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Role of microparticles in endothelial dysfunction and arterial hypertension

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Abstract

Microparticles are small cell vesicles that can be released by almost all eukaryotic cells during cellular stress and cell activation. Within the last 1-2 decades it has been shown that microparticles are useful blood surrogate markers for different pathological conditions, such as vascular inflammation, coagulation and tumour diseases. Several studies have investigated the abundance of microparticles of different cellular origins in multiple cardiovascular diseases. It thereby has been shown that microparticles released by platelets, leukocytes and endothelial cells can be found in conditions of endothelial dysfunction, acute and chronic vascular inflammation and hypercoagulation. In addition to their function as surrogate markers, several studies indicate that circulating microparticles can fuse with distinct target cells, such as endothelial cells or leukocyte, and thereby deliver cellular components of their parental cells to the target cells. Hence, microparticles are a novel entity of circulating, paracrine, biological vectors which can influence the phenotype, the function and presumably even the transcriptome of their target cells. This review article aims to give a brief overview about the microparticle biology with a focus on endothelial activation and arterial hypertension. More detailed information about the role of microparticles in patho-

physiology and disease can be found in already published work.

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Key words: Microparticles; Arterial hypertension; Endothelial dysfunction; Biological vectors; Inflammation

Core tip: Microparticles are small cell vesicles which can be released from many cells (*e.g.*, endothelial cells, platelets, leukocytes) into circulation and that can be quantified with flow cytometry. Several studies have shown that specific microparticles subtypes are increased in conditions enhanced vascular inflammation and coagulation. Thereby, microparticles have become surrogate markers, which can be used to assess for example leukocyte and endothelial cell activation. Additionally, by fusion with other cells, microparticles transfer cellular components of their parental cells to their target cells, which often results in altered function of the target cells.

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INTRODUCTION

What are microparticles?

During cell activation, multiple eukaryotic cells, such as endothelial cells or leukocytes, but also prokaryotes, have the ability to shed little cell blebs, so called microparticles^[1,2]. Microparticles consist of the cell membrane as well as of the cytoplasm of their maternal cells and can be classified by flow cytometry into for example endothelial microparticles (EMPs), leukocyte microparticles and

platelet microparticles (PMPs). When microparticles were first described by Wolf^[3] over 40 years ago, it was suggested that they are only a kind of cellular debris. However, within the last couple of years microparticles have gained increasing interest in different medical fields and recent effort has been undertaken to investigate the biology of microparticles, as well as the impact of microparticles on different diseases^[4-7]. It thereby has become evident that microparticles can be used as circulating surrogate markers for several pathophysiological conditions, such as inflammation, coagulation but also metastatic diseases and additionally are important circulating biological vectors^[1].

Microparticles as biological vectors in circulation

The biology of microparticles is still incompletely understood, but it is evident that microparticles have far more functions than only activating inflammatory cells and the coagulation cascade. It recently has been shown that they bind to and fuse with distinct target cells, a process that is at least partly mediated by specific interactions of microparticles with surface receptors (such as Mac-1) of the target cell^[8]. By fusion with their target cells, microparticles deliver cytoplasm as well as membrane anchored surface receptors to their destination cells. This process is frequently associated with changes of the target cells phenotype and function. Hence, microparticles are an own kind of biological vectors modulating the function of their target cells remote from the location where they initially had been released.

Elevated microparticle levels can often be found in pathological conditions which are associated with cell mediated inflammation and coagulation. To assess the inflammatory effect of platelet microparticles, which is the largest microparticle fraction in the blood, Jy *et al*^[9] investigated the effect of PMPs on neutrophils. They found that microparticles released from platelets attach to neutrophils and activate those. Hence, platelet microparticles may in fact be an additional link between vascular coagulation and inflammation in cardiovascular disease.

Hypothesizing that microparticles might not only influence the phenotype but also the transcriptome of their target cells, Hunter *et al*^[10] assessed whether microparticles from mononuclear cells contain microRNAs, which are small non-coding RNA molecules that regulate mRNA translation and thereby affect post transcriptional gene expression. In this ground breaking study, they found that microparticles indeed contain a broad spectrum of different microRNAs, which they might deliver to their target cells and presumably affect the target cells protein synthesis. Interestingly, when compared to microRNA patterns of their cells of origin, microparticles do not contain a random set of microRNAs of their paternal cells, but are loaded with a distinct, specific selection of miRNAs^[11]. These findings suggest that microparticle release is a highly regulated process in which cell vesicles are "loaded" from their cells of origin with specific RNA molecules which might eventually be transferred to their target cells. However, to date the underlying molecular

mechanisms of this loading process are not understood.

To what extent circulating microparticles are involved in intercellular signalling was demonstrated by a pivotal study of Janowska-Wieczorek *et al*^[12]. They found that PMPs transfer the platelet surface receptor glycoprotein (GP) II b/III a to the surfaces of different lung cancer cell lines. As the GP II b/III a integrin has a high affinity to (sub)endothelial antigens, tumour cells that were pre-incubated with platelet microparticles also showed increased metastasization. Hence, PMPs might be directly involved in the progression of tumour diseases.

