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Narrative Review

Cell-Derived Exosomes as Therapeutic Strategies: Investigating the Effect of Exosomes Derived from Various Types of Cells, Especially Nerve Cells, on Survival and Neuronal Differentiation

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Abstract

Nervous and brain cells injury is a complex, life-threatening condition that causes mortality and disability worldwide. No effective treatment has been clinically verified to date. Achieving effective drug delivery across the blood–brain barrier (BBB) presents a major challenge to therapeutic drug development for nervous and brain cells injury. Furthermore, the field of nerve damage biomarkers is rapidly developing to cope with the many aspects of pathology and enhance clinical management of this type of damage. Exosomes appear to be effective inter-cellular communicators delivering several types of molecules, such as proteins and RNAs, suggesting that they could influence types of stem cells differentiation. Exosomes are endogenous extracellular vehicles (EVs) containing various biological materials, including lipids, proteins, microRNAs, and other nucleic acids. Compelling evidence exists that Exos, such as stem cell-derived Exos and even neuron or glial cell-derived Exos, are promising treatment strategies for Nervous cells injury because they pass through the BBB and have the potential to deliver molecules to target lesions. Meanwhile, Exos have Fewer safety risks compared to intravenous injection or orthotopic transplantation of viable cells, such as microvascular occlusion or imbalanced growth of transplanted cells. These unique characteristics also make Exos contents, especially Exos-derived microRNAs, as appealing biomarkers in nervous and brain cells injury. In this review, we explore the potential impact of cell-derived Exos and exosome-derived contents on the diagnosis, therapy, and prognosis prediction of nerve damage. The associated challenges and opportunities are also discussed.

Keywords: Exosome, Nerve Cell, Differentiation

Introduction

Exosomes are a large component of the broader class of nanoparticles called extracellular vehicles (EVs).[1] Small extracellular vesicles containing transferrin receptors were first reported in 1983 by Johnstone and colleagues while culturing reticulocytes.[2] These vesicles were then named as "exosomes" by Johnstone in 1987.[3] With more studies conducted, now exosomes are generally accepted as small, cell-derived, single-membrane vesicles (30-150 nm) released by almost all types of cells into extracellular space via fusing plasma membrane and multivesicular bodies (MVBs).[4] Contents embedded in exosomes include nucleic acids, proteins, lipids, amino acids, metabolites, glycoconjugates, cytosolic and cell-membrane proteins.[5] Via releasing these contents to neighboring cells, as a form of paracrine signaling, and/or to distant cells, acting as a type of endocrine signaling, exosomes are able to regulate cell-to-cell communications and multiple autocrine and paracrine cellular phenotypes.[6]

The central nervous system is one of the most important systems, which coordinates and maintains the homeostasis of the human body. Exosomes are secreted by all cells in the brain, including neurons, and have been hypothesized to play a critical role in cell–cell communication.[7,8] Exosomes can signal over short range within brain tissue,[9] and can signal widely throughout the brain through the cerebrospinal fluid.[10,11] Strong evidence indicates that exosomes

impart biological activity to neurons.[9,12] For instance, in the Drosophila larval neuromuscular junction, exosome-mediated protein transport is required for coordinated development of pre- and postsynaptic components of the neuromuscular junction.[13,14] Exosomes secreted by oligodendrocytes affect firing rate, signaling pathways, and gene expression in cultured primary neurons.[15,16] Although there is evidence of biological roles of exosomes secreted by neurons and other cell types in the brain, the potential function of exosomes in neural circuit development is unclear. Research has shown that exosomes play a profound role in neural circuit development, leading to enhanced neural progenitor proliferation, neuronal differentiation, neurogenesis, synaptogenesis, and circuit connectivity.

