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REVIEW ARTICLE

# Exosomes and regenerative medicine: state of the art and perspectives

**HUI JING, XIAOMIN HE, and JINGHAO ZHENG**

**SHANGHAI, CHINA**

**Exosomes have attracted the attention of the scientific community in recent years due to their widespread distribution, their possible functions as biomarkers of disease, and their great potential to be applied as therapeutic agents. Exosomes carry proteins and nucleic acids that can facilitate their uptake by distant target cells through endocytosis, such that exosomes could be targeted to a specific cell or cells to enhance or interfere with specific biological processes. This review will mainly focus on their roles in tissue repair and regenerative processes. Exosomal engineering and their potential applications in tissue regeneration are also reviewed here as an outlook for future research. (Translational Research 2018;196:1–16)**

**Abbreviations:** adMSCs = adipose-derived MSCs; AIS = acute ischemic stroke; AKI = acute kidney injury; AMI = acute myocardial infarction; BMP-7 = bone morphogenetic protein 7; CCl4 = carbon tetrachloride; CDCs = cardiosphere-derived cells; CM = conditioned medium; CPCs = cardiac progenitor cells; CSCs = cardiac stem cells; DM = diabetes mellitus; DPSCs = dental pulp stem cells; ECs = endothelial cells; ECFCs = endothelial colony-forming cells; EPCs = endothelial progenitor cells; EGFR = epidermal growth factor receptor; EVs = extracellular vesicles; GPX1 = glutathione peroxidase1; hASCs = human adipose-derived stem cells; hBMSCs = human bone marrow mesenchymal stem cells; HCV = hepatitis C virus; hiPSC-MSCs = human-induced pluripotent stem cell-derived mesenchymal stromal cells; hMSCs = human bone marrow-derived stromal cells; hSkMs = human skeletal myoblasts; hSMMSCs = human synovial membrane MSCs; hUCMSCs = human umbilical cord mesenchymal stem cells; hUSCs = human urine-derived stem cells; IGF-1R = insulin-like growth factor-1 receptor; IL-1β = interleukin-1β; iMSCs = induced pluripotent stem cell-derived MSCs; MAPK = mitogen-activated protein kinase; mES = mouse embryonic stem cells; MSCs = mesenchymal stem cell; mRNAs = messenger RNAs; miRNAs = microRNAs; RGCs = retinal ganglion cells; PF = pericardial fluid; PRP = platelet-rich plasma; RARβ = retinoic acid receptor β; SCs = Schwann cells; SCIs = spinal cord injuries; SD rats = Sprague Dawley rats; siRNA = short-interfering RNA; SK2 = sphingosine kinase 2; TBI = traumatic brain injury; TGF-β1 = transforming growth factor-β1; TNF-α = tumor necrosis factor α; USCs = urine-derived stem cells; VEGF = vascular endothelial growth factor

**Xiaomin He, MD, PhD** *is an Attending Physician in the Department of Cardiothoracic Surgery at Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine. Dr. He's research focuses on novel regenerative strategies for tissue-engineered tracheas and myocardial patches.*

From the Department of Cardiothoracic Surgery, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China.

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Reprint requests: Jinghao Zheng or Xiaomin He, Department of Cardiothoracic Surgery, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, 1678 Dongfang Road, Shanghai 200127, China; e-mail: zhengjh210@163.com, mrxmhe@163.com.

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## INTRODUCTION

Paracrine signaling is of utmost importance in maintaining cellular homeostasis, and it also plays a key role in the onset and dissemination of many diseases.[1-4] In past decades, soluble factors secreted by cells, for instance cytokines and growth factors, were considered to be the principal form of paracrine communication between cells.[5-7] Recently, extracellular vesicles, particularly exosomes, have been identified as another vital mediator of paracrine communication.[8-12] A dramatic increase in the number of publications on exosomes highlights their growing importance in scientific research (Fig 1).

Exosomes, nanovesicles sizing ranging from 40 to 150 nm, were first discovered in the supernatants of cultured sheep erythrocytes.[13-15] It was then discovered, through advancements in biological science and technology, that these nanovesicles are widely biologically distributed. Presently, exosomes have already been found in almost all types of bodily fluids, including saliva, milk, amniotic fluid, serum or plasma, and urine.[14,16-21] The exosomes can be enriched from various fluids by differential centrifugation, density gradient isolation, and commercially available kits, and identified by specific biomarkers and particle diameters.[22-25]

Exosomes originate from the endosomes that are generated by endocytosis of the cytoplasmic membrane.[26] After further processing, exosomes are released through membrane fusion.[27] They are enveloped by a lipid bilayer enriched in cholesterol, sphingomyelin, and ceramide.[28,29] The membrane of exosomes is also abundant in some tetraspanins such as CD9, CD63, and CD81, which could be used as markers for identifying exosomes.[17,20,29-31] The internal contents of exosomes are enriched in special biomolecules, functional proteins, and nucleic acids, including microRNAs (miRNAs), messenger RNAs (mRNAs), and even DNA.[19,26,32,33]

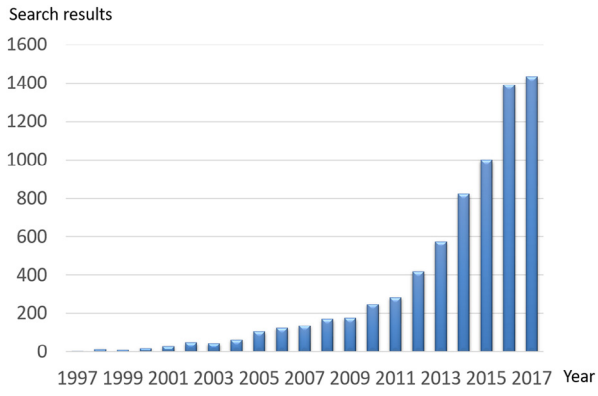


**Fig 1.** The dramatic increase in the number of publications on exosomes. The graph of "search results by year" is generated by searching "MeSH Terms: exosomes" in Pubmed, which indicates the growing importance of exosomes in scientific research the last decade.

Initially, exosomes were regarded as useless cellular metabolic waste, but it has since been recognized that they have many pivotal cellular functions. After release, exosomes can act upon special target cells in the vicinity of the parent cells in a paracrine manner, and they can also enter biological fluids, such as blood and urine, to be delivered to target cells far from the secreting cells, similar to the classical endocrine process.[19-21,33] When exosomes are absorbed by specific target cells, the exosomal contents, especially miRNAs, will mediate numerous biological processes. The potential functions of the miRNAs contained within exosomes have already largely been explored.[8,34-36] In detail, primary miRNAs are initially transcribed from genome of parental cells, processed by Drosha to pre-miRNA, and then transported into cytoplasm forming double-stranded mature miRNA. The mature miRNAs are integrated into late endosomes, and then miRNA-containing exosomes are released and captured by recipient cells. One strand of the exosomal miRNAs is integrated into Argonaute proteins which contain miRNA-induced silencing complex, and then interacts with target mRNA transcripts, which generally leads to the inhibition of corresponding gene expression.[26,32,37,38] Thus, some biomolecules in exosomes might be applied as biomarkers for disease diagnosis, prognosis, and even injury conditions, because their levels or contents might change following the occurrence of some diseases or injuries.[32,34,39-42]

Among the functions of exosomes reported thus far, their roles in cancer progression and immunoregulation have been predominantly studied.[32,34,43] In particular, cancer cell-derived exosomes have been found to promote tumor formation and metastasis in a variety of ways, for instance, by transferring tumorigenic factors to normal cells, remodeling the extracellular matrix, and mediating immune evasion.[19,32,35,44,45] Therefore, exosomes have been explored as potential biomarkers for cancer diagnoses and as special therapeutic vehicles for cancer treatments. In addition, immune cell-derived exosomes may function as proinflammatory or anti-inflammatory agents by transferring immunomodulatory cytokines, miRNAs, or other mediators between immune cells and other cell populations.[46-48]

Although exosomal functions have already been widely explored, the potential for regulating tissue repair and regeneration has not drawn nearly as much attention. Nevertheless, exosomes may be a promising substitute for many current cell and tissue engineering strategies.[49-51] The most striking evidence supporting this viewpoint originates from investigations focusing on mesenchymal stem cell (MSC) transplantation for tissue regeneration.[49,51-53] Definitely, it has been shown through a series of elegant studies that MSCs induce cellular changes mainly through paracrine signaling, especially

