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Review Article

The Enigmatic Regulators of Central Nervous System Diseases- Extracellular Vesicles Derived from Mesenchymal Stem Cell

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Abstract

Stem cells can spontaneously secret extracellular vesicle (EVs), which containing proteins, lipids, and nucleic acids. EVs have a broad prospect as a treatment of central nervous system (CNS) diseases, the release and uptake of EVs has important physiological functions and may also contribute to the development and propagation of inflammation, vascular, malignant, trauma and neurodegenerative diseases. This review will detail and discuss the characteristics of EVs and the potential challenges and strategies in the treatment of EVs-based therapies for CNS diseases in the future.

Keywords: Stem cells; Central nervous system; Extracellular vesicles; miRNA; Therapy

Introduction

CNS has complex anatomy and communicated with diverse cellular populations to respond to environmental stimuli and their metabolic requests. The diversity of CNS diseases can be caused by multifactor, and the existence of the blood-brain barrier has brought great difficulties to the treatment of CNS diseases. Currently, numerous of research developed to promote neurological recovery, but no drugs on the market is available. Increasing evidence is demonstrating that Mesenchymal stem cells (MSCs) derived EVs (MSCs-EVs) shown the positive effects and that the therapeutic value mainly attributed to the miRNA enriched EVs. This review summarized the characteristics of different components of EVs and the main mechanisms involved therapeutic approaches in CNS diseases, focusing on miRNA enriched MSCs-EVs, elucidating how and why miRNA enriched EVs could provide a unique opportunities in CNS diseases therapy, and discussed their clinical potential, neuro restoration could be a viable treatment strategy.

MSC Derived EVs

MSC

MSCs are usually obtained from adult bone marrow, peripheral blood, adipose tissue, and placenta, bone marrow is the most frequently used source [1,2]. They can promote tissue repair and remodeling through and secretion of cytokines [3-8], which has become a promising alternative strategy in treatment of CNS diseases [9]. However, the application of MSCs in clinical has some drawbacks, such as unstable phenotype, high costs of generation and processing, ectopic tissue formation [10]. In addition, lodged in the pulmonary microvasculature and caused infusion toxicity [11,12], and cellular rejection or unwanted implantation also have been reported recently [13]. In recent years, some scholars have found that MSCs affects tissue repair rather than cell replacement by stimulating tissue cells through paracrine factors [14]. The main aspect of MSCs response to the disease is the secretion of differ functional molecules stored in EVs and play a significant role in cell-to-cell communication, which generate important actions in development, regeneration, angiogenesis, homeostasis, et al. [15-19].

EVs

EVs comprise a large variety of membranous structures released from almost all types of cells. The accumulated historical data and recent research have indicated that the contents, EVs are heterogeneous and dynamic existed in EV's size, content, membrane composition and function, according to their cellular source, physiological status, and most importantly environmental conditions. Increasing research on EVs has increased understanding of their variety and complexity. EVs are lipid bilayer and comprise a heterogeneous population of membrane vesicles, by fusion of multivesicular bodies and the plasma membrane or formed from the direct budding or microvesicles. At present, three main subgroups of EVs have been defined by The International Society of Extracellular Vesicles, and they can be broadly classified based on size or origin: microvesicles (MVs, and exosomes) and apoptotic bodies [20,21]. MVs, which are typically larger in size (ranging from 100 to 1,000 nm) and are formed as the result of the outward budding of the plasma membrane. Exosomes generally representing smallest EVs of 150nm or less. Exosomes generally representing smallest EVs of 150nm or less, and derived from early endosomes by invagination of the recruited membrane, inward budding, and scission. Apoptotic bodies characterized by a

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dimension ranging from 1,000 to 5,000 nm, and that released as blebs from cells undergoing programmed death cell [22-24]. EVs contain various specific molecules, such as, DNA, miRNA, mRNA, long non-coding RNA, lipids, proteins, and genetic materials from viruses or prions, depending on the different cellular origin and the function of putative target [25,26]. The best characterized of EVs were firstly described in the early '80s [27]. Later, a small vesicle was founded in reticulocytes, It has a circular or concave cup shape under the electron microscope with a lipid bilayer structure, small vesicles fuse with the plasma membrane and release their contents to the outside of the cell in the process of exocytosis [28]. This was coined for 40-100 nm vesicles released during reticulocyte differentiation by fusion of multivesicular endosomes (MVEs) with the plasma membrane [29,30]. To unify the nomenclature throughout, we will, therefore, use the term EVs for all types of vesicles in this review.

