The study by Schneider et al confirms that FBXO11 regulates the stability of BCL6 but also raises some important questions. In this regard, the previously described role of phosphorylation in BCR signaling linked degradation of BCL6, but data presented in this article contradict the original findings by Duan et al,[3] which suggest that BCL6 degradation by FBXO11 does not require phosphorylation and may occur in the absence of BCR signaling.[3] In addition, the BCL6 degron has not been identified and thus there is not yet a full understanding of the mechanistic aspects of the role of FBXO11 in BCL6 regulation. It is anticipated that future studies identifying additional substrates for FBXO11 and delineating their degrons as well as elucidating the structure of FBXO11 will further enhance our understanding of the mechanisms by which FBXO11 plays a role in B-cell biology and DLBCL pathogenesis.

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

REFERENCES

1. Schneider C, Kon N, Amadori L, et al. FBXO11 inactivation leads to abnormal germinal-center formation and lymphoproliferative disease. *Blood.* 2016;128(5):660-666.

2. Fielenbach N, Guardavaccaro D, Neubert K, et al. DRE-1: an evolutionarily conserved F box protein that regulates C. elegans developmental age. *Dev Cell.* 2007; 12(3):443-455.

3. Duan S, Cermak L, Pagan JK, et al. FBXO11 targets BCL6 for degradation and is inactivated in diffuse large B-cell lymphomas. *Nature.* 2012;481(7379):90-93.

4. Cattoretti G, Pasqualucci L, Ballon G, et al. Deregulated BCL6 expression recapitulates the pathogenesis of human diffuse large B cell lymphomas in mice. *Cancer Cell.* 2005;7(5):445-455.

5. Horn M, Geisen C, Cermak L, et al. DRE-1/FBXO11-dependent degradation of BLMP-1/BLIMP-1 governs C. elegans developmental timing and maturation. *Dev Cell.* 2014;28(6):697-710.

6. Pasqualucci L, Compagno M, Houldsworth J, et al. Inactivation of the PRDM1/BLIMP1 gene in diffuse large B cell lymphoma. *J Exp Med.* 2006;203(2):311-317.

7. Tam W, Gomez M, Chadburn A, Lee JW, Chan WC, Knowles DM. Mutational analysis of PRDM1 indicates a tumor-suppressor role in diffuse large B-cell lymphomas. *Blood.* 2006;107(10):4090-4100.

8. Abbas T, Keaton M, Dutta A. Regulation of TGF-β signaling, exit from the cell cycle, and cellular migration through cullin cross-regulation: SCF-FBXO11 turns off CRL4–Cdt2. *Cell Cycle.* 2013;12(14):2175-2182.

9. Rossi M, Duan S, Jeong YT, et al. Regulation of the CRL4(Cdt2) ubiquitin ligase and cell-cycle exit by the SCF (Fbxo11) ubiquitin ligase. *Mol Cell.* 2013;49(6):1159-1166.

10. Mackintosh C, Ordóñez JL, García-Domínguez DJ, et al. 1q gain and CDT2 overexpression underlie an aggressive and highly proliferative form of Ewing sarcoma. *Oncogene.* 2012;31(10):1287-1298.

● ● ● LYMPHOID NEOPLASIA

Comment on Hope et al, page 680

Versican vs versikine: tolerance vs attack

Michael Schmitt   HEIDELBERG UNIVERSITY HOSPITAL

In this issue of *Blood*, Hope et al demonstrate the differential influence of versican and its proteolytic derivate, versikine, on the immune system. This discovery opens a new avenue for immunotherapies in multiple myeloma patients.[1]

Multiple myeloma is an (oligo)clonal plasma cell disease which can develop in the bone marrow and also, in some cases, as extramedullary disease in soft tissue. Tumor escape mechanisms in multiple myeloma still need to be identified. The graft-versus-myeloma effect observed after allogeneic stem cell transplantation clearly demonstrates that T lymphocyte can play a role in the antitumor defense of the immune system. In the last 2 decades, several tumor-associated antigens (TAAs) with therapeutic relevance have been defined.[2] Such TAA-specific T cells can be elicited and augmented, for example, by vaccination with tumor antigen–derived peptides.[3] These antimyeloma T-cell responses may be hampered by standard drugs used in myeloma therapy like steroids (prednisone, dexamethasone) which have a potent antiproliferative action. In modern myeloma therapy, thalidomide and its derivatives play a crucial role. These immunomodulatory drugs are not only antiproliferative agents, but they also exert effects on antigen-presenting cells (APCs) and T cells, thus modulating and enhancing or suppressing TAA-directed T-cell responses.[4]

