The neuroprotection effects of exosome in central nervous system injuries: A new target for therapeutic intervention

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Abstract

Central nervous system (CNS) injuries, including traumatic brain injury (TBI), spinal cord injury (SCI) and subarachnoid hemorrhage (SAH), are the most common cause of death and disability around the world. As a key subset of extracellular vesicles (EVs), exosomes have recently attracted great attentions due to their functions in remodeling extracellular matrix, and transmitting signals and molecules. A large number of studies have suggested that exosomes played an important role in brain development and involved in many neurological disorders, particularly in CNS injuries. It has been proposed that exosomes could improve cognition function, inhibit apoptosis, suppress inflammation, regulate autophagy and protect blood brain barrier (BBB) in CNS injuries via different molecules and pathways including microRNA (miRNA), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), ph1osphatidylinositol-4,5-bisphosphate 3-kinase/protein kinase B (PI3K/AKT), Notch1 and extracellular regulated protein kinases (ERK). Therefore, exosomes showed great promise as potential targets in CNS injuries. In this article, we present a review highlighting the applications of exosomes in CNS injuries. Hence, on the basis of these properties and effects, exosomes may be developed as therapeutic agents for CNS injury patients.

1. Introduction

Central nervous system (CNS) injuries and their potential long-term consequences are of major concern for public health. High rates of morbidity and mortality making them a global health challenge [1]. CNS is highly sensitive to external mechanical damage, such as traumatic brain injury (TBI), spinal cord injury (SCI), subarachnoid hemorrhage (SAH) and stroke, presenting a limited capacity for regeneration due to its inability to restore either damaged neurons or synaptic network [2]. Although some of the pathological processes of CNS injuries such as blood brain barrier (BBB) disruption, inflammation and oxidative stress have been elucidated, the detailed mechanisms driving these processes are poorly understood [3]. Despite the progress has been made in the prevention and treatment of CNS injuries in the past, patients suffering from CNS injuries usually end up with poor prognosis [4]. Therefore, it is urgently needed to find optimal therapies and improve patients' long-term neurological functioning after CNS injuries.

Extracellular vesicles (EVs) are lipid-bound vesicles that play a significant role in intracellular communication. EVs are classified into three main subtypes including microvesicles (MVs), apoptotic bodies and exosomes. Among EVs, exosomes are most broadly investigated. Exosomes are 30 to 120 nm endogenous nanovesicles containing proteins, lipids and nucleic acids [5]. The formation of exosomes includes the exocytosis of endosomes and they are secreted out of the cell following the fusion of multivesicular bodies with the plasma membrane (Fig. 1) [6]. Exosomes can cross the BBB and have the potential to specifically deliver molecules to CNS [7]. The initial function of exosomes is thought to be the elimination of non-functional proteins in cells, but the current view is that exosomes are vesicles that are cell-specifically secreted and are involved in intercellular communication [8]. Via cargo proteins, mRNAs, DNAs and miRNAs, exosomes can work locally or be stably transferred to recipient cells and act as key players in triggering, transferring and regulating immune responses to neighbouring cells [9]. Furthermore,

most cells in CNS have been reported to secrete exosomes into the extracellular environment [10, 11]. It has been shown that exosomes were involved in the brain development, functional diversification and contributed to diverse neurological disorders, such as CNS injuries [12, 13]. In this regard, exosomes could be a promising alternative to cell-based therapies, highlighting the potentially roles of exosomes in CNS injuries are important.

In the present study, we provide an overview of exosomes functions in CNS injuries and the associated molecular mechanisms. This review describes (1) the source of exosomes in CNS injuries; (2) the role of exosomes in CNS injuries; and (3) the downstream targets of exosomes.

2. The Source Of Exosomes In Cns Injuries

In 1983, Pan *et al.* isolated a small vesicle from the supernatant of sheep erythrocytes by ultracentrifugation, the vesicle was later named exosome [14]. This observation led to investigations into the potential role of exosomes in multiple models [15]. Recently, the effects of exosomes in CNS injuries were elucidated. Specifically, exosomes derived from astrocyte, microglia, mesenchymal stem cell (MSC), neuron cells and brain endothelial cells (BECs) were found to influence brain damage in CNS injury models (Table 1).

2.1 Astrocyte and microglia

Astrocytes and microglia are able to release cytokines, chemokines and growth factors in respond to brain damage [16]. These factors can affect the homeostatic balance of CNS and determine the degree of injury [17]. Recently, the astrocytes or microglia-derived exosomes have been demonstrated to regulate secondary brain injury after CNS injuries.

Astrocytes are the most abundant glial cells in the CNS. Normally, astrocytes play crucial roles in promoting the formation of BBB, maintaining the function of neural circuit, modulating synaptic circuits and neurotransmitter recycling as well as repairing and scarring process of the brain [18]. In addition to upholding normal brain activities, astrocytes can function as reactive astrogliosis following CNS injuries by regulation of gene expression, morphology and proliferative capacity [19]. Reactive astrogliosis are capable of secreting soluble factors such as transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), glial-derived neurotrophic factor (GDNF) and basic fibroblast growth factor (bFGF), which further activated inflammatory response after CNS injuries [20]. The diversity functions of astrocytes make them predominant among other cells in CNS [21, 22].

Microglia are brain-resident myeloid cells that regulate immune reaction and inflammatory response [23]. Microglial have been considered as the “gate-keepers” of CNS microenvironment with a large number of functions in development and remodeling of the nervous system [24]. Moreover, microglia modulate cell survival and neurological recovery in response to brain damage by release of trophic factors [25].Upon brain damage, microglia are activated and move toward the lesioned zone, secreting growth factors such as insulin-like growth factor I (IGF-I) and proinflammatory cytokines such as interleukin (IL)-1β, IL-6 and

tumor necrosis factor-α (TNF-α) [26]. Deficiency of microglial has been reported to participate in CNS injuries such as stroke, TBI and hypoxia-ischemia injury [27, 28].