In the past 20 years, EVs were demonstrated that be produced and released by B lymphocytes and dendritic cells through differential centrifugation and described the role of EVs in antigen presentation *in vivo* and able to induce T cell responses [31,32]. Recently research found that all cell types are able to secrete EVs, including mesenchymal stem cell (MSC) [33], hematopoietic stem cell [34], cardiac progenitor cells [35], embryonic stem cell [36], pancreatic cancer cell [37] and liver cancer cell [38] et al. EVs are also found in physiological and pathological fluids, including pleural effusions, plasma [39], ocular effluent and aqueous humor [40], breast milk [41], broncho-alveolar lavage [42], synovial fluid [43], bile [44], urine [45,46] and sputum [46], ascites [47], amniotic fluid [48], semen ("prostasomes" and "epididymosomes") [49-51], nasal secretions [52], CSF [53].

EVs have recently gained much attention for their application to CNS diseases, EVs participate in the regulation of normal physiological processes and disease pathology, not only including tissue homeostasis, such as stem cell maintenance, development, repair, regeneration, as well as pathophysiology [54-57], but also modulate immune system and protect apoptosis via multiple pathways [58,59]. In addition, EVS plays a significant role in cancer and cardiovascular disease [23]. Increasing interest in the development of EVs (Figure 1). Its therapeutic effect for central nervous system diseases have been used in pre-clinical and clinical settings over the last decade, administration of MSCs-EVs has beneficial effects in numerous animal models of CNS diseases, including stroke, intracerebral hemorrhage (ICH), traumatic brain injury (TBI), glioblastoma (GBM), spinal cord injury (SCI) et al. The therapeutic effect of EVs in CNS diseases can be ascribed to the modulation of variety processes, including angiogenesis, neurogenesis, apoptosis, immune response, and reprogram in physiological and pathological status [60]. Compare with MSCs: EVs are smaller diameter and less complex content, so they are easier to produce and store, and will be more potential to address contentious regulatory issues [61]. Interestingly, purified EVs from MSCs exerted most, the key mechanism by which MSC contribute to tissue repair and regeneration is through their paracrine function, EVs are one of the major factors that are secreted [62-64]. Other studies have also showed that the treatment effects of MSCs are mostly attributed to cell-secreted paracrine factors rather than target and direct action of transplanted cells [65-67]. Moreover, paracrine factors can induce revascularization and promote proliferation of tissue cells [68,69].

EV components

The database was developed based on published articles, such as, EVpedia (http://evpedia.info) and ExoCarta (http://exocarta.org) storing millions of the proteins, mRNAs, miRNAs, and lipids of mammalian EVs.

Nucleic acid content: Walking through the historical discovery of EVs mRNAs and miRNAs in humans and mice, 4,946 mRNA entries and 2,838 miRNAs from EVs from multi cells and body fluids have been identified (EVpedia, ExoCarta) [70,71]. Highly abundant small RNAs constituent of wide range of genetic materials in EVs, and many of them derived from ribosomal 18S and 28S rRNAs, tRNAs. By next-generation sequencing, diverse composition of small RNAs have been identified, not only contain commonly known RNA species, such as mRNAs, miRNAs, rRNAs, tRNA, vault RNA, long and short non-coding RNA, piwi-interacting RNA, and Y RNA also have been characterized [20,72-76]. Most of the RNA is generally shorter in size, around 200 nucleotides and smaller portion extending out to 4kb [77]. Interestingly, different types of RNA species can also be stably together with functional ribonucleoprotein (RNP) and depending on the isolation procedure, for example, high and low-density lipoproteins (HDLs and LDLs) participate in a mechanism of cell-sell communication involving the transport of miRNAs and enables their stability and delivery throughout the body, argonaute 2 (AGO2), which are essential to miRNA-induced silencing [78,79]. Multiple reports have implicated EVs serve as carriers of genetic information in cell-cell communication by carrying cell-specific mRNAs and miRNAs, especially in the treatment of CNS diseases. In some cases, genomic and mitochondrial DNA has been found, however, the therapeutic effects of not yet documented [80,81].