It has been reported that exosomes can be found in both adult and embryonic animal CSF.[17,18] Exosomes play an important role in synchronizing the intercellular communication between the glia and neurons.[19] Exosome-mediated interactions between neurons and the glia induce neurite outgrowth, which supports the survival of neurons.[20,21] MSC-derived exosomes containing miRNA-133b support the induction of neurite outgrowth and survival of neurons.[22] The exosome-mediated transfer of miRNAs in neuron-to-astrocyte signaling has been shown recently. Exosomes isolated from the neuronal conditioned medium contain abundant miRNAs and small RNAs. These exosomes can be directly internalized into astrocytes and increase astrocyte miRNA-124a and GLT1 protein levels, indicating that cell-to-cell interaction and/or communication within the central nervous system is also due to exosomes.[23]

Exosomes are secreted by many cell types and cell lines, including mast cells, B lymphocyte cell lines, dendritic cells, stem cells, endothelial cells, smooth muscle cells, neuronal cells, and cancer cells.[24] Exosomes are released from viable cells or diseased cell types either constitutively or upon activation into interstitial spaces as well as into body fluids. Interestingly, these exosomes are also released from cells *in vitro*.[25] Studies have also shown that exosomes can be used as a cell-free vaccine for various diseases.[26] Recently, the role of exosomes has been well documented both in normal physiological conditions such as lactation, immune response, and neuronal function and in pathophysiological conditions such as development and progression of liver diseases, neurodegenerative diseases, and cancer.[27] Based on the cell origin, exosomes attribute morphogen transporters in the creation of polarity during development and differentiation.[28] Predictable and reliable induction of lineage specific differentiation of stem cells is one of the key requirements for tissue engineering applications. In many cases, the biomaterial properties and choice of biomaterials are also dependent on this factor. Traditionally, growth factor delivery systems are used for induction of lineage specific differentiation of stem cells. The FDA has approved the use of growth factors such as bone morphogenetic factor 2 (BMP2) for clinical use. However, current clinical applications of growth factors have caused several adverse side effects and ectopic interactions. Many complications have been reported recently from BMP2 usage causing serious safety concerns among clinicians.[29,30] In an effort to develop biomimetic approaches that can circumvent growth factor usage and complex controlled release mechanisms, we explored the possibility of utilizing cell-type specific exosomes. Although these studies show the potential of exosomes for use in regenerative medicine, their ability to induce the differentiation of cells towards nerve cells has not been studied rigorously. Additionally, the effects of using exosomes from nerve cell on the overall biology of the recipient cell needs to be studied. We hypothesized that exosomes isolated from differentiated neural cells could be used to induce lineage specific differentiation of naïve MSCs.

Biogenesis Secretion Process of Exosomes

Exosomes are generated through a continuous process that involves double invagination of the plasma membrane and the formation of intracellular multivesicular bodies (MVBs).[31] Biogenesis of exosomes starts with the de novo formation of early-sorting endosomes (ESEs). At start, cell membrane invaginates and forms a cup-shaped structure that contains cell surface proteins and extracellular components, such as soluble proteins, lipids, metabolites, small molecules, and ions.[32] Then ESEs take shape and subsequently either fuse with the endoplasmic reticulum (ER), trans-Golgi network (TGN) or a preexisting ESE. ESEs next mature into late sorting endosomes (LSEs).[33] The second invagination in LSEs leads to the production of intraluminal vesicles (ILVs), which can further modify the load of future exosomes and allow cytoplasmic

components to enter the newly formed ILVs. LSEs are further transformed into multivesicular bodies (MVBs), which can be degraded by fusion with lysosomes or auto phagosomes, or they can be fused with plasma membrane to release ILVs as exosomes.[34] Exosomes are released by cells either as a reaction to specific stimuli, or under normal physiological conditions.[35] Released exosomes function as carriers of molecular information to transfer cargo molecules from parent to recipient cells and regulate cell-to-cell communications involving in physiological and pathological processes[36] (Figure 1).[37]