2.2 MSC

MSCs are stromal cells that have the ability to self-renew and also exhibit multilineage differentiation [29]. MSCs were first derived from bone marrow, subsequently they have been isolated from almost all tissues. MSCs can be isolated from adipose tissue, umbilical cord, menses blood and so on [30]. Recently, MSCs have been found in new sources, such as menstrual blood and endometrium [31]. Depending on different parameters such as tissue source, isolation method and medium composition, the role of MSCs are different [32]. MSCs have been an attractive choice for experimental and clinical application because of their relatively simple procedure for cell isolation, self-renewal and capable of differentiating into diverse cell lineages under specific culture conditions [33, 34]. Moreover, MSCs can secrete high levels of proteins, cytokines and immune-receptors that functions in immunoregulation, revascularization, cutaneous wound healing, angiogenesis and tissue regeneration [35]. In addition to secreted proteins, MSCs also release exosomes, which could be a promising therapeutic target in diseases [36].

2.3 Neuron cell

Neurons are specialized cells with a high level of polarization. The basic function of neurons is responsible for rapid communication of information by receiving, integrating, transmitting and outputting [37]. Neurons consist of three main structural and functional domains: the dendrites, a cell body or soma and an axon. These domains contain smaller compartments, such as the dendritic postsynaptic spines and the axonal presynaptic boutons, for neuronal functions [38, 39]. Neurons receive electrochemical signals from other neurons through dendrites, which then communicate information to target cells through the soma and along the axon [40]. Furthermore, neurons are also “excitable” cells, which produce different oscillatory activities that help to understand the transmitting and processing of signals in neural system [41]. The neuronal surface membrane contains ion channels that allow small charged atoms to pass. For example, the activation of potassium or sodium ion channel in neurons can determine firing activities. Therefore, recurrent firing activities as spike trains, sequence of regular or chaotic bursting and mixed-mode type of oscillations may emerge in a single neuron [42].

2.4 BECs

BECs are mesodermal derived modified simple squamous epithelial cells that form the walls of blood vessels [43]. A great number of studies have demonstrated that BECs play an important role in brain development, remodeling and repair [44]. Acute injuries, including trauma, cerebral hemorrhage and hypoxia-ischemia, can lead to BEC death, which further causes BBB disruption, inflammation and oxidative stress [45]. Thus, the homeostatic balance of BEC death and survival is vital to brain development and maturation. BECs have unique properties, they lack fenestrations, undergo low rates of transcytosis and are held together by tight junctions (TJs) [46]. These characteristics allow them to limit the vesicle-mediated transcellular movement of solutes and regulate the movement of cells, molecules

and ions between brain and blood [47]. Moreover, BECs prevent peripheral immune cells to CNS due to their low expression of adhesion molecules [48].

2.5 Other sources of exosomes

To date, the four sources of exosome have been well-studied in CNS injuries. However, there were also some other sources of exosome that have been explored such as human urine stem cell (USC) [49], circulating endothelial progenitor cell (cEPC) [50], neural stem cell (NSC) [51], macrophages [52] and dental pulp stem cell (DPSC) [53]. All these sources of exosome may provide neuroprotection in CNS injuries.

3. The Function Of Exosomes In Cns Injuries

Exosomes were firstly reported to exhibit neuroprotection on CNS injuries in 2012 [54]. Subsequently, many studies have demonstrated that exosomes could provide neuroprotective effects in CNS injuries. The neuroprotection of exosomes was reportedly attributed to their effects on improvement of cognitive function, inhibition of inflammation, suppression of apoptosis, regulation of autophagy, promotion of angiogenesis and protection of BBB (Table 2).

3.1 Cognitive function

In animals, cognitive function is considered to be the ability to learn, retain and recall information. However, in humans, it also represents a complex, multidimensional set of intellectual functions like judgment and evaluation [55]. Thus, in a broader context, cognitive function includes all mental abilities and processes related to knowledge including memory, reasoning, attention, comprehension and language production [56]. Cognitive function was originally thought to be regulated by CNS, but now other systems, for example, the immune system and the intestinal microbiome may also be involved [57]. Cognitive function impairment may occur in CNS injuries and neurodegenerative disease, which is characterized by problems in attention, thinking, memory, language and social communication. Peoples who suffer from cognitive decline experience poor quality of life and demand continuous care from their families and society, thus increasing the burden of family members and social insurance funds [58].

The effects of exosomes on cognitive function after CNS injuries have been explored. In a rat TBI model, MSCs-derived exosomes significant improved spatial learning as measured by the modified Morris water maze test and recovered sensorimotor function as evidenced by reduced neurological deficits and foot-fault frequency [59]. Furthermore, treatment with exosomes derived from mouse BECs significantly improved neurological and cognitive functional outcome as evaluated by adhesive removal test and odor test in a mouse stroke model [60]. In addition, it has been shown that exosomes from human umbilical cord MSCs attenuated stress-induced hippocampal dysfunctions and improved motor recovery in an acute brain disorder model [61].

The precise mechanisms underlying how exosomes regulated cognitive function were unclear. It has been revealed that cognitive function impairment involved selective neuronal loss in the hippocampus and cortex [62]. Therefore, exosomes may also improve cognitive function by intervene with these pathological processes.

3.2 Inflammation

Inflammation is one of the major determinants of secondary brain damage after CNS injuries [63]. In normal conditions, inflammation is a vital physiological immune response against noxious stimuli (such as injury or infection) and defends the host against pathogenic threats [64]. However, in respond to CNS injuries, excessive inflammation may provoke substantial detrimental effects. This process involves initiating microglia activation and sustaining astrocytic activation. Once activated, these cells can induce a series of events including activation of glial, recruitment of leukocyte, and release of pro-inflammatory cytokines (e.g., IL-1β, IL-2, IL-6, TNF-α, interferon γ (IFN-γ)) and chemokines (e.g., C-C motif chemokine ligand 2 (CCL2), C-X-C motif chemokine ligand 8 (CXCL8)) [65, 66]. These cytokines and chemokines recruit more inflammatory cells to amplify the inflammatory response, leading to BBB breakdown, cerebral edema and cell death [67].