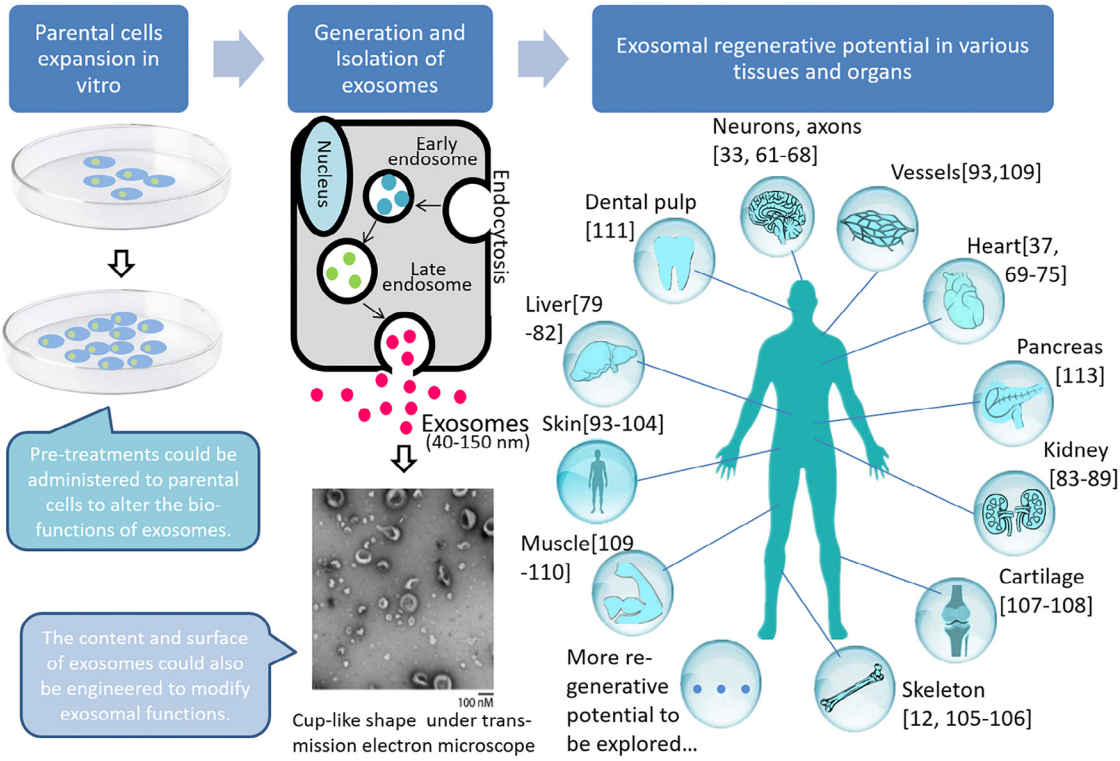


**Fig 2.** Exosomal generation and regenerative potential in various tissues and organs. Exosomes originate from the endosomes generated by endocytosis. After further processing, exosomes are released through membrane fusion. The regenerative potential of exosomes has been reported in many tissues and organs, such as nerve, heart, liver, kidney, skeleton, cartilage, muscle, pancreas, and dental pulp. It is reasonable to believe that more regenerative potential of exosomes will be discovered in the future.

via the exosomes they produce.[51-53] Therefore, we could reasonably visualize a cell-free therapy utilizing paracrine factors, such as exosomes, to promote tissue repair and regeneration (Fig 2), which would avoid the risks associated with direct stem cell transplantation, such as teratomas, immune rejection, and the reduced regenerative capacity of engrafted cells.[54-56]

## EXOSOMAL REGENERATIVE POTENTIAL IN DIFFERENT TISSUES AND ORGANS

Taking into consideration the critical roles of MSCs and their products in tissue regeneration, MSC-derived exosomes are particularly promising candidates for developing cell-free therapies.[49,51,53] In addition, exosomes released from immune cells (monocytes, leukocytes, granulocytes, and lymphocytes) are implicated in several fundamental biological processes, such as the recruitment of inflammatory cells, neovascularization, and coagulation.[57-59] Thus, they are also of vital importance in ensuring the appropriate inflammatory reaction after injury, which would boost tissue repair and regeneration (Table I). Hence, existing evidence as to the potential uses of exosomes in promoting tissue repair and regeneration will be reviewed in the following section.

**Neural regeneration.** It has been established that exosomes could be used as biomarkers for brain injuries. A proof of concept study conducted by Ji et al suggested that the serum exosomal miR-9 and miR-124 were promising biomarkers for diagnosing acute ischemic stroke (AIS) and evaluating the degree of damage caused by ischemic injury.[60] Furthermore, the regenerative effects of exosomes on neurons and nerves have been reported. Frohlich et al reported that exosomes derived from glutamate stimulated oligodendrocyte can promote survival in neurons deprived of oxygen and glucose.[61] In addition, Xin et al reported that exosomes extracted from multipotent mesenchymal stromal cells could deliver miRNA-133b to neural cells to boost neurite outgrowth, which was the first article revealing that communication occurs between MSCs and brain parenchymal cells.[62] Takeda et al found that treatment with exosomes derived from differentiating neuronal cells could induce neuronal differentiation in human MSCs.[63] This work also suggested that delivery of miR-125b via exosomes might be the possible underlying mechanism.

**Table I.** Regenerative potentials of exosomes and underlying mechanisms

| Target organs | Exosomal source | Regenerative potential of exosomes reported | Underlying mechanisms | In vitro/in vivo | References |
|---|---|---|---|---|---|
| Nerves | Multipotent mysenchymal stromal cells | Boosting neurite outgrowth. | Transferring miRNA-133b to neural cells via exosomes | In vitro | Xin et al, 2012 |
| | Differentiating neuronal cells | Inducing the neuronal differentiation of human MSCs | Delivery of miR-125b via exosomes | In vitro | Takeda et al, 2015 |
| | Human BMSCs | Enhancing endogenous angiogenesis and neurogenesis, and attenuating neuroinflammation in rats of traumatic brain injury (TBI) | Not mentioned | In vivo (TBI rat models) | Zhang et al, 2016 |
| | Human adipose-derived stem cells | Boosting neuronal survival and proliferation | MALAT1, a long noncoding RNA in exosomes mediated splicing of PKCδII thereby increasing neuronal survival | In vitro | El Bassit et al, 2016 |
| | BMSCs | Promoting survival of retinal ganglion cells and regeneration of their axons | Might be correlated with Argonaute-2, a key miRNA effector molecule | In vitro and in vivo (rat optic nerve crush models) | Mead et al, 2017 |
| | Dedifferentiated Schwann cells | Increasing axonal regeneration in vitro and enhancing regeneration after sciatic nerve injury in an SD rat model | Inhibiting activity of RhoA, a GTPase which could inhibit axonal elongation and promote growth cone collapse after being activated | In vitro | Lopez-Verrilli et al, 2013 |
| | RARβ-agonist-treated neurons | Inhibiting proliferation of astrocytes and leading them to arrange around the regenerating axons | Might be related with increased exosomal secretion of phosphatase and tensin homolog (PTEN) | In vitro and in vivo (rat cervical avulsion models) | Goncalves et al, 2015 |
| Heart | Cardiosphere-derived cells | Inhibiting apoptosis and promoting proliferation of cardiomyocytes in mouse hearts suffering from ischemia injury | Closely related with enrichment of miR-146a in exosomes | In vivo | Ibrahim et al, 2014 |
| | BMSC | Enhancing tube formation of human umbilical vein endothelial cells and inhibiting proliferation of T-cell in vitro, enhancing neovascularization and suppressing inflammation response in SD rats with acute myocardial infarction | Not mentioned | In vitro and in vivo | Teng et al, 2015 |
| | MSCs | Boosting the proliferation, migration, and angio-tube formation of cardiac stem cells | Not mentioned | In vitro and in vivo (rat myocardial infarction models) | Zhang et al, 2016 |
| | Mouse embryonic stem cell | Enhancing neovascularization and cardiomyocyte survival, suppressing myocardial fibrosis post infarction, promoting c-kit(+) cardiac progenitor cells survival and proliferation | Delivery of embryonic stem cell specific miR-294 to cardiac progenitor cells via exosomes | In vivo (mice models with acute myocardial infarction) | Khan et al, 2015 |
| | hUCMSCs | Protecting myocardial cells from apoptosis and promoting angiogenesis in rat model with acute myocardial infarction | Might be associated with modulating expression of Bcl-2 family | In vitro and in vivo | Zhao et al, 2015 |
| | Human cardiac progenitor cell | Decreasing fibrosis and improving angiogenesis a rat model suffering from myocardial ischemia reperfusion injury | Not mentioned | In vivo | Agarwal et al, 2017 |

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**Table I.** (*continued*)

| Target organs | Exosomal source | Regenerative potential of exosomes reported | Underlying mechanisms | In vitro/in vivo | References |
|---|---|---|---|---|---|
| Liver | Hepatocyte | Promoting the proliferation of hepatocyte in vitro and liver regeneration in vivo | Exosomal transfer of neutral ceramidase and sphingosine kinase 2 (SK2) to target hepatocytes | In vitro and in vivo (mouse models of ischemia/reperfusion injury and partial hepatectomy) | Nojima et al, 2016 |
| | MSCs | Activating of proliferative and regenerative responses | Not mentioned | In vitro and in vivo (liver injury mouse models) | Tan et al, 2014 |
| Kidney | hBMSCs | Promoting the proliferation of cisplatin-damaged proximal tubular epithelial cells | Horizontal transfer of IGF-1R mRNA via exosomes | In vitro | Tomasoni et al, 2013 |
| | tubular epithelial cells exposed to hypoxic conditions | Activating fibroblasts to initiate fibrotic repair response | Delivering TGF-β1 mRNA by exosomes | In vitro | Borges et al, 2013 |
| | hUCMSCs | Suppressing renal oxidative stress and apoptosis and increasing renal epithelial cell proliferation | Activation of the extracellular-signal-regulated kinase (ERK)1/2 pathway | In vitro and in vivo (rat models with cisplatin-induced acute kidney injury) | Zhou et al, 2013 |
| | Urine-derived stem cells | Inhibiting podocyte apoptosis and promoting vascular regeneration and cell survival of SD rats model with streptozotocin-induced kidney injury | Might be related with the enrichment of cytokines VEGF, TGF-β1, angiogenin, and BMP-7 in exosomes | In vitro and in vivo (rat models with streptozotocin-induced kidney injury) | Jiang et al, 2016 |
| Skin | Human urine-derived stem cells | Enhancing skin wound healing by promoting angiogenesis | Not mentioned | In vivo (rat models) | Yuan et al, 2016 |
| | hUCMSC | Boosting tissue repair by reversing the burn-induced inflammatory reaction | Weakening inflammation by downregulating the TLR4 signaling pathway | In vitro and in vivo (severe burn rat models) | Li et al, 2016 |
| | Human amniotic epithelial stem cells | Accelerating healing of full-thickness skin defect in rats by promoting the migration and proliferation of fibroblasts | Not mentioned | In vitro and in vivo (rat models with skin wound) | Zhao et al, 2017 |
| | Human umbilical cord blood-derived endothelial progenitor cells | Exerting proangiogenic and wound healing effects in diabetic rat model | Erk1/2 signaling pathway | In vitro and in vivo (rat models with streptozotocin-induced diabetic) | Zhang et al, 2016 |
| | Platelet-rich plasma | Inducing proliferation and migration of endothelial cells and fibroblasts to promote angiogenesis and re-epithelialization in chronic cutaneous wound healing process | Not mentioned | In vivo (diabetic rat modes with chronic cutaneous wounds) | Guo et al, 2017 |
| | Adipose-derived stem cells | Enhancing survival and capillary density of flaps subjected to ischemia-reperfusion injury | Not mentioned | In vitro and in vivo (mouse models with extended pectoral skin flaps) | Pu et al, 2017 |
| | Corneal epithelial cells | Inducing myofibroblast transformation after corneal wound occurred, and inducing the proliferation of endothelial cells and aortic ring sprouting | Not mentioned | In vitro | Han et al, 2017 |
| | hUCMSC | Repairing damaged skin tissue at the early stage of deep second-degree burn | Trigger the Wnt/β-catenin signaling pathway | In vitro and in vivo (rat skin burn models) | Zhang et al, 2015 |

