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REVIEW

Targetting Exosomes as a New Biomarker and Therapeutic Approach for Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is a neurodegenerative disease that mainly occurs in old age and involves progressive cognitive impairment. AD has become a major global issue for public health, with approximately 24 million people currently affected by the disease. Estimates indicted that this number will quadruple by 2050. Because of the high incidence of AD, there is an urgent need to develop new strategies to diagnose and treat AD. Many recent studies have indicated the multiple, yet somewhat controversial, roles of exosomes in AD. Although the underlying mechanisms by which exosomes play a role in AD are still unknown, current evidence suggests that exosomes can carry and spread toxic amyloid-beta, and hyperphosphorylated tau, between cells, and then induce apoptosis, thus contributing to the loss of neurons. In addition, exosomes appear to possess the ability to reduce brain amyloid-beta, and tau hyperphosphorylation, and transfer neuroprotective substances between neural cells. The accumulating data brings hope that the application of exosomes may be helpful for early diagnostics and the identification of new therapeutic targets for AD. Here, we summarized the various roles of exosomes, and how they might relate to the pathogenesis of AD. We also highlight the potential application of exosomes as a therapeutic option in AD therapy.

Keywords: exosomes, alzheimer's disease, biomarker, mesenchymal stem cells, therapeutic strategy

Introduction

Alzheimer's disease (AD) is the most prevalent form of dementia, and is accompanied by impaired cognition and behavior in elderly people over 65 years of age. AD affects approximately 24 million people globally, although current estimates indicate that this number is likely to quadruple by 2050.[1] AD has several neuropathological hallmarks, including the deposition of β-amyloid (Aβ) peptides in the extracellular matrix between neurons (known as amyloid plaques), the intracellular formation of neurofibrillary tangles (NFTs) arising from the accumulation of hyperphosphorylated tau protein in neurons, neuronal loss, neuroinflammation, and oxidative stress. Due to the high prevalence of AD, and its high economic burden to society, there is significant interest in developing new approaches to treat AD.[2,3]

Exosomes, a form of nanoscale vesicle, are commonly found in the biological fluids and tissues of the central nervous system, and may carry a small amount of molecular genetic material and proteins that play key roles in intercellular communication.[4] This form of vesicle transport may be related to the production, transport, and degradation of toxic proteins in AD.[5,6] In cellular and animal models of AD, exosomes have been

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shown to carry and spread toxic Aβ, and hyperphosphorylated tau, between neural cells, including neurons and glia,[7–9] and may then induce cell apoptosis, thus resulting in the loss of neurons.[10–12] On the other hand, exosomes may exert positive actions, including the reduction of brain amyloid-beta, or the transfer of neuroprotective substances between neural cells (neurons and glia).[13] Since neuron-derived exosomes (NDEs) exist in both cerebrospinal fluid and peripheral blood,[14–17] it is possible that targeting changes in the exosomes during the pathogenesis of AD might provide a new alternative approach with which to treat AD. In this review, we discuss the multiple roles of exosomes in AD, particularly the therapeutic strategies that use mesenchymal stem cells (MSCs) to treat AD, and the challenges associated with this practice in clinical scenarios.

Exosomes

Exosomes are single-lipid membrane vesicles that are secreted by all cell types, with diameters ranging from 30–150 nm.[18,19] Small vesicles are produced by the inward budding of the plasma membrane; these vesicles are then fused together to form the early endosome. During the process of endosome formation, proteins, lipids, RNAs, and other substances are enclosed into the lumen, and then accumulated within the late endosome, thus forming multi–vesicular bodies (MVBs); these are subsequently released into the extracellular milieu as "exosomes".[20] Evidence suggests that exosomes act as an important messenger for cellular communication, particularly between cells of the central nervous system.[21] Owing to their stable lipid bilayer membrane, exosomes are capable of transferring bioactive molecules (proteins, nucleic acids, and RNAs) between cells[21] (Figure 1). Because of the exchange of proteins and genetic materials, exosomes not only participate in normal physiological processes, including cell growth, immune regulation, angiogenesis, neuronal communication, and cell migration,[22] but also participate in the pathogenesis of various diseases, including AD.[23] Our recent study showed that kidney and brain protein (KIBRA), an adaptor-like protein, can regulate the secretion of exosomes through a Rab27A-dependent mechanism, and participate in the