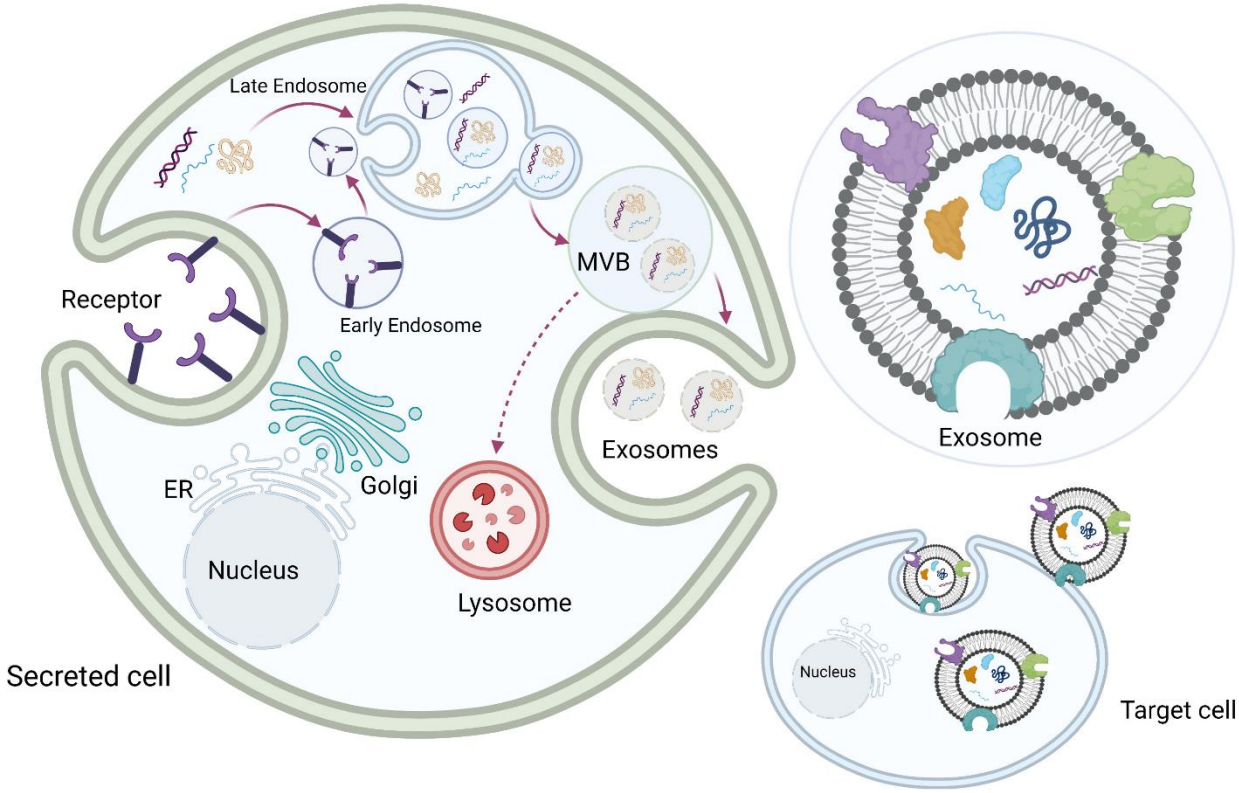

Figure 1. Exosome Biogenesis. Invagination of the cellular plasma membrane to generate early endosomes is the first step in the biogenesis of exosomes. After that, early endosomes develop into late endosomes, and the endosome membrane invaginates to create numerous intraluminal vesicles inside the endosome that eventually form a multivesicular body (MVB). (with courtesy to R. Harati et al.)[37]

Molecular Compositions of Exosomes

Exosomes carry a unique cargo of proteins, lipids, and RNAs that can be distinct, and reflect the cell of origin. However, exosomes from different cellular origins share some common characteristics, such as lipid bilayer, which has an exceptionally high cholesterol /phospholipid ratio, their size and density, and basic compositions of lipid and protein. The different protein compositions of exosomes have their specific roles: Annexin and flotillin are important for transport and fusion; tetraspanins are involved in cell targeting; and other proteins, such as Alix and TSG101, are involved in their biogenesis from multivesicular bodies. In addition, some protein kinases and heterotrimeric G-proteins are implicated in signaling transduction and lipid metabolism.[38] Exosome proteins also include those derived from the cytoplasm or membrane-bound proteins. Proteomic analyses have revealed the presence of structural components: (i) extracellular matrix and cell surface proteins, such as collagens, integrins, and galectin; (ii) cell surface receptors such as platelet-derived growth factor receptor B and epidermal growth factor receptor; and (iii) intracellular cytoskeletal components, including signaling molecules, metabolic enzymes and G-proteins.[39,40] Importantly, the lipid compositions of exosomes are enriched in cholesterol, ceramide, phosphoglycerides, and long and saturated fatty-acyl chains, because all of these compositions could provide structural stability for exosomes.[41] In addition,