Numerous studies have proposed that exosomes exerted a central effect in CNS injuries-induced inflammation. The effect of exosomes in CNS injuries-induced inflammation was firstly described by Zhang *et al.* in 2015 [59]. They found that the density of CD68 + and GFAP + cells was significantly increased in the lesion boundary zone after TBI. MSCs-derived exosomes treatment significantly reduced the CD68 + and GFAP + cells density in the injured cortex compared to the phosphate buffered saline (PBS) treatment, suggesting that MSCs-derived exosomes had anti-inflammatory effects in TBI [59]. Moreover, in a mouse model of SAH, bone marrow MSCs-derived exosomes suppressed the expression and activity of histone deacetylase 3 (HDAC3) and up-regulated the acetylation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) p65, thus attenuating neuroinflammation in early brain injury [68]. Furthermore, in ischemic stroke (IS) models, exosomes secreted from the lipopolysaccharide (LPS)-stimulated macrophage promoted microglial polarization from the M1 phenotype to the M2 phenotype and reduced the production of IL-1β, TNF-α *in vitro*, indicating the anti-inflammatory effect of exosomes [52]. In addition, in has been shown that plasma exosomes could enhance melatonin therapeutic effects against ischemia-induced inflammatory responses and inflammasome-mediated pyroptosis in ischemic stroke [69].

The underlying mechanisms of exosomes-mediated inflammation are immensely complicated. Studies have indicated that the NF-κB signaling pathway might be the key target and we will discuss the detailed mechanisms in our following sections.

3.3 Angiogenesis

Under physiological conditions, the brain vascular system is stable and contributes to the maintenance and growth of the tissue [70]. When brain vasculature is damage under pathological conditions including injuries, angiogenesis is activated. Angiogenesis is a tightly regulated process through which new blood

vessels are formed, it involves the participation of endothelial cells, extracellular matrix and vascular cells to form capillaries. This process requires an orchestrated interplay of many stimulators, inhibitors and matrix components [71, 72]. Angiogenesis facilitates the generation of new vasculature, which further accelerates highly coupled neurorestorative process and promotes tissue perfusion. Angiogenesis is controlled by vascular growth factors such as vascular endothelial growth factor (VEGF) [73]. VEGF owns a mitogenic effect on endothelial cells, thus increasing the vascular permeability and promoting cell migration. Besides its role in angiogenesis, VEGF also shows important effects in the neuronal development and physiological function [74]. VEGF can regulate the ion channels of the neuron membrane and accelerate the development of neurons and neural dendritic [75].

Since angiogenesis is benefit for CNS injuries-caused secondary injury, exosomes may attenuate brain damage by promoting angiogenesis. Consistent with this hypothesis, Zhang *et al.* proposed that MSCs-derived exosomes significantly increased the vascular density and angiogenesis as identified by EBA/BrdU + double labeling for newborn endothelial cells in the injured cortex [59]. Furthermore, bone marrow MSCs-derived exosomes increased the number of branch points as proven by tube formation assay in a rat hypoxic-ischemic injury model [76]. In another study, it was shown that miRNA-17-92 cluster-enriched exosomes derived from human bone marrow MSCs increased the formation of blood vessels after TBI, indicating that exosomes could promote angiogenesis[77]. Because angiogenesis is emerging as therapeutic target for CNS injuries, therefore, exosomes-based therapies by targeting angiogenesis might provide opportunities for the development of novel therapeutic strategies for CNS injuries.

3.4 Apoptosis

Apoptosis is a very tightly programmed cell death (PCD) occurring regularly to eliminate unnecessary and unwanted cells as well as to maintain a homeostatic balance between cell survival and cell death [78]. Apoptosis is critical to animals especially long-lived mammals that must integrate multiple physiological and pathological death signals. Apoptosis therefore represents a physiological and protective response to damage [79]. It has been shown that insufficient apoptosis can trigger cancer or autoimmunity, while excessive activation of apoptosis could be harmful and contribute to abnormal cell death, particularly in pathological conditions such as acute and chronic degenerative diseases, immunodeficiency and trauma [80]. Morphologically, apoptosis renders the cell with shrinkage, which is characterized by DNA fragmentation, chromatin condensation, cytoplasm compacting and plasma membrane blebbing. This is followed by nuclear fragmentation and formation of apoptotic bodies [81]. If apoptosis occurs in CNS injuries, it can cause secondary brain injury, aggravating the damage of brain [82].

The functions of exosomes in apoptosis have been studied. The results obtained by Song *et al.* demonstrated that microglia-derived exosomes significantly increased cell survival and decreased neuronal apoptosis in ischemia-reperfusion injury, as demonstrated by neuronal survival, TdT-mediated dUTP Nick-End labeling (TUNEL) staining and the lactate dehydrogenase (LDH) assay [83]. In addition, Ni *et al.* showed that in a mouse TBI model, bone marrow MSCs-derived exosomes up-regulated the expression of B-cell lymphoma-2 (Bcl-2) while down-regulated the expressions of Bcl-2-associated X

protein (Bax), suggesting that bone marrow MSCs-exosomes attenuated cell apoptosis [84]. In another study conducted by Lai *et al.*, they found that MSCs-derived exosomes decreased apoptosis in brain following SAH as shown by increased expression of Bcl-2 and decreased expression of caspase-3 [68]. In conclusion, these data suggested that exosomes could reduce cell apoptosis in models of CNS injury.

