In this issue of Blood, Keren and colleagues report the existence of novel aging-associated cross-talk between the peripheral B-cell compartment and progenitors in the bone marrow, which negatively regulates B-cell production.1 This pathway could represent a target for therapeutic intervention in aged individuals who suffer from recurrent infection caused by immunosenescence.

Aging is associated with alterations in the B-cell compartment resulting from decreased production of these important cells. However, despite this decline in B lymphopoiesis, absolute numbers of B cells remain unchanged in peripheral blood, spleen, and lymph nodes during aging.2,3 Published studies have clearly shown that this defective production of B cells is linked in part to acquired hematopoietic stem cell (HSC)–intrinsic defects4,5 and microenvironmental changes.6 Exploring the possibility that production of B cells might also be regulated by accumulated antigen-experienced cells, Keren and colleagues determined that elimination of peripheral B cells from aged mice results in increased production of B cells in the bone marrow. They did not demonstrate complete restoration of B-lymphopoietic rate, and thus did not exclude roles for intrinsic stem-cell or microenvironmental defects. Nonetheless, this study suggests the existence of aging-associated repressive cross-talk between the peripheral B-cell compartment and progenitors in the bone marrow that affects B-cell production, and supports the notion that the defective B lymphopoiesis in aging may be partially reversible (see figure).

The investigators used 3 B cell–depletion strategies to examine the effect of peripheral B-cell depletion on B-lymphopoietic activity. Taking advantage of B cell–activating factor receptor (BAFF–R) signaling requirements for the survival of mature B cells, they generated and studied mice homozygous for a targeted loxp-flanked Baff-r allele (BAFF-RFL/FL) and transgenic for cre-recombinase driven by the type-I interferon responsive promoter (Mx-cre). Elimination of B cells by conditional BAFF–R gene deletion led to significant restoration of B lymphopoiesis in old BAFF-RFL/FL Mx-cre mice, as suggested by the increased generation of proB, preB, and immature B cells in bone marrow. In a second approach they depleted B cells in aged animals by multiple rounds of treatment with antibodies reactive with B-cell surface markers. This approach also led to increased B lymphopoiesis. Finally, they used transgenic mice expressing human CD20 specifically in the B lineage (hCD20 Tg mice), eliminating B cells in aged animals with anti-huCD20 (Rituxan). Once again, peripheral B-cell deficiency enhanced B lymphopoiesis in the bone marrow of old mice with increases seen in early hematopoietic progenitor cells including multipotent primitive progenitors and common lymphoid progenitor stages.

Keren and colleagues next tested whether B-cell depletion in aged animals rejuvenates the repertoire of B-cell antigen-receptor specificity. To test this question, they used an immunoglobulin transgenic mouse model (3-83Tg mice).
previously used to monitor age-associated changes in the B-cell repertoire.2,3 Results indeed suggested that depletion of long-lived, antigen-experienced B cells in old 3- to 3Tg mice can, by reactivating B lymphopoiesis, give rise to a more young mouse–like repertoire.

One of the most biologically important aging–associated changes in the immune system is the failure to mount protective antibody responses on vaccination or infection by newly encountered pathogens.2 To test the competence of the rejuvenated peripheral B-cell compartment, the authors immunized aged mice that had been subjected to B-cell depletion. They observed a significant increase in the ability of the mice to mount a primary antibody response, although these responses were much reduced compared with those of young mice.

Rejuvenation by peripheral B-cell depletion is at odds with previous experiments in which hematopoietic stem cells from aged animals failed to reconstitute a young–like repertoire when transferred to lethally irradiated, therefore B cell–depleted, young recipients.5 In these earlier studies, it was further shown that simple reduction of the number of young HSCs transferred to irradiated recipients replicated the defect. This pointed to low frequency of lymphoid–competent HSCs in the old bone marrow as an underlying cause of the defect. Recent studies have shown that HSC populations may be composed of functionally distinct subsets characterized by distinct differentiation potential6–11 and that this composition is altered during aging with expansion of myeloid-biased HSCs.12 Thus, multiple factors are at play in aging–associated immuno-senescence.

A remaining question is explanation of the observed selective loss of B–versus T–lymphopoietic potential in HSCs from aged animals. Provided the thymus is functional, T lymphopoiesis is retained.5 Thus, immunologically aged progenitors seem to display a specific defect in B-cell production rather than a simple skewing of myeloid– and lymphoid-biased cells. Might the cross-talk observed by Keren et al contribute to this bias?

The findings of Keren et al are important in showing that defective B lymphopoiesis in aging may be partially reversed and that peripheral B-cell populations can speak to the lymphopoietic machinery. It is tempting to speculate about the existence of a soluble factor secreted in the periphery and sensed at the hematopoietic progenitor level. The next step will be to explore the nature of this activity.

Keren and colleagues’ work may constitute a breakthrough in our understanding of the molecular basis of the age-associated immune dysfunction. Of import to the common man is the possibility the clinical depletion of the source of this repressive activity may increase immune function in the aged.

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REFERENCES


Comment on Gay et al, page 3025

Toward deeper response in MM

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In this issue of Blood, Gay and colleagues report that in 1175 elderly myeloma patients treated with melphanal/prednisone plus novel agents, the achievement of complete remission was an independent predictor of outcome.1

Multiple myeloma (MM) is a proliferation of clonal bone marrow plasma cells (BMPCs) characterized by a high degree of resistance to chemotherapy. In fact, complete remission (CR) was rarely observed with the use of conventional chemotherapy. For many years stabilization of tumor load was considered a more powerful prognostic factor than degree of tumor reduction.2 More recently, it was shown that high-dose therapy followed by autologous stem–cell transplantation (ASCT) results in a higher tumor reduction, and a significant correlation between the degree of tumor decrease and survival was observed. This lead to the definition of CR by the European Blood and Marrow Transplantation (EBMT) group as negative immunofixation electrophoresis (IFE) in serum and urine, in the absence of increased BMPCs. More recently, the International Myeloma Working Group (IMWG) expanded the CR EBMT criteria by adding the category of stringent CR (sCR), defined by negative IFE in serum and urine with a normal serum free light chain (FLC) ratio plus the absence of clonal BMPCs by immunohistochemistry or immunofluorescence.3 The IMWG also introduced the concept of very good partial response (VGPR; ≥ 90% M-protein decrease) as a separate category of partial response (PR; ≥ 50% M-protein decrease). In addition to the EBMT and IMWG response criteria, the achievement of negative minimal residual disease (MRD) by multiparameter flow cytometry (MFC) or by molecular studies4 are essential for long-term remission duration and prolonged survival. Finally, between 10% and 40% of patients with MM in CR after ASCT develop oligoclonal bands, a fact likely resulting from a robust humoral response and associated with a favorable outcome.5
B cells talk to their progenitors

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