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Exosomes in Pathogenesis, Diagnosis, and Treatment of Alzheimer's Disease

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Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the accumulation of β-amyloid peptide 1-42 and phosphorylation of tau protein in the brain. Thus far, the transfer mechanism of these cytotoxic proteins between nerve cells remains unclear. Recent studies have shown that nanoscale extracellular vesicles (exosomes) originating from cells may play important roles in this transfer process. In addition, several genetic materials and proteins are also involved in intercellular communication by the secretion of the exosomes. That proposes novel avenues for early diagnosis and biological treatment in AD, based on exosome detection and intervention. In this review, exosome-related pathways of cytotoxic protein intercellular transfer in AD, and the effect of membrane proteins on exosomes targeting cells are first introduced. The advances in exosome-related biomarker detection in AD are summarized. Finally, the advantages and challenges of reducing cytotoxic protein accumulation via exosomal intervention for AD treatment are discussed. It is envisaged that future research in exosomes may well provide new insights into the pathogenesis, diagnosis, and treatment of AD.

MeSH Keywords: **Alzheimer Disease • Biological Markers • Exosomes**

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Background

Alzheimer's disease (AD) is a late-onset neurodegenerative disorder involving memory and other cognitive impairments. The initiating mechanism of its onset is related to poisoning, metabolism, genetic factors, and so on. Recent evidences have demonstrated that vascular, inflammatory and degenerative pathways critically interact and contribute to its pathology [1–3]. However, no hypothesis has yet managed to account for all symptoms and pathogenic mechanism in AD, it is commonly accepted that the main pathological features of AD involve amyloid β-peptide 1–42 (Aβ1–42) protein accumulation and phosphorylated tau protein (p-tau)-induced apoptosis in nerve cells. Aβ1–42 toxic protein accumulation may not be easily degraded and eliminated by ubiquitin or the autophagy pathway [4]. Moreover, abnormal p-tau tends to lose its function of maintaining microtubule stability [5,6]. The consequent microtubule assembly leads to microtubule associated axonal transport barriers, which interfere with the formation of lysosomes and contribute to the aggregation of toxic proteins in axons [7].

In another hand, AD familial studies have suggested that toxic proteins are associated with multiple specific gene mutations, such as the amyloid precursor protein gene (*APP*) and presenilin (*PS-1, PS-2*), which appear to facilitate Aβ1-42 assembly by promoting Aβ production [8–10]. However, AD genetic studies have indicated that several genes, such as *ApoE4* and *ApoJ*, affect the degradation of Aβ1–42 protein [11–13]. These results have provided the theoretical basis for diagnostic genetic factor-based biomarker discovery and gene therapy for AD.

In recent studies, the presence of Aβ1–42 protein and p-tau in the cerebrospinal fluid (CSF) of patients with AD was verified [14–16], suggesting that toxic proteins may penetrate into the extracellular fluid through nerve cell secretion. In addition, adding toxic proteins to cell culture medium or CSF induced pathological and behavioral changes both in nerve cells and animal models analogous to AD [17–19]. These results suggest that the transmission of toxic proteins between cells may be an important pathway for AD progression after the initiation of AD pathogenesis. However, the transfer mechanism of these toxic proteins between the cells and extracellular fluid remains unclear.

Exosomes, a kind of nanoscale vesicle widely present in various cells and the extracellular fluid, may carry small molecular genetic material and proteins involved in information transfer between cells [20,21]. This vesicle transport may relate to the toxic protein generation, transportation, and degradation process in AD [22–24]. This might provide a new line of research for revealing the disease's progressive pathogenesis and improving the current poor treatment status of AD. In this review, we focus on discussing the roles of exosomes in toxic protein production, transportation, and degradation, with a mind to providing new viewpoints to the pathogenesis, model establishment, and biological therapy of AD.

Biological Characteristics of Exosomes

Exosomes are a kind of single lipid membrane vesicles secreted by cells, with diameters ranging from 40 to 100 nm, and are widely distributed in body fluids [25]. Many kinds of cells such as neurons, glial, stem, and tumor cells may release exosomes to the extracellular fluid through direct fusion of the multivesicular bodies with the plasma membrane [26]. However, it was only in the last decade that exosomes were considered to play an important role in intercellular communication based on genetic content transport. Exosomes in the extracellular fluid can bind to target cells through membrane receptors, directly fuse with the plasma membrane, or be endocytosed to release their contents [20]. This process was verified by co-culture of R18-labeled exosomes and PKH-67-labeled cells; the membrane fusion process was observed under the fluorescence microscope [27]. Moreover, exosome microRNA transfer to target cells using fluorescent labeling has also been reported [28]. These findings confirmed the extracellular transport mechanism through exosomes.

