Editorial: Bone Marrow T Cells at the Center Stage in Immunological Memory

Francesca Di Rosa1* and Tania H. Watts2

1Institute of Molecular Biology and Pathology, Consiglio Nazionale delle Ricerche, c/o Department of Molecular Medicine, Sapienza University, Rome, Italy, 2Department of Immunology, University of Toronto, Toronto, ON, Canada

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Editorial on the Research Topic

Bone Marrow T Cells at the Center Stage in Immunological Memory

The notion that bone marrow (BM) T cells give a key contribution to adaptive immunity is increasingly recognized (1–3). Researchers now more often include the BM when analyzing T cell responses in experimental mouse models (4, 5) or when providing an overview of memory T cell compartmentalization (6). Translation of BM T cell knowledge into medicine has begun. Promising results of the first clinical trial using BM T cells in the treatment of multiple myeloma (MM) were reported last year (7). Further applications are expected in the near future, as BM T cells have been involved in a variety of processes, going from normal hematopoiesis to bone resorption in patients affected by hyperparathyroidism (8, 9).

This research topic on BM T cells contains two sections. The first one contains original research contributions on BM memory CD4 and CD8 T cells in mouse models (Hojyo et al.; Geerman et al.) and hosts a debate on the role of BM memory T cells in systemic or localized memory (Di Rosa; Sercan-Alp and Radbruch; Di Rosa and Gebhardt). In the second one, emerging scenarios in translational medicine in different fields (e.g., hematology, oncology, transplantation immunology, osteoimmunology, etc.) are discussed (Wakkach et al.; Borrello and Noonan; Szyska and Na; Pacifici; Bonomo et al.).

MEM or YT Cells

The BM harbors a high frequency of antigen-specific memory T cells against vaccines, pathogens, and tumors and is considered a major site for the maintenance of memory T cells (reviewed by Di Rosa and Gebhardt). In addition to conventional memory T cells, another class of non-recirculating subsets—the so-called tissue-resident memory T cells (Trm)—has recently been identified in several non-lymphoid organs including skin, gut, and brain (10, 11). These cells, which can provide a first-line defense against reinfection at barrier surfaces, are characterized by expression of CD69 as well as integrins such as CD103 and VLA1, which can contribute to their tissue retention (reviewed in Di Rosa and Gebhardt). BM has a high proportion of CD69+ memory T cells (2, 3, 12), as confirmed in an original report by Geerman et al. in this research topic. However, the expression of CD69 may not be sufficient to define these T cells as “tissue resident.” Di Rosa and Gebhardt discuss the evidence that BM T cells are largely circulatory, likely stopping over temporarily in BM niches where they receive survival signals, before re-entering the circulation.

An issue of some debate has been the extent of homeostatic proliferation of the memory T cells in these niches [Di Rosa; Sercan-Alp and Radbruch; (3, 13–16)]. Sercan-Alp and Radbruch have suggested (3) that the level of homeostatic proliferation measured by BrdU is overestimated. However,
this remains a point of contention. As often found when research groups disagree, the experimental details may offer a solution. One group found, for example, that MyD88 negative mice did not have unexpectedly high rates of BrdU incorporation (Sercan-Alp and Radbruch), suggesting that the BrdU may have been LPS contaminated. Another found that proliferation rates were similar with BrdU and CFSE labels (13). As documented by Di Rosa in her commentary, a variety of experimental approaches have provided evidence that the level of proliferation of memory T cells in the BM, while low, is higher than the level of homeostatic proliferation of T cells in spleen or LN. Thus, it is likely that the niches in the BM that are rich in cytokines such as IL-7 and IL-15, while largely providing survival signals may also induce a low level of proliferation, sufficient to at least partially support homeostasis. A recent hypothesis proposes that memory T cells circulating through the BM may stop to rest for a while in dedicated niches supporting quiescence and/or proliferate in distinct niches for self-renewal, before moving on (16).

In an original research article, Geerman et al. provide evidence that the frequency and phenotype of different subsets of memory T cells as well as their expression of cytokine receptors was similar in different bones in the steady state and after an acute systemic infection with lymphocytic choriomeningitis. This is reassuring for investigators who may wish to use different bones in their studies. Of note, the vertebrae, which contain the most BM cells, also provide the most abundant source of T cells.

In an original research contribution, Hojyo et al. focus on memory CD4 T cells and show that B cell depletion increases the number of CD49b+Tbet+ TCR transgenic CD4 memory T cells in the BM. Whether B cell depletion has a direct effect on the CD4 T cells or affects their access to another factor which in turn regulates their expression of CD49b+ and/or BM localization is not yet clear.

**BM T CELLS IN TRANSLATIONAL MEDICINE**

The activation state of freshly isolated BM T cells, e.g., resulting from exposure to IL-15 in the organ, together with their prompt response to in vitro stimulation makes these cells ideal candidates for adoptive transfers in conditions requiring highly active effectors (17–19). The article by Borrello and Noonan recapitulates concepts and results on the use of marrow-infiltrating lymphocytes (MILs) against MM in humans and discusses the unique opportunity to exploit BM T cells in adoptive T-cell therapy against both hematological and solid cancers. Moreover, MIL transfer might ameliorate bone disease in MM patients, by switching BM T cells from Th17 to Th1 [Borrello and Noonan; (20)].

By contrast, in HSCT transplantation (HSCT), donor T cell effector function against host BM stroma is detrimental for donor HSC seeding and hematopoiesis reconstitution. Starting with the recent recognition that BM is a major target organ in GVHD after allogeneic HSCT in leukemic patients (21), Szszya and Na discuss some possible mechanisms underlying this adverse effect, e.g., T-cell-derived cytolytic factors and cytokines can damage osteoblasts, endothelia, and surrounding cells, while replenishment of destroyed niches by hematopoietic cells is impaired.

Two articles link BM T cell-derived TNF-alpha and IL-17 to altered bone metabolism in human diseases. Pacifici discusses the evidence suggesting that catabolic effects of parathyroid hormone on bone in patients affected by hyperparathyroidism relies on Th17 cell-induced RANKL release by osteoblasts and osteocytes, with subsequent osteoclast-mediated bone resorption (9). Wakkach et al. give an overview of the mechanisms supporting bone destruction in inflammatory bowel disease and propose that TNF-alpha-producing Th17 cells in the BM sustain bone loss in patients with Crohn's disease (22).

Bonomo et al. review the evidence that BM T cells are at the cross-roads between immunity, bone metabolism, and hematopoiesis and propose that T cells act as messengers who “bring the news” from the periphery to the BM. According to this view, activated T cells enter the BM and modulate BM-resident cell function, ultimately tuning blood cell production and bone remodeling to the class of peripheral immune response (Bonomo et al.).

**AUTHOR CONTRIBUTIONS**

TW wrote the paragraph on memory T cells in the BM; FD wrote the paragraph on BM T cells in Translational Medicine; FD and TW together wrote the remaining parts and edited the final text.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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