(*continued on next page*)

**Table I.** (*continued*)

| Target organs | Exosomal source | Regenerative potential of exosomes reported | Underlying mechanisms | In vitro/in vivo | References |
|---|---|---|---|---|---|
| Skeleton | MSCs | Accelerating fracture healing process in a CD9$^{-/-}$ mice model with femur fractures | Not mentioned | In vivo | Furuta et al, 2016 |
| | Human-induced pluripotent stem cell-derived MSCs | Stimulating proliferation and osteogenic differentiation of BMSCs derived from ovariectomized rats in vitro and in vivo | PI3K/Akt signaling pathway | In vitro and in vivo (ovariectomized rats with critical size bone defects) | Qi et al, 2016 |
| Cartilage | Human embryonic MSCs | Promoting cartilage repair in a rat model with osteochondral defects on bilateral trochlear grooves | Not mentioned | In vivo | Zhang et al, 2016 |
| | Human synovial membrane MSCs<br>Induced pluripotent stem cell-derived MSCs | Stimulating chondrocyte migration and proliferation | Not mentioned | In vitro and in vivo (mouse models with collagenase-induced OA) | Zhu et al, 2017 |
| Muscle | MSCs | Promoting muscular regeneration in a mouse model with cardiotoxin-induced muscle injury | Might be mediated by miR-494 | In vitro and in vivo | Nakamura et al, 2015 |
| | Human skeletal myoblasts during myotube differentiation procedure | Inducing myogenesis response of human adipose-derived stem cells, accelerating skeletal muscle regeneration by reducing the collagen deposition and increasing the number of regenerated myofibers in injured muscles | Not mentioned | In vitro | Choi et al, 2016 |
| Other organs and tissues | Dental pulp cells cultured in odontogenic differentiation condition | Induce odontogenic differentiation of naive human dental pulp stem cells (DPSCs) and human bone marrow-derived stromal cells (HMSCs) to boost regeneration of dental pulp-like tissue | Trigger the p38 mitogen activated protein kinase (MAPK) pathway and increase expression of genes required for odontogenic differentiation | In vitro and in vivo (tooth root slice models) | Huang et al, 2016 |
| | Murine pancreatic β-cells | Promoting bone marrow cells in diabetic immunodeficiency mice to differentiate into pancreatic β-cells effectively | Not mentioned | In vivo | Oh et al, 2015 |

*Abbreviations: BMP-7,* bone morphogenetic protein 7; *BMSC,* bone marrow-derived mesenchymal stem cell; *hUCMSC,* human umbilical cord mesenchymal stem cell; *MSC,* mesenchymal stem cell; *OA,* osteoarthritis; *RARβ,* retinoic acid receptor β; *SD,* Sprague Dawley; *TGF-β1,* transforming growth factor-β1; *TLR4,* toll-like receptor 4; *VEGF,* vascular endothelial growth factor.
Reported exosomal regenerative potentials are arranged in the table according to different target tissues and organs. The corresponding exosomal sources and experimental modes are also presented, as well as some identified underlying mechanisms of exosomes-mediated regenerative potentials, if available.

Recently, Zhang et al had investigated the regenerative potential of exosomes derived from human bone marrow mesenchymal stem cells (hBMSCs) on traumatic brain injury (TBI) in rats.[64] They found that compared with the negative control, endogenous angiogenesis and neurogenesis of rats with TBI systemically administered hBMSC-generated exosomes was enhanced, whereas neuroinflammation was attenuated. These results suggest that the exosomes released by hBMSCs significantly improve functional recovery in rats after TBI. The same group also found that native exosomes secreted by MSCs can promote axonal growth while tailored MSC-exosomes carrying the elevated miR-17-92 cluster could further boost this effect, because tailored exosomes can selectively deliver their cargo miRNAs to recipient neurons and activate their target signals.[65] Furthermore, they also determined that neuronal internalization of MSC exosomes was accomplished mainly via the Soluble N-ethylmaleimide-Sensitive Factor Attachment Protein Receptor complex.

El Bassit et al also reported on the proregenerative effect of exosomes derived from human adipose-derived stem cells (hASCs) on HT22 neuronal cells post injury.[66] They found that exosomes derived from the hASCs boosted neuronal survival and proliferation by increasing expression of PKCδII in HT22 cells. They also found that MALAT1, a long noncoding RNA in hASCs-derived exosomes mediated splicing of PKCδII, thereby increasing its expression. Additional research by this group indicated that the regenerative effect of hASCs-derived exosomes could be further enhanced by insulin stimulation. More recently, it was reported by Mead et al that exosomes isolated from BMSCs could significantly promote the survival of retinal ganglion cells and regeneration of their axons; these beneficial effects might be correlated with argonaute-2, a key miRNA effector molecule.[33]

Spinal cord injuries often result in permanent damage due to the failure of axonal regeneration. In the peripheral nervous system, axonal regeneration is mainly supported by Schwann cells (SCs). After nervous damage, SCs can dedifferentiate, proliferate, and efficiently guide axons to their original target tissues. Lopez-Verrilli et al reported that exosomes derived from dedifferentiated SCs could be specifically internalized by axons, markedly increasing axonal regeneration in vitro and enhancing regeneration after sciatic nerve injury in a Sprague Dawley (SD) rat model.[67] Their research also indicated that SCs-derived exosomes promoted axonal regeneration by inhibiting activity of RhoA, a GTPase that could inhibit axonal elongation and promote growth cone collapse, but they did not mention the underlying molecular mechanism in the article. Goncalves et al found that the retinoic acid receptor β (RARβ) agonist could promote locomotor and sensory recovery in rat cervical avulsion models.[68] Further mechanism research revealed that in RARβ-agonist-treated neurons, activity of PTEN (a major negative regulator of neuronal regeneration) was obviously decreased by cytoplasmic phosphorylation. Moreover, the exosomal secretion of RARβ-agonist-treated neurons also increased. After being taken up by astrocytes, these exosomes could reduce the proliferation of astrocytes and cause them to arrange around the regenerating axons, preventing scar formation. Finally, the neuronal and neuronal-glial regenerative effects of RARβ signaling result in axonal regeneration into the spinal cord.

**Myocardial regeneration.** The potential protective effects of exosomes have already been explored in a series of myocardial ischemia reperfusion injury models. Ibrahim et al showed that exosomes isolated from cardiosphere-derived cells could inhibit apoptosis and promote the proliferation of cardiomyocytes when injected into mouse hearts suffering from ischemia injury.[69] They also found that these beneficial effects were closely related to the enrichment of miR-146a in exosomes. Teng et al reported that exosomes generated from BMSCs significantly enhanced tube formation of human umbilical vein endothelial cells and inhibited proliferation of T cell in vitro.[70] In addition, reduced infarct size and preserved cardiac function were also observed in SD rats with acute myocardial infarction due to enhanced neovascularization and suppressed inflammation response. Zhang et al also found that preconditioning with MSC exosomes could boost the proliferation, migration, and angio-tube formation of cardiac stem cells in a dose-dependent manner.[71]

It was reported by Khan and colleagues that mouse embryonic stem cell-derived exosomes (mES-Ex) possessed the ability to promote endogenous repair and enhance cardiac function after myocardial infarction.[72] They found that after mES-Ex were intramyocardially administered in mice at the time of myocardial infarction, both neovascularization and cardiomyocyte survival was enhanced, and myocardial fibrosis post infarction was evidently suppressed concurrent with enhanced c-kit(+) cardiac progenitor cells (CPCs) survival and proliferation. This research group also investigated the underlying mechanisms of these beneficial effects via microRNA array analysis. Their results indicated that the regenerative potential of mES-Ex was tied to the delivery of embryonic stem cell-specific miR-294 to CPCs, which could promote cell survival and proliferation of the latter.

Zhao et al showed that exosomes derived from human umbilical cord mesenchymal stem cells (hUCMSCs) possessed a protective effect in an acute myocardial infarction rat model.[73] They found that exosomes might improve cardiac systolic function by protecting myocardial cells from apoptosis and promoting angiogenesis. These beneficial effects were potentially associated with modulating

the expression of members of the Bcl-2 family. Vicencio et al also showed that a specific cardioprotective pathway, involving TLR4 and HSP27, could be activated by exosomes in plasma.[74]

Recently, Agarwal and coworkers evaluated the regenerative role of human CPCs-derived exosomes in a rat myocardial ischemia reperfusion injury model.[75] In their investigation, human CPCs obtained from children of different ages were isolated and cultured under hypoxic and normal conditions. Then, exosomes were isolated from the conditioned media and delivered to rats. Finally, their results indicated that exosomes released by neonate CPCs improved cardiac function by decreasing fibrosis and improving angiogenesis regardless of oxygen levels in culture conditions, whereas exosomes from older children could only gain reparative power when CPCs were subjected to hypoxic conditions. This is the first investigation demonstrating that donor age and hypoxia level can influence the therapeutic efficacy of human CPC-derived exosomes.

