The Neuroprotection Effects of Exosome in Central Nervous System Injuries: a New Target for Therapeutic Intervention

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Received: 2 December 2021 / Accepted: 5 September 2022 / Published online: 14 September 2022
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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), phosphatidylinositol-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.

Keywords Central nervous system injuries · Exosomes · Downstream molecules

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 [5]. Among EVs, exosomes are most broadly investigated. Exosomes are 30 to 120 nm endogenous nanovesicles containing proteins, lipids, and nucleic acids [6]. The exosome formation process mainly involves three steps: (1) the formation of early endosomes by invagination of the plasma membrane; (2) the early endosomes generate late endosomes and multivesicular bodies (MVBs) containing intraluminal vesicles. Upon fusion of MVBs with the plasma membrane, the vesicular contents are released, called exosomes; (3) if MVBs fuse with lysosomes, the MVBs are degraded. In addition, microvesicles are secreted by outward budding and splitting of plasma membrane, and apoptotic bodies containing DNAs, RNAs, proteins, and histone are produced by blebbing of apoptotic cells (Fig. 1) [7, 8]. Exosomes can cross the BBB and have the potential to specifically deliver molecules to CNS [9]. 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 involved in intercellular communication [10]. Via cargo proteins, mRNAs, DNAs, and microRNAs (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 neighboring cells [11]. Furthermore, most cells in CNS have been reported to secrete exosomes into the extracellular environment [12, 13]. It has been shown that exosomes were involved in the brain development, functional diversification, and contributed to diverse neurological disorders, such as CNS injuries [14, 15]. 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.

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 [16]. This observation led to investigations into the potential role of exosomes in multiple models [17]. Recently, the effects of exosomes in CNS injuries were elucidated. Although there are both exogenous and endogenous exosomes, the exosomes mentioned in our review were isolated from cells in vitro and used for the treatment of CNS injuries via intravenous injection or intracerebroventricular injection. Specifically, exosomes derived from astrocyte, microglia, neuron cells, mesenchymal stem cell (MSC), and brain endothelial cells (BECs) were found to influence brain damage in CNS injury models (Table 1).

Compared to direct cell transduction, exosomes also carry bioactive chemicals such as proteins, mRNAs, and miRNAs and have the same transduction functions of derived cells. In addition, exosomes own the diameter of nanoparticles and can cross the BBB, which are the key factors for the information transfer between derived cells and other cells. Studies have shown that most cells used to treat CNS diseases were attributed to their release of exosomes [18].

Astrocyte and Microglia

Astrocytes and microglia are able to release cytokines, chemokines, and growth factors in respond to brain damage [19]. These factors can affect the homeostatic balance of CNS and determine the degree of injury [20]. 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 [21]. 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 [22]. 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 [23]. Reactive astrogliosis is 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 activate inflammatory response after CNS injuries [24]. The diversified functions of astrocytes make them predominant among other cells in CNS [25, 26].

