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THEME | *Extracellular Vesicles in Cell Physiology*

Role of extracellular vesicles in stem cell biology

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Bruno S, Chiabotto G, Favaro E, Deregibus MC, Camussi G. Role of extracellular vesicles in stem cell biology. *Am J Physiol Cell Physiol* 317: C303–C313, 2019. First published May 15, 2019; doi:10.1152/ajpcell.00129.2019.—The extracellular vesicles (EVs) are membrane vesicles carrying proteins, nucleic acids, and bioactive lipids of the cell of origin. These vesicles released within the extracellular space and entering into the circulation may transfer their cargo to neighboring or distant cells and induce phenotypical and functional changes that may be relevant in several physiopathological conditions. In an attempt to define the biological properties of EVs, several investigations have focused on their cargo and on the effects elicited in recipient cells. EVs have been involved in modulation of tumor microenvironment and behavior, as well as in the immune and inflammatory response. In the present review, we address the paracrine action of EVs released by stem cells and their potential involvement in the activation of regenerative programs in injured cells.

cancer cells; exosomes; immune cells; microvesicles; stem cells

INTRODUCTION

In 2011, the term "extracellular vesicles" (EVs) was proposed to define all of the membrane vesicles containing cytosol enclosed into a lipid bilayer and secreted by cells (66). The secretion of EVs is well preserved throughout evolution; plants, prokaryotic cells, and all eukaryotes from amoeba to mammals can release vesicles into the extracellular space (117). In humans, EVs are present in different body fluids, such as blood, urine, amniotic fluid, breast milk, saliva, cerebrospinal fluid, semen, synovia, and tears. Several studies have shown the EV involvement in many physiological and pathological conditions. In particular, EVs exchange information among cells by carrying different types of molecules, such as proteins, lipids, and genetic materials (RNAs and DNA), which are selectively sorted inside vesicles.

BIOGENESIS AND CLASSIFICATION OF EXTRACELLULAR VESICLES

Vesicles, defined by the generic term of EVs, include heterogeneous populations that have originated from different subcellular compartments. Based on their size and subcellular origin, EVs are distinguished into exosomes and ectosomes (32). Exosomes are intraluminal vesicles with a diameter ranging from 30 to 100 nm, derived from the multivesicular bodies by budding of the endosomal membranes and secretion upon fusion with the cell surface (13). Ectosomes, also known as microvesicles (MVs) or microparticles, include different populations of vesicles, such as those derived from perfectly healthy cells, which are in the nano-range (50–200 nm), and larger vesicles (up to 1,000 nm), which include the preapoptotic vesicles. Ectosomes are generated by plasma membrane budding and are shed in the extracellular space (1, 133). Apoptotic bodies, with a diameter ranging from 1,000 to 5,000 nm, are a class of vesicles released by apoptotic cells that are mainly enriched with nuclear fragments (72).

The mechanisms involved in the biogenesis of different types of EVs are not yet fully understood. The components of the endosomal sorting complex required for transport (ESCRT) machinery and other auxiliary proteins (ALIX, TSG101, and VPS4) have been involved in exosome biogenesis. However, recent studies have shown the involvement of these molecules not exclusively in exosomes, but also in the formation of shedding vesicles. Moreover, an ESCRT-independent mechanism has been described in exosome formation (138). Several components of the RAB family of small GTPase proteins are involved in the interaction of the multivesicular bodies with the plasma membrane during exosome release (6, 50). In the formation of shedding vesicles, a rearrangement of cytoskeletal myosin and actin regulated by Ras-related GTPase ADP-ribosylation factor 6 (ARF6) signaling is implicated (139). Because molecules involved in biogenesis, such as ESCRT and tetraspanins, are commonly expressed by exosomes and ectosomes, these cannot be taken as a criterion of distinction (108). In addition, the same cell may release vesicles in the nano-range, either by exocytosis or by surface membrane budding, making difficult a punctual distinction of the origin of vesicles released by healthy cells. Whereas CD63, CD81, and CD9 members of tetraspanin family are enriched in exosomes,

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distinctive markers for ectosomes are lacking. However, a recent study suggests that annexin A1 is a marker for ectosomes (77). Surface-expressed molecules may indicate the cellular origin of vesicles. For instance, EVs derived from mesenchymal stem cells express on their surface mesenchymal markers, such as CD44, CD90, CD105, and CD146 (20).

