Extracellular vesicles in Alzheimer’s disease: from pathology to therapeutic approaches

Marta Garcia-Contreras, Avnesh S. Thakor*

Abstract
Alzheimer’s disease is a progressive and fatal neurodegenerative disorder that starts many years before the onset of cognitive symptoms. Identifying novel biomarkers for Alzheimer’s disease has the potential for patient risk stratification, early diagnosis, and disease monitoring in response to therapy. A novel class of biomarkers is extracellular vesicles given their sensitivity and specificity to specific diseases. In addition, extracellular vesicles can be used as novel biological therapeutics given their ability to efficiently and functionally deliver therapeutic cargo. This is critical given the huge unmet need for novel treatment strategies for Alzheimer’s disease. This review summarizes and discusses the most recent findings in this field.

Key Words: Alzheimer’s disease; brain; diagnostic; extracellular vesicles; isolation methods; microglia; neurodegenerative diseases; neuroinflammation; neurons; therapy

Extracellular Vesicles
EVs are a heterogeneous population of membrane-bound structures released by most cells into the extracellular space and can be found in most body fluids such as serum, plasma, urine, saliva, and cerebrospinal fluid (van Niel et al., 2018). EVs can be classified based on their size, origin markers, content, or source (Table 1).

Extracellular Vesicles Isolation Methods
EVs can be isolated from cell culture media or biological fluids including blood, urine, cerebrospinal fluid, tears, and saliva. Due to the complexity of biological fluids, current isolation methods isolate either exclusively exosomes or a mixture of EVs and other components. An overview of these methods can be found in Table 2.

Ultracentrifugation
Ultracentrifugation is the most commonly used method to isolate EVs. There are two types of ultracentrifugation methodologies: differential or density gradient. Differential centrifugation consists of sequential centrifugation steps: a 300 × g spin for 10 minutes followed by a 10,000 × g spin for 30 minutes to eliminate intact cells, dead cells, and cell debris. After depletion of cells and large apoptotic bodies by low-speed centrifugation, the EVs are pelleted in the final step at 100,000 × g for 70 minutes (Garcia-Contreras et al., 2017). Density gradient centrifugation is a combination of ultracentrifugation with a sucrose gradient to separate the EVs based on their density (Cvjetkovic et al., 2014).

Affinity-based capture
Affinity-based isolation enables the selective capture of specific EVs subpopulations using antibodies to specific membrane markers such as CD63, CD81, or CD9 (Kowal et al., 2016). For this reason, selecting a proper membrane marker is one of the most significant steps in these immunoassays. A bead-based affinity approach is a method that uses magnetic beads or latex beads for capturing and isolating EVs. Another affinity-based capture method is a lipid nanoprobe system, which labels the EVs with a labeling probe for magnetic enrichment using a capture probe (Bano et al., 2021).

Search Strategy and Selection Criteria
In this narrative review, we used PubMed and Google Scholar to search articles published from 1998 to 2021 with the following keywords: extracellular vesicles, neurodegeneration, Alzheimer’s, therapeutics, pathology, and biomarkers.

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Extracellular Vesicles Characterization Methods

**Electron microscopy**
Morphological characterization is carried out using electron microscopy. Transmission electron microscopy is a standard technique used to characterize EV preparations. EVs analyzed by transmission electron microscopy often show a cup-shaped appearance, which is an artifact of the preparation procedure. Transmission electron microscopy can be combined with immunogold staining using gold conjugated antibodies to detect the presence of specific markers. Scanning electron microscopy is another approach to analyze EV morphology and structure, while atomic force microscopy is a type of scanning microscopy that allows imaging of the topology of EV surfaces with nanometer resolution.

**Western blot assay and enzyme-linked immunosorbent protein assay**
Western blot assay is a widely used method to characterize and detect EV proteins. Enzyme-linked immunosorbent protein assays (ELISA) are also used to quantify the number of exosomes based on the level of the exosome-associated proteins including CD9, CD63, and CD81. ELISA is more sensitive and provides more accurate protein quantification compared to western blots.

**Flow Cytometry**
Flow cytometry or imaging flow cytometry of EVs is performed by using beads coupled to antibodies that detect EV surface markers. The use of beads is due to the small size of EVs and the difficulty to detect EVs with most conventional flow cytometers. The challenge with flow cytometry of EVs relates to their small particle size and low refractive index, which makes them difficult to separate from background signals.

**Nanoparticle Tracking Analysis**
Nanoparticle tracking analysis uses light diffraction patterns to measure the size and the concentration of EVs. Direct size and concentration quantification can also be performed using the tunable resistive pulse sensing principle.

