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Review on the roles of specific cell-derived exosomes in Alzheimer's disease

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Alzheimer's disease (AD) is the sixth leading cause of death worldwide and cannot be effectively cured or prevented; thus, early diagnosis, and intervention are important. The importance of exosomes, membrane-bound extracellular vesicles produced in the endosome of eukaryotic cells, in the development, diagnosis, and treatment of AD has been recognized; however, their specific functions remain controversial and even unclear. With the development of exosome extraction, isolation, and characterization, many studies have focused on exosomes derived from different cells and body fluids. In this study, we summarized the roles of exosomes derived from different body fluids and cells, such as neuron, glial, stem, and endothelial cells, in the development, diagnosis, monitoring, and treatment of AD. We also emphasize the necessity to focus on exosomes from biological fluids and specific cells that are less invasive to target. Moreover, aside from the concentrations of classic and novel biomarkers in exosomes, the size and number of exosomes may also influence early and differential diagnosis of AD.

KEYWORDS

Alzheimer's disease, mild cognitive impairment, exosome, biomarkers, neuron, glial cells

Introduction

Alzheimer's disease (AD) is one of the leading causes of death worldwide and the most common form of dementia, comprising 60–80% of all cases (Landeiro et al., 2018). The global number of patients with AD is expected to rise to 65.7 million in 2030 and 115.4 million in 2050, at a rate of one new case every 3 s (Prince et al., 2013). AD is characterized by the accumulation of amyloid plaques formed by extracellular aggregates of the amyloid- β ($A\beta$) peptide, neurofibrillary tangles formed of intracellular hyperphosphorylated microtubule-associated tau proteins, and axonal degeneration. It can affect memory, use of language, and behavior and may develop into a severe disability, causing a huge burden to both families and society (Ghidoni et al., 2018). Currently, more than 99% of clinical trials for AD therapy have failed

(Cummings et al., 2014), and only seven FDA-approved palliative drugs are available. Therefore, timely diagnosis and intervention are important in the early stages of AD.

According to the 2011 guidelines from the National Institute on Aging and the Alzheimer's Association (Jack et al., 2011), reliable biomarkers for AD only included the levels of A β 1-42, total tau, and phosphorylated tau in the cerebrospinal fluid (CSF), which are expensive, invasive, and infeasible for screening. It has been estimated that, even in high-income countries, only 20–50% of dementia cases were correctly recognized and documented in primary care (Zheng et al., 2016). However, neuropathological alterations in patients with AD were reported to begin 10–20 years before the development of clinical symptoms (Villemagne et al., 2013). Thus, it is necessary and meaningful to find reliable and feasible biomarkers to help effectively diagnose AD, especially in the early stages.

In the last decade, many studies have found that extracellular vehicles (EVs) play key roles in the management of normal physiological environments, including waste management, stem cell maintenance, and tissue repair, as well as in pathological processes, including AD (Ratajczak et al., 2006; Gatti et al., 2011; van der Pol et al., 2012; Watson et al., 2019). Exosomes, 30–150 nm in diameter, are main EVs that originate in the endosome, and can carry multifarious molecular cargo, such as nucleic acids, lipids, and proteins (DeLeo and Ikezu, 2018; Yokoi et al., 2019). In the central nervous system, exosomes are critical for intercellular communication, maintenance of myelination, synaptic plasticity, and trophic support of neurons (Hornung et al., 2020). Currently, exosomes play important roles in the development, diagnosis, and treatment of AD; however, their specific functions remain controversial and even unclear. For example, some study found that exosomes could help spread tau proteins and encourage A β aggregation (Song et al., 2020a; Ruan et al., 2021); however, other studies reported that neuronal exosomes could restrain A β oligomerization, accelerate A β fibril formation, and facilitate microglia-mediated A β clearance, implying that exosomes from different cell types might exhibit different effects on the development of AD (Yuyama et al., 2012, 2014; Asai et al., 2015; Dinkins et al., 2017). Since exosomes secreted from different cell types contain particular and different types of markers, it is possible to identify their origins and isolate them from a specific cell subgroup, and corresponding extraction and purification methods have also been developed in recent years (Goetzl et al., 2019; Hornung et al., 2020). Thus, it is feasible and meaningful to recognize, extract, and analyze specific cell-derived exosomes based on the features of the targeted diseases. Noticeably, because exosomes are the main type of EVs, many authors interchangeably used the terms EVs and exosomes (Hornung et al., 2020). Thus, we also include some important studies taking about EVs in this review. Moreover, it is still challenging for effective and specific extraction, isolation, and characterization of exosomes, thus, the

mentioned exosomes in many cases could also contain small amounts of other EVs.

Considering the above and based on previous published studies, in this review we mainly discuss and summarize the roles of exosomes derived from different body fluids and cells in the development, diagnosis, monitoring, and treatment of AD, as well as the remaining challenges in this field.

