**Novel players: tissue-resident memory B cells**

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The paper by Shlomchik and colleagues in this issue of Blood identifies a novel subset of human memory B cells (MBC), tissue-resident memory B (BRM) cells, with a unique gene expression signature and a function distinct from conventional CD27+ MBC 1.

The conventional approach to understanding the biology of the human memory B cell compartment has focused on studying peripheral blood and secondary lymphoid tissues, largely focusing on tonsil and spleen 2,3,4. Previous studies using gut-associated lymphoid tissues (GALT) led to increased understanding of MBC subsets and deeper understanding of B cell biology in lymphoid tissues but gut tissue itself was not evaluated 5.

Not until now has a comprehensive analysis of B cell lineages across multiple lymphoid and non-lymphoid tissues been performed. Shlomchik et al have carried out a deep phenotypic analysis of tissues which became available from multiple healthy donors. They enumerated the broader B cell subsets using conventional B-cell markers including CD38, CD27 and Ig isotype to identify immature, antigen-naïve and antigen-experienced memory B-cell and antibody-secreting subsets. This carefully conducted comparison provides a unique source of data on the distribution of multiple B cell lineages in the human body. A further focus on understanding the heterogeneity among MBC populations using CD45RB and CD69 as an early activation marker linked to residency in non-lymphoid tissues identified a double-positive CD45RB+CD69+ MBC population among CD27+ B cells. This was enriched in the gut and also present in secondary lymphoid tissues, in smaller proportions but was strikingly absent in the blood or bone marrow. In fact, the vast majority of MBC in the gut were CD45RB+CD69+ prompting the proposal that these markers identify gut BRM cells. Remarkably single positive, double positive and negative subsets were also distinctive in their functionality with the double-positive subset highly effective in generating antibody upon stimulation. These findings indicate that tissue-located B cells are distinctive and not in homeostasis with the more commonly studied circulating B cells.

RNAseq analysis comparing the four MBC subsets selected on the expression of CD45RB and CD69, and carefully isolated from ileum avoiding GALT and compared to splenic MBC, revealed a unique subset of genes exclusively expressed in the double-positive MBC in the intestine. Indicative of B cell effector function, the CD45RB+CD69+ BRM cell subset had increased expression of gene signatures consistent with B-cell differentiation into antibody-secreting plasmablasts and plasma cells.

Functional studies supported the fact that BRM cells differentiate into IgM antibody- secreting cells. In terms of their functional significance, these are most likely to give rise to IgM-secreting cells previously described in the gut to preserve commensal bacteria but may also play a role in protection against infectious disease 6. The question is whether gut BRM cells will undergo antibody isotype-switch and produce IgA or will continue as IgM remains to be answered. IGHV mutational analysis of this novel memory B cell subset will provide further insight into the differentiation status and will allow probing of the link between BRM cells and IgA+ B-cell memory. The further question is whether effective vaccines against enteric pathogens should aim to induce BRM cells, hence possibly requiring delivery via mucosal routes.

This study parallels one of BRM cells found in the lung in mice with distinctive properties but lacking the ability to circulate 7. For these lung BRM cells there was an apparent requirement for local antigenic challenge to fully differentiate into BRM. In the case of the gut BRM cells, the antigens are presumably local commensal or pathogenic bacteria.

BRM cells express genes associated with effector function ready to contribute to an early plasmablastic antibody response to antigens. In this respect there is a parallel with tissue-resident memory T (TRM) cells which are highly functional and express high levels of cytolytic and activation molecules 8, 9. The other striking parallel with TRM cells in lacking the ability to circulate points out that these highly functional lymphocytes may be best placed where they are needed to combat the ever-hostile encounters with pathogens or cancer or, in case of BRM cells, also to maintain microbiota 6.

Further insights into biology of normal BRM cells might provide insight into the cell of origin for B-cell malignancies which reflect these features, including those originating in mucosal sites.

**Conflict of interest**

Theauthors declarethat there isno conflict of interest.

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