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Extracellular Vesicles as an Emerging Paradigm of Cell-to-Cell Communication in Stem Cell Biology

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Abstract

Recently, a growing body of literature supports the novel concept that extracellular vesicles, including exosomes and microvesicles, play a significant role in intercellular communication. Extracellular vesicles are released from various cell types and physically internalized by other cells. The discoveries that extracellular vesicles carry functional molecules, such as proteins, lipids, and nucleic acids raise the possibility that they may dynamically modulate cellular activities of recipient cells by transferring their bioactive contents to target cells. In particular, it has been suggested that extracellular vesicles derived from stem cells may deliver specific signals to the microenvironment, regulating cell proliferation and differentiation and tissue regeneration. In this review, we will discuss the biomolecular characteristics of stem cell-derived extracellular vesicles and their potential application in regenerative medicine.

Keywords: Extracellular vesicles; Exosomes; Microvesicles; Stem cells; Cell-to-cell communication

Introduction

Cell-to-cell communication is the fundamental mechanism that enables multicellular organisms to maintain tissue homeostasis and normal cellular functions. Recent studies have demonstrated that extracellular vesicles (EVs), including exosomes and microvesicles, may act as a crucial mediator of intercellular communication. It is well-established that EVs are small membrane vesicles secreted from numerous cell types, including immune cells, tumor cells, and stem cells [1-3]. In addition, EVs have been found in various body fluids, such as blood, saliva, and urine [4,5]. EVs are secreted either in a constitutive or regulated manner. For instance, a number of tumor cells release EVs constitutively [6], whereas primary B cells secrete EVs when stimulated with potent activation signals, such as cytokine [7].

Initially, EVs became of interest because they are implicated in antigen presentation [8]. Thus, many studies have focused on the potential therapeutic effect of EVs as a cell-free vaccine for human malignancies [9]. More recently, the findings that EVs harbor bioactive molecules, such as proteins, lipids, and nucleic acids have shed new light on the role of EVs as a paracrine mediator of cell-to-cell communication. In particular, EVs contain genetic materials, such as mRNAs and microRNAs (miRNAs), enabling exchange of information between cells [10]. It has been documented that a number of cell types can epigenetically modulate their neighboring cells by transferring genetic information via EVs [11]. The message delivered by EVs varies, depending on the pathophysiological state of the cell of origin [12]. A recent study showed that hepatocellular carcinoma cell (HCC)-derived EVs contained a selected group of miRNAs, altering the behavior of recipient HCC cells [13]. In stem cell biology, the discovery of EV-mediated intercellular communication has spurred research on the therapeutic opportunities of stem cell-derived EVs in regenerative medicine.

Properties of EVs

Biogenesis of EVs

There is accumulating evidence that vesicles released from cells are heterogeneous in terms of biogenesis and size [14]. The first type of vesicles, known as exosomes, originates from multivesicular bodies and fuse with the plasma membrane, which leads to secretion to the extracellular space. Exosomes range from 40 nm to 100 nm in size and can be characterized by the expression of tetraspanins such as CD9, CD63, and CD81 [15]. Another class of vesicles is referred to as microvesicles which are distinguished from exosomes by the mechanisms of biogenesis. Microvesicles are produced by direct budding of the plasma membrane and this relies on dynamic interplay between phospholipid redistribution and cytoskeleton activation. These shedding vesicles are known to range from 100 nm to 1 μm in size [12]. However, the exact biogenesis and characterization of two different types of EVs remain to be explored. The traditional method employed to purify EVs is ultracentrifugation combined with sucrose density gradients. In addition, EVs isolation kits using EVs precipitation solutions have been developed. More detailed review has recently been published [16].

Molecular contents of EVs

Both types of EVs contain cellular molecules, including cell surface receptors, proteins, lipids, and nucleic acids. Recent advancements in mass spectrometry-based proteomic analysis revealed that EVs contain proteins that are characteristic of the cell of origin [17]. Moreover, disease-specific vesicular proteins may provide a better understanding of pathophysiological functions of EVs and help us to discover diagnostic and therapeutic target proteins [18]. For example, epidermal growth factor receptor (EGFR) expressed on exosomal membranes was investigated for a potential lung cancer biomarker [19].

