REVIEW

Role of mesenchymal stem cell-derived microvesicles in tissue repair

Stefania Bruno · Giovanni Camussi

Abstract Results from recent studies suggest that the beneficial effect of stem cell-based therapy is mainly dependent on a paracrine effect. The paracrine hypothesis implicates the ability of stem cells to limit injury or coordinate repair through the release of soluble factors. Among these factors microvesicles (MVs) have emerged as a mechanism through which stem cells may reprogram injured cells. In fact, MVs released from stem cells may deliver proteins, bio-active lipids and nucleic acids to injured cells. In particular, the transfer of transcripts derived from stem cells may induce phenotypic and functional changes in the recipient cells that promote the activation of regenerative programs.

Keywords Exosomes · Microvesicles · Extracellular vesicles · Mesenchymal stem cells

Introduction

Mesenchymal stem cells, also known as mesenchymal stromal cells (MSCs), are a heterogeneous multipotent cell population residing in the bone marrow that can be rapidly expanded in vitro while maintaining their multipotency [1]. A number of studies have focused on alternative sources of stem cells with multiple differentiating capabilities and easy accessibility [2]. MSCs obtained from adipose tissue or from umbilical cord vein, as well as from dental pulp have been investigated as a potential source of stem cells [3–5]. In the search for alternative sources of stem cells, the isolation of stem cells from human amniotic fluids (hAFSCs), and their subsequent differentiation into all three types of germ layer cells, has also been reported [6]. Since the recovery of hAFSC is considered ethically acceptable and does not involve the destruction of human embryos, hAFSCs present an attractive source of stem cells for tissue regeneration [7].

Although MSCs exhibit the capacity to migrate to injured sites and can therefore contribute to tissue repair, the extent of improvement of injured tissues has not been shown to correlate with cellular engraftment and differentiation of MSCs to tissue cells, suggesting that they may play an indirect role in tissue regeneration.

Growing evidence indicates that the therapeutic effect of MSCs depends primarily on their capacity to secrete soluble factors; these include a variety of growth factors, cytokines and chemokines that orchestrate interactions within the microenvironment and influence tissue regeneration. These factors can inhibit apoptosis, stimulate proliferation, promote vascularization and modulate the immune response [8]. In addition to soluble factors, MSCs also secrete extracellular vesicles which are small, spherical membrane fragments that are involved in cell-to-cell communication and are capable of altering the cell fate and phenotype of recipient cells [9].

Extracellular vesicles: origin and modes of action

Many different sub-populations of extracellular vesicles have been described and characterized in detail, including exosomes, ectosomes and apoptotic bodies. Exosomes,

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derived from endocytic vesicles, have a diameter of 30–100 nm and are generated following the fusion of multi-vesicular bodies with plasma membranes [10]. Shedding vesicles, also named ectosomes or membrane particles, tend to be 100 nm–1 μm in diameter and bud directly from the plasma membrane. These vesicles are shed into the extra-cellular space in a calcium flux- and calpain-dependent manner [11]. Most extracellular vesicles that are described in the literature, either released in vitro or present in biological fluids, are heterogeneous and consist of exosomes and shedding vesicles, collectively defined here as microvesicles (MVs).

MVs hold the signature of the cell of origin, as they contain proteins (e.g. receptors, adhesion molecules) and lipids of the cell membrane and cytoplasmic constituents [mRNA, microRNA (miRNA), DNA, proteins]. MVs can function as a cargo for delivering cellular components to other cells, thus inducing alterations in the phenotype and behavior of recipient cells [12]. The results of a recent study by Aliotta et al. [13] indicate that MVs can induce changes in cellular phenotypes that persist in vitro as well as in vivo for extended periods of time. Therefore, MVs may stably alter the phenotype of target cells [13].

The mechanisms whereby MVs influence the fate of target cells are varied. They may directly stimulate the cells by means of interactions with receptors and molecules that are expressed on their surface and which bind to specific ligands expressed by recipient cells [14]. Following ligand interaction, MVs may deliver their contents to the recipient cell. For example, MVs derived from endothelial cells can activate angiogenesis through the transfer of pro-angiogenic molecules, such as growth factors [15]. MVs may repro-gram mutant tissue by direct transfer of membrane-associated wildtype molecules. In particular, it has been recently demonstrated that MVs from different types of MSCs shuttle a cysteine-selective transport channel (cystinosin) that restores function in mutant target cells [16]. MVs may also mediate the horizontal transfer of ge-netic information, such as subsets of mRNA and microRNA (miRNA) specific to the cell of origin [17]. Ratajczak et al. [17] demonstrated that MVs may facilitate the transfer of mRNA and, as a result, influence the behavior of target cells. Specifically, these authors found that MVs produced by murine embryonic stem cells (ESCs) may reprogram hematopoietic progenitors. In particular, MVs may increase the pluripotency of hematopoietic progenitors by delivering mRNA for transcription factors involved in stem cell self-renewal, such as Oct-4, Rex-1, Nanog and GATA-2. The transferred mRNA then becomes translated into protein by recipient cells [17]. MVs can also contain mRNA for recep-tors of specific growth factors; for example, MVs released by bone marrow MSCs (BM-MSCs) contain mRNA for the insulin growth factor 1 (IGF-1) receptor [18]. In an in vitro

model of renal toxic injury induced by cisplatin, the transfer of IGF-1 receptor mRNA through MVs has been shown to increase the proliferation of damaged proximal tubular cells [18].

