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Review

Therapeutic potential of plasma membrane-derived microparticles

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Abstract:
In the past, plasma membrane-derived microparticles were considered "cellular dust." According to the literature, circulating levels of microparticles are increased in several cardiovascular diseases associated with inflammation, suggesting that microparticles are linked to deleterious effects such as endothelial dysfunction or thrombosis. However, very recent studies have shown that under several conditions microparticles can transfer biological messages between cells. Indeed, microparticles act as vectors of key information to maintain cell homeostasis or to favor cell repair and induce angiogenesis. For instance, microparticles of platelet origin are able to repair myocardial injury after myocardial infarction. Also, we have shown that engineered microparticles generated from human activated/apoptotic T cells promote angiogenesis through the up-regulation of adhesion proteins and pro-angiogenic factors in human endothelial cells. Interestingly, the effects induced by these microparticles on the formation of capillary-like structures, expression of adhesion molecules, and pro-angiogenic factors are reversed after silencing of the Sonic Hedgehog (Shh) morphogen pathway. In addition, the same type of microparticles is able to induce neo-vascularization in an ischemic hindlimb model. These effects are, at least in part, mediated by Shh and nitric oxide production. Taking into consideration these results and the most recent data concerning the ability of microparticles to transmit genetic information between cells through mRNA transfer, it is plausible that plasma membrane-derived microparticles could serve as tools with veritable therapeutic potential.

Key words: microvesicles, nitric oxide, oxidative stress, angiogenesis, endothelial cell

Membrane remodeling and microparticle formation

Described 30 years ago as inert "cellular dust." cell-derived microparticles (MPs) are considered to be microvesicles (0.05–1 μm) released through the process of exocytic budding of the plasma membrane following stimulation of different cell types [19, 40]. There are two well-known cellular processes that can lead to the formation of MPs: chemical and physical cell activation (by agonists or shear stress, respectively), and apoptosis (through the action of growth factor deprivation or apoptotic inducers) [37, 52]. However, the mechanisms that take place during MP formation are not completely elucidated.

An asymmetric distribution of phospholipids is generated during membrane biogenesis; this asymmetry is lost after cell stimulation, and several studies suggest that this is necessary for MP formation. Indeed, membrane remodeling and MP shedding seem to be fundamental processes of virtually all cell types that appeared at different evolutionary stages of multi-cellular organisms, such as in the elaboration of phagocytic and clotting functions [19]. In the resting

membrane, aminophospholipids, chiefly phosphatidylserine and phosphatidylethanolamine, are sequestered in the inner leaflet by specific transporters governing their inward or outward phospholipid translocation. After stimulation, aminophospholipids translocate to the outer leaflet; this process is controlled by the activation of specific phospholipid transporters referred as "floppases" and the inhibition of other transporters including the aminophospholipid translocase. This leads to the loss of the asymmetric distribution of aminophospholipids [53]. Membrane remodeling is associated with a significant and sustained increase of cytosolic Ca^{2+} accompanying cell stimulation that may lead to the collapse of membrane asymmetry by stimulating/inhibiting transporters. The most prominent change in lipid distribution is the surface exposure of phosphatidylserine, followed by MP release through cytoskeleton degradation by Ca^{2+} dependent proteolysis [19, 53]. By contrast, several studies showed that not all MPs contain phosphatidylserine, suggesting that the mechanisms implicated in MP formation may be more complex than suspected and could require supplemental intracellular pathways [1, 38]. In this respect, it has been shown that genes linked to cytoskeletal reorganization, such as Rho kinase-II, are involved in the formation of MPs by endothelial cells through a mechanism involving caspase-2 [44]. Alternatively, other authors have shown the involvement of caspase-3 and Rho kinase-I in MP formation [45].

The membrane composition of MPs reflects the plasma membrane of the original cell at the precise moment of MP production and thus allows the characterization of the cellular source [20]. In this review, we discuss the current knowledge of MP biological effects, as well as the mechanisms that they can modulate. An enhanced knowledge of these processes will likely open new therapeutic approaches with plasma membrane-derived MPs as tools for veritable therapeutic potential in the treatment of ischemic diseases by promoting neovascularization.

Deleterious biological effects of MPs

The physiological and pathophysiological roles of MPs are unclear [34]; they can be beneficial or deleterious, depending on situations and composition. Different phenotypes of MPs derived from platelets, erythrocytes, endothelial cells, monocytes, and smooth muscle cells have been identified in plasma and other physiological fluids. In general, circulating levels of MPs are increased in pathologies associated with systemic or local inflammation.

