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Review

Microparticles in cardiovascular diseases

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Abstract

Microparticles are membrane vesicles released from many different cell types. There are two mechanisms that can result in their formation, cell activation and apoptosis. In these two mechanisms, different pathways are involved in microparticle generation. Microparticle generation seems to be a well regulated process. Microparticles vary in size, phospholipid and protein composition. They have a potent pro-inflammatory effect, promote coagulation and affect vascular function. Since these processes are all involved in the pathogenesis of cardiovascular disease and circulating microparticle numbers are altered in many cardiovascular diseases, a role for microparticles in the pathogenesis of cardiovascular diseases is likely. Although hard evidence for a role of microparticles in cardiovascular diseases at present is still only limited, new evidence is accumulating rapidly to support this theory. Elucidation of the microparticle composition and the mechanisms involved in exertion of their effects will supply this evidence and enable us to develop additional intervention strategies for prevention and treatment of cardiovascular diseases.

Keywords: Coronary disease; Endothelial function; Hemostasis; Platelets; Thrombosis

1. Introduction

Microparticles were first described in 1967 when Wolf reported platelet membrane fragments in human plasma [1]. He called these fragments ‘platelet dust’. This ‘dust’ contained vesicles, smaller than 0.1 μm in diameter, which promoted coagulation. In past decades it has become apparent that many cell types can release microparticles and that these microparticles may not just be side effects of cellular processes, but may be actively involved in physiology and pathophysiology. In vitro, the release of microparticles has been shown from endothelial cells, vascular smooth muscle cells, platelets, leukocytes, lymphocytes and erythrocytes. Some of these microparticle populations occur in the blood of healthy individuals and patients. There are obvious changes in numbers, cellular origin and composition of microparticle populations in various disease states. The impact, however, of these changes on their in vivo effect is still insufficiently known. Microparticles have been implicated to play a role in inflammation, coagulation and vascular function. In this review, we will summarize recent information on microparticle formation, composition, and—most importantly—their putative physiological and pathological functions in cardiovascular diseases. Furthermore, we will discuss the evidence that some currently used therapies may in fact partially exert their effects via the blockade of microparticle formation.

2. Microparticle formation

There are two well-known cellular processes that can lead to the formation of microparticles, cell activation and apoptosis. At present we do not know whether cell

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activation and apoptosis lead to the formation of similar microparticles, in terms of size, lipid and protein composition and (patho-)physiological effects. There are, however, differences in the mechanisms resulting in their formation. The processes thought to be involved in microparticle formation during cell activation and apoptosis are presented schematically in Fig. 1.

2.1. Cell activation

Microparticles can be formed during cell activation by many agonists (Fig. 1, left panel). Platelets, for instance, are activated by thrombin, calcium ionophore A23187, ADP plus collagen, the terminal complement complex C5b-9 or shear stress [2–14]. Monocytes, endothelial cells, hepatocytes and arterial smooth muscle cells release microparticles upon activation by bacterial lipopolysaccharides, cytokines such as tumor necrosis factor-α or interleukin-1, the C5b-9 complex or hydroperoxide [15–20]. In general, the release of cell activation-associated microparticles is time- and calcium-dependent. The shedding starts within minutes after addition of an agonist [7,9,21]. One of the first signs of cell activation is the increase in cytosolic calcium concentration [10,12,18], especially at the site of vesiculation [22]. Subsequently, the increase in cytosolic calcium activates kinases, inhibits phosphatases and activates calpain [10,12,18,23–26]. Chelation of extracellular calcium ions by EGTA blocks the increase in cytosolic calcium as well as the release of microparticles [18]. Thus, the increase in cytosolic calcium is essential for microparticle release.

Microparticle formation requires the breakdown of the membrane skeleton, the subcellular system that provides the cell membrane with structural stability [27]. This membrane skeleton mainly consists of actin, vinculin and talin. The exact interaction between the cell membrane and the membrane skeleton, which prohibits microparticle formation, is currently unknown. Talin is degraded by calpain, which is one of the direct pathways through which the increased cytosolic calcium concentration facilitates microparticle formation [18] (Fig. 1, left panel).