Researches so far have only studied the role of exosomes on apoptosis in general. However, apoptosis can be divided into two pathways: the mitochondria-dependent pathway (the intrinsic pathway) and the death receptor-dependent pathway (the extrinsic pathway). The intrinsic pathway involves a chain of intracellular events occurring in the mitochondrion including the release of cytochrome c, formation of the apoptosome with apoptotic protease-activating factor 1 (APAF1), activation of caspase-9 and subsequent caspase-3. The release of cytochrome c is positively regulated by the pro-apoptotic Bcl-2 family members such as Bax, Bcl-2 antagonist killer 1 (Bak), Bid and negatively regulated by the anti-apoptotic Bcl-2 family members such as Bcl-2, B-cell lymphoma-extra large (Bcl-xL). In contrast, the extrinsic pathway is initiated by the binding of TNF ligand to TNF receptor and the binding of Fas ligand to Fas receptor. Upon ligand binding, the death receptors allow the binding of an initiator caspase-8 or -10 to form death inducing signaling complex (DISC) through its death effector domain (DED). The activation of caspase-8 relays the death signal to an execution caspase to bring about apoptosis [85, 86]. Thus, which apoptotic pathway is associated with the effects of exosomes in CNS injuries-induced apoptosis remains unclear and further studies are needed to clarify it.

3.5 Autophagy

Autophagy is an evolutionarily conserved lysosomal pathway for the degradation of cytoplasmic components [87]. In conditions of starvation response, cell differentiation and quality control, autophagy is activated and plays an important role in maintaining and regulating cell homeostasis by degrading intracellular components and providing degradation products to cells [88]. Autophagy begins with the formation of a membrane vesicle called the phagophore, which matures into a spherical lipid bilayer vesicle named the autophagosome. The autophagosome then fuses with a lysosome and degrades the contents in autolysosome [89]. Recent studies have revealed that the dysfunction of autophagy was implicated in CNS injuries and extensive activation of autophagy can lead to type II PCD [90]. Up to now, the dual role of autophagy in protective or destructive of CNS injuries remains controversial. Shi *et al.* found that in cerebral ischemia-reperfusion rats, inhibiting autophagy by sevoflurane attenuated brain damage, demonstrating a detrimental role of autophagy [91]. Conversely, Ahsan *et al.* reported that Urolithin A-activated autophagy protected against ischemic neuronal injury by inhibiting endoplasmic reticulum (ER) stress both *in vitro* and *in vivo*, suggesting that autophagy played a beneficial role in stroke [92].

There were also studies showing that exosomes could affect autophagy in CNS injuries. However, the roles of exosomes-regulated autophagy in CNS injuries were also controversial. Li *et al.* have shown that exosomes from neurons inhibited cell apoptosis and death in TBI by suppression of Rab11a-mediated autophagy, suggesting a detrimental role of autophagy in TBI [93]. Interestingly, in another study conducted by Yuan *et al.*, they found that bone marrow MSCs-derived exosomes decreased ER stress in

BV2 cells by induction of disabled homolog 2-interacting protein (DAB2IP)-mediated microglial cell autophagy, suggesting a protective role of exosomes and autophagy in brain injury [94]. The discrepancies may be due to the different source of exosomes and cell types used in these two studies. Taken together, by combination with the previous studies, we though that depending on different CNS injury models, sources of exosomes and cell types, autophagy and cell death may have inhibitory, additive or even synergistic effects.

3.6 BBB function

BBB is a highly specialized, semi-permeable physical barrier that locates at the interface between the CNS and the surrounding environment. It is instrumental in regulating the metabolism of brain, maintaining the microenvironmental homeostasis of CNS and coordinating the functions of peripheral organs [95]. In addition, BBB is a dynamic metabolic interface that can bi-directionally regulate the transport of fluids, solutes and cells [96]. Structurally, BBB is formed by BECs with TJ. Dysfunction of BBB is a common pathological feature in CNS injuries. Several underlying events are involved in BBB destruction, such as disruption of the TJ, breakdown of the BECs and degradation of the extracellular matrix [97]. In an *in vitro* model of IS, Pan *et al.* found that MSCs-derived exosomes alleviated BBB disruption in hypoxia/reoxygenation (H/R)-injured endothelial cells by analyzing the Evans blue dye extravasation and brain water content [98]. Moreover, Lai *et al.* suggested that bone marrow MSCs-derived exosomes attenuated BBB permeability in early brain injury after SAH [68]. Furthermore, another *in vivo* study confirmed the protective effects of exosomes on BBB in ischemia-reperfusion injury [99].

4. Downstream Molecules Of Exosomes In Cns Injuries

The specific mechanisms mediating the functions of exosomes in CNS injuries have yet to be fully explained, a number of downstream molecules of exosomes have been suggested which may explain their biological effects (Fig. 2).

4.1 MicroRNA (miRNA)

MiRNAs, a subset of non-coding RNAs, are 19 to 25 nucleotide long endogenously-initiated short RNA molecules [100]. MiRNAs modulate gene expression at the post-transcriptional level via translational inhibition or messenger RNA (mRNA) degradation and control a range of biological functions, including developmental timing and host-pathogen interactions as well as cell proliferation, apoptosis and tumorigenesis [101]. As a regulatory element, miRNA itself is also regulated by multiple effectors such as miRNA editing, circadian clock and methylation. However, illustrating the exact roles of miRNAs in these pathophysiological processes are difficult because of their complexity of actions [102]. Formation of a miRNA consists of two steps, from primary (pri) miRNA to precursor (pre) miRNAs mediated by Drosha in the nucleus and from pre-miRNAs to mature miRNAs mediated by Dicer in the cytoplasm [103].

MiRNAs contribute to nearly 1 % of all predicted genes in nematodes, flies and mammals. Because of their simple structure and ability to modulate cellular functions, an expanding body of evidences have

shown that miRNA-based therapies, either activating or inhibiting, hold great promise [104]. Recently, miRNAs have been identified in exosomes, which can be taken up by neighboring or distant cells and subsequently modulate recipient cells. Exosomal miRNAs play an important role in disease progression and provide neuroprotection in CNS injuries by stimulating angiogenesis, suppressing apoptosis and reduced inflammation. It has been shown that microglia-derived exosomes protected the mouse brain from ischemia-reperfusion injury via exosomal miRNA-124 [83]. Moreover, in a rat hypoxic-ischemic injury model, bone marrow MSCs-derived exosomal miRNA-29b-3p promoted angiogenesis and suppressed apoptosis in the brain [76]. Furthermore, MSCs-derived exosomal miRNA-193b-3p attenuated neuroinflammation in early brain injury after SAH [68].