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Exosomes secreted by the prostate was used as reservoirs of tumor-associated proteins for prostate cancer detection and progression [20]. Moreover, it has been documented that EVs harbor lipids, such as eicosanoids, fatty acids, cholesterol, and lipid-related enzymes [21]. Recent studies reported that EVs also contain DNA. Glioblastoma and astrocyte cells secreted microvesicles carrying mitochondrial DNA [22]. In addition, a set of mRNAs and miRNAs have been identified in EVs derived from numerous cell types, such as human renal cancer stem cells [23], tumor-associated macrophages [24], and adipocytes [25]. Based on these findings, it has been suggested that circulating miRNAs probably transported by EVs in cancer patients can serve as novel diagnostic markers. EV-encapsulated miRNAs are relatively stable since they are protected from extracellular degrading enzymes [26,27].

Cell-to-cell communication through EVs

The discoveries that EVs harbor bioactive contents, such as proteins and nucleic acids raise the possibility that EVs might play a significant role in cell-to-cell communication. Recent works indicated that EVs are able to convey proteins to the recipient cells. Active Wnt proteins secreted on exosomes activated the Wnt signaling pathway in target cells [28]. EGFR-bound exosomes induced tumor antigen-specific regulatory T cells [29]. More intriguingly, one elegant study elucidated the role of exosomes as a vehicle for exchange of genetic information [30]. The author's isolated exosomes from a mouse mast cell line MC/9 and a human mast cell line HMC-1, and primary bone marrow-derived mouse mast cells. Using microarray assessments, they identified 1,300 mRNAs and 120 miRNAs in these mast cell-derived exosomes. Surprisingly, many of them were exosome-specific as they were not detectable in the cytoplasm of the donor cell. The results proved that mRNAs in exosomes were intact and functional and they were transferable to other mouse and human mast cells. More importantly, their data showed that once mouse exosomal mRNAs were transferred to human mast cells, new mouse protein could be synthesized in human mast cells, suggesting that genetic materials shuttled by vesicles modify the behavior of the surrounding cells. Subsequently, a number of studies investigated the role of EVs in the context of immune responses, tumor development, and stem cell biology. Indeed, significant evidence has demonstrated that tumor-derived EVs have detrimental effects on the immune response, thus promoting the immunosuppressive microenvironment for their survival [31].

Stem-Derived EVs as a Paracrine Mediator

Embryonic stem cell-derived EVs

Ratajczak et al. [3] were the first to suggest that EVs derived from stem cells exert profound effects on the microenvironment by transferring stem cell-specific proteins and mRNAs. In their study, the authors demonstrated that microvesicles derived from embryonic stem cells (ESCs) contained Wnt-3 and mRNAs implicated in pluripotent transcription factors. These molecular components were transferred to the neighboring cells, thus reprogramming hematopoietic progenitors. In another study, ESC-derived microvesicles were engineered to carry green fluorescent protein (GFP) and these modified microvesicles fused with other ESCs, shuttling their GFP [32]. In addition, it was found that miRNAs were enriched in ESC-derived microvesicles and a subset of miRNAs was transferred to mouse embryonic fibroblasts. Recently, Katsman et al. [33] reported that microvesicles derived from ESCs induced de-differentiation and alterations in gene expression of Müller cells of the retina. They performed microarrays of Müller cells treated with ESC-derived microvesicles compared to untreated Müller cells. Müller cells incubated with ESC-derived microvesicles showed the up-regulation of genes and miRNAs associated with cellular proliferation and induction of pluripotency and the down-regulation of genes important to differentiation and cell cycle arrest.

Mesenchymal stem cell-derived EVs

Collino et al. [34] found that microvesicles generated by human mesenchymal stem cells (MSCs) and human liver stem cells harbored unique patterns of miRNAs associated with ribonucleoproteins known to be responsible for the intracellular trafficking of RNAs. They also contained proteins involved in the transport and stability of mRNAs such as Staufen1, Staufen2. In another study, it was found that specific miRNAs, such as hsa-let-7b and hsa-let-7g were present as their precursor forms in MSC-derived microvesicles [35]. These studies suggest that a dynamic regulation of RNA compartmentalization occurs during the biogenesis of stem cell-derived EVs and stem cells may modulate their neighboring cells by delivering RNA contents.