Interestingly, Beltrami et al found that the pericardial fluid (PF) also contained exosomes enriched with miRNAs co-expressed in the patient myocardium and vasculature vs peripheral plasma.[37] Amazingly, the specific exosomes in the PF could improve the survival, proliferation, and networking of endothelial cells (ECs) cultured in vitro and restore the angiogenic capacity of ECs depleted of endogenous miRNA profiles. Most importantly, the PF exosomes could improve blood flow recovery and angiogenesis after ischemic injury in the mouse model. Further investigation suggested that PF exosomes might orchestrate the vascular repair process by delivering miRNA let-7b-5p to ECs.

**Hepatic regeneration.** Exosomes have already been used as specific biomarkers for hepatocyte damage and inflammation in acute liver injury.[41,76-78] Momen-Heravi et al reported that the exosomal levels in the plasma of patients with alcoholic hepatitis were obviously higher than those of the healthy population, as were the specific miRNA profiles in their exosomes.[76]

The regenerative potential of exosomes on liver has also been investigated recently. In acute liver injury, Nojima et al found that hepatocyte-derived exosomes could promote the proliferation of hepatocytes in vitro and liver regeneration in vivo.[79] Their research suggested that the underlying mechanism might involve exosomal transfer of neutral ceramidase and sphingosine kinase 2 (SK2) to target hepatocytes. Moreover, they also found that the levels of circulating exosomes with proliferative effects also increased after liver injury. Tan et al also investigated the regenerative potential of MSCs-derived exosomes in a carbon tetrachloride ($CCl_4$)-induced liver injury mouse model. They reported that $CCl_4$-induced liver injury was notably attenuated by concurrent treatment with MSCs-exosomes, which might be achieved mainly through the activation of proliferative and regenerative responses.[80]

Recently, Yan and coworkers reported that systemic administration of hUCMSC-derived exosomes (hUCMSC-Ex) could effectively rescue mice from CCl4-induced liver failure; this protective effect was closely associated with hUCMSC-Ex-derived glutathione peroxidase1.[81] The antioxidant and antiapoptotic abilities of hUCMSC-Ex would diminish after knockdown of glutathione peroxidase1 in hUCMSCs. Nong et al also evaluated the regenerative potential of exosomes derived from human-induced pluripotent stem cell-derived mesenchymal stromal cells (hiPSC-MSCs-Exo) during hepatic ischemia-reperfusion injury.[82] Their results indicated that hiPSC-MSCs-Exo administration can alleviate warm hepatic ischemia-reperfusion injury by suppressing inflammatory responses, attenuating oxidative stress responses, and inhibiting cellular apoptosis. However, the molecular mechanism by which these effects occur was not further elucidated.

**Renal regeneration.** It was reported by Tomasoni et al that exosomes released by hBMSCs could promote the proliferation of cisplatin-damaged proximal tubular epithelial cells via horizontal transfer of IGF-1 receptor mRNA.[83] Zhou and colleagues also demonstrated that exosomes derived from hUCMSCs could alleviate acute kidney injuries induced by cisplatin in rats by suppressing renal oxidative stress and apoptosis, while increasing renal epithelial cell proliferation.[84] Borges et al found that tubular epithelial cells exposed to hypoxic conditions can produce exosomes enriched in transforming growth factor-β1 (TGF-β1) mRNA, which can activate fibroblasts to initiate the fibrotic repair response.[85] This study suggested that TGF-β1 mRNA delivered by exosomes constituted a rapid response to initiate tissue-regenerative responses after hypoxia injury. Their finding also enlightens the potential for exosome-targeted therapies to control tissue fibrosis.

Burger et al examined the therapeutic potential of human umbilical cord blood-derived endothelial colony-forming cells (ECFCs) and ECFC-derived exosomes in a mouse model of ischemic acute kidney injury (AKI).[86] They found that intravenous administration of ECFCs can attenuate renal injuries in mice with ischemic AKI, while direct intravenous administration of ECFC-derived exosomes had the same effect. Recently, this group demonstrated that exosomes derived from ECFCs were enriched in miR-486-5p and delivery of ECFC-derived exosomes could reduce ischemic AKI via transfer of miR-486-5p targeting PTEN.[87]

In addition, Wang et al found that MSCs that were engineered to overexpress miRNA-let7c could selectively localize to injured kidneys and upregulate miR-let7c gene expression to attenuate kidney injury.[88] The exosomes

derived from these engineered MSCs were also able to selectively transfer miR-let7c to damaged kidney cells to achieve antifibrotic functions. Jiang et al also investigated the therapeutic potential of exosomes from urine-derived stem cells (USCs-Exo) on kidney injury repair in an SD rat model.[89] Their results suggested that streptozotocin-induced kidney injury could be alleviated by weekly intravenous tail injections of USCs-Exo, which could obviously inhibit podocyte apoptosis and promote vascular regeneration and cell survival. They also deduced from an USCs-Exo contents assay that the regenerative potential might be related to the enrichment of cytokines vascular endothelial growth factor (VEGF), TGF-β1, angiogenin, and bone morphogenetic protein 7 in USCs-Exo.

**Cutaneous regeneration.** Angiogenesis is of crucial importance in various physiological processes including cutaneous wound healing and tissue regeneration. It has already been established that exosomes released from cancer cells can modify the tumor environment to enable the metastasis of cancer cells and promote angiogenesis, which was reviewed in other articles.[90-92] This type of beneficial effect might also be found in exosomes derived from other sources, beyond cancer cells.

Liang et al found that exosomes released by human adipose-derived MSCs (adMSCs) can significantly promote endothelial cell angiogenesis in vitro and in vivo.[93] Further investigation indicated that exosomes derived from adipose-derived MSCs could transfer miR-125a to endothelial cells, resulting in the downregulation of angiogenic inhibitor delta-like 4. Yuan et al also demonstrated that exosomes extracted from human urine derived stem cells could enhance skin wound healing by promoting angiogenesis in vitro and in vivo.[94] However, they did not determine the underlying molecular mechanisms of this beneficial effect.

Burn injury, one of the most common causes of cutaneous damage, could significantly intensify the inflammatory reaction, including increased tumor necrosis factor α and interleukin-1β (IL-1β) levels, and decreased IL-10 levels.[95-97] Li et al found that administration of hUCMSC-exosomes could successfully reverse the burn-induced inflammatory reaction.[95] Further research suggested that miR-181c in hUCMSC-exosomes weakened inflammation by downregulating the TLR4 signaling pathway following burn injury, which could attenuate excessive inflammation and boost tissue repair.

Zhao et al investigated the regenerative potential of exosomes derived from human amniotic epithelial stem cells on the healing of full-thickness skin defects in rats.[98,99] Exosomes were isolated and then different concentrations were subcutaneously injected around the wound site. Eventually, they found that exosomes released by human amniotic epithelial stem cells could promote the migration and proliferation of fibroblasts, accelerating healing of full-thickness skin defect in a dose-dependent manner. Zhang et al also demonstrated that exosomes from human umbilical cord blood-derived endothelial progenitor cells possessed robust proangiogenic and wound healing effects in a diabetic rat model.[100] Microarray analyses indicated that exosomes markedly altered the expression of a series of genes involved in the Erk1/2 signaling pathway, and functional studies further confirmed that this signaling pathway was of vital importance during the exosome-induced angiogenic responses of endothelial cells. Recently, Guo and colleagues demonstrated that exosomes derived from platelet-rich plasma can effectively induce the proliferation and migration of endothelial cells and fibroblasts to promote angiogenesis and re-epithelialization in chronic cutaneous wound healing processes, highlighting the healing of chronic ulcers.[101]

Pu and colleagues reported that the survival and capillary density of flaps subjected to ischemia-reperfusion injury were significantly enhanced via the injection of exosomes released by adipose-derived stem cells.[102] Han et al had also found that exosomes derived from corneal epithelial cells could fuse to keratocytes and induce myofibroblast transformation after a corneal wound occurred.[103] Furthermore, corneal epithelial cell-derived exosomes can induce the proliferation of endothelial cells and aortic ring sprouting in vitro. Their results indicated that epithelial cell-derived exosomes might be involved in corneal wound healing and neovascularization processes, which may be applied as therapeutic interventions in the future.

Exosomes could also orchestrate controlled cutaneous regeneration in a bipolar manner. Zhang et al showed that exosomes derived from hUCMSCs could trigger the Wnt/β-catenin signaling pathway to repair damaged skin tissue during the early stages of deep second-degree burn healing, and they could also inhibit Wnt/β-catenin signaling through the induction of YAP phosphorylation to circumvent excessive skin cell expansion and collagen deposition after the remodeling phase.[104]

**Skeletal regeneration.** Bone regeneration using MSCs and tissue engineering strategies is one of the most widely researched fields in regenerative medicine. Furuta and colleagues evaluated the therapeutic effects of exosomes isolated from MSC-conditioned medium (CM) in the fracture healing process in a $CD9^{-/-}$ mice model, which produces low levels of exosomes. Identical femur fractures were created in both test and control groups. Then mice in the test group were injected with exosomes, while controls were injected with exosome-free CM. The bone union rates were measured, and the results suggested that the exosomes in MSC-CM could accelerate the fracture healing process.[12]

Recently, Zhang et al investigated the pro-osteogenic potential of hiPSC-MSC-Exos.[105,106] They showed that the isolated exosomes could effectively stimulate the proliferation and osteogenic differentiation of bone marrow MSCs derived from ovariectomized rats in vitro and in vivo. These results also suggested that the therapeutic effects of hiPSC-MSC-Exos could be intensified by increasing their exosomal concentration. Bioinformatics analyses further confirmed that the PI3K/Akt signaling pathway was the principal regulator during the hiPSC-MSC-Exos-induced osteogenic differentiation of BMSCs.