Microparticle formation in platelets is also in some way linked to the glycoprotein IIb–IIIa complex. This complex, in its active conformation, is the main fibrinogen receptor on the platelet surface. The most important binding site within the fibrinogen molecule for binding to the glycoprotein IIb–IIIa is the amino acid sequence arg–gly–asp (RGD). It has been shown that addition of artificial RGD-containing peptides not only blocks fibrinogen binding to activated platelets, but also the release of microparticles [9]. Thus, binding of fibrinogen to the activated glycoprotein IIb–IIIa complex facilitates the release of microparticles. The role of the glycoprotein IIb–IIIa complex in platelet microparticle formation is supported by studies on platelets from patients with Glanzmann's thrombasthenia. These platelets have reduced amounts or complete absence of functional glycoprotein IIb–IIIa and an impaired ability to vesiculate [9]. Thus, the bleeding tendency of these patients may not only be caused by the defect in platelet

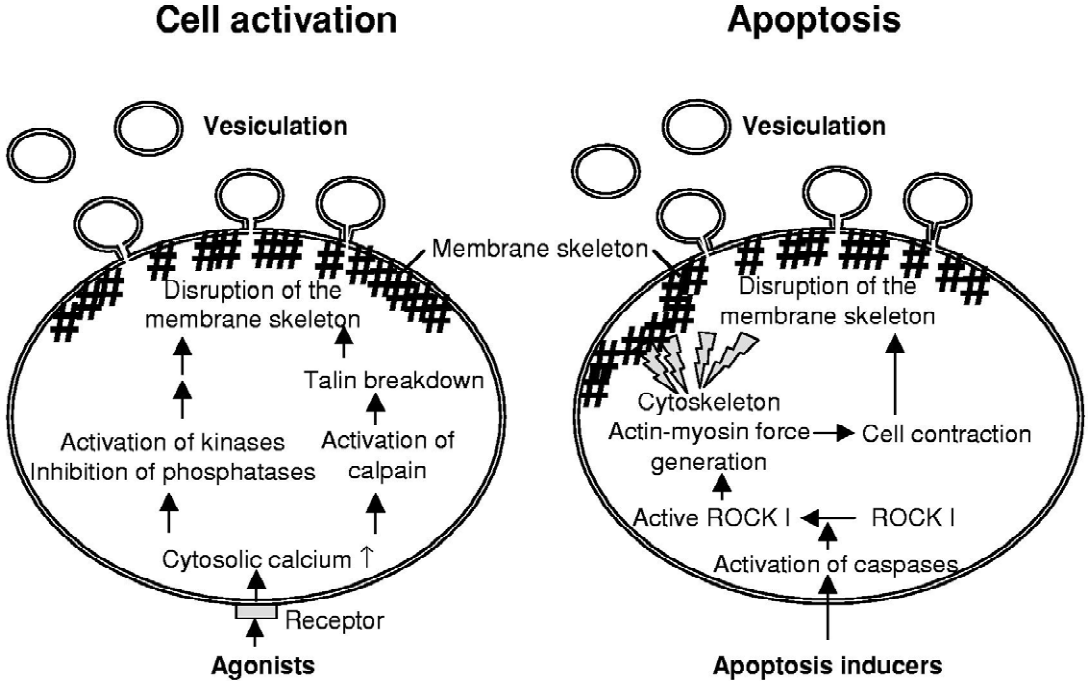

Fig. 1. Schematic representation of general mechanisms involved in microparticle formation during cell activation (left panel) and apoptosis (right panel).

cross-linking via fibrinogen, but also by their decreased ability to generate microparticles.

2.2. Cell apoptosis

Apoptosis is characterized by cell contraction, DNA fragmentation, and dynamic membrane blebbing [23,28]. Such blebs may differ from microparticles formed by cell activation in size, lipid and protein composition and (patho-)physiological effects. The contractile force, generated by actin–myosin cytoskeletal structures, is thought to drive the formation of membrane blebs (Fig. 1, right panel) [29,30]. Apoptotic membrane blebbing depends on activation of the Rho-associated kinase, ROCK I [23]. ROCK I promotes increased actin–myosin force generation and couples actin–myosin filaments to the plasma membrane [31]. During apoptosis, ROCK I is cleaved by activated caspases and becomes activated. ROCK I activity and, as a consequence, membrane blebbing are required for redistribution of fragmented DNA from the nuclear region into the membrane blebs and apoptotic bodies [23]. Thus, microparticle formation during apoptosis results from ROCK I activity and the resulting disruption of the membrane skeleton structure. Such microparticles may contain fragmented DNA (Fig. 1, right panel).