Endothelial progenitor cell-derived EVs

It has been suggested that the molecular contents present in EVs are specific to the donor cells. Deregibus et al. [36] reported that microvesicles secreted from endothelial progenitor cells (EPCs) enhanced angiogenesis. The data indicated that EPC-derived microvesicles were taken up by endothelial cells, which resulted in enhancement of endothelial cell survival, proliferation and tube formation. Microarray analysis and quantitative reverse transcription-polymerase chain reaction (RT-PCR) showed that EPC-derived microvesicles conveyed mRNAs involved in the PI3K/AKT signaling pathway, triggering an angiogenic program in endothelial cells. More recently, the same group demonstrated that miR-126 and miR-296, known as pro-angiogenic miRNAs, were enriched in EPC-derived microvesicles and these might contribute to the up-regulation of pro-angiogenic pathways in the recipient cells [37,38].

Cancer stem cell-derived EVs

A recent work showed that microvesicles derived from cancer stem cells (CSCs) act as a transporter for exchange of information between

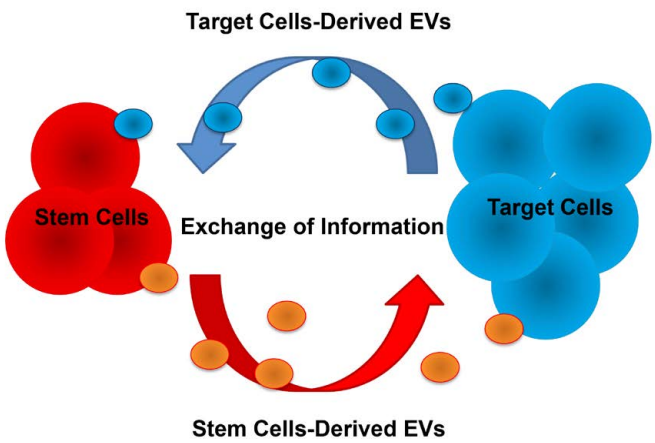

Figure 1: Reciprocal exchange of information between stem and target cells via EVs. Stem cell-derived EVs can deliver stem-cell specific bioactive molecules, including proteins, mRNAs, and miRNAs, to target cells. Thus, they may trigger a regenerative program in injured cells in a paracrine manner. Conversely, target cells may stimulate stem cells by secreting vesicle-encapsulated genetic materials.

tumors and their surrounding cells, thus engendering a favorable microenvironment for cancer progression [23]. In this study, the authors found that only CD105-positive CSC-derived microvesicles activated an angiogenic program in normal human endothelial cells, stimulating their growth and vessel formation. Moreover, treating SCID mice with CSC-derived microvesicles significantly enhanced lung metastases. The molecular characterization of CSC-derived microvesicles displayed a set of pro-angiogenic mRNAs and miRNAs implicated in tumor development and metastases.

Application of Stem Cell-Derived EVs

Stem cell-derived EVs and tissue repair

There is increasing evidence that stem cell-derived EVs contribute to tissue remodeling and have profound effects on the recipient cells in a paracrine manner (Figure 1). In this context, it has been suggested that EVs released from stem cells play a critical role in exchange of information between stem cells and tissue-injured cells [12]. Thus, the potential application of stem cell-derived EVs in regenerative medicine has been tested in a variety of experimental models. EVs secreted from tissue resident stem cells alter the behavior of the target cells. Herrera et al. [39] demonstrated that microvesicles derived from human liver stem cells facilitated hepatic regeneration after hepatectomy in rats by activating proliferation and apoptosis resistance of hepatocytes. In this study, the authors indicated that human liver stem cell-derived microvesicles shuttled a subset of mRNAs implicated in the control of proliferation and apoptosis. Over the past decade, the role of MSCs in regenerative medicine and their potential use as vehicles for gene delivery have been intensely investigated since it is well-established that MSCs migrate to injured tissues and participate in wound healing and tissue repair [40,41]. Accumulating evidence supports the notion that MSC-derived EVs help to repair tissue damage. For instance, purified exosomes from MSCs reduced infarct size in a myocardial ischemia/reperfusion injury mouse model [42]. Furthermore, using an acute myocardial infarction rat model, Bian et al. [43] demonstrated that EVs secreted from human bone marrow MSCs enhanced proliferation, migration, and tube formation of endothelial cells in a dose-dependent manner. Several studies reported that administration of MSC-derived microvesicles improved the recovery from acute kidney injury by stimulating proliferation of tubular cells in different renal injury models [44-46]. In addition, it has been suggested that MSC-derived EVs exert therapeutic effects on neurological diseases [47]. A recent study indicated that microvesicles produced by MSCs promoted sciatic nerve regeneration in rats, suggesting MSC-derived microvesicles as a novel approach to peripheral nerve cell therapy [48]. Also, MSC-derived exosomes delivered miR-133b to neural cells, which resulted in enhancement of neurite outgrowth [49]. In another study, systemic injection of MSC-derived exosomes improved neurovascular remodeling and neurogenesis after stroke in rats, implying that MSC-derived EVs may provide a potential therapeutic benefit for the treatment of neurological diseases [50].

