**EDITORIAL COMMENT**

**Microparticles, Debris That Hurts**

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Microparticles (MPs) are fragments of cell membranes released from stimulated or apoptotic cells that have long been considered innocent remnants of cell destruction. Evidence is accumulating, however, that the circulating and tissue-derived MPs may elicit a strong thrombogenic and inflammatory response (1). In addition to MPs, activated cells can also release smaller vesicle-denominated exosomes that are relatively unexplored in the research area of vascular biology (2).

Circulating MPs are being explored as a potential source for biomarker discovery. Platelet MPs have been associated with clinically evident atherosclerotic disease in diabetes type II patients (3), and leukocyte-derived MPs are predictive of subclinical atherosclerosis in asymptomatic patients (4).

Experimental and clinical data consistently point to a causal role for MPs in atherosclerosis development and progression. Recent reports revealed their contribution to hemostatic and inflammatory responses, vascular remodeling and angiogenesis, cell survival, and apoptosis, well-known processes involved in atherothrombosis. Platelets constitute the main source of circulating procoagulant MPs under many pathophysiological situations. These MPs encompass functional membrane or cytoplasmic effectors that play an important role in platelet aggregation and harbor effectors like glycoprotein IIb/IIIa, glycoprotein Ib, von Willebrand factor, arachidonic acid, and thromboxane A2 (1). The procoagulant MPs are less prevalent in healthy individuals. Recently, the presence of functionally active tissue factor in platelets has been reported by several groups, which could play an important role in the initiation of thrombus formation (5). Although the exact source of this platelet-derived tissue factor is unknown, one of the concepts is that tissue factor is taken up in the form of circulating MPs potentially derived from monocytes.

A role for MPs in inflammatory responses in the vascular wall has been suggested. Plaque-derived MPs enhance the cell surface processing of the TACE/ADAM17 substrate tumor necrosis factor and the receptor TNFR-1, suggesting that MPs could regulate the inflammatory balance in the atherosclerotic lesion (6).

In this issue of the _Journal_, Leroyer et al. (7) report another mechanism by which MPs can contribute to a local inflammatory response and subsequent plaque destabilization. They show that MPs that are isolated from human atherosclerotic lesions express CD40 ligand (CD40L). In an experimental setup, they nicely demonstrate that plaque-derived CD40L+ particles hide proangiogenic properties in vitro and in vivo. It has been shown previously that platelet-derived MPs induce angiogenesis in vitro and in vivo (8). These studies pointed to a beneficial role for circulating MPs in revascularization after myocardial ischemia. Leroyer et al. (7) show that CD40+ MPs with angiogenic properties are associated with plaques from patients suffering from symptomatic carotid artery disease, and they propose a role for plaque neovascularization, a plaque−destabilizing feature.

CD40−CD40L interactions play a central role in atherosclerosis progression. In mice studies, inhibition of CD40L signaling results in a significant decrease of plaque development (9,10). CD40 and CD40L are coexpressed by most, if not all, cells that are known to play a role in atherosclerotic disease such as endothelial cells, smooth muscle cells, macrophages, and platelets. CD40L on platelets is rapidly translocated onto the cell surface after activation. Interestingly, more than 95% of the circulating CD40L is derived from platelets (11). Platelet-derived CD40L has been examined as a biomarker for unstable coronary artery disease and stroke, but it is still debated whether increased circulating CD40L levels reflect the local vascular thrombus formation or are more likely a consequence of the clinical event.

Literature consistently reports that platelets are the main source of functionally active MPs and circulating CD40L. Surprisingly, Leroyer et al. (7) describe that plaque-derived MPs are mainly of leucocyte origin and do not originate from platelets. Moreover, in atherosclerotic plaques, CD40L was not observed on platelet-derived MPs. This is rather unexpected since intraplaque bleeding is regularly observed in carotid plaques, and the presented study reports the presence of erythrocyte-derived particles in atherosclerotic lesions. The authors did demonstrate that the angiogenic properties of plaque- and leucocyte-derived MPs were not shared by circulating MPs, which are more likely platelet MPs, when samples were compared that were obtained from the identical patients.

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The reported evidence supports the concept that intraplaque apoptosis results in MP accumulation and subsequent endothelial cell proliferation and intraplaque neovascularization, and will further stimulate the search for inflammatory pathways that play a dominant role in atherosclerotic plaque destabilization. Whether CD40L+ MPs are dominant players in lesion progression and thrombosis remains to be elucidated. For instance, it is unclear to what extent MP-associated CD40L contributes to lesion progression compared with other cell-based sources of CD40L.

In addition, the absence of an effect on endothelial cell proliferation using MPs from the circulation may conflict with previous reports (8), since a proangiogenic effect has been described for blood-derived platelet MPs. As mentioned earlier, the complete lack of platelet-derived MPs in plaques, while platelets are the dominant source of CD40L+ MPs in the circulation, is rather unexpected.

The implications of the presented data for pathogenesis research are evident. However, it is more difficult to indicate the clinical implications of the presented research. First, MPs were obtained from a relatively small cohort of symptomatic and asymptomatic patients. Effects on MP-related functions by medication use, established risk factors, or delay between symptoms and surgery could, therefore, not be taken into account. Second, it could be suggested that blocking CD40L might stabilize plaques by inhibition of plaque neovascularization. However, the use of CD40L antibodies may result in unwanted complications that could be detrimental in patients suffering from cardiovascular disease since human trials revealed an increase in thrombotic complications when a monoclonal antibody against CD40L was administered (12). Third, tissue MPs may be difficult to target therapeutically. However, circulating MPs are considered a therapeutic target in cardiovascular disease (13). Recent patents regarding circulating MPs and exosomes are related to their procoagulant potential.

In summary, MPs should not be appreciated as innocent debris since they may hide procoagulant and inflammatory activity that may influence atherothrombosis and lesion progression. The different functional characteristics of circulating MPs and atherosclerotic plaque-derived MPs are intriguing and deserve more detailed research.

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REFERENCES


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