prostaglandins that are bound to the exosomal membrane for delivery to target cells can potentially enhance their biological activities.[42] It is increasingly recognized that RNA, especially microRNAs, contained in exosomes are the important signaling messengers that can be transferred between cells.[43] MicroRNAs released within exosomes, as a subset of the cellular RNA, can be unique or tissue specific.[44] In addition, many exosomes contain major histocompatibility complex class I and class II molecules that are involved in antigen binding and presentation.[45,46] It is important to note that proteins like integrins and annexins as compositions of exosomes play important roles in cell adhesion to recipient cells, as do tetraspanins, which can direct targeting to specific cells such as endothelial cells to promote angiogenesis and vasculogenesis.[47] The long-range targeting and tissue uptake of exosomes and their stability in the circulation or in other biological fluids make exosomes attractive as a biomarker as well as a therapeutic vehicle in the treatment of various diseases.

Neuroprotective Effects of Exosomes

Exosomes are parts of those vesicle-producing cells. Quantity and contents of exosomes reflect the state of their cells of origin. Besides, exosomes provide a mechanism by which cells can manipulate the molecular composition and function of extracellular matrix (ECM).[48] In addition, exosomes transmit signals and molecules via a pathway of intercellular vesicle traffic, exerting local paracrine or distal systemic effects.[49] Exosome-mediated responses can be either disease promoting or restraining, depending on the composition and cell state. Furthermore, engineered exosomes can deliver diverse therapeutic payloads, including short interfering RNAs, antisense oligonucleotides, chemotherapeutic agents, and immune modulators.[50] The biological functions of exosomes span a large swath of biology. Exosomes released by neurons, glia and other cells in CNS contribute to the complex network of interconnected messages that underlie both the physiology and the pathology of this system.[51] Protective mechanisms of exosomes in CNS physiology include angiogenesis promotion, immune regulation, inhibiting the apoptosis of neurons and promoting the formation of myelin sheath and axon growth.[52]

In addition to promoting angiogenesis, exosomes also exhibited neuroprotective effects to reduce the damage caused by ischemia via other mechanisms.[53] Doeppner et al.[54] showed that exosomes derived from MSC exhibit the same neuroprotective effects as the derived MSCs. In addition, EV injection avoided the side effects related to stem cell transplantation, such as abnormal differentiation, immune rejection, and difficulty in operation.[55] Kuang et al. showed that miR-25-3p contained in exosomes produced by adipose-derived MSC exhibited neuroprotective effects by reducing neuron autophagy.[56] In addition to MSCs, exosomes secreted by many other cells also have neuroprotective effects. MiR-137 contained in endothelial progenitor cell-derived exosomes boosts the neuroprotective effect of oxyhemoglobin-treated SH-SY5Y cells partially via COX2/PGE2 pathway.[57] M2 microglia-derived exosome treatment attenuated neuronal apoptosis induced by oxygen–glucose deprivation (OGD). The underlying pathway involved exosomal miR-124 and its downstream target USP14.[58] However, pro-inflammatory exosomes were found to accumulate in rat brains 72 h post focal cerebral ischemia. These exosomes were secreted by activated microglia with high expression of glutaminase 1 (GLS1).[59] Applying exosome secretion inhibitor, GW4869, displayed similar anti-inflammatory effects to that of a glutaminase inhibitor, CB839. This study suggested that GLS1-mediated exosome release may play an important role in the formation of neuroinflammatory microenvironment.[59]

