Journal of Inflammation Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Unveiling the Complex Role of Exosomes in Alzheimer's Disease

Mingyue Sun, Zhuoyou Chen

Department of Neurology, The Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, Changzhou, 213000, People's Republic of China

Correspondence: Zhuoyou Chen, Email neuro1972@163.com

Abstract: Alzheimer's disease (AD) is the most common neurodegenerative illness, characterized by memory loss and cognitive decline, accounting for 60–80% of dementia cases. AD is characterized by senile plaques made up of amyloid β (Aβ) protein, intracellular neurofibrillary tangles caused by hyperphosphorylation of tau protein linked with microtubules, and neuronal loss. Currently, therapeutic treatments and nanotechnological developments are effective in treating the symptoms of AD, but a cure for the illness has not yet been found. Recently, the increased study of extracellular vesicles (EVs) has led to a growing awareness of their significant involvement in neurodegenerative disorders, including AD. Exosomes are small extracellular vesicles that transport various components including messenger RNAs, non-coding RNAs, proteins, lipids, DNA, and other bioactive compounds from one cell to another, facilitating information transmission and material movement. There is growing evidence indicating that exosomes have complex functions in AD. Exosomes may have a dual role in Alzheimer's disease by contributing to neuronal death and also helping to alleviate the pathological progression of the disease. Therefore, the primary aim of this review is to outline the updated understandings on exosomes biogenesis and many functions of exosomes in the generation, conveyance, distribution, and elimination of hazardous proteins related to Alzheimer's disease. This review is intended to provide novel insights for understanding the development, specific treatment, and early detection of Alzheimer's disease.

Keywords: Alzheimer's disease, exosomes, pathogenesis, diagnosis, treatment

Introduction

Alzheimer's disease (AD), commonly referred to as senile dementia, is a common central neurodegenerative disorder. AD primarily manifests as a slow reduction in self-care abilities, increasing memory loss, and cognitive impairment, along with neuropsychiatric disorders, significantly impacting the quality of life of patients.[1] AD accounts for over 60% of dementia cases. Sporadic cases account for over 90% of cases. The disease progresses through memory and cognitive disabilities, causing mood swings, agitation, irritability, and reduced vital functions.[2–4] Amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFTs) are key factors in Alzheimer's disease (AD) pathophysiology.[5] These plaques form when extracellular Aβ monomers are handled by secretases, leading to inflammatory response and damaging neurons.[6] Defective hyperphosphorylation as well as incorrectly folded tau also produce intracellular NFTs, impairing neuronal signal.[7] The researchers have dedicated significant resources to investigate etiology of AD, but it remains incompletely understood, and there is now no viable medication to halt the progression of AD. Food and Drug Administration (FDA)-approved drugs do not provide a definitive therapy for the pathophysiology of AD, but they do give symptomatic relief by slowing down the course of the disease. Treatment for Alzheimer's disease often involves targeting the increase of Acetylcholine levels to avoid its degradation, hence protecting memory and cognitive abilities.[8] Recent advancements in therapy, such as disease-modified AD medications, have been developed to overcome the limitations of traditional treatments. This technique requires a thorough understanding of metabolic pathways and utilizes several targeted tactics to provide effective medicine.[5] As research on extracellular vesicles (EVs) advances, it has become evident that a specific kind of tiny EVs known as exosomes are significant in the pathogenic process of AD.

Received: 1 March 2024
Accepted: 11 June 2024
Published: 18 June 2024

Exosomes are nanosized extracellular vesicles released upon the exocytosis of a MVB, characterized by a bilayer membrane structure. Exosomes may be secreted by the majority of cell types and are often found in bodily fluids.[9] Exosomes in the central nervous system (CNS) transmit messages locally inside cells and extensively across the brain via the cerebrospinal fluid (CSF).[10] Exosomes, containing proteins, lipids, and nucleic acid molecules, are transported from donor cells to distant recipient cells through mechanisms like phagocytosis, pinocytosis, endocytosis, or plasma membrane fusion, containing specific cargoes.[11] Additionally, exosomes are seen as carrier vehicles that may travel actively between cells, facilitating material and information exchange. Research indicates several cells within the CNS, such as neurons, astrocytes, oligodendrocytes, microglia, and endothelial cells, are capable of releasing exosomes. These exosomes may have positive or negative effects in both normal and diseased states.[12]

Exosomes are increasingly shown to play a crucial role in the formation as well as dissemination of two pathological hallmarks in AD, senile plaques and intracellular neurofibrillary tangles, which are characterized by the deposition of extracellular amyloid β protein and the hyperphosphorylation of microtubule-related tau protein.[13] Exosomes associated with AD were first discovered while studying the buildup of APP cleavage in MVBs,[14,15] which are considered as progenitors of exosomes. Later research discovered that Aβ peptides are present in exosomes,[16] providing more evidence that exosomes play a role in the progression of Alzheimer's disease. Interestingly, exosomes derived from impaired nerve cells can play a dual role in AD. They can transfer APP, γ/β-secretase, Aβ peptide, and tau protein to healthy neurons, accelerating the death of peripheral neurons and spreading pathological features of AD.[17,18] Additionally, exosomes can promote Aβ clearance, transporting Aβ to microglia's lysosomes and degrading in them.[19] Therefore, the primary aim of our work is to outline the updated understandings on exosomes biogenesis and many functions of exosomes in the generation, conveyance, distribution, and elimination of hazardous proteins related to Alzheimer's disease. This is intended to provide novel insights for understanding the development, specific treatment, and early detection of Alzheimer's disease.

Overview of Exosomes: Biogenesis, Secretion, Sources, Isolation, and Biological Characteristics

The Biogenesis and Secretion of Exosomes

Three primary categories of EVs, exosomes, microvesicles (MVs), and apoptotic bodies, have been identified according to their size and origin. Microvesicles (MVs) are generated by budding off the plasma membrane and typically range in diameter from 100 to 1000 nm.[20,21] Apoptotic bodies, ranging from 100 to 2000 nm in diameter, are generated by the plasma membrane of apoptotic cells. They are not often engaged in cellular communication since they are ingested by phagocytic cells.[22] Exosomes are the smallest extracellular vesicles formed during endocytosis, typically ranging in size from 40 to 160 nm in diameter.[9,23] Exosome development starts in the endosomal system and is linked to the processing of membrane organelles such as the transGolgi network, endoplasmic reticulum, lysosomes, and autophagosomes.[24] Endosomes are formed during endocytosis, aiding cells in absorbing substances (such as proteins, lipids, and molecules) through engulfing.[25,26] Intracellular endocytosis occurs from an early endosome involving the plasma membrane and external cargos. The trans-Golgi network and endoplasmic reticulum play a role in the formation of early endosomes. The early endosome transitions into the late endosome as it matures. Endosomes undergo further invagination to create intraluminal vesicles (ILVs),[7,27] leading to the formation of multivesicular bodies (MVBs). Multi-vesicular bodies (MVBs) may merge with the plasma membrane to expel intraluminal vesicles (ILVs) as exosomes.[28,29] Alternatively, multivesicular bodies (MVBs) may merge directly with lysosomes or autophagosomes (Figure 1).

