Evolving Role of Microparticles in the Pathophysiology of Endothelial Dysfunction

Fina Lovren and Subodh Verma

BACKGROUND: Endothelial dysfunction is an early event in the development and progression of a wide range of cardiovascular diseases. Various human studies have identified that measures of endothelial dysfunction may offer prognostic information with respect to vascular events. Microparticles (MPs) are a heterogeneous population of small membrane fragments shed from various cell types. The endothelium is one of the primary targets of circulating MPs, and MPs isolated from blood have been considered biomarkers of vascular injury and inflammation.

CONTENT: This review summarizes current knowledge of the potential functional role of circulating MPs in promoting endothelial dysfunction. Cells exposed to different stimuli such as shear stress, physiological agonists, proapoptotic stimulation, or damage release MPs, which contribute to endothelial dysfunction and the development of cardiovascular diseases. Numerous studies indicate that MPs may trigger endothelial dysfunction by disrupting production of nitric oxide release from vascular endothelial cells and subsequently modifying vascular tone. Circulating MPs affect both proinflammatory and proatherosclerotic processes in endothelial cells. In addition, MPs can promote coagulation and inflammation or alter angiogenesis and apoptosis in endothelial cells.

SUMMARY: MPs play an important role in promoting endothelial dysfunction and may prove to be true biomarkers of disease state and progression.

The endothelium plays an important role in maintaining cardiovascular homeostasis by secreting endothelium-derived relaxing and endothelium-derived contracting factors (1–3). Nitric oxide (NO) (3) is the key endothelium-derived relaxing factor and plays a pivotal role in the maintenance of vascular tone and reactivity (4). In addition to being the main determinant of basal vascular smooth muscle tone, NO is an inhibitor of coagulation, inflammation, and oxidative stress (5). Diminished production or availability of NO and/or imbalance in the relative contribution of endothelium-derived relaxing and contracting factors have been described in endothelial dysfunction (6). Endothelial dysfunction is commonly associated with the development and progression of a wide range of cardiovascular diseases. Dysfunction of endothelial cells is also the earliest event in the process of lesion formation and atherosclerosis (7). Various human studies have identified that measures of endothelial dysfunction may offer prognostic information with respect to vascular events (2, 3, 8).

Extracellular vesicles are a heterogeneous population of particles released from various cell types into the extracellular space under both normal and stressed conditions. These particles are divided into 3 categories—exosomes, apoptotic bodies, and microparticles (MPs)—on the basis of their size, content, and mechanism of formation. Exosomes, which are between 40 and 100 nm in diameter, are the smallest of the extracellular vesicles. Exosomes are formed through inward budding of endosomal membranes and are enclosed within intracellular particles that subsequently release their contents into the extracellular environment (9). Apoptotic bodies are approximately 1–5 μm in size and are formed during the late stages of apoptosis by all cell types (9). MPs are small membrane fragments that are shed from various cell types and range between 0.1 and 1.0 μm. The release of MPs is a highly controlled process that is driven by different

3 Nonstandard abbreviations: NO, nitric oxide; MP, microparticle; eNOS, endothelial nitric oxide synthase; PKB, phosphatidylinositol-3-kinase; ERK1/2, extracellular signal-regulated kinase 1/2; NF-k, nuclear factor κ-light-chain enhancer of activated B cell; ROS, reactive oxygen species; NAD(P)H, nicotinamide adenine dinucleotide (phosphate) oxidase; MCP-1, monocyte chemotactic protein-1; Akt, protein kinase B; IL-6, interleukin-6; ICAM-1, intracellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; RANTES, regulated on activation, normal T cells expressed and secreted; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; bFGF, basic fibroblast growth factor; TNF-α, tumor necrosis factor-alpha; TF, tissue factor.
stimuli such as shear stress, physiological agonists, pro-apoptotic stimulation, and damage (9). Under basal conditions, cells may also release MPs spontaneously (10).

MPs typically express membrane and cytoplasmic proteins as well as cytoplasmic content such as transcription factors, RNA, microRNA, lipids, and organelles, all of which reflect their cell of origin and stimuli that lead to their generation (11). Long considered as inert debris, MPs are now appreciated as an important transcellular delivery system in the exchange of biological signals. MPs may transfer information from the parent cell to various target cells by direct cell-to-cell contact or alternatively through secretion of soluble mediators and effectors (11).