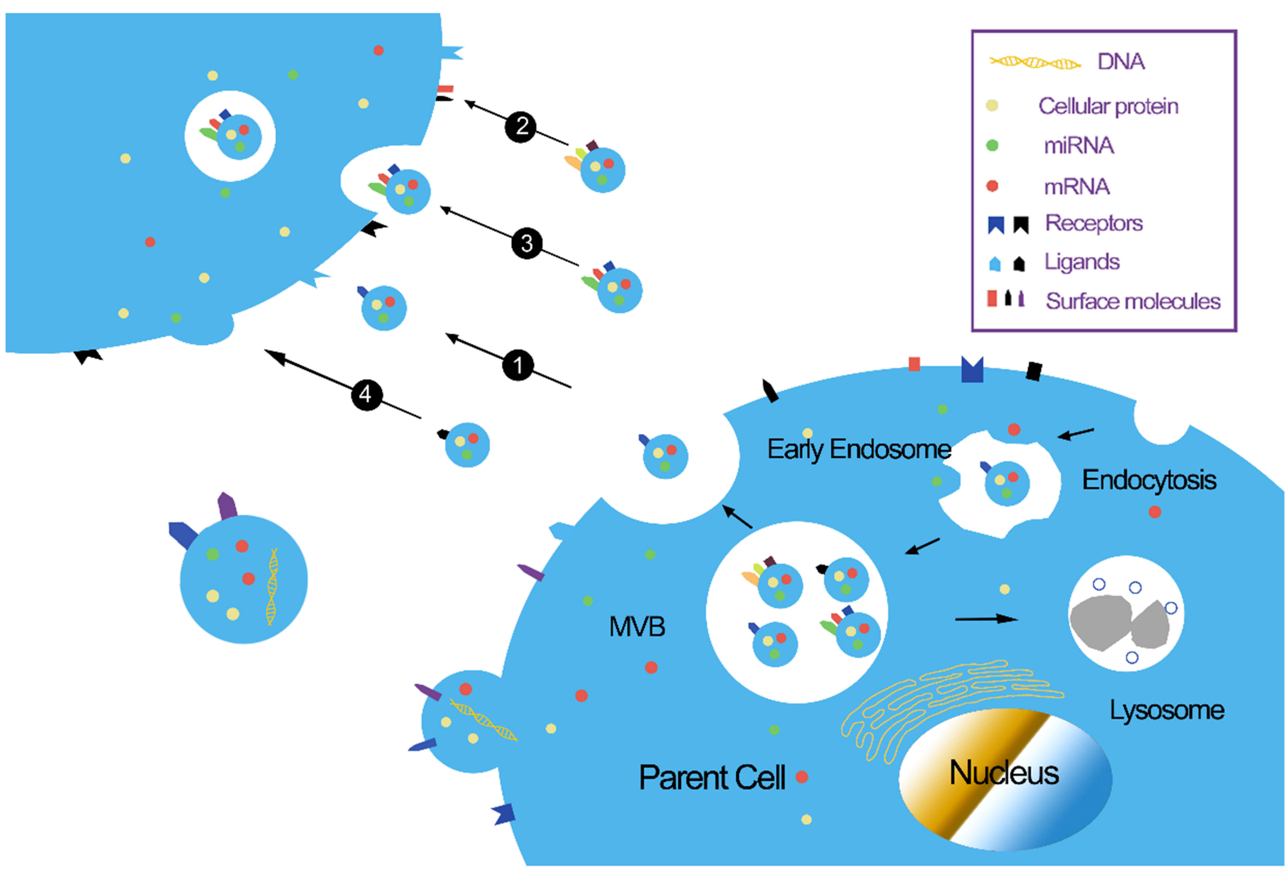

Figure 1 Biological functions of exosomes. (1) Stimulation of recipient cells by functioning as signal complexes; (2) Transfer of surface receptors or lipids into recipient cells; (3) Delivery of cytoplasmic proteins and nucleic acids via the endocytic pathway; (4) Delivery of cytoplasmic proteins and nucleic acids by membrane fusion.
Abbreviations: miRNA, micro RNA; MVB, multivesicular body.

progression of AD pathology.[24,25] Another of our recent studies indicated that the up-regulation of mammalian target of rapamycin (mTOR) facilitates the release of tau into the extracellular space in an exosome-independent manner in SH-SY5Y cells.[26] More recently, research has shown that the mTOR complex 1 (mTORC1) also regulates the release of exosomes through a Rab27A-dependent mechanism. mTORC1 activation inhibits exosome release, while the inhibition of mTORC1 induces the release of exosomes without significantly changing cargo content, thus indicating that mTORC1 controls the release of exosomes, but not formation.[27] Due to their ability to cross the blood–brain barrier (BBB),[28] it follows that exosomes might represent an important approach for exploring new treatment options for AD.

Markers and Contents in Exosomes

Exosomes are microvesicles that are typically enclosed in a lipid bilayer membrane that is used for transport and serves to protect the luminal cargo against damage from severe extracellular environments.