS signaling is impeded [78,87]. Evidence that BLyS has a role in the appropriate evolution of primary humoral responses also comes from findings that suggest both BLyS and APRIL may influence isotype switching either directly, or indirectly by extending survival [59,88].

A direct link between the BLyS/BLyS receptor family and antigen-experienced pools was forged through detailed analyses of the BCMA knockout, which revealed a lack of long-lived marrow plasma cells and truncated memory responses in these mice. Inasmuch as T dependent costimulation and germinal center formation are requisites for establishing humoral memory, it seems likely that the switch from BR3 to BCMA follows from these events. However, the detailed timing and inducers of this shift await further investigation.

7. Does the BLyS family receptor phenotype of a B cell define its functional niche of independent homeostatic regulation?

The conversion from a BR3- to a BCMA-centered survival system indicates that, unlike their pre-immune counterparts, memory plasma cells can use either APRIL or BLyS for survival. This switch thus provides a means for independent homeostatic control of antigen-experienced B cells, as well as a competitive advantage over primary FO and MZ pools. Extending this principle suggests a mechanism of homeostatic compartmentalization whereby a B cell's niche is determined by the spectrum of BLyS receptors expressed. Since the BLyS receptor array will specify the possible resources and the balance of negative versus positive signals; both the biological "space" for which a cell competes, as well as its relative fitness within that space, could be established via this mechanism (schematized in Fig. 1). This model further suggests that the activation signals directing cells into particular niches may act, at least in part, by specifying the overall pattern and extent of BLyS receptor expression. For example, stimulation that yields transient AFC responses might target responding clones to short-lived fates determined by their array of BLyS receptors; whereas stimuli engendering memory cell formation would specify BLyS receptor expression patterns commensurate with enhanced fitness and longevity.

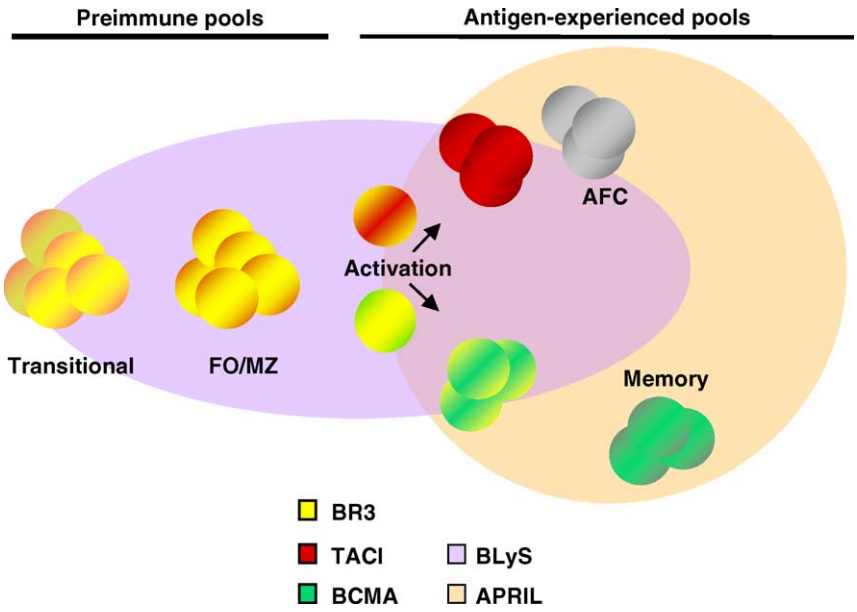

Fig. 1. Schematic representation of a model for niche specification by differential BLyS receptor expression. In this model, the reservoirs of available BLyS and APRIL define independent but partially overlapping homeostatic niches. The differential expression of the three BLyS family receptors (TACI, BCMA, and BR3) determines the niche a cell is able to occupy, as well as its relative ability to compete within that niche. Both maturation and activation are accompanied by shifts in BLyS receptor expression, with niche specification and alternative fates being determined by the quality of exogenous cues driving these processes.

8. Innate and adaptive receptors can mediate differential BLyS receptor regulation

We previously showed that anti-IgM mediated BCR cross-linking induces increased BLyS binding capacity through the upregulation of BR3 [89], consistent with the notion that exogenous stimuli can vary the levels of BLyS receptors. Whether activation via alternative receptor systems might yield contrasting changes in BLyS receptor expression remains unexplored. One category of such alternative stimuli are the Toll like receptor (TLR) ligands. Murine FO B cells respond to several TLR ligands, including unmethylated CpG DNA sequences that act via TLR9 [90,91]. B cells responding in vivo to CpG stimulation proliferate and secrete IgM, yielding transient protection from otherwise lethal challenge with certain bacteria [92,93]. Accordingly, we have begun initial characterization of BLyS binding capacity and receptor expression following CpG stimulation. Following CpG stimulation, mature FO B cells increase BLyS binding in a dose-dependent fashion to an equal or greater extent than after BCR stimulation alone. Interestingly, this increase in BLyS binding primarily reflects increased TACI expression. Given the current view that TACI serves a negative regulatory role in the BLyS family, it is tempting to speculate that elevated TACI—either alone or in the absence of sustained or increased BR3 and/or BCMA expression—might specify a comparatively rapid demise of clonal progeny yielding the characteristic short-lived response to CpG stimulation. Overall, these findings are consistent with the possibility that levels of each BLyS receptor might be differentially influenced by various exogenous stimuli, yielding an overall BLyS receptor phenotype that specifies both competitive niche and survival probability.

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