**Direct Counting of Single Extracellular Vesicles**
There are new techniques that allow the study of single EVs, thereby enabling the study of specific EV subpopulations. Super-resolution microscopy allows separating focal spots to visualize and directly count the number of single EVs as well as quantify their content. Other than fluorescence-based EV visualization, there is an interferometric reflectance imaging method for single EVs. EVs can also be captured in an antibody array on a chip followed by the acquisition of interferometric images by a chip reader where the number and size of EVs can be acquired.

**Extracellular Vesicles in the Pathogenesis of Alzheimer’s Disease**
EVs are membrane-bound structures that transport cargo between cells in the body. They have been shown to be involved in several neurodegenerative diseases such as Alzheimer’s disease (AD), Parkinson’s disease, and amyotrophic lateral sclerosis. AD is characterized by the intracellular accumulation of amyloid-β (Aβ) plaques associated with neurofibrillary tangles. In contrast, Parkinson’s disease is associated with the deposition of Lewy bodies, which are aggregates of α-synuclein. While EVs have been implicated in the pathogenesis of AD, Parkinson’s disease, and amyotrophic lateral sclerosis, the mechanisms by which EVs contribute to disease progression are not fully understood. These findings highlight the importance of EVs in the context of neurodegenerative diseases and underscore the potential of EVs as therapeutic targets.
and Aβ aggregates are less efficiently cleared and degraded by astrocytes and microglia (Dinkins et al., 2016), thereby contributing to their dysregulation in AD. Tau aggregates are another major hallmark of AD (Villemagne et al., 2018) and EVs from the CSF of AD patients have been shown to contain Tau and can be transmitted to neurons where they induce Tau aggregation (Saman et al., 2012; Fiandaca et al., 2015; Wang et al., 2017). In neurodegenerative conditions, microglia have been shown to release higher levels of EVs 



**Extracellular Vesicles as Biomarkers of Alzheimer’s Disease**

**Proteins cargo**

Several proteins have been found to be altered in EVs derived from AD patient samples (Muraoka et al., 2020). Specifically, neuron-derived EVs in AD patients have been shown to have increased levels of alpha-globin, beta-globin, and delta-globin compared to healthy controls by liquid chromatography-tandem mass spectrometry proteomics analysis (Ariz et al., 2021). In addition, lysosomal proteins are also altered in neural-derived plasma EVs in preclinical AD samples. These autolysosomal proteins could distinguish preclinical AD patients from controls (Goetzl et al., 2015). Synaptic proteins such as NPTX2, AMPA4, NGN1, and NRXN2a have also been reported to be decreased in neuron derived EVs from plasma of patients with AD. These proteins decreased significantly from the time of normal cognition in preclinical AD to the time of the development of AD dementia (Goetzl et al., 2018). Moreover, astrocyte-derived EVs have been shown to contain dysregulated protein cargo in AD samples such as β-site amyloid precursor protein-cleaving enzyme 1 and soluble amyloid precursor protein β (Goetzl et al., 2016). Microglia-derived EVs also have been shown to have altered protein cargo in AD mouse models and these appear to correlate with disease progression (Muraoka et al., 2021).

**miRNAs and mRNAs cargo**

miRNAs in circulating EVs have been shown to serve as biomarkers for age-related cognitive decline. Several miRNAs are dysregulated in AD samples from plasma, serum, CSF, and brain tissue (Lugli et al., 2015; Cheng et al., 2020). Specific miRNAs such as miR-132 and miR-212 are dysregulated in neural EV samples from AD patients compared to controls (Cha et al., 2019), while miR-9-5p and miR-598 have also been found in EVs obtained from the CSF of AD patients (Saman et al., 2012) (Table 3).

**Table 3 | Studies showing EVs involved in Alzheimer’s pathology**

| Specimen type | Species | Primary EV isolation method | Findings | References |
|---------------|---------|-----------------------------|----------|------------|
| CSF and cell culture media | Human | Ultracentrifugation | Exosome-mediated secretion of phosphorylated tau | Saman et al., 2012 |
| Brain and serum | Mouse | Ultracentrifugation | Exosomes stimulate the aggregation of Aβ_{1-42} in vitro and in vivo | Dinkins et al., 2014 |
| Brain and cell culture media | Mouse | Ultracentrifugation | Microglia-derived exosomes help propagate tau pathology in the mammalian brain | Asai et al., 2015 |
| Cell culture media and serum | Mouse | Ultracentrifugation and ExoQuick | Ceramide-enriched exosomes exacerbate AD-related brain pathology by promoting the aggregation of Aβ | Dinkins et al., 2016 |
| Plasma | Human | Ultracentrifugation | Exosomes mediate the propagation of Tau aggregation between cells. | Wang et al., 2017 |
| Brain (temporal neocortex) | Human | Ultracentrifugation | AD brains contain increased levels of Aβ oligomers and can act as vehicles for the neuron-to-neuron transfer of Aβ to recipient neurons in culture | Sardar Sinha et al., 2018 |
| Brain | Mouse | Exoasy Isolation | Exosomes enhance Aβ induced neurotoxicity in vivo. | Elsherbini et al., 2020 |
| iPSCs culture media | Mouse | ExoQuick-TC | AD familial A246E mutant form of presenilin 1 alters neuronal iPSCs EV cargo | Podvin et al., 2021 |
| Brain | Mouse | Ultracentrifugation | Spread of tau in hippocampal GABAergic interneurons via brain-derived extracellular vesicles | Ruan et al., 2021 |