Recently, Quesenberry and Aliotta suggested that MVs released in the microenvironment around injured cells may represent a signal for stem cell differentiation [19]. In fact, MVs derived from the damaged murine lung may enter into bone marrow cells where they induce a lung-specific phe-notype in these cells [20, 21]. Signals from injured cells may therefore induce stem cell recruitment and differentiation in specific cells of injured organs.

Our group has focused on MVs released from human BM-MSCs, demonstrating that they are responsible for shuttling a specific subset of cellular mRNA, including tran-scripts that are characteristic of mesenchymal cell lineages, as well as transcripts related to several different cell func-tions (e.g. for the control of transcription, cell proliferation and immune regulation) [22]. In addition to mRNA, MVs may also transfer miRNA, a function confirmed by experi-ments demonstrating that the conditioned medium produced by human MSCs derived from ESCs contains MVs that shuttle specific pre-miRNA [23] and miRNA [24]. Specifically, we have shown that MVs released from human BM-MSCs contain mature functional miRNA that can be transferred to target renal tubular cells [25]. Gene ontology analysis has shown that the highly expressed miRNAs in MVs from BM-MSCs are involved in multi-organ develop-ment, cell survival and differentiation.

The protein content of MVs from MSCs has also been characterized recently [26]. MVs from MSCs contain pro-teins that are characteristic of MSCs (e.g. CD29, CD73, CD44, CD105), proteins associated with intra-cellular MV biogenesis and trafficking (RAB protein family) and pro-teins associated with MSC self-renewal and differentiation (TGF-β, MAPK, PPAR, etc.). Gene ontology analyses of such proteins indicate that several biological processes are represented, including vesicle-mediated transport, cell cycle and proliferation, cell migration, morphogenesis and devel-opmental processes.

MSCs and MSC-derived MVs favor renal regeneration

It has been reported that MSC administration effectively ameliorates experimental acute kidney injury (AKI) [27–31] and induces functional improvements in chronic kidney disease (CKD) [32]. MSCs can migrate to injured tissues when transplanted systemically. Homing of MSCs into injured tissues depends on their ability to migrate and interact with the local microenvironment. The triggering of the chemokine receptor CXCR4 by its ligand, stromal de-rived factor, plays an important role in the homing of MSCs

to the sites of injury [33, 34]. Moreover, it has been shown that CD44 and glycosaminoglycan hyaluronan (HA) interaction is involved in MSC migratory capacity [35]. The expression of CD44 is involved in the localization of exogenous MSCs to injured renal tissue, based on the observations that loss of CD44 expression by mutant MSCs results in reduced MSC localization to injured tissue and subsequent prevention of renal repair [30]. After systemic administration, MSCs accumulate in the injured kidney, but only few of these permanently engraft within the tubules [27–30]. The beneficial effect of MSC administration is due to transient localization to the damaged tissue. In rats with ischemia and reperfusion injury, MSCs were found to localize to the peritubular capillaries and further migrate to the tubular interstitium 24 h after systemic administration. However, after 3 days, none of the administered MSC had differentiated into tubular or endothelial cells [36]. In the model of glycerol-induced AKI, the majority of injected MSCs disappeared from the kidney after just 5 days [37]. This experimental evidence indicates that MSCs do not replace renal tubular cells, but mitigate injury by providing paracrine support for repair. This hypothesis is sustained by experiments showing that conditioned medium (CM) from murine MSCs mimics the beneficial effects of the cells of origin in the experimental model of cisplatin-induced AKI [38]. In this study, the intraperitoneal administration of MSC-CM limited renal injury by diminishing tubular cell apoptosis and increasing tubular cell survival. It can therefore be concluded that bio-active factors secreted by MSCs are responsible for their capacity to ameliorate kidney function and morphology. In particular, IGF-1 and vascular endothelial growth factor (VEGF) were suggested to be involved in the renal-protective effect of MSC administration. Injection of IGF-1 gene-silenced MSCs in the murine model of cisplatin-induced AKI reduced the beneficial effect of MSCs [39]; VEGF knockdown by small interfering RNA

(siRNA) also reduced the effects of MSC infusion in ischemia and reperfusion AKI [40].