Protein content: Proteomic profiling of the EVs underwent a significant development in recent years, 41,860 protein entries from EVs have been identified, including annexin (Annexins I, II, IV, V and VII), cytoskeletal components (actin, alanine, tubulin, coenzyme), small GTPase family members Rab7 and Rab11, and EVS marker proteins Alix, TSG101, CD9, CD63 [82,83]. Alix, Syntenin-1, integrins, tetraspanins, cytoskeletal proteins, Tsg101, HSPs, annexins, Rab proteins, metabolic enzymes, and ribosomal proteins were categorized as common EVs protein [84,85]. As more EVs proteomes are identified, the inclusion or exclusion of cellular protein packaging is governed by protein-sorting mechanism during production of EVs [86].

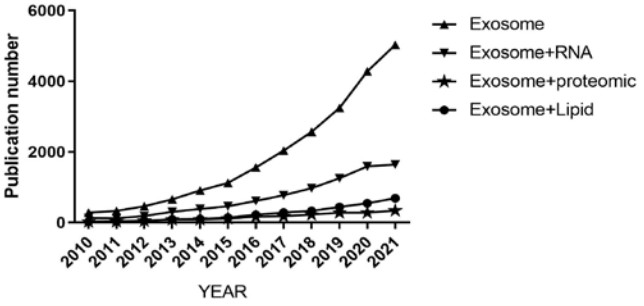

Figure 1: Publication in exosome research annually since 2010 retrieved from a PubMed search of the term "exosome", "exosome + RNA", "exosome + Lipid", "exosome + Proteomic".

During the last 20 years, extensive research has investigated in the protein composition of MSC-EVs (MSC derived EVs) by various proteomic analysis, including immunoelectron microscopy, fluorescence-activated cell sorting and Western blotting, there have been over 900 proteins identified in MSC-EVs [82,87]. Recent studies have shown that MSC-EVs can improve the recovery of damaged tissues [84], and identified 730 proteins by LC coupled MS/MS analysis, 43 surface receptors as well as signaling molecules are characterized, which is responsible for self-renewal and differentiation. Some other analysis indicated that MSCs-EVs proteins contributed to cell proliferation, migration, adhesion, and morphogenesis [88,89]. Self-renewal ability and differentiation potentiality of MSCs can be associated with the therapeutic effects, which is regulated by the integration of related genes, including signaling molecules (CDC42, VAV2); surface receptors (PDGFRB, EGFR, and PLAUR); antigens (CD109, CD248, CD151 and CD276) [84].

Lipid content: In addition to the abundance of proteins and nucleic acid within EVs, similarly, the lipid composition has also been investigated quite extensively [90-92]. A total of 1116 lipids have been identified (http://exocarta.org) in various settings. While there does not appear to similar lipid composition for EVs derived from different cells types, all of EVs lipid bilayer mainly contains the components plasma membrane lipids (sphingomyelin, phospholipids, ganglioside GM3, and cholesterol) [93,94]. Among them, glycerophospholipids accounted for 91.5% of the total lipid ion abundance, followed by sphingolipids (5.3%), sterols (1.9%) and glycerol (1.4%) [95]. Glycerol phospholipids mainly include phosphatidylserine and phosphatidylglycerol. The former is a recruiter of negative charge activators and signaling proteins [96], and the latter involved in transmembrane transport [97,98]; sphingomyelin is related to the construction of outer membrane [99]; sterols are associated with vesicles and plasma membranes [100].