CONTENT OF EXTRACELLULAR VESICLES AND MECHANISMS OF ACTION

The nature and abundance of EV contents vary with respect to cell type, biogenesis, physiologic, or pathological conditions, as well as with the protocol used to purify EVs. Different databases collecting the results of EV content are actually available and publicly accessible: EVpedia (86), Exocarta (103), and Vesiclepedia (82). All available databases include not only the nucleic acid, lipid, and protein content of EVs, but also the isolation procedure used by different researchers. Comparative analyses indicate an enrichment of specific subsets of RNAs, proteins, and lipids in EVs, in respect to the cells of origin (90, 140).

Several studies have characterized the protein cargo of the EV populations produced by different cell types (35, 58, 59, 126, 132). Proteins commonly found in EVs include proteins associated with the endosomal pathway, such as the ESCRT components (e.g., Alix, TSG101), proteins involved in EV formation and release (e.g., RAB27A and ARF 6), proteins involved in signal transduction, different types of tetraspanins, proteins involved in antigen presentation (major histocompatibility complex I and II), transcription factors (Notch and Wnt), growth factors [e.g., hepatocyte growth factor (HGF) and insulin-like growth factor 1 (IGF-1)], and cytokines.

By lipidomic analysis, EVs share common lipid composition with the cells of origin and lipids differentially expressed in respect to cells. For example, EV membranes are enriched in cholesterol, unsaturated lipids, sphingomyelin, ganglioside GM3, phosphatidylserine, and ceramide (96). At variance, EVs contain a reduced amount of diacyl-glycerol and phosphatidylcholine compared with the cell of origin. The ratio of sphingomyelin and phosphatidylcholine in EVs is twice as high as in the producing cells (89). These differences in composition of lipids depend on EV biogenesis.

Various genetic materials are present in EVs. In some cases, genomic (7) and mitochondrial (64, 65) DNAs have been found. A recent study on exosomal subfractions of EVs suggests that DNA is secreted by an autophagy- and multivesicular-endosome-dependent mechanism and not by exosomes (77). In general, the EVs are enriched with RNAs, in particular, with small RNAs. In addition to the ordinarily known RNA types, like mRNAs, microRNAs, and ribosomal RNAs, EVs may contain long- and short-noncoding RNAs, fragments of tRNA, piwi-interacting-RNA, Y-RNA, and vault RNA (30, 40, 70, 73, 112). Several RNAs present in EVs are around 200 nucleotides (9), suggesting that probably they are fragments. Notably, circular RNAs are also present in EVs (92). The encapsulation of nucleic acids within EV membranes confers protection from the degrading enzymes present in the extracellular space. However, it should be noted that RNA-binding proteins not associated with EVs may also confer protection from ectonucleases (49).

After release, EVs may induce a variety of effects in neighboring or distant cells by diffusing in biological fluids. EVs may interact with target cells by different mechanisms, including direct membrane fusion, ligand-receptor interaction, and internalization. The most common mode of entry of EVs into cells seems to be clathrin-dependent or clathrin-independent endocytosis (44, 106, 135). Once entered into the recipient cells, EVs may follow the endocytic pathway, which conducts to lysosomes or they may escape lysosomal digestion and release their content into the cytoplasm of the target cells. However, the modality of cell membrane-EV interaction, the mechanisms allowing transfer of EV-cargo, and the downstream effects triggered by EVs, are only partly understood and depend on the origin of EVs and on the type and activation state of target cells.

CANCER CELL-DERIVED EXTRACELLULAR VESICLES AND TUMOR MICROENVIRONMENT MODULATION

By secreting EVs, cancer cells may communicate with nearby stromal cells, such as endothelial cells, cancer-associated fibroblasts (CAFs), and by entering into the circulation, they may interact with distant cells. Cancer EVs are able to orchestrate several processes, such as angiogenesis (124), extracellular matrix remodeling (110, 125), and induction of epithelial-mesenchymal transition (EMT), promoting tumor aggressiveness, invasiveness, and metastatic potential (48, 54–56, 111, 142). In turn, tumor stroma cells by secreting EVs may influence tumor progression. In fact, CAF-derived EVs are able to stimulate proliferation, motility, and metastatic potential of tumor cells, thus providing evidence for a bidirectional crosstalk between tumor and environmental cells (99, 123).

Recently, it has been shown that tumor-derived EVs play a functional role in the resistance to chemotherapy of prostate, non-small cell lung, breast, and ovarian cancers (29, 36, 41, 115, 143). CAFs, which are innately resistant to chemotherapy, may secrete EVs that contain factors promoting chemoresistance into recipient cancer cells, thus inhibiting tumor cell apoptosis and favoring tumor growth (5, 14, 121).