As MVs can influence the behavior of recipient cells by shuttling bio-active molecules, our group and others have recently exploited the possible effects of MSC-derived MVs in tissue regeneration, in different experimental animal models of renal injury (Table 1).

MSC-derived MVs express several adhesion molecules of MSCs, such as CD44, CD29 (β1-integrin), α4- and α5 integrins and CD73 [22]. In this study [22], CD44 and CD29 were shown to be instrumental in MV internalization into tubular epithelial cells, as treatment with specific blocking antibodies was found to prevent MV incorporation. Moreover, pretreatment of MSC-derived MVs with annexin V abrogated their uptake and effect on target cells [16].

In studies carried out by our group, we found that human BM-MSC-derived MVs stimulated the proliferation and apoptosis resistance of tubular epithelial cells in vitro [22, 41]. In vivo, MV treatment accelerated the morphological and functional recovery of glycerol-induced-AKI in SCID mice [22]. In this experimental model, the effect of MV injection was comparable to that obtained with MSCs, indicating that MVs mimic the beneficial effects of the cells of origin. This in turn suggests that MVs may mediate, at least in part, the MSC-regenerative potential. In the lethal model of AKI induced by cisplatin, a single administration of MVs improved the survival of SCID mice, without preventing chronic tubular injury. Multiple injections of MVs, at different time points after injury, not only further improved the survival of SCID mice but also completely prevented chronic tubular injury [41]. We also found that a single administration of MVs immediately after ischemia and reperfusion injury protected rats from AKI and prevented CKD [42]. After injection, MVs transiently localize within glomeruli and proximal tubules in animals with ischemia and reperfusion injury (Fig. 1). In contrast, in normal rats, MVs are

Table 1 Evidence for microvesicle involvement in tissue regeneration

Microvesicle cell sources	Animal models	Reference
Bone marrow mesenchymal stem cells	Mouse glycerol-induced AKI	[22]
	Rat renal ischemia and reperfusion injury	[42]
	Mouse cisplatin-induced AKI	[41]
	Mouse remnant kidney model	[43]
	Rat gentamicin-induced AKI	[44]
	Rat middle cerebral artery occlusion	[47]
Embryonic stem cell-derived mesenchymal stem cells	Mouse myocardial ischemia and reperfusion injury	[45]
Human liver stem cells	Rat hepatectomy	[49]
Endothelial progenitors cells	Rat renal ischemia and reperfusion injury	[51]
	Mouse hind limb ischemia	[52]

AKI, Acute kidney injury
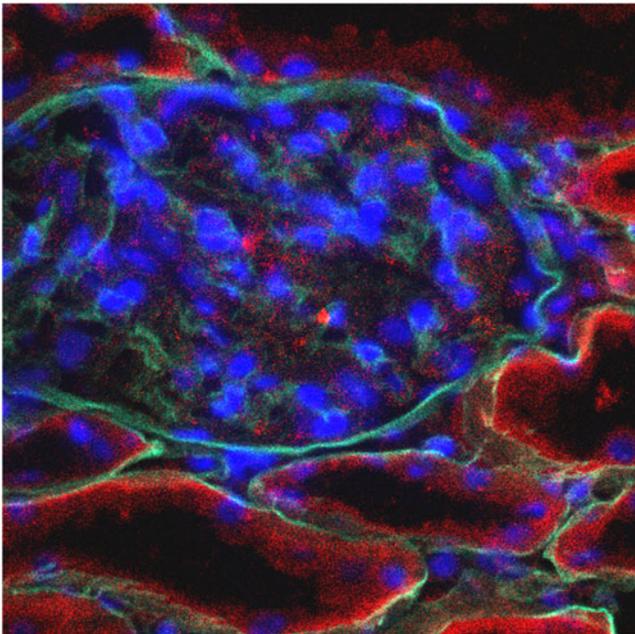
Fig. 1 Representative confocal microscopy showing the localization of PKH26-labeled microvesicles (MVs) within the glomerulus and proximal tubules in a rat with ischemia and reperfusion injury, 2 h after MV injection. MVs are seen within the glomerulus and, in particular, in the tubular epithelial cells. Magnification: ×600

captured by the liver and do not accumulate within the kidney [42]. The mechanism of protection has mainly been ascribed to the stimulation of cell proliferation and inhibition of apoptosis. In particular, we found that inhibition of in vitro apoptosis of cisplatin-treated tubular cells was associated with the down-regulation of genes involved in the execution phase of cell apoptosis (caspase 1 and 8) and with the up-regulation of anti-apoptotic genes (Bcl-xL and Bcl2) [41]. The in vitro and in vivo effects of MVs have been partially attributed to RNA delivery, as the inactivation of RNA has been found to abate their properties [22, 40, 41]. Moreover, the transfer of specific miRNA and mRNA and its subsequent translation into proteins in renal tubular cells has been shown both in vitro and in vivo [22, 41].