Ischemic preconditioning (IPC) has a protective effect on ischemic brain injury. But the mechanism remains unclear.[60] Studies showed that exosomes derived from OGD preconditioned astrocytes contained an increased level of miR-92b-3p. These exosomes can be taken up by neurons and attenuate OGD-induced neuron death and apoptosis.[61] Similarly, exosomes derived from hypoxic BMSCs were found to reduce rescue OGD-induced injury in neural cells by suppressing NLRP3 inflammasome-mediated pyroptosis and modulating microglial polarization.[62,63] Studies had also shown that ischemic-preconditioned astrocyte-derived exosomes (IPAS-EXOs) contained high level of circSHOC2. This exosome-shuttled circSHOC2 from IPASs protected neurons from autophagy and ameliorated ischemic brain injury via the miR-7670-3p/SIRT1 axis.[64] Moreover, exosomes are crucial in protecting neurons from ischemia–reperfusion injury. Wu et al. showed that astrocyte-derived exosome-transported microRNA-34c was neuroprotective against

cerebral ischemia/reperfusion injury via TLR7 and the NF-κB/MAPK pathways.[65] Mathew et al.'s research on retinal ischemia highlights the potential of MSC-EV as biomaterials for neuroprotective and regenerative therapy in retinal disorders.[66] Their results showed that administration of MSC-EVs into the vitreous humor 24 h after retinal ischemia in a rat model significantly enhanced functional recovery, and decreased neuro-inflammation and apoptosis.[66] *In vitro* experiments have shown that vascular endothelial cell-derived Evs reduced cell apoptosis and promoted neural progenitor cell proliferation after ischemia–reperfusion.[67]

Compared with other stem cells, human-induced pluripotent stem cell-derived neural progenitor cells (iPSC-NPCs) are more similar to cortical neurons in morphology and immunohistochemistry. Thus, they have greater potential for promoting the survival and growth of neurons and alleviating the proliferation of astrocytes. Transplantation of stem cell exosomes and stem cells themselves have both been shown to effectively repair nerve injury. However, there is no study on the protective effects of exosomes derived from iPSC-NPCs on oxygen and glucose deprived neurons.

Lee et al in a study established an oxygen-glucose deprivation model in embryonic cortical neurons of the rat by culturing the neurons in an atmosphere of 95% N2 and 5% CO_2 for 1 hour and then treating them with iPSC-NPC-derived exosomes for 30 minutes. Their results showed that iPSC-NPC-derived exosomes increased the survival of oxygen- and glucose-deprived neurons and the level of brain-derived neurotrophic factor in the culture medium. Additionally, it attenuated oxygen and glucose deprivation-induced changes in the expression of the PTEN/AKT signaling pathway as well as synaptic plasticity-related proteins in the neurons. Further, it increased the length of the longest neurite in the oxygen- and glucose-deprived neurons. These findings validate the hypothesis that exosomes from iPSC-NPCs exhibit a neuroprotective effect on oxygen- and glucose-deprived neurons by regulating the PTEN/AKT signaling pathway and neurite outgrowth.[68]