Different mechanisms are involved in the proangiogenic effect of cancer EVs. Breast cancer cell-derived EVs contain a unique 90-kDa form of vascular endothelial growth factor (VEGF), which is resistant to anti-VEGF antibodies, and activates VEGF receptors on endothelial cells promoting tumor angiogenesis (53). Under hypoxic conditions, EVs from colorectal cancer shuttled Wnt4, a member of the Wnt family. Wnt4 increases β-catenin nuclear translocation and activates Wnt/β-catenin signaling pathway, which triggers endothelial cell proliferation and migration (74). Moreover, cancer EVs may contribute to new blood vessel formation by transferring proangiogenic microRNAs (miRNAs) into recipient fibroblasts and endothelial cells (155). In particular, it has been demonstrated that the exosome expression of miR-155, miR-210, and miR-494 is under regulation of the hypoxia-inducible factor 1α (HIF-1α) (42, 45, 101, 102). In turn, miR-155 and miR-210 stabilize HIF-1α expression under hypoxic conditions, suggesting a positive feedback loop that supports angiogenesis in fibroblasts and endothelial cells (45, 102).

A growing body of evidence shows that EVs are involved not only in primary tumor establishment, but also in metastasis spreading. In fact, tumor-derived EVs can reach distant organs

through blood and lymphatic vessels. As showed by Hoshino et al. (71), this process is directed by specific exosome integrin expression, allowing targeting of specific organs, thereby supporting the formation of the so-called "premetastatic niche". For example, lung metastasis associates with the expression of exosome α6β4 and α6β1 integrins, whereas liver metastasis associates with exosome αvβ5 integrin expression (71). EVs can induce the expression of promigratory and proinflammatory mediators, resulting in stromal cell activation, extracellular matrix deposition, and bone marrow-derived myeloid cell recruitment, which play a crucial role in tumor cell implantation (39, 113).

CANCER STEM CELL-DERIVED EXTRACELLULAR VESICLES

A minor population of cells that is present in cancer responsible for tumor recurrence and resistance to therapy (37, 149) has been defined as cancer stem cells (CSCs). The presence of CSCs has been described in several tumors (22, 37, 46, 79, 149). This population of immature cells may differentiate in all tumor cell types and may favor tumor growth, invasion, and metastases (37). A clonogenic CSC population has been described in renal carcinomas (23). These cells retain self-renewal properties and are capable of differentiating into more mature tumor cells and to favoring metastasis and resistance to therapy. Renal CSCs express several mesenchymal markers, such as CD73, CD90, CD44, CD29, CD146, vimentin, and, in particular, CD105, which has been used to purify this population from primary tumors (22). Moreover, they express the embryonic renal Pax2 and OCT4, NANOG, Nestin, and Musashi embryonic stem cell markers. Renal CSCs are clonogenic, generate spheres in culture, and display tumor-initiating capabilities in vivo. Another characteristic of these cells is to recapitulate the morphological aspects of the tumor of origin and to generate serially transplantable tumors, when implanted in a very low number in SCID mice. Moreover, CSCs have been shown to contribute to vessel formation since several human endothelial cells are detectable within the neo-formed tumor (22). Grange et al. (60) characterized EVs derived from renal CSCs and EVs derived from non-stem cell populations of the same tumors. When compared, these two populations are similar for size (10–100 nm) and zeta potential (22.4 ± 3.5 mV). By FACS analysis, both EV types express CD44 and α5- and α6-integrins, whereas only CSC-derived EVs express CD105. The analysis of RNA content shows an enrichment of small RNAs in both EVs but by miRNoma analysis, CSC-derived EVs express a different pattern in respect to EVs derived from non-stem cell populations (60). In particular, CSC-EVs are enriched in miR-200c, miR-92, and miR-141, which are known to be expressed in several carcinomas (16, 76, 105, 129) and in miR-29a, miR-650, and miR-151, which correlate with tumor and metastases (57, 98, 152). By gene ontology analysis, the authors showed that 24 miRNAs enriched in CSC-derived EVs associate with cell proliferation, cell adhesion, transcription, and several metabolic processes. In addition, EVs derived from CSCs exclusively carry proangiogenic mRNAs, such as fibroblast growth factor 2 (FGF2), angiopoietin 1, MMP2, MMP9, ephrin, and VEGF. EVs derived from CSCs, but not those derived from non-stem renal cancer cells, promote in vitro formation of capillary-like structures in Matrigel, tumor cell invasion, and tumor cell adhesion to the endothelium, and inhibit doxorubicin-induced apoptosis. In vivo, CSC-derived EVs stimulate angiogenesis and induce the formation of premetastatic niche. The latter is associated with an enhanced expression by lung endothelial cells of VEGFR1 and VEGF and MMP2 (60).