The Sources of Exosomes

Exosomes are prevalent in several bodily fluids including bronchioalveolar lavage, synovium, saliva, urine, bile, cerebrospinal fluid (CSF), breast milk, and plasma. They have distinct cell-derived components on their surfaces and are secreted by different cell types such as nerve cells, mesenchymal cells, reticulocytes, fibrin, epithelium, endothelium, thrombocytes, allophycocyanins, and cancer cells. It is currently understood that the majority of cell types, including brain cells, produce exosomes. Dendritic cells and β-lymphocytes were also found to produce similar vesicles. Exosomes from multiple cell types contain identical

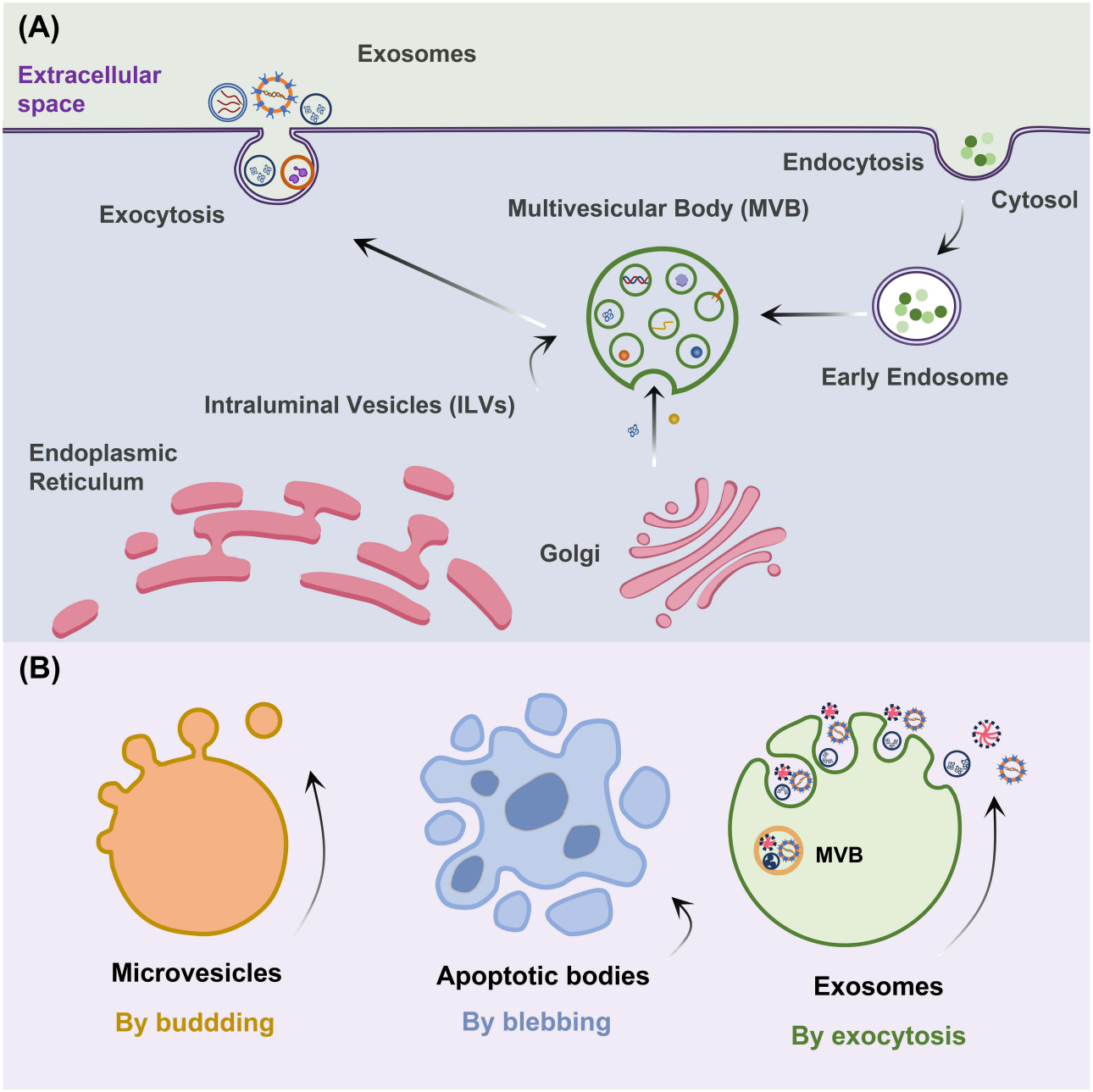

Figure 1 Three categories of extracellular vesicles and exosome biogenesis. (**A**) Endocytosis creates an early endosome via the plasma membrane's invagination to internalize cargo from the extracellular space. The early endosome is situated near the endoplasmic reticulum (ER) and the trans-Golgi network to assist in the internalization and modification of intracellular cargo. The early endosome transitions into a multivesicular body (MVB) or multivesicular endosome (MVE). Cytosolic molecules like as proteins and RNA are taken up by the multivesicular body (MVB) by membrane invagination, resulting in the creation of intra luminal vesicles (ILVs) inside the MVB. The multivesicular body combines with the plasma membrane and releases intraluminal vesicles known as exosomes into the extracellular matrix by exocytosis. (**B**) Three kinds of extracellular vesicles (EVs) are differentiated by their production and size. 1) Apoptotic bodies, ranging from 1000 to 5000 nm in diameter, are generated by the process of "blebbing" from the cellular membrane of a cell undergoing apoptosis. 2) Microvesicles are created by protruding from the plasma membrane and have a diameter ranging from 100 to 1000 nm. 3) Exosomes, with a diameter between 30 and 150 nm, come from the endosomal system.

substances. The structure usually comprises a lipid bilayer with transmembrane proteins and distinct protein markers, encircling a core comprising enzymes, extracellular matrix proteins, lipids, nucleic acids (DNA and RNA), and transcription factors.[30]

The Isolation of Exosomes

Various techniques have been used to extract exosomes and vesicles that resemble them from both plants and animal, and detailed procedures for isolating exosomes have been recently reviewed by Kandimalla et al.[30] Exosomes are isolated

using methods such as ultracentrifugation, isoelectric precipitation, ultrafiltration, polymer-based precipitation, size-exclusion chromatography, and microfluidic technologies.[31]

Since it is both simple and inexpensive, ultracentrifugation (UC) has become the method of choice for separating and purifying exosomes and particles that resemble them. While the process does increase purity, it reduces the amount of isolated exosomes.[32] An attempt was made to rectify this shortcoming by increasing the efficiency of the exosomes separation method while preserving a higher level of purity and yield. To enhance the exosomes yield, UC was slowed down by the use of ultrafiltration, which separates biomolecules according to their sizes. The extra stage in this process, however, makes it more susceptible to contamination and drives up manufacturing costs.[32,33] To separate exosomes according to their sizes, size-exclusion liquid chromatography (SEC) is useful. It gets rid of the need to pellet exosomes at high speeds, yields a very pure product, and works well with serum or plasma purification.[34] Nevertheless, additional procedures are required when using SEC to prevent sample-lipoprotein interference and protein aggregation.[35] To guarantee very pure separation, the immuno-isolation method employs magnetic beads coated with antibodies to target proteins on the exosomes surface. Problems with this approach persist, however, due to our incomplete understanding of exosomal architecture, surface components, and systemic problems.[36] A chemical conjugation approach may be used to modify the surface of paper in order to generate an immunoaffinity system that is based on paper. Antibody with strong affinity for particular EV is selected as the capture molecule. Consequently, this method requires a small sample size and is easy to implement.[35–37] Because of its many benefits, including high-purity separation, economy, and reduced processing time, microfluidics has recently emerged as a cutting-edge method for isolating exosomes. These benefits are based on the device's architecture that has a high surface-to-volume ratio. This reduces the volume required for important samples, and speeds up the response time by performing many phases at once.[32,35] According to the Minimal information for studies of extracellular vesicles 2018 guidelines, it is recommended to use a combined approach for isolating exosomes.[38]

The Biological Characteristics of Exosomes

Exosomes were first reported in the early 1980s to analyse vesicles released by various cultured cells, with a size range of 40 to 1000 nm. In the next years, this phrase may describe endosomal vesicles with diameters between 30 and 100 nanometers.[39,40] Exosome membranes are mostly phospholipids and proteins, with flag molecules including CD9, CD63, CD81, CD82, adhesion proteins, integrins, and glycoproteins on the surface. They can transport microRNAs, mRNA, DNA, heat shock proteins, lipid-associated proteins, sphingolipids, and phospholipids.[41] Exosomes have comparable cargoes, but also exhibit cell specificity determined by the chemicals in their source cells and the physiological or pathological circumstances during exosome synthesis. Exosome contents may vary under diverse stimuli and can be identified via proteomics, lipidomics, sequencing, and PCR.[12] Thorough investigation and comprehension of exosomes have improved the knowledge of their roles in three areas: 1) Exosomes carry unique contents that facilitate cell-cell communication as well as cellular processes. 2) Exosomes are present in cerebrospinal fluid, blood, urine, and other bodily fluids, making them useful as diagnostic markers. 3) Exosomes also play a role in delivering drugs.

