Int J Hematol (2013) 98:8–9
DOI 10.1007/s12185-013-1384-y

Guest editorial: Pathophysiology and management of thrombocytopenia: possible clinical application of TPO receptor agonists

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Received: 11 June 2013 / Revised: 12 June 2013 / Accepted: 12 June 2013 / Published online: 21 June 2013

Platelets are small, anucleated blood cells that exhibit a discoid shape when non-activated. Platelets play a crucial role in the formation of a pathologic thrombus as well as a normal hemostatic plug formation. Platelets express several adhesion receptors, such as GPIb–IX and GPIIb–IIIa, and circulate passively throughout the vascular tree covered by an intact monolayer of endothelial cells. In the initial step of hemostasis (and thrombus formation), platelets adhere to exposed subendothelial matrices at sites of vascular injury (or altered vascular surfaces). Following adhesion, they become activated, change shape, secrete granule contents, and aggregate to form a primary hemostatic plug and provide a catalytic surface to enhance blood coagulation. Platelets are released by megakaryocytes (MKs). Platelet counts are 130–320 $\times$ 10^3/μL in peripheral blood, and their average life span is 7–10 days. Red blood cell (RBC) counts in peripheral blood (4.4–5.6 $\times$ 10^6/μL) are approximately 20 times more than platelet counts, whereas their average life span is 120 days (approximately 12 times longer than that of platelets). Thus, the amounts of daily platelet production and RBC production in human body appear to be on the same order of magnitude. Essentially, only one mature blood cell is produced from a single progenitor cell within the bone marrow; e.g., one erythroblast differentiates to one mature erythrocyte. Bone marrow aspiration shows that erythroid progenitors are present at a concentration of approximately 100 $\times$ 10^3/μL. In sharp contrast, only 50–150 MKs/μL are present in the bone marrow, suggesting that roughly 1,000 platelets are generated from a single MK. For many years, the mechanism of thrombopoiesis remained largely obscure due to the paucity of MKs. The cloning and characterization of the primary regulator of thrombopoiesis, thrombopoietin (TPO), in 1994 greatly facilitated our understanding of platelet production.

Thrombopoiesis is a complex process that induces the commitment of multipotent stem cells to the MK lineage, MK progenitor proliferation, and terminal differentiation, inducing platelet production [1]. TPO controls thrombopoiesis by affecting the proliferation and/or apoptosis of progenitor cells, as well as MKs ploidy. Moreover, TPO supports the proliferation of hematopoietic stem cells (HSCs) and progenitor cells. In vitro colony assays using bone marrow from $TPO^{-/-}$ and/or c-$Mpl^{-/-}$ mice show a reduction of CFU-mix, CFU-GM and BFU-E progenitors. Although RBC and white blood cell (WBC) counts in peripheral blood are normal in $TPO^{-/-}$ and c-$Mpl^{-/-}$ mice, despite the marked thrombocytopenia, and do not reflect the multilineage effect of TPO, TPO can shorten the duration of anemia and leukopenia in an experimental mouse model under myelosuppressive conditions [2]. In addition to TPO, MK-active chemokines, stromal-derived factor (SDF)-1, and a fibroblast growth factor (FGF-4), direct MK interaction with the bone marrow stroma and regulate TPO-independent cell maturation, and restore thrombopoiesis in $TPO^{-/-}$ and c-$Mpl^{-/-}$ mice [3]. A recent report of in vivo imaging of thrombopoiesis in mouse bone marrow revealed that MKs are enriched at bone marrow sinusoids and observed as sessile cells that extend dynamic proplatelet-like protrusions into microvessels, and that these cells routinely release heterogeneous particles, with properties resembling immature proplatelets, into BM microvessels [4].

In this issue of IJH, in light of the approval of TPO receptor agonists in the treatment of primary immune thrombocytopenia and significant advances in the field of

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megakaryopoiesis and thrombopoiesis, we focus on the pathophysiology of various thrombocytopenic disorders, including primary immune thrombocytopenia, inherited thrombocytopenias, aplastic anemia, and myelodysplastic syndromes, and the possible clinical application of TPO receptor agonists to these pathological conditions, following a comprehensive and informative overview of the biology of TPO and TPO receptor agonists. As a member of the editorial board, it is my hope that our readers will enjoy the excellent review articles in this PIH series and gain a better understanding of the pathophysiology these thrombocytopenic disorders.

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