Since inflammation is characterized by interactions among platelets, leukocytes, and endothelial cells, levels of MPs from these cells are elevated in pathologies such as vascular and immune diseases or cancer. In recent years, a large amount of data has provided evidence that MPs contribute, at least in part, to the pathogenesis of cardiovascular diseases with an important local or systemic inflammatory component, mainly through their potent pro-inflammatory effects, the promotion of coagulation, and their ability to modify vascular function (Fig. 1).

Pro-inflammatory effects associated with MPs

Several pro-inflammatory enzymes, as well as their metabolites, are up-regulated by the direct action of MPs. The first studies of the effects of platelet MPs on endothelial cells showed that arachidonic acid transported by MPs leads to an increase in cyclooxygenase-2 (COX-2) and intercellular adhesion molecule-1 (ICAM-1) expression [6, 7]. In addition, MPs can facilitate interactions between leukocytes and endothelium. Indeed, platelet MPs or MPs from leukocyte origin participate in the release of several cytokines from endothelial cells [interleukin (IL)-1, IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1)] and monocytes (IL-1, tumor necrosis factor (TNF)-α, and IL-8) [31]. Furthermore, circulating MPs from preeclamptic patients with endothelial dysfunction [42] and MPs from isolated lymphocytes are able to elicit inducible nitric oxide synthase (iNOS) and COX-2, as well as activate the NF-κB pathway, indicating that MPs can act as pro-inflammatory effectors [33].

Role of MPs in hemostasis/thrombosis

One of the first described roles for MPs was in the initiation and amplification of the coagulation cascade and, under pathological conditions, in thrombosis. Recent studies have emphasized the possibility of MPs as diagnostic and investigative tools in hemostatic and vascular diseases. MPs originating from circulating cells or vascular endothelial cells have been implicated in the pathogenesis of thrombosis. Essen-

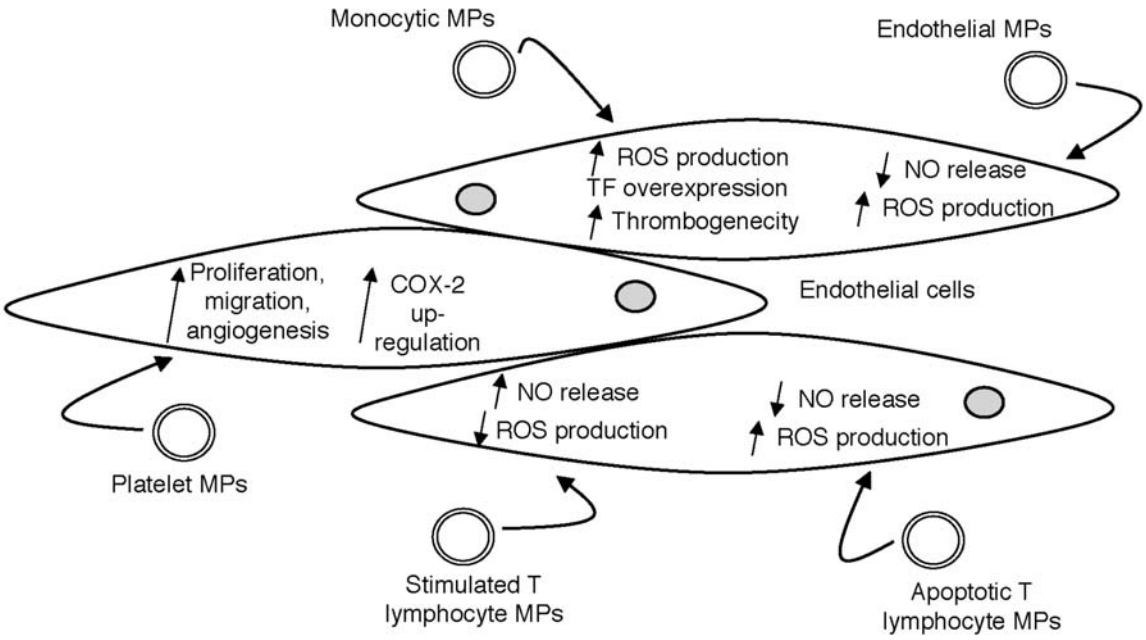

Fig. 1. Microparticle (MP) effects on endothelial cells. Depending on the cell origin and the stimulation used for their generation, MPs have different effects on endothelial cell function. MPs can have beneficial or deleterious effects by acting on the nitric oxide pathway, pro-inflammatory enzymes, reactive oxidative species production, and angiogenesis. COX-2, inducible cyclo-oxygenase; NO, nitric oxide; ROS, reactive oxygen species; TF, tissue factor