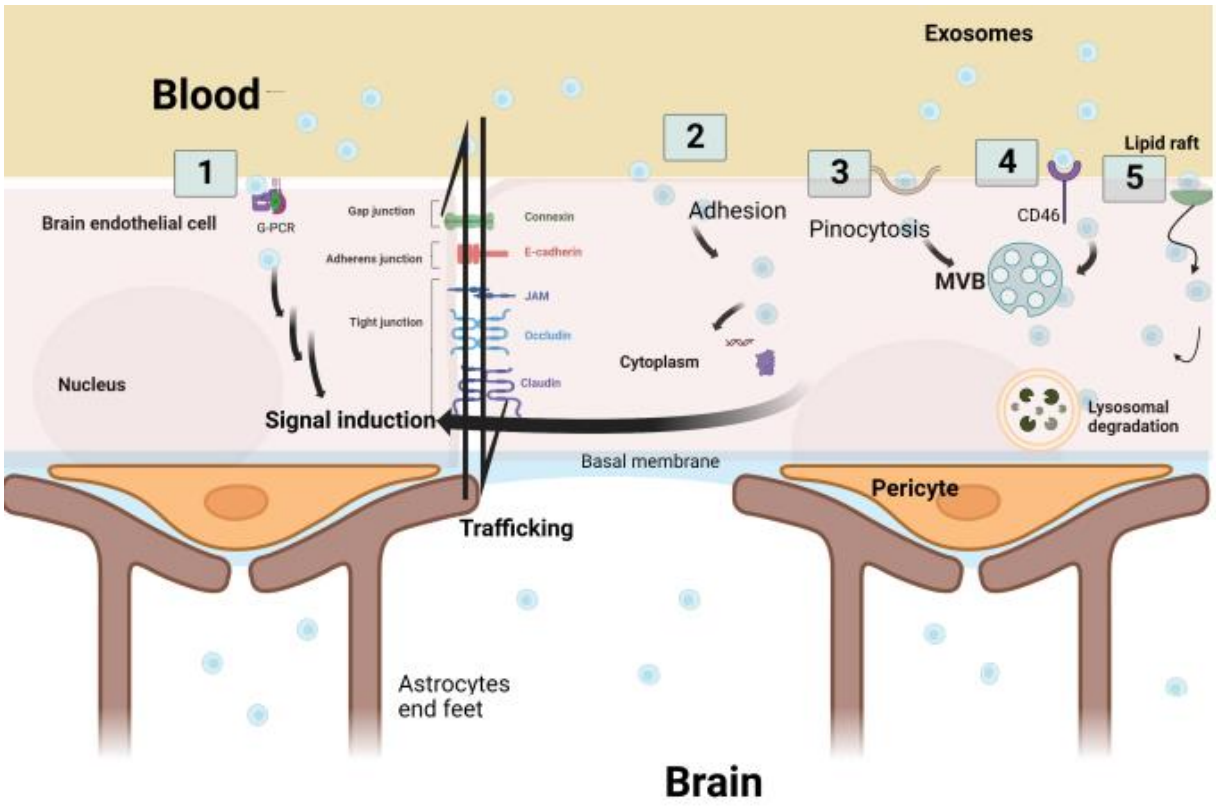

Figure 2. Diagram Showing the Five Potential Pathways for Exosome Transcytosis Across the Endothelium of Blood–Brain Barrier's. (1) Blood exosomes attach to the brain endothelium's G-protein coupled receptor (GPCR) to initiate downstream signaling cascade pathways. (2) Exosome cargo is secreted into the cytoplasm to trigger signal cascades after adhering to and fusing through the endothelial cell membrane. (3) Incorporation of exosomes into cells occurs through inverse membrane invagination. (4) Blood exosomes attach to receptors such CD46, allowing the exosomes to enter the cell. (5) A non-specific lipid raft that binds to exosomes and facilitates their integration. (with courtesy to R. Harati et al.)[37]

Exosome Transport across the Brain-Blood Barrier

Successfully delivering therapeutic agents to the brain is difficult because of the blood-brain barrier (BBB), which is a highly selective membrane separating the brain's extracellular fluid from circulating blood. Treating neurological diseases is notoriously difficult due to the barrier's stringent selectivity. Over 98% of small-molecule drugs and nearly 100% of large-molecule drugs, such as peptides, recombinant proteins, monoclonal antibodies, genes, and short interfering RNAs (siRNAs), are unable to pass through the BBB.[69] Exosomes have recently become a promising way for delivering therapeutics across the BBB, offering hope for treating Alzheimer's, Parkinson's, epilepsy, mental disorders, and more.[70] The BBB relies on different mechanisms to facilitate compound movement across the brain and to prevent the entry of harmful substances, which is essential for proper neuronal function.[71] Tight junctions between endothelial cells limit passive diffusion of water-soluble agents across the BBB, but O_2 and CO_2 can diffuse freely. Since bases are cationic, they interact with the negatively charged head groups of phospholipids more readily than acids can, allowing lipid-soluble molecules to diffuse more effectively through the BBB than in compounds with polar surfaces.[70,71] Via receptor- or adsorptive-mediated transcytosis pathways, high molecular weight substances like peptides and proteins can pass through the blood-brain barrier (BBB) (Figure 2).[37]