In summary, microparticles are small cell blebs that represent a novel way of intercellular communication, which seems to be particularly relevant for inflammatory and pro-coagulatory diseases. Due to the effects on their target cells, microparticles are able to change the phenotype, the function and presumably also the transcriptome of their target cells and might be involved in the pathogenesis of several cardiovascular diseases^[1].

ARTERIAL HYPERTENSION

Arterial hypertension is a strong risk factor for atherosclerosis and vascular mortality and often starts with endothelial dysfunction^[13,14]. Early diagnosis of impaired endothelial function is crucial to allow medical anti-inflammatory, endothelium-protective treatment at an early disease stage. Reflecting endothelial dysfunction, endothelial microparticles might be a valuable tool to assess endothelial dysfunction, particularly in asymptomatic patients.

Microparticles in endothelial dysfunction and arterial hypertension

Arterial hypertension is a multifactor disease that is strongly promoted by endothelial dysfunction^[15,16]. Recent data indicate that altered, activated endothelial cells release endothelial microparticles into circulation. EMPs can be used as cellular surrogate markers for endothelial dysfunction and are increased in several diseases with an altered endothelial function, such as atherosclerosis, aortic valve stenosis and pulmonary hypertension^[17-20]. It recently was published that endothelial microparticles are even associated with several cardiovascular risk factors in the Framingham Heart Study^[21].

However, besides their role as surrogate markers, microparticles are furthermore involved in the progression of impaired endothelial function as well as in angiogenesis^[22,23]. For example Burger *et al*^[24] assessed the effect of microparticles on endothelial inflammation and found that microparticles themselves induce endothelial expression of vascular cell adhesion molecule 1, platelet endothelial cell adhesion molecule and adhesion of J774A.1 cells, which is a cell line with macrophage characteristics^[24]. Along the same line of evidence, Boulanger *et al*^[25] investigated the mechanisms how microparticles induce endothelial dysfunction and found that MPs from patients with myocardial infarction, but not from healthy

controls, induced endothelial dysfunction by impairing the endothelial nitric oxide transduction pathway. These data were confirmed by Martin *et al*^[26] who discovered that T cell microparticles reduced endothelial nitric oxide- and prostacyclin mediated vasodilatation and decreased expression levels of endothelial nitric oxide synthase.

One of the few studies investigating the interconnection between microparticles and arterial hypertension was performed by Preston *et al*^[20]. They assessed the abundance of endothelial microparticles in patients with untreated severe hypertension *vs* those with mild hypertension compared to normotensive individuals. It was found that microparticles released from endothelial cells and platelets were significantly increased in patients with severe arterial hypertension and that endothelial microparticles correlated strongly with the level of both systolic and diastolic blood pressures. Thus, it can be suggested that EMPs and PMPs can be used as circulating markers for endothelial injury in arterial hypertension. The findings described by Preston *et al*^[20] are supported by studies, in which increased levels of circulating endothelial microparticles had been found in patients with pre-eclampsia, a disease that is characterized by vascular inflammation, altered endothelial function and arterial hypertension^[27,28].

The Renin Angiotensin System (RAS) plays a key role in arterial hypertension and is the target for anti-hypertensive medical treatment. It has been supposed that angiotensin II, which is the final effector of the RAS, not only affects the blood pressure but furthermore induces a pro-thrombotic state. Hypothesizing that the RAS might be involved in the generation of pro-thrombotic microparticles, Cordazzo *et al*^[29] investigated the effect of angiotensin II on the release of microparticles from mononuclear cells. They found that angiotensin II indeed induces shedding of pro-thrombotic MP from mononuclear cells. The data of Cordazzo support the suggestion that microparticles might in fact be the link between the activation of the renin angiotensin system and a pro-thrombotic state, which can be found in patients suffering from arterial hypertension.

End-organ damage, such as hypertensive nephropathy with impaired kidney function, is a common complication of patients with arterial hypertension. To assess whether endothelial microparticles might be involved in impaired renal function under arterial hypertension, Hsu *et al*^[30] measured endothelial microparticles, endothelial progenitor cells (EPCs) and the glomerular filtration rate in patients suffering from arterial hypertension. They found that elevated EMPs to EPCs ratios are associated with a decline of the glomerular filtration rate in hypertensive patients. These data underline the impact of endothelial damage assessed by the EMP to EPC ratio on the progression of impaired kidney functions in arterial hypertensive patients.

In conclusion, particularly endothelial microparticles can be found in several conditions that are associated with arterial hypertension. EMPs are not only valuable

surrogate markers reflecting the extent of endothelial cell dysfunction but additionally might promote the progression of arterial hypertension and its complications.

WHAT BRINGS THE FUTURE?

