that constitutively overexpress G-CSF develop a nonfatal myeloproliferative phenotype that is very similar to that observed in GαS-osteocytes–deleted mice, including neutrophilia, splenomegaly, and osteopenia.[4]

This provocative study raises several important questions. The authors show that impaired parathyroid home/parathyroid hormone-related protein receptor signaling in osteocytes is not responsible for the MPD-like phenotype. Which, then, of the approximately 50 G protein–coupled receptors that are expressed in osteocytes, are responsible for the myeloproliferative-like phenotype? While likely contributing to the neutrophilia, the elevated level of G-CSF is unlikely to cause thrombocytosis, and the factor(s) that are stimulating thrombopoiesis are unclear. Finally, these data raise the possibility that inherited disorders of osteocytes may contribute to the pathogenesis of certain blood disorders.

The important study by Fulzele and colleagues adds osteocytes to the list of bone marrow stromal cells that regulate hematopoiesis. Osteocytes play an essential role in sensing and responding to mechanical stress on bone. Thus, osteocytes may provide a mechanism by which mechanical and other stresses on bone regulate hematopoiesis.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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● ● ● IMMUNOBIOLOGY

Comment on Loria et al, page 940

Arenaviruses bite the "dust"

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In this issue of *Blood*, Loria and colleagues present new aspects on the role of platelets in protecting against both lethal hemorrhagic diathesis and virus replication in viral hemorrhagic fever (VHF), using a murine model of lymphocytic choriomeningitis virus (LMCV) infection.[1]

The natural mouse pathogen LCMV is a member of the Arenaviridae family that sporadically infects humans. Several arenaviruses are etiologic agents of VHF in humans, a syndrome characterized by fever, headache, general malaise, impaired cellular immunity, and hemostatic alterations including thrombocytopenia that may ultimately lead to shock and death.[2]

Clinical manifestations of VHF are not fully recapitulated in mice after infection with any arenavirus, including LCMV. This limits the utility of this animal model in studying the pathogenic mechanisms of bleeding disorders observed in human VHF. Infection of adult mice with the Armstrong LCMV strain induces a fully protective cytotoxic T lymphocyte (CTL) response that is able to clear the infection within 1 week. In contrast, other LCMV strains such as clone-13 produce an acute thrombocytopenia without bleeding, and chronic, persistent infection occurs with the virus replicating to high titers in multiple organs associated with a deficient CTL response. Although subtle changes in host cell function occur with LCMV replication, LCMV is essentially considered to be a noncytolytic virus that indicates that the major signs of LCMV-associated pathology are mostly attributable to the host response to infection.[3]

In 2008, 2 major advances shed light on the role of platelets in VHF, using mice as experimental models. First, it was demonstrated that mice rendered thrombocytopenic only suffered localized hemorrhages at sites undergoing noninfectious inflammatory processes, and that low numbers of circulating platelets were able to prevent such inflammation-induced hemorrhages.[4] Second, Iannacone et al reported that platelet-depleted mice infected with the LCMV Armstrong strain developed a syndrome similar to VHFs, with mucocutaneous bleeding, vascular leakage, anemia, uncontrolled viral replication, suboptimal immune responses, and animal death.[5] Remarkably, lethal hemorrhage was less associated with thrombocytopenia and instead was more closely associated with platelet dysfunction mediated by high interferon (IFN)–I levels.

In the current paper, Loria et al induced a finely tuned platelet depletion using antibodies, and confirmed and extended previous findings. They show that mice profoundly depleted of platelets (> 95% depletion) and infected with the Armstrong LCMV strain developed hemorrhagic spots in several organs along with high viral titers, generalized splenic necrosis, and increased mortality. Interestingly, they also found that the presence of 15% of platelets (partial depletion) was sufficient to prevent vascular damage but not viral replication, necrotic destruction of innate and adaptive immune splenocytes, or CTL exhaustion. These observations not only confirm the novel notion that platelets are necessary to protect vascular integrity and are critical mediators of viral clearance, but also underscore an underappreciated relationship among platelet-mediated hemostasis, viral infection, and immunosuppression. Furthermore, the authors perceptively suggest that the higher circulating platelet levels in humans compared with other species explain why mice are not suitable experimental models to study VHF and offer a simple alternative model to study the pathophysiology of VHF and other infectious diseases.