MSC-derived EVs as a vehicle for gene delivery

Recently, several studies evaluated MSC-derived EVs as a potential vehicle for gene delivery. Katakowski et al. [51] isolated exosomes released by the MSCs transfected with a miR-146b, known as an anti-tumor miRNA, expressing vector. The authors showed that injection of miR-146b-expressing exosomes derived from the transfected MSCs significantly inhibited glioma growth in a rat model. Furthermore, Munoz et al. [52] reported that the delivery of synthetic anti-miR-9 by MSC-derived exosomes to the Glioblastoma Multiforme (GBM) cells reversed the chemoresistance of GBM cells. The data showed that anti-miR-9 shuttled by MSC-derived exosomes down-regulated the expression of the multidrug transporter, thus sensitizing the GBM cells to temozolomide. Since EVs are bi-lipid and non-synthetic structure that protects molecules from degradation, they are regarded as an ideal gene delivery vector. However, it is challenging to purify uniform EVs because EVs are heterogeneous population and a subset of molecular contents transported by EVs may vary in a context-dependent manner.

Stem cell-derived EVs and tumor

More recently, the effect of stem cell-derived EVs on tumor growth has been explored. Human liver stem cell-derived microvesicles suppressed hepatoma growth in SCID mice by transferring tumor suppressor miRNAs [53]. In addition, we demonstrated that MSC-derived exosomes significantly down-regulated the expression of vascular endothelial growth factor (VEGF) in breast cancer cells, thus suppressing angiogenesis *in vitro* and *in vivo* [54]. The results indicated that MSC-derived exosomes delivered miR-16, a miRNA known to target VEGF, and miR-16 was involved in the anti-tumor effect of MSC-derived exosomes. Furthermore, Bruno et al. [55] reported that MSC-derived microvesicles suppressed different types of tumor progression *in vitro* and *in vivo*. The authors treated MSC-derived microvesicles with HepG2 hepatoma, Kaposi's sarcoma, and Skov-3 ovarian tumor cell lines. The data demonstrated that MSC-derived microvesicles promoted cell cycle arrest in all cell lines and induced apoptosis in HepG2 and Kaposi's cells and necrosis in Skov-3. In contrast, a recent study found that exosomes from human bone marrow MSCs promoted angiogenesis in tumors by activating the extracellular signal-regulated kinase1/2 (ERK1/2) pathway *in vivo* [56]. Thus, whether stem cell-derived EVs are pro- or anti-tumorigenic has been a matter of debate. Nevertheless, these observations suggest that stem cell-derived EVs serve as an important mediator of intercellular communication in the tumor microenvironment.

Conclusions

Based on the accumulating evidence that EVs secreted from stem cells convey bioactive components to the recipient cells, EVs have emerged as a key player of cell-to-cell communication in stem cell biology. The molecular contents delivered by EVs may differ, depending on the state of the cells in the microenvironment. Since stem cell-derived EVs can transport stem-cell specific genetic materials, including mRNAs and miRNAs, they may trigger a regenerative program in injured cells in a paracrine manner. Conversely, EVs released from injured cells may induce stem cell differentiation. However, the exact characteristics and biological functions of stem cell-derived EVs are not fully elucidated. In addition, the effect of stem cell-derived EVs on tumor development is currently controversial. Thus, in order to harness stem cell-derived EVs as a therapeutic option, further studies are required.

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Competing Interest Statement

Authors have no conflict of interest.