Exosomes as a Player in AD Pathogenesis

Alzheimer's disease (AD) is the predominant cause of dementia and the most prevalent neurodegenerative disorder that worsens with time. Symptoms include memory loss, mobility difficulties, learning impairment, speech and motor deficiencies, psychological disruption, etc. Alzheimer's disease has a complex pathogenesis, which is characterized by the accumulation of insoluble Aβ-amyloid deposits outside cells, the presence of tau fibrils forming NFTs within cells, and neuronal death.[42,43] The release of amyloid-β protein from cultured cells and the accumulation of exosomal proteins like Alix and Flotillin-1 surrounding amyloid plaques in AD patients demonstrate the link between exosomes and the illness.[44] Extracellular deposits seen in the brains of Alzheimer's disease patients, known as amyloid plaques, mostly consist of Aβ. Amyloid fibrils and Aβ oligomers are entangled to form aggregates in a regular pattern in the plaques.[45] The evolution of AD may include soluble Aβ oligomeric forms.[46] Aβ peptides are APP's proteolytic derivatives. The endosomal pathway controls this process, which may occur at various parts of the cell and is also important for making exosomes.[47]

Despite the fact that our knowledge of exosome activity in AD is still limited, there is mounting evidence from both new and existing studies indicating exosomes have diverse functions in the disease.[48] Research shows that exosomes

have many roles in AD pathogenesis. Exosomes may remove and oligomerize Aβ, contributing to plaque formation. Exosomes carry both harmful and beneficial payloads throughout the brain, including Aβ, tau, inflammatory compounds, and enkephalins, insulin-degrading enzymes. Glial cells and neurons may also take up exosomes. Due to their capacity to communicate and control neuron-glial cell interactions, exosomes contribute to Alzheimer's disease (AD).

The exact function of exosomes in the degenerative process of Alzheimer's disease is still unclear, despite the fact that their involvement in the disease is well-established. According to several researchers, exosomes in AD enhance the spread of Aβ as well as p-tau, leading to neurotoxicity.[18,49–51] Contrarily, there is evidence that exosome production may ameliorate the pathogenic phenotype of AD, according to some studies (Figure 2).[19,52–55]

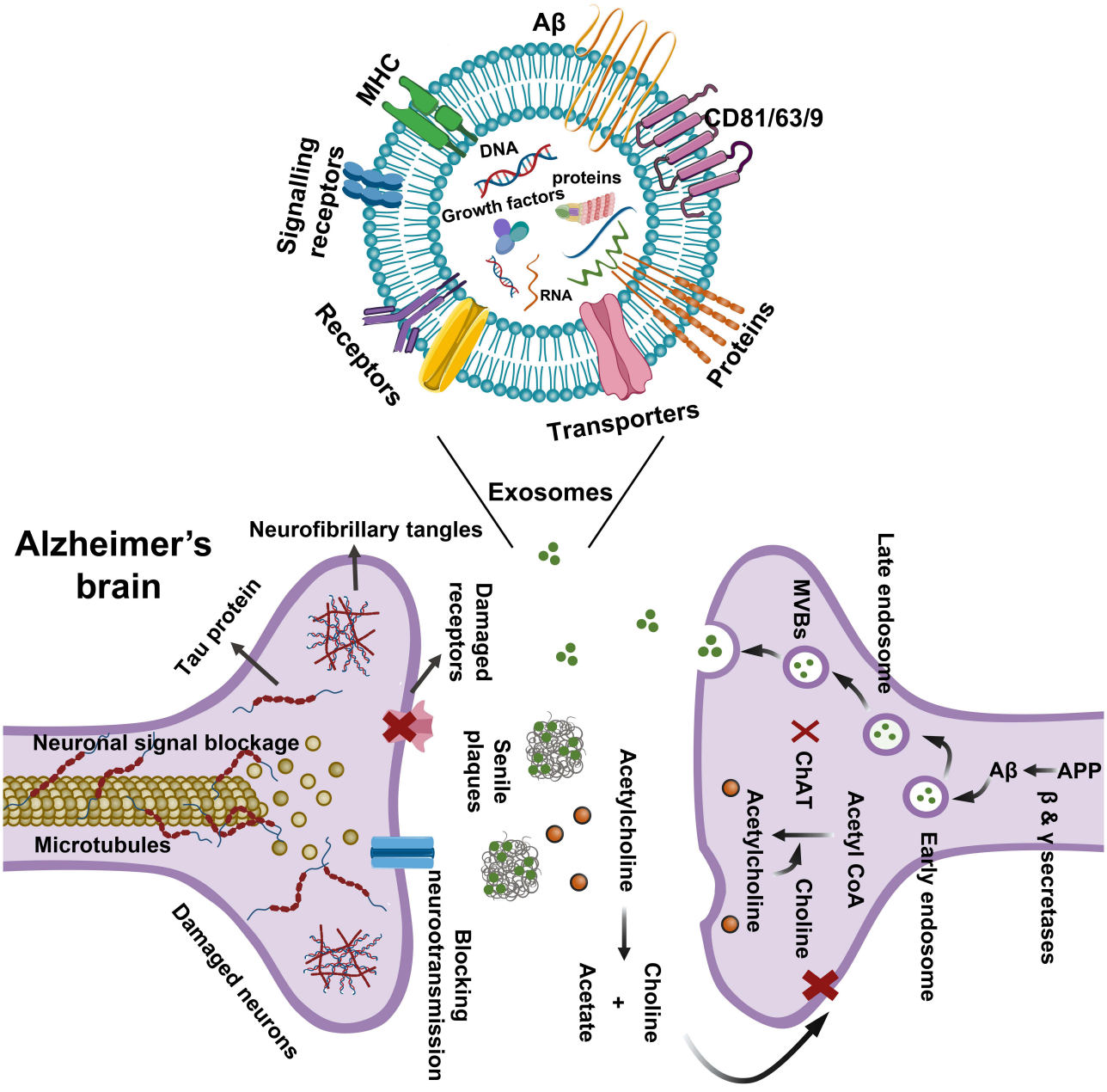

Figure 2 Alzheimer's disease pathophysiology and the involvement of exosomes. The breakdown of amyloid precursor protein creates amyloid beta (Aβ), which is deposited on the exosome surface by early endosomes. Exosomes with Aβ in the synaptic cleft cause AD by inducing senile plaque development and inhibiting neurotransmission. Unstable micro tubules in recipient neurons release tau and form neurofibrillary tangles, which harm neurons and receptors. Choline acetyltransferase (ChAT) synthesis is inhibited by damaged neurons, which limit acetyl-CoA and choline interaction. Aβ and neurofibrillary tangles destroy neuronal cells and hinder neurotransmission, producing brain dysfunction and advancing AD.

Exosomes are Involved in the APP Metabolic Process, Aβ Aggregation and Plaque Formation, the Spread of Aβ and Tau

Intracellular Aβ is typically destroyed via the endosomal-lysosomal route. Inhibition of the Aβ degradation pathway, particularly key molecules like metalloproteinase endothelin-converting enzyme, can cause intracellular Aβ accumulation, facilitating exosome encapsulation and release of Aβ and APP metabolites.[54] Exosomes regularly contain APP, CTFs-APP, and various proteases involved in APP processing.[56] APP cleavage by β- and γ-secretase in early endosomes releases Aβ to MVBs. The export of Aβ to exosomes was produced by a small fraction of the peptide being sorted into intraluminal vesicles in MVBs.[57] Numerous studies reveal APP-associated proteins and metabolites in exosomes of AD cell models and patients during Aβ production. Rajendran et al noticed APP in exosomes and β-secretase cleavage in early endosomes. APP-transfected cells may leak a tiny quantity of Aβ into the culture medium via exosomes. Brain slices from all AD patients show exosome marker Alix enrichment around small neuritic plaques, indicating exosome deposition around amyloid plaques.[16] Vingtdeux et al found that MVBs are necessary for APP metabolism and can secrete all APP metabolites.[58] Exosomes may also house critical members of the secretase family, including β-site APP cleaving enzyme 1, presenilin 1, and disintegrin.[56] Zheng et al stereotactically injected HEK293-APP Swe/Ind cell conditioned media exosomes into the hippocampus dentate gyrus. Exosomes harboring pathogenic proteins were more neurotoxic and impaired hippocampal neurogenesis.[59] In addition to direct engagement in APP metabolism, exosomes may also participate indirectly. Recent research found that exosome-mediated miR-185-5p distribution regulates APP expression in various cells. Exosomes from AD mice and APP-overexpressed N2a cell cultures dramatically boosted recipient cell APP expression. Exosomes do not directly transport APP gene products to destination cells, which is surprising. Instead, exosome miR-185-5p expression decreases.[60] More data is needed to establish that indirect regulation has expanded the complexity of APP metabolism exosomes.

