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Review

Peripheral B cell survival

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Abstract. Recent findings suggest that lymphocyte survival is a continuous active process and support the role of B cell receptor engagement in B cell survival. In this context the conflict of survival interests between the diverse B cells gives rise to a pattern of interactions which mimics the behavior of complex ecological systems. In response to competition lymphocytes modify their survival requirements and diverge to occupy different immunological niches through differentiation. Thus naive and memory-activated B cell populations show independent homeostatic regulation. We discuss how niche differentiation allows the coexistence of different cell types and guarantees both repertoire diversity and efficient immune responses.

Key words. B lymphocytes; survival; competition; homeostasis; B cell receptor.

Introduction

In adult mice the total number of lymphocytes remains constant and shows a 'return tendency, due to a density dependent process to approach a stationary distribution of population densities', usually referred to as homeostasis. B lymphocytes are, however, produced continuously in either the primary lymphoid organs or, to a much lower extent, by peripheral cell division: it follows that each newly formed lymphocyte can only persist if another resident lymphocyte dies. In an immune system where the total number of cells is limited, cell survival cannot be a passive phenomenon, but rather must be a continuous active process where each lymphocyte must compete with other lymphocytes [1, 2]. It can be said that lymphocytes follow the Red Queen hypothesis postulate that 'it takes all the running you can do to keep in the same place' [2]. In fact, continuous signaling by B cell antigen receptors (BCRs) appears to be critical for both B cell development and for the survival of mature B cells in the peripheral lymphoid tissues.

B cell development

B cells are generated from hematopoietic multipotential stem cells (HSCs) in the para-aortic splanchnopleura, omentum, liver and spleen during fetal life, and in the bone marrow in the adult. B cell development follows different stages of differentiation according to the steps of rearrangement of the immunoglobulin heavy chain locus, the expression of specific cell surface markers and growth factor requirements.

Commitment of HSCs into the B cell differentiation pathway critically requires the B cell-specific activator protein (BSAP) coded by the Pax5 gene [3] as well as the basic helix-loop-helix proteins encoded by the E2A gene [4] and the early B cell factor (EBF) [5]. Early progenitor B cells (pro-B) can be identified by the surface expression of the CD45R isoform B220, CD43, CD25 and c-kit. According to the differential expres-

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sion of CD24 (heat-stable antigen, HSA) and BP-1 we can discriminate different fractions of pro-B cells [6, 7]. At this stage of development expression of the recombinase activity genes 1 and 2 (Rag1 and Rag2) leads to DNA rearrangements in the immunoglobulin H (IgH) chain locus. Absence of either of these genes leads to the block of B cell development at the pro-B stage [8]. These gene recombination events occur sequentially, first D_H to J_H rearrangements, later followed by V_H to D_HJ_H rearrangements. Productive $V_HD_HJ_H$ rearrangements result in the expression of μH chain protein in the cytoplasm, which if capable of associating with a $V_{preB}/\lambda 5$ surrogate L chain [9] and together with Igα and Igβ assembles a functional pre-B cell receptor at the membrane. Expression of this surrogate receptor promotes the transit of a pro-B cell into a pre-B cell which enters into active cell division. The presence of a functional pre-B cell receptor at the cell surface prevents further H chain rearrangements, ensuring IgH allelic exclusion and triggering IgL chain rearrangement [10–12]. If successful, L chain recombination allows the production of a conventional IgL chain and leads to the expression of an IgM BCR at the cell surface. Progression of pre-B cells to the immature B cell stage is therefore strictly dependent on signaling by a functional pre-B cell receptor [10]. Immature IgM^+ B cells migrate to the periphery, where they complete their maturation after different transitional steps [13]. These include the gain-of-surface IgD and CD23 expression, the progressive shutdown of Rag enzymatic activity [14] and the loss of expression of the 493 marker [15].