Exosomes and Neurogenesis

Exosomes deliver functional proteins and genetic materials to neighboring cells, and have potential applications for tissue regeneration. One possible mechanism of exosome-promoted tissue regeneration is through the delivery of microRNA.[72,73] In a study by Mu et al., they hypothesized that exosomes derived from neuronal progenitor cells contain miRNAs that promote neuronal differentiation. They treated mesenchymal stem cells (MSCs) daily with exosomes derived from PC12 cells, a neuronal cell line, for 1 week. After the treatment with PC12-derived exosomes, MSCs developed neuron-like morphology; and gene and protein expressions of neuronal markers were upregulated. Microarray analysis showed that the expression of miR-125b, which is known to play a role in neuronal differentiation of stem cells, was much higher in PC12-derived exosomes than in exosomes from B16-F10 melanoma cells. These results suggest that the delivery of miRNAs contained in PC12-derived exosomes is a possible mechanism explaining the neuronal differentiation of MSC.[74]

Axonal regeneration in the peripheral nervous system is greatly supported by Schwann cells (SCs). After nerve injury, SCs dedifferentiate to a progenitor-like state and efficiently guide axons to their original target tissues. Contact and soluble factors participate in the crosstalk between SCs and axons during axonal regeneration. Lopez et al.[75] showed that dedifferentiated SCs secrete nano-vesicles known as exosomes which are specifically internalized by axons. Surprisingly, SC-derived exosomes markedly increase axonal regeneration in vitro and enhance regeneration after sciatic nerve injury in vivo. Exosomes shift the growth cone morphology to a pro-regenerating phenotype and decrease the activity of the GTPase RhoA, involved in growth cone collapse and axon retraction. Interestingly, exosome internalization by axons was selective for SCs but not for fibroblast-derived exosomes, probably reflecting the presence of specific molecules on the exosomal surface, allowing their differential recognition by axons. Selective transfer of exosomes has been previously reported. In the CNS, oligodendrocyte-derived exosomes are taken by microglial cells but not by neurons or astrocytes.[76]

Neural stem/progenitor cells (NPCs) are known to have potent therapeutic effects in neurological disorders through secreting exosomes. The limited numbers of NPCs in adult brain and the decline of NPC pool in many neurological disorders restrain the further use of exosomes in treating these diseases. The direct conversion of somatic cells into induced NPCs (iNPCs) provides abundant NPC-like cells to study the therapeutic effects of NPCs-originated exosomes (EXOs).[77] A recent study by Ma et al. demonstrated that iNPCs-derived exosomes (iEXOs) exhibit distinct potential in facilitating the proliferation of NPCs, compared to EXOs, indicating the need importance to investigate the effects of EXOs and iEXOs on the differentiation of NPCs, which remains unknown. Their results suggest that EXOs, but not iEXOs, promoted neuronal differentiation and neither of them had effect on glial generation.[78] The NPCs used in their studies were isolated from mouse cortical tissue at embryonic day 14, when robust neurogenesis takes place in vivo. Although cultured in growth factors-containing medium to promote proliferation, those NPCs retain the innate "developmental program"

which preserves the neurogenic microenvironment by releasing exosomes that promote neuronal differentiation. As gliogenesis generally initiates since the postnatal stage, mouse embryonic NPCs do not release exosomes with high gliogenic potential. It also explains the reason why iEXOs exhibit no potential to facilitate neurogenesis, since this innate "developmental program" is missing. Microarray analysis revealed different miRNA signatures in EXOs and iEXOs, in which miR-21a was highly enriched in EXOs. Perturbation of function assay demonstrated the key roles of miR-21a in the generation of neurons and mediating the neurogenic potential of exosomes. Their data suggest that EXOs and iEXOs may achieve their therapeutic effects in promoting neurogenesis through transferring key miRNAs, which sheds light on the development of highly efficient cell-free therapeutic strategies for treating neurological diseases.[78]

Sharma et al.[79] explored function of exosomes in brain development. They tested whether neural exosomes can regulate the development of neural circuits. They showed that exosome treatment increases proliferation in developing neural cultures and in vivo in dentate gyrus of P4 mouse brain. They compared the protein cargo and signaling bioactivity of exosomes released by hiPSC-derived neural cultures lacking MECP2, a model of the neurodevelopmental disorder Rett syndrome, with exosomes released by isogenic rescue control neural cultures. Quantitative proteomic analysis indicates that control exosomes contain multiple functional signaling networks known to be important for neuronal circuit development. Treating MECP2-knockdown human primary neural cultures with control exosomes rescues deficits in neuronal proliferation, differentiation, synaptogenesis, and synchronized firing, whereas exosomes from MECP2-deficient hiPSC neural cultures lack this capability.[79] These data indicate that exosomes carry signaling information required to regulate neural circuit development.

