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SPECIAL MINI REVIEW

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Rethinking 'immunological memory': Local and systemic immunity provided by bone marrow-resident memory cells

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Abstract

It has been 25 years since we first described long-lived memory plasma cells of the bone marrow, 13 years since we identified bone marrow resident memory T cells and 2 years since we showed that the bone marrow is also a preferred location of resident memory B cells. The bone marrow is increasingly recognized as a fundamental component of long-lasting immunological memory, not only providing protective immunity but also fuelling chronic inflammation. We now understand that the bone marrow functions as the 'backbone' of immunological memory, hosting the memory plasma cells which provide not only humoral immunity but also memory B and T cells, which constitute 'reactive memory'. This knowledge now allows us to define true cellular 'correlates of protection' for systemic immunity, its quality and duration, as induced by infection and vaccination, something that has never been more important given the recent SARS-CoV-2 pandemic. While memory plasma cells of the bone marrow indicate long-lasting humoral protection, memory T (and B) cells mobilized into the blood in secondary immune reactions indicate the strength of reactive memory. In this review, we have contextualized many of our own findings from the last two decades that have contributed to our understanding of how bone marrow-resident memory cells provide local and systemic immunity.

1 | INTRODUCTION

This year marks 25 years since we first published the identification of long-lived memory plasma cells in the bone marrow (BM) as a correlate of long-lasting humoral immunity.[1] While immunological memory has always been a 'hot topic' of debate for immunologists, since the outbreak of the SARS-CoV-2 pandemic in 2020, it has also attracted considerable public interest. Reassuringly, many of the published reports concerning the immune response to SARS-CoV-2 (both the initial reaction and the memory phase) hold true to several major pillars of what we already knew concerning the formation and maintenance of immunological memory. And although we are far from a concise systemic understanding of how immunological memory provides immunity, in practical terms, we believe that we can now define resident memory cells as a 'cellular correlate of protection', allowing us to predict that systemic immunity to SARS-CoV-2, as induced by infection or vaccination, will be effective and long-lasting. In this review, we will put our own findings together with those from others into context, illustrating how local and systemic immunity is provided by BM-resident memory cells.

2 | THE BM ATTRACTS PLASMABLASTS AND MAINTAINS LONG-LIVED MEMORY PLASMA CELLS

Our journey studying the organization and maintenance of immunological memory started with the discovery that murine plasma cells survive in the BM for up to 120 days following a systemic immune reaction in mice.[1] These cells were found to be 'resting', a term now commonly used, meaning that they were not proliferating. This was critical as it showed that the stable number of BM plasma cells seen in our experiments was due to long-term maintenance of the cells, rather than continuous death and regeneration of short-lived plasma cells, as had been previously thought. The term 'memory plasma cells' was coined following these experiments, because the cells maintained the information on specific antibody production in the absence of continued instruction by antigen.[2] Rafi Ahmed's lab also confirmed and extended our findings in a different experimental setup.[3] Together, these papers have formed one of the central pillars in our understanding of the maintenance of long-term immunological memory – the BM is key.

These initial breakthroughs opened a Pandora's Box of questions regarding the generation and maintenance of immunological memory. For example, how do newly generated plasma cells migrate from the secondary lymphoid organs to the BM? Jason Cyster's laboratory showed that newly generated plasma cells exit the spleen and lymph nodes via a coordinated change in the expression of several chemokine receptors. This involves downregulation of CXCR5 and CCR7[4] and upregulation of the sphingosine-1-phosphate receptor-1 (S1P1),[5] thereby allowing such cells to sense sphingosine-1-phosphate in the blood. Expression of CXCR4 (for the ligand CXCL12) was also found to be important for migration into the BM as shown by both CXCR4-deficient plasma cells, which did not accumulate normally in the BM, and by pre-treatment of plasma cells with the CXCR4 inhibitor AMD3100, which resulted in less BM seeding after adoptive transfer.[4,6] Interestingly, work from Anja Hauser and Rudi Manz also showed a temporal dynamic in the migratory responsiveness of newly generated plasmablasts to chemokines including CXCL12, despite continued expression of CXCR4. While plasmablasts were found to migrate in response to CXCL12, plasma cells did not.[7] This non-responsiveness of BM plasma cells may be important for ensuring that they remain resident, in contact with CXCL12-expressing stromal cells.[8,9]