3. Microparticle composition

Microparticle membranes consist mainly of lipids and proteins. Their composition depends on the cellular origin and the cellular processes triggering their formation. Hardly any information is available on the intravesicular contents of microparticles. A schematic representation of the composition of microparticle membranes is presented in Fig. 2.

3.1. Lipids

Microparticles are surrounded by a phospholipid bilayer. In resting cells the various phospholipid species are distributed asymmetrically in the bilayer. This asymmetrical phospholipid distribution is usually disturbed during microparticle formation [32], leading to exposure of negatively charged phospholipids such as phosphatidylserine and phosphatidylethanolamine on the microparticles. This exposure likely plays a role in the in vivo effects of microparticles since phosphatidylserine efficiently binds coagulation factors [33].

Only limited information is available on the phospholipid composition of microparticles in health and disease. The phospholipid composition of microparticles from healthy humans consists mainly of phosphatidylcholine (approximately 60%), with the remainder being comprised of sphingomyelin, phosphatidylethanolamine and phosphatidylserine [34]. Although these microparticles are mainly derived from platelets [35], their phospholipid composition clearly differs from that of platelet plasma membranes. This could be due to contamination by microparticles from other cells and/or from the selective release of phospholipids into microparticle membranes.

Fourcade and coworkers reported that microparticles from synovial fluids of inflamed joints of arthritis patients contain phosphatidylcholine, phosphatidylethanolamine, sphingomyelin, and lysophospholipids (all 20–25%) and small amounts of phosphatidylserine [14]. This composition clearly differs from that of microparticles isolated from blood of healthy humans [34]. Microparticles in the synovial fluids are mainly derived from leukocytes rather

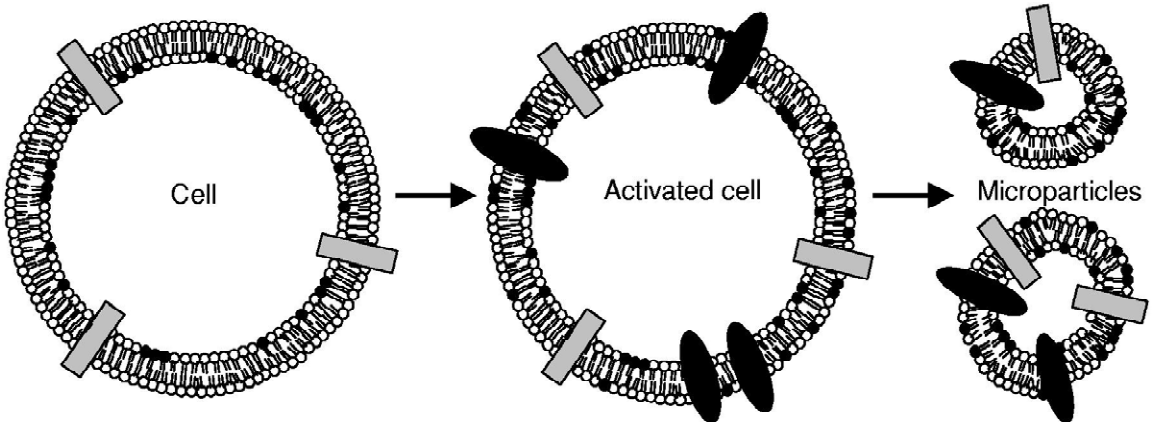

Fig. 2. Schematic representation of microparticle generation and composition. Negatively charged phospholipids are presented by the black dots. In the resting cell the negatively charged phospholipids, such as phosphatidylserine and phosphatidylethanolamine, are located only in the inner layer. The grey rectangles represent cell-specific antigens, e.g., CD4 for T-helper cells. In the activated cells and microparticles negatively charged phospholipids are relocated and are also present in the outer layer. The black ovals represent molecules that have been upregulated by cell activation on the cell membrane and the microparticles.

than platelets [36]. This may indicate that the phospholipid composition of microparticles differs between various cell types, or alternatively, that inflammatory stimuli produce microparticles with a different phospholipid composition. Huber and coworkers recently reported the presence of oxidized phospholipids in microparticles from endothelial cells that had been exposed to an oxidative stress stimulus, whereas such phospholipids were absent in microparticles from calcium ionophore stimulated endothelial cells [21]. Thus, the phospholipid composition and their oxidation status differ between microparticles.