References

1. D'Souza-Schorey C, Clancy JW (2012) Tumor-derived microvesicles: shedding light on novel microenvironment modulators and prospective cancer biomarkers. Genes Dev 26(12): 1287-1299.[PubMed]

2. Hwang I (2013) Cell-cell communication via extracellular membrane vesicles and its role in the immune response. Mol Cells 36(2): 105-111.[PubMed]

3. Ratajczak J, Miekus K, Kucia M, Zhang J, Reca R, et al. (2006) Embryonic stem cell-derived microvesicles reprogram hematopoietic progenitors: evidence for horizontal transfer of mRNA and protein delivery. Leukemia 20(5): 847-856. [PubMed]

4. Gallo A, Tandon M, Alevizos I, Illei GG (2012) The majority of microRNAs detectable in serum and saliva is concentrated in exosomes. PLoS One 7(3): e30679.[PubMed]

5. Pisitkun T, Shen RF, Knepper MA (2004) Identification and proteomic profiling of exosomes in human urine. Proc Natl Acad Sci U S A 101(36): 13368-13373. [PubMed]

6. Record M, Subra C, Silvente-Poirot S, Poirot M (2011) Exosomes as intercellular signalosomes and pharmacological effectors. Biochem Pharmacol 81(10): 1171-1182.[PubMed]

7. Saunderson SC, Schuberth PC, Dunn AC, Miller L, Hock BD, et al. (2008) Induction of exosome release in primary B cells stimulated via CD40 and the IL-4 receptor. J Immunol 180(2): 8146-8152.[PubMed]

8. Raposo G, Nijman HW, Stoorvogel W, Liejendekker R, Harding CV, et al. (1996) B lymphocytes secrete antigen-presenting vesicles. J Exp Med 183(3): 1161-1172.[PubMed]

9. Viaud S, Ullrich E, Zitvogel L, Chaput N (2008) Exosomes for the treatment of human malignancies. Horm Metab Res 40(2): 82-88.[PubMed]

10. Camussi G, Deregibus MC, Bruno S, Grange C, Fonsato V, et al. (2011) Exosome/microvesicle-mediated epigenetic reprogramming of cells. Am J Cancer Res 1(1): 98-110.[PubMed]

11. Camussi G, Deregibus MC, Tetta C (2013) Tumor-derived microvesicles and the cancer microenvironment. Curr Mol Med 13(1): 58-67.[PubMed]

12. Camussi G, Deregibus MC, Cantaluppi V (2013) Role of stem-cell-derived microvesicles in the paracrine action of stem cells. Biochem Soc Trans 41(1): 283-287.[PubMed]

13. Kogure T, Lin WL, Yan IK, Braconi C, Patel T (2011) Intercellular nanovesicle-mediated microRNA transfer: a mechanism of environmental modulation of hepatocellular cancer cell growth. Hepatology 54(4): 1237-1248.[PubMed]

14. Akers JC, Gonda D, Kim R, Carter BS, Chen CC (2013) Biogenesis of extracellular vesicles (EV): exosomes, microvesicles, retrovirus-like vesicles, and apoptotic bodies. J Neurooncol 113(1): 1-11.[PubMed]

15. Simons M, Raposo G (2009) Exosomes--vesicular carriers for intercellular communication. Curr Opin Cell Biol 21(4): 575-581.[PubMed]

16. Momen-Heravi F, Balaj L, Alian S, Mantel PY, Halleck AE, et al. (2013) Current methods for the isolation of extracellular vesicles. Biol Chem 394(10): 1253-1262.[PubMed]

17. Choi DS, Kim DK, Kim YK, Gho YS (2013) Proteomics, transcriptomics and lipidomics of exosomes and ectosomes. Proteomics 13(10-11): 1554-1571. [PubMed]

18. Choi DS, Kim DK, Kim YK, Gho YS (2014) Proteomics of extracellular vesicles: exosomes and ectosomes. Mass Spectrom Rev.[PubMed]

19. Yamashita T, Kamada H, Kanasaki S, Maeda Y, Nagano K, et al. (2013) Epidermal growth factor receptor localized to exosome membranes as a possible biomarker for lung cancer diagnosis. Pharmazie 68(12): 969-973. [PubMed]

20. Drake RR, Kislinger T (2014) The proteomics of prostate cancer exosomes. Expert Rev Proteomics 11(2): 167-177.[PubMed]

21. Record M, Carayon K, Poirot M, Silvente-Poirot S (2014) Exosomes as new vesicular lipid transporters involved in cell-cell communication and various pathophysiologies. Biochim Biophys Acta 1841(1): 108-120.[PubMed]

22. Guescini M, Genedani S, Stocchi V, Agnati LF (2010) Astrocytes and glioblastoma cells release exosomes carrying mtDNA. J Neural Transm 117(1): 1-4.[PubMed]