| Sources | Models | Animals and/or cells | Beneficial functions of exosomes | Molecular targets |
|---------|--------|----------------------|----------------------------------|-------------------|
| Astrocyte | TBI | Mice, mouse neurons | Improve neurological deficits, decrease inflammation and apoptosis | ERK, NF-κB, GJA1-20 k |
| | IS | Mouse neurons | Suppress neuronal apoptosis, regulate autophagy | miR-7670-3p, SIRT1 |
| | I/R injury | Rats, N2a cells | Promote cell proliferation, inhibit apoptosis | miR-34c, miR-361, NF-κB |
| | OGD/R injury | Mouse neurons, OPCs | Induce cell differentiation and migration, reduce apoptosis | miR-424-5p |
| Microglia | I/R injury | Mice, mouse neurons | Attenuate behavioral deficits, infarct volume and apoptosis | miR-124, USP14 |
| | TBI | Mouse neurons, BV2 cells | Inhibit neuronal inflammation, contribute to neurite outgrowth | miR-124-3p, miR-5121 |
| | IS | Mouse neurons | Decrease infarct volume, behavioral deficits, and apoptosis | miRNA-137, Notch1 |
| | OGD/R injury | BMECs, mouse neurons | Reduce neurological dysfunctions and cell injury | miR-424-5p, miR-92b-3p |
| | ICH | Rats, rat neurons | Suppress neuronal necroptosis | miR-383-3p, ATF4 |
| Umbilical MSC | HIBD | Ovine fetuses | Reduce the neurological sequelae and BBB damage | / |
| | PBI | Rat pups, BV2 cells | Rescue normal myelination and mature oligodendroglia | NF-κB |
| Bone marrow MSC | TBI | Mice, mouse neurons | Improve cognitive function and angiogenesis, reduce inflammation | miR-124-3p, miR-5121 |
| | IS | Mice, mouse neurons, BV2 cells | Promote new regeneration, prevent immunosuppression | miR-34c, miR-361, NF-κB |
| | SCI | Rats, BMECs, mouse neurons | Reduce neurological dysfunctions and cell injury | NS-424-5p, miR-92b-3p |
| Adipose MSC | TBI | Rats | Facilitate functional recovery, inhibit inflammation | ERK, NF-κB, p38 |
| Neuron | TBI | BV2 cells | Inhibit inflammation and apoptosis, promote neurite growth | miR-21-5p |
| | SAH | Mouse | Mitigate brain edema and BBB injury, reduce inflammation | miR-193b-3p |
| BEC | I/R injury | Mice, PC12 cells | Promote functional motor recovery, decrease apoptosis | miR-126-3p |
| USC | SCI | Mouse | Enhance neurological functional recovery, promote angiogenesis | PI3K/AKT |
| cEPC | IS | Mouse | Reduce infarct volume and apoptosis, promote angiogenesis | miR-126, PI3K/AKT |
| NSC | SCI | Rats, PC12 cells | Inhibit neuroinflammation and apoptosis | miR-219a-2-3p, NF-κB |
| Macrophages | IS | Rats, SH-SY5Y cells | Improve neurological function, decrease inflammation | / |
| DPSC | I/R injury | Mice | Alleviate brain edema, cerebral infarction, and inflammation | NF-κB |

CNS central nervous system, TBI traumatic brain injury, ERK extracellular regulated protein kinase, NF-κB nuclear factor kappa-light-chain-enhancer of activated B, GJA1-20 k gap junction alpha 1-20 k, IS ischemic stroke, miRNA microRNA, SIRT1 sirtuin-1, I/R ischemia–reperfusion, OGD/R oxygen–glucose deprivation/reoxygenation, UPS14 ubiquitin-specific protease 14, BMEC brain microvascular endothelial cell, ICH intracerebral hemorrhage, ATF4 activating transcription factor 4, MSC mesenchymal stem cell, HIBD hypoxic/ischemic brain damage, BBB blood–brain barrier, PBI perinatal brain injury, SCI spinal cord injury, BSCB blood-spinal cord barrier, SAH subarachnoid hemorrhage, BEC brain endothelial cell, USC urine stem cell, PI3K/AKT phosphatidylinositol-4,5-bisphosphate 3-kinase/protein kinase B, cEPC circulating endothelial progenitor cell, NSC neural stem cell, DPSC dental pulp stem cell.

astrocytes can function as reactive astrogliosis following CNS injuries by regulation of gene expression, morphology, and proliferative capacity [23]. Reactive astrogliosis is 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 activate inflammatory response after CNS injuries [24]. The diversified functions of astrocytes make them predominant among other cells in CNS [25, 26].
Microglia are brain-resident myeloid cells that regulate immune reaction and inflammatory response [27]. Microglia have been considered as the "gate-keepers" of CNS microenvironment with a large number of functions in development and remodeling of the nervous system [28]. Moreover, microglia modulate cell survival and neurological recovery in response to brain damage by release of trophic factors [29]. 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) [30]. Deficiency of microglia has been reported to participate in CNS injuries such as stroke, TBI, and hypoxia–ischemia injury [31, 32].

In physiological conditions, astrocyte or microglia-derived exosomes are enriched with various biological molecules including genes, miRNA, and proteins. Conversely, in pathological conditions such as oxidative stress, inflammation, and nutrient deficiency, astrocyte or microglia-derived exosomes exert neuroprotective effects and promote neurite regeneration and outgrowth [33, 34]. Besides, the exosomes can be isolated from astrocyte or microglia in vitro. Firstly, supernatants collected from cultured astrocyte or microglia were filtered with a 0.2-μm filter to remove the large debris and dead cells. Then, small cell debris were removed by centrifugation at 10,000 g for 30 min and the supernatants were further recentrifuged at 100,000 g for 3 h. The supernatants were used as exosome-free controls and stored at 4 °C. The pellets were resuspended in phosphate buffered saline (PBS) and stored at −80 °C [35, 36].

