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Homeostatic control of B lymphocyte subsets

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Abstract

Lymphocyte homeostasis poses a multi-faceted biological puzzle, because steady pre-immune populations must be maintained at an acceptable steady state to yield effective protection, despite stringent selective events during their generation. In addition, activated, memory and both short- and long-term effectors must be governed by independent homeostatic mechanisms. Finally, advancing age is accompanied by substantial changes that impact the dynamics and behavior of these pools, leading to cumulative homeostatic perturbations and compensation. Our laboratory has focused on the overarching role of BLyS family ligands and receptors in these processes. These studies have led to a conceptual framework within which distinct homeostatic niches are specified by BLyS receptor signatures, which define the BLyS family ligands that can afford survival. The cues for establishing these receptor signatures, as well as the downstream survival mechanisms involved, are integrated with cell extrinsic inputs via cross talk among downstream mediators. A refined understanding of these relationships should yield insight into the selection and maintenance of B cell subsets, as well as an appreciation of how homeostatic mechanisms may contribute to immunosenescence.

Keywords

B lymphocyte; Homeostasis; Aging

Introduction

Cells of the immune system operate under strict homeostatic controls, as evidenced by the relatively constant pool sizes of various lymphocyte pools, as well as aberrant repertoires and autoimmunity associated with homeostatic perturbations. A growing literature indicates that limitations in both survival-promoting resources and physical space underlie these homeostatic constraints [1]. Within the B lymphocyte lineage, the B cell antigen receptor (BCR) plays a major role in determining B cell survival [2,3]. More recently, the B lymphocyte stimulator (BLyS) family of cytokines and receptors has been revealed as an equally important determinant of B cell homeostatic regulation [4,5]. We have explored the mechanisms through which molecules of this family act, as well as how homeostatic demands shift with age. Based on this work, we have forwarded the notion that BLyS family receptors and ligands act largely by mediating survival and that signals via these receptors integrate with other exogenous inputs, particularly those via the BCR, through downstream cross talk. In addition, others and we have shown a differential distribution of BLyS family receptors among primary and antigen-experienced B cell subsets. This has led to the idea that BLyS receptor "signatures" define

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independent homeostatic niches and that exogenous activation cues direct the acquisition of particular BLyS receptor profiles. Finally, since the production rates and dynamics of B cell subsets shift with age, some aspects of immunosenescence likely reflect ongoing and cumulative effects of these homeostatic mechanisms. In this overview, we briefly address the basis for these ideas and comment on remaining questions.

Pre-immune and antigen-experienced B cell pools occupy distinct homeostatic niches

B cells arise from bone marrow (BM) progenitors that rearrange their immunoglobulin genes, culminating in the expression of a functional BCR [6,7]. These newly formed immature (IMM) B cells exit the BM to join the transitional (TR) compartment before entering the follicular (FO) or marginal zone (MZ) pools [8–10]. Once steady state is achieved, the sizes of FO and MZ B cell subsets remain relatively constant, suggesting they are under strict homeostatic control. BCR signaling plays a major role in the selection of cells within the IMM and TR pools through the elimination or editing of potentially autoreactive clones [11–15], as well as the differentiative failure of cells that do not meet a minimum level of BCR signal strength [16,17]. In addition, BCR signaling is a critical determinant of longevity among mature primary B cells, which continue to rely on sub-threshold BCR signaling—termed “tonic” signaling—for their survival [2,3,18].

