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. 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. Although mechanisms of platelet-driven atherosclerosis have been studied widely, little is known about their production during atherosclerosis-promoting conditions.

See accompanying article on page 751

In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Murphy et al1 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 of platelet-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 a related channel, namely ABCG4. ABCG4 expressed in megakaryocyte progenitors controls thrombopoiesis by promoting cholesterol efflux to high-density lipoprotein, thus reducing membrane cholesterol content and thrombopoietin signaling. Therapeutically, this earlier finding could be instructed by infusion of recombinant high-density lipoprotein or lipid-free apolipoprotein A-I to restrict platelet-dictated inflammatory responses in atherosclerosis. ABCB6, in contrast, is not expressed in the Golgi apparatus and does not regulate cholesterol efflux mechanisms. Although the precise biological role of ABCB6 is not fully understood, its importance in facilitating phorphyrin import into the mitochondria has been established. 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.

Although the data presented here are certainly important and surprising, further studies are needed to explore how these findings can be used for therapeutic targeting. Current platelet-targeted therapies are mostly based on the direct inhibition of functions of circulating platelets, including the administration of COX1 inhibitors, ADP receptor antagonists, and inhibitors of αIIbβ3. Although the appropriate tools are currently not available, it is conceivable that the interference with ABCB6 would possibly allow for directing 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 relevant platelet activity, this could be a new target for future therapeutic strategies.

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.

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*Arterioscler Thromb Vasc Biol* is available at [http://atvb.ahajournals.org](http://atvb.ahajournals.org)

DOI: 10.1161/ATVBAHA.114.303365
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.

Sources of Funding
The author’s research is supported by the NWO (VIDI project 91712303), the DFG (SOr876/3-1, SOr876/6-1, FOR809, SFB914 TPB08), the Else Kröner Fresenius Stiftung, and the LMUexcellence program of the Ludwig-Maximilians-University Munich.

Disclosures
None.

References


Key Words: Editorials • atherosclerosis • blood platelets • chemokines
The ABC of Thrombopoiesis
Oliver Soehnlein

Arterioscler Thromb Vasc Biol. 2014;34:700-701
doi: 10.1161/ATVBAHA.114.303365
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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