Interleukin-7 (IL-7) is also an essential requirement for B cell development (reviewed in [16]). Pro-B cells express interleukin-7 receptors (IL-7R), and their growth is strictly dependent on direct interactions with (IL-7)-producing stromal cells. Mice deficient for either IL-7 [17], IL-7R α chain [18] or the common γc chain [19] show a block of B cell development at the pro-B cell stage. Studies in IL-7R$\alpha -/-$ mice showed that IL-7 controls expression of Pax5 and Pax5-dependent genes [20] essential for the HSC commitment to the B cell lineage [3]. These genes are not required for D_H to J_H rearrangement but control the germ-line transcription of distal unrearranged V_H gene segments which is believed to be necessary for recombination [20]. Thus, by enhancing V_H to D_HJ_H recombination IL-7 expands the diversity of the B cell repertoire. IL-7 is also essential for pre-B cell growth [21]. In fact, in IL-7-deficient mice the different steps of B cell development are unimpaired, but expansion of pre-B cells is abolished. In these mice as in the common γc chain-deficient mice very few B cells are found at the periphery [18, 19]. At later stages of differentiation withdrawal from IL-7 leads to the pre-B to B cell transition in the absence of cell division. The amplitude and type of response of B lineage cells to IL-7 is modulated by the expression of the pre-B receptor and the BCR [22, 23].

In summary, B cell development is regulated by signals given via IL-7R and pre-B or B cell receptors. It is not yet clear whether the role of pre-B cell receptor signalling in B cell development is merely constitutive [24] or whether it requires ligand recognition. It is nevertheless clear that the signal thresholds of the pre-B and B cell receptors will vary according to the stage of differentiation [25] and according to the presence or absence of different accessory molecules (CD19, CD45) and coreceptors (CD21, CD22) [26]. Antigen signalling via the BCR complements constitutive signals, and by inducing positive selection, survival, growth and expansion or apoptosis and anergy will determine the final fate of mature B cells.

The role of the BCR in peripheral B cell survival

Resting B cells

Survival of naive B cells in the peripheral pools appears to involve interactions between the BCR and yet unidentified ligand(s). The role of the BCR in the survival of mature resting B cells was first investigated by experiments in which a transgenic BCR could be ablated by an inducible Cre-LoxP recombination event [27]. In these studies it was reported that after BCR ablation, B cells were rapidly lost from the peripheral pools. These studies, however, did not allow direct correlation of BCR signalling and peripheral B cell survival. In fact, BCR ablation also leads to the arrest of new B cell production in the bone marrow [10], and in the absence of the newly formed bone marrow (BM) migrants a significant fraction of the peripheral B cells are rapidly lost [28, 29]. It has also been shown that in mice with a deletion mutation of the Igα cytoplasmic tail, early B cell development in the BM exhibits only a small impairment, but the generation of the peripheral B cell pool was severely reduced [30]. The question remained whether the mere presence of a signalling complex, e.g. IgM-Igα-Igβ or some other complex, at the cell surface suffices to signal B cell survival, or whether B cell survival requires ligand recognition. We have addressed directly the role of ligand-mediated recognition in peripheral B cell survival. We found that B cells lacking the V region of the IgM receptor have a very short life expectancy [31]. Thus, although the presence of a truncated membrane IgM transgene, lacking the V region, can provide constitutive signals that suffice to signal allelic exclusion and can promote pre-B-cell development in the absence of the surrogate light chain $\lambda 5$ [32], it is nevertheless unable to support long-term survival of the Tg B cells. More important, by directly comparing the fate of two populations of Tg B

cells, either lacking or expressing an Ig V-region, we were able to assign the poorest competitive ability and the short peripheral survival of the B cells to the lack of an antigen-combining site. These results support the involvement of ligand recognition in the persistence of peripheral B cell populations.

Differences in the antibody repertoires expressed by pre-B and peripheral B cells can also be invoked to suggest the involvement of ligand-mediated recognition in peripheral B cell positive selection and persistence [33–36]. In contrast to T cells in which T-cell-receptor (TCR) survival signaling seems to require the recognition of major histocompatibility complex (MHC) class I or class II molecules (see review in [2]), the nature of the ligand(s) that might be involved in B cell survival remains elusive. Analysis of V_H-gene family expression has provided evidence for a very conserved pattern of V_H-gene family usage that is independent of the V_H-gene number, is strain- and tissue-specific, and is tightly regulated during B cell differentiation [33]. After B cell generation in the BM, naive B cell survival is associated with a strong peripheral selection of B cells expressing particular V_H-gene families [34, 36]. These observations suggest that the recognition interactions related to B cell survival may not require the involvement of the full antigen-binding site and might be exclusively V_H-mediated. It is possible that this type of ligand recognition may not lead to full cell activation and that low avidity interactions suffice to promote cell survival. It was recently shown that the BCR is capable of differential signalling, and that B cell responses may differ depending upon the properties of the antigen. Thus, whereas some B cell responses were better correlated with antigen-BCR affinity than with receptor occupancy, others were only weakly dependent on antigen affinity [37].

