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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