AD: Alzheimer’s disease; Aβ: amyloid-β; CSF: cerebrospinal fluid; EVs: extracellular vesicles; iPSCs: induced pluripotent stem cells.

**Table 4 | Studies of findings on extracellular vesicles biomarkers in Alzheimer’s disease**

| Specimen type | Species | Biomarker | Primary EV isolation method | Findings | References |
|---------------|---------|-----------|-----------------------------|----------|------------|
| Astrocytes, cell culture media | Human | Ceramide | Ultracentrifugation | Ceramide composition in amyloid-induced astrocytes is altered. | Wang et al., 2012 |
| Serum | Human | miRNAs | Plasma/ Serum exosomal RNA isolation kit | AD-specific 16-miRNA signature | Cheng et al., 2015 |
| Blood and CSF | Human | Lysosomal proteins | ExoQuick and immunoprecipitation | Autolysosomal proteins in neurally derived blood exosomes distinguish patients with AD from control samples | Goetzl et al., 2015 |
| Plasma | Human | miRNAs | Ultracentrifugation | Screening of individual loci indicated that 20 miRNAs showed differential expression in AD | Lugli et al., 2015 |
| Serum | Human | miRNAs | Total exosome isolation reagent | miR-1353a, 193b, and 384 potential biomarkers for early AD diagnosis | Yang et al., 2018 |
| Brain, iPSCs, CSF, and blood | Human | miRNAs | ExoQuick and immunoprecipitation | miR-132 and miR-212 dysregulated in AD neural EVs | Cha et al., 2019 |
| Plasma | Human | Protein | Ultracentrifugation | EV-bound Aβ measurement could better reflect PET imaging of brain amyloid plaques and differentiate various clinical groups. | Lim et al., 2019 |
| Brain and serum | Human | Small RNA and miRNAs | Sucrose gradient and exosomal RNA isolation kit | BDEVs have differential RNA biotypes compared to a heterogeneous population of EVs and provide a better representation of the total brain. | Cheng et al., 2020 |
| CSF | Human | Proteins | MagCapture exosome isolation kit | HSPLA1, NPEP5, and PTGFRN were significantly increased in AD CSF EVs. | Muraoka et al., 2020 |
| Blood | Human | Hemoglobin | Immunoprecipitation | Hemoglobin subunits and other peptides are altered in AD patients. | Arioz et al., 2021 |
| Brain | Mouse | Proteins | Sucrose gradient, ultracentrifugation | Enrichment of pTyr, APP, and PhD and reduction of WdR61, Pompca, Aldh1a2, C4I, Amp32b, Actn4, and Nduv2 | Muraoka et al., 2021 |
| Human frontal cortices | Human | Lids | Ultracentrifugation and density gradient | AD BDEVs have a unique lipid signature that distinguishes them from BDEVs of the CTL frontal cortex. | Su et al., 2021 |

AD: Alzheimer’s disease; BDEVs: brain-derived extracellular vesicles; CSF: cerebrospinal fluid; CTL: age-matched controls; EVs: extracellular vesicles; iPSCs: induced pluripotent stem cells; PET: positron emission tomography; SEC: size exclusion chromatography.
Extracellular Vesicles as a Therapeutic Tool in Alzheimer’s Disease