[29] The lipid bilayer contains proteins, some of which have been identified as relatively specific exosomal markers, including CD9, Alix, CD63, and TSG101.[30] All of these markers, together with CD81, can be used to identify exosomes; otherwise, they could be mistaken for other forms of extracellular vesicles.[31] The lipids in exosomes can regulate the exosomal sorting of small RNAs and proteins.[32,33] In addition to proteins and lipids, there are a number of other genetic materials found in exosomes, including DNA, mRNA, miRNA, ribosomal RNA (rRNA), circular RNA, and long noncoding RNA (lncRNA).[34,35] Exosomes can carry and transmit these genetic materials to play a part in normal physiological processes and diseases.[36–38] Exosomes contain RNAs that are involved in many aspects of neurological function, including synaptic transmission, angiogenesis, neurite outgrowth, axonal growth, and neuronal differentiation from neural stem cells.[39]

In addition to RNA, DNA, and proteins, exosomes have been shown to contain bioactive lipids, such as ceramide, cholesterol, phosphatidylserine, and sphingolipids[40,41] (Figure 2).

The Role of Exosomes in AD

The Pathogenic Role of Exosomes in AD

Evidence has emerged recently to indicate that exosomes play a harmful role in the aggregation and deposition of specific misfolded proteins, such as Aβ, tau, prions, and α-synuclein; these subnormal proteins are all core features in neurodegenerative disorders.[12,42–44] Exosomes have been shown to carry different disease-causing cargos,