3 | HOW THE BM STROMA AND SOLUBLE FACTORS ACT AS A BACKBONE TO SUPPORT MEMORY PLASMA CELLS

The existence of BM survival niches may explain how a tissue such as the BM, with its ever-changing cellularity, can support the long-term maintenance of memory lymphocytes. It is also clear that certain factors are essential for the survival of plasma cells, as they die almost immediately after isolating them from the BM.[10] Although some plasma cell survival factors had been documented, including cytokines and adhesion molecules,[11–13] recreation of the BM niche ex vivo to analyse plasma cell survival in molecular detail was a complex task. This involved culturing the isolated BM plasma cells under hypoxic conditions, providing direct stromal cell contact (in our case the stromal cell line ST2) and the addition of the cytokine APRIL (A Proliferation-inducing ligand), which signals via the receptors B cell maturation antigen (BCMA) and transmembrane activator and CAML-interactor (TACI) on plasma cells.[14] In such ex vivo niches, stromal cell contact and APRIL-induced signalling were both necessary and sufficient to maintain the survival of BM memory plasma cells. Stromal cell contact was found to activate the PI3K signalling pathway (and prevented activation of caspases 3 and 7), while APRIL activated the NFkB pathway (and prevented activation of caspase 11). Thus, stromal cells and APRIL synergise to provide the memory plasma cells with resilience to mitochondrial and endoplasmic reticulum stress resulting from the extensive antibody synthesis of the plasma cells. It

remains to be shown whether a soluble survival factor such as APRIL directly binds to its receptor in this form in vivo in order to mediate its effects. However, it is interesting to note that that APRIL can also bind to the extracellular matrix, with the immobilized form of the cytokine being capable of triggering the receptor.[15]

While the maintenance of memory lymphocytes in the BM clearly depends on cellular contact with stromal cells, these vital supporting cells themselves have remained enigmatic. Single cell sequencing of more than 1000 primary murine BM stromal cells revealed an astonishingly high level of heterogeneity in the cells analysed, in particular with respect to the expression of genes coding for secreted proteins, such as cytokines and chemokines.[16] Three populations of *Cxcl12*-expressing stromal cells were uncovered, according to high, medium and low levels of expression, hinting towards the possibility that these subpopulations could support different haematopoietic cells according to their varying needs. Furthermore, 14 subsets of stromal cells were distinguished based on their expression of a cytokine or chemokine, including cytokines known to play a role in memory T cell survival such as IL-7 and IL-15. Taken together, these results clearly indicate that the BM is highly specialized in supporting different types of memory lymphocytes, in part due to the heterogeneity of its stromal cells.

One intriguing possibility concerning BM stromal cells relates to their possible function in controlling the number of memory lymphocytes in the BM. Although it remains to be shown whether this is directly controlled by the stromal cells or not, as we generally only see one memory cell contacting one stromal cell, this could theoretically mean there is a limit to the number of memory lymphocytes which can be supported at any one time. Further research is needed to understand what would happen if all the niches become occupied, or how the composition of memory cells changes following a new antigen challenge.

4 | THE BM MAINTAINS POPULATIONS OF RESTING, RESIDENT MEMORY T CELLS SPECIFIC FOR SYSTEMIC ANTIGENS

'Antigen-experienced' BM CD4+ T cells, derived following exposure to environmental antigens, had been documented in mice already in 1999[17]; however, the relationship of these cells to memory cells in the periphery and the role that they played in recall responses was not clear. Using a murine adoptive transfer model system, Koji Tokoyoda showed that unlike memory T cells in the secondary lymphoid organs (SLOs) which decreased over time, antigen-specific BM memory T cells accumulated in number before plateauing approximately 2 months after exposure to antigen.[18] These BM memory T cells were found to be in contact with IL-7-expressing stromal cells and were 'resting' in terms of proliferation. Moreover, they provided B cell help for the generation of high-affinity antibodies and were prolific cytokine producers, proving their status as 'professional' memory T cells. Follow-up studies documented the importance of integrin alpha 2[18,19] and CD69[20] in mediating the homing to and persistence of memory T cells in the BM.