EVs can also function as a novel therapeutic tool for neurodegenerative diseases given they can efficiently target the brain and penetrate through the blood-brain barrier (BBB) (Alvarez-Erviti et al., 2011). Specifically, stem cell-derived EVs have been shown to have neuroprotective and immunomodulatory properties in neurodegenerative diseases (Niu et al., 2020; Garcia-Contreras and Thakor, 2021; Kim et al., 2021). In AD, the mechanism of Aβ degradation by glial cells is altered, including the production of proteases (such as neprilysin), which can hydrolyze Aβ at different cleavage sites. Previous studies have shown that administration of mesenchymal stem cell (MSC) derived EVs overexpressing neprilysin reduced plaque deposition in AD mice models (Katsuda et al., 2013). Furthermore, MSC-derived EVs have shown to be neuroprotective in animal models of AD by protecting neurons against Aβ-induced oxidative stress and synaptic damage (de Godoy et al., 2018; Ma et al., 2020). This neuroprotection can be mediated by the delivery of MSC-EV specific cargo such as miR-23a-3p to neurons, which then inhibits BACE1 expression while activating the Wnt/B-catenin pathway (Sha et al., 2021). Neural stem cell-derived EVs have also been shown to have neuroprotective effects and can restore fear extinction memory consolidation and reduce anxiety-related behaviors (Apodaca et al., 2021). Finally, given that a lack of physical exercise contributes to several cerebral diseases, including AD, increasing EVs in the brain in response to physical exercise has been proposed as a potential therapeutic strategy (Zhang et al., 2021). New emerging engineering strategies are being developed to explore the specific targeting of EVs (Jang et al., 2021). EVs can be modified by manipulating their cargo, with changes then subsequently incorporated into the secreted EVs for specific delivery/targeting (Dooley et al., 2021) (Table 5).

| Mechanism | Findings                                                                 | References                     |
|-----------|--------------------------------------------------------------------------|--------------------------------|
| Dendritic cell-derived EVs as siRNA delivery vehicle | EVs mediate siRNA delivery by protein (62%) knockdown of BACE1, a therapeutic target in AD, in wild-type mice | Alvarez-Erviti et al., 2011 |
| MSC neprilysin-bound exosomes | Administration of exosomes in the brain of AD mice causes a decrease in plaque deposition | Katsuda et al., 2013 |
| Sphingomyelinase inhibitor (GW4869) | Decreased EV levels are associated with less Aβ plaque deposition | Dinkins et al., 2014 |
| MSC-derived EVs | Protect neurons against AβO-induced oxidative stress and synapse damage. | de Godoy et al., 2018 |
| ADSC-derived EVs | Alleviate neuronal damage and promote neurogenesis. | Ma et al., 2020 |
| Neural stem cell-derived EVs | Restored fear extinction memory consolidation and reduced anxiety-related behaviors. EV treatment also significantly reduced dense core Aβ plaque accumulation and microglial activation. | Apodaca et al., 2021 |
| MSC-derived EVs | Reduced Aβ expression and restored the expression of neuronal memory/synaptic plasticity-related genes in the cell model. Improvement in brain glucose metabolism and cognitive function in AD transgenic mice. | Chen et al., 2021 |
| Bone marrow MSC-EVs | BM-MSC-EVs delivered miR-29c-3p to neurons to inhibit BACE1 expression and activate the Wnt/B-catenin pathway. | Sha et al., 2021 |
| Exercise | Physical exercise increases EVs in the brain. | Zhang et al., 2021 |

Conclusion

AD is an increasingly common form of dementia that worsens over time. While Aβ and tau are recognized as key factors in AD, many important details remain unknown. EVs could provide new insights into the underlying drivers of AD, with dysregulated EV cargo possibly representing an underappreciated driver of AD pathology. In addition, some of these EV cargos could also be reflective on the disease stage of AD and thus be used as biomarkers. Existing efforts in the field are trying to investigate how to analyze cell-type-specific EV content. Current biomarkers for AD are obtained from the CSF, which is obtained in an invasive manner and sometimes is not able to differentiate AD from other types of dementia. In contrast, EVs could be obtained from blood in a minimally invasive manner with studies suggesting they could even reflect the disease stage of AD (Goetzl et al., 2015; Lugli et al., 2015). Brain-derived EVs are thought to be present in the circulation given that neuroinflammatory responses and pro-inflammatory cytokines promote the breakdown of the BBB. However, given their low concentrations, the development of highly sensitive methods for EV detection and extraction is needed.

Existing AD treatments have a low efficacy partially due to the difficulties in crossing the BBB. However, EV-based therapies could represent a more efficient, specific, and functional delivery system. EVs have the ability to cross the BBB by interacting with the endothelial cells (the first line of defense in the brain). There is an urgent unmet need to develop new treatments to delay or prevent AD. Promising results using different types of EVs have been obtained, and these include reducing Aβ plaque deposition, oxidative stress, synaptic damage, and/or microglial activation (Katsuda et al., 2013; de Godoy et al., 2018; Apodaca et al., 2021). New engineering strategies to over-express EVs can also function as a novel therapeutic tool for neurodegenerative diseases such as AD.

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