In healthy humans, circulating MPs are mainly derived from platelets and to a lesser extent leukocyte and endothelial cells (12). Increased concentrations of MPs have been demonstrated under some physiological and pathophysiological conditions (13). MPs isolated from blood have been considered as biomarkers of vascular injury and inflammation in several cardiovascular pathologies including, acute myocardial infarction, diabetes, atherothrombosis, preeclampsia, hypertension, and metabolic syndrome (13–16).

In this review we examine the implications of circulating MPs. Endothelial responses to MPs can be acute, resulting from the release of several factors, or prolonged, implying changes in the expression of genes involved in the structural and functional regulation of the vascular wall (17). Under normal conditions, MPs contribute to the regulation of endothelial cell functions, including coagulation and inflammation (18). Under stress, cells release MPs that differ in numbers, composition, and function, thereby contributing to a procoagulant and proinflammatory phenotype that leads to endothelial dysfunction and the development of cardiovascular diseases (19).

In this review we examine the implications of circulating MPs in endothelial dysfunction, focusing on the endothelial NO bioavailability and oxidative stress, inflammation, and cell proliferation.

**MPs Modify Vascular Function by Promoting Oxidative Stress and Reducing NO Concentrations in Endothelial Cells**

Several studies have demonstrated that MPs may impair NO release from vascular endothelial cells and subsequently modify vascular tone. MPs from T lymphocytes decrease NO production and increase oxidative stress in endothelial cells (20). These effects are associated with reduced endothelial NO synthase (eNOS) activity, which depends on phosphatidylinositol-3-kinase (PI3K), extracellular signal–regulated kinase 1/2 (ERK1/2), and nuclear factor κ-light-chain-enhancer of activated B cell (NFκB) pathways (20). Furthermore, aorta from mice injected with T-lymphocyte MPs shows an impaired acetylcholine-evoked endothelial relaxation due to a decline in NO and an increase in the production of reactive oxygen species (ROS) (20).

Similarly, circulating T lymphocyte–derived MPs, at concentrations that are reached in pathological disorders, produce endothelial dysfunction in conductance and small resistance arteries, in response to agonist and shear stress (21). Of particular interest is that MP treatment reduces the NO- and prostacyclin-derived but not the endothelium-derived hyperpolarizing-mediated dilation. This MP effect is associated not only with decreased NOS expression, but also with overexpression of caveolin-1 (21).

Furthermore, a recent study has shown that the incubation of human endothelial cells with MPs released from activated monocytes has deleterious effects on endothelial function, although the production of NO is enhanced and the generation of superoxide is not affected (22). These MPs increase the nitration of several proteins in endothelial cells and activate multiple pathways related to nitrosative stress by activating both PI3K and ERK1/2 and regulating calveolin-1 expression but not its phosphorylation (22).

Endothelial MPs alone can also aggravate endothelial dysfunction. MPs generated from endothelial cells impair endothelium-dependent relaxation in the rat aorta (23). This effect is accompanied by increased superoxide production in aortic rings, which may reduce the bioavailability of NO.

On their own, endothelial MPs produce detectable amounts of superoxide and contain nicotinamide adenine dinucleotide (phosphate) oxidase [NAD(P)H] oxidase (24). In addition to the oxidative stress, endothelial MPs also enhance expression of the cell adhesion proteins in cultured endothelial cells (24).

MPs isolated from patients with cardiovascular diseases may diminish vascular function and promote endothelial dysfunction (13–15). Boulanger and colleagues have shown that MPs from patients with acute myocardial infarction suppress endothelium-dependent relaxation in isolated arteries (13). In contrast, MPs isolated from patients with nonischemic chest pain do not affect arterial responses (13). MPs from women with preeclampsia induce impaired endothelium-dependent relaxation in isolated resistance arteries (16). Furthermore, reduced flow-mediated dilation has been associated with the presence of endothelial MPs in clinical samples from conditions such as end-stage renal failure (14) and type 2 diabetes (15). In these conditions, circulating human endothelial MPs appear to induce endothelial dysfunc-
tion by diminishing NO release without changing eNOS expression (14, 16).