Different platelet requirements for controlling vascular integrity and immune response is an interesting novel concept and suggests that these 2 events may involve different platelet-mediated mechanisms. Based on the recent findings concerning platelet maintenance of vascular integrity,[4] Loria et al suggest that the extreme efficiency of a small number of platelets in preventing these vascular defects may involve delivery to the endothelium vasoactive compounds from the platelet granules rather than platelet adhesion or aggregation. On the other hand, the marked disarray of the splenic cytoarchitecture allows profuse transmigration of immune cells that may open holes in the vascular wall and promote platelet

adhesion and activation. Therefore, the authors suggest that the need for physical contact between platelets and the subendothelium would explain the higher numbers of platelets required to prevent splenic necrosis than to provide systemic hemostasis. In this sense, the observation that platelets expressing integrin β3 and CD40L are required for LCMV clearance through CTLs[5] implies a physical interaction between platelets and immune cells and gives further support to the idea that more platelets are necessary to prevent splenic necrosis and viral replication than bleeding.

Loria et al also analyzed platelet involvement in the immunosuppression after LCMV clone-13 infection of mice by increasing the number of circulating platelets with thrombopoietin treatment. Even though the number of platelets was significantly increased, no differences were seen in LCMV viral titers, suggesting that other mechanisms mediate the deficient immune response seen in LCMV clone-13 infections.

From their present results, Loria et al propose interesting future lines of research, including an evaluation of the abilities of vasoactive molecules to prevent hemorrhage and death in experimentally platelet-depleted mice. They also propose that mice genetically deficient in thrombopoietin signaling, which have platelet levels similar to those found in humans, are a more appropriate experimental model for studying the pathology of VHF. They further suggest that the selective inactivation of IFN-I signaling in megakaryocytes, while preserving important IFN-I antiviral activity in immune and stromal cells, might completely overcome the thrombocytopenia induced by LCMV clone-13 infection. This interesting proposal could be more generalized as thrombocytopenia mediated by IFN-I might be involved in several viral infections.[6] Additionally and in line with this hypothesis, it was recently demonstrated that megakaryocytes express functional IFN-I receptors.[7] Finally, an important issue that requires further clarification is the molecular basis governing platelet interaction with immune cells in VHF.

After being discovered in 1882 by Giulio Bizzozero, platelets were considered to be cytoplasmic "dust" derived from megakaryocytes. During the 20th century, enormous basic and clinical evidence entrenched platelets as critical mediators of physiologic hemostasis and pathologic thrombosis. In the present century, they are additionally appreciated as key amplifiers of the inflammatory response and, more recently, important regulators of the immune response. Along these lines, the study by Loria et al strongly supports the concept that, regardless of the apparent "simplicity" of platelets, these cells play critical roles in several cellular processes beyond hemostasis.

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

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● ● ● MYELOID NEOPLASIA

Comment on McNerney et al, page 975

CUX1 in leukemia: dosage matters

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In this issue of *Blood*, McNerney and colleagues identify *CUX1* as a tumor suppressor gene (TSG) on the long arm of chromosome 7, showing frequent inactivation in acute myeloid leukemia (AML).[1]

Complete loss of chromosome 7 (monosomy 7) and partial deletion of the long arm of chromosome 7 [del(7q)] are recurring karyotypic abnormalities in malignant myeloid disorders, including the myelodysplastic syndromes (MDS) and AML, and are associated with a poor prognosis.[2,3] The del(7q) in MDS and AML is considered to mark the location for a gene or genes the loss of which may affect important processes such as growth control and normal hematopoiesis. The identification of significant genes associated with chromosome deletions, including the del(7q), in human leukemia has proven challenging, however.

The basis for research on deletions such as the del(7q) in MDS and AML is well known. The first step is to characterize the deletions and to identify the commonly deleted region (CDR), the region of deletion shared by all patients, as this localizes the gene(s) for further study. Over the years several CDRs mapping to 7q have been identified in MDS and AML, including CDRs at 7q22, 7q32-33, and 7q35-36.[2-4] The next step typically involves the sequencing of all the candidate genes that map within the CDR in a group of affected patients. The gene sequencing is critical to our understanding of the disease pathogenesis; if the Knudsen 2-hit model applies, there would be loss of 1 allele of a gene and a mutation of the remaining copy of the same gene. The lack of recurrent mutations identified in the genes mapping to the various CDRs identified on 7q in MDS and AML patients with −7/del(7q) suggests that haploinsufficiency, a dosage effect resulting from the loss of a single allele of a gene,[5] may be the molecular mechanism relevant in this group of malignancies. There has been growing recognition of haploinsufficiency as a cancer model over the past decade and the importance of this model in the context of myeloid disorders is supported by recent studies concerning MDS patients with the 5q− syndrome.[6]

Interest in the *CUX1* (*CUTL1*) gene, encoding a transcription factor, as a possible candidate gene in malignant myeloid disorders with abnormalities of chromosome 7, stretches back to the mid-1990s when it was first mapped to the CDR at 7q22 by investigators.[2,7] Most recently *CUX1*, normally highly expressed in multipotent hematopoietic progenitors, was shown to be expressed at reduced levels in $CD34^+$ cells from patients with MDS with −7/del(7q).[4] McNerney and colleagues

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