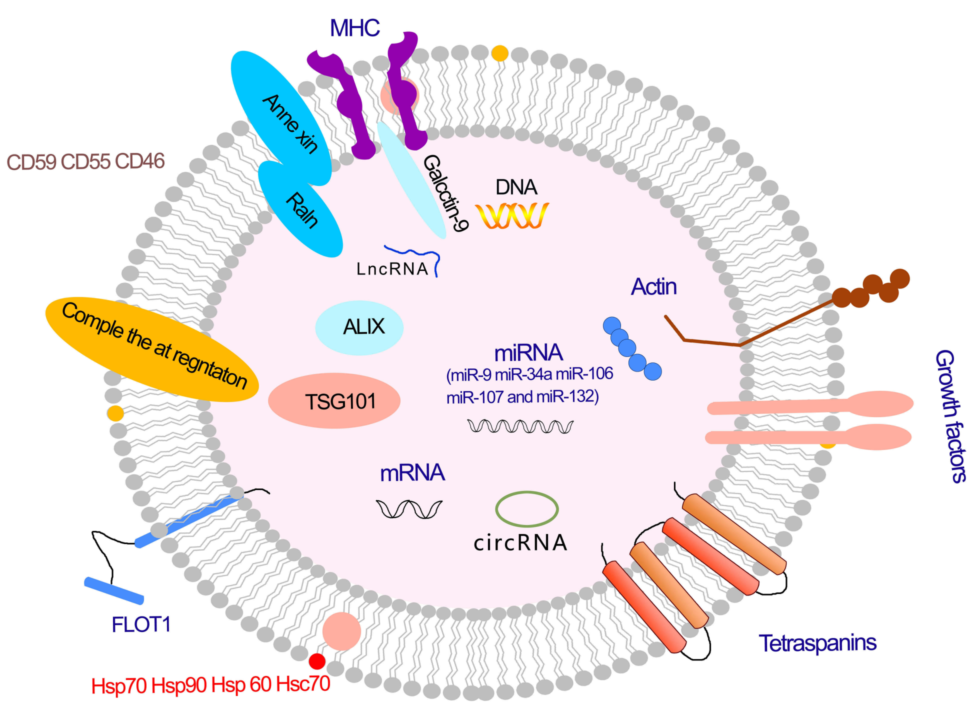

Figure 2 Exosome and its cargo.
Abbreviations: MHC, major histocompatibility complex; mRNA, messenger RNA; miRNA, microRNA; LncRNA, long non-coding RNA; circRNA, circular RNA.

including proteins, RNA, and miRNA.[45] Importantly, exosomes can carry Aβ, tau, prions, and α-synuclein, and can spread pathogenic proteins across the brain.[8,46–50] On the other hand, exosomes have generated immense interest after their discovery as mediators for the delivery of important proteins and microRNAs during intercellular communication, suggesting that exosomes may serve as an early biomarker of AD.[51,52]

Aβ is produced by the successive hydrolysis of amyloid precursor protein (APP) by β-secretase (BACE) and γ-secretase; the β-cleavage of APP mainly occurs in early endosomes.[53,54] Soluble amyloid precursor protein beta (sAPPβ), APP, and BACE, have been shown to be co-localized with early endosomal markers (Rab5), and early endosomal antigen-1, in APP mutant HeLa cells by immunofluorescence.[53] The accumulated Aβ in MVBs can be released into the extracellular space through exosomes.[54] HEK cells expressing APP Swe/Ind were previously shown to be capable of efficiently transferring APP to normal primary neurons by exosomes.[55] Plasma exosomes containing AA amyloid oligomers were previously shown to exhibit amyloid-enhancing factor activity in a murine transfer model of AA amyloidosis.[56] Plasma NDEs from AD patients induce AD-like neuropathology, including Aβ deposition and tau phosphorylation, in normal mouse brain.[57] Meanwhile, in vivo studies have shown that the reduction of exosomes contributes to lower senile plaque deposit in the 5XFAD mouse model, a mouse line that expresses five mutations of familial AD.[12] These lines of evidence have confirmed that exosomes promote Aβ aggregation, and accelerate amyloid plaque formation.[30] Exosomes might be one of the main mediators participating in the progression of AD neuropathology.[58] Accordingly, exosomes from blood,[59] CSF,[60,61] and cell cultures[62] have been shown to contain monomeric Aβ and tau.