He et al. recently reported that MSC-derived MVs also protect against renal injury in the mouse remnant kidney model [43]. In this model of 5/6 subtotal nephrectomy, a single MV administration preserves the function of the remnant kidney, ameliorated renal injury and prevented renal fibrosis. Reis et al. [44] have recently reported that BM-MSCs, as well as CM or purified MVs, minimize gentamicin-induced AKI. When CM or MVs were incubated with RNase, the in vivo effects were blunted, confirming that regenerative properties are mediated by RNAs carried by MVs [44].

The therapeutic effect of MVs produced by MSCs has also been reported in experimental models of myocardial ischemia and reperfusion injury (Table 1). In two studies, CM from human ESC-derived MSCs significantly reduced infarct size

in pig and mouse models of myocardial infarction [45, 46]. The results of electron microscopy, ultracentrifugation, mass spectrometry and biochemical studies/assays demonstrated that the active components of CM are exosomes [45]. Therefore, in these cases as well, the authors attributed the therapeutic activity of MSC-CM to exosomes.

MSCs also have a potential therapeutic benefit for the treatment of neurological disease and injury. In a recent study, Xin et al. [47] reported that MSC treatment of rats subjected to middle cerebral artery occlusion leads to a significant increase in miR-133b levels in the ipsilateral hemisphere by exosome-mediated delivery. This study is the first to demonstrate that MSCs communicate with brain parenchymal cells and regulate neurite outgrowth by transfer of miRNA to neural cells via exosomes [47].

MVs derived from other cell sources may contribute to tissue regeneration

As shown in Table 1, MVs produced by other stem/progenitor cell sources have been studied as potential therapeutic agents in different animal models of tissue injury.

Human liver stem cells (HLSCs) represent a population of MSCs resident in the adult human liver, with a partial hepatic commitment [48]. HLSC-derived MVs induce in vitro proliferation and apoptosis resistance in human and rat hepatocytes [49]. Moreover, in vivo MVs accelerate morphological and functional recovery of the liver in a model of 70 % hepatectomy in rats [49]. In this case as well, the activities of MVs have been found to be at least partly RNA-dependent: RNase pre-treatment reduces their protective effects [49]. In addition, in the same study, specific human proteins translated from MV-transported mRNA were detected in vitro and in vivo in rat hepatocytes.

Endothelial progenitor cells (EPCs), obtained from the peripheral blood of healthy donors are also able to produce MVs which, after internalization in normal endothelial cells, activate an angiogenic program by the horizontal transfer of mRNA [50]. The administration of a single dose of EPC-MVs immediately after renal ischemia and reperfusion injury in rats was found to confer functional and morphological protection from AKI by improving proliferation and reducing apoptosis of the renal tubular cells [51]. Moreover, EPC-MVs are able to protect against CKD by inhibiting capillary rarefaction, glomerulosclerosis and tubulo-interstitial fibrosis. Non-specific depletion of miRNA content in MVs by Dicer knock-down in EPCs or depletion of specific proangiogenic miRNA (miR-126 and miR-296) by transfection of EPCs with specific antagomir reduced the renal protective effect of EPC-MVs [51]. Moreover, EPC-MVs also reduced injury and enhanced reperfusion in a murine model of hind limb ischemia [52].

Conclusions

Based on the fact that, in regenerative therapies MVs mimic the beneficial effects of the cells from which they originate, MVs could represent an important potential therapeutic tool. As they may influence the behavior of recipient cells by delivering their bioactive cargo, it may be possible to exploit this effect in tissue regeneration and repair. MVs for use in regenerative therapy could be obtained on a large scale from producer stem/progenitor cells and suitably altered to obtain engineered MVs to enhance tissue regeneration. For example, producer cells might be modified to over-express specific antigens capable of delivering MVs to a specific organ or tissue. Moreover, the use of MVs in place of stem/progenitor cells could represent a novel therapeutic strategy, avoiding the possible adverse effects of cell administration, such as pulmonary occlusion at the moment of systemic cell delivery, or long-term mal-differentiation of transplanted cells.

However, several problems need to be addressed before MSC-released MVs can be considered as a potential therapeutic tool. First, it is necessary to develop strategies to obtain sufficient amounts of MVs. A preliminary kinetic study we undertook based on NanoSight detection of MVs in MSC-conditioned medium revealed that the timing of collection is critical. In fact, in our study, after 12 h, a single MSC released about 7,000 MVs, whereas after 24 h only 2,500 MV/cell were detectable, due to a re-uptake of MVs by MSCs. In addition, an enhanced release could be obtained after appropriate stimulation of MSCs. Moreover, further studies are needed to define biosafety, fields of application and effective doses.

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