Immunotherapy, with breakthrough potential, has also reached myeloma therapy: treatment of myeloma with monoclonal antibodies against signaling lymphocytic
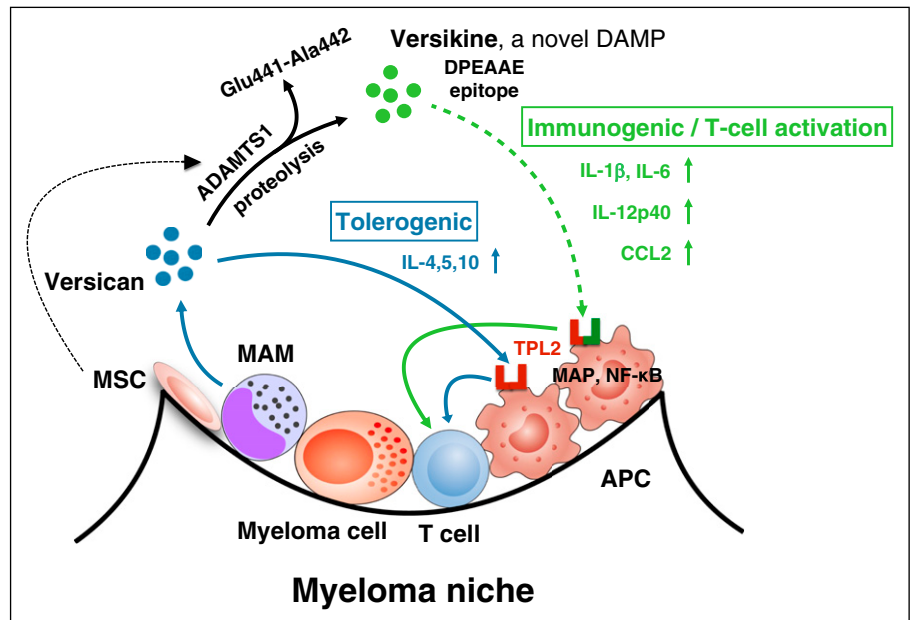
MAMs secrete the matrix proteoglycan versican which can be cut into versikine and a small peptide dimer (glutamine position 441–alanine position 442; Glu[441]-Ala[442]) by ADAMTS1. This ADAMTS1 is produced by mesenchymal stroma cells (MSCs). Both versican (blue lines) and versikine (green lines) exert an influence on T cells: while versican binds to TLR2 on APCs which block T cells through type II cytokines (interleukin-4 [IL-4], IL-5, and IL-10). On the other hand, versikine, a novel damage-associated molecular pattern (DAMP), binds to TLR2 but perhaps also other receptors, subsequently using intracellular mitogen-activated protein (MAP) and nuclear factor κB (NF-κB) thus mediating T-cell activation through type I cytokines like IL-1β, IL-6, IL-12p40, and CCL2.

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 Glu^{441}-Ala^{442} 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 chemotactic mediators like CCL2. Like IL-27, versikine can upregulate interferon regulatory factor 8 on tumor cells which makes them prone to apoptosis. Using immunohistochemistry, Hope et al could demonstrate that, in case of high versikine expression with the neoepitope DPEAAE, a high frequency of $CD8^+$ T cells could also be observed in the respective tissue. The interaction of macrophages and T cells creates a type I cytokine inflammatory milieu which enhances T-cell (and likely also innate) immune responses against myeloma cells. Therefore, versikine creates a novel bioactive DAMP stimulating an antimyeloma response by the immune system.

Versikine will be tested as an adjuvant in future trials with T-cell epitope peptide vaccination, CAR, and other T-cell therapies.

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

REFERENCES

1. Hope C, Foulcer S, Jagodinsky J, et al. Immunoregulatory roles of versican proteolysis in the myeloma microenvironment. *Blood*. 2016;128(5):680-685.

2. Wang L, Jin N, Schmitt A, et al. T cell–based targeted immunotherapies for patients with multiple myeloma. *Int J Cancer*. 2015;136(8):1751-1768.

3. Schmitt M, Schmitt A, Rojewski MT, et al. RHAMM-R3 peptide vaccination in patients with acute myeloid leukemia, myelodysplastic syndrome, and multiple myeloma elicits immunologic and clinical responses. *Blood*. 2008;111(3):1357-1365.

4. Neuber B, Herth I, Tolliver C, et al. Lenalidomide enhances antigen-specific activity and decreases CD45RA expression of T cells from patients with multiple myeloma. *J Immunol*. 2011;187(2):1047-1056.

5. van de Donk NW, Moreau P, Plesner T, et al. Clinical efficacy and management of monoclonal antibodies targeting CD38 and SLAMF7 in multiple myeloma. *Blood*. 2016;127(6):681-695.

6. Hope C, Ollar SJ, Heninger E, et al. TPL2 kinase regulates the inflammatory milieu of the myeloma niche. *Blood*. 2014;123(21):3305-3315.

7. Tang M, Diao J, Gu H, Khatri I, Zhao J, Cattral MS. Toll-like receptor 2 activation promotes tumor dendritic cell dysfunction by regulating IL-6 and IL-10 receptor signaling. *Cell Reports*. 2015;13(12):2851-2864.

● ● ● **PLATELETS AND THROMBOPOIESIS**

ROS: novel regulators of thrombopoiesis

Bing Zhang and James L. Zehnder STANFORD UNIVERSITY SCHOOL OF MEDICINE

In this issue of *Blood*, Wu et al describe a novel dominant negative loss-of-function mutation (*BLVRB* S111L) in a heme catabolic 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.[4,5] The delicate maintenance of platelet homeostasis has initially been explained by the "autoregulation" model, which postulates that TPO is produced at a constant rate and cleared by binding to TPO receptors on platelets followed by internalization and degradation.[6] However, a growing body of evidence suggests the presence of other regulatory mechanisms in TPO production. Recently, the hepatic Ashwell-Morrell receptor (AMR) was shown to mediate the removal of desialylated platelets and regulate hepatic TPO synthesis, providing a better understanding of the transcriptional regulation of TPO production[7,8] (see figure).

Previous work has provided evidence for the existence of additional pathways in the regulation of thrombopoiesis. Choi et al[9] 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 al[10] reported that mice lacking MPL expression on MKs and platelets, but with preserved MPL expression on stem/progenitor cells, displayed profound megakaryocytosis and thrombocytosis 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