Interestingly, unlike the situation we had previously described for memory plasma cells and CD4+ T cells, other groups had reported that for memory CD8+ T cells in the BM, (homeostatic) proliferation may play a major role in their maintenance, with the half-life of such cells amounting to approximately 14 days in mice.[21–23] However, using flow cytometric analysis of Ki-67, an antigen only expressed in proliferating cells, we found the vast majority of antigen-specific BM memory CD8+ T cells were resting in the G0 phase of the cell cycle.[24] Moreover, we examined the proliferation status of antigen-specific memory CD8+ T cells over a longer period of time by treating mice with cyclophosphamide for 14 days in order to deplete any proliferating cells during this two-week window. While this did not result in a significant decrease in the number of antigen-specific CD8+ BM memory T cells, their splenic counterparts were reduced by approximately 50%.[25] Therefore, while a large number of splenic memory CD8+ T cells may be maintained by proliferation, this was not the case for BM memory CD8+ T cells. One possible explanation for the conflicting results between our studies and those of others relating to the proliferation status of BM memory CD8+ T cells could be due to the use of Bromodeoxyuridine (BrdU) to mark proliferating CD8+ T cells,[21–23] as we could show that BrdU itself induced proliferation in these cells.[24] Therefore, the use of BrdU should be avoided when examining the proliferation profiles of BM memory CD8+ T cells in favour of other methods, such as Ki-67 staining.

Before the term 'tissue-resident' memory T cells existed, we had an inkling that BM memory T cells were most likely long-term tissue inhabitants.[18] Comparison of antigen-specific memory CD4+ T cells in the blood and BM of individual humans showed that the BM is home to resting memory T lymphocytes, which maintain long-term memory to systemic (e.g. measles, mumps, rubella; MMR), but not to cutaneous antigens.[26] Confirming their 'resident' status, such BM memory CD4+ T cells were maintained in the tissue even when they were no longer detectable in the blood.[26] Therefore, analysis of circulating memory cells in the blood (particularly in humans) is a poor indication of immunological memory existing in the tissues.

A major breakthrough in understanding the residency of memory T cells in tissues came following studies examining the inhibitory nature of the relationship between the activation marker CD69 and the chemokine receptor S1P1 and their dual control in lymphocyte trafficking.[27,28] Rather than acting as an early activation marker as previously thought, expression of CD69 acts as a 'stop signal', preventing surface expression of S1P1 and thereby counteracting the recruitment of cells into the blood.[29,30] Two terms were coined to distinguish memory T cells in the blood (which do not express CD69) from the CD69-expressing memory cells in the tissues: 'Circulating' and 'Tissue Resident' memory (TRM) T cells, respectively.[31–33] In humans, CD69 is expressed on approximately 30% of CD4+ and 60% of CD8+ BM memory T cells,[26] while in mice, 30%–40% of CD8+ BM memory T cells[24] and 40%–50% of CD4+ BM memory T cells express it.[20,34] Gene expression analysis of CD69± human and murine BM memory CD4+ T cells[35] revealed that only the CD69+ memory T cells expressed typical transcripts associated with a TRM phenotype previously described for TRM cells from other tissues,[36,37] while CD69− cells did not. Therefore, while in both humans and mice, CD69+ memory T cells constitute a population of resting, resident memory cells which protect the local tissue from systemic pathogens, the jury remains out on the role of CD69− BM memory T cells.

5 | DISTINCT POPULATIONS OF MEMORY B CELLS ARE MAINTAINED IN THE BM AND SLOS

As with CD4+ T cells, 'antigen experienced' B cells had been detected in the BM[38]; however, the presence of BM memory B cells was reported to be more indicative of a larger circulating population, rather than a specific 'resident' BM population.[39] Comparison of isotype-switched memory B cells (Bsm) from the spleen and BM in mice revealed that many of the features of memory plasma cells and T cells also held true for Bsm in that they were also resting in terms of proliferation and were found to be docked onto stromal cells.[40] Moreover, the B cell receptor repertoires of Bsm from the spleen and BM in individual mice were significantly different, proving that rather than only being a fraction of circulating memory B cells, they constituted distinct populations of resident memory cells, with cells of only one such population being migratory.[40] It remains to be shown how these different populations of Bsm in SLOs and BM contribute to secondary immune responses.