A database of exosomes content was roughly established by large-scale analysis of various tissues, and there were11261 protein entries, 2375 mRNA entries and 764 miRNA entries in exosomes [29]. In addition, modified exosomes successfully delivered exogenous siRNA into the brain tissue of mice after intravenous administration, indicating that modified exosomes may cross biological barriers, such as the blood-brain barrier (BBB) [30]. The technology of exosomes content detection and exogenous genetic material modify may deliver exogenous hereditary materials to acting sites on nerve cells and create new avenues for disease biomarkers detection and gene therapy for neurological diseases such as AD.

Furthermore, the issue of how exosomes function on target cells with high selectivity remains a challenge for targeted treatment. In several studies, the rabies virus glycoprotein (RVG) peptide was bound to the extra-exosomal N terminus of murine Lamp2b [30,31], a protein found abundantly in exosomal membranes [32], in order to selectively act on neural cells. It is noted that modified exosomes have successfully delivered exogenous interfering RNA exclusively into neural cells *in vivo* [30]. At the same time, the exosomes of homologous cells have immunogenicity, which can effectively avoid inducing immune response. In addition, through the fluorescent labeling of exosomes and animal imaging technology, the acting sites of exosomes can be dynamically tracked, which makes it possible to provide effective technical support for accurate gene therapy.

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Exosomes in the Pathogenesis of AD

Exosomes are believed to be involved in the spread of many neurodegenerative diseases, including Parkinson's disease (PD) and AD [33]. After the occurrence of AD initiating factors, Aβ may be secreted from cells in association with exosomes and be released to the extracellular space. However, most tau proteins released into extracellular fluids are cut-off mid-region tau [34,35], lacking tail ends that cause tau aggregation. Therefore, Full-length tau in exosomes via endocytosis or axonal transmission may be the main vector of abnormal tau transmission [36]. Polanco et al. established a simple model of neural circuit with hippocampal neurons. They observed the exosomes spreading in the interconnected neurons and found the exosomes can spread the Aβ and tau protein by endosomal pathway and axonal transport [37]. Moreover, in the plaques of patients with AD, enriched accumulation was found in Aβ and specific exosomal proteins, such as Alix, indicating the Aβ in the plaques may constitute the contents of the exosomes secreted from neural cells in AD [38]. In addition, research on tau protein has reported that the concentration of abnormal p-tau in exosomes isolated from the CSF of patients with AD at the mild/severe stage (Braak stages 3–6) was significantly higher than that from patients with AD at the early stage (Braak stages 0–2). This phenomenon indicated that exosome-mediated secretion of p-tau might play a significant role in the abnormal processing of tau and in the increase of CSF tau during early AD [39]. Furthermore, hypophosphorylated tau protein-rich exosomes extracted from CSF of AD patients can promote the aggregation of tau protein in neurons and microglia [40]. Exosomes play a similar role in other neurodegenerative diseases. For instance, α-synuclein was released from exosomes to the extracellular fluid, based on a calcium dependent mechanism, which aggravates and propagates PD-related pathological features [41]. Moreover, exosomes may wrap prion proteins and be secreted from the infected cells to the extracellular fluid, and deliver prion proteins to the target cells by membrane fusion [42]. This is similar to the pathological mechanism in AD and PD.

In addition, exosomes are also involved nerve cell injury in AD. The mutation of the *PS* gene could downregulate cystatin C in exosomes, a protein targeting the classical secretory pathway by its signal peptide sequence and providing a neuroprotective function in AD [43], which induced the decrease of soluble APP and increase of Aβ1–42 [44]. In contrast, lysosomes play an important role in neurodegenerative diseases by degrading unnecessary proteins [45]. Lysosomal dysfunction promotes exosome secretion from nerve cells in neurodegenerative diseases and aggravates extracellular toxic protein accumulation [41].

Not only the exosomes of neurons aggravate the progress of AD, but also the exosomes in astrocytic apoptosis involved in AD pathogenesis. In the central nervous system (CNS), astrocytes are indispensable for the support of neurons. However, astrocytes may also activate inflammatory and proapoptotic signaling pathways if they are triggered to migrate and proliferate [46–48]. Astrocytic reactivation has been observed in many neurodegenerative diseases, including AD [49,50]. Glial apoptosis has been reported to be correlated with the number of senile plaques, and caspases activation has been suggested to contribute to astrocytic damage [51,52]. Bieberich et al. found that expression of prostate apoptosis response 4 (PAR-4) and the simultaneous elevation of ceramide can induce apoptosis in neural progenitor cells [53,54], and they verified that Aβ could induce apoptosis in astrocytes *in vitro* through a PAR-4-dependent mechanism. They also suggested that the mechanism of astrocytic apoptosis in AD may be associated with the secretion of PAR-4/ceramide-containing exosomes, which could induce cell death [55]. Furthermore, they found neutral sphingomyelinase 2 (nSMase2) deficient astrocytes were protected from Aβ induced apoptosis, and nSMase2 could modulate the secretion of exosomes [24].