tially, MPs from platelets harbor coagulation-associated molecules on their surfaces that favor the generation of thrombin. Elevated platelet MPs associated with calpain activity have been documented in plasma of patients with thrombotic thrombocytopenic purpura [23]. Because MPs accumulate in the lipid core of atherosclerotic plaques and are a major determinant of its thrombogenicity, MPs could be triggers of a vicious cycle that promotes prothrombogenic and proinflammatory responses, as well as cellular dysfunction within the vascular compartment [27]. MPs may play an important procoagulant role in other diseases including acute myocardial infarction, antiphospholipid syndrome, preeclampsia, rheumatoid arthritis, hemolytic uremic syndrome, vasculitis, heparin-induced thrombocytopenia, and paroxysmal nocturnal hemoglobinuria [18]. In contrast, procoagulant activity from circulating MPs may be beneficial in autoimmune thrombocytopenia, and may explain why many patients with that disorder have a relatively low bleeding tendency for their degree of thrombocytopenia [21].

Endothelial MPs express ultra-large von Willebrand factor (vWF) multimers, which promote platelet aggregation and increase their stability. vWF bound to endothelial MPs has been reported to bind more readily to platelet vWF receptors than soluble vWF [22]. Furthermore, many properties of MPs provide additional prothrombotic potential: expression of P-selectin on platelet MP surfaces, and the expression of tissue factor and P-selectin glycoprotein ligand 1 (PSGL-1) on the surface of monocyte-derived MPs [11]. Recently, Del Conde et al. [12] postulated that tissue factor on monocyte MPs plays a key role in normal coagulation physiology.

MPs and vascular function

Endothelial dysfunction is the primary event leading to the failure of vasoactive, anticoagulant, and anti-inflammatory effects of healthy endothelium. The most important mechanism for endothelial dysfunction is the decrease in nitric oxide (NO) bioavailability through the decrease of its production, by an increase of its breakdown to nitrite/nitrate, and/or its reaction with reactive oxygen species leading to the neutralization of its effect.

Because endothelial dysfunction and arterial stiffness are major determinants of cardiovascular risk, several groups have investigated the effects of circulating MP on vascular function. Circulating MPs, rich

in endothelial and platelet surface markers, from patients with acute myocardial infarction cause severe endothelial dysfunction in rat aorta by affecting the endothelial NO transduction pathway but not endothelial NO synthase (eNOS) expression. In contrast, MPs isolated from venous blood of patients with non-ischemic chest pain had no such effect [8]. In diabetes, the presence of circulating endothelial MPs bearing vascular endothelial-cadherin seem to be the most significant risk factor for coronary heart disease with respect to well-known markers of atherothrombosis and may provide a quantitative estimate of endothelial cell dysfunction [26]. In a recent study, we observed increased levels of circulating MPs in metabolic syndrome patients compared with healthy subjects. In addition, *in vitro* treatment of endothelial cells with MPs from metabolic syndrome patients decreased both NO and superoxide anion (O_2^-) production, resulting in protein tyrosine nitration. The reduction of O_2^- was linked to both reduced expression of p47phox of NADPH oxidase and over-expression of extracellular superoxide dismutase. The decrease in NO production was triggered by non-platelet derived MPs. These results indicate that circulating MPs account for, at least partially, endothelial dysfunction in metabolic syndrome [1].

In vitro generated MPs from endothelial cells impair endothelium-dependent relaxation and NO production in the rat aorta. It has also been shown that the effect induced by endothelial MPs on endothelial cells is related to an increase in O_2^- production, which might reduce the bioavailability of NO [10]. Thus, MPs of endothelial origin may reflect cellular injury, for instance apoptosis, or cell activation, and may serve as circulating markers for vascular dysfunction that are easily measured in the blood.