In contrast to the tonic BCR signals required for developing and quiescent B cell survival, strong BCR ligation in mature B cells can yield widely divergent outcomes based on the avidity and extent of BCR-ligand interactions, as well as the availability and timing of costimulatory second signals. T-dependent (TD) responses generally involve FO B cells and arise following concomitant stimulation via the BCR and CD40. These responses are characterized by the rapid emergence of relatively short-lived primary antibody forming cells (AFCs) and the concomitant initiation of germinal centers (GCs). The naïve B cells recruited into a TD response undergo selective expansion and preservation (reviewed in [19]), ultimately yielding long-lived memory (MEM) B cells. Although these are a small proportion of total B cells, they persist indefinitely, indicating substantially slower turnover rates than those of pre-immune B cells. The disparate lifespan characteristics of naive versus antigen-experienced B cells suggests that activation releases responding cells from homeostatic constraints operative in pre-immune populations and fosters divergence into niches that are under alternative homeostatic control. For example, among FO B cells, BCR engagement with CD40 ligation initiates germinal center (GC) formation, affinity maturation, efficient class switch recombination, and the establishment of long-lived memory pools. In contrast, T-independent responses generally yield comparatively short-lived AFC clones. This overall conceptual framework—whereby the nature of activation cues and the source of the responding B cell clones determines the homeostatic niche targeted for subsequent occupation—implies that the mediators of peripheral B cell homeostasis must not only afford coordinated control over the size and composition of pre-and post-immune pools, but must also provide a means through which the differentiative events following activation appropriately direct responding cells.

The BLyS family of cytokines and receptors

The BLyS family includes two cytokines, BLyS [4,20–22] and A proliferation-inducing ligand (APRIL) [21,23], both of which are now recognized as central players in B cell homeostasis. Through differential interactions with several receptors, these two ligands profoundly influence multiple aspects of B cell biology, such as the selection, differentiation, and homeostasis of primary B cells (reviewed in [24]). These largely B lineage-specific activities, coupled with clear relevance to both autoimmunity and neoplasia, have focused intense scrutiny on BLyS, APRIL, and their corresponding receptors. This work has already yielded considerable insight

into fundamental aspects of B cell biology and has revealed several promising therapeutic targets.

BLyS can bind three receptors: transmembrane activator and cyclophilin ligand inter-actor (TACI), B cell maturation antigen (BCMA), and BLyS receptor 3 (BR3) [25–28]. Two of these receptors, TACI and BCMA, can also bind APRIL [26,29]. All three receptors are type III transmembrane proteins with cysteine-rich domains (CRDs) that mediate ligand binding. While TACI possesses two CRDs, BCMA and BR3 have only a single or a partial CRD [30, 31]. This variation, along with differences in combining site residues, yields different affinities for the two ligands. BR3 interacts solely and strongly with BLyS, as evidenced by affinity measurements and biological findings. BCMA, on the other hand, has a nearly 1000-fold greater affinity for APRIL than for BLyS [32,33]. Between these extremes, TACI interacts appreciably with both BLyS and APRIL [26,34]. Finally, sulfated proteoglycans have been shown to bind APRIL, although the physiological role of this relationship awaits clarification [35]. In addition, differential interactions of trimeric versus oligomeric forms of BLyS have recently been described [36]. For example, BR3 can bind to soluble trimeric BLyS, while only the BLyS 60-mer is an efficient TACI agonist.

BLyS binding capacity and responsiveness arise with primary B cell maturation

BLyS family members play little role in early B lineage commitment and differentiation. Thus, B lineage subsets prior to the bone marrow immature stage do not bind BLyS and do not express any of the three receptors [37]. In contrast, all B lineage subsets subsequent to the BM IMM stage bind BLyS and express one or more of the BLyS family receptors. Within the IMM pool, minimal BLyS binding is observed within the $CD23^{-}$ fraction, whereas somewhat higher levels of BLyS binding are seen in the $CD23^{+}$ IMM cells [37]. As these exit the marrow and pass through the TR stages, BLyS binding capacity increases, reflecting increased levels of both BR3 and TACI [37]. Cells in the FO and MZ compartments display the greatest and most sharply defined BLyS binding capacities, reflecting uniformly high levels of both TACI and BR3.

BLyS mediates selection and survival of primary B cells

BLyS serves as a limited resource that defines the limits of biological “space” for naive B cells, such that when BLyS consumption equals availability, the set point for primary B cell numbers is reached (reviewed in [1]). Indeed, experiments with mixed BM chimeras [38] showed that BR3 mutant B cells compete poorly in the presence of wild-type (WT) B cells. This notion of competition links BLyS availability with the thresholds for both positive and negative selection within TR subsets. Consistent with this, exogenous BLyS administration enhances the success of TR differentiation, and BLyS transgenic mice display B cell hyperplasia and humoral autoimmune manifestations. More recent studies, using several transgenic models in which self-reactive B cells are eliminated at the late TR stages, have directly demonstrated that excess BLyS can rescue these autoreactive cells and allows them to mature [39–41].