Exosomes from various body fluids provide possibilities for the early diagnosis and intervention of Alzheimer's disease

Cerebrospinal fluid-derived exosomes

A review reported that a large percentage of modulated proteins originate from exosomes, most of which are involved in the growth, development, maturation, and migration of neurons and neurotransmitter-mediated cellular communication (Bastos et al., 2017). Thus, CSF-derived exosomes have been widely studied, and their proteome has been recognized as a potential new reservoir for biomarker discovery in neurological disorders, including AD (Street et al., 2012). It has also been reported that more than 400 unique proteins mainly involved in AD, as well as the aging and telomere length pathway, were considerably enriched in CSF-derived EVs (Muraoka et al., 2019), and some proteins such as HSPA1A, NPEPPS, and PTGFRN could be used to monitor the progression of mild cognitive impairment (MCI) converted to AD (Muraoka et al., 2020). Moreover, the levels of total tau and p-181-tau in CSF-derived EVs were not only positively correlated with, but also higher than those in total CSF in individuals with AD (Guix et al., 2018; Muraoka et al., 2019). Thus, CSF-derived exosomes (or EVs) play important roles in the early and differential diagnosis of AD. However, the techniques used to derive exosomes from CSF still require refinement to reduce volume and variability.

Blood-derived exosomes

Since the collection of exosomes from the CSF is invasive, it is necessary and urgent to find less or non-invasive biomarkers from other body fluids. Exosomes consist of a lipid bilayer encapsulating the cytosol and have an efficient capability to cross the blood-brain barrier without the loss of their biomarkers, thereby reaching many biological fluids, such as blood, urine, saliva, and synovial fluid (Colombo et al., 2012). Thus, the exosomes in these body fluids could dynamically reflect the pathological changes occurring in some inaccessible sites, such as the brain, making them promising biomarkers for the first step of multistage diagnoses.

Of these different body fluids, plasma and serum are the most widely used for the extraction of exosomes. Interestingly, previous studies have shown that the levels of exosome-bound A β could correlate better with PET imaging of brain amyloid plaques and differentiate various clinical stages of dementia compared to unbound or total circulating A β (Lim et al., 2019). Further extensive analyses of abnormal protein levels in neural cell-derived exosomes could identify patients with AD up to a decade ahead of clinically detectable cognitive losses (Goetzl, 2020). These reports imply that the levels of biomarkers in brain-derived, blood-borne exosomes can better reflect alterations occurring in the brain (Guix et al., 2018; Lim et al., 2019). It was also reported that the levels of A β 1-42, total tau, p-181-tau, and p-S396-tau in neuron-derived exosomes (NDEs) from plasma were highly correlated with those in CSF and could differentiate patients with AD from those with MCI and/or controls with an accuracy of up to 96.4% (Fiandaca et al., 2015; Jia et al., 2019). Moreover, it was reported that patients who eventually developed AD had considerably higher levels of 181-tau and/or p-S396-tau in their NDEs compared to their plasma, even 10 years prior to diagnosis, compared to those who did not develop AD (Fiandaca et al., 2015; Winston et al., 2016).

Apart from the classic biomarkers, many other promising biomarkers such as lysosomal proteins, GAP43, neurogranin, SNAP25, and synaptotagmin 1 in NDEs from plasma could predict the development of AD at least 5 years before cognitive impairment and differentiate AD from frontotemporal dementia with 95.8% accuracy (Goetzl et al., 2015a; Jia et al., 2021). Another study also found that neuro-protective transcription factors such as repressor element 1 silencing transcription factor, low-density lipoprotein receptor-related protein 6, and heat shock factor 1 in NDEs from plasma decreased 2–10 years before the onset of clinical AD symptoms, implying a possible early pathogenic contribution of increased neuronal susceptibility to neurotoxic proteins in AD rather than higher levels of pathogenic proteins (Goetzl et al., 2015b). Furthermore, miRNAs such as miR-9-5p, miR-598, miR-125b, miR-29, miR-342-3p, and miR-193b, which are highly stable and resistant to degradation in exosomes, could be promising biomarkers for early clinical diagnosis and monitoring of AD (Riancho et al., 2017; Chen et al., 2019; Dong et al., 2020). Recently, a meta-analysis found that exosome-derived markers in serum had a higher diagnostic value for AD and MCI than those in plasma, implying that isolating exosomes from serum is a more accurate and non-invasive detection method (Xing et al., 2021).

Exosomes derived from urine and other body fluids

A pilot study found that the levels of A β 1-42 and p-S396-tau in urinary exosomes were higher in patients with