MPs from apoptotic T lymphocytes or from diabetic patients impair endothelium-dependent relaxation, independently of CD11a-CD18 or Fas-FasL pathways. This impairment is linked to alterations in the eNOS/caveolin-1 pathway [28]. In fact, MPs from apoptotic T cells decrease NO production *via* the phosphoinositide 3-kinase (PI3-kinase) pathway [36]. Indeed, incubation of endothelial cells with these MPs is associated with enhanced phosphorylation of eNOS at its inhibitory site and over-expression of caveolin-1, resulting in diminished NO release. In addition, lymphocytic MPs enhance reactive oxygen species by a mechanism sensitive to xanthine oxidase inhibitors, which could decrease NO bioavailability [36]. In another model, MPs from apoptotic smooth muscle cells evoked endothelial dysfunction *via* diminished redox-sensitive NO production. In addition, pre-treatment of endothelial cells with abciximab or eptifibatide, two blockers of β3-integrins, restored NO production, suggesting that β3-integrins are implicated in the effects of smooth muscle MPs [14].

In inflammatory diseases, circulating MPs from lymphocytic origin could promote *ex vivo* vascular hyporeactivity through the release of vasodilatory active factors (NO and prostacyclin) from smooth muscle cells, prompted by the up-regulation of inducible NO synthase and COX-2. The recruitment of such MPs into the media was confirmed in mice injected with human $CD4^+$-lymphocyte-derived MPs. In this paracrine pathway, Fas-FasL interactions between lymphocyte-derived MPs and targeted smooth muscle cells appear mandatory and involve NF-κB [50]. Interestingly, MP-mediated NO and pro-inflammatory cytokine production, as well as activation of NF-κB, are completely prevented by *in vitro* treatment or after oral administration of the selective agonist of peroxisome proliferator-activated receptor (PPAR)-γ, rosiglitazone. The current paradigm involving enhanced participation of MPs in vascular diseases indicates that rosiglitazone prevents MP-induced vascular hyporeactivity through the regulation of proinflammatory proteins [49]. This finding highlights a therapeutic perspective of targeting MPs as hallmarks of vascular diseases.

Taken together, these results show that, depending on their origin, MPs can be not only considered as a surrogate marker of endothelial dysfunction or injury but also as effectors able to amplify pre-existing vascular dysfunction.

Beneficial effects of microparticles

Protective role of MPs on vascular and blood cells

In the majority of pathologies in which MP levels are elevated, the pathogenesis and/or risk factors of these diseases are positively correlated with MP concentration; however, recent data indicate that MPs can also exert protective effects, even when MP levels are in-

creased. For instance, elevated levels of circulating MPs, mainly derived from platelets, erythrocytes, and endothelial cells, have been found in the blood of septic patients [38, 39]. However, Soriano et al. [47] have shown that the presence of MPs and MP-cell conjugates may predict a more favorable outcome in severe sepsis. An explanation of this inverse correlation between MP level and survival in sepsis was provided by Mostefai et al. [38]. These authors reported that circulating levels of MPs, derived from platelets and endothelium, as well as P-selectin+ and L-selectin+ MPs, are increased in septic patients. Surprisingly, septic MPs enhanced the contraction of mouse aortic rings in response to serotonin, without reducing sensitivity. This effect is not linked to increased calcium entry or mechanisms sensitive to Rho-kinase inhibitors. In addition, the effect of septic MPs is not affected by NOS or COX-2 inhibitors, and is not associated with NO or O_2^- overproduction. The non-selective COX inhibitor indomethacin reduces or abolishes contraction in aorta from mice treated with healthy or septic MPs, respectively. The effect of septic MPs is associated with increased thromboxane-A_2 production. Altogether, the reported data provide evidence that increased circulating MPs are protective against vascular hyporeactivity, accounting for hypotension in patients with septic shock [38].

Another example of a beneficial role for MPs is the idea that MPs can expand undifferentiated cells since MPs possess key molecules for cell proliferation and differentiation. Several reports have confirmed this observation. Martinez et al. [29] demonstrated that MPs generated from activated/apoptotic human T lymphocytes harbor Sonic hedgehog (Shh), a morphogen that acts as an inter-cellular signal responsible for multiple cellular fate decisions during development and adult life [for review see ref. 41], and for the induction of megakaryocyte differentiation [29]. Furthermore, MPs from human activated/apoptotic T lymphocytes carrying Shh act directly on endothelial cells to improve endothelial function, and prevent endothelial dysfunction induced by ischemia/reperfusion *via* NO release. These effects are associated with changes in expression and phosphorylation of enzymes related to the NO pathway, and the reduction of reactive oxygen species [2]. Altogether, Agouni and colleagues [2] suggested that the biological message carried by MPs harboring Shh may represent a new therapeutic approach against endothelial dysfunction during acute severe endothelial injury.