3.2. Proteins

Microparticles expose membrane antigens that are specific for the 'parent cell' they originate from. These identification antigens are always present on the cell surface, irrespective of the activation or apoptosis status of the parent cell, and enable the determination of their cellular source, e.g., CD4 for microparticles from T-helper cells [37].

Microparticle membranes may also contain molecules that have been upregulated or translocated by cell activation or apoptosis [16]. For instance, activated cultured endothelial cells release microparticles displaying E-selectin (unpublished data). Platelet microparticles expose molecules such as P-selectin and glycoprotein 53 that both originate from intracellular granule membranes [3,11]. These microparticles are also highly enriched in α-granule-derived factor Va [11]. Similar observations were done in T-cell-derived microparticles, which displayed glycoprotein 53 from endocytic origin [38].

Several differences in antigen exposure between microparticles and their parent cell seem not directly related to activation. For example, T-cell-derived microparticles lack the proteins CD28 and CD45 (leukocyte common antigen), which are among the most abundantly present proteins of the parent cell membrane [38]. Stimulation of platelets with complement complex C5b-9 produces microparticles that, compared to the platelets, are highly enriched in the C9-neoantigen [11] and have a 1000-fold higher surface density of C5b-9, suggesting that these microparticles are shed from the site of insertion of the C5b-9 complex [11]. Also, erythrocyte-derived microparticles are specifically enriched in various antigens and receptors [40,41]. Taken together, these differences indicate that microparticle shedding must be a well-regulated process [38,39]. This is illustrated by the finding that some proteins present in lipid rafts, specific subdomains of the cell membrane that are enriched in cholesterol and sphingomyelin as well as particular proteins, of the erythrocyte membrane are transferred into microparticles, while others are not [39].

The microparticle composition is also agonist dependent. T-cells produce microparticles that are enriched in CD3ε- and ζ-chains only upon activation of the T-cell antigen receptor and not upon activation by ionomycin plus *p*-methoxyamphetamine hydrochloride [38]. Microparticles from thrombin- or collagen-activated platelets expose glycoprotein IIb–IIIa complexes that bind fibrinogen, in contrast to microparticles produced by platelets incubated with C5b-9, which do not bind fibrinogen [3]. Finally, even microparticles released by one cell type in response to a single agonist still can form a heterogeneous population. For instance, microparticles released from platelets after stimulation with serum from patients with heparin-induced thrombocytopenia are heterogeneous in size and in exposure of glycoprotein IIb–IIIa [42].

Thus, microparticles vary in size, phospholipid and protein composition and therefore their functional capacity and activity. The shedding seems to be a well regulated process, that creates particular microparticle characteristics under various (patho)physiological conditions.

4. Microparticle function

We described the numbers and cellular origin of microparticles in the blood of healthy men [35] and women [43]. Circulating microparticles were mainly derived from platelets, but also from erythrocytes, leukocytes and endothelial cells [35,43]. These microparticles initiated thrombin generation in vitro [35,43]. Microparticles have also been studied in various disease states, in which numbers, cellular source and composition are altered. Although many aspects of microparticle function are still unclear, a picture develops in which microparticles play an important role in inflammation, coagulation, and vascular (dys-)function. Theoretically, microparticles may have various (patho-)physiological functions, namely transport of membrane components from the parent cell to other cells and (in-)direct activation of inflammation, coagulation or vascular function. Since inflammation, coagulation and vascular function are all involved in the pathogenesis of cardiovascular diseases, we will discuss how microparticles are involved in these processes (see Fig. 3).