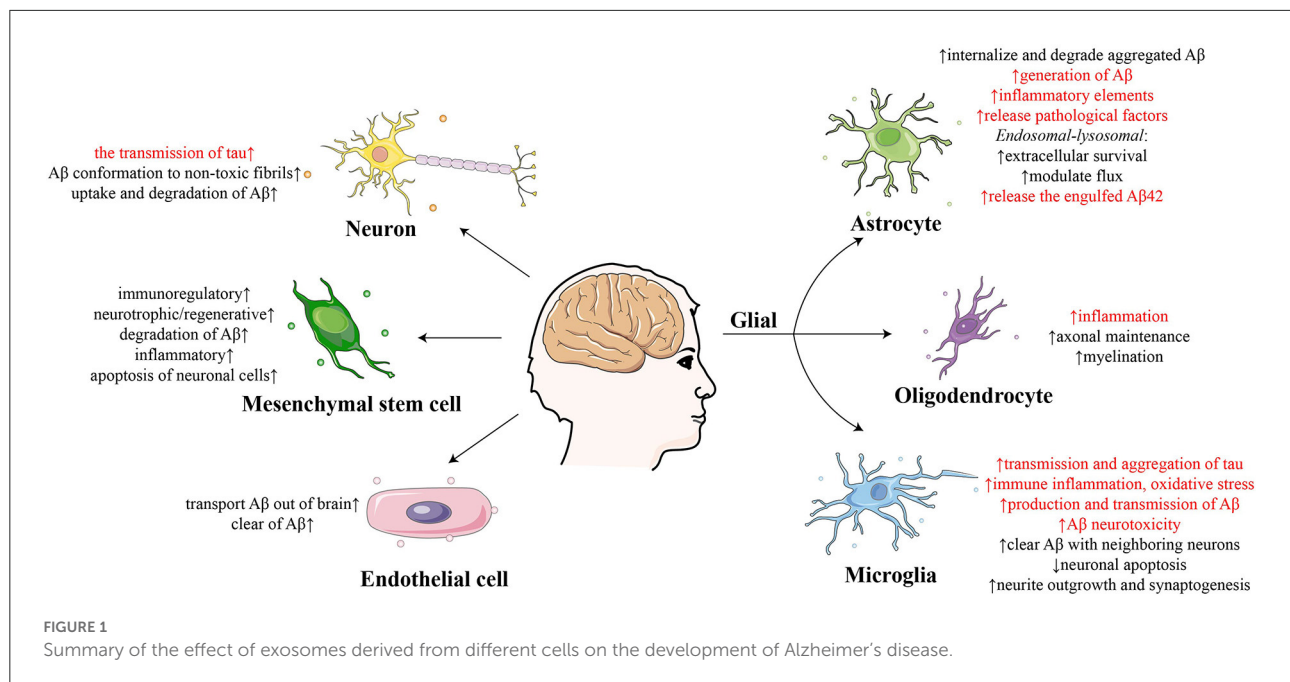
AD than in controls, suggesting that it is a promising non-invasive biomarker (Sun et al., 2019). Comprehensive proteomic profiling analysis identified 336 differentially expressed proteins, including 44 brain cell biomarkers in urinary exosomes, of which 22 were further verified. Notably, annexin 2 and clusterin were markedly decreased in AD mouse models compared to control mice (Song et al., 2020b). Moreover, 48 differentially expressed miRNAs in urinary exosomes, including 18 upregulated and 30 downregulated ones, were identified and verified prior to the identification of A β plaque deposition, which was predicted to display gene targets and important signaling pathways closely associated with AD pathogenesis (Song et al., 2021). Furthermore, other non-invasive body fluids, such as saliva-derived exosomes (Han et al., 2018; Rani et al., 2021) are also promising for the early diagnosis of AD. However, associated studies are limited and need to be further explored, and the collections of saliva samples needs to be further standardized in clinical application.

Exosomes derived from different cells play different roles in the development, diagnosis, and treatment of Alzheimer's disease

Exosomes derived from neural cells play multifaceted roles in the nervous system, including in synaptic plasticity, the neuron-glia interface, neuroregeneration, neuroprotection, and the dissemination of neuropathological molecules (Upadhyay et al., 2020). It has also been reported that exosomes derived from various types of neural cells, including neurons, glia, stem cells and so on, play different roles in the development of AD (Figure 1) (Song et al., 2020a); therefore, it is vital to distinguish and analyze specific cell-derived exosomes.

Neuron-derived exosomes

As the basic structural and functional unit of the nervous system, neurons mediate various neural activities such as the conduction of excitation. Proteins in exosomes are released from affected neurons and propagate along neuroanatomically connected regions of the brain, leading to the spread of neurodegenerative diseases. Full-length tau proteins, which are more prone to aggregation, were found to be higher inside NDEs than in their free form (Guix et al., 2018), implying that NDEs could promote the transmission of tau. Moreover, the levels of P-S396-tau and P-T181-tau in NDEs can predict the development of AD up to 10 years before the clinical onset of sporadic AD (Fiandaca et al., 2015). Furthermore, a recent study demonstrated that NDEs, but not total exosomes, in plasma samples of AD patients could induce complement-mediated



neurotoxicity, leading to the decrease of cell viability (Nogueras-Ortiz et al., 2020).

However, beneficial effects of NDEs on extracellular Aβ have also been found. NDEs may drive conformational changes in Aβ to form non-toxic amyloid fibrils and promote uptake and degradation by microglia (Yuyama et al., 2012). With enriched expression of glycosphingolipids, ceramide, and the GPI-anchored protein PrPc, NDEs showed stronger affinity for Aβ than other origin-derived exosomes, such as those from glial cells (Joshi et al., 2015; Yuyama et al., 2015). Moreover, it was reported that intracerebral infusion of NDEs into mouse brains could decrease the levels of Aβ and attenuate Aβ-induced synaptic density toxicity in the hippocampus (Yuyama et al., 2014, 2015), which implies that supplementation or promotion of NDE generation could be a novel therapeutic approach for AD (Yuyama et al., 2019).