In another context, platelet MPs increase adhesion of mobilized hematopoietic stem/progenitor cells to endothelium, and accelerate their homing into the bone marrow, suggesting a potential role for MPs in the optimization of transplantation [20]. The same group has described that binding of platelet MPs to hematopoietic cells enhanced engraftment by stimulating proliferation, survival, adhesion, and chemotaxis, although the active component(s) of these MPs that trigger(s) the message has not been identified [5, 20].

Taking into consideration that MPs from platelets accelerate thrombin generation and adhere to collagen, vWF, fibrinogen, and surface-adherent platelets, they may be beneficial in maintaining normal hemostasis in diseases associated with reduced platelet function [24]. Platelet MPs have also been described as stimulators of the mitogenic activity of bone cells, thereby contributing to the regeneration of mineralized tissues [17].

MPs in angiogenesis and related diseases

Angiogenesis is a complex, multi-step process that can be modified by MPs at different levels depending on the MP components. Therapeutic angiogenesis remains an attractive treatment for peripheral vascular diseases and chronic tissue ischemia. Numerous mediators, including growth and transcription factors, and signaling molecules have been reported to augment chronic ischemia-induced angiogenesis in animal models [35]. However, clinical trials of proangiogenic agents have revealed little or no efficacy in patients suffering from such disorders [52].

Endothelial MPs can promote matrix degradation and favor new vessel formation through the metalloproteinase (MMP) activity that they harbor [48]. In contrast, Mezentsev et al. documented anti-angiogenic properties of endothelial MPs [32]. Thus, low concentrations of endothelial MP could promote angiogenesis, whereas high concentrations could suppress angiogenesis by increasing the production of reactive oxygen species.

Platelet-derived MP exhibit pro-angiogenic activity by promoting almost all of the steps involved in angiogenesis, including the proliferation, survival, migration, and formation of capillary-like structures by endothelial cells, through the activation of both PI3-kinase and extracellular signal-regulated kinase (ERK) pathways [25]. Also, *in vitro* platelet MPs evoke sprouting in aortic rings *via* the PI3-kinase and

ERK pathways [9] and, most interestingly, they stimulate post-ischemic neovascularization after chronic ischemia, suggesting a key role for platelet MPs in blood vessel neoformation [9].

As mentioned above, human lymphocytic MPs generated *in vitro* and bearing Shh (MPs^{Shh+}) correct endothelial injury by triggering the release of NO from endothelial cells [2]. NO is a potent vasodilator and plays a key role in regulating VEGF-induced angiogenesis [15]. In agreement with these observations, we have found that treatment of endothelial cells with MPs^{Shh+} induces and accelerates the formation of capillary-like structures in an *in vitro* model of angiogenesis [46]. Besides, these MPs regulate cell proliferation, adhesion molecule expression, and endothelial cell migration. Importantly, mRNA levels of pro-angiogenic factors, such as VEGF, HGF, and FLT-1, are markedly increased by MPs^{Shh+} as measured by q-PCR [46]. Expression of adhesion molecules and pro-angiogenic factors are reversed after supression of the Shh receptor by siRNA or when Shh signaling is pharmacologically inhibited with cyclopamine. Moreover, after induction of hindlimb ischemia in mice by ligation of the left common femoral artery, MPs^{Shh+} increase blood flow recovery by a mechanism involving eNOS activation and other downstream potential angiogenic factors such as VEGF. These findings demonstrate that MPs^{Shh+} may represent a potent tool in stimulating neovascularization. Further studies are required to evaluate and confirm the efficacy of MPs as a tool of "therapy" in other disease states associated with impaired angiogenesis.

Future directions: microparticles as a cross-link between cells and therapeutic tools

Until now, the detection and measurement of MP levels in different pathologies have not been cemented into therapeutic or diagnostic strategies in the man-