Research indicates that exosomes may expedite the production of amyloid plaques by promoting Aβ aggregation. Exosomes are linked to Aβ fibrosis, since Yuyama et al demonstrated that exosomes from PC12 cells given chloroquine and KCl increase Aβ assembly. Cholera toxin B subunit blocking and endoglycoceramidase-treated glycolysis in vitro investigations revealed that exosome glycosphingolipids (GSLs) glycochains significantly influence Aβ fibril formation.[19] On the outer layer of exosomal membranes, glycochain membrane lipids (GSLs) expose their glycans to the environment. After traversing the cell membrane, GSLs form dense clusters that monomeric Aβ can detect and attach to.[61] Research suggests that GM1 ganglioside, found in GSLs, may bind to Aβ and enhance aggregation.[62,63] Especially NDE exosomes enrich GSLs. Exosomes may serve seeds for Aβ aggregation, and plaque development. GSLs and cellular prion protein (PrP(C)) are significantly loaded in exosomes. Glycosylphosphatidylinositol-anchored surface glycoprotein PrP(C) is found on neuron and exosome outer leaflets. Research suggests that exosomes attach to Aβ via PrP(C), which has the strongest affinity for dimeric, pentameric, and oligomeric Aβ species, accelerating fibrosis and lowering neurotoxic effects.[64] Results indicate that NDEs may capture Aβ via GSLs and PrP(C) in a single or synergistic way, promoting Aβ aggregation and amyloid plaque formation.

With more and more proof Aβ and tau spread in the brain, the idea that exosomes might be the means by which Aβ and tau are transmitted is becoming more popular.[65–67] Normal mouse brains are subjected to AD-like neuropathology when exosomes produced from plasma neuronal cells of AD patients seed tau aggregation.[51] Results from some investigations show that tau clumps may multiply and spread throughout the brain by exosomes, much like prion diseases. Pathological tau "seeds" transported by exosomes cause tau misfolding into a harmful conformation in cells that take them up.[68] Only exosomes and tau seeds devoid of vesicles have been shown to transmit across synapses in neuronal networks, according to recent literatures.[69] Aβ enhances the seeding activity of the majority of the exosomal tau produced by AD synapses, which is oligomeric and has its C-terminal truncated form.[70] Additionally, studies have shown that exosomes enriched with tau or isolated from tau transgenic rTg4510 mice brains can promote tau aggregation in recipient cells, as well as increase tau phosphorylation and soluble oligomer formation.[49,50,71] Release of tau-containing exosomes is another way in which microglia aid in the spread of tau. By encouraging microglia production of tau-enriched exosomes, BIN1 (another gene associated with AD) contributes to advancement of tau pathology in AD.[72] In mice, exosomes derived from cerebrospinal fluid (CSF) of Alzheimer's disease (AD) patients that include

BIN1-associated genetic variations that cause AD expedite the spread of tau.[73] Inhibiting exosome formation or reducing microglia numbers considerably slows tau propagation in both laboratory and living organism studies.[74] Glial cell-derived exosomes have the potential to promote Aβ aggregation in the brains of 5XFAD mice, along with spreading tau. The cognitive deficits in the 5XFAD mouse model can be alleviated by reducing Aβ1−42 and amyloid plaques in the brain. Even more crucially, exosomes retrieved from AD patients, such as blood and cerebrospinal fluid, display an abnormally high level of soluble Aβ1−42, Aβ oligomer, p-T181-tau, and p-S396-tau. What's more, these abnormalities could be identified prior to a clinical diagnosis, suggesting that exosomes could be used as a way to diagnose AD. Also, neurons in culture may be exposed to these harmful substances via exosomes produced by Alzheimer's disease patients, which have elevated quantities of Aβ oligomer. Crucially, oligomer spread and associated toxicity were reduced when two ESCRT proteins, TSG101 and VPS4A, were knocked down, which inhibited exosome production, secretion, or absorption.[18] These evidences suggest that exosomes have a role in the dissemination of tau and Aβ, which in turn leads to pathological damage in AD, when considered collectively.

Exosomes are Involved in Neuroinflammation, Oxidative Stress, Angiogenesis, and Neuronal Dysfunction in AD

An inflammatory response including free radicals, cytokines released by microglia and astrocytes, and other factors is associated with the development of Alzheimer's disease.[75] Exosomes play a large role in neuroinflammation as a natural nanocarrier of harmful inflammatory chemicals. Furthermore, they aid in the advancement of inflammation in brain cells and speed up the production of amyloid plaques by releasing Aβ.[75,76] The prevailing belief is that Aβ plaques cause cellular-level downstream consequences such oxidative stress, microglial activation, local inflammation, and tau protein hyperphosphorylation, which ultimately result in cell death and dysfunctional synaptic transmission.[77–79] The levels of complement, which include C1q, C4b, and C3d, as well as pro-inflammatory markers (IL-1, TNF-α, and IL-1β), were noticeably greater in AD patients compared to matched controls.[80] Patients in the CE 2 stage had lower levels of regulatory proteins and greater levels of complement proteins compared to those in the CE 1 preclinical stage, adding to the mounting evidence linking inflammatory chemicals in exosomes to AD by showing that levels of complement proteins in exosomes produced from astrocytes are correlated with disease stage.[80] In neuroinflammatory illnesses like AD, synaptic dysfunction may be one of the first mechanisms impacted.[81,82] A study found that EV produced by Aβ1−42 activates microglia, which in turn causes a significant reduction in the density of dendritic spines in hippocampal neurons both in living organisms and in laboratory settings. One possible explanation is that EV contains a large number of miRNAs that control the expression of important synaptic proteins.[83] Aβ treatment in astrocytes leads to the production of the proapoptotic PAR-4 protein, leading to increased cell death in cultured astrocytes.[84] Both serum and brain tissue from 5XFAD mice and Alzheimer's patients contain ceramide-enriched and astrocyte-derived exosomes connected to Aβ pathology. These exosomes were transferred to mitochondria by bypassing neurones in vitro or in vivo, causing mitochondria to cluster and increase DRP1 levels. Aβ-linked exosomes promoted the binding of Aβ to VDAC1. After binding, caspase triggered neurite breakdown and neuronal cell death.[85,86]

Interestingly, peripheral exosomal contents may potentiate CNS inflammation, which may play a part in explaining how a peripheral pro-inflammatory state such as depression, obesity, diabetes can be risk factors for AD. Li et al[87] investigated the involvement of serum-derived exosomes in the process of neuroinflammation by utilizing the endotoxemia model with lipopolysaccharide (LPS). The findings indicated that the mice that received exosomes derived from LPS-challenged mice experienced heightened activation of microglia and astrogliosis. Additionally, there was an increase in the production of pro-inflammatory cytokines in the body and an elevated expression of pro-inflammatory cytokine mRNA and the inflammation-associated microRNA (miR-155) in the CNS of these recipient mice. Gene expression study verified that several inflammatory microRNAs (miR-15a, miR-15b, miR-21, miR-27b, miR-125a, miR-146a, miR-155) exhibited a substantial increase in expression inside the isolated exosomes when exposed to LPS-induced conditions. Accumulated signaling within the microglia of mice that received tail-vein injections of fluorescently labeled exosomes were also observed, suggesting that peripheral exosomes may act as a neuroinflammatory mediator in systemic inflammation.[87] Another study examined whether exosomes generated during the peripheral inflammatory process have

the ability to trigger neuroinflammation.[88] It was demonstrated that proinflammatory exosomes could cross the blood–brain barrier and trigger neuroinflammation when injected intravenously. Results suggest that peripheral cholinergic signals may play a role in regulating proinflammatory exosomes-mediated signaling from the periphery to the brain.[88] Exosomes secreted during a peripheral pro-inflammatory state such as depression, obesity, and diabetes may serves as a key mechanism linking to AD.[89–91]