Exosomes can not only spread AD pathological proteins; they are also suggested to play a harmful role in impairing neuronal functions by other means in AD. For example, exosome contents have been proposed to induce neuronal apoptosis in astrocytes exposed to amyloid protein, and in 5XFAD mouse models of AD.[12,63] Amyloid peptides could activate neutral sphingomyelinase 2 (nSMase2), and induce an increase in the secretion of ceramide-containing exosomes in astrocytes.[63] In contrast, these secreted exosomes could be captured by astrocytes, and subsequently cause neural apoptosis.[63,64] GW4869, an inhibitor of nSMase2, was shown to reduce Aβ in a mouse model of AD by preventing the secretion of exosomes,[12] thus indicating that the ceramide generated by nSMase2 may be critical for the formation of exosomes. Aβ and exosomes were also found to co-localize inside neurons, thus suggesting that exosomes participate in Aβ sorting and oligomerization.[65]

Tau is a core protein associated with the pathogenesis of AD and is secreted in exosomes.[66] Our previous study showed that the up-regulation of mTOR facilitates the release of tau into the extracellular space in an exosome-independent fashion in SH-SY5Y cells.[26] Furthermore, a recent study showed that tau protein is released via exosomes from cultured primary neurons, and N2a cells overexpressing different tau constructs or CSF in AD and control subjects.[67] These results indicated that intracellular tau is secreted into the extracellular space in an exosome independent manner. Research has also shown that exosomes isolated from CSF samples diagnosed with AD contained higher levels of tau phosphorylation at the epitope Thr-181, indicating that exosomal tau may contribute to abnormal tau phosphorylation.[68] Interestingly, tau is phosphorylated at epitope Thr-181, the site that is most enriched in exosomal tau; this epitope therefore represents a specific biomarker for the elevated tau seen in early AD.[61,68,69] Another study showed that microglial cells play a significant role in phagocytosis and the secretion of tau in exosomes; the depletion of microglia in two diverse tauopathy mouse models showed that the propagation of tau could be inhibited, and that the inhibition of exosome synthesis reduced the propagation of tau compared with a control group, both in vitro and in vivo.[61] Based on these results, exosomes derived from microglia are efficient carriers for spreading tau between neurons. A recent study also showed that exosomes from the CSF of AD patients, containing monomeric and oligomeric tau, can also result in the aggregation of tau in cultured cells.[67]

Beneficial Actions of Exosomes in AD

Although several studies have shown that exosomes can be harmful for AD, there is a growing body of evidence demonstrating that they also possess beneficial actions that may be of importance in the development of AD. For example, the up-regulation of exosomes containing nSMase2 secretion enhances Aβ uptake in microglia and signifcantly reduces the extracellular levels of Aβ.[70] Exosomes from the neuronal genetically modified neuroblastoma cell line (N2a cells) have the capacity to neutralize Aβ-induced disruptions in synaptic plasticity and prevent Aβ-induced neuronal apoptosis.[71] In another study, neuroblastoma-derived exosomes were injected into the right hippocampus of AβPP/PS1 transgenic mice; these exosomes were shown to bind to Aβ and subsequently be incorporated into microglia.[72] Interestingly, the continuous injection of exogenous exosomes resulted in a marked reduction of Aβ deposition and neurotoxicity in AβPP/PS1 transgenic mice.[72] In summary, numerous studies have focused on the neuroprotection functions of exosomes with regard to the reduction and clearance of Aβ.