Moreover, it has been shown that CSC-EVs may modify phenotype and function of MSCs. MSC interaction with tumor is bivalent. In some instances, it has been reported that MSCs inhibit tumor development, in others, their involvement in tumor progression and angiogenesis (15, 81, 95, 146). CSC-EVs were shown to precondition MSCs toward a protumorigenic and angiogenic phenotype (93). Indeed, COL4A3, MMP1-3, CXCR4, and CXCR7 are significantly upregulated in MSCs pretreated with CSC-EVs.

Recently, it has been shown that osteosarcoma-derived EVs induce epigenetic changes in MSCs, influencing their function in the tumor microenvironment (100). In addition, cancer EVs could interfere with the immune system favoring the immune escape of tumors (130). The EV-mediated repression of innate immune responses may occur through mobilization of the myeloid-derived suppressor cells (27) and activation of tumor-associated macrophages (10) and neutrophils (12).

Tumor EVs promote differentiation of monocytes into monocyte-derived suppressors, which defeat T-cell proliferation and function (137). These EVs have been shown to express membrane PD-L1 and transforming growth factor-β (TGF-β) immunosuppressive cytokine (28, 131, 148) and to inhibit proliferation and cytotoxic activity of natural killer (NK) cells (4, 94, 97). Moreover, cancer EVs suppress adaptive immune responses by repressing antigen-presenting cells (147) and by blocking cytotoxic T-cell activation and proliferation, through the regulation of immune function-related genes (43, 107). In fact, the presence of Fas ligand and tumor necrosis factor-related apoptosis-inducing ligand on colorectal and prostate cancer-derived EVs can induce apoptosis in CD8+ T lymphocytes (2, 75). The immune modulatory activity of EVs is retained by CSC-derived EVs. In fact, it has been shown that CSC-EVs express the immunomodulatory nonclassical human leukocyte antigen G (HLA-G) that suppresses dendritic cell (DC) maturation (61). CSC-EVs reduce the expression of several markers of activation of monocyte-derived DC, such as CD40, CD80, and CD86 costimulatory molecules, CD83, HLA-DR, and several T-cell adhesion molecules. This altered phenotype results in impairment of CD3 + lymphocyte proliferation and associates with an enhanced production of interleukin-10 (IL-10) in respect to control DCs. CSC-EVs also stimulate the release of soluble HLA-G by monocyte-derived DCs. HLA-G has been shown to inhibit natural killer (NK) cells, T cells, and DCs (8) and has been linked to the immune escape of cancer (87). Of interest, CSC-EVs express significantly more HLA-G in respect to cancer cells deprived of the stem cell population. When CSC-EVs were incubated with an anti-HLA-G antibody, the DC phenotype of monocyte-derived cells was restored, and the immune inhibition reverted.

Recently, colorectal cancer stem cells have been shown to secrete EVs by a β-catenin/Tcf-4-activated RAB27B-dependent mechanism, exhibiting a switch of exosome RNAs from retrotransposons to microRNAs (miRNAs) (31). In particular, miR-146a may promote stem-like properties and tumorigenesis in colon cancer cells by targeting Numb. Moreover, these EVs facilitate an immunosuppressive tumor microenvironment.

PARACRINE ACTION OF STEM/PROGENITOR CELL-DERIVED EXTRACELLULAR VESICLES

Stem cell-derived EVs (SC-EVs) contain stem cell-associated transcription factors, such as Nanog and Oct-4 (119), express typical mesenchymal stromal cell (MSC) markers (CD105, CD29, CD73), and other stem cell markers such as CD133 (118) and c-KIT (144). SC-EVs express also Wnt and Hedgehog, which have a possible role in stem cell biology (99). Ratajczak et al. (119) demonstrated that SC-EVs may regulate stemness, self-renewal, and differentiation of stem/progenitor cells. In fact, EVs released from embryonic stem cells sustain the self-renewal of hematopoietic stem cells, by delivering specific proteins and mRNAs, which induce the upregulation of specific genes of pluripotency (119) (Table 1). In addition, EVs derived from other types of stem/progenitor cells shuttle mRNAs that are able to induce reprogramming of target cells. In particular, EVs from endothelial progenitor cells (EPCs) induce a proangiogenic phenotype in terminally differentiated endothelial cells and promote angiogenesis (49).