4.1. Inflammation

4.1.1. In vitro evidence

An increased inflammatory response is involved in the pathogenesis of cardiovascular diseases. Adhesion of monocytes and neutrophils to the endothelium is an early event in vascular inflammatory syndromes and, together with the subsequent transendothelial migration of the leukocytes, a crucial step in the development of atherosclerosis [44]. Specific adhesion receptors exposed on endothelial cells attract various classes of leukocytes to the vascular wall. The ligands for these receptors are present on leukocytes as well as on the leukocyte-derived microparticles. Which of these ligands are involved in the

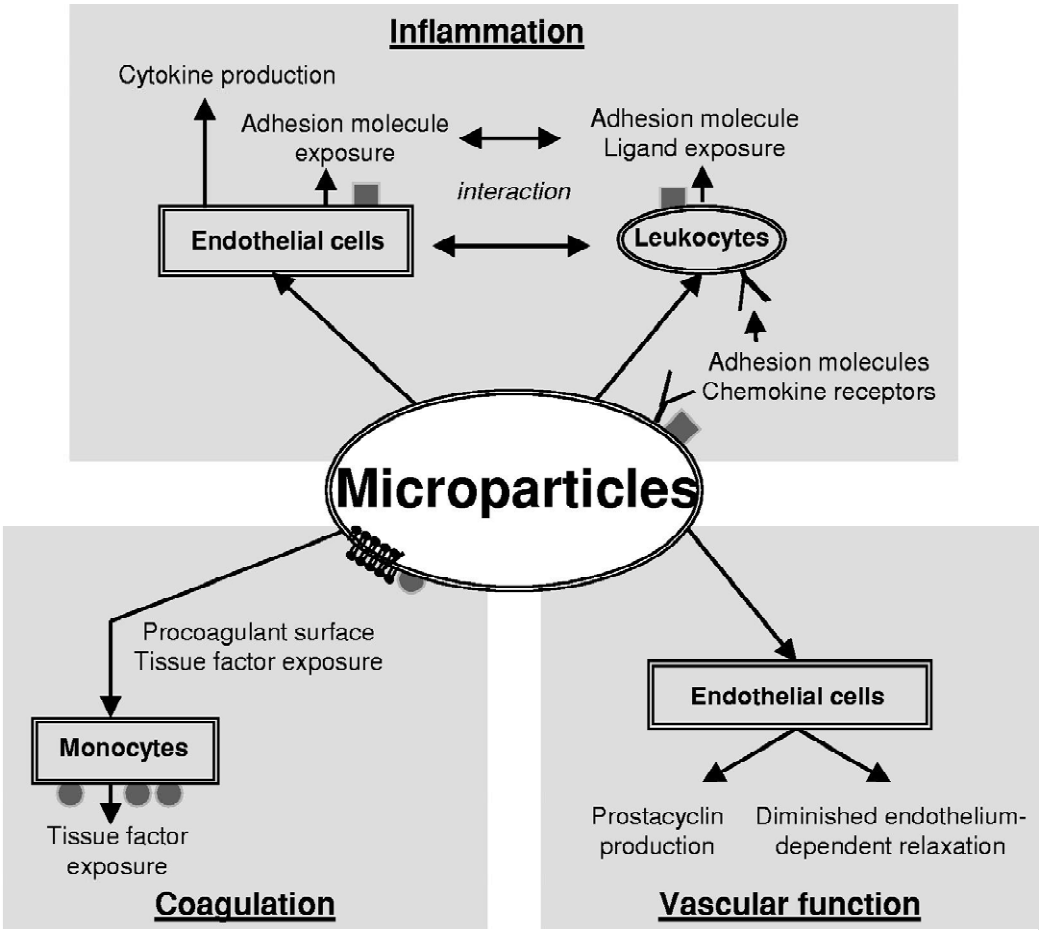

Fig. 3. Schematic representation of functions attributed to microparticles.

adhesion of leukocyte-derived microparticles to endothelial cells, however, is unknown at present.

Platelet-derived microparticles may initiate inflammation. Barry and coworkers showed that platelet microparticles deliver arachidonic acid to endothelial cells, which results in upregulation of CD54 (intercellular adhesion molecule-1; ICAM-1) and the subsequent adhesion of monocytes [45]. Once leukocytes are bound to the vascular wall they migrate into the intima, where they secrete cytokines and growth factors that promote the migration and proliferation of vascular smooth muscle cells and thus plaque formation. The release of cytokines by endothelial cells, which attracts leukocytes to the endothelium, is also triggered by microparticles [46,47]. Studies describing the role of microparticles in the interaction between endothelial cells and leukocytes are summarized in Table 1. Fig. 3 shows schematically how microparticles promote the inflammatory response.