Among the many approaches adopted to treat AD, stem cell therapy and, particularly, the use of mesenchymal stem cells (MSCs) is receiving significant attention. This is because MSCs are involved in multiple biological processes, including neurogenesis, oligodendrogenesis, axonal connectivity, and myelin formation.[73–76] Around eight years ago, a research study showed that the intravenous delivery of MSCs allowed transport across the blood–brain barrier and subsequent migration to sites of neural injury without inducing tumorigenic or immune responses.[77] MSCs have also been shown to promote cognitive function in various pathological conditions,[78–80] including neuro-regeneration,[72] neuroprotection,[79] the reduction of Aβ deposits and tau-related cell death,[80] and the down-regulation of pro-inflammatory cytokines, such as TNF-a and IL-1β.[81] Research attention has re-focused on exosomes recently because a study found that MSCs may exert their therapeutic effects via exosomes;[82–84] these observations were made in a range of studies, including the experimental treatment of collagenase-induced osteoarthritis in a mouse model,[84] wound healing in diabetic skin ulcerations or extensive burns,[85] and limb ischemia in mice.[86] Multiple studies have found that MSC-derived exosomes are good candidates for the treatment of AD. Indeed, the co-culture of human adipose-derived mesenchymal stem cells (ADSCs), with N2a cells that overproduced human Aβ, showed reductions in both extracellular and intracellular Aβ levels in N2a cells. These authors also found that exosomes secreted from ADSCs carry enzymatically active neprilysin, the most important Aβ-degrading enzyme in the brain, thus suggesting a potential new treatment for AD.[72,87] Hao et al co-cultured injured cortical neurons with ADSCs, and found that ADSCs secreted exosomes that exerted direct neuroprotective effects by inhibiting neuronal cell apoptosis, thus promoting the regeneration and repair of the central nervous system (CNS), and hence restoring bioenergy following energy depletion caused by glutamate excitotoxicity.[88] In another study, Ahmed et al demonstrated the detection of neprilysin in exosomes secreted by dental pulp stem cell (DPSC) and that these exosomes were able to degrade Aβ1-42 and to reduce Aβ-induced neurotoxicity in SH-SY5Y neuroblastoma cells in vitro.[89] In another study, MSC-derived exosomes were shown to improve learning and memory function in APP/PS1 transgenic mice, reduce Aβ accumulation, and increase the expression of synaptic protein in the brains of APP/PS1 transgenic mice.[90,91] Furthermore, treatment with exosomes derived from MSCs were shown to reduce the activation of glial cells, and the levels of inflammatory factors involved in the regulation of the STAT3 and NF-kB pathways.[91] A very recent study further showed that the injection of exosomes derived from human umbilical cord mesenchymal stem cells (hucMSCs) into the brain could repair cognitive dysfunction and facilitate the clearance of Aβ deposition in the AβPP/PS1 transgenic mouse model.[92] Therefore, MSC-derived exosomes have emerged as an appealing approach for the delivery of therapeutics for AD.

Given the available evidence, it is evident that exosomes may play a vital neuroprotective role in neurodegenerative diseases, including AD, and may, therefore, represent a new therapeutic approach for AD in clinic. Table 1 summarizes our current understanding of the various roles of exosomes in AD.

Future Directions: The Clinical Value of Exosomes

Exosomes as Biomarkers

In AD, exosomes can be synthesized and released from brain cells, pass through the BBB, and can be detected in the peripheral blood or in CSF;[93] these properties render exosomes as ideal biomarkers to reflect the pathological progress of AD. Changes in the contents of exosomes that are circulating in the blood may serve as early biomarkers for the diagnosis and treatment of AD.[94] For example, NDEs have

Table 1 Multiple Roles of Exosomes in AD

Harmful actions	Spreading Aβ and P-tau[10,43,53–57] Stimulation of aggregation of extracellular Aβ[10,43]
	Mediating neuron-to-neuron propagation of oAß[6–10]
	Induction of neuronal apoptosis[10]
Beneficial actions	Binding extracellular Aβ and promoting its degradation[70,92]
	Neutralizing Aβ induced disruption in synaptic plasticity[71]
	Carrying nucleic acids with gene expression regulating abilities[90,100–102]
	Serving as therapeutic vehicles of drug delivery for AD[108–110]

Abbreviations: AD, Alzheimer's disease; APP, amyloid precursor protein; oAß, ß-amyloid oligomers.