Among exosomal cargo biomolecules, miRNAs obtain the most attention due to their regulative effects in gene expression. Studies have shown that miRNAs are not randomly incorporated into exosomes, a subset of miRNAs may preferentially enter exosomes [105]. Although the precise mechanisms of sorting miRNAs into exosomes remain unclear so far, four potential modes have been suggested. These include: (1) The neural sphingomyelinase 2 (nSMase2)-dependent pathway. (2) The miRNA motif and sumoylated heterogeneous nuclear ribonucleoproteins (hnRNPs)-dependent pathway. (3) The 3’-end of the miRNA sequence-dependent pathway. (4) The miRNA induced silencing complex (miRISC)-related pathway [106]. However, further studies are needed to prove which mode is associated with the incorporation of miRNAs into exosomes in CNS injuries.

4.2 Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)

NF-κB is a family of dimeric transcription factors that involved in inflammatory responses, innate and adaptive immunity as well as cell proliferation and differentiation [107]. NF-κB can protect cells against inflammation and cell death by regulating the transcription of genes including cytokines, chemokines and adhesion molecules [108]. There are mainly two pathways for NF-κB activation, the “canonical” pathway and the “alternative” pathway. The “canonical” pathway is triggered by microbial products and proinflammatory cytokines such as IL-1 and TNF-α, leading to the activation of RelA- or cRel- containing complexes. The “alternative” pathway is initiated by TNF-family cytokines, B cell activating factor and receptor activator of NF-κB ligand, resulting in activation of RelB/p52 complexes [109, 110].

NF-κB is tightly regulated, and activation of NF-κB has been implicated in CNS injuries. Exosomes were also shown to modulate inflammatory response in CNS injuries by activation of NF-κB. In ischemia-reperfusion injury models, the inflammatory response reflexed by the levels of TNF-α, IL-1β, IL-6 and their mediator, NF-κB were suppressed by DPSCs-derived exosomes [53]. Furthermore, in *in vivo* and *in vitro* SCI models, NSCs-derived exosomes downregulated the NF-κB-p65 axis in rats and PC12 cells respectively, thus inhibiting the inflammatory response [51]. Similar results were found in SCI models using bone marrow MSCs-derived exosomes both *in vivo* and *in vitro* [111]. Therefore, functional exosomes are important to regulate inflammation via regulation of NF-κB in CNS injuries.

How exosomes regulated NF-κB in CNS injuries have not been well characterized. There were reports showing that long noncoding RNAs (lncRNAs) and miRNAs may be involved. For example, stem cell-derived exosomes could prevent aging-induced cardiac dysfunction through the lncRNA MALAT1/NF-κB signaling pathway [112]. The regulation of NF-κB by lncRNAs can be mediated by the interaction between lncRNAs and the p65 subunit of NF-κB. LncRNAs bind with the p65 subunit of NF-κB and IkB to form a stable lncRNAs/NF-κB/IkB complex. Then, the phosphorylation sited of IkB is masked, thus inhibiting IkB kinases (IKK)-induced IkB phosphorylation and NF-κB activation [113]. In addition, it has been shown that miRNAs could regulate NF-κB by interfere with the signaling components upstream of NF-κB such as affecting the phosphorylation of IKK and IkB. For example, activation of miR-214-3p decreased cell apoptosis and inflammation in osteoarthritis (OA) by downregulated the IKK-β expression and led to the dysfunction of NF-κB signaling pathway [114]. Therefore, we speculated that exosomes might also regulate NF-κB via lncRNAs and miRNAs in CNS injuries. However, further studies were needed to confirm our hypothesis.

4.3 Phosphatidylinositol-4,5-bisphosphate 3-kinase/protein kinase B (PI3K/AKT) pathway

The PI3K/AKT is an intracellular signaling pathway that participates in a broad range of cellular processes including cell proliferation, differentiation, metabolism and quiescence [115]. The PI3K/AKT pathway can be activated by ligands, including cytokines, hormones and growth factors. These ligands further bind to receptors, such as epidermal growth factor receptor (EGFR), receptor tyrosine kinase (RTK) and G-protein-coupled receptor (GPCR). Activation of these receptors firstly activates class I PI3K, then phosphorylates phosphatidylinositol 4,5-biphosphate (PIP2) to phosphatidylinositol 3,4,5-triphosphate (PIP3) and recruits signaling proteins, including AKT [116].The PI3K/AKT pathway can also be activated by loss of phosphatase and tensin homolog (PTEN). PTEN is a main negative regulator of the PI3K that dephosphorylates PIP3 to PIP2 [117].

Exosomes have been found to exhibit protective effects in CNS injuries by activation of the PI3K/AKT pathway. It has been identified that MSCs-derived exosomes decreased ROS production, apoptosis and TJ disruption in H/R-injured endothelial cells. Moreover, MSCs-derived exosomes activated PI3K/AKT pathway and inhibition of PI3K by its inhibitor LY294002 ameliorated the protective effects of exosomes [98]. Moreover, Cao *et al.* revealed that USC-derived exosomes harboring ANGPTL3 enhanced spinal cord functional recovery after SCI by activation of the PI3K/AKT pathway [49]. Furthermore, Wang *et al.* indicated that cEPCs-derived exosomes had beneficial effects on mouse IS by attenuating infarct volume and cell apoptosis, increasing the microvessel density and promoting axon growth ability via activating the PI3K/AKT pathway [50].