**Chondral regeneration.** Zhang et al showed the therapeutic effects of exosomes derived from human embryonic mesenchymal stem cells on cartilage repair. Osteochondral defects were created on bilateral trochlear grooves in a rat model. One defect was weekly intra-articularly injected with human embryonic MSC-derived exosomes for 12 weeks, and the contralateral defect was injected with phosphate-buffered saline. Eventually, complete restorations of cartilage were observed in defects treated with exosomes, whereas only fibrous repair tissues were found in the control group.[107] However, this research did not exclude the possibility that exosome injected into the trochlear groove might be transferred to the contralateral defect through blood circulation, thereby interfering with the outcome of control group.

Recently, Zhu and coworkers evaluated the regenerative potential of exosomes secreted by human synovial membrane MSCs (SMMSC-Exos) and induced pluripotent stem cell-derived MSCs (iMSC-Exos) on osteoarthritis, which is induced by failure of articular cartilage regeneration in a rat model.[108] They found that both iMSC-Exos and SMMSC-Exos could attenuate osteoarthritis by stimulating chondrocyte migration and proliferation, while the regenerative power of iMSC-Exos was stronger than that of SMMSC-Exos. This inspiring work also provided new perspectives for cell-free therapies for cartilage injury and osteoarthritis.

**Muscular regeneration.** Nakamura et al showed that exosomes derived from MSCs could promote myogenesis and angiogenesis in vitro.[109] They verified that MSC-derived exosomes promoted muscle regeneration in a mouse model of cardiotoxin-induced muscle injury, which might be mediated by miR-494. Recently, Choi and colleagues also found that exosomes derived from human skeletal myoblasts during myotube differentiation could effectively induce a myogenesis response in hASCs.[110] Moreover, a laceration mouse model verified that exosomes derived from differentiating human skeletal myoblasts could accelerate skeletal muscle regeneration by reducing collagen deposition and increasing the number of regenerated myofibers in injured muscles.

**Regeneration of other tissues and organs.** The regenerative potential of exosomes has also been investigated in other tissues and organs such as in dental pulp tissue and pancreas. Huang and colleagues have evaluated the potential of exosomes derived from dental pulp cells cultured under odontogenic differentiation conditions to induce odontogenic differentiation in naive human dental pulp stem cells and human bone marrow-derived stromal cells in vitro and in vivo.[111] After being taken up by human dental pulp stem cells and human bone marrow-derived stromal cells, exosomes could trigger the p38 mitogen-activated protein kinase pathway and increase the expression of genes required for odontogenic differentiation in a dose-dependent and saturable manner via the caveolar endocytic mechanism, boosting the regeneration of dental pulp-like tissue collectively. In addition, they found that exosomes could bind to matrix proteins such as type I collagen and fibronectin, which enabled exosomes to be tethered to biomaterials.

Diabetes mellitus is a complex metabolic disease characterized by glucose overproduction and underutilization, constituting one of the most important global health problems. Insulin, which functions to decrease blood glucose, is synthesized and secreted by pancreatic β-cells. Reductions in the amount and function of pancreatic β-cells result in relative or absolute insufficient insulin secretion, contributing to the pathophysiology underlying diabetes.[112] Oh et al investigated the regenerative potential of extracellular vesicles, including exosomes and microvesicles, derived from a murine pancreatic β-cell line.[113] They found that bone marrow cells in diabetic immunodeficient mice can effectively differentiate into pancreatic β-cells when cultured with exosomes. This inspiring finding might provide an ideal solution to the dilemma that sources of functional islets for transplantation are particularly limited.

## EXOSOMAL ENGINEERING FOR TISSUE REPAIR AND REGENERATION

Recent evidence indicates that exosomes secreted by most cell types can mediate transfer of proteins, mRNAs, and microRNAs; theoretically, endogenous exosomes could be promising candidates for natural drug delivery due to their small size, low immunogenicity, nontoxicity, permeability of physiological barriers, and stability in circulation.[114-117] Emerging exosomal engineering strategies have achieved this miraculous aim.

Reported investigations proved that exosomes could be specially preloaded with therapeutic agents, such as short-interfering RNA (siRNA), miRNA, DNA, and some proteins and compounds.[115,117] By this means, the desired agents can be protected from degradation and deactivation after administration, and effectively transferred to target cells for special medical purposes. Besides, the surface of exosomes could also be engineered with

particular ligands with affinity to specific cell types, ensuring that the engineered exosomes can be efficiently and selectively captured by target cells to evade the off-target effects.[118] Generally, modifying exosomal content and surface markers will not interfere with the other natural features of exosomes. Moreover, it has been recognized that the microenvironment, which parental cells are exposed to, can influence the functional potential of the exosomes these cells produce.[119,120] Existing evidence regarding exosomal engineering strategies is presented in the following section, and the potential applications in regenerative medicine will also be discussed herein.

**Engineering the exosomal content with compounds.** Zhuang et al were the first to encapsulate an anti-inflammatory compound, curcumin, into exosomes derived from EL-4, a murine lymphoma cell line.[121] After incubation with exosomes loaded with curcumin, RAW 264.7 cells, a murine macrophage cell line, released lower levels of proinflammatory cytokines IL-6 and tumor necrosis factor α compared with cells incubated with curcumin alone. Additionally, they demonstrated that the curcumin delivered by exosomes is more stable and more highly concentrated in blood circulation. They found that the solubility, stability, and bioavailability of curcumin were significantly increased after they were encapsulated in exosomes. Moreover, intranasal administration of exosomes encapsulating curcumin leads to rapid delivery of curcumin to the brain, because the modified exosomes were selectively taken up by microglial cells, and subsequently induced apoptosis of microglial cells. In contrast, curcumin is difficult to penetrate the blood-brain barrier when it is delivered alone. Therefore, the exosomes-mediated curcumin delivery is superior to delivery of curcumin alone. This proof-of-concept investigation successfully validated that exosomes could be modified to deliver specific therapeutic agents to target cells. In the future, with assistance from exosomes engineered with anti-inflammatory compounds, clinicians might be able to beneficially modulate the inflammatory response as soon as tissue damage occurs. It is also reasonable to imagine that engineering exosomes with compounds that can boost tissue regeneration may help improve overall tissue repair.

**Engineering the exosomal content with nucleic acids.** Another exosomal engineering strategy would be encapsulating nucleic acids into exosomes. Alvarez-Erviti and colleagues demonstrated that systemic injection of engineered exosomes containing siRNA against GAPDH or BACE1 could be effectively delivered to mouse brain tissues and that the expression of target genes in recipient cells could be repressed; these findings indicate that efficient in vivo delivery of nucleic acids through exosomes is feasible.[122]

Recently, de Rivero Vaccari et al isolated exosomes from embryonic cortical neuronal cultures and loaded them with an siRNA against apoptosis speck-like protein containing a caspase recruitment domain (ASC) and administered the exosomes to spinal cord-injured animals.[123] Surprisingly, they found that neuronal-derived exosomes could cross the injured blood-spinal cord barrier and deliver their cargo in vivo, resulting in the knockdown of ASC protein levels. These findings also indicate that exosomal siRNA delivery might be a promising route to block the devastating inflammation activation that occurs after CNS injury. In the future, proregeneration nucleic acids, such as proinflammatory, antiproliferation, or antiangiogenic genes might also be transferred via engineered exosomes to promote tissue repair.

**Engineering the exosomal surface.** Exosomes are enveloped by a lipid bilayer that is also abundant in some tetraspanins such as CD9, CD63, and CD81. In theory, the surface of exosomes can also be engineered to target specific cell types. Ohno et al engineered the surface of exosomes with peptides with affinity to epidermal growth factor receptor (EGFR) and successfully showed that antitumor miRNAs could be efficiently transferred to breast cancer cells with high EGFR expression via systemic injection of these modified exosomes.[118] It can be inspired that modifying the surface of exosomes by adding proteins with affinity to injured cells and tissues could precisely drive exosomes to a target site.

**Engineering exosomes via interfering with parental cells.** It is also interesting to note that the exosomes secreted by a particular cell are often heterogeneous in composition, such that several subpopulations of exosomes with distinct biological functions can be generated from the same cell.[124,125] At the same time, the subpopulations of exosomes can be enriched in different specific contents to target desired cell types.[124] Another recent study reported on the immunoregulatory potential of exosomes derived from lipopolysaccharide (LPS)-treated MSCs, suggesting that LPS-treated cells have stronger immunoregulatory properties than untreated MSCs.[120] miRNA microarray analysis demonstrated that let-7b, miR-1180, miR-550b, and miR-133a were unique to exosomes derived from LPS-treated MSCs. The following functional investigation attributed their better immunotherapeutic potential to the subsequent upregulation of the TLR4/NF-κB/STAT3/AKT signaling pathway.

Huang et al also found that exosomes released by colorectal cancer cells under hypoxic conditions can promote the proliferation and migration of endothelial cells.[119] The underlying mechanism likely involves an exosomally mediated Wnt/β-catenin signaling pathway. Garcia et al also reported that exosomes derived from cardiomyocytes cultured under glucose deprivation induce

the proliferation and angiogenesis of endothelial cells.[126] Thus, it might be concluded that the microenvironment, which parental cells are exposed to, can influence the functional potential of exosomes these cells produce. There is every reason to believe that the exosomes could carry stronger therapeutic potential for tissue regeneration through modulating the microenvironment of their parental cells in some special ways.

## LIMITATIONS AND PROSPECT

Despite extensive study, the potential roles of exosomes in tissue repair and regeneration have not been fully elucidated. It is still unclear which contents or properties of exosomes are capable of promoting tissue regeneration. Fully addressing this question could unlock the "proregeneration message" of exosomes, which could therapeutically be particularly valuable for patients who cannot produce such signals or produce insufficient levels. It would also be of great significance in illuminating the variations in exosomal amounts following injury, because excessive exosome recruitment might lead to further tissue damage by perpetuating the inflammatory response.

