use in oncology clinical trials of immunotherapy to avoid stopping immunotherapy too early in those patients deriving benefit despite imaging that generates concern for progression. Unfortunately, as planned, this study did not meet its planned number of CRs per a Simon 2-stage design, which leaves another gap on whether an enriched population with high PD-L1 expression per the used score would have achieved similar responses and durability. The recurring reports of hyperprogression in the studies of the uncommon forms of NHL with relatively small sample size calls for further investigation into underlying mechanisms of such responses. The risk-benefit balance is critical in this scenario and would have an impact on timing for using such therapy (earlier vs later lines of therapy) because only a small percentage of patients are expected to be salvageable if they develop hyperprogression with these agents.

In summary, this report adds to the body of evidence for the activity of checkpoint (PD-1 and now PD-L1) inhibitors in ENKTL and serves as a useful reminder of the spectrum of responses of such agents, reconsideration of clinical trial design with particular agents, and the continued pursuit of filling our knowledge gaps in uncommon diseases.

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IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Weisel et al, page 2774

Novel players: tissue-resident memory B cells

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The paper by Weisel and colleagues in this issue of *Blood* identifies a novel subset of human memory B cells (MBCs), tissue-resident memory B (BRM) cells, with a unique gene expression signature and a function distinct from conventional CD27$^+$ MBCs.[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.[2-4] Previous studies using gut-associated lymphoid tissues (GALTs) 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 nonlymphoid tissues been performed. Shlomchik et al have carried out a deep phenotypic analysis of tissues that became available from multiple healthy donors. They enumerated the broader B-cell subsets using conventional B-cell markers, including CD38, CD27, and immunoglobulin isotype, to identify immature, antigen-naive, 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 nonlymphoid tissues identified a double-positive CD45RB$^+$ CD69$^+$ MBC population among CD27$^+$ B cells. This was enriched in the gut and present in secondary lymphoid tissues, in smaller proportions, but was strikingly absent in the blood or bone marrow. In fact, most MBCs 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 4 MBC subsets selected on the expression of CD45RB and CD69, and carefully isolated from ileum avoiding GALTs and compared with splenic MBCs, revealed a unique subset of genes exclusively expressed in the double-positive MBCs 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 immunoglobulin M (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. Immunoglobulin heavy-chain gene variable region 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 cells. 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 the case of BRM cells, also to maintain microbiota.[6]

Further insights into the 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.

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LYMPHOID NEOPLASIA

Comment on Oberbeck et al, page 2786

TCL1 and TCR collaborate to drive T-PLL

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In this issue of *Blood*, Oberbeck et al[1] have undertaken a comprehensive evaluation of the biology and genetics of T-cell prolymphocytic leukemia (T-PLL), focusing on the cooperation between the T-cell receptor (TCR) and the proto-oncogene T-cell leukemia 1A (*TCL1A*) in promoting the growth and survival of T-PLL cells.

T-PLL is a rare, aggressive, and ultimately fatal malignancy. To date, understanding of the pathogenesis of T-PLL has been elusive, and successful therapy even more so. In this paper, Oberbeck et al report the results of a series of elegant experiments on a large collection of 188 primary T-PLL cells, supplemented by murine models to validate their findings. First, the authors confirm that surface marker and gene expression reveal a central memory T-cell phenotype in the majority of T-PLL samples, albeit with some heterogeneity, which is distinct from normal naive T cells. Second, they show that the T-PLL cells have an activated phenotype, with overexpression of proliferation markers, such as CD38, CD69, CD40L, and Ki67. Interestingly, this does not appear to change during disease progression, although further longitudinal studies may be required to confirm this. This activation state is maintained by constant low-level antigen stimulation via the TCR and is coupled to downregulation of inhibitory coreceptors (eg, CTLA4), resulting in persistence of the T-PLL clone. Resting memory T cells depend on low-level TCR input, but the threshold for activation is much lower in T-PLL than in normal T cells. Third, Oberbeck et al interrogated the role of TCL1A, which has been recognized for >20 years as the most frequently occurring genetic alteration in T-PLL.[2] This antiapoptotic protooncogene has a twofold impact (see figure). It enhances the response to T-cell stimulation leading to a growth advantage over normal T cells and facilitates transformation. In addition, it promotes resistance to activation-induced programmed cell death (AICD) via its interaction with the prosurvival kinase AKT. The fact that most T-PLL cells are ataxia telangiectasia mutated (ATM) deficient further compromises the intracellular apoptotic machinery.[3] All of these features, memory T-cell phenotype, activation markers, and high expression of TCL1 protein, are associated with poor clinical outcome when queried in the patient cohort. For example, overall survival was