Although exosomes are involved in nerve cell injury in AD, in the nervous system they are active messengers, protecting neurons from oxidative stress [56]. Similar neuroprotective effects are found in neurodegenerative diseases. In AD research, it was found that exosomes both played a role in toxic protein spread and acted on Aβ to reduce injury in the nervous system. In the extracellular fluid, exosomes derived from N2a cells may abrogate the synaptic-plasticity-disrupting activity of both synthetic and AD brain-derived Aβ, and rescue long-term potentiation from Aβ-mediated impairment *in vivo*. These effects are mainly due to the sequestration of Aβ oligomers via exosomal surface proteins, such as the p75 neurotrophin receptor (PrPc), which has high affinity to Aβ oligomers [57]. Furthermore, in the CNS, microglia around the neurons can remove damaged structures, including exosomes-delivered Aβ. Enhancement of exosome secretion could efficiently reduce extracellular levels of Aβ by the glycosphingolipids (GSLs) on its surface [24].

Exosomes as Biomarkers in the Diagnosis of AD

Biomarkers are necessary for improving diagnostic sensitivity and specificity and for monitoring the biological activities of AD, prior to apparent clinical symptom manifestation. Toxic proteins in exosomes can be detected in the early stage of the disease, and exosomes are carriers of specific toxic proteins between cells and the extracellular fluid in a variety of neurodegenerative diseases. Therefore, the detection of specific toxic proteins in peripheral exosomes from body fluids is expected to become a biomarker-based method in the diagnosis of early stage AD and other neurodegenerative diseases.

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Recently, the combination of CSF p-tau and CSF Aβ1–42 has widely been studied as a diagnostic biomarker capable of distinguishing AD from other dementia in the early stages. Comparing the AD, dementia with Lewy bodies, and vascular dementia, concentration of CSF p-tau, it was highest in patients with AD [14,15,58]. Although CSF p-tau detection can help distinguish AD from other types of dementia, comparing p-tau concentrations in exosomes is more helpful for identifying the degree and stage of AD by combining symptoms based on the positive correlation between the amount of p-tau in CSF exosomes and the severity of AD. Moreover, as p-tau can be found in CSF exosomes in the early stage, it is helpful for the early diagnosis of AD [39]. Recent study has found that the full-length tau to mid-region tau in CSF and plasma exosomes of AD patients was much higher than free solution, while the CSF and plasma exosomes of healthy people did not contain full-length tau [36]. Therefore, CSF exosomes may be used as a biomarker in the diagnosis of AD. But at present, p-tau can also be identified in a small amount of CSF [59]. Detection of specific tau in CSF exosomes for diagnosis of AD does not show better application prospects.

There have been several studies on the detection of Aβ1-42 in the CSF and plasma of patients with AD at the early stage [60–63]. Current investigations suggest that Aβ accumulation could bring forward the diagnosis of AD by more than 15 years [64]. However, the detection rate of Aβ1–42 in the CSF in early stage AD was only 40%–50%, and the concentrations remained stable over a period of 12 months [65]. Furthermore, the accumulation of Aβ1–42 in the plasma was dissimilar to that in the CSF [66], and there was no variation in plasma Aβ over time in patients with AD [67]. Therefore, plasma Aβ cannot be utilized as an AD biomarker in previous viewpoint. As CSF Aβ is mainly derived from the exosomes secreted by lesion cells, detection of Aβ1–42 in CSF exosomes is prospected to improve the diagnostic sensitivity of AD. In the study of combined detection of CSF p-tau and Aβ1–42, sensitivity and specificity were higher than 86% [68]. Other studies have reported that the combined detection of CSF Aβ1–42 and p-tau might help assist early diagnosis for AD 10 years prior to clinical onset and differentiate early stage AD from frontotemporal lobar degeneration [69,70]. Therefore, the combined detection of these two potential biomarkers in CSF exosomes may be more valuable for the early diagnosis of AD.

In recent years, advantages of miRNAs in disease diagnosis have attracted research attention to miRNA detection. miRNA could be a biomarker for AD diagnosis. As miRNA secreted by the host cells is rich in exosomes, there have been several studies in which exosomes were extracted from different types of body fluids for miRNA micro-quantitative determination. In a case study, five miRNAs were found to be significantly different in CSF exosomes from the normal control group (two upregulated, three downregulated) [71]. More miRNAs were found to be abnormal in AD plasma exosomes (19 upregulated, 33 downregulated) [72,73]. In the downregulated miRNAs, mir-342-3p was also significantly reduced in the blood of patients with AD [74]. Other microRNAs, such as miR-9-5p and miR-598, could be detected rich in the exosomes delivered from CSF of AD patients [75]. The comparison of these results could provide accurate early diagnosis for AD.