How are BR3 and BCR signaling integrated?

The molecular processes whereby BR3 signaling promotes primary B cell viability and—perhaps more importantly—how these signals are integrated with BCR-mediated selection, are the objects of intense investigation. Accumulating evidence indicates links between BLyS signaling and Bcl-2 family member expression via NF-κB transcriptional regulatory pathways [42–44]. Thus, ectopic expression of BLyS leads to increased levels of several anti-apoptotic Bcl-2 family members among peripheral B cells, and some defects in BR3 mutant or TACI-

Ig transgenic mice are repaired through ectopic of Bcl-2 or Bcl-xL expression. In addition, the expression of pro-apoptotic genes may be lessened or attenuated by BLyS signaling via BR3. A connection between cell cycle control and BLyS-mediated signaling has more recently emerged, suggesting a potential relationship between cell cycle control systems and the homeostatic maintenance of peripheral pools [45].

Although these observations shed light on the ultimate mediators of BLyS-mediated survival in primary B cells, they do not address a remaining fundamental question: If the BCR and BR3 signals can cross-modulate one another—as evidenced by the plasticity in TR selection revealed in the experiments outlined above—what molecular mechanisms afford this integration? Although the precise details of this relationship remain elusive, a growing literature suggests that cross talk among downstream mediators of these pathways, particularly the NF-κB system of transcriptional regulatory elements, are involved (reviewed in [46,47]. Because the BCR primarily drives the classical NF-κB pathway, whereas BR3 leads to non-classical NF-κB pathway activation, the engagement of interacting downstream systems may prove critical to BLyS-mediated survival. Indeed, disruption of either the classical or non-classical NF-κB pathways blocks peripheral B cell development, mirroring the dual requisite for both BCR and BR3 signaling for primary B cell survival. The nature of this potential cross talk is not yet understood, but several clues have emerged. Recent studies demonstrated that all major components of the non-classical NF-κB pathway are critical for BLyS-mediated survival. Further, while the phenotypes of knock-out mice for various NF-κB components vary somewhat, nearly all are similar to BLyS$^{-/-}$ or BR3$^{-/-}$ mice. Thus, it seems likely that the BCR and BR3 may be coupled through these two signaling systems, either via simultaneous activation targeting separate promoters of survival, or through direct cross talk. Regardless of exact mechanism, determining the details of this relationship should eventually afford the opportunity to deliberately manipulate selection and survival within peripheral B cell subsets.

Do BLyS family molecules influence antigen-experienced B cell subsets?

In addition to their profound influence on the selection, formation, and longevity of pre-immune B cell populations, members of the BLyS–BLyS receptor family also play important roles following 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 [48,49]. Moreover, while rudimentary germinal centers form following immunization in these mice, they fail to evolve normally; consistent with reports indicating compromised germinal center formation when BLyS signaling is impeded [50]. 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 [51,52].

The TACI receptor may also play a regulatory role in the selection of antigen-responsive clones. TACI KO mice have increased peripheral B cell numbers, enhanced antibody responses to TD and TI-1 antigens, and exhibit hallmarks of humoral autoimmunity [53,54]. These data suggest that in the absence of TACI, negative selection fails, indicative of TACI as a negative regulator. However, the production of antibodies resulting from TI-2 stimuli is impaired in these mice, suggesting the role of TACI may be more complex. A direct link between the BCMA receptor and antigen-experienced pools was shown through analyses of the BCMA KO mouse, which revealed a lack of LLPCs and truncated memory responses in these mice [55]. Inasmuch as TD co-stimulation and GC formation are requisites for establishing humoral memory, it seems likely that the switch from BR3 to BCMA dependence is also requisite for at least one arm of the memory B cell response.

Does BLyS receptor phenotype define homeostatic niche?