Several studies have shown that SC-EVs may mimic the effect of stem cells in various experimental models of tissue injuries (Table 1). In fact, EVs produced by stem cells carry biological messages that can influence the behavior and the fate of the target cells. This observation stimulated a number of studies aimed at evaluating whether SC-EVs may substitute stem cell-based therapies. SC-EVs from various cell sources have been investigated as potential therapeutic agents in cardiovascular diseases. SC-EVs improve heart function and vessel formation by inhibiting cardiomyocyte apoptosis and inflammation, and by promoting angiogenesis. In fact, EVs from MSCs are able to reduce inflammation and ameliorate myocardial functions in the course of ischemia-reperfusion injury (IRI), by triggering phosphatidylinositol 3-kinase (PI3K)/Akt prosurvival signaling and by restoring bioenergetics (3). Moreover, it has been shown that MSC-EVs reduce the infarct size and promote angiogenesis (11). Similarly, EVs secreted by cardiomyocyte progenitor cells (141) and from embryonic stem cells (84) were shown to improve cardiac function by promoting neovascularization of ischemic heart and cardiomyocyte survival. EV treatment also reduces fibrosis after infarction by the delivery to cardiomyocytes of miR-294, which increases cell survival and proliferation (84).

Numerous studies reported that SC-EVs have potent renal-regenerative properties. In particular, MSC-EVs mimic the effect of the cell of origin in inducing renal regeneration in a model of acute kidney injury (AKI) (17). MSC-EVs induce proliferation of renal tubular cells accelerating the reparative process of damaged tubules (17) (Fig. 1) and protect tubular cells from apoptosis (18) through upregulation of specific antiapoptotic genes and downregulation of proapoptotic genes. MSC-EVs shuttled mRNAs that can be translated into proteins, both in vitro and in vivo, stimulating reentry of damaged tubular cells into cell cycle (17, 18). Gradient separation of exosomes and MVs shows a distinct molecular signature and function on renal tubular cells (34), and exosomes retain the majority renal regenerative activity in AKI (20). It has also been reported that MSC-EVs mediate the transfer of human IGF-1 receptor mRNA to tubular cells, increasing the cell sensitivity to the proproliferative actions of IGF-1 (136). In addition, miRNAs carried by MSC-EVs have a relevant role in proregenerative effect of EVs. In fact, miRNA-depleted EVs, released by Drosha-knockdown MSCs, failed to induce renal regeneration in AKI (33). Other sources of SC-EVs have been studied in various experimental models of AKI. In particular, EVs from umbilical cord blood (CB) MSCs (154), EVs obtained from human liver stem cells (HLSCs) (69), and EVs from glomerular MSCs (116) are protective in AKI. EVs obtained from CB-MSCs stimulate tubular cell proliferation by the horizontal transfer of human HGF and by the induction of HGF production (80). Wharton's Jelly-derived MSC-EVs reduce inflammation and apoptosis via mitochondrial protection (63). EPC-EVs administered after renal IRI prevent the development of renal injury by enhancing tubular cell proliferation and reducing apoptosis and leukocyte infiltration (24). Moreover, EPC-EVs have been tested also in a rat model of experimental anti-Thy1.1 glomerulonephritis induced by a complement-mediated mesangial injury. In this model, EPC-EVs are able to inhibit the infiltration of leukocytes, the activation of mesangial cells, and the activation of serum complement, to decrease proteinuria and to improve renal function (25). EVs derived from endothelial cell-forming colonies, in particular, exosomes, significantly attenuate renal injury in a model of renal IRI (21). SC-EVs have also been studied in different animal models of chronic kidney diseases (CKD). EVs isolated from urinary MSCs are able to reduce the urinary volume and micro-albumin excretion in a rat model of diabetic nephropathy (DN) induced by streptozotocin injection (78). Moreover, the direct injection of MSC-exosomes under the renal capsule in the streptozotocin-induced DN model prompts a rapid improvement of renal morphology (109). EVs derived from MSCs and from HLSCs not only interfere with the progression but also revert to the renal fibrosis in a model of DN induced by streptozotocin. The antifibrotic effect correlates with the downregulation of several profibrotic genes in renal tissues (62, 85). In fact, HLSC-EVs contain a pattern of antifibrotic miRNAs able to downregulate profibrotic genes, restoring normal renal function in different animal models of CKD (62, 85).