Recent findings suggest that B cell survival may be also related to the levels of receptor occupancy and cross-linking. We have compared directly the fate of dual receptor B cells with single receptor B cells by accessing the development of these two B cell populations in several different lines of mixed BM chimeras [M. M. Rosado and A. A. Freitas, unpublished). It was found that when alone, dual and single receptor B cells show an identical behavior and generate peripheral pools of similar size. When mixed in the same host, a preferential peripheral selection of the single receptor-expressing B cells out-competed dual-receptor B cells. The dilution of a specific BCR at the cell surface seems to reduce the capacity of the cell to capture survival signals.

If B cell survival signals involve antigen-specific receptors, implying some type of ligand recognition [31], it could be predicted that the size of each B cell clone would be limited by the levels of exploitable 'epitopes' present at the periphery. A diverse population of B cells exploiting multiple 'epitopes' should therefore occupy a larger niche than a monoclonal population, and the maximal peripheral cell number should vary for each B cell clone, cell numbers being limited by intraspecific competition. By crossing several Ig transgenic mice with C57Bl/6-Rag2-deficient mice, we derived different lines of mice bearing homogeneous populations of monoclonal B cells. Studies in these monoclonal B mice seem to confirm both predictions. We have found that the number of resting B cells in mice containing a single B cell clone was diminished compared with wild-type mice and varied according to the monoclonal line studied [M. M. Rosado and A. A. Freitas, unpublished]. These results, although supporting the role of BCR specificity in the control of peripheral cell numbers, do not exclude the contribution of other 'nonspecific' trophic factors in B cell homeostasis.

Indeed, peripheral B cell survival is likely to involve multiple mechanisms. Different signals may engage different cell surface receptors using the same or different survival pathways. The constitutive expression of the Ebstein-Barr virus LMP2A protein in transgenic mice bypasses BCR signaling and allows the survival of receptorless B cells in the peripheral pools [38]. Downstream of the BCR signaling pathway defects in CD45 [39], Btk [40], Syk [41] or NF-κB [42], or in the OBF-1 transcription factor [43] also affect peripheral B cell maintenance. Lymphocyte survival is also modified through the balance between different apoptotic and antiapoptotic proteins [44–46]. It has been shown that BCR signaling and increased levels of intracellular bcl-2 ensure lymphocyte survival through independent pathways [31, 47]. It is possible that the expression of bcl-2 may simply increase cell efficiency by lowering the threshold of resource requirements for survival. B cell survival requirements may still vary according to the state of activation.

Memory/activated B cells

Memory B cells not only show phenotypic changes and express a hypermutated BCR of a different isotype with an increased avidity for antigen, but show also a higher rate of cell division and a lower threshold of activation, and occupy a different habitat within the secondary lymphoid organs. Studying memory responses to both thymus-dependent and -independent antigens and using different cell transfer systems, it has been claimed that the long-term persistence of B cell memory required continuous cell division in the presence of antigen [48–50]. Recent observations in mice in which an inducible Cre-loxP-mediated gene inversion was used to change the specificity of the BCR contradict these results. In these experiments it was shown that after antigenic stimulation and the generation of memory B cells, memory cells survived even after expressing a new BCR

unable to bind to the original activating antigen [I. Maruyama, K.-P. Lam and K. Rajewsky, personal communication]. These findings suggest that antigen may only be required at early steps of cell activation and selection of high-affinity B cells in the germinal centers. Once these B cells acquire a 'memory phenotype', they may no longer require antigen recognition for long-term survival.

In this context it is important to recall that the difference in the interactions required for the survival of B and T cells may explain the different rate of mutation of B and T cell receptors. Since T cell survival requires recognition of ubiquitous MHC molecules, somatic mutation of the TCR might always be disadvantageous as it may cause loss of MHC recognition and thus cell death. In contrast somatic mutation may increase the BCR-ligand avidity and favor selection of high-affinity B cells which, compared with the initial population of nonmutated B cells, have a competitive survival advantage within the germinal center. In their flight for survival, B cells are still able to use mechanisms of V-gene replacement [51, 52], receptor editing [53–55] and change BCR specificity to escape cell death, and perhaps gain a survival advantage over other rival cells. B cell survival may therefore be also strictly dependent on mechanisms that regulate rates of B cell production and peripheral B cell numbers.