recently been proposed as potential biomarkers for AD; Fiandaca et al found that NDEs in patients with AD showed significantly higher levels of amyloid β 1–42 (Aβ1-42) than those from case controls 1 to 10 years before diagnosis; this test could be developed as a valuable predictor of AD.[60] In another paper, Jia et al reported that the levels of Aβ1-42, total tau, p-T181 tau, and p-S396 tau, in NDEs that were isolated from the plasma of AD patients were significantly higher when compared with controls, thus providing a good predictor for disease development during the preclinical stage.[95] A recent study also found that extracellular vesicles in the circulatory system can respond to the state of the central nervous system, and that levels of Aβ 42, T-tau, and PT181-tau in NDEs may reflect the pathological changes associated with AD in the brain, and therefore exhibit the same capacity to diagnose AD as those in the CSF.[96] In addition, miRNAs, which play significant roles in the regulation of various biological processes, and even the diagnosis of many diseases, are therefore considered as candidates for blood-based exosomal biomarkers for dementia. However, the standardization of exosomes extracted from blood components (plasma or serum) for the development of miRNA biomarkers is complicated.[39,97] The literature relating to exosome-associated miRNAs as biomarkers for AD is very limited, and current understanding requires further validation in different cohorts. One of the highlights of existing exosomal research is the characterization of their molecular properties in specific diseases. Extensive attention is now being afforded to exosome-derived biomarkers in the blood of AD biomarker research. However, the development of exosomal biomarkers for AD requires further verification.

Exosomes for Therapeutic Application

Exosomes have the ability to transfer bioactive molecules between cells across the BBB, and can be used as effective natural carriers for the therapeutic delivery of potential-disease modifying molecules.[93] Compared with traditional gene therapy candidate vectors such as viruses, polyethylenimine nanoparticles, and liposomes, exosomes have greater advantages in terms of therapeutic efficacy, good levels of safety, a low immune response, and offer the possibility of targeting.[97] Exosomes are naturally secreted components of body cells and are widely found in extracellular fluids.[18] Exosomes for therapeutic treatment can be obtained from the medium of cultured MSCs with reduced levels of cell immunogenicity.[84] The availability of MSCs in a variety of tissues, their ease of isolation, and their significant ability to propagate in vitro have made MSCs desirable potential producers of exosomes.[98] The adaptability of these MSCs to genetic modification further enables them to produce exosomes that are rich in the required therapeutic factors. Proteomic analysis of MSC-derived exosomes showed similar immunotolerance characteristics as MSCs,[99] further enhancing the importance of these cells as allogeneic and autogenous natural delivery vehicles. Furthermore, it has been suggested that the therapeutic effect of MSCs with regard to targeting pathological regions is exerted via the exosomes that they secrete.[100] A recent study has demonstrated that exosomes secreted by MSCs have remarkable migration and homing abilities towards specific areas of neuropathology, and specifically to neurons, and that neuroinflammation plays a vital role in these homing mechanisms.[101] These authors also found that 24 hrs after intranasal administration, exosomes derived from MSCs were found to have been transported to the hippocampus, the central region associated with AD.[101] Thus, the specific migration and homing abilities of MSC-derived exosomes could pave the way for their use as multifunctional theranostic agents in AD.

Several studies have suggested that exosomes derived from MSCs transfer their therapeutic factors, particularly miRNAs, to recipient cells, thereby altering gene expression and thus promoting a therapeutic response.[21,42] Exosomes have also been studied as a delivery platform for encapsulation, or short interfering RNAs (siRNA).[90] For example, Alvarez-Erviti et al showed that the delivery of BACE-1 siRNA mediated by exosomes, which specifically targeted β-secretase, resulted in a 60% knockdown of the BACE-1 gene, thus leading to a 55% reduction of Aβ levels in the mouse brain.[102] Aβ is derived from the cleavage of Aβ precursor protein (APP) by β- and γ-secretases; MSCs can be genetically modified to secrete exosomes that are enriched with therapeutic factors, such as siRNAs, that specifically target β- and γ-secretase enzymes, such that exosomes can be exploited as valuable nanotechnological approaches that exert vital neuroprotective effects on AD.[103,104] This approach has been explored experimentally in an attempt to improve functional recovery after stroke, enhance neurovascular plasticity, and repair injured brain tissue after traumatic brain injury.[105–108] Thus, it may be possible to use MSC-derived exosomes as a cell-free therapy for the treatment of AD.[109]