23. Grange C, Tapparo M, Collino F, Vitillo L, Damasco C, et al. (2011) Microvesicles released from human renal cancer stem cells stimulate angiogenesis and formation of lung premetastatic niche. Cancer Res 71(15): 5346-5356.[PubMed]

24. Yang M, Chen J, Su F, Yu B, Su F, et al. (2011) Microvesicles secreted by macrophages shuttle invasion-potentiating microRNAs into breast cancer cells. Mol Cancer 10: 117.[PubMed]

25. Ogawa R, Tanaka C, Sato M, Nagasaki H, Sugimura K, et al. (2010) Adipocyte-derived microvesicles contain RNA that is transported into macrophages and might be secreted into blood circulation. Biochem Biophys Res Commun 398(4): 723-729.[PubMed]

26. Kosaka N, Iguchi H, Ochiya T (2010) Circulating microRNA in body fluid: a new potential biomarker for cancer diagnosis and prognosis. Cancer Sci 101(10): 2087-2092.[PubMed]

27. Yang C, Wang C, Chen X, Chen S, Zhang Y, et al. (2013) Identification of seven serum microRNAs from a genome-wide serum microRNA expression profile as potential noninvasive biomarkers for malignant astrocytomas. Int J Cancer 132(1): 116-127.[PubMed]

28. Gross JC, Chaudhary V, Bartscherer K, Boutros M (2012) Active Wnt proteins are secreted on exosomes. Nat Cell Biol 14(10): 1036-1045.[PubMed]

29. Huang SH, Li Y, Zhang J, Rong J, Ye S (2013) Epidermal growth factor receptor-containing exosomes induce tumor-specific regulatory T cells. Cancer Invest 31(5): 330-335.[PubMed]

30. Valadi H, Ekstrom K, Bossios A, Sjostrand M, Lee JJ, et al. (2007) Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nat Cell Biol 9(6): 654-659.[PubMed]

31. Taylor DD, Gercel-Taylor C (2011) Exosomes/microvesicles: mediators of cancer-associated immunosuppressive microenvironments. Semin Immunopathol 33(5): 441-454.[PubMed]

32. Yuan A, Farber EL, Rapoport AL, Tejada D, Deniskin R, et al. (2009) Transfer of microRNAs by embryonic stem cell microvesicles. PLoS One 4(3): e4722. [PubMed]

33. Katsman D, Stackpole EJ, Domin DR, Farber DB (2012) Embryonic stem cell-derived microvesicles induce gene expression changes in Muller cells of the retina. PLoS One 7(11): e50417.[PubMed]

34. Collino F, Deregibus MC, Bruno S, Sterpone L, Aghemo G, et al. (2010) Microvesicles derived from adult human bone marrow and tissue specific mesenchymal stem cells shuttle selected pattern of miRNAs. PLoS One 5(7): e11803.[PubMed]

35. Chen TS, Lai RC, Lee MM, Choo AB, Lee CN, et al. (2010) Mesenchymal stem cell secretes microparticles enriched in pre-microRNAs. Nucleic Acids Res 38(1): 215-224.[PubMed]

36. Deregibus MC, Cantaluppi V, Calogero R, Lo Iacono M, Tetta C, et al. (2007) Endothelial progenitor cell derived microvesicles activate an angiogenic program in endothelial cells by a horizontal transfer of mRNA. Blood 110(7): 2440-2448.[PubMed]

37. Cantaluppi V, Biancone L, Figliolini F, Beltramo S, Medica D, et al. (2012) Microvesicles derived from endothelial progenitor cells enhance neoangiogenesis of human pancreatic islets. Cell Transplant 21(6): 1305-1320. [PubMed]

38. Cantaluppi V, Gatti S, Medica D, Figliolini F, Bruno S, et al. (2012) Microvesicles derived from endothelial progenitor cells protect the kidney from ischemia-reperfusion injury by microRNA-dependent reprogramming of resident renal cells. Kidney Int 82(4): 412-427.[PubMed]

39. Herrera MB, Fonsato V, Gatti S, Deregibus MC, Sordi A, et al. (2010) Human liver stem cell-derived microvesicles accelerate hepatic regeneration in hepatectomized rats. J Cell Mol Med 14(6B): 1605-1618.[PubMed]

40. Bergfeld SA, DeClerck YA (2010) Bone marrow-derived mesenchymal stem cells and the tumor microenvironment. Cancer Metastasis Rev 29(2): 249-261. [PubMed]