Moreover, NDEs can also be used to diagnose AD. A meta-analysis showed that the area under the curve (AUC, 95% confidence interval) of miRNA and other biomarkers in NDEs for the diagnosis of AD or MCI was up to 0.89 (0.86–0.92), and a sub-group analysis found that NDEs from plasma had a higher AUC value (Xing et al., 2021). Higher levels of alpha-globin, beta-globin, and delta-globin in NDEs were found in patients with AD compared to those in controls (Arioz et al., 2021). The levels of presynaptic proteins, including synaptotagmin and synaptophysin, as well as postsynaptic proteins, including synaptopodin and neurogranin, in plasma NDEs were reported to be markedly lower in patients with AD, which was also correlated with the extent of cognitive loss (Goetzl et al., 2016a, 2018a). Many other biomarkers in NDEs were also found to be markedly different between patients with AD and controls,

such as the level of Ser/Tyr phosphorylation of the insulin receptor substrate 1 (indicating insulin resistance), lysosomal enzymes and ubiquitin (indicating lysosomal dysfunction), and cellular survival factors (indicating impaired cellular stress responses) (Goetzl et al., 2015a,b; Kapogiannis et al., 2015). Furthermore, with the specific expression of neuronal, L1, or neural cell adhesion molecules, NDEs could be effectively isolated from total plasma/serum exosomes using a precipitation or immunoaffinity method with according antibodies (Fiandaca et al., 2015). With this isolation method, NDEs were found to comprise up to 15% of total plasma exosomes (Kapogiannis et al., 2015).

Glial cell-derived exosomes

Brain function depends on coordinated interactions between neurons and glial cells, including astrocytes, microglia, and oligodendrocytes. However, the specific functions of glial cells and their derived exosomes remain controversial. For example, it has been reported that exosomes in glia could be transferred into neurons via cargo molecule-dependent and membrane contact-dependent mechanisms, which could benefit neurons or reversely disseminate the disease (Brites and Fernandes, 2015).

Astrocyte-derived exosomes

As the most abundant type of glial cells in the brain, astrocytes accumulate at sites of Aβ peptide deposition, internalizing and degrading aggregated peptides, which is considered a protective process (Wyss-Coray et al., 2003).

Cellular experiments have shown that A β 1-42 can inhibit exosome release from astrocytes by activating the c-Jun N-terminal kinase signaling pathway, thereby increasing the levels of astrocyte-derived exosomes (ADEs) via ultrasound stimulation can reverse oligomeric A β -induced cytotoxicity and help the clearance of A β plaques *in vitro* (Abdullah et al., 2016; Deng et al., 2021). Moreover, neuroprotective proteins such as synapsin 1, angiogenesis-associated molecules such as vascular endothelial growth factor, and matrix metalloproteinases involved in extracellular matrix proteolysis have been found in ADEs or astrocyte-derived EVs (Proia et al., 2008; Sbai et al., 2010; Wang et al., 2011). ADEs could also prolong the extracellular survival of protective endosomal-lysosomal cargo, such as the cysteine-protease inhibitor cystatin C, with their limiting membrane (Mathews and Levy, 2019). Efficient exosome release would help modulate flux via the neuronal-endosomal pathway by decompressing potential “traffic jams” and contributing to the degradation of neuronal debris (Mathews and Levy, 2019).

However, when a large amount of A β accumulates within astrocytes for a prolonged period without degradation, severe endosomal-lysosomal defects would occur in the astrocytes. Astrocytes can then release engulfed A β 1-42 protofibrils through exosomes, leading to severe neurotoxicity to neighboring neurons (Söllvander et al., 2016). Animal experiments have also revealed that A β and tau released into the serum are most likely from ADEs in the brain (Rosas-Hernandez et al., 2019). Moreover, reducing the secretion of ADEs by neutral sphingomyelinase 2 loss-of-function could improve pathology and cognition in the 5XFAD mouse model (Dinkins et al., 2016). Recently, it was reported that some subsets of astrocytes contain amyloid precursor proteins (APP), β -secretase, and γ -secretase, which are required for the generation of A β peptides. These components are increased by fibrillary A β 1-42 and several inflammatory cytokines (Zhao et al., 2011; Goetzl et al., 2016b). Furthermore, certain inflammatory and neurodegenerative reactions would elicit a coordinated response, leading to astrocyte hyperplasia and their conversion into reactive phenotypes, which could increase the expression of pro-inflammatory elements and damage both synapses and neurons (Liddelow and Barres, 2017; Goetzl et al., 2018b). Astrocytes can also release pathological factors such as S100 β , a protein enriched in the brain of patients with AD that contributes to peri-plaque pathology (Mrak et al., 1996). Recently, a deep RNA sequencing study reported that ADEs influence neurodegenerative diseases mainly through metabolic and ubiquitin-dependent protein balance (Xie et al., 2022). Therefore, it is hard to deem the effect of astrocytes and ADEs on the development of AD as either “protective” or “disruptive.”

Currently, studies on the ability of classic biomarkers in ADEs to help in the diagnosis of AD are still lacking. The levels of complement proteins such as C1q, C3b, C3d, and cytokines including IL-6, TNF- α , and IL-1 β in ADEs were found to be

considerably different between patients with AD and controls, which could also distinguish between moderate and preclinical stage AD (Goetzl et al., 2018b; Goetzl, 2020). As components of neurotoxic neuroinflammation, complement proteins in plasma ADEs could be predictive biomarkers of patients with MCI progressing into AD, with considerably higher levels of C1q, C4b, factor D, fragment Bb, C5b, C3b, and C5b-C9 in converters within 3 years (Winston et al., 2019). The expression of the anti-human glutamine aspartate transporter has been widely used for the isolation of ADEs (Goetzl et al., 2018b). Moreover, plasma ADEs prominently express higher levels of glial fibrillary acidic protein and glutamine synthetase than NDEs, which could be used to distinguish between ADEs and NDEs (Goetzl et al., 2016b). Since, the cargos in exosomes derived from human neuron and astrocyte cells were mainly recognized as useful biomarkers for the diagnosis of AD, thus related results from previous studies were summarized in Table 1.