Neuron Cell

Neurons are specialized cells with a high level of polarization, and the basic function of neurons is responsible for rapid communication of information [37]. Under normal or pathological conditions, neurons can secret exosomes and mediate a variety of different effects, including nutritional metabolic support, nerve regeneration, inflammatory responds, and the propagation of toxic components, playing an important role in health and neurodegenerative diseases [38]. The exosomes can also be isolated from neuron in vitro as described in the literature [39]. Interestingly, recent studies have shown that neuron-derived exosomes might be isolated by a precipitation/immunoaffinity approach using antibodies against neuronal cell adhesion molecule L1 cell adhesion molecule (L1CAM) [40].

The exosomes secreted by neuron, astrocyte, and microglia could affect the interactions and the physiology of these cells by transmitting lipids, proteins, and RNAs, thus supporting their metabolic requests and responding to environmental stimuli [41]. Neuron exosomes can interact with astrocyte exosomes that sense and respond to neuronal activity and participate in the re-uptake of neurotransmitters [42]. For example, astrocyte exosomes regulate nutrients delivery through BBB based on neuronal activity [43]. Neuron exosomes could also affect microglia exosomes. It has been shown that exosomes release by neurons facilitated microglial removal of degenerating neurites by up-regulating the complement molecule C3 in microglia exosomes [34]. Moreover, microglia-derived exosomes interact with neuron exosomes by promoting neuronal production of ceramide and sphingosine, which positively affects excitatory neurotransmission [44]. Furthermore, microglia-derived exosomes drive the enrichment in proteins implicated in cell adhesion/extracellular matrix organization and cellular metabolism, which in turn affect the cellular response of recipient astrocyte exosomes [45]. In addition, through the capillaries, astrocyte exosomes can participate to the inflammatory response upon interact with neuron and microglia exosomes [46].

MSC

MSCs are stromal cells that have the ability to self-renew and also exhibit multilineage differentiation [47]. 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 [48]. Recently, MSCs have been found in new sources, such as menstrual blood and endometrium [49]. Depending on different parameters such as tissue source, isolation method, and medium composition, the role of MSCs is different [50]. MSCs can secrete high levels of proteins, cytokines, and immune-receptors that functions in immunoregulation, revascularization, cutaneous wound healing, angiogenesis, and tissue regeneration [51]. In addition to secret proteins, MSCs also release exosomes, which could be a promising therapeutic target in diseases [52].

MSCs have the ability to generate large number of exosomes; the generation rate of exosomes is associated with the proliferation rate of MSCs [53]. There are a lot of methods that have been discovered to isolate exosomes from MSCs such as ultracentrifugation (UC), size-exclusion chromatography (SEC), filtration, and immunoaffinity isolation methods. Of these methods, UC was the most widely used. UC is to obtain purified exosomes by repeated differential centrifugation, filtration, and washing. However, membrane damage of exosomes may occur during centrifugation [54].

Very recent preclinical studies have identified exosomes as a dominant player in the MSC-mediated repair process of injured tissues [55]. MSC-derived exosomes coordinate intercellular communication and tissue repair through transfer of proteins, DNA, RNA, and lipids between cells, which is likely to constitute a novel mode of intercellular communication [56].
BECs

BECs are mesodermal derived modified simple squamous epithelial cells that form the walls of blood vessels [57]. A great number of studies have demonstrated that BECs play an important role in brain development, remodeling, and repair [58]. Acute injuries, including trauma, cerebral hemorrhage, and hypoxia–ischemia, can lead to BEC death, which further causes BBB disruption, inflammation, and oxidative stress [33]. 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) [59]. 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 [60]. Moreover, BECs prevent peripheral immune cells to CNS due to their low expression of adhesion molecules [61].

BECs also secret exosomes. Normally, BEC-derived exosomes can increase the proliferation, migration, and secretion of matrix metalloproteinase (MMP)-1 and MMP-3 in the mesenchymal stem cells, stimulating local trophic support. Moreover, in CNS injuries, BEC-derived exosomes can protect brain from damage [62]. The isolation of exosomes from BECs in vitro is also centrifugation, filtration, and washing as described in the literature [63].