Patients with metabolic syndrome have increased circulating concentrations of MPs compared to healthy patients (17). In vivo injection of MPs from these patients into mice leads to impaired endothelium-dependent relaxation in aorta and decreased eNOS expression. This finding provides evidence that circulating MPs from patients with metabolic syndrome influence endothelial dysfunction (17). Moreover, MPs from metabolic syndrome patients induce an ex vivo vascular dysfunction by increasing both ROS and NO release and by altering cyclooxygenase metabolites and monocyte chemotactic protein-1 (MCP-1) through the Fas/Fas-ligand pathway (25).

In patients with obstructive sleep apnea, circulating endothelial MP concentrations negatively correlate with flow-mediated vasodilation and carotid-intima thickness (26). An increase in plasma endothelial MPs has also been observed in patients who were briefly exposed to second-hand smoke (27). A summary of MP-induced endothelial dysfunction in relation to cardiovascular disorders is provided in Table 1.

In a rat model, MPs from pulmonary hypertensive rats have been reported to inhibit endothelial NO production and endothelium-dependent vasorelaxation (28). In some instances, MPs have been found to have a positive effect on endothelial function. Hedgehog morphogens are associated with MPs shed from the plasma membrane of apoptotic stimulated T cells. Mice injected with these MPs show improved acetylcholine-evoked relaxation of the aorta and induce NO production directly by the hedgehog morphogen pathway, which involves PI3K and protein kinase B (Akt) (29). Finally, in a mouse ischemia/reperfusion model, impaired coronary relaxations are restored after administration of hedgehog morphogens containing MPs (30). This effect indicates that T-cell MPs may preserve coronary endothelial integrity and functionality in severe acute endothelial injury (30), which is accompanied by an increase in NO production in both tissue and blood, following ischemia/reperfusion (31).

**MPs Trigger Endothelial Inflammation**

Circulating blood contains MPs derived mainly from platelets and to a lesser extent from leukocytes and endothelial cells (32). These MPs can affect both proinflammatory and antiinflammatory processes in endothelial cells.

The effects of platelet MPs have been studied extensively. Their biological role extends beyond their participation in coagulation. MPs interact with endothelial and blood cells and are involved in the regulation of endothelial function (33). Stimulation of endothelial cells by platelet MPs in vitro results in the release of cytokines, interleukin-6 (IL-6), and IL-8, and a rise in the expression of intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin (34).

In addition to RANTES, platelet MPs contain substantial amounts of RANTES (regulated on activation, normal T cells expressed and secreted) (35). This proinflammatory cytokine can be deposited on activated endothelium, as can be observed in atherosclerotic lesions in mice carotid arteries (36). Thus, the transcellular delivery of RANTES promotes leukocyte recruitment to atherosclerotic plaques and subsequently induces progression of atherosclerosis in mice (35).

Furthermore, platelet MPs deliver arachidonic acid in a transcellular manner, inducing cyclooxygenase-2 production and ICAM-1 in endothelial cells, which then activate platelets (37). Endothelial cells exposed to platelet MPs may in turn deliver arachidonic acid to platelet MPs. The arachi-
donic acid is then metabolized to thromboxane A2, which elicits contraction in pulmonary arteries (38).

An alternative mechanism of endothelial cell activation with platelet MPs occurs through an active cytokine, IL-1β. Platelets synthesize pro–IL-1β, which is shed in its mature form within the platelet MPs. These platelet MPs then induce neutrophil–endothelial cell adhesion (39).

Leukocyte MPs may originate from monocytes, neutrophils, and B and T lymphocytes. A recent study has shown that monocyte MPs generated from lipopolysaccharide-stimulated monocytes contain IL-1β and inflammasome (40). These monocyte MPs bind and internalize with human endothelial cells and activate endothelial cell adhesion molecules in ERK1/2- and NFκB-dependent pathways, promoting inflammation responses in endothelial cells (40).

MPs from freshly isolated leukocytes act on the endothelium as a competent inflammatory agonist, stimulating inflammatory gene expression, release of cytokines IL-6 and IL-8, and upregulation of the leukocyte–endothelial cell adhesion molecules ICAM-1, VCAM-1, and E-selectin. Among the activated pathways, leukocyte MPs stimulate the secretion of IL-6 in endothelial cells through the phosphorylation of c-Jun N-terminal kinase 1 without the involvement of NFκB or the ERK1/2 pathways (41).