HLSC-EVs participate also in accelerating the morphological and functional rescue of injured liver cells (68). Similarly, injection of EVs produced by human umbilical CB-MSCs diminishes inflammation in fibrotic liver. EVs inhibit hepatic fibrosis and protect hepatocytes by inhibition of EMT (91). Moreover, MSC-EVs stimulate liver regeneration following drug-induced injury (128).

Recent studies have demonstrated that SC-EVs have a neuroprotective effect similar to cells of origin. In particular, MSC-EVs by transfer of miRNAs (miR-133b) are able to promote neural plasticity and recovery of glia cells and of neurons in rats with stroke (145). On the other hand, treatment with EVs derived from neuronal cells under differentiation could induce human MSCs to differentiate into neuron-like cells through the transfer of miR-125b, thus confirming a two-way synergistic interaction (127). EVs obtained from MSCs enhanced endogenous angiogenesis and neurogenesis, and attenuated neuroinflammation in a rat model of traumatic brain injury (153). Moreover, EV-MSCs significantly promote the survival of retinal ganglion cells together with the axon regeneration (104). EVs derived from human adipose stem cells (ADSCs) enhance both neuronal survival and proliferation in vitro (51). Interestingly, in an in vivo model of Alzhei-

Table 1. *Biological roles of stem/progenitor cell-derived extracellular vesicles*

Biological Effect	Mechanism of Action	Cell Source	Target	Reference
Regulation of stemness, self-renewal, and differentiation	– Transfer of proteins and mRNAs – Upregulation of pluripotency-related gene expression	Mouse embryonic stem cells	Hematopoietic progenitor cells	(119)
Proangiogenic effect	– Transfer of specific proteins, mRNAs and miRNAs (miR-126 and miR-296) – Activation of PI3K/Akt pathway – Inhibition of apoptosis	EPCs	Endothelial cells	(24, 49)
Improvement of myocardial function and regeneration after IRI	– Transfer of pluripotency-related miRNAs (e.g., miR-294) – Activation of PI3K/Akt pathway – Inhibition of apoptosis – Decreased oxidative stress and increased ATP and NADH production – Reduction of inflammation, infarct size, and fibrosis	MSCs, cardiomyocyte progenitor cells, mouse embryonic stem cells	Cardiomyocites, inflammatory cells	(3, 84, 141)
Improvement of renal function and regeneration after AKI	– Transfer of specific proteins, mRNAs, and miRNAs – Transfer of mRNA coding for IGF-1 receptor and HGF which increase cell proliferation – Inhibition of apoptosis – Reduction of inflammation	MSCs from bone marrow, renal glomeruli, Wharton's jelly, umbilical cord, HLSCs, EPCs, and tubular progenitor cells	Renal tubular epithelial cells, inflammatory cells	(17, 18, 20, 21, 24, 33, 34, 63, 69, 80, 116, 136, 154)
Improvement of renal function in experimental anti-Thy1.1 glomerulonephritis	– Transfer of mRNA coding for the complement inhibitors Factor H, CD55 and CD59 – Reduction of complement-mediated mesangial injury – Reduction of inflammation and histopathological changes	EPCs	Mesangial cells	(25)
Improvement of renal function in CKD (e.g., aristolochic acid-induced kidney fibrosis, DN)	– Transfer of specific miRNAs which downregulate pro-fibrotic genes – Transfer of VEGF, TGF-β1, angiogenin which increase glomerular cell proliferation – Transfer of BMP-7 which inhibits apoptosis – Reduction of fibrosis, inflammation, and histopathological changes	MSCs from bone marrow, urine, HLSCs	Renal fibrosis, podocytes and renal tubular epithelial cells	(62, 78, 85, 109)
Stimulation of liver regeneration after acute injury	– Transfer of specific mRNAs – Increase of hepatocyte proliferation and apoptosis resistance	HLSCs	Hepatocytes	(68)
Improvement of liver function and regeneration after chronic injury	– Increase of proliferation-related protein expression – Inhibition of apoptosis through upregulation of Bcl-xL – EMT inhibition – Reduction of fibrosis and inflammation	MSCs from umbilical cord and embryonic stem cells	Hepatic fibrosis	(91, 128)
Neuroprotective effect (e.g., Alzheimer's disease, stroke)	– Transfer of specific miRNAs involved in axon regeneration (e.g., miR-17-92, miR-21, miR-133, miR-146a) – Transfer of long non-coding RNAs which increase cell proliferation(e.g., MALAT1) – Transfer of neprilysin which contributes to β-amyloid peptide clearance in the brain – Increase of angiogenesis and neurogenesis – Reduction of neuroinflammation	MSCs from adipose tissue and bone marrow	Glia, hippocampal neurons, retinal ganglion and neuroblastoma cells	(51, 83, 104, 145, 153)
Immunomodulation	– Increase of CD4+CD25+FoxP3+ Tregs which inhibit graft-versus-host disease – Reduction of Th17 and NK cells – Downregulation of Th1 responses – Upregulation of anti-inflammatory genes (e.g., TGF-β1 and IL-10) – Downregulation of proinflammatory genes (e.g., IL-1β, IL-12P40, IL-6 and tumor necrosis factor)	MSCs from bone marrow	CD4+ T cells, synovial leukocytes	(26, 150, 151)