Microparticles are promising surrogate markers for a variety of pathological conditions, particularly in conditions that are associated with impaired endothelial function and arterial hypertension (Table 1). However, a lack of standardization of microparticle definitions and methods used to quantify microparticles makes it difficult to compare results from different research groups. As microparticles have a highly complex molecular architecture, they are more fragile than for example blood proteins, which are often used as clinical surrogate parameters. Hence, the way how blood samples for microparticle measurements are taken, such as the diameter and the length of the needle that was used, is critical and can significantly influence flow cytometric analysis of microparticles. Finally, even technical characteristics of the flow cytometry used to analysis microparticles can influence measurement results. Therefore, the International Society on Thrombosis and Haemostasis (www.isth.org) and the International Society for Extracellular Vesicles (<http://www.isev.org>) are working on recommendations for standardized protocols for microparticle measurements. Standardized studies will need to assess the diagnostic value of microparticles as surrogate markers in arterial hypertension.

As microparticles reflect a variety of different pathological changes in the vascular system (*e.g.*, inflammation, coagulation, activation of different cell types, *etc.*) they might represent a broader spectrum of cellular changes in circulation than measuring only one distinct soluble marker protein. Furthermore, besides their role as vascular surrogate markers, microparticle measurement can presumably be used to monitor the success of medical treatments of diseases that are associated with vascular inflammation. However, large clinical multicentre studies are necessary to assess whether microparticles of different cellular origin can be used as surrogate markers and as tools for drug monitoring in different cardiovascular diseases.

Until now, only very few studies have investigated the effect of different drugs on circulating microparticles. Nomura *et al*^[31] found that eicosapentaenoic acid, which is an omega-3 fatty acid, reduces endothelial derived microparticles in patients suffering from type 2 diabetes. Trantomano *et al*^[32] described that fluvastatin has a protective effect on endothelial cells and inhibits EMP release and Morel *et al*^[33] reports that vitamin C reduces endothelial and platelet derived microparticles in patients with myocardial infarction. Even if these data are promising, their results need to be confirmed by randomized multicentre studies and it needs to be assessed whether a reduction of microparticle levels is associated with a beneficial patient outcome.

In conclusion, microparticles are small cell vesicles re-

Table 1 Overview about studies investigating the interrelation between microparticles and endothelial dysfunction/arterial hypertension

Study subjects	Flow cytometric MP characteristics	Findings	Ref.
Framingham offspring cohort	CD144 ⁺ CD31 ⁺ /CD41 ⁻	Increased CD144 ⁺ MP correlate with Arterial hypertension Elevated triglycerides Metabolic syndrome Increased CD31 ⁺ /CD41 ⁻ correlate with elevated triglycerides	Amabile <i>et al</i> ^[21]
MPs of AMI patients	Isolated blood MPs	MPs from AMI patients impair the endothelial nitric oxide pathway	Boulanger <i>et al</i> ^[25]
Ang II stimulated mouse aortic endothelial cells	Annexin V ⁺ CD144 ⁺	Ang II induces EMP release EMPs increase endothelial expression of VCAM-1, PCAM and adhesion of J774A.1 cells	Burger <i>et al</i> ^[24]
(Microparticles of) human mononuclear cells	Microparticles from mononuclear cells	Ang II induces MP release of mononuclear cells Angiotensin receptor type 2 inhibitors reduce Ang II induced MP release	Cordazzo <i>et al</i> ^[29]
MPs of human lymphoid CEM T cell line	Isolated cell culture MPs	MPs decrease expression levels of eNOS MPs induce endothelial dysfunction by altering the NO- and prostacyclin pathways	Martin <i>et al</i> ^[26]
EMPs of women with pre-eclampsia	CD62E ⁺ CD31 ⁺ /42b ⁻	Women with preeclampsia have higher EMP levels than those with gestational hypertension and controls	González-Quintero <i>et al</i> ^[28]
MPs levels of patients with art Hypertension	CD31 ⁺ /CD42 ⁺ CD41 ⁺	Increased EMPs and PMPs in patients with severe arterial hypertension EMPs and PMPs levels correlate with blood pressure	Preston <i>et al</i> ^[20]

EMPs: Example endothelial microparticles; PMPs: Platelet microparticles; Ang II: Angiotensin II; MPs: Microparticles; eNOS: Endothelial nitric oxide synthase; VCAM-1: Vascular cell adhesion molecule 1; PCAM: Platelet endothelial cell adhesion molecule; AMI: Acute myocardial infarction; NO: Nitric oxide.

leased by a huge variety of cells reflecting the state of activation of their parental cells. Besides functioning as surrogate markers for example for endothelial dysfunction, recent evidence indicates that they additionally influence the progression of several cardiovascular diseases. Hence, circulating microparticles might not only be valuable surrogate markers for different pathological conditions but furthermore be novel therapeutic targets by which the progression of microparticle mediated diseases might be influenced.

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