Besides, it has been proved that exosomes derived from hepatitis C virus (HCV)-infected human hepatoma cells could mediate HCV transmitting infection through delivery of exosomal full-length viral RNAs.[127] Therefore, the obtained exosomes must be compulsively screened for some specific viral RNAs before clinical applications for tissue regeneration. Apart from this, some limitations associated with the exosomal isolation techniques also exists. Differential ultracentrifugation can enrich exosomes with high purity, thus being regarded as golden criterion for exosomal isolation; however, the obtaining rate is barely satisfactory, and the collapse and damage of exosomal membranes or aggregation of exosomes might be induced.[22] Besides, a series of commercialized isolation kits have been developed to improve the exosomal obtaining rate; however, purity of exosomes extracted by kits is compromising.[25] Great efforts still need to be dedicated to develop some optimized methods for exosomal isolation and purification.

Although there is much that remains to be learned in the field of exosomal research, the unique properties of exosomes clearly represent new therapeutic opportunities for tissue repair and regeneration. The reported regenerative potential of exosomes will be clinically utilized for regeneration in various target tissues and organs after further translational research. And it is reasonable to believe that more regenerative potential of exosomes will be discovered in the future. Moreover, by virtue of exosomal engineering, we might be able to modify the contents of exosomes by adding therapeutic drugs or compounds to enhance their regenerative potential. In addition, modulating the microenvironment of the parental cells is another promising approach to strengthen exosomal regenerative potential. Furthermore, the exosomal surface can also be modified to achieve accurate delivery, circumventing off-target effects. Innovative strategies using exosomes have paved the way for new options in regenerative medicine, which are worthy of further investigation.

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### REFERENCES

1. Muller E, Wang W, Qiao W, et al. Distinguishing autocrine and paracrine signals in hematopoietic stem cell culture using a biofunctional microcavity platform. Sci Rep 2016;6:31951.
2. Cho KI, Yoon D, Qiu S, et al. Loss of Ranbp2 in motor neurons causes the disruption of nucleocytoplasmic and chemokine signaling and proteostasis of hnRNPH3 and Mmp28, and the development of amyotrophic lateral sclerosis (ALS)-like syndromes. Dis Model Mech 2017;10:559–79.
3. Civitarese RA, Kapus A, McCulloch CA, Connelly KA. Role of integrins in mediating cardiac fibroblast-cardiomyocyte cross talk: a dynamic relationship in cardiac biology and pathophysiology. Basic Res Cardiol 2017;112:6.
4. Plotnikov EY, Silachev DN, Popkov VA, et al. Intercellular signalling cross-talk: to kill, to heal and to rejuvenate. Heart Lung Circ 2017;26:648–59.
5. Parascandolo A, Rappa F, Cappello F, et al. Extracellular superoxide dismutase expression in papillary thyroid cancer mesenchymal stem/stromal cells modulates cancer cell growth and migration. Sci Rep 2017;7:41416.
6. Wang J, Sun B, Tian L, et al. Evaluation of the potential of rhTGF-beta3 encapsulated P(LLA-CL)/collagen nanofibers for tracheal cartilage regeneration using mesenchymal stems cells derived from Wharton's jelly of human umbilical cord. Mater Sci Eng C Mater Biol Appl 2017;70:637–45.
7. Blondiaux E, Pidial L, Autret G, et al. Bone marrow-derived mesenchymal stem cell-loaded fibrin patches act as a reservoir of paracrine factors in chronic myocardial infarction. J Tissue Eng Regen Med 2017;11:3417–27.
8. Zhang Y, Yu M, Dai M, et al. miR-450a-5p within rat adipose tissue exosome-like vesicles promotes adipogenic differentiation by targeting WISP2. J Cell Sci 2017;130:1158–68.
9. Collino F, Pomatto M, Bruno S, et al. Exosome and microvesicle-enriched fractions isolated from mesenchymal stem cells by

gradient separation showed different molecular signatures and functions on renal tubular epithelial cells. Stem Cell Rev 2017;13:226–43.
10. Goloviznina NA, Verghese SC, Yoon YM, Taratula O, Marks DL, Kurre P. Mesenchymal stromal cell-derived extracellular vesicles promote myeloid-biased multipotent hematopoietic progenitor expansion via toll-like receptor engagement. J Biol Chem 2016;291:24607–17.
11. Lee M, Ban JJ, Kim KY, et al. Adipose-derived stem cell exosomes alleviate pathology of amyotrophic lateral sclerosis in vitro. Biochem Biophys Res Commun 2016;479:434–9.
12. Furuta T, Miyaki S, Ishitobi H, et al. Mesenchymal stem cell-derived exosomes promote fracture healing in a mouse model. Stem Cells Transl Med 2016;5:1620–30.
13. Johnstone RM, Adam M, Hammond JR, Orr L, Turbide C. Vesicle formation during reticulocyte maturation. Association of plasma membrane activities with released vesicles (exosomes). J Biol Chem 1987;262:9412–20.
14. Geminard C, Nault F, Johnstone RM, Vidal M. Characteristics of the interaction between Hsc70 and the transferrin receptor in exosomes released during reticulocyte maturation. J Biol Chem 2001;276:9910–6.
15. Johnstone RM. Cleavage of the transferrin receptor by human granulocytes: differential proteolysis of the exosome-bound TFR. J Cell Physiol 1996;168:333–45.
16. Katsiougiannis S, Chia D, Kim Y, Singh RP, Wong DT. Saliva exosomes from pancreatic tumor-bearing mice modulate NK cell phenotype and antitumor cytotoxicity. FASEB J 2017;31:998–1010.
17. Hock A, Miyake H, Li B, et al. Breast milk-derived exosomes promote intestinal epithelial cell growth. J Pediatr Surg 2017;52:755–9.
18. Xiao GY, Cheng CC, Chiang YS, Cheng WT, Liu IH, Wu SC. Exosomal miR-10a derived from amniotic fluid stem cells preserves ovarian follicles after chemotherapy. Sci Rep 2016;6:23120.
19. An M, Lohse I, Tan Z, et al. Quantitative proteomic analysis of serum exosomes from patients with locally advanced pancreatic cancer undergoing chemoradiotherapy. J Proteome Res 2017;16:1763–72.
20. Domenyuk V, Zhong Z, Stark A, et al. Plasma exosome profiling of cancer patients by a next generation systems biology approach. Sci Rep 2017;7:42741.
21. Sun H, Yao W, Tang Y, et al. Urinary exosomes as a novel biomarker for evaluation of alpha-lipoic acid's protective effect in early diabetic nephropathy. J Clin Lab Anal 2017;doi:10.1002/jcla.22129.
22. Lee MJ, Park DH, Kang JH. Exosomes as the source of biomarkers of metabolic diseases. Ann Pediatr Endocrinol Metab 2016;21:119–25.
23. Mitchell P, Tollervey D. Finding the exosome. Adv Exp Med Biol 2010;702:1–8.
24. Kastelowitz N, Yin H. Exosomes and microvesicles: identification and targeting by particle size and lipid chemical probes. Chembiochem 2014;15:923–8.
25. Wang D, Sun W. Urinary extracellular microvesicles: isolation methods and prospects for urinary proteome. Proteomics 2014;14:1922–32.
26. Stahl PD, Barbieri MA. Multivesicular bodies and multivesicular endosomes: the "ins and outs" of endosomal traffic. Sci STKE 2002;2002:pe32.
27. Montecalvo A, Larregina AT, Morelli AE. Methods of purification of CTL-derived exosomes. Methods Mol Biol 2014;1186:87–102.
28. Rog T, Orlowski A, Llorente A, et al. Interdigitation of long-chain sphingomyelin induces coupling of membrane leaflets in a cholesterol dependent manner. Biochim Biophys Acta 2016;1858:281–8.
29. Simbari F, McCaskill J, Coakley G, et al. Plasmalogen enrichment in exosomes secreted by a nematode parasite versus those derived from its mouse host: implications for exosome stability and biology. J Extracell Vesicles 2016;5:30741.
30. Zhou Q, Rahimian A, Son K, Shin DS, Patel T, Revzin A. Development of an aptasensor for electrochemical detection of exosomes. Methods 2016;97:88–93.
31. Oliveira-Rodriguez M, Lopez-Cobo S, Reyburn HT, et al. Development of a rapid lateral flow immunoassay test for detection of exosomes previously enriched from cell culture medium and body fluids. J Extracell Vesicles 2016;5:31803.
32. Lai X, Wang M, McElyea SD, Sherman S, House M, Korc M. A microRNA signature in circulating exosomes is superior to exosomal glypican-1 levels for diagnosing pancreatic cancer. Cancer Lett 2017;393:86–93.
33. Mead B, Tomarev S. Bone marrow-derived mesenchymal stem cells-derived exosomes promote survival of retinal ganglion cells through miRNA-dependent mechanisms. Stem Cells Transl Med 2017;6:1273–85.
34. Li J, Chen Y, Guo X, et al. GPC1 exosome and its regulatory miRNAs are specific markers for the detection and target therapy of colorectal cancer. J Cell Mol Med 2017;21:838–47.
35. Teng Y, Ren Y, Hu X, et al. MVP-mediated exosomal sorting of miR-193a promotes colon cancer progression. Nat Commun 2017;8:14448.
36. Lim JH, Song MK, Cho Y, Kim W, Han SO, Ryu JC. Comparative analysis of microRNA and mRNA expression profiles in cells and exosomes under toluene exposure. Toxicol In Vitro 2017;41:92–101.
37. Beltrami C, Besnier M, Shantikumar S, et al. Human pericardial fluid contains exosomes enriched with cardiovascular-expressed MicroRNAs and promotes therapeutic angiogenesis. Mol Ther 2017;25:679–93.
38. Yu X, Odenthal M, Fries JW. Exosomes as miRNA carriers: formation-function-future. Int J Mol Sci 2016;17.
39. Khoontawad J, Pairojku C, Rucksaken R, et al. Differential protein expression marks the transition from infection with *Opisthorchis viverrini* to cholangiocarcinoma. Mol Cell Proteomics 2017;16:911–23.
40. Cao XY, Lu JM, Zhao ZQ, et al. MicroRNA biomarkers of Parkinson's disease in serum exosome-like microvesicles. Neurosci Lett 2017;644:94–9.
41. Cho YE, Kim SH, Lee BH, Baek MC. Circulating plasma and exosomal microRNAs as indicators of drug-induced organ injury in rodent models. Biomol Ther (Seoul) 2017;25:367–73.
42. Panich T, Chancharoenthana W, Somparn P, Issara-Amphorn J, Hirankarn N, Leelahavanichkul A. Urinary exosomal activating transcriptional factor 3 as the early diagnostic biomarker for sepsis-induced acute kidney injury. BMC Nephrol 2017;18:10.
43. Rong L, Li R, Li S, Luo R. Immunosuppression of breast cancer cells mediated by transforming growth factor-beta in exosomes from cancer cells. Oncol Lett 2016;11:500–4.
44. Hu Y, Li D, Wu A, et al. TWEAK-stimulated macrophages inhibit metastasis of epithelial ovarian cancer via exosomal shuttling of microRNA. Cancer Lett 2017;393:60–7.
45. Min H, Sun X, Yang X, et al. Exosomes derived from irradiated esophageal carcinoma-infiltrating T cells promote metastasis by inducing the epithelial-mesenchymal transition in esophageal cancer cells. Pathol Oncol Res 2018;24:11–8.