B Cell production

At the periphery, B cell pools represent transit compartments where there is an input of newly formed cells, proliferation due to antigenic stimulation and a cellular output due to cell death and terminal differentiation [28]. The number of peripheral B cells could therefore be a function of the rates of B cell production [28]. This turned out not to be the case. B cell production in the BM was accessed either by studying the rate of precursor cell division after incorporation of the thymidine analogs ^{3}[H]-thymidine [56] or BrdU [57], or by statmokinetic methods [58]. Estimates based on these studies indicate a daily production of about $1.5–2 \times 10^{7}$ B cells, which should suffice to replenish a peripheral B cell compartment of 10^{8} B cells in 5–6 days [56]. It is claimed, however, that a majority of these newly formed B cells are counterselected [59], die 'in situ' [60] or soon after leaving the marrow [61], and never incorporate the peripheral pool [35, 62, 63]. In this case the size of the B cell pool would be limited by the insufficient 'effective' production of new B cells. In contrast it has also been claimed that a significant fraction of the peripheral B cell pool is continuously renewed from incoming newly formed cells [28].

To study the role of B cell production in the control of peripheral B cell numbers and homeostasis, we created a mouse model in which BM B cell production could be limited [64]. For this purpose we generated chimeras grafting Rag2-deficient mice with mixtures of BM cells from normal mice and from mice with a developmental block of B cell development (μMT or Rag2-deficient) [8, 10]. In these chimeras the number of pre-B cells can be reduced by diluting normal BM cells among incompetent BM cells from the B cell-deficient donors. We found that the number of pre-B cells was strictly dependent on the ratio of 'normal' progenitors present in the inoculum [64]. More important, we found that a normal-sized peripheral B cell pool was generated in mice containing only 30% of the normal number of pre-B cells and one-third of the normal daily B cell production [64]. These results demonstrate that about one-third of the normal number of BM B cell precursors suffices to maintain the peripheral B cell pool size. A similar conclusion was obtained after parabiosis between one normal and two or three B-cell-deficient mice [64]. In these circumstances B cell production was restricted to the BM of the normal mouse. In mouse triads it was found that each individual mouse had physiological B cell numbers, i.e. the B cell production of one mouse was sufficient to populate the peripheral pools of three mice. In conclusion, in adult mice the potential to produce new B lymphocytes in the primary lymphoid organs largely exceeds the number required to replenish the peripheral B cell pools.

B cell competition

In an immune system where new lymphocytes are continuously produced in excess but their total numbers are kept constant, newly generated cells are likely to compete with other newly produced or resident cells to survive. Competition can be defined as 'an interaction between two populations, in which, for each, the birth rates are depressed or the death rates increased by the presence of the other population' [65].

There are several established criteria accepted as evidence of competition among populations [66]: (i) the presence of competitors should modify the equilibrium size of a population, and (ii) the presence of competitors should alter the dynamics, e.g. the growth kinetics and life expectancy of a population.

The question of whether competition arises between B cells was addressed by comparing the development and the fate of BCR transgenic (Tg) and non-Tg populations in several different lines of mouse BM chimeras [67]. Briefly, host mice were lethally irradiated and reconstituted with BM cells from different non-Tg and Ig-Tg donor mice mixed at variable ratios. At different

times after reconstitution the total number of peripheral lymphocytes, the kinetics of the host population by the several donor cell lineages, their relative representation in the precursor, peripheral mature and effector cell compartments, and their relative life spans were evaluated.

It was found that (i) when injected alone, transgenic (Tg) and non-Tg cell populations show an identical behavior and generate peripheral pools of similar size, and (ii) when Tg and non-Tg cells are mixed in the same host they initially accumulate at the same rate. However, after reaching equilibrium at steady-state numbers, there is a preferential selection of the non-Tg cells at the periphery [67]. These observations fulfil the first criteria for competition since they demonstrate that the presence of non-Tg populations modifies the number of the Tg cells.

In these experiments, by comparing the kinetics of accumulation of BrdU-labeled cells among Tg and non-Tg B cell populations in different BM chimeras, it was also found that that the life expectancy of the Tg B cells varied according to the presence and the type of other competing cells [67]. These latter findings fulfil the second criteria required for the definition of competition as they prove that the presence of competitors alters the life span of a population.

