the disease but at the risk of severe GVHD. Separation of GVL reactivity from GVHD would improve cancer therapy in the context of hematopoietic stem cell transplantation with no or limited toxicity. Previously, the potential effectiveness of in vitro–selected and –expanded virus-specific T cells has been illustrated.[5] Infusion of ex vivo–selected and –expanded T cells recognizing (leukemic) hematopoietic cells from the patient, but not nonhematopoietic cells, is being explored to more effectively provide GVL reactivity.[6,7]

As reported in this issue of *Blood*, Warren and colleagues have explored the adoptive transfer of T cells selected ex vivo to recognize minor histocompatibility antigens for the treatment of patients with relapsed leukemia after allogeneic hematopoietic stem cell transplantation.[8] By selecting T cells that recognize mHAgs preferentially expressed on recipient hematopoietic cells, they attempted to separate GVL reactivity from GVHD. Recognition of hematopoietic cells from recipient origin and absence of recognition of skin fibroblasts were evaluated as the criteria for selecting T-cell responses that do not elicit GVHD. They evaluated whether in vitro expansion of such mHAg-specific T cells to large numbers was feasible and could lead to in vivo persistence and migration of the cells to the bone marrow, resulting in a specific therapeutic effect.

The authors demonstrate that despite the logistic complexity of in vitro isolation, characterization, and expansion of clonal mHAg-specific T cells, they were capable of generating therapeutic doses of T cells, resulting in a strong biologic effect in patients. Unfortunately, the selection criteria did not result in the prevention of GVHD. Pulmonary toxicity was the most frequent sign of undesired GVHD, illustrating that more stringent selection of the right specificity is necessary, which was further substantiated by successful molecular characterization of some of the mHAgs. Although the side effects were obviously disappointing, the authors demonstrate in their paper proof of principle that antigen-specific T cells can be isolated, expanded, and infused and can elicit a clinical effect. The antileukemic effects unfortunately did not persist, possibly due to exhaustion of the T cells resulting in relatively short in vivo survival.

The clinical study of Warren and colleagues is an important study that demonstrates the feasibility of adoptively transferring in vitro–selected and –expanded mHAg-specific T cells in the context of allogeneic stem cell transplantation. Combining various strategies—for example, first depleting alloreactive T cells from the graft (T-cell depletion), followed by administration of more stringently selected T cells recognizing mHAgs specifically expressed on hematopoietic cells—and better selection of T-cell subsets as previously suggested by the authors[9] may lead in the future to separation of GVL from GVHD and better outcome of allogeneic hematopoietic stem cell transplantation.

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● ● ● HEMATOPOIESIS & STEM CELLS

Comment on Gomes et al, page 3886

Cholesterol activates vascular niche and hematopoiesis

Shahin Rafii and Daniel Nolan WEILL-CORNELL MEDICAL COLLEGE

In this issue of *Blood*, Gomes and colleagues demonstrate that hypercholesterolemia in mice for 30 days induces dramatic alterations in hematopoiesis through CXCL12 (SDF-1)–mediated enhanced interaction of the hematopoietic cells with specialized bone marrow sinusoidal endothelial cells.[1] This results in thrombocytosis, lymphocytosis, and increased mobilization of the progenitor cells to the peripheral circulation, possibly contributing to atherosclerosis.

Hypercholesterolemia has been associated with acceleration of atherosclerosis, resulting in ischemic heart and peripheral vascular diseases. It is believed that hypercholesterolemia through induction of inflammation promotes atheromas.[2,3] However, the precise mechanism by which high cholesterol and LDL levels would foster atheroma formation remains known. In this report, it is demonstrated that hypercholesterolemia stimulates the release of CXCL12 (also known as stromal derived factor-1, SDF-1), which by stimulation of its receptor CXCR4 (CD184) increases the interaction of the megakaryocytes with the bone marrow sinusoidal endothelial cells, leading to increased thrombopoiesis. Elevation of CXCL12 within the bone marrow and circulation also augments the mobilization of CXCR4$^+$ B lymphocytes and proangiogenic CXCR4-responsive hematopoietic progenitor cells (HPCs), known as hemangiocytes,[4] to the peripheral circulation leading to significant lymphocytosis, while partially depleting myeloid precursors within the bone marrow. These data provide an explanation for the previously unrecognized etiology of thrombocytosis, lymphocytosis, and alteration in monocyte levels observed in hypercholesterolemic patients.[2,3]

High cholesterol primarily affects blood vessels within myocardium and large vessels. This is the first report linking hypercholesterolemia to functional alterations of a specialized vascular bed, such as sinusoidal endothelium within the bone marrow. The bone marrow vascular niche, demarcated by VEGFR3$^+$ sinusoidal endothelial cells, has recently been shown to be essential for the maintenance and reconstitution of hematopoiesis,[5] including thrombopoiesis.[6-8] This report indicates that sinusoidal endothelial cells are not immune to hypercholesterolemia and their activation through alteration of hematopoietic equilibrium, such as induction of thrombocytosis and mobilization of the inflammatory cells, could contribute to systemic complications associated with hypercholesterolemia.