Microglia-derived exosomes

As the primary innate immune cells in the brain, microglia can detect tissue damage and microbial infection, and phagocytose not only dying cells and, protein aggregates, but living neurons, and synapses (Neumann et al., 2009; Schafer et al., 2012). It was also found that exosomes added to mixed brain cultures containing all major cell types were preferentially taken up by microglia (Fitzner et al., 2011). Moreover, microglial-derived EVs could influence neurite outgrowth and modulate neuronal activity (Delpech et al., 2019; Paolicelli et al., 2019). However, it is relatively difficult to define the function of microglia as “protective” or “disruptive”, because they can dynamically switch between different phenotypes depending on the stage of the disease (Guo et al., 2021).

Microglia can phagocytize tau-containing cytopathic neurons or synapses and efficiently transmit tau to neurons via phagocytosis and exosomes. Thus, microglia and microglia-derived exosomes (MDEs) are positively correlated with tau pathology, and their depletion dramatically suppresses the propagation of tau and reduces excitability in the dentate gyrus (Schafer et al., 2012; Asai et al., 2015; Ruan et al., 2020). When tau-containing MDEs are taken up by neurons, abnormal aggregation of tau is further triggered (Asai et al., 2015). Moreover, reactive microglia may release exosomes carrying the inflammatory markers, including iNOS, IL-1 β , TNF- α , MHC class II, IL-6, miR-155, miR-146a and miR-124, and pro-resolving genes, including IL-10 and arginase 1, leading to a more damaging pro-inflammatory state throughout the brain (Frühbeis et al., 2013; Fernandes et al., 2018). Deep RNA sequencing also demonstrated that MDEs influence neurodegenerative diseases through immune inflammation and oxidative stress (Xie et al., 2022). Suppressing the expression of miR-21-5p is considered a promising novel strategy for the treatment of neuroinflammation (Yin et al., 2020). Furthermore,

TABLE 1 Exosomes derived from human neuron and astrocyte cells as AD biomarkers in previous studies.

	References	Disease group	Control group	Body fluid	Cell source	Isolation method	Validation techniques	Cargo change
1	Fiandaca et al. (2015)	AD, <i>n</i> = 57	Cognitively normal controls, <i>n</i> = 57	Serum	Neuron	anti-NCAM	ELISA	↑total tau, P-S396-tau, P-T181-tau, Aβ1-42
2	Goetzl et al. (2016a)	AD, <i>n</i> = 24	Cognitively normal (1–10 years before the diagnosis of AD), <i>n</i> = 24	EDTA plasma	Neuron	anti-L1CAM	ELISA	↑P-S396-tau, P-T181-tau, Aβ1-42
3	Winston et al. (2016)	AD, <i>n</i> = 10	Cognitively normal controls, <i>n</i> = 10	Plasma	Neuron	anti-L1CAM	ELISA	↑P-S396-tau, P-T181-tau, Aβ1-42 ↓neurogranin, repressor element 1-silencing transcription factor
		Progressed to AD within 36 months, <i>n</i> = 20	Stable MCI, <i>n</i> = 20					
4	Jia et al. (2019)	AD, <i>n</i> = 28	Amnesic MCI, <i>n</i> = 15; healthy controls, <i>n</i> = 29	Plasma	Neuron	anti-NCAM	ELISA	↑Aβ42, T-tau, P-T181-tau
5	Arioz et al. (2021)	AD, <i>n</i> = 20	Healthy controls, <i>n</i> = 20	Serum	Neuron	anti-L1CAM	LC-MS/MS	↑alpha-globin, beta-globin, delta-globin
6	Goetzl et al. (2017)	AD, <i>n</i> = 28	Cognitively normal controls, <i>n</i> = 28	EDTA plasma	Neuron	anti-L1CAM	ELISA	↓neuronal pentraxin 2, neurexin 2a, GluA4-containing glutamate receptor, neuroligin 1
		AD, <i>n</i> = 18	Cognitively normal (6–11 years before the diagnosis of AD), <i>n</i> = 18					neurexin 2a, GluA4-containing glutamate receptor, neuroligin 1
7	Goetzl et al. (2016b)	AD, <i>n</i> = 12	Cognitively normal controls, <i>n</i> = 28	EDTA plasma	Neuron	anti-L1CAM	ELISA	↓synaptophysin, synaptopodin, synaptotagmin, neurogranin, growth-associated protein 43
		AD, <i>n</i> = 9	Cognitively intact or with MCI (1–10 years before the diagnosis of AD), <i>n</i> = 9					
8	Kapogiannis et al. (2015)	AD, <i>n</i> = 26	AD normal controls, <i>n</i> = 26	Plasma	Neuron	anti-L1CAM	ELISA	↑P-serine 312-IRS-1 ↓P-pan-tyrosine-IRS-1
		AD, <i>n</i> = 22	Cognitively normal (1–10 years before the diagnosis of AD), <i>n</i> = 22					

(Continued)