Other Sources of Exosomes

To date, the four sources of exosome have been well-studied in CNS injuries. However, there are also some other sources of exosome that have been explored such as human urine stem cell (USC) [64], circulating endothelial progenitor cell (cEPC) [65], neural stem cell (NSC) [66], macrophages [67], and dental pulp stem cell (DPSC) [68]. All these sources of exosome may provide neuroprotection in CNS injuries.

The Function of Exosomes in CNS Injuries

Exosomes were firstly reported to exhibit neuroprotection on CNS injuries in 2012 [69]. 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). In CNS injuries such as SCI, TBI, and SAH, the relationships among cognition function, apoptosis, inflammation, angiogenesis, and autophagy have been clarified. It has been suggested that regulation of autophagy could decrease apoptosis, inflammation, and promote angiogenesis, resulting in improvement of cognition function [70, 71].

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 [72]. Thus, in a broader context, cognitive function includes all mental abilities and processes related to knowledge including memory, reasoning, attention, comprehension, and language production [73]. 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 [74]. Cognitive function impairment may occur in CNS injuries and neurodegenerative disease, which is characterized by problems in attention, thinking, memory, language, and social communication [75]. People 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 [76].

Table 2  Mechanisms of exosomes in CNS injuries

| Mechanisms                     | Factors                                      | Associated molecules                          |
|--------------------------------|----------------------------------------------|-----------------------------------------------|
| Improve cognitive function     | Reduce neuronal loss in cortex and hippocampus| /                                             |
| Promote angiogenesis           | Induce endothelial proliferation and augment vasopermeability | VEGF                                          |
| Suppress apoptosis             | Reduce chromosomal DNA fragmentation and formation of apoptotic bodies | Bcl-2, Bax, caspase-3                          |
| Inhibit inflammation           | Decrease inflammatory factors and attenuate inflammatory response | NF-κB, TNF-α, IL-1β, IL-4, IL-10               |
| Affect autophagy               | Increase the expression of LC3-II and promote the formation of autophagosome | Beclin-1, LC3                                  |
| Protect BBB function           | Reduce endothelial cell markers and tight junction protein loss | GSTo3, GPx                                     |

CNS central nervous system, VEGF vascular endothelial growth factor, DNA deoxyribonucleic acid, Bcl-2 B-cell lymphoma-2, Bax Bcl-2-associated X protein, NF-κB Nuclear factor kappa-light-chain-enhancer of activated B cells, TNF-α tumor necrosis factor-α, IL-1β interleukin-1β, IL-4 interleukin-4, IL-10 interleukin-10, LC3 microtubule-associated protein light chain 3, BBB blood–brain barrier, GSTo3 glutathione S-transferase alpha 3, GPx glutathione peroxidase

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The effects of exosomes on cognitive function after CNS injuries have been explored. In a rat TBI model, MSC-derived exosomes significantly 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 [77]. 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 [63]. 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 [78].

The precise mechanisms underlying how exosomes regulated cognitive function were unclear. Chen et al. found that exosomes derived from human adipose MSCs were mainly taken up by microglia/macrophages. They suggested that human adipose MSC-derived exosomes specifically entered microglia/macrophages and suppressed their activation during brain injury, thus facilitating functional recovery [79]. So, exosomes may improve cognitive function by regulation of microglia/macrophages activation. Moreover, it has been revealed that cognitive function impairment involved selective neuronal loss in the hippocampus and cortex [80]. Therefore, exosomes may improve cognitive function by intervene with these pathological processes.

**Inflammation**

Inflammation is one of the major determinants of secondary brain damage after CNS injuries [81]. 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 [82]. However, in respond to CNS injuries, excessive inflammation may provoke substantial detrimental effects [83]. 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)) [84, 85]. These cytokines and chemokines recruit more inflammatory cells to amplify the inflammatory response, leading to BBB breakdown, cerebral edema, and cell death [86].