More study has focused on exosomes as neuron-glial cell communication mediators. Zhu et al[92] found that deleting the Trem2 gene in mice (Trem2 KO) can increase the spread of tau protein from the medial entorhinal cortex (MEC) to the hippocampus. This spread of tau is accompanied with a decline in synaptic function and memory behavior. Deleting Trem2 in microglia increases the spread of tau protein throughout different layers of neurons cultivated in a microfluidic chamber. Additionally, inhibiting exosomes can effectively decrease the amount of tau found in exosomes and the surrounding fluid released by microglia containing tau. While the deletion of microglial Trem2 does not impact the absorption of tau, it does improve the distribution of tau to endosomal and cellular pre-exosomal compartments once it is taken up. Trem2 deletion has been found to influence alterations in the microglial proteomic landscape in the presence of tau and LPS/ATP therapy, leading to the activation of exosomes. In addition, exosomes derived from microglia without the Trem2 gene exhibit increased amounts of tau protein and have a greater ability to induce tau aggregation in a tau FRET reporter line, as compared to exosomes from microglia with the Trem2 gene.[92] Exosomes contain inflammation-causing payloads to cause neuroinflammation.[93] Research indicates that Aβ buildup and tau hyperphosphorylation activate microglia and astrocytes, leading to inflammation.[94] Exosomes may contain harmful proteins like Aβ or tau, and activated glial or neuronal cells could release them into environment, exacerbating neuroinflammatory effects.[95] MicroRNAs, an essential exosome cargo, also induce neuroinflammation. NDEs expressing miR-21-5p may be phagocytosed by microglia and promote M1 polarization. This increases neuroinflammatory factors, neurite outgrowth inhibition, P-tau accumulation, and PC12 cell apoptosis.[96] Exosomes enhance and disseminate extracellular microenvironment inflammation and may also reduce it. Due to its carrier transport, simplicity of modification, and therapeutic drug encapsulation, exosomes have been shown to treat inflammation. Related investigations have shown that AD is tightly linked to NLRP3 inflammasome activation.[97] Ginger rhizome exosomes limit NLRP3 inflammasome activation, IL-1β and 18 release, and pyroptotic cell death by preventing NLRP3 inflammasome assembly.[98] Microglia exosomes may sometimes decrease inflammation. Upregulated miR-124-3p in microglial exosomes induces anti-inflammatory M2 polarization, reduces neuronal inflammation, and is transferred to neurons to boost neurite outgrowth after traumatic brain injury.[99] Overall, exosomes may enhance or inhibit the inflammatory response depending on the stimuli and cell types that create them. More study is required to determine the process.

A thorough investigation found a link between oxidative stress and AD growth. A self-sustaining cycle of oxidative stress and inflammatory reactions may cause persistent neuronal damage and dysfunction in AD.[100] Changing environmental circumstances deposit free radicals, causing oxidative stress, mitochondrial malfunction, and inflammation. Essential free radicals, reactive oxygen species, cause tissue failure and oxidative stress.[101] To promote cell development and govern metabolism, the reactive oxygen species level must maintain signalling pathways such the Ras/AMPK, and Protein kinase-C pathways. Oxidative stress may cause amyloid-β and neurofibrillary tangles.[102] Furthermore, intracellular amyloid-β accumulation triggers oxidative and inflammatory pathways, creating a loop of oxidation and amyloid-β production.[103] Numerous studies show that neuroinflammation-induced oxidative stress increases Aβ production by increasing β and γ-secretase activity.[104] Oxidative stress triggers Aβ formation via p38 mitogen-stimulated protein kinase signaling, NFκB binding, or lipid peroxidation. Several Aβ techniques increase oxidative stress by overexpressing reactive oxygen species in cells.[105] Metal ion-chelated Amyloid β may regenerate O2 by a three-step process including reduction to superoxide and oxygen peroxide, generation of OH radical, and the release of reactive oxygen species as byproducts. Amyloid-β may induce oxidative stress via endoplasmic reticulum damage, lipid buildup, and mitochondrial malfunction.[106] Studies indicate that monomeric units and micro-oligomers Aβ are responsible for generating oxidative stress, which results in cell damage and neuronal death, rather than plaques.[107] Also, oxidative stress might alter the process of biogenesis, the release, and the composition of exosomes. Exosomes generated under oxidative stress contain biologically active chemicals that might potentially affect the regulation of both challenged cells and nearby cells.[108–112] In addition, exosomes obtained from cells exposed to oxidative stress exhibited a reduction in the levels of proteins that

promote cell survival and an increase in proteins that induce cell death. These findings align with previous reports indicating that oxidative stress can modify the phosphorylation process of proteins involved in cell activity.[113] Oxidative stress has been found to change the lipid content of exosomes, specifically affecting the amounts of oxidized lipids, and their transfer across cells. Exosomes have been demonstrated to have both proinflammatory and anti-inflammatory effects on nearby cells through the production or transport of oxidatively changed lipids.[114] Establishing a two-way connection is essential for preserving cellular balance in the face of oxidative stress. Alterations in redox state stimulate an increase in the quantity of exosomes, which can be done by either enhancing their release or reducing their breakdown. Elevated autophagy conditions redirect MVBs toward lysosomes rather than the plasma membrane, impeding the secretion of exosomes.[115,116] Conversely, inhibiting autophagic trafficking facilitates exosome secretion.[117] Studies have demonstrated that oxidative stress can lead to an increased release of exosomes in several types of cultured cells.[118–121] Furthermore, the presence of nanoparticles, mechanical damage, or chemicals has been shown to cause oxidative stress, leading to an increase in the quantity of exosomes, which may also be accompanied by morphological alterations.[121]

Regionally raised capillary concentration, vascular loop growth, glomeruloid vascular structure creation, and VEGF and TNF release are biochemical and morphological signs of angiogenesis. A study suggests that angiogenic activation of the brain endothelium in AD leads to the formation of Aβ plaques and neurotoxic protein that damages cortical neurons.[122] Angiogenesis, the formation of new blood vessels from pre-existing vessels, is a complex and coordinated process that involves vascular degradation. Increasing vascular basement membrane endothelial cell and neovasculature development.[123,124] Research indicates that microglia-produced inflammatory cytokines, regulated by Amyloid-β protein, accelerate AD development.[125] Angiopathy in cardiovascular illnesses and AD is linked to amyloid, resulting in altered artery walls and increased microcapillary thickness in Aβ deposits.[126] The high incidence of vascular problems in AD, Aβ's regulation of endothelial inflammation, and the close link between capillaries and amyloid-β deposits lead to cerebral vasculature involvement.[127] Using DNA sequencing and proteomics to analyze gene expression levels supports the Aβ-inflammation-angiogenesis theory in AD.[128] Interestingly, several genetic factor translation products promote angiogenesis. This study suggests that damaged brain arteries may upregulate angiogenesis and its components and that unique DNA array information plays a role in AD pathogenesis.[129] VEGF controls brain angiogenesis and BBB integrity.[130] VEGF binds to VEGF receptor-2, activating it. VEGF exists in less active membrane-bound and inactive soluble forms, inhibiting pro-angiogenic signaling. Deficit in angiogenic response to VEGF in Alzheimer's disease may be mediated by VEGF receptor expression.[131] Earlier stages of AD also show TGF-1 signalling pathway dysfunction and reduced downregulation of transforming growth factor-II receptor in neurons.[132]

Collectively, these results suggest that exosomes may transport pathogenic proteins associated with Alzheimer's disease and lead to dysfunction in neuronal activity. Hence, pharmaceutical treatments that block exosome release might provide a novel therapeutic approach for Alzheimer's disease.

