Platelet microparticles: reinforcing the hegemony of platelets in atherothrombosis

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Microparticles (MPs) represent a heterogeneous population of vesicles with a diameter of 100 to 1,000 nm that are released by budding of the plasma membrane (ectocytosis) and express antigens specific of their parental cells (1). Generation and release of MPs occurs not only during cellular activation following stimulation with proinflammatory, prothrombotic or proapoptotic substances or exposure to high shear stress, but also during cellular differentiation and apoptosis (2). While MPs are present in peripheral blood of healthy individuals, with platelet MPs representing 70–90% of all circulating MPs, significant elevations have been reported in many disease states including atherosclerosis, diabetes, sepsis, autoimmune disorders, and malignancies (1, 2). MPs may participate in several hemostatic and inflammatory responses, vascular remodeling and angiogenesis, cell survival, and apoptosis, processes which are partly also involved in atherothrombosis (3, 4).

MPs display an opulent spectrum of bioactive substances and recent studies provided compelling evidence that MPs represent an efficient shuttle system for the intercellular exchange of biological signals and information (5, 6). Indeed, MPs may transfer their components and content to elicit profound effects on selectively responsive targets cells not only in their local environment but also throughout the circulatory system, resulting in cell activation, phenotypic modification, and reprogramming of cell function. Such a transcellular delivery system establishes an integrated communication network in which information and properties among cells can be selectively shared and enable the coordination of complex cellular responses as well as the maintenance of the homeostasis equation.

As documented by numerous studies in the last 25 years, a key feature of MPs is their procoagulant potential enabling them to play a relevant role both in haemostasis and thrombosis (7). In this respect it has been shown that the surface of platelet-derived MPs is approximately 50- to 100-fold more procoagulant than the surface of activated platelets and that procoagulant MPs are capable of correcting the bleeding phenotype in mice with severe haemophilia A (8, 9). In general, two major molecular properties in varying degrees convey the procoagulant function of MPs: abundant exposure of membrane phosphatidylserine and functional tissue factor (TF) (7). In the course of cellular activation or apoptotic breakdown, extensive membrane remodeling including translocation of anionic phosphatidylserine to the exoplasmic leaflet is observed and membrane budding is ultimately resolved into the release of phosphatidylserine-enriched MPs. Phosphatidylserine serves as a highly potent surface for the assembly of coagulation factors and thus provides a catalytic environment optimal for the generation of thrombin (10). TF is an integral membrane protein of crucial importance for the initiation of blood coagulation as its interaction with plasma factor VIIa initiates enzymatic cascade reactions culminating in the formation of thrombin and subsequent conversion of fibrinogen to fibrin (11). The recent finding that some MPs represent a rich reservoir of circulating, “blood-borne” TF challenged the traditional model of blood coagulation which implied that blood does not contain significant TF levels and emphasised the role of subvascular TF which forms a “haemostatic envelope” around blood vessels and is only exposed following vascular injury (11, 12). Accordingly, in a murine model analyzing the laser-induced injury of the cremaster artery, deposition of activated platelets at the site of injury as well as rapid and P-selectin/PSGL-1 dependent accumulation of infused and TF-enriched MPs within the leading edge of the developing thrombus could be observed (13). Of note, the cellular origin of blood-borne TF is still not ultimately defined although it appears that MPs derived from stimulated monocytes display the most relevant amount of TF. Complicating the interpretation of data on the assessment of MP-associated TF is the observation that TF-expression by MPs most likely varies within the pathophysiological context and that MP membranes containing TF might be exchanged and shared among different cell lines. Furthermore encryption and de-encryption of TF appears to be operative in the regulation of blood-borne TF activity (7).

Acute thrombus formation on disrupted atherosclerotic plaques plays a key role during the onset of acute coronary syndromes. In the December 2012 issue of Thrombosis and Haemostasis, the study of Suades et al. revealed that MPs contribute to the formation and progression of arterial thrombi in the context of manifest atherosclerosis and following injury of the vessel wall (14). Platelet adhesion under conditions of high shear stress, as present in stenotic arteries, is central for the development of arterial thrombosis. Suades et al. now convincingly demonstrate that circulating and in particular platelet-derived


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MPs enhance the deposition of platelets and fibrin to the injured or atherosclerotic arterial vessel wall. MPs may also bind to already adhered platelets under high shear rate conditions and may locate within the thrombus, thus possibly serving as a "sticky surface" to further support recruitment of platelets. Moreover, the authors demonstrate that MPs induce activation of platelets and amplify their aggregation, decrease clotting time and markedly increase thrombus size. Following the argumentation by Suades et al, it appears that under certain pathophysiological conditions platelets may engage a functional autocrine, self-amplifying loop mechanism to successfully reinforce and disseminate their procoagulatory potential. Such mechanism might be particularly deleterious in the scenario of advanced atherosclerosis with plaque rupture, as circulating MPs (mainly originating from activated platelets) may cooperate with platelet MPs to amplify arterial thrombus formation. Indeed, it has been shown that the atherosclerotic plaque constitutes an opulent source of sequestered MPs, in particular of leukocyte origin with an even more profound expression of TF (10).

Altogether, the study of Suades et al. presented in the December 2012 issue of *Thrombosis and Haemostasis* provides another aspect of MPs as an element linking atherosclerosis, inflammation as well as thrombosis and in particular substantiates the concept that elevated levels of circulating and/or platelet-derived MPs reflect "vulnerable blood", referring to a hypercoagulable state with increased blood thrombogenity and augmented risk for atherothrombotic events (15, 16). According to such a concept, evaluation of MPs may help to detect patients at risk for such events and for an adverse outcome. However, to establish a valid MP-based risk stratification tool many obstacles still need to be overcome. Until now, studies on human MPs in cardiovascular disease models were mostly observational in their nature, with only limited studies determining the prognostic role of MPs and their subsets. Before starting large-scale and prospective studies though, a standardised methodological procedure for probe sampling as well as quantification of MPs is urgently needed. Considering the variability of the molecular composition and content of MPs, which results in a broad spectrum of MP functional properties (e.g. proinflammatory and procoagulant potential), a more extensive characterisation of MPs and their subsets beyond the mere quantification is required in addition. Indeed, a multitude of induction pathways together with complex inclusive or exclusive sorting mechanisms are operative during the generation of MPs and the molecular profile of these MPs appears to be relevantly dependent on the cellular stimulus and the microenvironment of the parental cell (5). Therefore, in order to establish new diagnostic strategies based on the evaluation of MPs, further efforts are necessary in analysing determinants and consequences of different induction pathways, to decipher the signature of circulating MP subsets as well as to assess and compare the functional properties of MPs in selected diseases and different stages of disease progression, e.g. in patients with atherosclerosis or cancer.

**Conflicts of interest**

None declared.

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**References**