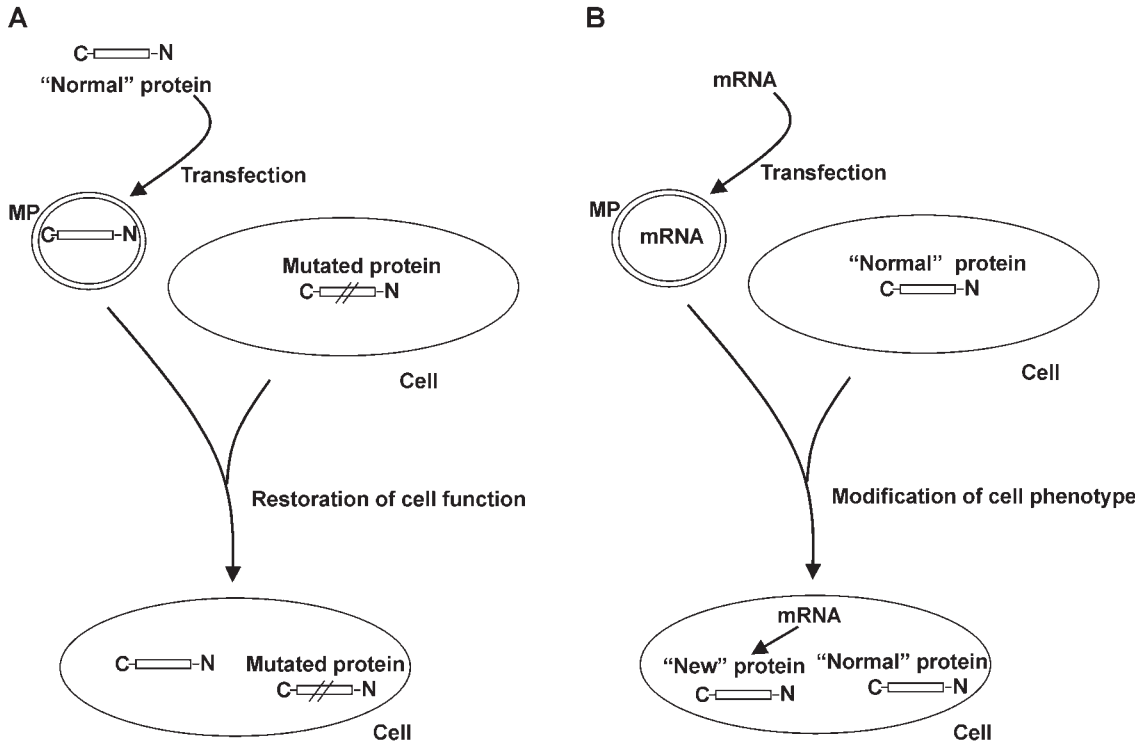

Fig. 2. Schematic representation of the use of microparticles (MPs) as potential therapeutic tools. **(A)** Engineered MPs can over-express several "normal" proteins that can be transferred to target cells and consequently, rescue the function of a mutated protein. **(B)** MPs can modify cell phenotypes by transferring mRNA into target cells; there, mRNA is translated into corresponding "new" proteins

agement of relevant diseases. However, they have helped to shift the understanding of the pathophysiological mechanisms governing several diseases. As described above, MPs, due to their pro-coagulant activity, may ameliorate platelet function when it is impaired, in diseases such as thrombocytopenia, by restoring hemostasis [16, 24].

In our point of the view, the most promising use of MPs as therapeutic tools is the ability to generate *in vitro* engineered MPs (Fig. 2). Indeed, it has been shown that engineered MPs can over-express several proteins by forcing the cells from which they originate to synthesize them. Furthermore, MPs can transfer and incorporate mRNA into target cells and therefore, modify their phenotype. Supporting the first approach, we have shown that engineered MPs^{Shh+} exhibit pro-angiogenic abilities and may be used as a tool in diseases associated with defective angiogenesis (see above). Recently, it has been reported that transfection of glioma cells with the oncogenic form of the epidermal growth factor receptor (EGFR) induces MPs over-expressing EGFR, which can be transferred to cells lacking this receptor [4]. A similar approach may be used to transfer proteins to target cells in which function is impaired due to a mutated protein, for instance. Although no reports, until now, have studied this possibility, future research should be conducted.

Concerning the ability of MPs to carry mRNA, it has been reported that MPs from lung cells contain mRNA which can be released into bone marrow cells, thereby modulating their phenotype [3]. Also, Deregibus et al. [13] have shown that MPs from endothelial progenitor cells are able to stimulate pro-angiogenic activities in endothelial cells *via* horizontal PI3-kinase/Akt-associated mRNA transfer. Ratajczak and colleagues [43] have shown that embryonic stem cell-derived MPs can deliver mRNA for several pluripotent transcription factors into hematopoietic progenitors, favoring their reprogramming since mRNA is translated into the corresponding proteins. As described above for the overexpression of proteins, transfection of MPs with mRNA and subsequent mRNA delivery may represent a new opportunity to transfer a "desired" biological message into target cells and modify their phenotype.

The interest of all these studies highlights the potential role of MPs in the modulation of cell functions. Future studies will dissect the molecular requirement(s) of MP-cell interactions and mRNA transfer to target therapy.

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