4.1.2. In vivo evidence

During various systemic inflammatory conditions, microparticle numbers are increased in the systemic circulation, as summarized in Table 2. Furthermore, there is direct evidence for a role of microparticles in inflammatory processes available from in vivo studies. Mesri and coworkers described a heterogeneous microparticle population in healthy humans, which doubled in size by administration of *N*-formyl-Met–Leu–Phe, an inflammatory stimulus. The resulting microparticle population contained both leukocyte- and platelet-derived microparticles [48]. The leukocyte microparticles in this mixed population stimulated cultured endothelial cells, resulting in the production of interleukin-6, monocyte chemoattractant protein-1 and tissue factor [48].

4.1.3. Microparticle components involved in inflammation

Oxidized phospholipids may form (one of) the biologically active components of microparticles that cause monocyte adherence to endothelial cells and neutrophil activation [21]. Patel and coworkers showed that microparticles from hydroperoxide-treated endothelial cells contain oxidized phospholipids [17]. These oxidized phospholipids are present in microparticles released from endothelial cells subjected to oxidative stress, but absent in microparticles released in response to a non-oxidative stimulus such as calcium ionophore [21]. Also apoptosis is accompanied by oxidative stress [49], and microparticles

Table 1
Effects of microparticles on leukocytes, endothelial cells and the interactions between these cells

Microparticle source	Effects	Refs.
Endothelial cells	Promote monocyte–endothelial cell binding	[21]
Platelets	Upregulation of CD11a/CD18[a] and CD11b/CD18[b] on monocytes and ICAM-1 on endothelial cells resulting in increased cellular interaction	[45]
Platelets	Upregulation of CD11b on leukocytes, resulting in increased phagocytic activity and increased leukocyte–leukocyte binding	[2,83]
Endothelial cells	Neutrophil activation	[17]
Endothelial cells, leukocytes	Chemotactic attraction of leukocytes	[46,47]
Peripheral mononuclear cells, monocytes	Chemokine receptor transfer to peripheral mononuclear cells, monocytes and endothelial cells	[84]

[a] Lymphocyte function antigen-1.
[b] Macrophage antigen-1.

from endothelial cells undergoing apoptosis contain oxidized phospholipids [21]. Oxidative stress and apoptosis are well-recognized phenomena in many cardiovascular diseases, such as cardiomyopathy, myocarditis, acute myocardial infarction, atherosclerosis and pre-eclampsia (reviews see [28,50–52]). Furthermore, oxidized phospholipids in low density lipoproteins are implicated in the pathogenesis of atherosclerosis (for reviews see [50,53]). Therefore, the occurrence of oxidized phospholipids in apoptotic microparticles and in microparticles formed in the presence of oxidative stress may be an important mechanism in the pathogenesis of these diseases.

Oxidized phospholipids exert their actions through platelet activating factor (PAF) receptors [17,54], which are exposed on both endothelial cells and leukocytes [55]. The exact pathways through which the effects of oxidized phospholipids are accomplished after their interaction with the PAF receptor are not yet clarified, and may or may not be similar to the actions of PAF on its receptor [56,57]. Microparticles are also capable of delivering arachidonic acid to endothelial cells, monocytes and platelets [6,45]. Thus, microparticles are actively involved in inflammatory processes and thus in cardiovascular diseases.

4.2. Coagulation

4.2.1. In vitro evidence

Patients with cardiovascular diseases have an increased risk of thrombosis, which can manifest itself as acute myocardial infarction or stroke [58]. There is substantial in vitro evidence for microparticle involvement in activation of the coagulation system. Coagulation requires not only

Table 2
Diseases in which total microparticle numbers or numbers of subgroups of microparticles in the venous circulation are increased

Disease	Increased microparticles	Refs
Acute coronary syndromes	Total, endothelium, platelet	[85,86]
Arteriosclerosis obliterans	Platelet	[78]
Diabetes	Total and platelet	[87,88]
Hypertension	Platelet	[87]
Idiopathic thrombocytopenia	Platelet	[89,90]
Lupus anticoagulant	Endothelium	[16]
Paroxysmal nocturnal hemoglobinuria	Total and platelet	[91]
Pre-eclampsia	Leukocyte	[43]
Sepsis	Leukocyte	[60,64]
Systemic inflammation after trauma or sepsis	Platelet	[92]
Uremia	Platelet	[87]