Exosomes are Involved in the Aβ Clearance Process, the Remission of AD Pathology, and Exert a Protective Role in AD

Despite the fact that exosomes were thought to cause AD, a substantial amount of new research suggests they may actually help prevent the disease. In particular, exosomes may carry chemicals that restore neuronal functioning or remove Aβ, which may have protective effects on Alzheimer's disease. Exosomes include proteins with several powerful protective roles for neurons, such as Cystatin C.[133,134] Neprilysin (NEP) and insulin-degrading enzyme (IDE), two enzymes involved in the breakdown of Aβ, are also found in exosomes. New evidence from the following studies supports the idea that exosomes' protective impact is directly related to IDE.[52,55]

Released into the extracellular environment by exosomes, metalloproteases endothelin-converting enzyme (ECE)-1 and −2 may facilitate the breakdown of Aβ. Increasing Aβ levels and facilitating the intracellular production of Aβ oligomers may be achieved by the inhibition of metalloproteases, which disrupts Aβ catabolism.[54] Exosomes produced from neuroblastoma cells/ human cerebrospinal fluid were shown to be able to inhibit Aβ's ability to alter synaptic plasticity, according to another investigation. The main factor determining these effects is the ability of exosomal surface proteins, including PrP, to sequester Aβ oligomers.[135] Exosomes facilitate tau secretion in response to overexpression,

and this released tau does not cause cell death in contrast to cytoplasmic tau, according to one study.[136] This finding provides further evidence that tau-secreting exosomes could mitigate the harmful effects of tau overexpression in cells. Furthermore, it has been shown that neuronal cells may decrease Aβ oligomerization in vitro by improving microglia-mediated Aβ clearance via the production of exosomes. Microglia secrete mutant tau into the central nervous system via exosomes, according to a recent research.[137] Reducing microglia numbers and blocking exosomal secretory routes decreases tau growth in both in vivo and in vitro experiments. Neuronal exosomes, when injected into the brains of APP transgenic mice, reduce the buildup of Aβ and amyloid. A possible explanation might be neuronal exosomes capture Aβ via the membrane's rich glycosphingolipids, transfer it to microglia, and therefore reduce Aβ pathogenesis. Exosomes produced by hypoxia-preconditioned mesenchymal stromal cells may reverse the cognitive loss in APP/PS1 mice according to a newly published research.

A recent research found that microglia exosomes may secrete their contents by activating receptor expressed on myeloid cells 2 (TREM2). In order to change the inflammatory levels around Aβ and enhance microglia cell detection and phagocytosis of Aβ, pure microglia exosomes may attach to Aβ via TREM2, releasing chemokines.[138] Furthermore, TREM2 may influence tau pathology along with its functions in Aβ clearance. The enhancement of tau trafficking, dispersion, and pathogenic dissemination via microglia exosomes may be achieved by deleting Trem2, as previously mentioned.[92,139] On the flip side, microglial overexpression of TREM2 reduces neuronal tau hyperphosphorylation pathology and the inflammatory response.[140] These findings lend credence to the idea that TREM2 may prevent tau pathogenesis by way of microglia exosomes. Microglial enrichment of the ATP-gated cationic channel P2X purinoceptor 7 (P2RX7) enhances exosome secretion. Giving P301S tau mice the P2RX7-specific inhibitor GSK1482160 improves their working and contextual memory by reducing the quantity of exosomes and tau.[141] Potentially new avenues for enhancing tau pathology include inhibiting P2RX7 to decrease exosome expression.

Role of Exosomes in AD Diagnosis

AD is usually detected late in life, making treatment challenging. MRI, CT, and PET scans are the main AD diagnostic methods. Biochemical AD diagnostics are not used clinically despite their development. Reliable biochemical tests for early AD detection may enhance AD treatment throughout age.

A biomarker is a characteristic that could be reliably measured and studied as a sign for treatment-related physiological effects, pathogenic activities, or normal bioactivities.[142] Possible Alzheimer's disease biomarker data comes from a wide range of places, including clinical memory impairment tests, analyses of bodily fluids or organs, imaging of neurons, and olfactory tests.[143] More and more research is focusing on exosomes as potential biomarkers to differentiate between healthy and diseased states, due to their unique biological properties. Exosomes provide several distinct benefits as a diagnostic tool for diseases. The first advantage is that exosomes may be easily and painlessly retrieved from most bodily fluids, meaning that the organism is not harmed in any way during the sampling process. Furthermore, the payloads housed inside exosomes are able to retain their biological activity and structural integrity due to the protective nature of their membranes. Plus, the exosome cargoes are process-related and change depending on the illness state. Surprisingly, exosomes may traverse the BBB via their bilayer lipid structure and end up in peripheral circulation. Researchers are focusing their efforts on searching for biomarkers from blood exosomes since blood samples are so common. More importantly, the content of patient samples may be preserved for future biomarker investigation because to the excellent stability of these exosomes. Blood, urine, CSF, saliva, synovial fluid, breast milk, semen, amniotic fluid, ascites, lymph, and as many other bodily fluids as possible contain exosomes.

Early AD diagnosis and disease progression prediction using biochemical biomarkers has been described.[144] Aβ1−42, total tau (T-tau), and p-tau protein levels in cerebrospinal fluid (CSF) are the most commonly acknowledged AD biomarkers.[145,146] Even in the early to mid-stages of AD, these biomarkers could provide diagnostically useful information.[147] The CSF sample approach has limited dissemination and applicability in clinical practice due to its invasiveness. It has been discovered that exosomes may be produced in the brain, released into the bloodstream, and identified in the peripheral circulation after crossing the blood-brain barrier.[148] There has been recent speculation that exosomes generated from neurons might be indications for AD. It has been discovered that exosomes secreted from the central nervous system and amyloid-β precursor protein are components of neurons in plasma.[149] Identified the onset of

Alzheimer's disease up to five years prior to the onset of the illness, amyloid-β, which is present in neuronal generated exosomes removed from serum. Research on exosome biomarkers is therefore driven by the requirement to diagnose AD at an earlier stage.[150] Exosomes are potential biomarkers for tracking the degenerative progression of Alzheimer's disease because of this quality.

Almost every biomolecule derived from the parent cells is present in exosomes. Urine is one of the physiological fluids that contains exosomes, and it is easy and non-invasive to collect this fluid. Consequently, the most typical and effective specimens for liquid biopsy are exosomes of urine. In a preliminary investigation, Sun et al[151] assessed the concentrations of Aβ1−42 and P-S396-tau in urine exosomes. According to the results of this investigation, the amounts of these pathogenic proteins in urine exosomes were much higher in people with AD as compared to healthy controls. A new, non-invasive, and inexpensive way to measure salivary exosome content was developed by Rani et al using nanoparticle tracking analysis. Patients with cognitive impairment and AD may have considerably elevated salivary exosomal levels, according to this research. Cognitively impaired people may be able to differentiate between Alzheimer's disease and other dementias using cerebrospinal fluid biomarkers. Although the absolute levels of CSF Aβ40 and Aβ38 are not very useful for AD diagnosis, there are a number of benefits to using the Aβ42/AỤ40 or Aβ42/Aβ38 ratios. The ratios of CSF Aβ42 to AỤ40 and Aβ42 to AỤ38 may serve as more accurate indicators of target engagement in amyloid-based therapeutic clinical trials compared to CSF AỤ42 alone. As well as protein markers, exosomal nucleic acids may detect AD. APP processing, tau phosphorylation, and apoptosis activation by exosomal miRNA may impact AD progression. An AD prognostic serum miRNA signature was described by Cheng et al. Intergroup differences in miRNA modification were reported between AD and control groups.[152] miR-193b may reduce APP mRNA and protein content. MiR-193b level was similar in AD patients and controls, while exosomal levels were much lower. Also, exosomal miR193b and Aβ42 were adversely linked to AD, suggesting exosomal miR193b level a biomarker for AD.[153] Another AD-related biomarker is blood or CSF exosomal miR-451a. In several investigations, AD patients had lower blood and CSF exosomal miR-451a levels than controls.[154–156] Yang et al[157] measured serum miR-135a, −193b, and −384 levels using qRT-PCR in 2018. MCI and AD groups had higher miR-135a and miR-384 levels than the control group. MCI and AD patients have lower serum exosomal miR-193b levels. Using Solexa sequencing and qRT-PCR, Dong et al[158] identified blood exosome miRNAs such miR-31, miR-93, miR-143, and miR-146a for AD diagnosis. During the stages of AD, miR-132-3p showed the highest dysregulation of all of these. It is worth noting that nerve cells show a decline in miRNA-132-3p and a rise in P-tau as the illness progresses, suggesting that miRNA-132-3p is dysregulated and might be used as a new disease biomarker.[159] The AD patients had significantly lower levels of these four miRNAs than the controls.