46. Momen-Heravi F, Bala S, Kodys K, Szabo G. Exosomes derived from alcohol-treated hepatocytes horizontally transfer liver specific miRNA-122 and sensitize monocytes to LPS. Sci Rep 2015;5:9991.
47. Sukma Dewi I, Celik S, Karlsson A, et al. Exosomal miR-142-3p is increased during cardiac allograft rejection and augments vascular permeability through down-regulation of endothelial RAB11FIP2 expression. Cardiovasc Res 2017;113:440–52.
48. Ellwanger JH, Crovella S, Dos Reis EC, Pontillo A, Chies JA. Exosomes are possibly used as a tool of immune regulation during the dendritic cell-based immune therapy against HIV-I. Med Hypotheses 2016;95:67–70.
49. Toh WS, Lai RC, Hui JH, Lim SK. MSC exosome as a cell-free MSC therapy for cartilage regeneration: implications for osteoarthritis treatment. Semin Cell Dev Biol 2017;67: 56–64.
50. Prathipati P, Nandi SS, Mishra PK. Stem cell-derived exosomes, autophagy, extracellular matrix turnover, and miRNAs in cardiac regeneration during stem cell therapy. Stem Cell Rev 2017;13:79–91.
51. Pashoutan Sarvar D, Shamsasenjan K, Akbarzadehlaleh P. Mesenchymal stem cell-derived exosomes: new opportunity in cell-free therapy. Adv Pharm Bull 2016;6:293–9.
52. Liu S, Liu D, Chen C, et al. MSC transplantation improves osteopenia via epigenetic regulation of notch signaling in lupus. Cell Metab 2015;22:606–18.
53. Tan SS, Yin Y, Lee T, et al. Therapeutic MSC exosomes are derived from lipid raft microdomains in the plasma membrane. J Extracell Vesicles 2013;2.
54. Park S, Choi Y, Jung N, et al. Myogenic differentiation potential of human tonsil-derived mesenchymal stem cells and their potential for use to promote skeletal muscle regeneration. Int J Mol Med 2016;37:1209–20.
55. Iwai S, Sakonju I, Okano S, et al. Impact of ex vivo administration of mesenchymal stem cells on the function of kidney grafts from cardiac death donors in rat. Transplant Proc 2014;46:1578–84.
56. Merino A, Ripoll E, de Ramon L, et al. The timing of immunomodulation induced by mesenchymal stromal cells determines the outcome of the graft in experimental renal allotransplantation. Cell Transplant 2017;26:1017–30.
57. Aharon A, Tamari T, Brenner B. Monocyte-derived microparticles and exosomes induce procoagulant and apoptotic effects on endothelial cells. Thromb Haemost 2008;100:878–85.
58. Li F, Wang Y, Lin L, et al. Mast cell-derived exosomes promote Th2 cell differentiation via OX40L-OX40 ligation. J Immunol Res 2016;2016:3623898.
59. Liu H, Gao W, Yuan J, et al. Exosomes derived from dendritic cells improve cardiac function via activation of CD4(+) T lymphocytes after myocardial infarction. J Mol Cell Cardiol 2016;91:123–33.
60. Ji Q, Ji Y, Peng J, et al. Increased brain-specific MiR-9 and MiR-124 in the serum exosomes of acute ischemic stroke patients. PLoS ONE 2016;11:e0163645.
61. Frohlich D, Kuo WP, Fruhbeis C, et al. Multifaceted effects of oligodendroglial exosomes on neurons: impact on neuronal firing rate, signal transduction and gene regulation. Philos Trans R Soc Lond B Biol Sci 2014;369.
62. Xin H, Li Y, Buller B, et al. Exosome-mediated transfer of miR-133b from multipotent mesenchymal stromal cells to neural cells contributes to neurite outgrowth. Stem Cells 2012;30:1556–64.
63. Takeda YS, Xu Q. Neuronal differentiation of human mesenchymal stem cells using exosomes derived from differentiating neuronal cells. PLoS ONE 2015;10:e0135111.
64. Zhang Y, Chopp M, Zhang ZG, et al. Systemic administration of cell-free exosomes generated by human bone marrow derived mesenchymal stem cells cultured under 2D and 3D conditions improves functional recovery in rats after traumatic brain injury. Neurochem Int 2017;111:69–81.
65. Zhang Y, Chopp M, Liu XS, et al. Exosomes derived from mesenchymal stromal cells promote axonal growth of cortical neurons. Mol Neurobiol 2017;54:2659–73.
66. El Bassit G, Patel RS, Carter G, et al. MALAT1 in human adipose stem cells modulates survival and alternative splicing of PKCdeltaII in HT22 cells. Endocrinology 2017;158:183–95. en20161819.
67. Lopez-Verrilli MA, Picou F, Court FA. Schwann cell-derived exosomes enhance axonal regeneration in the peripheral nervous system. Glia 2013;61:1795–806.
68. Goncalves MB, Malmqvist T, Clarke E, et al. Neuronal RARbeta signaling modulates PTEN activity directly in neurons and via exosome transfer in astrocytes to prevent glial scar formation and induce spinal cord regeneration. J Neurosci 2015;35:15731–45.
69. Ibrahim AG, Cheng K, Marban E. Exosomes as critical agents of cardiac regeneration triggered by cell therapy. Stem Cell Reports 2014;2:606–19.
70. Teng X, Chen L, Chen W, Yang J, Yang Z, Shen Z. Mesenchymal stem cell-derived exosomes improve the microenvironment of infarcted myocardium contributing to angiogenesis and anti-inflammation. Cell Physiol Biochem 2015;37:2415–24.
71. Zhang Z, Yang J, Yan W, Li Y, Shen Z, Asahara T. Pretreatment of cardiac stem cells with exosomes derived from mesenchymal stem cells enhances myocardial repair. J Am Heart Assoc 2016;5.
72. Khan M, Nickoloff E, Abramova T, et al. Embryonic stem cell-derived exosomes promote endogenous repair mechanisms and enhance cardiac function following myocardial infarction. Circ Res 2015;117:52–64.
73. Zhao Y, Sun X, Cao W, et al. Exosomes derived from human umbilical cord mesenchymal stem cells relieve acute myocardial ischemic injury. Stem Cells Int 2015;2015:761643.
74. Vicencio JM, Yellon DM, Sivaraman V, et al. Plasma exosomes protect the myocardium from ischemia-reperfusion injury. J Am Coll Cardiol 2015;65:1525–36.
75. Agarwal U, George A, Bhutani S, et al. Experimental, systems, and computational approaches to understanding the MicroRNA-mediated reparative potential of cardiac progenitor cell-derived exosomes from pediatric patients. Circ Res 2017;120:701–12.
76. Momen-Heravi F, Saha B, Kodys K, Catalano D, Satishchandran A, Szabo G. Increased number of circulating exosomes and their microRNA cargos are potential novel biomarkers in alcoholic hepatitis. J Transl Med 2015;13:261.
77. Thulin P, Hornby RJ, Auli M, et al. A longitudinal assessment of miR-122 and GLDH as biomarkers of drug-induced liver injury in the rat. Biomarkers 2016;1–9.
78. Povero D, Eguchi A, Li H, et al. Circulating extracellular vesicles with specific proteome and liver microRNAs are potential biomarkers for liver injury in experimental fatty liver disease. PLoS ONE 2014;9:e113651.
79. Nojima H, Freeman CM, Schuster RM, et al. Hepatocyte exosomes mediate liver repair and regeneration via sphingosine-1-phosphate. J Hepatol 2016;64:60–8.
80. Tan CY, Lai RC, Wong W, Dan YY, Lim SK, Ho HK. Mesenchymal stem cell-derived exosomes promote hepatic regeneration in drug-induced liver injury models. Stem Cell Res Ther 2014;5:76.