(activated) coagulation factors and calcium ions, but also membranes exposing negatively charged phospholipids, such as phosphatidylserine. Exposure of phosphatidylserine facilitates binding of (activated) coagulation factors to the membrane, thereby enabling the formation of tenase- and prothrombinase-complexes. Subsequently, blood coagulation can start, especially when tissue factor—a transmembrane protein that initiates coagulation through the extrinsic coagulation pathway—is exposed. Microparticles have a negatively charged phospholipid surface [32], readily bind activated coagulation factors [3,7,11,59] and expose tissue factor in various conditions [15,20,60–63]. Both in vitro prepared and in vivo generated microparticles initiate and support thrombin generation in vitro [16,33,35,36,60,61,63,64]. Furthermore, infusion of artificially prepared phospholipid vesicles triggers the development of severe disseminated intravascular coagulation in primates [65], and infusion of these vesicles in pregnant rats induces placental congestion and growth restriction in the offspring [66].

Besides these direct effects of microparticles on the coagulation system, microparticles may also indirectly promote coagulation. For instance, purified P-selectin or P-selectin-exposing platelets trigger the expression of tissue factor on monocytes [67]. Since P-selectin is often present on platelet-derived microparticles, these microparticles are likely to induce tissue factor expression by monocytes (see Fig. 3).

4.2.2. In vivo evidence

The evidence that microparticles indeed contribute to coagulation in vivo is mainly circumstantial. First, microparticle numbers are elevated in different types of disease involving hypercoagulation, such as idiopathic thrombocytopenia, paroxysmal nocturnal hemoglobinuria, lupus anticoagulant and acute coronary syndromes (see Table 2). Second, microparticle generation is reduced in several bleeding disorders, such as Scott Syndrome [3], Castaman's defect [68] and Glanzmann's disease [9]. Platelets from patients with the Scott syndrome and Glanzmann's disease have a decreased microparticle generating capacity in response to agonists [3,9] and have reduced numbers and function of inducible factor Va receptors [3]. Third, microparticles expose tissue factor in several clinical conditions that are strongly associated with hypercoagulation, such as pericardial wound blood [63], the blood of patients with disseminated intravascular coagulation [64], and synovial fluid from inflamed arthritic joints [36].

Since hypercoagulation is one of the characteristics of cardiovascular diseases, and altered numbers and procoagulant behaviour of microparticles were reported in several cardiovascular diseases, microparticles are likely to play a causal role in the development of hypercoagulation in cardiovascular disease.

4.3. Vascular function

4.3.1. In vitro evidence

Diminished vascular function, especially endothelial dysfunction, has been reported in many cardiovascular diseases. Well known examples are the pathogenesis of cardiac failure [69], atherosclerosis [70], acute coronary syndromes [71], hypertension [72], and pre-eclampsia [73]. Several studies reported the effects of microparticles on endothelial cell activation and function in vitro. Recently, Boulanger and coworkers described that microparticles from patients with acute myocardial infarction diminished endothelium-dependent relaxation in isolated arteries [74]. In contrast, microparticles isolated from the venous blood of patients with non-ischemic chest pain had no such effect [74]. This was the first demonstration of a direct effect of microparticles on vascular function. Recently, we demonstrated also that microparticles from venous blood of women with pre-eclampsia diminished endothelium-dependent relaxation in isolated resistance arteries [75] (see Fig. 3). On the other hand, microparticles may also have beneficial effects on vascular function. For instance, transfer of arachidonic acid to endothelial cells by platelet microparticles induced the expression of cyclooxygenase-2 expression and the production of prostacyclin [6]. Prostacyclin induces vasodilatation and diminishes platelet reactiveness. The platelet microparticles used in these experiments were pretreated with secretory phospholipase A_2, an acute phase reactant, which occurs in the circulation at strongly increased concentrations during diseases like sepsis and pre-eclampsia. Whether or not untreated platelet microparticles have the same effects is unknown.

