Regulation of megakaryopoiesis by bone marrow macrophage polarization

Ming Hou

Qilu Hospital of Shandong University, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by increased bleeding tendency and thrombocytopenia. The main mechanisms include the loss of immune tolerance, accelerated platelet destruction, impaired bone marrow (BM) microenvironment, and decreased platelet production.[1–5] The processes of megakaryocytopoiesis and thrombocytopoiesis occur within a complex BM microenvironment. Macrophages (MΦs) are crucial regulators of normal hematopoiesis in the BM microenvironment, whereas very few studies focus on the effect of BM MΦs on megakaryopoiesis, especially the MΦ polarization subsets in thrombocytopenic disease. Prolonged thrombocytopenia (PT) after hematopoietic stem cell transplantation is a strong risk factor for transplantation-related morbidity and mortality, and no standard treatment guideline exists. Meanwhile, PT, characterized by dysfunctional megakaryocyte (MK) maturation and thrombocytopenia, not only provides a paradigm for understanding the relationship between MK development and BM microenvironment but also an ideal disease model for studying thrombocytopenia.

In a recent SIGNAL TRANSDUCT TARGET THER publication, Zhao et al investigated the mechanistic link between BM MΦ polarization and megakaryopoiesis in PT patients, in vitro and in an MΦ specific PI3K-knockdown murine model.[6] In the BM microenvironment of PT patients, a significantly higher M1/M2 ratio was observed, which was associated with remarkable downregulation of the PI3K-AKT pathway. The authors also demonstrated that M1 MΦs and M2 MΦs exerted opposing effects on megakaryopoiesis. M1 MΦs suppress whereas M2 MΦs promote MK maturation and platelet release in a PI3K-AKT pathway-dependent manner. Enhanced BM M1 MΦ polarization leads to the impaired megakaryopoiesis-supporting ability of BM MΦs in PT patients, which could be rescued by PI3K-AKT pathway activators in vitro. These data demonstrate for the first time that altering PI3K-AKT pathway activity to modulate M1/M2 MΦ polarization and function could be a potential therapeutic approach to enhance megakaryopoiesis and platelet production in patients with thrombocytopenia.

Address correspondence: Dr. Ming Hou, PhD, MD, Qilu Hospital of Shandong University, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China. E-mail address: qlhouming@sina.com (M. Hou).

Blood Science, (2021) 3, 149-150

Received September 6, 2021; Accepted September 7, 2021.

http://dx.doi.org/10.1097/BS9.0000000000000090

In terms of both phenotype and function, MΦs have remarkable heterogeneity, which reflects the specialization of tissue-resident MΦs in microenvironments. Two well-established polarized phenotypes are often referred to as classically activated MΦs (M1) and alternatively activated MΦs (M2). Aberrant M1/M2 polarization has been involved in the pathogenesis of a variety of human diseases. A confocal laser scanning microscopy study revealed an increased number of $CD68^+iNOS^+$ M1 MΦs and a decreased number of $CD68^+CD163^+$ M2 MΦs in the spleens of ITP patients compared with non-ITP control patients, providing clues that M1 MΦs and M2 MΦs have different roles in regulating platelet turnover.[7] Zhao et al found $CD68^+CCR2^+$M1 MΦs suppress, whereas $CD163^+CX3CR1^+$ M2 MΦs supported MK maturation and platelet release,[6] shedding new light on the regulation of hematopoiesis by BM MΦ subsets. Besides M1/M2 MΦs, other BM-derived MΦ subtypes also modulate megakaryopoiesis. For example, mesenchymal stem cells-reprogrammed BM resident $Arg1^+$ MΦs, with tissue-repair features, improved thrombopoiesis in leukemia-bearing mice.[8] However, the data are still incomplete and far from being systematic, and our knowledge of the specific function and mechanistic basis of a specific subtype of MΦs is still very rudimentary. Future studies to assign definitive biochemical markers to each of the different MΦ populations are needed so that individual populations of MΦs can be manipulated, selectively depleted, or targeted by cell-specific therapeutics.

The PI3K-AKT pathway converges multiple extracellular and intracellular signals to regulate MΦ biology that includes the production of pro- and anti-inflammatory cytokines, phagocytosis, autophagy, and polarization. Moreover, Zhao et al provide further evidence that the PI3K-AKT pathway plays a critical role in regulating the megakaryopoiesis-supporting ability of M2 MΦs. Activation of the PI3K-AKT pathway corrected the impaired ability of MΦs from PT patients to support megakaryopoiesis in vitro.[6] Therefore, the PI3K-AKT pathway might be a potential therapeutic target for the management of PT patients. However, it should be noted that the PI3K-AKT pathway is one of the most frequently dysregulated pathways in cancers. Considering the double-edged sword effects of PI3K-AKT pathway activators, further clinical studies are needed to validate the preliminary findings in the future.

Strengths of Dr. Xiao-Jun Huang and Dr. Yuan Kong group work are that they reveal firstly the specific effect and mechanism of MΦ polarization subsets on MKs, which provide new insights into the pathogenesis of thrombocytopenia and offer a potential therapeutic target as well as a good study paradigm for patients with thrombocytopenia. A major area of research in the future, now made possible by advances in genomic technologies, will be the pairwise definition of the transcriptomes and chromatin

landscapes (epigenomes) of MΦs and MKs obtained from BM in both normal and diseased conditions.

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