But how exosomes regulated the PI3K/AKT pathway in CNS injuries was uncertain. Recently, in many cancer models, it has been proposed that the regulation of the PI3K/AKT pathway by exosomes might be associated with the miRNA/PTEN pathway [118–120]. That means, exosomes firstly controlled miRNAs, which further regulated PTEN and the downstream PI3K/AKT pathway. For example, colorectal cancer

(CRC) cell-derived exosomal miRNA-934 induced M2 macrophage polarization by downregulating PTEN expression and activating the PI3K/AKT signaling pathway [121]. In another case, exosomal miRNA-223 derived from macrophages promoted the drug resistance of epithelial ovarian cancer (EOC) cells via the PTEN-PI3K/AKT pathway. In addition, exosomal miRNA-32-5p induced multidrug resistance in hepatocellular carcinoma by down-regulation of PTEN to activate the PI3K/AKT signaling pathway [122]. Therefore, combined with these literatures, we speculated that exosomes may also regulate the PI3K/AKT pathway via miRNAs-PTEN axis in CNS injuries. Further studies are needed to explore it.

4.4 Notch1

Notch1 is a class I transmembrane protein that directly transduces extracellular signals into cells. Notch1 modulates interactions between physically adjacent cells and plays an essential role in cell fate decisions and tissue homeostasis by binding to its ligands [123]. Notch1 signaling is initiated by interaction of the receptor with its ligands Delta-1 or Jagged-1. This ligand-receptor interaction triggers Notch1 intracellular cytoplasmic domain (NICD) which translocates into the nucleus. There, nuclear Notch1 associates with the transcription factor recombining binding protein suppressor of hairless (RBP-Jκ), activates the expression of target genes and regulates a variety of cellular metabolisms [124]. Recent studies have demonstrated that the Notch1 signaling pathway was involved in CNS injuries such as cerebral ischemic injury. Blockage of the Notch1 signaling pathway could reduce neuronal cell apoptosis, suppress inflammatory response, promote angiogenesis and improve prognosis in CNS injuries [125, 126]. Exosomes also facilitated Notch1 to provide neuroprotection in ischemic brain injury. It has been suggested that down-regulation of Notch1 induced by microglia-derived exosomes was associated with decreased neurobehavioral deficits, fewer infarct areas in the brain and less apoptosis in ischemia-reperfusion injury. In addition, the Notch1 inhibitor Cren further enhanced the effects [127].

The underlying mechanism of how exosomes regulate Notch1 may involve miRNAs. It has been shown that miRNA-137 could mediate the function of microglia-derived exosomes by binding to the 3’ untranslated region (UTR) of Notch1 [127]. In another case, Liu *et al.* found that in bone marrow MSCs, exosomes secreted by mesenchymal stem cell transplantation (MSCT) reduced intracellular levels of miR-29b, which resulted in recovery of DNA methyltransferase 1 (Dnmt1)-mediated Notch1 promoter hypomethylation and inhibition of Notch1 signaling [128]. These data indicated a critical role of miRNAs between exosomes and Notch1 signaling. However, the clear mechanisms of how exosomes regulate Nothch1 in CNS injuries are unknow, which is an interesting aspect worth exploring.

The Notch family consists of four receptors, classified as Notch1, Notch2, Notch3, and Notch4 receptors. Notch1 and Notch2 are expressed widely in tissues throughout development. Notch3 is expressed mainly in pericytes and vascular smooth muscle, and Notch4 is most abundant in endothelium [129]. The distribution differences make the functions of the Notch receptors variants rather distinct. Notch1 mutation leads to vascular malformations, Notch2 mutation causes vascular and renal defects, Notch3 mutation induces viable and fertile and Notch4 is dispensable for embryonic development [130]. Since Notch1 can be controlled by exosomes in ischemic brain injury, further studies are needed to clarify whether other Notch receptors such as Notch2 and Notch3 can be regulated by exosomes in CNS injuries.

4.5 Extracellular signal-regulated kinase (ERK)

ERK is a serine/threonine protein kinase that belongs to the mitogen-activated protein kinase (MAPK) family It is widely expressed in eukaryotic cells [131]. Various stimuli, such as trauma, oxidative stress and inflammation, activate tyrosine kinases and transmit the signal to rat sarcoma virus (Ras). Ras-guanosine triphosphate (GTP) binds to rapidly accelerated fibrosarcoma (Raf) and induces its translocation to cell membrane from cytoplasm. Activated Raf phosphorylates serine residues of mitogen-activated protein kinase kinase (MEK) in its catalytic region, which further phosphorylates ERK. Phosphorylated ERK moves to the nucleus, activates many transcription factors, and results in regulation of cell proliferation, differentiation, gene expression and various physiological processes [132]. In physiological states, ERK is essential for normal development and functional plasticity of the CNS. However, in pathological states such as cerebral ischemia, brain trauma and ischemia-reperfusion injury, abnormally expression of ERK may play a detrimental role by promoting cell apoptosis and oxidative stress [133]. Exosomes have been shown to regulate ERK by affecting its phosphorylation. Long *et al.* implied that astrocyte-derived exosomes significantly inhibited lipopolysaccharide (LPS)-induced microglial M1 phenotype transformation and the subsequent inflammation through decreased phosphorylation of ERK [134].

5. Other Aspects Of Exosome Research In Cns Injuries

CNS injuries, caused by cerebrovascular pathologies or mechanical contusions, comprise a diverse group of pathological processes, including glutamate excitotoxicity, oxidative stress, apoptosis and autophagy [135]. Although the functions of exosomes on CNS injuries-induced cognitive function, inflammation, angiogenesis, apoptosis, autophagy and BBB disruption have been widely described, its roles in excitotoxicity and oxidative stress have not been fully illustrated.