MPs from apoptotic human T cells attenuate vascular contractions to the agonists (42). MP-induced vascular hyporeactivity is associated with vascular inflammation and is linked to an increase in NO and prostacyclin production. These effects are a result of the upregulation of the proinflammatory proteins inducible NO synthase (iNOS) and cyclooxygenase-2 (COX-2) through NFκB-dependent transcription (42).

Experiments in cultured endothelial cells have demonstrated that the release of endothelial MPs is associated with IL-6 secretion (43). The same study showed that interaction between endothelial MPs and naive endothelial cells also triggers ICAM-1 upregulation and proinflammatory responses—effects not observed with endothelial MPs from unstimulated cells. Also, inflamed endothelial cells alone can cause the release of proinflammatory MPs from circulating blood cells. This release of MPs could then contribute to prolonged endothelial activation and atherosclerotic changes in blood vessels subjected to inflammatory insult (43).

Furthermore, human atherosclerotic plaque contains large amounts of MPs originating from various cells (44, 45). MPs isolated from human atherosclerotic plaque regulate the inflammatory responses in endothelial cells, enhancing the adhesion of monocytes to endothelial cells and increasing the transendothelial migration—both of which promote atherosclerotic plaque progression (45).

Some MPs have been shown to promote antiinflammatory activity. Neutrophil MPs contain the functionally active antiinflammatory protein annexin-1 and may inhibit the interaction between leukocytes and endothelial cells both in vitro and in vivo (46). Also, endothelial MPs generated by activated protein C, and carrying the endothelial protein C receptor, may modulate inflammation and increase cell survival (47).

Activated protein C and the MP endothelial protein C receptor form a complex that influences the expression of endothelial genes involved in apoptosis and inflammation, through the activation of protease-activated receptor 1 (47).

**MPs Alter Endothelial Cell Survival and Angiogenesis**

Contradictory data have been reported regarding the effect of MPs on angiogenesis. It has been reported that platelet MPs may stimulate angiogenesis, but it has also been reported that lymphocyte and endothelial MPs may stimulate as well as inhibit angiogenesis.

Platelet MPs from healthy individuals promote proliferation, migration, and tube formation in cultured endothelial cells (48). The latter effects of MPs are mediated by their lipid components, likely sphingosine 1-phosphate. The ability of platelet MPs to induce angiogenesis is related to the activation of ERK1/2 and PI3K pathways (48). Another study also demonstrated that platelet MPs enhance endothelial cell migration and induce tube formation (49). Platelet components, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor, basic fibroblast growth factor (bFGF), and heparanase, have all been shown to be involved in mediating these endothelial functions (49).

Local injections of platelet MPs isolated after left coronary artery ligation in rats increase the capillary formation in the ischemic region. This effect is abolished by selective inhibition of VEGF and basic bFGF. Similarly, endothelial migration induced with the platelet MPs may be completely abolished by an inhibitor of VEGF receptor tyrosine phosphorylation or an inhibitor of heparanase (50).

Lymphocyte MPs may have proangiogenic effects via their capacity to stimulate NO release from endothelial cells (30). However, these MPs may also have antiangiogenic effects due to the development of oxidative stress associated with a reduced release of NO from endothelial cells (20).

Leukocyte MPs generated from apoptotic human T lymphocyte possess strong antiangiogenic effects, suppressing the sprouting of the aortic ring microvessel
in vitro and corneal neovascularization in vivo (51). In endothelial cells, this effect is linked to the downregulation of VEGF receptor type 2 expression, ERK1/2 phosphorylation, and an increase in ROS production (51).

MPs generated from the activated T-lymphocyte, harboring the morphogen Sonic Hedgehog, regulate angiogenesis through both direct and indirect mechanisms (52). These MPs increase capillary-like formation and proliferation but inhibit migration in endothelial cell culture. Proteins involved in these processes, such as ICAM-1 and Rho A, and the activation of focal adhesion kinase and VEGF, are upregulated in endothelial cells treated with MPs containing morphogen Sonic Hedgehog (52).