Numerous studies have proposed that exosomes exerted a central effect in CNS injury–induced inflammation. The effect of exosomes in CNS injury–induced inflammation was firstly described by Zhang et al. in 2015 [77]. They found that the density of CD68 + and GFAP + cells, which respectively represents inflammatory response and astrocyte activation, was significantly increased in the lesion boundary zone after TBI. MSC-derived exosomes treatment significantly reduced the CD68 + and GFAP + cells density in the injured cortex compared to the PBS treatment, suggesting that MSC-derived exosomes had anti-inflammatory effects in TBI [77]. Moreover, in a mouse model of SAH, bone marrow MSC-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 [87]. 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 and TNF-α in vitro, indicating the anti-inflammatory effect of exosomes [67]. In addition, it has been shown that plasma exosomes could enhance melatonin therapeutic effects against ischemia-induced inflammatory responses and inflammasome-mediated pyroptosis in ischemic stroke [88].

The underlying mechanisms of exosome-mediated inflammation are immensely complicated. Studies have indicated that the NF-κB signaling pathway might be the key target. It has been shown that exosomes suppressed microglia/macrophage activation by inhibiting NF-κB and p38 mitogen–activated protein kinase (MAPK) signaling, thus suppressing inflammation [79]. Furthermore, exosomes inhibited LPS-induced microglial M1 phenotype transformation and the subsequent inflammation through decreased phosphorylation of extracellular signal-regulated kinase (ERK) and NF-κB p65 [35]. In addition, exosomes could interfere within the Toll-like receptor 4 (TLR4) signaling of microglia and prevent the degradation of the NF-κB inhibitor IκBα and the phosphorylation of molecules of the MAPK family in response to LPS stimulation [89].

**Angiogenesis**

Under physiological conditions, the brain vascular system is stable and contributes to the maintenance and growth of the tissue [90]. When brain vasculature is damaged 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 [91]. This process requires an orchestrated interplay of many stimulators, inhibitors, and matrix components [92, 93]. Angiogenesis facilitates the generation of new vasculature, which further accelerates highly coupled neurorestorative process and promotes tissue perfusion [94]. Angiogenesis is controlled by vascular growth factors such as vascular endothelial growth factor (VEGF) [95]. VEGF owns a mitogenic effect on endothelial
cells, thus increasing the vascular permeability and promoting cell migration [96].

Since angiogenesis is beneficial for CNS injury–caused secondary injury, exosomes may attenuate brain damage by promoting angiogenesis. Consistent with this hypothesis, Zhang et al. proposed that MSC-derived exosomes significantly increased the vascular density and angiogenesis as identified by EBA/BrdU + double labeling for newborn endothelial cells in the injured cortex [77]. Furthermore, bone marrow MSC-derived exosomes increased the number of branch points as proven by tube formation assay in a rat hypoxic-ischemic injury model [97]. 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 [98].

Because angiogenesis is emerging as a therapeutic target for CNS injuries, therefore, exosome-based therapies by targeting angiogenesis might provide opportunities for the development of novel therapeutic strategies for CNS injuries. Recently, exosome-based therapies have already been applied successfully for angiogenesis-mediated tissue regeneration in TBI and stroke [99]. However, the potential mechanisms have not been fully explained. It has been proposed that exosomes could promote angiogenesis by regulation of VEGFR2. VEGFR2 is responsible for most downstream angiogenic effects of VEGF, binding of VEGF to VEGFR2-activated survival and migration pathways such as focal adhesion kinase. Exosomes improved angiogenesis and neurogenesis in the peri-infarct area of mice by upregulation of VEGFR2 [100]. Furthermore, exosomes could promote the migration of brain microvascular endothelial cells (BMECs), resulting in the activation of vascular cells and angiogenesis under the anoxic condition [101]. In addition, exosome-derived communication between BECs was responsible for the induction of local neo-vascularization in brain injury [102].

**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 [103, 104]. 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 [71, 105]. If apoptosis occurs in CNS injuries, it can cause secondary brain injury, aggravating the damage of the brain [106].

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 [36]. In addition, Ni et al. showed that in a mouse TBI model, bone marrow MSC-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 MSC-derived exosomes attenuated cell apoptosis [107]. In another study conducted by Lai et al., they found that MSC-derived exosomes decreased apoptosis in the brain following SAH as shown by increased expression of Bcl-2 and decreased expression of caspase-3 [87]. In conclusion, these data suggested that exosomes could reduce cell apoptosis in models of CNS injury.