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 homeostatic niche is determined by the spectrum of BLyS receptors expressed (discussed in [56,57]). Since the BLyS receptor signature will specify the possible resources (e.g., BLyS versus APRIL) 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, might be established via this mechanism. This prompts a working model in which BLyS signaling via BR3 provides homeostatic control over pre-immune subsets, including the TR, FO, and MZ pools; and shifts in BLyS receptor expression during immune responses channel cells into alternative homeostatic niches. Thus, short-lived AFCs are characterized by high levels of TACI, whereas GC B cells express high BR3 levels and LLPCs express BCMA.

Consistent with these ideas, we have recently found that primary B cells and responses are eliminated by treatment with neutralizing anti-BLyS antibody in vivo, but memory B cells memory responses and LLPC numbers are essentially unaffected (J. Scholz and J. Crowley, submitted).

Do exogenous regulatory cues modulate BLyS receptor expression?

The notion that BLyS receptor signature defines the homeostatic niche and competitive fitness suggests that the activation signals directing differentiative fate specify the pattern and extent of BLyS receptor expression. For example, stimulation that yields transient AFC responses might triage 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.

We previously showed that anti-IgM-mediated BCR cross linking induces increased BLyS binding capacity through the upregulation of BR3, 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 positive stimuli is the Toll like receptor (TLR) ligands. Murine FO B cells respond to several TLR ligands, including unmethylated CpG DNA sequences that act via TLR9. B cells responding in vivo to CpG stimulation proliferate and secrete IgM, yielding transient protection from otherwise lethal challenge with certain bacteria. Accordingly, we have recently characterized BLyS binding capacity and receptor expression following CpG stimulation [57]. 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. It is thus 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 end-stage differentiation of clonal progeny, yielding the characteristic short-lived antibody forming response to CpG stimulation.

We have also begun analyses of the impact of negative regulatory cues on BLyS receptor expression and responsiveness, by examining the influence of FcγRIIB signaling (Crowley et al, submitted). Our results indicate that FcγRIIB ligation attenuates BCR-mediated BLyS receptor upregulation. This effect requires FcγRIIB co-ligation with the BCR and operates via a SHIP-dependent mechanism. Downstream BLyS signaling pathways are dampened following FcγRIIB/BCR co-ligation, blunting the survival-promoting effects of BLyS.

Overall, these findings are consistent with the possibility that levels of each BLyS receptor are differentially influenced by exogenous stimuli, yielding an overall BLyS receptor phenotype that specifies both competitive niche and survival probability.

Are homeostatic relationships perturbed with age?

Advancing age is associated with a broad spectrum of changes in immune system status, including failures of B cell progenitor pools and their microenvironments, shifts in repertoire composition, changes in the dynamics of B cell pools, and a general decline in immune responsiveness (see the volume associated with [58] for review and commentary). Both lineage intrinsic and microenvironmental changes contribute to shifts in B cell commitment with age, but the overall result is diminished generation rates of IMM and TR B cells. Interestingly, although the generation of TR B cells is reduced, residency time in the TR pools is extended. In addition, the turnover rate of the FO pool slows as much as twofold—apparently compensating for the reduced input of newly formed cells.

These changes in the dynamics of peripheral B cell populations are provocative. For example, because thresholds for TR selection vary based on available BLyS and competitive cohort, such reduced throughput and increased residency times may afford the maturation of polyreactive and autoreactive clonotypes. Moreover, these changes in FO subset turnover may indicate that B cells in aged mice are a highly selected pool with exceptional ability to compete for these resources. We have begun to test this idea by determining the competitive survival capacities, as well as the BLyS receptor profiles, of B cells from aged versus young mice (Hao, unpublished observations). Our data show that after adoptive co-transfer into either replete or lymphopenic hosts, aged B cells display increased longevity and expansion capacity compared to young B cells. In addition, we have observed an age-related shift in the BLyS receptor profiles of FO B cells: the ratio of $TACI^{hi}$ to $TACI^{lo}$ B cells is 2-fold higher in aged individuals (Scholz and Hao, unpublished observation). Together these findings suggest that mature B cell pools in aged individuals are enriched for highly fit competitors bearing distinct BLyS receptor profiles.

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