MPs of endothelial origin can elicit angiogenesis, but the mechanisms by which they mediate their effects are different from those reported for other MPs. Low concentrations of endothelial-derived MPs stimulate angiogenesis through matrix metalloproteinase activity and extracellular matrix remodelling. It has been reported that endothelial cells release MPs containing matrix metalloproteinases (53). Metalloproteinases released by endothelial MPs regulate the focalized proteolytic activity essential for invasion during neovascular structure formation (54). High concentrations of endothelial-derived MPs have been reported to avert angiogenesis because they decrease the formation of capillary-like structures through the production of ROS (55). Moreover, high doses of endothelial MPs also negatively regulate proliferation and migration in valvular endothelial cells, leading to endothelial dysfunction and valvular disease (56).

In contrast to these findings, MPs derived from ischemic tissues, which are mostly from endothelial origin, can induce differentiation of progenitor cells to endothelial cells and promote vasculogenesis, although they produce high concentrations of ROS and overexpress NADPH oxidase subunits (57).

In addition to endothelial and other disease-related cells, adipocytes have been recently reported to secrete MPs (58). Adipocyte-derived MPs are associated with multiple angiogenic factors and play a role in angiogenesis in adipose tissue. Leptin, tumor necrosis factor-α (TNF-α), and bFGF from adipocyte-derived MPs are involved in endothelial cell migration and tube formation (58).

MPs derived from human circulating endothelial progenitor cells activate angiogenesis in mature quiescent endothelial cells. Endothelial progenitor cell MPs express several adhesion molecules that are crucial in the internalization of MPs into endothelial cells and are required for their biological activity. The effects of endothelial progenitor cell MPs are associated with the PI3K/Akt signaling pathway and eNOS activation (59).

Treatment with endothelial progenitor cell MPs improves neovascularization and favors regeneration in severe mouse hind limb ischemia, suggesting a possible use of these MPs for treatment of peripheral arterial disease (60).

Macrophage MPs represent a major determinant of intraplaque neovascularization and plaque vulnerability. MPs isolated from macrophages located within human atherosclerotic lesions express the CD40 ligand and stimulate endothelial cell proliferation after CD40 ligation, thereby promoting angiogenesis within the plaque (61).

Procoagulant and Antiapoptotic Role of MPs in Endothelial Cells

Endothelial cell dysfunction, disruption of vascular homeostasis, apoptosis, and coagulation all appear to be associated with MPs (62). Experimental data show that active generation of monocyte MPs results in the disruption of endothelial cell integrity and increases endothelial thrombogenicity (63). Enhancing coagulation activity by stimulation with monocyte MPs is associated with an increased expression of the endothelial tissue factor (TF) and a reduced expression of anticoagulant TF pathway inhibitor and thrombomodulin (63, 64).

Furthermore, monocyte MPs induce endothelial cell apoptosis (63), which results in the loss of anticoagulant membrane components and subsequently leads to procoagulant activation (65). MPs released from endothelial cells contain a substantial quantity of caspase-3, and by disposing of caspase-3 in MPs, endothelial cells are protected from detachment and apoptosis (62). In addition, endothelial MPs protect endothelial cells against apoptosis in an annexin I/phosphatidylserine receptor-dependent manner. Endothelial MP-mediated protection against apoptosis is associated with inhibition of p38 activity (66).

Fig. 1 summarizes the signaling pathway activated by various MPs in endothelial cells.

Clinical Implications

MPs have damaging effects on endothelial cell function, which can in turn contribute to the development of cardiovascular diseases. Accordingly, strategies that focus on the removal of MPs or the inhibition of their functions could represent novel therapeutic directions. Indeed, some existing and effective pharmacotherapies have led to a decrease in circulating MP concentrations, albeit inadvertently.

In this regard, statins and 3-hydroxy-3-methylglutaryl-coenzyme A–reductase inhibitors may
through their antiinflammatory effects on endothelial cells cause a reduction in endothelial MP release (67). Conversely, another in vitro study has shown that statins stimulate endothelial detachment and MP release by inhibiting prenylation (68).

Peroxisome proliferator activated receptor agonists (e.g., rosiglitazone) present an alternative approach to targeting deleterious MP functions in inflammatory diseases. Rosiglitazone inhibits leukocyte MP-mediated vascular dysfunction and decreases the release of proinflammatory proteins from isolated murine aortae (69). Peroxisome proliferator activated receptor treatment also reduces the ability of MPs to evoke an increase in NFκB and subsequently counteracts vascular dysfunction associated with increased release of proinflammatory proteins elicited by MPs in mice (70).