MSC-EVs-miRNA in CNS Disease Therapy

Accumulating evidence reveals that modification of exosomal miRNAs content can be a promising tool in the development of CNS diseases therapeutic. In addition, exosomes can penetrate the blood-brain barrier to enhance the therapeutic effect of miRNAs. Evidence from extensive studies in the last decade has indicated that exosomes from MSCs carrying miRNAs were found to be effective against several CNS disease targets and were reported to enhance chemosensitivity while suppress angiogenesis. Moreover, Exosomes express miRNAs regulate the expression of related genes in receptor cells and promote the regeneration and repair of receptor cells. Exosomal miRNAs currently studied in CNS diseases mainly include miRNA-126, miRNA-21, miRNA-17-92, miRNA-133b, and miRNA-124 (Figure 2).

Stroke

Compared to native MSC, MSC-EVs-miR-17-92 cluster can further enhanced axonal growth in stroke mice, which activated the PTEN/mTOR signaling pathway [101]. Similarly, Xin et al, suggest that MSC-EVs-miR-17-92 cluster also increased neural plasticity and improved functional recovery *via* the PI3K/Akt/mTOR/GSK-3β signaling pathway [102]. In another study, miR-21, which increased the expression in MSC-derived EVs, improved learning and memory capabilities via the PTEN/Akt pathway. Moreover, EVs have been shown to increase miR-21 level in AD mice, which restored the cognitive deficits in APP/PS1 mic [103]. Additionally, c(RGDyK)-conjugated EVs (cRGD-Exo) loaded with cholesterol-modified miR-210 (RGD-exo-miR-210) targets the ischemic brain contributing to miR-210 increase in the lesion region, which increased vascular endothelial growth factor (VEGF) and CD34 and shown neural protection in middle cerebral artery occlusion (MCAO) mouse [104]. What's more, obtained evidence indicated that, overexpression of miR-138-5p was observed to promotes the proliferation and migration of astrocytes injured because of hypoxia and glucose deprivation, while BMSCs-EVs-miR138-5p promote proliferation which was achieved by inhibiting the apoptosis of astrocytes via downregulate LCN2 [105]. After oxygen-glucose deprivation (OGD) treatment, BMSCs-derived miR-134 EVs suppressed oligodendrocytes (OLs) apoptosis through a caspase-8-dependent apoptosis pathway [106].

Traumatic brain injury (TBI)

Some studies demonstrated for the first time that EVs from MSCs improve nerve functional recovery, stimulate angiogenesis, and promote neurogenesis in traumatic brain injury (TBI) [107]. In the latter, MSCs-EVs have been found to reduce neurological impairment in a transient intraluminal MCAO. MSCs-EVs -miR133b could regulates the expression of connective tissue growth factor (CTGF), a major inhibitor of axonal growth at injury sites, in astrocytes and the Ras homolog gene family member A (RhoA) expression in the IBZ, it also increased the expression of von Willebrand factor (vWF) in stroke rat, which demonstrated that MSCs communicate with brain parenchymal cells by transfer miR-133b to neural cells via EVs [108,109]. EVs from MSCs cultured in 3D conditions showed better outcome than 2D, EVs derived from 3D scaffolds provided better spatial learning, hMSC-generated EVs promoted endogenous angiogenesis, neurogenesis, and improved functional recovery in rats after TBI [110]. Moreover, EVs-miR124 could play a crucial role in the microglial polarization, and move it towards to anti-inflammatory phenotype (M2) state by inhibiting TLR4 pathway, thus improving neurogenesis and enhancing functional recovery in the hippocampus [111]. Recently research demonstrated that, MSCs-EVs-miR-17-92 improved functional recovery after TBI by reducing neuroinflammation and enhancing endogenous angiogenesis and neurogenesis, providing a novel therapeutic strategy for TBI.