These results establish a novel concept as to how hypercholesterolemia through CXCL12-mediated recruitment of inflammatory and thrombotic cells might contribute to the development of atherosclerosis or even predispose patients to inflammatory-dependent malignancies. Hence, this report sets forth the provocative notion that therapeutic targeting of CXCR4 signaling might diminish certain end-organ complications associated with chronic hypercholesterolemia. Whether cholesterol-lowering agents commonly used to treat hypercholesterolemia also modulate the expression of CXCL12 or CXCR4 and decrease inflammation-dependent atheroma is not known.

These interesting findings notwithstanding, there are many unanswered questions. For example, the mechanism by which high cholesterol or LDH levels provoke CXCL12 release by the endothelial cells or other stromal cells needs to be determined. It is conceivable that HDL might prevent CXCL12-driven activation of hematopoiesis, thereby attenuating atheroma formation. The consequences of CXCL12-mediated lymphocytosis in the setting of hypercholesterolemia and progression of atherosclerosis requires further investigation. Nonetheless, this study has unraveled a drugable chemokine pathway that if targeted properly could benefit patients who suffer from complications associated with hypercholesterolemia.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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● ● ● LYMPHOID NEOPLASIA

Comment on Palamarchuk et al, page 3916

Coding and noncoding: the CLL mix

Deepa Sampath and George A. Calin M. D. ANDERSON CANCER CENTER

In this issue of *Blood*, Palamarchuk and colleagues present interesting evidence that deletions in chromosome 13q result in a loss of expression of both the protein coding gene, *dleu7* as well as the noncoding RNA cluster *miR-15a-16-1*. dleu7 and miR15a-16-1 may both have a role in the pathogenesis of CLL.

Chronic lymphocytic leukemia (CLL) is characterized by multiple and recurrent chromosomal abnormalities, of which deletions in chromosome 13q (del13q14) are the most frequent.[1] Monoallelic and biallelic deletions at the 13q14 locus occur in 55% and 16%, respectively, of all CLL, are of varying lengths, and at the very least involve a minimally deleted region of approximately 30 kb that was previously shown to lead to the loss of expression of the microRNAs, *miR-15a-16-1*.[2] This cluster is located in an intron of the *dleu2* gene within the 13q14 chromosomal locus and is down-regulated in the majority of CLLs.[2] Loss of the cluster led to the spontaneous generation of CLL in mice,[3] whereas ectopic expression of miR-15a-16 induced apoptosis in cell lines and suppressed tumorigenesis in xenograft models.[4] The tumor suppressor function of miR-15a and miR-16-1 was linked to its ability to target the antiapoptotic survival proteins Bcl-2[5] and Mcl-1.[4] Bcl-2 and Mcl-1 function by sequestering proapoptotic members of the Bcl-2 family so as to prevent mitochondrial dysfunction and cell death. Consequently, loss of miR15a-16-1 is associated with enhanced survival.[3,4]

CLL is also characterized by the deregulated expression of the B-cell activating factor (BAFF), a potent regulator of normal B-cell development and function and a proliferation-inducing ligand (APRIL). Ligation of BAFF and APRIL to their cognate receptors, the B-cell maturation antigen (BCMA) and transmembrane activator or the calcium modulator and cyclophilin ligand-interactor (TACI) trigger the activation of nuclear factor of κB (NF-κB) that in turn activates signaling cascades that promote CLL survival.[6]

A high-resolution map of 13q14 deletions in CLL identified that the minimally deleted region contained the protein coding gene *dleu7* in addition to *dleu2-miR15a-16-1* noncoding gene.[7] This study by Palamarchuk et al identified that the protein product of *dleu7* directly bound to and inhibited the function of BCMA and TACI.[8] Consequently, dleu7 functioned as a potent inhibitor of NF-κB signaling, an action that is likely to compromise CLL survival. The NF-κB suppressive action of dleu7 may in part explain its ability to function as a tumor suppressor in CLL. This paper highlights in a convincing manner the finding that cytogenetic abnormalities in CLL often result in the concomitant loss of proteins and noncoding RNAs such as dleu7 and miR15a-16-1 in del13q that function in parallel to suppress tumorigenesis. A very recent study takes into account the cellular consequences of losing dleu2 expression, the host gene on which miR-15a-16-1 reside: mice engineered to lose dleu2 in addition to miR15a-16-1 developed a more aggressive phenotype of CLL in contrast to mice that lost miR15a-16-1 alone,[3] suggesting