TABLE 1 Continued

	References	Disease group	Control group	Body fluid	Cell source	Isolation method	Validation techniques	Cargo change
9	Goetzl et al. (2015a)	AD, <i>n</i> = 26	AD normal controls, <i>n</i> = 26	Plasma	Neuron	anti-L1CAM	ELISA	↑cathepsin D, lysosome-associated membrane protein 1, ubiquitinated proteins ↓heat-shock protein 70
		AD, <i>n</i> = 20	Cognitively normal (1–10 years before the diagnosis of AD), <i>n</i> = 20					
10	Goetzl et al. (2015b)	AD, <i>n</i> = 24	AD normal controls, <i>n</i> = 24	Heparin plasma	Neuron	anti-L1CAM	ELISA	↓low-density lipoprotein receptor-related protein 6, heat-shock factor-1, repressor element 1-silencing transcription factor
		Preclinical AD (1–10 years before diagnosis of AD), <i>n</i> = 16	Cognitively normal controls, <i>n</i> = 16					
11	Goetzl et al. (2016a)	Amnesic MCI or early AD, <i>n</i> = 12	Cognitively normal controls, <i>n</i> = 10	EDTA plasma	Astrocyte	anti-ACSA-1	ELISA	↑β-secretase 1, sAPPb, Aβ42 ↓septin-8, GDNF
12	Goetzl et al. (2018a)	Early AD, <i>n</i> = 28	Cognitively normal controls, <i>n</i> = 28	EDTA plasma	Astrocyte	anti-ACSA-1	ELISA	↑IL-6, TNF-α, IL-1β, C1q, C4b, factor B, factor D, Bb, C3b, C3d, C5b-C9 terminal complement complex ↓CR1, CD46, CD59, DAF ↑C4b, C3d, factor B, Bb, C3b, C5b-C9 terminal complement complex, TNF-α, IL-1β ↓CD59, DAF
		AD, <i>n</i> = 16	Cognitively normal (5–12 years before the diagnosis of AD), <i>n</i> = 16					
13	Winston et al. (2019)	AD, <i>n</i> = 20	Cognitively normal controls, <i>n</i> = 20	EDTA plasma	Astrocyte	anti-ACSA-1	ELISA	↑C1q, C4b, factor D, Bb, C5b, C3b, C5b-C9
		Progressed to AD within 3 years, <i>n</i> = 20	Stable MCI during the 36-month study, <i>n</i> = 20					

AD, Alzheimer's disease; MCI, mild cognitive impairment; L1CAM, L1 cell adhesion molecule; NCAM, neural cell adhesion molecule; ACSA-1, human glutamine aspartate transporter.

it was demonstrated that MDEs and microglia-derived EVs not only had higher APP and A β 1-40 production, carried oligomeric A β , and mediated A β transmission, but also promoted the extracellular aggregation of A β 1-42 to form small soluble neurotoxic species, which strongly increased A β neurotoxicity (Joshi et al., 2014; Fernandes et al., 2018; Gouwens et al., 2018). However, it has been reported that microglia and neighboring neurons could work together to clear A β peptides via exosomes (Guo et al., 2021). Microglia-depleted mice had increased levels of soluble A β in the brain, and statins could promote the degradation of extracellular A β by stimulating the secretion of MDE-associated insulin-degrading enzymes, indicating a beneficial role of microglia in the metabolism of extracellular A β (Fuhrmann et al., 2010; Tamboli et al., 2010). Furthermore, cargo molecules in microglia derived EVs, including trombospondin-1 and 4, can suppress neuronal apoptosis and promote neurite outgrowth and synaptogenesis, implying a neuroprotective role (Drago et al., 2017). Thus, further investigation of the roles of microglia and MDEs in central nervous system disorders is required.

Recently, advances in single-cell RNA sequencing have helped unravel some questions in the field of microglia through the discovery of a new phenotype called “disease-associated microglia.” These accumulate around plaques and exhibit upregulated gene expression of apolipoprotein E (APOE) and trigger the receptors expressed on myeloid cells 2 (TREM2), which are considered genetic risk factors for AD (Keren-Shaul et al., 2017). However, another study found that TREM2 knockout ameliorated amyloid pathology in the early stages of AD, but exacerbated it later in the disease process (Jay et al., 2017), which highlights the roles of microglia and MDEs in AD pathology depending on the stage of the disease. Furthermore, a reproducible and efficient method for yielding purified primary microglia cells and effectively isolating and characterization of MDEs based on CD11b/c has been proposed in recent years (Murgoci et al., 2018), which is beneficial for further studies on MDEs.

Oligodendrocyte-derived exosomes

Although few studies have focused on the potential roles of oligodendrocytes in AD pathogenesis, some gene variants that increase the risk of AD have been found to be predominantly expressed in oligodendrocytes. Interact with axon, oligodendrocyte played an important role in neuronal integrity. Oligodendrocyte-derived exosomes (ODEs) may be internalized by neurons through endocytosis, which could contribute to neuroprotection and long-term axonal maintenance under normal, or oxygen and glucose-deprived conditions (Frühbeis et al., 2012; Fröhlich et al., 2014). Moreover, it was reported that markedly increased numbers of both newly generated and mature oligodendrocytes following treatment with mesenchymal stromal cell-derived exosomes

considerably decreased amyloid- β precursor protein density and improved neurological outcomes (Zhang et al., 2021). ODEs can also participate in the management of oxidative stress by transferring human superoxide dismutase and catalase. When stress resistance occurs following ischemia, neurons take up more ODEs (Krämer-Albers et al., 2007). Notably, alterations in the composition of ODEs under some pathological conditions may switch immunologically inert exosomes into active ones, which may trigger inflammatory reactions in the brain. Furthermore, an immunocapture protocol based on common oligodendrocyte biomarkers, such as 2,3-cyclic nucleotide-3-phosphodiesterase, can extract and isolate ODEs for further study (Yu et al., 2020).