AKI, acute kidney injury; BMP-7, bone morphogenetic protein-7; CKD, chronic kidney disease; DN, diabetic nephropathy; EMT, epithelial-mesenchymal transition; EPCs, endothelial progenitor cells; HLSCs, human liver stem cells; IGF-1, insulin-like growth factor 1; IRI, ischemia-reperfusion injury; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; miRNAs, microRNAs; MSCs, mesenchymal stromal cells; NK, natural killer; PI3K, phosphatidylinositol 3-kinase; TGF-β1, transforming growth factor-β1; VEGF, vascular endothelial growth factor.

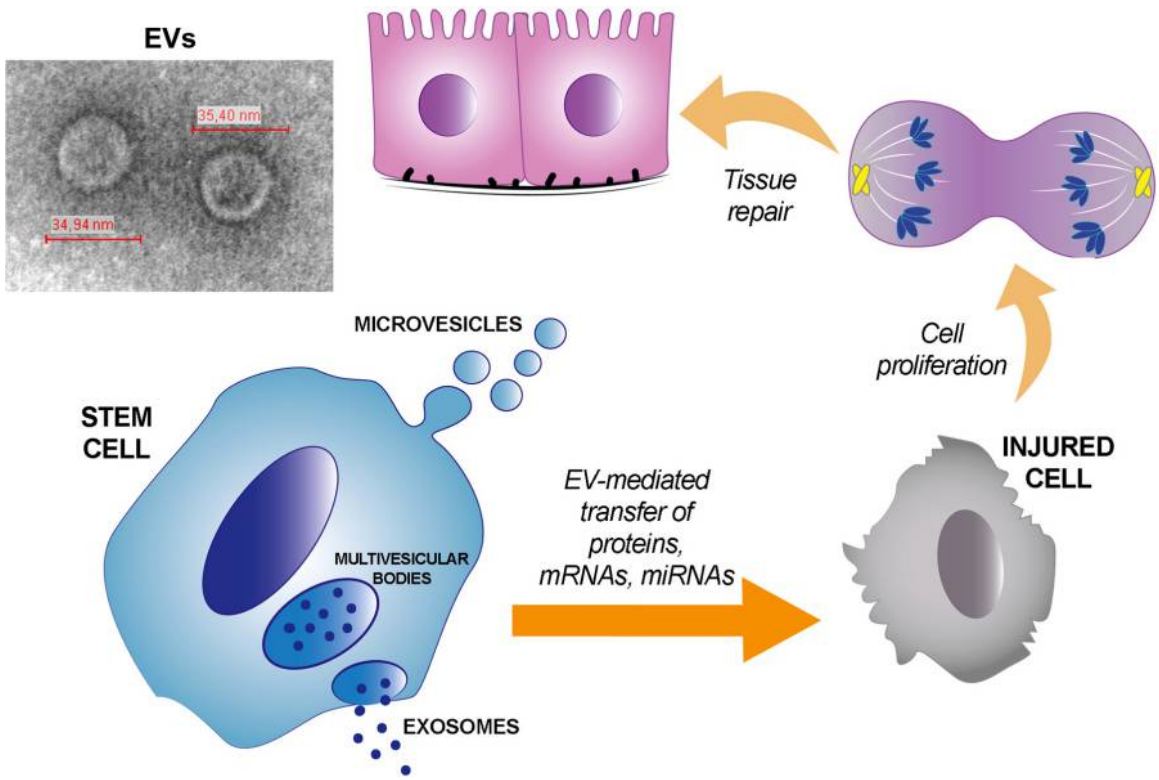

Fig. 1. Stem cell-derived extracellular vesicles (SC-EVs) contribution to tissue repair. Stem cells release EVs that accumulate at the site of tissue injury and deliver proteins and specific patterns of mRNAs and microRNAs (miRNAs) to injured cells. When incorporated into damaged cells, SC-EVs activate regenerative programs, which accelerate tissue recovery and include cell dedifferentiation, cell cycle reentry, proliferation, and redifferentiation. *Inset*: representative transmission electron microscopy image of EVs (original magnification ×250,000).

mer's disease, the positive effect of ADSC-EV administration has been attributed to their content in neprilysin, an enzyme involved in degradation of β-amyloid peptide in brain (83).