6 | REACTIVATED BM MEMORY T CELLS PARTICIPATE IN SECONDARY IMMUNE RESPONSES BOTH LOCALLY AND SYSTEMICALLY

The work from Koji Tokoyoda had already hinted to the role of (CD4+) memory T cells following reactivation – at least in terms of their cytokine production and their ability to provide help for high affinity antibody production following adoptive transfer.[18] As no germinal centres were found in the BM during recall responses, it was assumed that reactivated BM memory CD4+ T cells left the BM to participate in the secondary immune reaction in SLOs. It was therefore surprising to see that antigen-specific memory CD4+ T cells in the BM vigorously proliferated 3 days after in vivo reactivation with cognate antigen, with the number of such cells increasing more than 25-fold.[34] Use of the S1P1 inhibitor FTY70, to trap cells in the tissues before injecting the reactivating antigen, showed that this proliferation of BM memory T cells was independent of circulating cells. Moreover, 'immune clusters' (previously described following priming of naive T cells in the BM[41]), composed of activated T cells and antigen presenting cells, formed exclusively in the BM in the days immediately following reactivation. The early appearance of these clusters, lacking apparent cellular organization, were in stark contrast to the typical germinal centres seen later in the spleen.[34] Following cessation of the reactivation response, the BM memory CD4+ T cells went back to their resting phenotype, albeit in increased numbers, thereby maintaining and reinforcing the local immunity in the tissue. While we were the first to show this specifically for the BM, the fact that secondary recall responses were not diminished following removal of circulating lymphocytes had been known for many years,[42] again emphasizing the importance of maintaining tissue-resident memory T cells for ensuring successful reactivation responses.

However, as BM memory CD4+ T cells had also been shown to be capable of providing help in the generation of high-affinity antibodies outside of the BM,[18] presumably some BM TRM cells could be mobilized following reactivation to participate in recall responses in the SLOs. As the murine system did not lend itself easily to allow for determining whether BM TRM cells responded in such a way, we examined recall responses in humans following vaccination against MMR to assess the role of such cells in systemic immune reactions. Within 24 h, there was a rapid mobilization of antigen-specific memory CD4+ T cells into the blood following booster immunization of healthy adults with the MMR vaccine.[43] Examination of the epigenetic signature of circulating antigen-specific

CD4+ memory T cells before and after reactivation showed that while before activation, the circulating cells had a signature of splenic TRM cells, after activation the signature resembled BM TRM cells. Moreover, approximately 1 day after reactivation, the newly mobilized circulating cells were not yet proliferating (something not seen until several days later) – indicating that the initial reactivation resulted in a fast emigration of TRM cells from the BM into the circulation.[43] These mobilized TRM cells then disappeared from the circulation 2–4 days after challenge, before newly generated, still proliferating memory T cells exited into the blood, containing clonal offspring of the initially mobilized TRM cells.[43] Analysis of mobilized and circulating memory T cells on day one after a systemic recall challenge thus provides a unique measurement of the strength of the reactive memory towards this challenge.

7 | DOES THE BM PLAY A ROLE IN MAINTAINING LONG-TERM MEMORY TO SARS-CoV-2?

Defining the extent and duration of protective memory after infection from or vaccination against SARS-CoV-2 has become similar to the quest for the 'Holy Grail'. According to our concept that the BM maintains long-term memory to systemic antigens, this would presumably also be the case for systemic immune memory to SARS-CoV-2. Indeed, publications from the group of Ali Ellebedy have shown that long-lived memory plasma cells reside in the BM of individuals up to 11 months after infection,[44] and also more than 6 months after two doses of mRNA vaccination, in numbers roughly equivalent to those plasma cells secreting tetanus- or diphtheria-specific antibodies.[45] As for memory CD4+ T cells, SARS-CoV-2-specific polyfunctional memory CD4+ T cells were found to reside in the BM of vaccinated but also unexposed individuals, pointing to an eminent cross-reaction between T cells recognizing SARS-CoV-2 and common antigens of our environment.[46] The SARS-CoV-2-reactive BM memory CD4+ cells outnumbered their circulating counterparts, and were as frequent as those reactive to tetanus. This is particularly important given the emergence of the Omicron variant with its immune escape in relation to neutralizing antibodies.[47,48] For systemic immunity, this escape is of little relevance, given the robustness of T cell memory and overall humoral memory towards the mutations of Omicron.[49] Predictably, the long-term maintenance of (tissue-resident) memory B and T cells in the BM is vital in preserving the continued protection the vaccines provide from severe disease and death.[49,50]

8 | CONCLUSIONS

Over the past two decades, we have built up a body of work showing that long-term immunological memory is maintained in tissues such as the BM. Ignoring such tissues and assaying only memory cells from SLOs in mice or blood in humans leads to a false representation of immunological memory, and explains why defining correlates of protection against diseases has failed previously. Today, we can be confident that resident memory plasma cells of the BM secreting protective antibodies are a true 'correlate of humoral protection',[44,45] and that mobilized and circulating memory T cells assayed on day one after recall challenge are a true 'correlate of reactive memory',[43] of course in conjunction with the cellular and humoral response generated in those secondary immune reactions.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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