In a recent study, TNF-α inhibition attenuated inflammation in endothelial cells and improved vascular function by suppressing MP production, NFκB activation, and endothelial cell expression of adhesion molecules (71).

Calcium channel blockers improve endothelial cell function, and it has been suggested that this improvement may be in part be due to MP attenuation. Patients with type 2 diabetes who were treated with the calcium channel antagonist nifedipine had reduced concentrations of endothelial MPs (72). Similarly, hypertensive patients with type 2 diabetes administered benidipine, another calcium channel blocker, exhibited decreased concentrations of endothelial MPs (73).

Both platelet and endothelial MPs are significantly increased in patients with hypertension regardless of whether they had type 2 diabetes (74). In patients with hypertension and type 2 diabetes, losartan (an angiotensin II receptor blocker) therapy led to a decrease in platelet and endothelial MPs, and soluble adhesion markers were all decreased by losartan monotherapy (74).

Observations from studies using a variety of pharmacological interventions indicate that such manipulations can eliminate or reduce MP generation, which may in turn prevent or retard the progression of endothelial dysfunction and the development of cardiovascular diseases. In particular, treatments that lower oxidative stress and inflammation would be expected to lower circulating MP concentrations and subsequently diminish what damaging effects MPs exert on endothelial cells. Consequently, MPs represent a potential new therapeutic target in the treatment of diseases that stem at least in part from disarray within the endothelial cell layer.

**Summary and Future Directions**

Endothelial dysfunction is an early event in the pathogenesis of cardiovascular diseases. In endothelial dysfunction the multiple functions of endothelial cells are compromised. These functions include antiinflammation and anticoagulation, regulation of vascular tone, vascular wall permeability, and cell growth. The most prevailing mechanism of endothelial dysfunction is the
loss of NO biosynthesis and/or biological activity, which results in exaggerated ROS generation and oxidative stress.

Numerous studies indicate that MPs may trigger endothelial dysfunction by disrupting production of NO, promoting coagulation and inflammation, or altering angiogenesis and apoptosis. Endothelial MPs may induce endothelial dysfunction, but at the same time it has also been suggested that endothelial MPs are novel markers of endothelial dysfunction.

However, endothelial MPs as well as circulating MPs from all other cells have all been shown to induce endothelial dysfunction. Therefore, an evaluation of circulating MPs may provide information regarding endothelial health and functions, and may serve as an additional method of assessing endothelial dysfunction.

It is clear that to achieve a comprehensive understanding of how MPs are involved in modulating vascular health, a more cohesive and standardized means of defining and characterizing MPs is necessary. The size of the MP population studied is infrequently defined in published studies, and depending on the study this term may encompass one, some, or all of the heterogeneous population of extracellular vesicles. This lack of clear definition and characterization has resulted in inconsistencies in the literature and illustrates the critical need for adherence to strict nomenclature with clear definitions.

Another challenge is posed by the low circulating concentrations of some MPs (e.g., endothelial and leukocyte MPs). Although flow cytometry is the current gold standard for examining and assessing MPs, microscopy, enzyme-linked immunoassays, and specific functional assays are routinely used although these methods do not quite provide the same quality of information as flow cytometry. Recognizing that although a user is able, through flow cytometry, to separate and identify all circulating MPs and that much improvement is still essential to obtain more accurate analysis, an international collaboration has been established to address standardization of MP detection and quantification methods via flow cytometry.

Proteomic studies have revealed that even within a distinct, single MP population, there is a certain element of heterogeneity in which MPs may contain different protein components and exhibit different functional activities. Using a comparative proteomics approach, it has been demonstrated that endothelial MPs induced by in vitro exposure to TNF-α are dramatically different from plasminogen activator inhibitor-1–induced MPs. Analysis of proteomic and functional characteristics should be considered as a potential requirement to facilitate identification of active components in MPs and clarify their roles in specific pathophysiology.

The role of MPs on endothelial cell function has been studied extensively in vitro and ex vivo. In contrast, there have been few translational and clinical studies focused on the topic. Future translational and clinical studies that delve into the biochemical and functional role of MPs in endothelial cell dysfunction are clearly warranted.

With standardized MP nomenclature and clear definitions, as well as proteomic and functional characterization of MPs in patient populations, MPs may prove to be true biomarkers of disease state and progression.

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