In the past decades, apoptosis was considered to release extracellular vesicles such as apoptotic bodies and microvesicles; however, exosome release due to apoptosis has not been accepted because defining exosomes in apoptosis is difficult [108]. Recently, the release of exosomes in apoptosis has been proposed and was named ApoExos. Besides the roles in intercellular communication, ApoExos share common features of exosomes such as size and density and express the typical exosomal marker such as CD63 and sphingosine 1-phosphate receptors 1/3 (S1PR1/3) [109]. It has been reported that the caspase 3-dependent formation of MVBs and the release of ApoExos in endothelial cells could lead to the delivery of translationally controlled tumor protein (TCTP) [110]. Therefore, exogenous exosomes may suppress apoptosis in CNS injuries through inhibiting the release of ApoExos. However, none of the studies has explained it in CNS injuries and this is a significant aspect worth investigating.

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) [111]. 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 [112]. 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), and Bid and negatively regulated by the anti-apoptotic Bcl-2 family members such as Bcl-2 and B-cell lymphoma-extra large (Bcl-xL) [113]. 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 [71]. Upon ligand binding, the death receptors allow the binding of an initiator caspase-8 or caspase-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 [114, 115]. Thus, which apoptotic pathway is associated with the effects of exosomes in CNS injury–induced apoptosis remains unclear and further studies are needed to clarify it.

**Autophagy**

Autophagy is an evolutionarily conserved lysosomal pathway for the degradation of cytoplasmic components [116]. 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 [117–119]. 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 [120]. 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 [121]. 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 [122].

There were also studies showing that exosomes could affect autophagy in CNS injuries. However, the roles of exosome-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 [123]. Interestingly, another study conducted by Yuan et al., they found that bone marrow MSC-derived exosomes decreased ER stress in BV2 cells by induction of disabled homolog 2-interacting protein (DAB2IP)–mediated microglia autophagy, suggesting a protective role of exosomes and autophagy in brain injury [124]. 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 thought 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.

Both exosomes and autophagy share crosslink not only at function but also at molecular signaling and vesicular levels [125]. Autophagy can be activated in recipient cells after internalization of exosomes through the following ways: (1) Exosomes containing autophagic component induced autophagy via transferring the autophagic components or via the autophagic regulators in target cells, which called exosome-induced autophagy [125]. (2) Besides the autophagic component, exosome-related miRNAs including miR-19b, miR-20a/b, and miR-21 have been indicated to regulate the dynamic of autophagy and affect autophagy flux in target cells via modulation of phosphatidylinositol-4,5-bisphosphate 3-kinase/protein kinase B (PI3K/akt)/mTOR, TLR, and AMPK signaling pathway as well as downstream autophagic molecules such as ATG, LC3, Beclin-1, P62, and ULK1 [126]. (3) Exosomes can affect autophagic degradation by changing the fusion of lysosomes with both MVBs and autophagosomes and the interference with transport or fusion of the organelles [127].

**BBB Function**

BBB is a highly specialized, semi-permeable physical barrier that locates at the interface between the CNS and the surrounding environment [128]. It is instrumental in regulating the metabolism of the brain, maintaining the micro-environmental homeostasis of CNS, and coordinating the functions of peripheral organs [128]. In addition, BBB is a dynamic metabolic interface that can bi-directionally regulate the transport of fluids, solutes, and cells [129]. 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 [130]. In an in vitro model of IS, Pan et al. found that MSC-derived exosomes alleviated BBB disruption in hypoxia/reoxygenation (H/R)-injured endothelial cells by analyzing the Evans blue dye extravasation and brain water content [131]. Moreover, Lai et al. suggested that bone marrow MSC-derived exosomes attenuated BBB permeability in early brain injury after SAH [87]. Furthermore, another in vivo study confirmed the protective effects of exosomes on BBB in ischemia–reperfusion injury [132]. It has been suggested that exosomes could protect BBB by attenuating the disturbances in BEC function, decreasing permeability and disruption of tight junctions, suppressing adhesion molecule expression, and increasing endothelial nitric oxide synthase expression [133, 134].

**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). The mechanisms described are not unique to those only from...
MiRNAs, a subset of non-coding RNAs, are 19 to 25 nucleotide long endogenously initiated short RNA molecules [135]. 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 [136].