Exosomes in the Treatment of AD

In the nervous system, exosomes are active messengers, protecting neurons from oxidative stress [56]. As mentioned before, exogenous exosomes can assist in the degradation of Aβ1–42 in AD and other neurodegenerative diseases. Hao et al. co-cultured injured cortical neurons with human adipose-derived mesenchymal stem cells (ADSCs) using a semi-porous membrane, and the results demonstrated that AMSCs-conditioned medium, enriched with exosomes, mediates direct neuroprotection by inhibiting neuronal cell apoptosis, promoting nerve regeneration and repair, and restoring bioenergy following energy depletion caused by glutamate excitotoxicity [76]. In another study, exosomes were extracted from mesenchymal stromal cell (MSC)-conditioned medium and injected into a rat stroke model; it was found that exosomes could reduce nerve cell injury [77]. These results suggest that exosomes originating from ADSCs, and other exogenous stem cells, could be used for the treatment of nervous system diseases. In the exosomes isolated from ADSCs, the content of Neprilysin (NEP) was significantly higher than that of nerve cells [78], and this neutral endopeptidase was related to the degradation of Aβ [79,80]. The exosomes isolated from rat primary neurons contained cystatin C, which is also involved in the degradation of Aβ [81–83]. The physiological high concentration of cystatin C in the CSF and its proliferative effect on neural rat stem cells suggested it could exert a trophic function in the brain [84]. Therefore, exogenous exosomes are considered to be potential agents for the treatment of AD.

Owing to their RNA transport capacity, stable presence in body fluids, and capability of crossing the BBB, exosomes can be used as carriers to deliver nucleic acid fragments, such as miRNA and siRNA, for the treatment of AD. In 2011, a study first reported successful treatment in AD mice by using exosomes carrying siRNA [30]. Purified RVG-targeted exosomes were loaded with exogenous siRNA by electroporation. Significantly decreased protein expression and Aβ deposition in the AD mouse brain were confirmed. This provided evidence for the validity of exosome therapy for neurodegenerative diseases through siRNA delivery. In another study, delivery of miR-124a through exosomes enhanced the expression of excitatory amino acid transporter 2 (GLT1) on the surface of astrocytes, for modulating

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synapse activity and improving glutamate uptake [85]. This method is expected to alleviate neuronal apoptosis in AD.

Compared to traditional candidate vectors for gene therapy, such as viruses, polyethylenimine nanoparticles, and liposomes, exosomes show greater advantages in therapeutic effect, targeting ability, low immune response, and safety [86]. Exosomes are naturally secreted components from body cells, and are widely present in the extracellular fluid [25]. Exosomes for therapeutic treatment can be obtained from the culture medium of MSCs or self-derived dendritic cells with reduced cell immunogenicity [30,87,88]. Exosomes can prevent the activation of the immune system and phagocytosis by mononuclear macrophages due to the expression of CD55 and CD59 [89]. Therefore, exosomes may be safely applied in AD therapy.

Conclusions

Exosomes have been confirmed as an important agent in AD pathogenesis progression. Elucidating the underlying mechanisms involved will promote AD model establishment, early stage diagnosis, and gene therapy. It may also provide insights into potential therapies for other neurodegenerative diseases.

As small genetic fragments and toxic proteins could be carried by exosomes and transported between cells and extracellular fluids, which might also be the mechanism of the slow progress of neurodegenerative diseases, it can be assumed that in the co-culture system of nerve cells and isolated exosomes from plasma or CSF of patients with AD, nerve cells may be induced into AD-like injury cells. Furthermore, applying specific amounts of exosomes from AD to the CSF may induce AD symptoms in animal models. Intracerebral aggregation of alpha-synuclein can be induced by injecting exosomes extracted from brain tissues of dementia with Lewy bodies patients in animal model brains [90]; in another study, exosomes containing pathogenic proteins from the conditioned medium of HEK293-APP Swe/Ind cells showed high neurotoxicity to the hippocampal dentate gyrus region *in vivo* [91]. These results would promote a new approach for establishing AD and other neurodegenerative disease models. Compared to the existing AD models, exosome-based cell and animal models more closely resemble the actual pathogenesis.

In the early stage of AD, the combined detection of p-tau and Aβ1–42 can effectively enhance diagnostic sensitivity and specificity, as these two potential biomarkers are more likely delivered to extracellular fluids by exosomes. With the development of clinical laboratory technology, toxic proteins can be detected in a small amount of CSF, which offsets the advantages of CSF exosomes. Detection of toxic proteins and specific microRNA in plasma exosomes will improve the convenience of early diagnosis of AD.

Finally, exosomes will become a new hot spot in molecular treatment of AD due to their security, selectivity to target cells, and their capacity for small molecule drug delivery. In addition, exosome diffusion is not restricted by biological barriers, providing more options for exosome administration.

Conflicts of interest

None.

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