Spinal cord injury (SCI)

A significant recovery of hindlimb function was observed in spinal cord injury (SCI) rats after MSCs-EVs-miR133b administration. Additionally, MSCs-EVs-miR133b promoted the regeneration of axons, protected neuronal cells, and reduced the volume of the lesion, which targeted RhoA and decreased the expression. Moreover, it also activated signaling pathway proteins, which involved in the survival of neurons and the regeneration of axons, such as ERK1/2, STAT3, and CREB, could be an effective strategy [112]. Other research reported that, hMSCs-EVs-miR-21 and miR-19b regulated PTEN mRNA and protein as well as the value of cell apoptosis index, involved in the apoptosis and differentiation of neuron cells in SCI [113]. Further studies reveal that, EVs with miR-21 deficiency would not exert protective effects against SCI [114]. Interestingly, miR-21-5p was up-regulated after SCI, motor function and apoptosis were significantly increased in spinal cord post-SCI after miR-21-5p in MSCs-EVs transplantation therapy, an effect which was associated

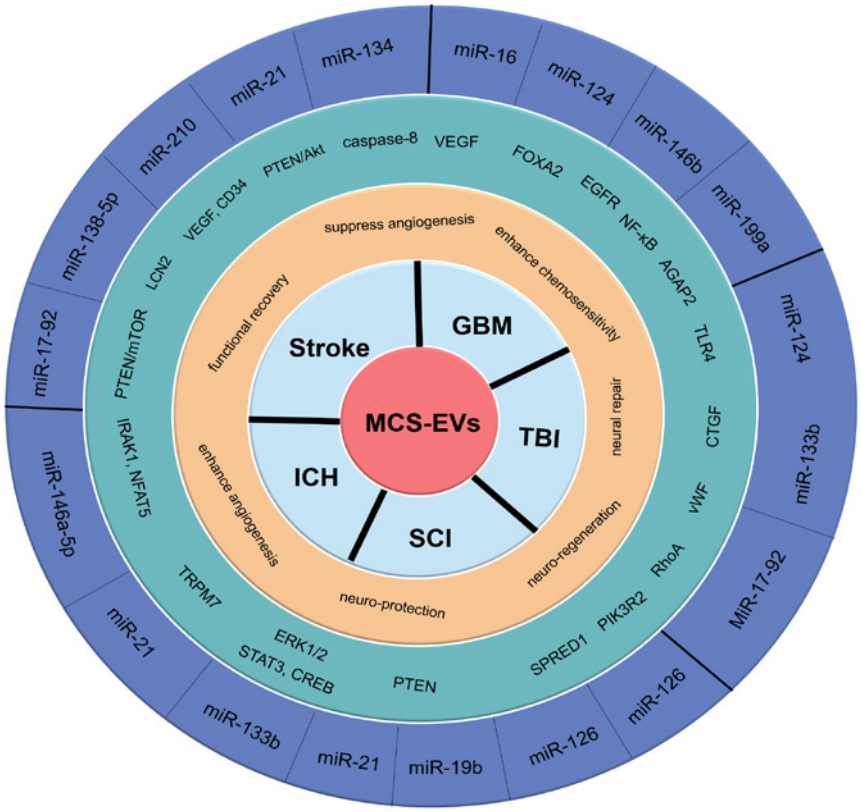

Figure 2: Schematic representation of possible routes of MSC-EVs-miRNA to improve CNS diseases.

with increased the proportion of TUNEL-positive cells [115]. *In vitro* analysis indicated that, MSCs-EVs-miR-126, a key regulator, promoted the angiogenesis and migration of human umbilical venous endothelial cells (HUVECs), through inhibiting the expression of SPRED1 and PIK3R2 [116].