Many studies indicate that stem cells and, in particular, MSCs secrete immunosuppressive EVs (19, 38, 47, 52, 120). MSC-EVs in vitro increase the CD4+CD25+FoxP3+Treg population, downregulate Th1 responses, and reduce the number of Th17 and NK cells (151). In vivo, the anti-inflammatory effect of MSC-derived EVs is observed in many mouse models of inflammatory and autoimmune diseases (114). The expression of anti-inflammatory transcripts, such as TGF-β1 and IL-10 is upregulated by MSC-EVs, whereas the expression of proinflammatory transcripts, such as IL-1β, IL-12, P40, IL-6, and tumor necrosis factor are reduced. Moreover, MSC-EVs inhibit rejection of allogenic skin graft in mice by inducing an enhanced expression of regulatory T cells (150). This immunosuppressive effect renders MSC-EVs good candidates as surrogate of MSC-based therapy (26, 67, 120). Finally, a first in human study with MSC-derived EVs has shown improvement of graft versus host disease symptoms in a therapy-resistant patient (88).

CONCLUSIONS AND FUTURE PROSPECTS

Overall, the studies summarized in this review indicate an increased awareness of the physiological and pathological role of EVs in different contexts. This newly described mechanism of cell-to-cell communication is based on the transfer of molecular information from an EV donor cell to a recipient cell. Since EV cargo has the signature of the cell of origin, the transfer of bioactive molecules to the recipient cells may induce epigenetic changes and functional modifications in the latter. In the context of tumor microenvironment, a bidirectional exchange of information between stroma and cancer stem cells may create conditions for tumor invasion and progression. Therefore, the search for potential biomarkers in tumor-derived EVs may open diagnostic and prognostic perspectives. Moreover, increasing evidence indicates that EVs are implicated in the physiological and pathological immune and inflammatory responses. A better understanding of these mechanisms may allow the development of new strategies aimed to modulate immunity and inflammation. In fact, EVs may be exploited to either enhance or inhibit immune/inflammatory responses, but this bifunctional role of EVs may also result in unpredictable adverse effects (151). It has been reported that the immune-modulatory action of EVs is related to the different state of maturation and activation of immune cells. For instance, dendritic and antigen-presenting cells may release EVs that modulate positively or negatively the nonspecific and/or antigen-specific immune responses (122). Moreover, the MHC-class I and II, and CD80 and CD86 costimulatory molecule expression may differentially modulate immunogenicity (134). A limitation of all these studies is that purification of EVs has been performed using different methods, and this may influence the characterization of EV content. Moreover, it should be taken into account that many studies described in the literature have been performed with cell lines that do not necessarily reflect the physiopathological conditions.

Several preclinical studies have shown that SC-derived EVs may mimic the beneficial effect of stem cells. It is now accepted that the regenerative potential of adult stem cells is related to paracrine mechanisms and a critical role of their secretome has been described. It may be difficult in this context to discriminate the exact contribution of EVs in respect to the bulk of cytokines and growth factors produced by stem cells. Therefore, a better understanding of the mechanisms related to the EV effects may contribute to the design of new therapeutic strategies. Furthermore, to envisage an EV-based therapy, further studies are needed to develop an upscale production of EVs under good manufacturing practice protocols of isolation and characterization, and to define their pharmacokinetics and pharmacodynamics. Nevertheless, EV-mediated transfer of nucleic acids could permit potentially versatile therapeutic approaches (122). For instance, EVs can be engineered and used as a vehicle for the delivery of miRNAs or of small interfering RNAs (siRNAs) to modulate different biological processes.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

G. Chiabotto prepared figures; S.B. and E.F. drafted manuscript; G. Chiabotto, M.C.D., and G. Camussi edited and revised manuscript; S.B., G. Chiabotto, E.F., M.C.D., and G. Camussi approved final version of manuscript.

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