Role of Exosomes in Parkinson Disease

Exosome treatment has also been proven to rescue dopaminergic neurons in substantia nigra and striatum of Parkinson Disease model mice. According to molecular studies conducted on PD model mice, exosome treatment restores hemostasis of oxidative stress, Neuroinflammation, and apoptosis. The role of exosomes in pathogenesis of PD is two-fold. The first and more widely investigated is their role as mediators of α-synuclein transmission between cells, a molecule whose accumulation is a notable feature of PD pathology. The second role of exosomes in PD pathology is to transport PD-implicated miRNA between cells. These results indicate that exosomes play major roles in PD pathogenesis. They are hence promising targets in PD treatment, as tools for modulation of PD pathology, and perhaps as tools for detection of encapsulated biomarkers.[80] NLM citations–made by hand.

Exosomes in Ageing and Motor Neuron Disease

Exosomes derived from skeletal muscles contribute to the neuroskeletal muscle function and mediate crosstalk between these different cell types. Myoblasts and myotubes have been reported to secrete exosomes, which could play a role in neuronal cell survival, myogenesis, myoblast differentiation, and muscle ageing.[81] There is evidence in multiple studies of crosstalk between myoblast-myotubes mediated by exosomes. Reportedly, C_2C_{12} myotube-derived exosomes decreased myoblast proliferation and induced differentiation, while negatively regulating Sirt1 expression in C_2C_{12} myoblasts.[81]

Furthermore, contribution of exosomes to pathology of Amyotrophic lateral sclerosis (ALS), the most frequent of motor diseases, has been brought to attention. Exosomes' propagation of misfolded proteins and aggregates, as well as their use as prognostic or diagnostic biomarkers in this disease is being increasingly investigated.[81,82]

Role of MSCs-Derived Exosomes in Neuroinflammation and in TBI

Numerous studies have reported the vital role of mesenchymal stem cells (MSCs) in neuroinflammation, neurogenic niches and neurogenesis, and therapeutic strategy of neurological studies. Subsequent to sudden external force trauma, a set of secondary pathological and/or functional alterations occur within the brain, which are referred to as traumatic brain injury (TBI). In the past decade, multiple studies have assessed the potential of MSCs derived from some kinds of multipotent cells by exosomes to act as an effective therapy for brain injury, in both models of TBI, and in clinical practice. Studies have shown that MSCs-derived exosomes can improve functional recovery, ameliorate spatial learning impairments, improve neurovascular remodeling and reduce neuroinflammation in animal models of TBI, although the underlying

mechanisms involved are not yet clear.[83]

Study Limitations

Although the results of previous proof-of-concept studies are very encouraging, it is just a beginning for us to understand the potential of exosomes as a viable therapeutic intervention in neurologic and traumatic brain injuries. Hence, much work should be conducted to take full advantages of MSCs-derived exosomes and support their potential to be a new strategy for the treatment of neurological disease in the future.

Conclusion

Exosomes present a complex composition and strongly contribute to the paracrine effects of stem cells. In regenerative therapies, EVs mimic the beneficial effects of the cells from which they originate, and could represent an important potential therapeutic tool. Therefore, the use of MSC-derived exosomes represents an interesting alternative for nerve cells repair, which may overcome the limitations and risks commonly associated with cell-therapy approaches. Engineering or modification of the EV surface antigen and internal content through preconditioning or engineering parent cells will enable EVs to target other more complex and specific diseases.

Conflict of Interest

The authors declare no conflicts of interest.

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