41. Ren G, Chen X, Dong F, Li W, Ren X, et al. (2012) Concise review: mesenchymal stem cells and translational medicine: emerging issues. Stem Cells Transl Med 1(1): 51-58.[PubMed]

42. Lai RC, Arslan F, Lee MM, Sze NS, Choo A, et al. (2010) Exosome secreted by MSC reduces myocardial ischemia/reperfusion injury. Stem Cell Res 4(3): 214-222.[PubMed]

43. Bian S, Zhang L, Duan L, Wang X, Min Y, et al. (2014) Extracellular vesicles derived from human bone marrow mesenchymal stem cells promote angiogenesis in a rat myocardial infarction model. J Mol Med (Berl) 92(4): 387-397.[PubMed]

44. Bruno S, Grange C, Collino F, Deregibus MC, Cantaluppi V, et al. (2012) Microvesicles derived from mesenchymal stem cells enhance survival in a lethal model of acute kidney injury. PLoS One 7(3): e33115.[PubMed]

45. Bruno S, Grange C, Deregibus MC, Calogero RA, Saviozzi S, et al. (2009) Mesenchymal stem cell-derived microvesicles protect against acute tubular injury. J Am Soc Nephrol 20(5): 1053-1067.[PubMed]

46. Gatti S, Bruno S, Deregibus MC, Sordi A, Cantaluppi V, et al. (2011) Microvesicles derived from human adult mesenchymal stem cells protect against ischaemia-reperfusion-induced acute and chronic kidney injury. Nephrol Dial Transplant 26(5): 1474-1483.[PubMed]

47. Yu B, Zhang X, Li X (2014) Exosomes derived from mesenchymal stem cells. Int J Mol Sci 15(3): 4142-4157.[PubMed]

48. Raisi A, Azizi S, Delirezh N, Heshmatian B, Farshid AA, et al. (2014) The mesenchymal stem cell-derived microvesicles enhance sciatic nerve regeneration in rat: A novel approach in peripheral nerve cell therapy. J Trauma Acute Care Surg 76(4): 991-997.[PubMed]

49. Xin H, Li Y, Buller B, Katakowski M, Zhang Y, et al. (2012) Exosome-mediated transfer of miR-133b from multipotent mesenchymal stromal cells to neural cells contributes to neurite outgrowth. Stem Cells 30(7): 1556-1564.[PubMed]

50. Xin H, Li Y, Cui Y, Yang JJ, Zhang ZG, et al. (2013) Systemic administration of exosomes released from mesenchymal stromal cells promote functional recovery and neurovascular plasticity after stroke in rats. J Cereb Blood Flow Metab 33(11): 1711-1715.[PubMed]

51. Katakowski M, Buller B, Zheng X, Lu Y, Rogers T, et al. (2013) Exosomes from marrow stromal cells expressing miR-146b inhibit glioma growth. Cancer Lett 335(1): 201-204.[PubMed]

52. Munoz JL, Bliss SA, Greco SJ, Ramkissoon SH, Ligon KL, et al. (2013) Delivery of Functional Anti-miR-9 by Mesenchymal Stem Cell-derived Exosomes to Glioblastoma Multiforme Cells Conferred Chemosensitivity. Mol Ther Nucleic Acids 2: e126.[PubMed]

53. Fonsato V, Collino F, Herrera MB, Cavallari C, Deregibus MC, et al. (2012) Human liver stem cell-derived microvesicles inhibit hepatoma growth in SCID mice by delivering antitumor microRNAs. Stem Cells 30(9): 1985-1998. [PubMed]

54. Lee JK, Park SR, Jung BK, Jeon YK, Lee YS, et al. (2013) Exosomes derived from mesenchymal stem cells suppress angiogenesis by down-regulating VEGF expression in breast cancer cells. PLoS One 8(12): e84256.[PubMed]

55. Bruno S, Collino F, Deregibus MC, Grange C, Tetta C, et al. (2013) Microvesicles derived from human bone marrow mesenchymal stem cells inhibit tumor growth. Stem Cells Dev 22(5): 758-771.[PubMed]

56. Zhu W, Huang L, Li Y, Zhang X, Gu J, et al. (2012) Exosomes derived from human bone marrow mesenchymal stem cells promote tumor growth in vivo. Cancer Lett 315(1): 28-37.[PubMed]