Types of competition and resources

Competition may arise through different processes [65]. In apparent competition two prey species attacked by a predator resemble the dynamic behavior of two competing populations. An example of apparent competition has been reported for cells of the immune system. In chimeras reconstituted with mixed populations of BM cells from male and female donors, the injection of TCR Tg CD8 T cells specific for the HY male antigen leads to the elimination of the cells from male origin and consequently to an augmentation of the number of cells from female origin [68].

In interference competition populations may interact directly with each other, or one population can prevent a second population from occupying a habitat and from exploiting the resources in it. Thus, although interference competition may occur for a resource, it is 'only loosely related to the resource level'.

In exploitation competition different populations have a common need for resources present in limited supply. In this case competition is directly related to the level of resources available.

We may define 'resource', in a broad sense, as any factor which is 'used' by a cell and for that reason is no longer available to other cells [66]. Resources may be trophic factors that ensure cell survival or stimulators like antigen that promote cell growth and expansion.

There is ample evidence for the role of resources in B cell competition.

1. The kinetics of accumulation of transgenic (Tg) and non-Tg populations after reconstitution in different groups of mouse chimeras follow the Monod density-dependent growth curve, i.e. 'it increases in a saturating manner with resource availability' [69]. During the expansion phase of cell reconstitution, resources are abundant, and both Tg and non-Tg populations accumulate at the same rate. When population growth reaches equilibrium, non-Tg populations become dominant, i.e. competition only occurs when resources are limiting [67].
2. Changes in resource level alter the balance between populations; antigenic administration to chimeras hosting different Tg cell populations favors dominance by the antigen-specific cells [70, 71].
3. Experiments demonstrating that the total numbers of peripheral B cells are not determined by rates of new cell production, but are limited at the periphery, also support the existence of resource competition [64].

In the immune system many molecules may function as resources, e.g. antigen, ligands for costimulatory and adhesion molecules, mitogens, interleukins, chemokines, hormones and other growth factors and so on. Resources can be external to the immune system or be produced by the lymphocytes themselves. By producing their own resources, lymphocytes also contribute to generate their own ecological 'space'. The problem is now to establish an hierarchical value for each of the multiple resources.

Resource availability shapes lymphocyte populations

Resource competition may regulate the size of peripheral lymphocyte pools [70]; if peripheral resources are plenty, many more newly generated B cells are able to survive. Any manipulation of resources may modify lymphocyte populations.

When resources are used by many cell types, changes in these common resources will modify overall cell numbers. Hormones and mitogens are examples of pleiotropic resources [1]. In axenic mice lymphocyte numbers are reduced, and lymphocytes expressing activation or memory markers are rare or absent [B. Rocha, personal communication].

Activated lymphocytes and antigen-presenting cells (APCs) are major producers of their own resources. Antigen stimulation increases resource availability by inducing macrophage and lymphocyte activation and the production of numerous cytokines. In this context, lymphocytes can increase in numbers as during the expansion phase of the immune response [72]. Once

antigen is eliminated, cytokine production decreases. Reduced resource levels are unable to maintain the same number of lymphocytes: most will die during the contraction phase of the immune response [72]. Antigen can also be considered as an example of a private resource, i.e. that used by a particular cell set. Changes in the levels of private resources modify the composition of lymphocyte populations, as when antigen injection to chimeras carrying mixtures of two different Tg B cells or of Tg and non-Tg B cells shifted the balance between populations to favor the antigen-specific Tg B cells [70, 71].

In conditions of resource competition one would also expect changes in the 'morphology' of a population in response to the presence of competitors: a process known as character displacement [73]. The IgM secreted into the serum by a population of normal B cells exhibits different binding patterns according to the presence or absence of a population of Tg B cells [70]. This implies that the presence of the Tg B cells leads to changes in the selection of the non-Tg B cell clones, a process that at a population level may be considered to mimic character displacement.

The ecological niche

The variety of resources and the heterogeneity of anatomical structures in the lymphoid organs allows different lymphocyte types to find an ecological niche and survive. The inability of the cell to migrate into the niche may compromise survival: exclusion of B cells from follicular niches in the secondary lymphoid organs has been claimed to result in cell death [61]. Niches may also play a role in homeostasis and in the control of cell numbers by forcing B cells to migrate into the primary follicles [74] where they must compete for trophic factors present in limited supply.

Lymphocytes may help to define their appropriate niches. The maturation of splenic follicular dendritic cell networks and the organization of B cell follicles depend on the expression of LTα and -β and tumor necrosis factor (TNF) by B lymphocytes [75–77].