In addition, the exciting potential of exosomes as therapeutic vehicles lies in drug delivery and development strategies to design and modify both the surface and content of these valuable biological structures. A recent study showed that exosomes derived from curcumin-treated (primed) cells (Exo-cur) can relieve the symptoms of AD by inhibiting the phosphorylation of Tau protein and help to prevent neuronal death both in vitro and in vivo.[110] With regard to exosomal-mediated protein delivery, the incorporation of catalase into exosomes (ExoCAT) has further revealed significant neuroprotective effects for Parkinson's disease in both in vitro and in vivo models.[111] In recent years, an exosome-based delivery system developed exosomes for protein loading via optically reversible protein-protein interactions (EXPLORs). This research integrated a reversible protein-protein interaction module that was controlled by blue light, and used an endogenous process for exosome biogenesis; exosomes generated by this process could be readily loaded with cargo.[112] Using the EXPLOR technique, most intracellular proteins, including transcription factors, signal transducers, and enzymes, can be efficiently targeted by EXPLOR-based therapeutics.[113] Thus, exosomes may hold significant potential to improve targeted drug delivery and neuronal functional recovery in AD therapy.

Challenges and Limitations

Although there is a growing body of literature relating to the rapid development of exosomes derived from MSCs, the therapeutic use of these exosomes remains in its infancy. Many issues need to be resolved before MSC-derived exosomes can be used for clinical treatments. Significant research is still required in order to guarantee the long-term biological safety of these exosomes, and confirm the potential adverse effects and efficacy of exosome administration in patients with AD.[114] We also need to know more about the time of administration, the most effective route of administration, including dose-response experiments, before considering MSC-derived exosomes for clinical application.

One of the key issues for the future development of exosomes for clinical application is to scale up the production of appropriate exosomes. The inherent properties of MSCs are advantageous to the large-scale production of exosomes. The large-scale production of clinically normative MSCs for the generation of exosomes is one of the key factors in translating MSC-derived exosomes for clinical application. There are still many problems to be resolved if we are to improve the production of MSC-derived exosomes. The large-scale production of MSC-derived exosomes requires new techniques, and the experimental protocol for extracting exosomes from MSCs still needs to be standardized. However, based on the promising results achieved from preclinical studies thus far, exosome-based therapies are steadily making their way towards clinical application.[97,115]

Moreover, the precise content of MSC-derived exosomes remains largely unknown because these exosomes contain many molecules that are yet to be identified. The exosome contents have been determined with microarray and proteomics techniques. However, exosome might have different contents according to the origin of the MSCs or their culture conditions. Our understanding of exosome-related therapies is rapidly expanding although exosomes have already been approved for application in several clinical trials. Table 2 summarizes the advantages and challenges of MSC based therapy and MSC exosome based therapy.

Conclusions

In recent years, exosomes have been gradually viewed as multipotent therapeutic targets and potential biomarkers of various diseases including AD. Thus, the development of genetically modified MSC exosomes might open a novel horizon for therapeutic strategies in AD. In this paper, we have reviewed the possible functions and applications of exosomes in AD. Together, these findings indicate that exosomes have a therapeutic potential for treating AD by enhancing neuroprotection mechanisms and being therapeutic vehicles, and exosomes may be have a vital biomarker role in AD preclinical and clinical studies.

Table 2 Advantages and Challenges of MSC Based Therapy and MSC Exosome Based Therapy

Type of Therapy	Advantages	Challenges
MSC based therapy	Potential of proliferation and differentiation, release of exosomes and other biological factors	Malignant transformation, tumor generation, microvascular obstruction
MSC Exosome based therapy	No apparent adverse effects, capability to cross the blood brain barrier, no vascular obstructive effects, easy to be stored and engineered	Determine the specific benefits and mechanisms of exosome administration, indepth study of exosome contents, potential side effects: tumor promotion

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Disclosure

The authors declare no conflicts of interest in this work.

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