Recently, miRNAs have been identified in exosomes, which can be taken up by neighboring or distant cells and subsequently modulate recipient cells [137]. Exosomal miRNAs play an important role in disease progression and provide neuroprotection in CNS injuries [17, 138]. It has been shown that microglia-derived exosomes could attenuate behavioral deficits and neuronal apoptosis via exosomal miRNA-124, thus protecting the mouse brain from ischemia–reperfusion injury [36]. Moreover, in a rat hypoxic-ischemic injury model, bone marrow MSC-derived exosomal miRNA-29b-3p promoted angiogenesis and suppressed apoptosis in the brain [97]. Furthermore, MSC-derived exosomal miRNA-193b-3p attenuated neuroinflammation in early brain injury after SAH [87]. In addition, exosomes derived from bone marrow MSCs reduced cell apoptosis and neuroinflammation after TBI by the action of miRNA-181b [139].

Among exosomal cargo biomolecules, miRNAs obtain the most attention due to their regulative effects in gene expression [140]. Studies have shown that miRNAs are not randomly incorporated into exosomes; a subset of miRNAs may preferentially enter exosomes [141]. Although the precise mechanisms of sorting miRNAs into exosomes remain unclear so far, four potential modes have been suggested. These include the following: (1) the neural sphingomyelinase 2 (nSMase2)-dependent pathway, (2) the miRNA motif and sumoylated heterogeneous nuclear ribonucleoprotein (hnRNP)–dependent pathway, (3) the 3′-end of the miRNA sequence-dependent pathway, (4) The miRNA-induced silencing complex (miRISC)–related pathway [142]. However, further studies are needed to prove which mode is associated with the incorporation of miRNAs into exosomes in CNS injuries.

**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 [143]. NF-κB can protect cells against inflammation and cell death by regulating the transcription of genes including cytokines, chemokines, and adhesion molecules [144].
Exosomes were also shown to modulate inflammatory response in CNS injuries by activation of NF-κB. In ischemia–reperfusion injury models, the inflammatory response reflected by the levels of TNF-α, IL-1β, IL-6, and their mediator, NF-κB, was suppressed by DPSC-derived exosomes [68]. Moreover, adipose-derived stem cell (ADSC)–derived exosomes could inhibit the activation of microglia cells and prevent neuroinflammation by suppressing NF-κB in lipopolysaccharide (LPS)-induced neural injury [145]. Furthermore, in in vivo and in vitro SCI models, NSC-derived exosomes downregulated the NF-κB-p65 axis in rats and PC12 cells respectively, thus inhibiting the BBB damage and inflammation [66]. Similar results were found in SCI models using bone marrow MSC-derived exosomes both in vivo and in vitro, bone marrow MSC-derived exosomes reduced brain cell death, enhanced neuronal survival, and improved motor function via down-regulation of NF-κB p65 signaling [146]. 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 [147]. 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 IκB to form a stable lncRNAs/NF-κB/IκB complex. Then, the phosphorylation sited of IκB is masked, thus inhibiting IκB kinase (IKK)–induced IκB phosphorylation and NF-κB activation [148]. 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 IκB. 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 [149]. 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.

**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 [150]. The PI3K/AKT pathway can be activated by ligands, including cytokines, hormones, and growth factors [151]. This 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 [152].

Exosomes have been found to exhibit protective effects in CNS injuries by activation of the PI3K/AKT pathway. It has been identified that MSC-derived exosomes decreased ROS production, apoptosis, and TJ disruption in H/R-injured endothelial cells. Moreover, MSC-derived exosomes activated PI3K/AKT pathway and inhibition of PI3K by its inhibitor LY294002 ameliorated the protective effects of exosomes [131]. 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 [64]. Furthermore, Wang et al. indicated that cEPC-derived exosomes had beneficial effects on mouse IS by attenuating infarct volume and cell apoptosis, increasing angiogenesis, and promoting axon growth ability via activating the PI3K/AKT pathway [65]. In addition, Zhang et al. proposed that stem cell–derived exosomes improved cognitive function, decreased mitochondrial apoptosis, and inhibited inflammatory response via the PI3K/AKT pathway in a model of focal cerebral ischemia–reperfusion [153].

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 [154–156]. 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 [157]. 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 [158]. 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.

**Notch1**

Notch1 is a class I transmembrane protein that directly transduces extracellular signals into cells [159]. Notch1 modulates interactions between physically adjacent cells and plays an essential role in cell fate decisions and tissue homeostasis by binding to its ligands [160].