Intracerebral hemorrhage (ICH)

Interestingly, intracerebral hemorrhage (ICH) could induce an increase of EVs level in the brain, inhibition of EVs release augmented neurological deficits and brain edema [117]. Proteomics analysis of the EVs identified 2416 proteins that have been implicated in regulating number of cell functions, EVs derived from MSC therapy work in ICH as paracrine effectors responsible for brain repair processes, improved functional recovery, more axons, a higher expression of oligodendrocyte formation markers [118]. Regarding functional recovery, previous studies demonstrated that miR-21 is downregulated in blood and brain tissue after ICH, MSCs-EVs-miR-21 can be transported to neurons and that it plays a crucial role in alleviate neuronal injury via targeting transient receptor potential melastatin 7 (TRPM7) [119]. Recent evidence indicated that improvement in functional outcome after miR-146a-5p-riched BMSCs-EVs administration following ICH, which could be associated with the inhibition of M1/M2 polarization transitions via downregulating the expression level of IRAK1 and NFAT5 [120]. In addition, it was also suggested that the expression of miR-133b levels were negatively correlated with RhoA expression and that the effect of MSCs-EVs-miR-133b play a significant role in neuroprotection *via* targeting RhoA and activating ERK1/2 [121].

Glioblastomas (GBM)

MSC-EVs are associated with mixed effects on tumor initiation and progression, being able either to favor angiogenesis and tumor initiation, or to inhibit metabolic signaling and progression of established tumors. These biological rationale for this response is likely attributable to their microenvironment. MSC-EVs, as the pivotal mediators of communication in the tumor microenvironment, play essential roles in cell-to-cell communication, and suppress angiogenesis by directly transferring anti-angiogenic molecules, MSC-EVs-miR-16 suppressed the expression of VEGF, to lead to the inhibition of angiogenesis and tumor progression [122]. Other research found that MSC-EVs-miR146b effectively reduced glioma xenograft growth in rat brain, it is likely that inhibition of factors EGFR and NF-κB protein in glioma cells underpins the anti-tumor [123]. When administered systemically, EVs-miR [124] is capable of downregulating FOXA2 and induced apoptotic cell death, which may correlate with FOXA2-mediated aberrant intracellular lipid accumulation [124]. In addition, EVs-miR9 was linked to temozolomide resistance in glioblastoma, when transfer this anti-miRNA into co-cultured- GBM cells, it was be able to affect GBM cells at a considerable distance [125]. MSC-EVs- miR199a enhanced the chemosensitivity to temozolomide and inhibited the tumor growth, besides, it suppressed the proliferation, invasion, as well as migration of glioma cells by down-regulating the expression of AGAP2 [126]. In a separate study, further research showed that the known targets of the miR-302-367 cell-to-cell transfer resulted in the inhibition of cyclin A, SHH, cyclin Dand, E2F1 and CXCR4/SDF1, and prevented growth of GBM stem-like or progenitor cells [127]. Some studies have

suggested that MSC-EVs promote tumorigenesis and metastasis, for example, it promoted the metastasis of the breast cancer, human renal cell carcinoma and bladder cancer [128-130].

Discussion

EVs, vectors of biological information, are involved in cell-cell communication in both physiological and pathological processes by delivering miRNAs to recipient cells that transferring beneficial mediators in CNS diseases. MSCs-EVs target housekeeping processes by their secreted EVs containing different miRNA to promote angiogenesis and neurogenesis, protect neurons, suppresses t neuron apoptosis, and increase neural plasticity. MSCs-EVs can also inhibit tumor proliferation, migration, and invasion, as well as enhance the chemosensitivity (Figure 2). The MSCs-EVs therapy, easier to cross the blood-brain barrier and avoiding the risk of iatrogenic tumor formation as well as intravenous administration-induced pulmonary embolisms, is a promising alternative to overcome the obstacles of cell-therapy. Despite numerous studies and literature reports, challenges are remaining for clinical application of MSCs-EVs-based therapy. Further studies of the cellular and molecular mechanisms of MSCs-EVs are necessary to maximize its clinical benefits in CNS diseases. Development and standardization of technologies in the manufacture, detection, and characterization of MSC-EVs are also indispensable for its clinical application. In conclusion, once these critical issues around MSC-EVs are settled, MSC-derived EVs can be harnessed as powerful therapeutic agents in CNS diseases.

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