Stem cell-derived exosomes

Stem cell-derived exosomes play important roles in the therapy for AD (Vasic et al., 2019; Sivandzade and Cucullo, 2021). Compared with traditional stem cell transplantation, stem cell-derived exosomes are relatively easier to manage, have lower immunogenicity, and have a lower risk of tumor formation, making them a potential therapeutic method (Guo et al., 2020). When the unique functionalities of exosome-derived membranes are combined with synthetic gold nanoparticles (AuNPs), efficient brain targeting can be achieved (Khongkow et al., 2019). In 5xFAD accelerated transgenic mouse model of AD, human neural stem cell-derived EVs showed the regenerative potential on the neurocognitive and neuropathologic hallmarks, and significantly reduced dense core A β plaque accumulation and microglial activation in the AD brain (Apodaca et al., 2021).

Mesenchymal stem cells (MSCs), a type of adult pluripotent stem cell, are derived from connective tissue especially adipose tissue. MSCs can reduce the A β plaque burden by the internalization and degradation of A β oligomers via the endosomal-lysosomal pathway. Electron microscopy and proteomic analysis further revealed that the therapeutic effect of MSCs was due to their exosomes (Lai et al., 2010). With well-characterized immunoregulatory neurotrophic and regenerative properties, MSC-derived exosomes were considered as a promising candidate for AD therapy and most widely studied. In mouse models, MSC-derived exosome administration via the lateral ventricle or intravenous injection could reduce A β expression and improve AD-like behaviors (Chen et al., 2021; Liu et al., 2022). Enzymatically active neprilysin, the most important A β -degrading enzyme in the brain, is also found in MSC-derived exosomes (Joshi et al., 2015). Moreover, MSC-derived EVs were considered as the best cell-free candidates for promoting a reparative process by activating positive responses in the brain microenvironment via intercellular communication (Elia et al., 2019). MiRNA-22-loaded exosomes derived from adipose-derived MSCs can decrease the release of inflammatory

factors, thereby playing a synergetic therapeutic role in AD (Zhai et al., 2021). Moreover, miR-223 loaded MSC-derived exosomes protected neuronal cells from apoptosis via the PTEN-PI3K/AKT pathway, providing a potential therapeutic approach for AD (Wei et al., 2020). Furthermore, a previous study proved the safety of MSC-derived EVs (Nassar et al., 2016), and a clinical trial was conducted to evaluate their safety and effectiveness in patients with mild to moderate dementia (www.clinicaltrials.gov, NCT04388982). It is worth noting that the efficacy was dosage-dependent, and the lower dose of exosomes was found to be more neuroprotective (Venugopal et al., 2017). Moreover, specific MSC-related molecules, such as CD29, CD44, CD90, and CD73, could help recognize and isolate MSC-derived exosomes.

Noticeably, even if EVs derived from native stem cells have potential in the treatment of neurodegenerative diseases including AD, its clinical application is still limited due to the short half-life, limited targeting, rapid clearance after application, and insufficient payload (Bang and Kim, 2022). Some strategies such as engineered EVs by genetic modification could improve stability, targeting ability and EVs tracking (Lino et al., 2021), thus, associated technologies need to be further explored and developed to prompt the clinical therapeutic application of stem cell-derived exosomes.

Endothelial cell-derived exosomes

Exosomes derived from endothelial cells (EDEs) of the human brain microvasculature contain P-glycoprotein, a member of the ABC transporter family, which can effectively transport A β out of the brain. Thus, it has been reported that EDEs can greatly facilitate the cerebral clearance of A β and potentially ameliorate cognitive dysfunction in AD mice (Pan et al., 2020). CD81-normalized levels of A β 1-40 and A β 1-42 in plasma EDEs were also found to be considerably higher in the preclinical AD/MCI group with small cerebral vascular disease than in controls, which often occurs before the presentation of neuronal and other cellular changes in AD (Abner et al., 2020). Moreover, endothelial proteins such as vascular cell adhesion molecule-1 and endothelial nitric oxide synthase can be used for the precipitation and enrichment of EDEs when using immune-specific absorption procedures for the analysis of cargo proteins (Goetzl et al., 2017).

The size and number of exosomes could be promising biomarkers for the diagnosis of AD

A recent study found that not only the constitution A β and p-S396-tau in exosomes markedly differed between patients with AD compared to the controls, but the exosomes from patients

with AD were smaller and lower in quantity, as determined by transmission electron microscopy (TEM) and nanoparticle tracking analysis (NTA), contributing to the early diagnosis of AD (Sun et al., 2020). Since TEM and NTA technology are widely used to visualize and characterize extracted exosomes, it is feasible to combine information on the size and number of exosomes with biomarker levels for the early and differential diagnosis of AD (Szatanek et al., 2017).