4.3.2. In vivo evidence

Only circumstantial evidence is presently available for a role of microparticles in vascular dysfunction in vivo. Microparticle numbers are elevated or the composition of the microparticle population is altered in cardiovascular diseases that are characterized by endothelial dysfunction, such as acute coronary syndromes, hypertension, atherosclerosis and pre-eclampsia (see Table 2). Also, high levels of presumably apoptotic microparticles are present in atherosclerotic plaques [76]. These microparticles are mainly derived from monocytes and lymphocytes. Almost all TF activity in the plaque is located on these microparticles. Therefore, the procoagulant activity of atherosclerotic plaques can be explained by their enclosed microparticles.

4.3.3. Microparticle components

Almost nothing is known about the microparticle components that impair endothelial functions. We suspect that oxidized phospholipids may be involved, especially since oxidized phosphatidylcholine induces endothelial dysfunction in isolated arteries [77]. However, future research addressing this question is needed.

5. Are microparticles cause or consequence of cardiovascular diseases?

In the previous paragraphs we summarized the evidence that microparticles contribute to the pathogenesis of cardiovascular disease; their potent pro-inflammatory effect, their promotion of coagulation, and their effect on vascular function. However, it remains to be established whether microparticles play a causal role in the pathogenesis of these diseases or whether they are a consequence of the disease. In the previous paragraphs several facts were discussed that indicate an active, causal role of microparticles in the pathogenesis of cardiovascular diseases. The strongest evidence for this hypothesis is provided by the studies that showed a direct effect of microparticles on endothelial function. Furthermore, the fact that in vivo and in vitro prepared microparticles induce increased adhesion of leukocytes to endothelial cells, trigger cytokine production and expose tissue factor or P-selectin, strongly suggests an active role of microparticles in inflammation and coagulation. However, increased microparticle numbers can also result from inflammation, hypercoagulation or vascular dysfunction. For instance, cytokines as well as thrombin can trigger microparticle generation [16,20] or enhance the already existing microparticle generation [3,4,8,9,46,59,78,79].

6. Effects of currently used therapies on microparticles

The recognition of a role of microparticles may not only be important for our understanding of the pathogenesis of cardiovascular disease, but may also have implications for the prevention and treatment of these diseases. Some currently used therapies are known to affect microparticle generation. For instance, abciximab (ReoPro®), a glycoprotein IIb–IIIa receptor antagonist that is currently used as an antiplatelet drug in prevention of ischemic complications after percutaneous coronary intervention, also almost completely blocks platelet vesiculation in vitro [80]. Thus, the anticoagulant effect of abciximab may not be solely due to inhibition of ligand binding to glycoprotein IIb–IIIa, but may also result from reduced release of microparticles from platelets. No in vivo studies have been performed that investigated this mechanism so far. Treatment of patients suffering from transient ischemic attacks with calcium channel blockers also decreased microparticle generation [81]. Furthermore, a randomized, placebo-controlled, double blind trial showed that treatment of patients with congestive heart failure (NYHA class II or higher) with vitamin C decreased the number of circulating microparticles [82]. After a 2.5-g intravenous bolus, followed by 3 days of treatment with 2 g twice daily, microparticle numbers were decreased with 70% on the fifth day. Since vitamin C is an antioxidant, prevention of generation of oxidized phospholipids in microparticles may also be an effect of this therapy. However, no data are available on these effects.

Thus, there are some therapies that are currently used for treatment of diseases that also affect microparticle numbers. Whether these effects on microparticles contribute to the therapeutic action remains to be established. With ongoing research on microparticles in cardiovascular disease, more of these effects on microparticles are likely to be discovered. Such information may prove useful in prevention or treatment of these diseases.

7. Concluding remarks

In this review we discussed the current knowledge available on microparticle formation, composition and function. Considerable evidence suggests that microparticles play a role in the processes of inflammation, coagulation and vascular function, all processes involved in the pathogenesis of cardiovascular diseases. Future studies are needed to provide additional evidence whether the role of microparticles in these disease processes is indeed a causal one. Clarification of the microparticle composition and the underlying mechanisms involved in exertion of the effects of microparticles will hopefully supply us with this evidence and enable us to develop additional intervention strategies for prevention and treatment of cardiovascular diseases.

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