Platelets play an important role in atherogenesis and atherothrombosis. At early stages of atherosclerosis, platelet-borne chemokines and platelet–leukocyte complexes contribute to the recruitment of neutrophils and monocytes to inflamed arteries.1,2 At late stages, platelets orchestrate additional processes such as thrombosis by direct mechanisms and possibly by indirect mechanisms such as the induction of neutrophil extracellular traps.3,4 Although mechanisms of platelet-driven atherosclerosis have been studied widely, little is known about their production during atherosclerosis-promoting conditions.

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In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Murphy et al5 show that the lack of ABCB6 in the bone marrow leads to thrombocytosis, enhanced proinflammatory platelet activity, and accelerated atherosclerosis in atherosclerosis-prone hyperlipidemic low-density lipoprotein receptor–deficient mice (see the Figure). Interestingly, ABCB6 was found to be highly expressed in bone marrow megakaryocyte progenitors. A lack of ABCB6 in bone marrow cells led to increased oxidative stress and subsequently unleashed platelet production. Consequent thrombocytosis enhances arterial deposition of the potent myeloid cell attracting chemokine CCL5 (RANTES), ultimately fueling atherosclerotic lesion development. Although the downstream mechanism ofplatelet-driven atherosclerosis in mice lacking ABCB6 in the bone marrow is dependent on well-understood mechanisms, the involvement of ABCB6 transporters in platelet production is novel and contrasts other findings on atherosclerosis-promoting conditions. ErP indicates megakaryocyte progenitors overexpressing ABCB6. In addition, based on this study, one would presume that ABCB6 exclusively contributes to thrombopoiesis under inflammatory conditions initiated by hypercholesterolemia. However, further studies are required to substantiate this. Should ABCB6 be found to control platelet production in the bone marrow, the overexpression or activation of ABCB6 could be an interesting and novel strategy to reduce arterial inflammation and coagulation orchestrated by platelets. However, before pursuing such approaches, platelet dysfunction should be excluded in platelets obtained from megakaryocytes overexpressing ABCB6. In addition, based on this study, one would presume that ABCB6 exclusively contributes to thrombopoiesis under inflammatory conditions initiated by hypercholesterolemia. However, further studies are required to substantiate this. Should ABCB6 be found to control facilitating phorphyrin import into the mitochondria has been established.7 Thus, data presented by Murphy et al establish an unexpected link between heme synthesis in megakaryocyte progenitors and platelet production. Although not demonstrated in the study, the deletion of ABCB6 should lead to cytoplasmatic accumulation of coproporphyrinogen III and, more importantly, to reduced heme synthesis. Previous studies have shown that the suppression of ABCB6 expression sensitized cells to stress, whereas the overexpression of ABCB6 protected against cellular stress.8

Figure. ABCB6 deficiency stimulates platelet production and promotes atherosclerosis. The lack of ABCB6 in bone marrow cells enhances the production of reactive oxygen species in megakaryocyte progenitors (MkP), thus stimulating megakaryopoiesis. The peripheral increase in circulating platelets is an important factor for the arterial recruitment of myeloid cells because platelets deposit the chemokine CCL5 (RANTES) and activate leukocyte by complexes formation. Overall, these mechanisms stimulate platelet-driven atherosclerosis. ErP indicates erythroid–progenitor cell; and MEP, megakaryocyte–erythroid progenitor cell.
thrombopoiesis also under acute inflammatory conditions, one might envision broader targeting approaches in settings of acute inflammation with importance of platelet-derived chemokines such as acute lung injury. Finally, it may also be of interest to test whether the reverse approach, namely the therapeutic inhibition of ABCB6 function, can promote megakaryopoiesis and increase platelet counts in patients with thrombocytopenia.

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References

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