Rhesus macaque B cell subsets are differentially distributed

Editorial: Where’s the B in NHP?

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REFERENCES


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Editorial:

NHP are the missing link in translating biomedical research from bench to bedside. Indeed, they are often the strongest models for preclinical testing of therapeutic and vaccine candidates, likely providing the most accurate surrogates for whether candidate agents will—or will not—operate effectively in humans. The last decade has witnessed a growing appreciation for B cells as key targets in the development of therapeutics for autoimmune diseases, and B cells are, of course, the sole source of antibody titers required for effective prophylactic vaccines. Accordingly, extending B cell subset hierarchies established in mouse models to nonhuman primates—and then to analogous subsets defined in humans—will be key to leveraging information gained from studies in higher vertebrates.

Surprisingly, despite widespread use of NHP for preclinical and basic studies in diabetes, transplantation, cancer, and infection, detailed information about the numbers and representation, as well as the anatomic locales of B cell and plasma cell subsets, has remained rudimentary. For example, macaca species are commonly used models of human antibody responses to herpes virus, EBV, and SIV infection, yet most published reports to date have used comparatively minimal B cell subset analyses and/or small cohorts of uninfected animals. In this issue of JLB, Neumann et al. [1] take a step toward rectifying this with their report on B cell and plasmablast/plasma cell subsets in primary and secondary lymphoid tissues of healthy rhesus macaques. In addition to providing much-needed, basic information about subset representation, their findings reveal intriguing, previously unappreciated, disparities in proportional representation of B-lineage populations from different anatomic sites. Furthermore, they provide a valuable comparison of fresh versus preserved blood and bone marrow from the same animals, revealing a preferential loss of CD27+ B cells incurred after cryogenic storage.

Similar to other recent reports, Neumann et al. [1] apply multicolor flow cytometry to rhesus macaque B cell subsetting and, like a concurrent report [2], include assessments of activation molecules, chemokine receptors, and Igs in their analyses. In addition, the authors follow phenotyping schemes applied to human B cells and plasmablasts/plasma cells (reviewed in ref. [3]). Three observations are noteworthy and foster thought about future applications. First, the distribution of B cells and plasma cells in bone marrow and secondary lymphoid organs is not necessarily mirrored in blood, consistent with findings in prior studies. A second and unexpected observation is that marrow from a flat bone shows a strikingly different B cell and plasmablast/plasma cell distribution pattern compared with marrow from a long bone. Finally, Neumann et al. [1] show that freezing blood or bone marrow samples leads to loss of CD27+ B cell subsets.

The proportions and phenotypes of peripheral blood B cell subsets do not necessarily reflect those in primary or secondary lymphoid organs. In confirming and extending other reports, Neumann et al. [1] find moderate to large differences in B cell subset and plasmablast/plasma cell frequencies when blood and other anatomic sites are compared [2, 4] (Fig. 1). For example, naïve B cells comprise approximately one-

Abbreviations: BMca = bone marrow from iliac crest aspiration, BMfem = femoral bone marrow, NHP = nonhuman primate(s)
quarter of CD20+ B cells in blood but nearly one-half in spleen and about three-quarters in lymph nodes. Average numbers of cells/ml reported by Neumann et al. [1] are generally concordant with frequencies, although variance in cell number was much greater, particularly for low-frequency memory B cell and plasmablast/plasma cell subsets. The importance of baseline information in healthy individuals is highlighted by several recent reports of proportional and numerical changes in memory B cell subsets following SIV or HIV infection (for example, see refs. [5, 6]). Furthermore, B cells in different locations may undergo no significant change in memory B cell number or in preexisting antibody-producing cells.

Thus, whereas B cells in blood are generally the most approachable for longitudinal studies, blood or PBMCs may not directly reflect global B cell status or anatomic distribution. Whereas this sounds a cautionary note—particularly for studies where expectations include ablations or shifts in B cell subset numbers—these findings might also be leveraged to an advantage; if the relative distributions of B cell subsets in the bone marrow and secondary lymphoid organs are consistent, then the same may be true for humans. This, in turn, suggests that if these relationships can be defined rigorously, then they would allow improved prediction of global B cell status without the need for biopsy or necropsy sampling. For example, if the proportion of a rare subset, such as resting memory, is consistently 2–3 times higher in secondary lymphoid organs compared with blood, then the resting memory B cell count in blood—perhaps paired with a noninvasive measurement of splenic or lymph node mass and cellularity—would yield an estimate of the number of resting memory B cells in the periphery.