Exosomal contents can be used as biomarkers to differentiate AD from normal controls, MCI as well as other forms of dementia such as fronto-temporal dementia. In a study by Krishna et al,[160] the synaptic and organellar markers in AD and frontotemporal dementia (FTD) are investigated by assessing the levels of synaptic protein, neurogranin (Ng), and organellar proteins, mitofusin-2 (MFN-2), lysosomal associated membrane protein-2 (LAMP2), and golgin A4 from neuronal exosomes. Exosomes obtained from the plasma of healthy controls (HC), AD and FTD subjects were analyzed. Neurodegenerative status was assessed by measurement of neurofilament light chain (NfL). Analyzed in this study were the pooled exosomal extracts from each group for the presence of Ng, MFN-2, LAMP-2, and golgin A4. As a result, the densitometric analysis of immunoreactive bands revealed a 65% decrease in Ng in individuals with AD and a 53% decrease in individuals with FTD. The mitochondrial protein MFN-2 shown a notable decrease of 32% in AD and 46% in FTD. The levels of Lysosomal LAMP-2 and Golgi complex related golgin A4 were significantly elevated in both AD and FTD. These findings indicate that alterations in Ng may be indicative of the progressive breakdown of synaptic connections, which is associated with cognitive impairments in AD and FTD. Crucially, alterations in the levels of synaptic protein, neurogranin (Ng) and MFN-2, LAMP2, and golgin A4 from neuronal exosomes are helpful to distinguish AD from normal controls and FTD.[160] The two-stage-sectional investigation by Jia et al[161] examined the potential of exosomal synaptic proteins as a predictor of asymptomatic Alzheimer's disease. The first trial included participants with preclinical AD and controls, while the second study confirmed the findings in familial AD. As compared to controls, AD patients had reduced quantities of growth associated protein 43 (GAP43), neurogranin, synaptosome associated protein 25 (SNAP25), and synaptotagmin 1. They found a correlation between the levels of

exosomal biomarkers and those in CSF. Adverse events were recognized five to seven years before to cognitive impairment by combining exosomal biomarkers. This study revealed that exosomal GAP43, neurogranin, SNAP25, and synaptotagmin 1 act as effective biomarkers to differentiate AD from normal controls and MCI.[161]

More credible biomarkers for early diagnosis have just been proposed, namely, exosomes in the blood that are generated from neurons and astrocytes.[162–164] In plasma neuron-derived exosome extracts, the levels of p-S396-tau, p-T181-tau, and Aβ1−42 are noticeably greater in Alzheimer's disease (AD) patients compared to controls. This reliably predicts AD start up to 10 years before clinical manifestation and progression from MCI to AD dementia.[51,165] It is worth noting that new studies have shown that the AD group had greater levels of neuron-derived exosomal Aβ1−42, T-tau, and p-T181-tau, which coincided with the levels in CSF. This indicates that these exosomal markers may be used for AD diagnosis much as the ones in CSF.[166] The APEX technology, developed by a group of researchers, analyses various populations of circulating Aβ proteins as well as exosomes that are bound or unattached to these proteins directly in the blood. When measuring Aβ linked to exosomes, as opposed to unbound or completely circulating Aβ, it is possible to more accurately represent PET imaging of brain amyloid plaques and differentiate between different groups.[167]

It has been postulated that proteins associated with neuroinflammation found in astrocyte and stem cell derived blood exosome extracts might serve as AD biomarkers.[168,169] Evidence suggests that these cells secreted exosomes from AD patients include much greater quantities of pro-inflammatory factors and complement factors.[80,170] There is an association between elevated levels of GABARAP, prion proteins (PrP), and APP with the presence of damaged mitochondrial organelles in extracellular vesicles (EV) isolated from the brains of preclinical AD patients. The presence of these dysfunctional mitochondrial organelles provides further evidence that defective autophagy in the temporal lobe plays a role in the transmission of AD neuropathology via EV.[171] And since exosomes contain a great deal of tiny miRNAs, assessing their expression is being investigated as a possible diagnostic tool in Alzheimer's disease.[172–174] Taken together, the aforementioned research provide credence to the idea that exosomes might be useful as biomarkers for AD (Table 1).

However, certain concerns remain: 1) Exosomes as AD biomarkers may not be reliable due to the small amount of pathological proteins that cross the blood-brain barrier and the influence of various organs on blood contents. 2) Antibodies targeting proteins may immunoprecipitate plasma neuronal exosomes, but same proteins are also produced in other tissues, necessitating the development of more specific protein markers. 3) Inconsistent experimental results due

Table 1 The Expression of miRNAs in Peripheral Blood and Cerebrospinal Fluids (CSF) Derived from AD Patients

miRNA Profile	Sample	Expression Pattern	Utility	Reference
miR-112, miR-161, miR-let-7d-3p, miR-5010-3p, miR-151a-3p	Blood	Upregulated	These miRNAs can discriminate AD patients from healthy controls.	[175]
miR-103a-3p, miR-107, miR-532–5p, miR-26b- 5p, miR-let-7f-5p		Downregulated		
miR-9-5p, miR-106a-5p, miR-106b-5p, miR-107	Blood	Downregulated	A reduction in whole-blood expression of these miRNAs was significantly associated with an increased risk of AD.	[176]
miR-let-7i-5p, miR-125a-5p, miR-1233-5p	Blood	Downregulated	Downregulation of miR-1233-5p as a pathologic marker for Aβ(+) MCI.	[177]
miR-98-5p, miR-885-5p, miR-483-3p, miR342-3p, miR-191-5p, miR-let-7d-5p	Serum	Downregulated	These miRNAs are downregulated in AD patients and is correlated to MMSE score.	[178]
miR-501-3p	Serum	Downregulated	The level of this miRNA is decreased in the serum of AD patients. Its lower levels are associated with lower MMSE scores.	[179]

(*Continued*)

Table 1 (Continued).

miRNA Profile	Sample	Expression Pattern	Utility	Reference
miR-210	Serum	Downregulated	The level of this miRNA is downregulated in the serum of AD patients, distinguishing AD individuals from healthy controls.	[180]
miR-519	Serum	Upregulated	The level of these miRNA in the serum of AD patients could be used to distinguish AD individuals from healthy controls.	[181]
miR-29, miR-125b, miR-223		Downregulated		
miR-125b	Serum	Downregulated	The level of this miRNA is downregulated in the serum of AD patients, distinguishing AD individuals from healthy controls and is correlated with the MMSE in AD patients.	[182]
miR-125b, miR-23a, and miR-26b	Serum	Downregulated	The levels of these miRNAs are decreased in the serum of AD patients, and serum miR-125 levels can distinguish AD individuals from healthy controls.	[183]
miR-613	Serum	Upregulated	The level of this miRNA is upregulated in the serum of AD patients and animals, and could be used to predict AD.	[184]
miR-455-3p, miR-4668-5p	Serum	Upregulated	The level of this miRNA is increased in the serum of AD individuals and can distinguish AD patients from healthy controls.	[185]
miR-195-5p, miR-146a-5p, miR-106b-3p, miR20b-5p, miR-497-5p	Serum	Upregulated	The level of these miRNAs in the serum of AD individuals and can distinguish AD patients from healthy controls.	[186]
miR-93-5p, miR-29c-3p, miR-125b-3p, miR19b-3p		Downregulated		
miR-28-3p	Serum	Upregulated	miR-28-3p level can be used as an early diagnosis and prognosis evaluation of AD patients.	[187]
miR-331-3p	Serum	Downregulated	Serum expression of miR-331-3p is decreased in AD patients, and is correlated with the MMSE scores and proinflammatory cytokine levels of AD patients.	[188]
miR-31, miR-93, miR-143, and miR-146a	Serum	Downregulated	The levels of these miRNAs are decreased in the serum of AD patients, and this panel can be used to distinguish AD individuals from healthy controls.	[158]
miR-6761-3p, miR-6747-3p, miR-6875-3p, miR-6754-3p, miR-6736-3p, miR-6762-3p, miR-6787-3p, miR-208a-5p, miR-6740-3p, miR-6778-3p, miR-6753-3p, miR-6716-3p, miR-4747-3p, miR-3646, miR-595, miR-4435	Serum	Upregulated	The level of these miRNA in the serum of AD individuals and can distinguish AD patients from healthy controls.	[189,190]
miR-125a-3p, ***miR-22-3p***, miR-24-3p, miR-6131, miR-125b-1-3p		Downregulated		

