activation molecule F7 (SLAMF7; also called CS1) and CD38 has been approved by regulatory authorities.5

Therapeutic approaches using the innate immune system, like natural killer cells and TAA-specific T-cell approaches with chimeric antigen receptors (CARs),2 are being investigated clinically. Therefore, there is a fervent need for a better understanding of the interaction of the myeloma niche with the immune system to further improve immunotherapies for myeloma patients.

Hope et al have previously described the effect of macrophages on myeloma cells and demonstrated the regulation of the inflammatory milieu in the myeloma niche through the tumor progression locus 2 (TPL2) kinase.6 In their work in the present issue, the group investigated the proteolysis of the matrix proteoglycan versican which is abundantly produced by myeloma-associated macrophages (MAMs). Versican itself causes tolerogenic polarization of APCs through the Toll-like receptor (TLR2).7 Mesenchymal stromal cell–derived protease ADAMTS1 (a disintegrin and metalloproteinase with thrombospondin motifs 1) cleaves the Glu441-Ala442 from versican, creating a molecule called versikine (see figure). Versikine induces proinflammatory IL-6 which is partially independent of TLR2 and does not interfere with expression of IL-1β. Versikine induces IL-12p40 through bone marrow–derived macrophages. The action is signaled through the MAP3K Tpl2.

T cells are attracted to the myeloma niche by inflammatory IL-6 which is partially autoregulation of thrombopoiesis.2,3 TPO, produced primarily in the liver, is the major physiological regulator of platelet production and its level is inversely correlated with platelet count (mass). MPL, the receptor of TPO, is predominantly expressed in hematopoietic tissues with a higher density on MKs and platelets, but with preserved MPL expression mice lacking MPL expression on MKs and platelets from subjects with essential thrombocythemia (ET) phenotype. Choi et al9 reported that the final stages of platelet formation and release appeared to be TPO independent, because withdrawal of TPO from late-stage MK culture did not eliminate proplatelet formation. Ng et al10 reported that mice lacking MPL expression on MKs and platelets, but with preserved MPL expression on stem/progenitor cells, displayed profound megakaryocyte deficiency and thrombocytopenia with expansion of progenitor cells.

In this issue of Blood, Wu et al describe a novel dominant negative loss-of-function mutation (BLVRB S111L) in a heme catalytic pathway deregulating reactive oxygen species (ROS) and associated with thrombocytosis.1

The critical role of platelets in hemostasis and their origin from marrow megakaryocytes (MKs) were first established in the early 20th century. The identification and characterization of the MPL proto-oncogene (MPL, or c-Mpl) followed by thrombopoietin (TPO) are milestones in unraveling the regulation of thrombopoiesis.2,3 TPO, produced primarily in the liver, is the major physiological regulator of platelet production and its level is inversely correlated with platelet count (mass). MPL, the receptor of TPO, is predominantly expressed in hematopoietic tissues with a higher density on MKs and platelets, but with preserved MPL expression mice lacking MPL expression on MKs and platelets, but with preserved MPL expression on stem/progenitor cells, displayed profound megakaryocyte deficiency and thrombocytopenia with expansion of progenitor cells.

The study performed by Wu et al opens a new window in understanding the regulation of thrombopoiesis beyond the TPO pathway. Specifically, the authors concluded that increased ROS accumulation as a result of defective redox coupling leads to differential hematopoietic lineage commitment and enhanced thrombopoiesis. RNAseq analysis of highly purified platelets from subjects with essential thrombocythemia (ET) and healthy controls identified 5 single nucleotide variants (SNVs) associated with the ET phenotype. To restrict the SNVs to only the modifiers of platelet production independent of molecular abnormalities associated with

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ROS: novel regulators of thrombopoiesis

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In this issue of Blood, Wu et al describe a novel dominant negative loss-of-function mutation (BLVRB S111L) in a heme catalytic pathway deregulating reactive oxygen species (ROS) and associated with thrombocytosis.1

The critical role of platelets in hemostasis and their origin from marrow megakaryocytes (MKs) were first established in the early 20th century. The identification and characterization of the MPL proto-oncogene (MPL, or c-Mpl) followed by thrombopoietin (TPO) are milestones in unraveling the regulation of thrombopoiesis.2,3 TPO, produced primarily in the liver, is the major physiological regulator of platelet production and its level is inversely correlated with platelet count (mass). MPL, the receptor of TPO, is predominantly expressed in hematopoietic tissues with a higher density on MKs and platelets, but with preserved MPL expression mice lacking MPL expression on MKs and platelets, but with preserved MPL expression on stem/progenitor cells, displayed profound megakaryocyte deficiency and thrombocytopenia with expansion of progenitor cells.

Previous work has provided evidence for the existence of additional pathways in the regulation of thrombopoiesis. Choi et al9 reported that the final stages of platelet formation and release appeared to be TPO independent, because withdrawal of TPO from late-stage MK culture did not eliminate proplatelet formation. Ng et al10 reported that mice lacking MPL expression on MKs and platelets, but with preserved MPL expression on stem/progenitor cells, displayed profound megakaryocyte deficiency and thrombocytopenia with expansion of progenitor cells.

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myeloproliferative neoplasms (such as \textit{JAK2} V617F), the authors genotyped a separate cohort of subjects with reactive thrombocytosis (RT). Only the \textit{BLVRB} S111L variant retained its significance as a thrombocytosis risk allele in both ET and RT subjects. This variant was subsequently functionally characterized to be a loss-of-function mutation leading to defective redox coupling of the enzyme. These findings established the first physiologically relevant function of \textit{BLVRB} in the heme degradation pathway, and a possible role of redox signaling in terminal megakaryocytopoiesis (see figure).

The authors present a convincing argument for this mutation uncoupling a redox reaction with generation of increased ROS and an association with thrombocytosis. Although much work remains to be done to fully understand the precise mechanism, this study opens an exciting line of inquiry, which should lead to a better understanding of normal and pathologic thrombopoiesis. This pathway also represents a potential therapeutic target for treatment of pathological thrombocytosis; the utility of intervention in this novel pathway remains to be tested.

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ROS: novel regulators of thrombopoiesis

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