Shifts in B cell subset representation following SIV or HIV infection or B ablative therapy are well documented, but these shifts may not underlie numerical changes. The distinction is key to interpreting and understanding humoral immunity in health and disease. For example, patients treated with a B ablative therapy that targets mature, naïve B cells show greatly increased frequencies of circulating memory B cells but undergo no significant change in memory B cell number or in preexisting vaccine-associated antibody titers [8].

Likewise, enhanced representation of transitional B cells in SIV- or HIV-infected individuals (e.g., ref. [9]) may reflect losses (lymphopenia) in the normally more predominant, mature, naïve B cell subset, rather than increased numbers of transitional B cells. Thus, more robust and detailed data sets on B cell and plasmablast/plasma cell numbers in healthy animals should afford an improved understanding of the effects of infection or various therapies on the persistence of memory and antibody-producing cells.

Bone marrow B cell subset and plasmablast/plasma cell representation differ in flat versus long bones. There is growing literature on memory B cell subset distributions in rhesus macaque, which generally parallel distributions and phenotypes observed in humans. In both species, CD20+ B cells are defined further as naïve (CD21+ CD27–), resting memory (CD21+ CD27+), activated memory (CD21– CD27+/hi), and tissue-like or double-negative memory (CD21– CD27–) [2, 4–6]. Neumann et al. [1] follow this scheme and include CD10 as a marker of immature/transitional B cells. Their observations indicate that BMca and BMfem differ widely in the proportion of immature, naïve, and resting memory subsets (Fig. 1). The 5-fold higher proportion of CD10+ cells in BMfem is particularly striking. In contrast, B cell subset proportions are similar when axillary and mesenteric lymph nodes are compared.

There are fewer reports on plasmablasts/plasma cells in rhesus macaque and ongoing debate regarding the surface marker phenotype and roles of these cells in NHP and humans. Human plasmablasts and plasma cells can be distinguished phenotypically based on cell size (plasma cells are larger) and differential expression of surface markers. Both groups are CD19+ but CD20lo/– and express surface CD27, CD38, and/or CD138; however, the pattern and expression level of these markers in these subsets are under debate [3, 10]. With the use of the human phenotyping scheme for plasmablasts/plasma cells, Neumann et al. [1] again find distinct plasmablast/plasma cell subset frequencies between the 2 bone marrow sites examined. For example, the frequency of CD38++ CD138++ plasmablast/plasma cells in

Figure 1. Distribution of B cell subsets and plasmablasts/plasma cells in iliac crest bone marrow (upper left), femoral bone marrow (lower left), spleen (upper right), axillary lymph node (lower right), and blood (center). Pie charts show average frequencies of immature (IMM), mature naïve, and memory B cell subsets, and bar graphs show average frequencies of CD38+/hi + CD138+/hi plasmablasts/plasma cells in each locale, as reported by Neumann et al. [1].
BMfem was ~5 times higher on average compared with BMca (Fig. 1). In addition, the frequency of cells within this group that are also CD27++ differed significantly (72% for cells from BMca; 37% for BMfem). Other phenotypic differences include the proportion of CD38++ CD138++ cells that are positive for the activation marker CD95, which is somewhat less frequent in BMfem, whereas cells positive for the chemokine receptor CXCR4 (CD184) are much more frequent in BMfem.

These unexpected differences in bone marrow from different sites indicate that not all bones are equivalent with respect to the generation of B cell precursors or the specific B cell/plasma cell subsets harbored. Accordingly, the cursors or the specific site for the generation of B cell precursors or the specific sites harbored. Thus, it may be worthwhile to explore means through which information from a peripheral blood sample, along with data from imaging or other technologies, might eventually be used to extrapolate accurately the status of B cell subsets in central or peripheral lymphoid sites—thus, affording improved longitudinal assessments of B cell–targeted interventions.

REFERENCES


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