81. Yan Y, Jiang W, Tan Y, et al. hucMSC exosome-derived GPX1 is required for the recovery of hepatic oxidant injury. Mol Ther 2017;25:465–79.
82. Nong K, Wang W, Niu X, et al. Hepatoprotective effect of exosomes from human-induced pluripotent stem cell-derived mesenchymal stromal cells against hepatic ischemia-reperfusion injury in rats. Cytotherapy 2016;18:1548–59.
83. Tomasoni S, Longaretti L, Rota C, et al. Transfer of growth factor receptor mRNA via exosomes unravels the regenerative effect of mesenchymal stem cells. Stem Cells Dev 2013;22:772–80.
84. Zhou Y, Xu H, Xu W, et al. Exosomes released by human umbilical cord mesenchymal stem cells protect against cisplatin-induced renal oxidative stress and apoptosis in vivo and in vitro. Stem Cell Res Ther 2013;4:34.
85. Borges FT, Melo SA, Ozdemir BC, et al. TGF-beta1-containing exosomes from injured epithelial cells activate fibroblasts to initiate tissue regenerative responses and fibrosis. J Am Soc Nephrol 2013;24:385–92.
86. Burger D, Vinas JL, Akbari S, et al. Human endothelial colony-forming cells protect against acute kidney injury: role of exosomes. Am J Pathol 2015;185:2309–23.
87. Vinas JL, Burger D, Zimpelmann J, et al. Transfer of microRNA-486-5p from human endothelial colony forming cell-derived exosomes reduces ischemic kidney injury. Kidney Int 2016;90:1238–50.
88. Wang B, Yao K, Huuskes BM, et al. Mesenchymal stem cells deliver exogenous MicroRNA-let7c via exosomes to attenuate renal fibrosis. Mol Ther 2016;24:1290–301.
89. Jiang ZZ, Liu YM, Niu X, et al. Exosomes secreted by human urine-derived stem cells could prevent kidney complications from type I diabetes in rats. Stem Cell Res Ther 2016;7:24.
90. Salem KZ, Moschetta M, Sacco A, et al. Exosomes in tumor angiogenesis. Methods Mol Biol 2016;1464:25–34.
91. Wang Z, Chen JQ, Liu JL, Tian L. Exosomes in tumor microenvironment: novel transporters and biomarkers. J Transl Med 2016;14:297.
92. Gopal SK, Greening DW, Rai A, et al. Extracellular vesicles: their role in cancer biology and epithelial-mesenchymal transition. Biochem J 2017;474:21–45.
93. Liang X, Zhang L, Wang S, Han Q, Zhao RC. Exosomes secreted by mesenchymal stem cells promote endothelial cell angiogenesis by transferring miR-125a. J Cell Sci 2016;129:2182–9.
94. Yuan H, Guan J, Zhang J, Zhang R, Li M. Exosomes secreted by human urine-derived stem cells accelerate skin wound healing by promoting angiogenesis in rat. Cell Biol Int 2016;doi:10.1002/cbin.10615.
95. Li X, Liu L, Yang J, et al. Exosome derived from human umbilical cord mesenchymal stem cell mediates MiR-181c attenuating burn-induced excessive inflammation. EBioMedicine 2016;8:72–82.
96. Burns C, Hall ST, Smith R, Blackwell C. Cytokine levels in late pregnancy: are female infants better protected against inflammation? Front Immunol 2015;6:318.
97. Guo SX, Jin YY, Fang Q, et al. Beneficial effects of hydrogen-rich saline on early burn-wound progression in rats. PLoS ONE 2015;10:e0124897.
98. Zhao B, Zhang Y, Han S, et al. Exosomes derived from human amniotic epithelial cells accelerate wound healing and inhibit scar formation. J Mol Histol 2017;48:121–32.
99. Zhao B, Wu GF, Zhang YJ, et al. [Effects of human amniotic epithelial stem cells-derived exosomes on healing of wound with full-thickness skin defect in rats]. Zhonghua Shao Shang Za Zhi 2017;33:18–23.
100. Zhang J, Chen C, Hu B, et al. Exosomes derived from human endothelial progenitor cells accelerate cutaneous wound healing by promoting angiogenesis through Erk1/2 signaling. Int J Biol Sci 2016;12:1472–87.
101. Guo SC, Tao SC, Yin WJ, Qi X, Yuan T, Zhang CQ. Exosomes derived from platelet-rich plasma promote the re-epithelization of chronic cutaneous wounds via activation of YAP in a diabetic rat model. Theranostics 2017;7:81–96.
102. Pu CM, Liu CW, Liang CJ, et al. Adipose-derived stem cells protect skin flaps against ischemia/reperfusion injury via interleukin-6 expression. J Invest Dermatol 2017;137:1353–62.
103. Han KY, Tran JA, Chang JH, Azar DT, Zieske JD. Potential role of corneal epithelial cell-derived exosomes in corneal wound healing and neovascularization. Sci Rep 2017;7:40548.
104. Zhang B, Wu X, Zhang X, et al. Human umbilical cord mesenchymal stem cell exosomes enhance angiogenesis through the Wnt4/beta-catenin pathway. Stem Cells Transl Med 2015;4:513–22.
105. Zhang J, Liu X, Li H, et al. Exosomes/tricalcium phosphate combination scaffolds can enhance bone regeneration by activating the PI3K/Akt signaling pathway. Stem Cell Res Ther 2016;7:136.
106. Qi X, Zhang J, Yuan H, et al. Exosomes secreted by human-induced pluripotent stem cell-derived mesenchymal stem cells repair critical-sized bone defects through enhanced angiogenesis and osteogenesis in osteoporotic rats. Int J Biol Sci 2016;12:836–49.
107. Zhang S, Chu WC, Lai RC, Lim SK, Hui JH, Toh WS. Exosomes derived from human embryonic mesenchymal stem cells promote osteochondral regeneration. Osteoarthritis Cartilage 2016;24:2135–40.
108. Zhu Y, Wang Y, Zhao B, et al. Comparison of exosomes secreted by induced pluripotent stem cell-derived mesenchymal stem cells and synovial membrane-derived mesenchymal stem cells for the treatment of osteoarthritis. Stem Cell Res Ther 2017;8:64.
109. Nakamura Y, Miyaki S, Ishitobi H, et al. Mesenchymal-stem-cell-derived exosomes accelerate skeletal muscle regeneration. FEBS Lett 2015;589:1257–65.
110. Choi JS, Yoon HI, Lee KS, et al. Exosomes from differentiating human skeletal muscle cells trigger myogenesis of stem cells and provide biochemical cues for skeletal muscle regeneration. J Control Release 2016;222:107–15.
111. Huang CC, Narayanan R, Alapati S, Ravindran S. Exosomes as biomimetic tools for stem cell differentiation: applications in dental pulp tissue regeneration. Biomaterials 2016;111:103–15.
112. Ellis C, Ramzy A, Kieffer TJ. Regenerative medicine and cell-based approaches to restore pancreatic function. Nat Rev Gastroenterol Hepatol 2017;14:612–28.
113. Oh K, Kim SR, Kim DK, et al. In vivo differentiation of therapeutic insulin-producing cells from bone marrow cells via extracellular vesicle-mimetic nanovesicles. ACS Nano 2015;9:11718–27.
114. Mikamori M, Yamada D, Eguchi H, et al. MicroRNA-155 controls exosome synthesis and promotes gemcitabine resistance in pancreatic ductal adenocarcinoma. Sci Rep 2017;7:42339.
115. Rayner S, Bruhn S, Vallhov H, Andersson A, Billmyre RB, Scheynius A. Identification of small RNAs in extracellular vesicles from the commensal yeast *Malassezia sympodialis*. Sci Rep 2017;7:39742.
116. Jiang J, Kao CY, Papoutsakis ET. How do megakaryocytic microparticles target and deliver cargo to alter the fate of hematopoietic stem cells? J Control Release 2017;247:1–18.
117. Sun D, Zhuang X, Xiang X, et al. A novel nanoparticle drug delivery system: the anti-inflammatory activity of curcumin is

enhanced when encapsulated in exosomes. Mol Ther 2010;18:1606–14.
118. Ohno SI, Takanashi M, Sudo K, et al. Systemically injected exosomes targeted to EGFR deliver antitumor MicroRNA to breast cancer cells. Mol Ther 2013;21:185–91.
119. Huang Z, Feng Y. Exosomes derived from hypoxic colorectal cancer cells promotes angiogenesis through Wnt4 induced beta-catenin signaling in endothelial cells. Oncol Res 2016;25:651–61.
120. Ti D, Hao H, Tong C, et al. LPS-preconditioned mesenchymal stromal cells modify macrophage polarization for resolution of chronic inflammation via exosome-shuttled let-7b. J Transl Med 2015;13:308.
121. Zhuang X, Xiang X, Grizzle W, et al. Treatment of brain inflammatory diseases by delivering exosome encapsulated anti-inflammatory drugs from the nasal region to the brain. Mol Ther 2011;19:1769–79.
122. Alvarez-Erviti L, Seow Y, Yin H, Betts C, Lakhal S, Wood MJ. Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. Nat Biotechnol 2011;29:341–5.
123. de Rivero Vaccari JP, Brand F 3rd, Adamczak S, et al. Exosome-mediated inflammasome signaling after central nervous system injury. J Neurochem 2016;136(suppl 1):39–48.
124. Kowal J, Arras G, Colombo M, et al. Proteomic comparison defines novel markers to characterize heterogeneous populations of extracellular vesicle subtypes. Proc Natl Acad Sci USA 2016;113:E968–77.
125. Santana SM, Antonyak MA, Cerione RA, Kirby BJ. Microfluidic isolation of cancer-cell-derived microvesicles from heterogeneous extracellular shed vesicle populations. Biomed Microdevices 2014;16:869–77.
126. Garcia NA, Ontoria-Oviedo I, Gonzalez-King H, Diez-Juan A, Sepulveda P. Glucose starvation in cardiomyocytes enhances exosome secretion and promotes angiogenesis in endothelial cells. PLoS ONE 2015;10:e0138849.
127. Ramakrishnaiah V, Thumann C, Fofana I, et al. Exosome-mediated transmission of hepatitis C virus between human hepatoma Huh7.5 cells. Proc Natl Acad Sci USA 2013;110:13109–13.