Recent studies have demonstrated that the Notch1 signaling pathway was involved in CNS injuries such as cerebral ischemic injury [161, 162]. 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 Crenigacestat further enhanced the effects [163].

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 [163]. 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 [164]. These data indicated a critical role of miRNAs between exosomes and Notch1 signaling. However, the clear mechanisms of how exosomes regulate Notch1 in CNS injuries are unknown, which is an interesting aspect worth exploring.

**ERK**

ERK is a serine/threonine protein kinase that belongs to the MAPK family; it is widely expressed in eukaryotic cells [165]. 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 [166].

Exosomes have been shown to regulate ERK by affecting its phosphorylation. Long et al. implied that astrocyte-derived exosomes significantly inhibited LPS-induced microglial M1 phenotype transformation and the subsequent inflammation through decreased phosphorylation of ERK [35]. Besides, Chen et al. suggested that glia-derived exosomes increased the phosphorylation of glial gap junction protein connexin 43 (Cx43) via ERK signaling activation, leading to the recovery of brain functional and protection of BBB after TBI [167].

**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 [168]. Although the functions of exosomes on CNS injury–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.

**Excitotoxicity**

Excitotoxicity is a phenomenon that describes the damage of cells due to exacerbated exposure to excitatory amino acids [169]. The underlying mechanisms of excitotoxicity include alterations in glutamate and Ca2+ metabolism, dysfunction of glutamate transporters, and malfunction of glutamate receptors [170]. 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 [171]. However, excessive or prolonged activation of glutamate causes the imbalance of neuronal Ca2+ homeostasis and final excitotoxicity, leading to mitochondrial destruction, neuronal damage, and oxidative stress [172].

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 [173]. Besides, astrocyte-derived exosomes suppressed glutatione-induced hippocampal neuron death in an in vitro glutamate excitotoxicity model [174]. Furthermore, 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 Ca2+ handling and mitochondrial function and rendered neurons vulnerable to excitotoxicity [175]. In addition, MSC-derived exosomes inhibited glutamate excitotoxicity in amyotrophic lateral sclerosis (ALS), a fatal neurodegenerative disease [176]. Therefore, exosomes may also intervene excitotoxicity in CNS injuries. However, further studies are needed to verify it.

**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) [177]. Under physiological conditions, both ROS and RNS are generated at moderate concentrations and act as second messengers to regulate signal transduction pathways [178]. 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 [178]. Oxidative stress has been reported in CNS...
injury models and contributed to the secondary brain damage such as brain edema, BBB damage and apoptosis [179, 180].

There were also researches indicating that exosomes could regulate oxidative stress. Zhang et al. suggested that astrocyte-derived exosomes markedly reduced oxidative stress in the hippocampal neurons of TBI rats by increasing the activity of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) [181]. Moreover, Du et al. proposed that astrocyte-derived exosomes could protect neonatal rats from hypoxic-ischemic brain damage (HIBD)–induced oxidative stress by inhibiting BNIP-2 expression [182]. In addition, adipose MSC-derived exosomes protected brain against sepsis syndrome in rats by decreasing the protein expressions of oxidative stress (NOX-1/NOX-2/oxidized protein) [183]. Therefore, the role of exosomes in CNS injury–induced oxidative stress is needed to be further studied.

**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. Exploratory research on the participation of apoptosis, inflammation, and autophagy in CNS injuries may identify common and diverse mechanisms underlying exosomes. Moreover, microarray, proteomic, and metabolomic analyses of the downstream moleculars of exosomes may offer new avenues for restoring normal neuronal network and blocking the vital nodes promoting brain damage. In addition, these targets in the molecular pathways may serve as novel markers for exosomes. We consider that exosomes can 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.

**Author Contribution** 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.

**Funding** This work was supported by Grants from the construction of Key Medical Subjects of Jiangsu Province (No. ZDXKB2016023) from Handong Wang.

**Data Availability** All data generated during this review are included in this article.

**Code Availability** Not applicable.

** Declarations**

**Additional Declarations for Articles in Life Science Journals That Report the Results of Studies Involving Humans and/or Animals** Not applicable.

**Ethics Approval** Not applicable.

**Consent to Participate** Not applicable.

**Consent for Publication** Not applicable.

**Conflict of Interest** The authors declare no competing interests.

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