Germinal centers that develop in the B cell follicles during T-cell-dependent antibody responses are one of the best characterized ecological niche in immunology [78, 79]. Germinal centers are oligoclonal; the B cells that give rise to germinal centers are initially activated outside follicles, and on the average three B cells colonize each follicle. Massive clonal expansion of the initial founder cells, driven by antigen held by follicular dendritic cells, prevents colonization of the germinal center by B cells specific for a second unrelated antigen. Expansion of the B cells is accompanied by BCR hypermutation. Competition among the proliferating B cells based on their ability to interact with antigen held on follicular dendritic cells (FDCs), will lead to the preferential survival of the cells capable of high-affinity recognition and to the death by apoptosis of other cells. Germinal centers therefore play a critical role in the maturation of immune responses by selecting cells with high avidity for antigen binding. They seem to have evolved to provide the appropriate niche for selecting B cells which attempt to gain competitive advantage for survival by somatic hypermutation. Indeed, somatic hypermutation is present in philogeny [80] well before the development of the affinity maturation of immune responses [81]. Affinity maturation of the immune response, however, is only present in species capable of germinal center formation.

B cell niche differentiation

In response to the presence of competitors a population of cells can modify its survival requirements, e.g. adapt to a new ecological niche. It has been shown that niche differentiation is dependent on interactions with the cells of the immune system, in particular naive and activated/memory populations of lymphocytes [82, 83]. Populations of resting and activated B cells are independently regulated [64, 82]. In fact, B cell homeostasis operates differently according to B cell life-history stages. In the central compartments the number of pre-B cells is dependent on the number of immediate precursors, and the rate of pre-B cell and B cell production is constant. At the periphery the size of the naive B cell pool is determined by the amount of available 'resources'. Indeed, in physiological conditions there is an excess of B cell production, which suffices to fill up the peripheral compartments of three mice [64]. Maintenance of normal-sized peripheral B cell pool requires a minimal continuous input of new B cells, since mouse chimeras with a 10-fold reduced B cell production show diminished B cell numbers [64]. Abrogation of new B cell production leads to a rapid decrease in the total number of peripheral B cells [28, 29]. Thus, replacement of resting B cells occurs continuously.

Activated IgM-secreting B cells do not represent a constant fraction of the number of resting B cells, but rather an autonomous compartment with different homeostatic controls. In mice with reduced B cell numbers the number of IgM-secreting cells and the serum IgM levels are as in normal mice [64, 82, 84]. Renewal of these activated Ig-secreting B cells follows the rule 'first come, first served'. Once established, the population of activated B cells has a founder advantage, resists replacement, persists even in the presence of a new cohort of B cells and is able to feedback-regulate the entry of new B cells into the activated pool [82]. The process of feedback regulation may occur through an

active mechanism mediated by the secretion of inhibitory factors, e.g. Igs, γ-IFN, IL-10, or indirectly due to a 'priority effect' in which the cells established first occupy the niche required for the survival of cells arriving late and prevent colonization of that niche by the incoming population. This effect is called interference competition [65].

The independent homeostatic regulation of the resting and activated B cell compartments implies an hierarchical organization of the immune system. In fact, peripheral mature resting B cells only accumulate once the activated pool is replenished, suggesting that the first priority of the system is the maintenance of normal serum IgM levels [82]. The immune system seems to be organized to ensure several alternative sources for the production of the natural antibodies, which constitutes the first barrier of protection. Every newly formed B cell has the ability to differentiate into a plasma cell, but this process is dependent on the nature and the number of cells already present at the periphery. Early during the development and expansion of the immune system an initial pool of activated B cells is selected which may resist replacement. Cellular competition based on BCR diversity and antigenic environment eventually leads to the substitution of the initially selected population by new specificities formed in the BM.

The independent homeostatic regulation of the resting and activated B cell compartments also implies that these two populations occupy different niches and suggest that they may differ in their requirements for survival.

Conclusion

In an immune system where the total number of cells is limited, lymphocyte repertoires will be shaped by the differential ability of lymphocytes to survive. Lymphocyte survival relies on cell/ligand interactions, the availability of other resources, and the nature and number of competing rivals. In order to survive, lymphocytes must acquire a selective advantage over their competitors. They must adapt to the immediate environment by modifying their survival thresholds and/or requirements through differentiation. The immune system shows therefore an hierarchical organization where the independent regulation of the naive and activated/memory cells pools allows the maintenance of both strong memory responses and the continuous availability of new diversity.

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