5.1 Excitotoxicity

Excitotoxicity is a phenomenon that describes the damage of cells due to exacerbated exposure to excitatory amino acids [136]. The underlying mechanisms of excitotoxicity includes alterations in glutamate and Ca^{2+} metabolism, dysfunction of glutamate transporters and malfunction of glutamate receptors [137]. In this process, glutamate is the main factor that induces excitotoxic cell damage. Normally, glutamate plays crucial roles in neuronal growth, axon guidance and synaptic plasticity. However, excessive or prolonged activation of glutamate causes the imbalance of neuronal Ca^{2+} homeostasis and final excitotoxicity, leading to mitochondrial destruction, neuronal damage and oxidative stress [138].

The functions of exosomes in excitotoxicity have also been well established. It has been shown that long-term secretion of exosomes protected neurons from excitotoxic damage in the model of trophic factors deprivation [139]. Besides, astrocyte-derived exosomes suppressed glutamate-induced hippocampal neuron death in an *in vitro* glutamate excitotoxicity model [140]. In addition, in Alzheimer's disease (AD)

models, exosomes isolated from AD patient cerebrospinal fluid (CSF) and plasma, from the plasma of AD mouse models, and from the medium of neural cells expressing familial AD presenilin 1 mutation impaired neuronal Ca^{2+} handling and mitochondrial function, and render neurons vulnerable to excitotoxicity [141]. Therefore, exosomes may also intervene excitotoxicity in CNS injuries. However, further studies are needed to verify it.

5.2 Oxidative stress

Oxidative stress, defined as imbalance between the biological systems leading to the generation of oxidant (free) radicals and the systems responsible for the removal of free radicals, is harmful to cells due to the excessive generation of oxidant compounds such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) [142]. Under physiological conditions, both ROS and RNS are generated at moderate concentrations and act as second messengers to regulate signal transduction pathways. However, the excessive generation of ROS and RNS due to depletion of the antioxidant system or excitotoxicity leads to the oxidation of biological molecules such as lipids, proteins, and DNA, resulting in oxidative damage in cells, tissues and organs [143]. Oxidative stress has been reported in CNS injury models and contributed to the secondary brain damage such as brain edema, BBB damage and apoptosis [144, 145].

There were also researches indicating that exosomes could regulate oxidative stress. Wang *et al.* suggested that MSCs-derived exosomes could protect against oxidative stress-induced skin injury via adaptive regulation of the nuclear factor erythroid 2-related factor 2 (Nrf2) defense system [146]. Moreover, Arslan *et al.* proposed that MSCs-derived exosomes increased adenosine triphosphate (ATP) levels, decreased oxidative stress, enhanced myocardial viability and prevented adverse remodeling after myocardial ischemia/reperfusion injury by activating the PI3K/AKT pathway [147]. In addition, strawberry-derived exosomes prevented oxidative stress in human mesenchymal stromal cells [148]. Therefore, whether exosomes could regulate oxidative stress in CNS injuries needed to be further studied.

6. Concluding Remarks

Exosomes play essential roles in CNS injuries and participate in a number of cellular and molecular processes of CNS injuries. In this review, we summarize the sources of exosomes, the functions of exosomes as well as some downstream moleculars of exosomes in CNS injuries. These observations make exosomes to be attractive therapeutic targets for patients suffering from CNS injuries. Continued discoveries in this field will bring novel insights on exosomes involved in biological functions and disease progression. Ultimately, exosomes may hold promise for clinical challenges.

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Conflict of interest statement

The authors declare no conflict of interest.

Availability of data and material

All data generated during this review are included in this article.

Code availability

Not applicable.

Authors' contributions

Professor Handong Wang conceived the whole work design and played a vital role in paper submission. Li Zhang finished the original manuscript including figures and tables. Lei Mao revised the manuscript.