The size of exosomes

One study reported that the size of plasma exosomes was smaller in an AD group than in the control group, which is beneficial for early diagnosis of AD (Sun et al., 2020). However, some studies found larger size of plasma EVs in patients with AD than in controls, which could be induced by the uptake and accumulation of A β (Longobardi et al., 2021). Moreover, in another study, no significant difference was observed in the diameters of EVs in the CSF between patients with AD and the controls (Saugstad et al., 2017). These inconsistent results are likely to be due to the differences in exosome types and sources. Thus, further studies need to be conducted to explore the roles of specific exosomes in the diagnosis of AD.

The number of exosomes

Some studies have reported markedly lower concentrations of plasma exosomes in patients with AD compared to those in controls (Sun et al., 2020; Longobardi et al., 2021). Considering both the size and concentration of exosomes, the diagnostic performance to distinguish between dementia and controls was high, with a sensitivity of 83.3% and specificity of 86.7% (Longobardi et al., 2021). Moreover, APOE4 was found to drive the downregulation of brain exosome biosynthesis and release, which plays an important role in endosomal and lysosomal deficits and could lead to a higher risk of AD development (Peng et al., 2019). However, other studies found that astrocytes in AD could induce an increased release of exosomes containing toxic proteins, and exposure to amyloid *in vitro* could increase the production of cell-derived exosomes (Dinkins et al., 2014; Chiarini et al., 2017). Another study found that the number of serum exosomes in transgenic mice with AD was considerably higher than that in wild-type mice, with increased ADEs and decreased EDEs (Rosas-Hernandez et al., 2019). Moreover, NDEs from participants with Down syndrome, who had characteristic neuropathological features of AD at the age of 40 years and eventually developed AD, had 39% higher levels of exosomes on average than those from the control group [(1,433 \pm 87 pg/ml) vs. (1,027 \pm 87 pg/ml)] (Hamlett et al., 2018). It was also reported that upregulation of exosome release was recognized as a useful mechanism to help clear these

deleterious proteins, which could also be recognized in urine samples (Sun et al., 2019). Furthermore, a basic study found that preventing exosome secretion could reduce the formation of amyloid plaques *in vivo*; thus, drugs interfering with exosome secretion, such as neutral nSMase2, could be used as potential drug targets in AD (Dinkins et al., 2014, 2015).

These inconsistent results could also be related to the differences in exosome types and sources, as well as different efficacies of extraction across different samples. Thus, more studies are needed to reach a definite conclusion in which the standardized process of exosome extraction, isolation, and characterization plays an important role. Moreover, the released exosomes were mostly recognized by the CD81 marker, which could be interfered with possible increased soluble CD81 levels per exosome. Thus, an accurate count of exosome numbers is important. NTA using ALIX as an exosome marker or other burgeoning high-sensitivity exosome-counting systems, such as Exo-counter and single molecule array, has been proven to be more accurate for the determination of exosome amounts (Fiandaca et al., 2015; Kapogiannis et al., 2015; Eitan et al., 2017; Yokose et al., 2020; Ter-Ovanesyan et al., 2021).

Conclusion

The role of specific cell-derived exosomes in the development, diagnosis, monitoring, and treatment of AD has attracted increasing attention in recent years. However, the conclusions of different studies are largely inconsistent and many mechanisms remain unclear. Thus, we summarize the roles of exosomes derived from different body fluids and cells in the development, diagnosis, monitoring, and treatment of AD in this study, and emphasize the necessity to focus on exosomes from specific cells and less-invasive biological fluids. Moreover, aside from the concentrations of classic and novel biomarkers in exosomes, we recognized and summarized the roles of the size and number of exosomes play in early and differential diagnosis of AD at first.

Interestingly, a recent study pointed out that a few proteins that had not yet been reported to be expressed in neurons were highly expressed in NDEs, implying that some NDEs may originate in non-neuronal tissues (Pulliam et al., 2019). Thus, the process and mechanism of specific cell-derived exosomes, from their origin, formation, and transportation to their ultimate roles in AD, still need to be further studied. Second, the standardization and automation of the whole process of extraction, isolation, and characterization, including the size and number of specific cell-derived exosomes, remain a challenge (Doyle and Wang, 2019; Guo et al., 2020; Hornung et al., 2020) and need to be developed and optimized. Moreover, methods which is time-saving, low-cost, and convenient, must be explored for clinical applications. Furthermore, it is crucial to accurately measure

the levels of promising biomarkers in exosomes, particularly classical A β and tau, which are of great importance for their clinical application. The levels of A β 1-42 in NDEs are <10 pg/ml, and that of p-181-tau is ~100 pg/ml, which is difficult to accurately determine with the traditional ELISA method. Therefore, automatic detection platforms, such as electrochemiluminescence instruments and single molecule arrays, and technologies with stronger anti-interference abilities, such as mass spectra, need to be developed. Except for the exosomes in CSF, further studies should focus on specific cell-derived exosomes in plasma, urine, and other non-invasive fluids, considering not only their internal biomarkers, but also their sizes and numbers.

Author contributions

LQ and SY mainly guided the study. YZ mainly wrote this manuscript. DM mainly drawn the figure. XM, JZ, DW, and JG made suggestions for revision of the manuscript. All authors reviewed the manuscript and approved the submission.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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