

Editorial

## Microparticles: Surrogate Markers & Biological Vectors in Cardiovascular Diseases

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Microparticles are small (<1.5 µm), anuclear cell vesicles that are released by several cell types during cell activation and apoptosis and that can be associated by their surface receptors to their cells of origin (e.g. platelets, endothelial cells, leukocytes) using flow cytometry [1-3]. Initially, it was believed that microparticles are a kind of cell debris without any distinct pathological function [4]. However, an increasing number of publications indicate that MP release is a highly regulated process and that circulating microparticles indeed have multiple distinct functions in haemostasis and vascular inflammation [5]. Even though the precise molecular mechanisms of microparticle release are still incompletely understood, it is evident that this process starts with a Ca<sup>2+</sup> influx into the maternal cells. This Ca<sup>2+</sup> influx results in an inactivation of the *flippase*, an enzyme that is essential for the asymmetric distribution of phosphatidylserine of the bilayer cell membrane, and an activation of calpain leading to a dissociation of cytosceletal protein actin with glycoproteins of the cell membrane. These two Ca2+ triggered effects finally result in cell bleb formation and microparticle release into circulation. As a consequence of the decreased flippase activity, the outer microparticle membrane is rich of Phosphatidylserine (PS), a unique characteristic that can be used to stain microparticles for flow cytometric analysis but furthermore results in a strong pro-thrombotic microparticle effect, as it activates pro-thrombin to thrombin.

Within the last decades it has become evident that microparticles are potent promoters of vascular inflammation and coagulation [6,7]. Consequently, increased levels of microparticles have been found in multiple inflammation triggered disease, such as sepsis, SIRS occurring after cardiopulmonary resuscitation, joint diseases, pulmonary hypertension and aortic valve stenosis [8-12].

As the early beginning, as well as the progression of several cardiovascular diseases is mainly influenced by platelet and leukocyte activation and endothelial dysfunction, microparticles of these cells have been found to be valuable surrogate markers in these diseases allowing detection of sub clinical changes in blood haemostasis. One exemplarily study, which underlines the importance of microparticles as surrogate markers, was performed by Chironi et al. [13]. They investigated leukocyte derived microparticles in patients without cardiovascular diseases and found that microparticles of leukocyte origin correlate well with sub clinical atherosclerosis. In the same line of evidence, Bernal-Mizrachi et al. assessed endothelial derived microparticles in patients with Coronary Artery Disease (CAD) [14]. They found that endothelial microparticles are increased in patients with CAD in comparison to controls and that patients with an acute coronary syndrome had higher levels of EMP than patients with stable CAD. However, even if there is strong evidence that microparticles can be used as surrogate markers in different inflammatory diseases, these data need to be confirmed by large clinical multicenter studies using standardized methods to assess quantity and surface characteristics of circulating microparticles.

Microparticles can not only be used as surrogate markers but also act as inflammatory biological vectors in circulation. It has been found that microparticles bind to and fuse with distinct target cells suggesting that that they thereby deliver cytoplasm and presumably also specific surface receptors to their destination cells [15]. As the adhesion of

microparticles to their target cells is believed to be at least to some extent receptor mediated, microparticles of a specific cell type affect most likely only a distinct subset of target cells, for example endothelial cells or leukocytes. Supporting this hypothesis, Jy et al. assessed the effect of platelet microparticles on leukocytes [16]. They found that PMP bind to leukocytes, activated those and thereby contribute mainly to cellular mediated vascular inflammation. This data was supported by Barry et al., who showed that platelet microparticles increase the adhesion of monocytes to endothelial cells in a time-and dose-dependent manner [17]. Sabatier and colleges investigated the impact of endothelial microparticles on the monocytotic cell line THP-1[18]. They showed that EMP induce a pro-coagulatory state in THP-1 cells, which was inhibited by blocking the endothelial surface receptor ICAM-1 and the leukocyte counterpart  $\beta 2$  integrins and thereby support the hypothesis of a receptor specific binding behaviour of microparticles to their target cells. This MP-induced paracrine activation of leukocytes might be the reason, why microparticles have been described in several inflammatory and coagulatory cardiovascular diseases, such as the aortic valve stenosis, acute coronary syndrome and pulmonary hypertension [11,12,14].

A novel mechanism of microparticle triggered vascular inflammation has been described by Habersberger et al. [19]. They found that *pentameric* C Reactive Protein (pCRP), which is the nonactive form of CRP, dissociates on the surface of PMP into active *monomeric* CRP. These data nicely show that circulating microparticles not only induce cellular inflammation, but also act on plasmatic inflammation. However, as it has been shown that microparticles even contain mRNA, as well as microRNA, microparticles might even be able to directly influence protein synthesis and post-translational gene regulation in their target cells [20].

In conclusion, microparticles are small cell vesicles that can be used as inflammatory and coagulatory surrogate markers in several cardiovascular diseases. Additionally, they represent an elegant way of intercellular communication by which biomolecules, protected by a lipid membrane from degradation by serum enzymes, can be transferred from a paternal cell to a target cell. Consequently, microparticles are able to change the phenotype and presumably even the gene expressions of their target cells. Future studies are required to assess whether a therapeutic reduction of distinct microparticle subtypes are associated with a beneficial effect for patients with cardiovascular diseases.

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Received December 04, 2013; Accepted December 05, 2013; Published December 09, 2013

Citation: Moser M, Helbing T, Fink K, Bode C, Diehl P (2013) Microparticles: Surrogate Markers & Biological Vectors in Cardiovascular Diseases. Transl Med 3: e126. doi:10.4172/2161-1025.1000e126

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