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Figures

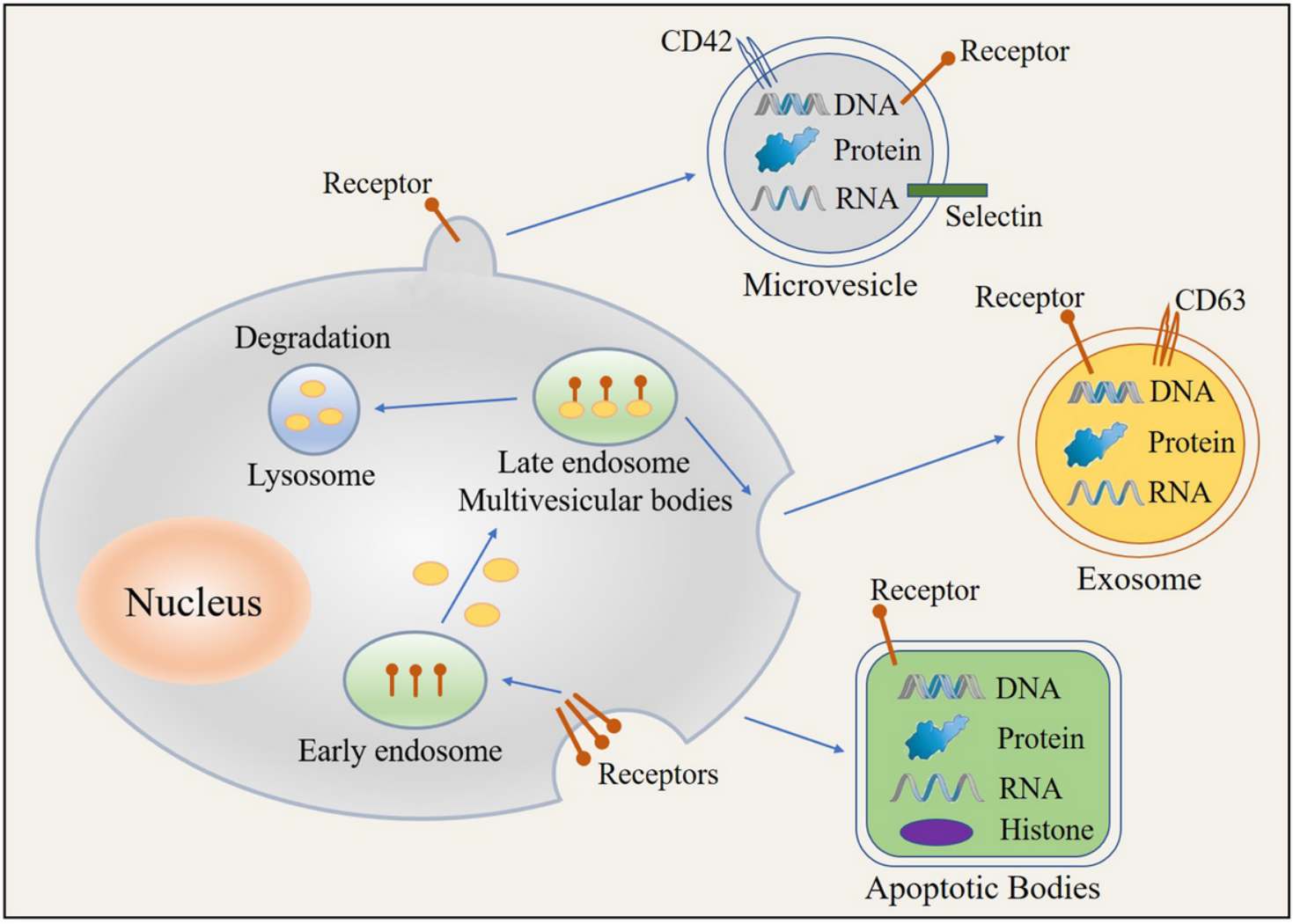

Figure 1

The biogenesis of extracellular vesicles. Exosomes containing DNAs, RNAs and proteins firstly fuse into early endosomes to form late endosomes (multivesicular bodies, MVBs). Late MVBs then fuse with lysosomes for degradation or fuse with plasma membrane to release exosomes. Microvesicles are secreted by outward budding and splitting of plasma membrane. Apoptotic bodies are produced by blebbing of apoptotic cells. They contain DNAs, RNAs, proteins and histone.

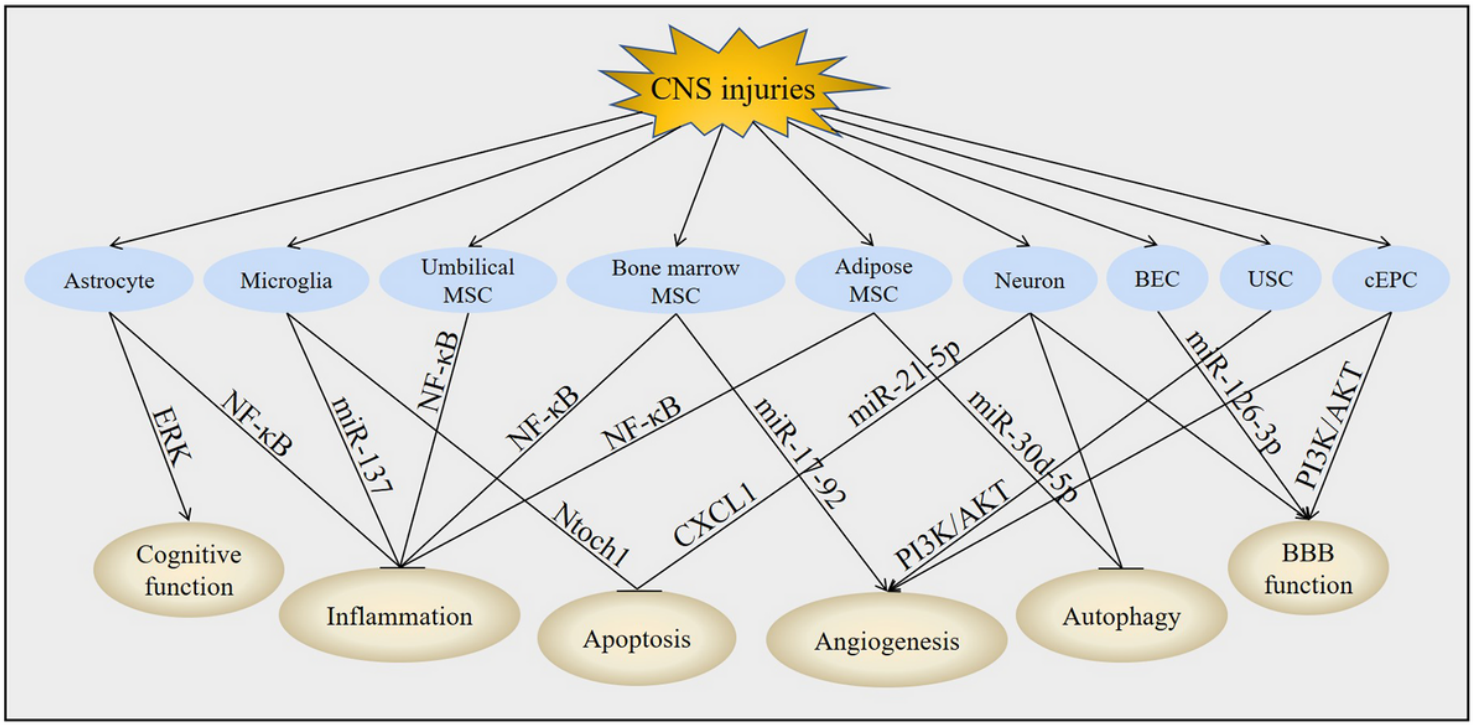

Figure 2

Downstream molecules of exosomes in CNS injuries. In CNS injuries, astrocyte, microglia, umbilical MSC, bone marrow MSC, adipose MSC, neuron, BEC, USC and cEPC-derived exosomes lead to the modulation of miRNAs, activation of PI3K/AKT and inhibition of ERK, NF-κB, Notch1, CXCL1. These downstream molecules subsequently improved cognitive function, promoted angiogenesis, regulated autophagy, protected BBB function, and suppressed apoptosis and inflammation post-CNS injuries.