(*Continued*)

Table 1 (Continued).

miRNA Profile	Sample	Expression Pattern	Utility	Reference
miR-128	Serum	Upregulated	miR-128 was significantly upregulated in the serum samples of AD patients compared with controls, and that this upregulation was negatively correlated with MMSE scores.	[191]
miR-let-7d-5p, miR-let-7g-5p, miR-15b-5p, miR-142-3p, miR-191-5p, miR-545-3p, miR-301a-3p	Plasma	Downregulated	These 7 signature miRNAs are downregulated in the plasma of AD patients and can discriminate AD individuals from healthy controls.	[192]
miR-34c	Plasma	Upregulated	The level of these miRNA in the serum of AD individuals can distinguish AD patients from healthy controls.	[193]
miR-92a-3p, miR-181c-5p, and miR-210-3p	Plasma	Upregulated	The levels of these miRNAs are increased in the plasma of AD patients and can distinguish AD individuals from healthy controls.	[194]
miR-34a-5p and miR-545-3p	Plasma	Downregulated	These miRNAs are downregulated in AD samples and show suitable diagnostic accuracy to distinguish AD patients from healthy controls.	[195]
miR-34a, miR-146a	Plasma	Downregulated	These miRNAs are downregulated in AD samples and show suitable diagnostic accuracy to distinguish AD patients from healthy controls.	[196]
miR-384	Plasma	Downregulated	The level of this miRNA in the plasma of AD individuals can distinguish AD patients from healthy controls.	[197]
miR-483-5p, miR-486-5p, miR-200a-3p, miR502-3p	Plasma	Upregulated	These miRNAs can distinguish AD patients from healthy controls.	[198]
miR-30b-5p, miR-142-3p		Downregulated		
miR-1908	Plasma	Upregulated	The level of this miRNA is increased in the plasma of AD patients and can distinguish AD patients from healthy controls.	[199]
miR-206	Plasma	Upregulated	The level of this miRNA is increased in the plasma of AD patients and can predict cognitive decline using the MMSE test.	[200]
miR-103, miR-107	Plasma	Downregulated	The level of these miRNAs are downregulated in the plasma of AD patients and can distinguish AD patients from healthy controls.	[201]
miR-135a, ***miR-384***	Serum (Exosome)	Upregulated	These miRNAs can be used to distinguish AD patients from healthy controls.	[157]
miR-193b		Downregulated		

(*Continued*)

Table 1 (Continued).

miRNA Profile	Sample	Expression Pattern	Utility	Reference
miR-22-3p, miR-378a-3p	Serum (Exosome)	Upregulated	These miRNAs can be used to distinguish AD patients from healthy controls.	[202]
miR-30b-5p		Downregulated		
miR-342-5p	Serum (Exosome)	Downregulated	The level of this miRNA is downregulated in the plasma of AD patients and can distinguish AD patients from healthy controls.	[203]
miR-342-3p, miR-141-3p, miR-342-5p, miR-23b-3p, miR-125b-5p, miR-24–3p, miR152–3p	Plasma (Exosome)	Downregulated	These miRNAs can predict AD status.	[204]
miR-423-5p, miR-369-5p, miR-23a-5p	Plasma (Exosome)	Upregulated	These miRNAs can be used to distinguish AD patients from healthy controls.	[205]
miR-204-5p, ***miR-125a-5p***, miR-1468-5p, miR375, miR-let-7e-5p		Downregulated		
miR-let-7b	Cerebrospinal fluids	Upregulated	miR-let-7b can function as signaling molecules and identify TLR7 as an essential element in a pathway that contributes to the spread of CNS damage.	[206]
miR-27a-3p	Cerebrospinal fluids	Downregulated	miR-27a-3p can be used to distinguish AD patients from healthy controls.	[207]
miR-29a, miR-29b	Cerebrospinal fluids	Upregulated	These miRNAs show suitable diagnostic accuracy to distinguish AD patients from healthy controls.	[196]
miR-34a, miR-125b, ***miR-146a***		Downregulated		
miR-384	Cerebrospinal fluids	Downregulated	The level of this miRNA in the cerebrospinal fluids of AD individuals can distinguish AD patients from healthy controls.	[197]
miR-146a, miR-100, miR-505#, miR-4467, miR-766, miR-3622b-3p, miR-296	Cerebrospinal fluids	Upregulated	The level of these miRNAs in the cerebrospinal fluids of AD individuals can distinguish AD patients from healthy controls.	[208]
miR-1274a, miR-375, miR-708, miR-219, miR-103		Downregulated		
miR-210	Cerebrospinal fluids	Downregulated	The level of this miRNA is downregulated in the cerebrospinal fluids of AD patients, distinguishing AD individuals from healthy controls.	[180]
miR-613	Cerebrospinal fluids	Upregulated	The level of this miRNA is upregulated in the cerebrospinal fluids of AD patients and animals, and could be used to predict AD.	[184]
miR-29a	Cerebrospinal fluids	Upregulated	The level of this miRNA is upregulated in the cerebrospinal fluids of AD patients and animals, and could be used to predict AD.	[209]
miR-378a-3p, miR-1291	Cerebrospinal fluids	Upregulated	The level of these miRNAs in the cerebrospinal fluids of AD individuals can distinguish AD patients from healthy controls.	[210]
miR-143-3p, miR-142-3p, miR-328-3p, miR193a-5p, miR-19b-3p, miR-30d-5p, miR-340- 5p, miR-140-5p, ***miR-125b-5p***, miR-223-3p		Downregulated		

(*Continued*)

Table 1 (Continued).

miRNA Profile	Sample	Expression Pattern	Utility	Reference
miR-let-7b, miR-let-7e	Cerebrospinal fluids	Upregulated	The level of this miRNA is upregulated in the cerebrospinal fluids of AD patients and animals, and could be used to predict AD.	[211]
miR-125-5p	Cerebrospinal fluids	Upregulated	These miRNAs represent novel targets for uncovering disease mechanisms and for biomarker development in both young-onset AD and late-onset AD.	[156]
miR-451a, miR-605-5p		Downregulated		
miR-455-3p	Cerebrospinal fluids	Upregulated	The level of this miRNA is upregulated in the cerebrospinal fluids of AD patients, and could be used to predict AD.	[212]
miR-16-5p, ***miR-331-3p***, miR-409-3p, miR-454-3p	Cerebrospinal fluids	Upregulated	The miRNA cargo in cerebrospinal fluid (CSF) is associated with of sex and APOE-e4 in AD.	[213]

Note: The contradictory result is displayed in italics and bold (miRNA).
Abbreviations: MMSE, Mini-Mental State Examination; MCI, mild cognitive impairment.

to potential contamination, inconsistent extraction methods, and potential errors in the quantification of exosomes. Future studies aimed at resolving these issues should provide further evidence to aid in the diagnosis of AD.

Role of Exosomes in AD Treatment

Exosomes can carry miRNA and siRNA for AD therapy due to their RNA transport capacity, stability in bodily fluids, and BBB crossing.[214] Neuron-derived exosomes influence extracellular Aβ structure, resulting in non-toxic fibrils that promote microglia absorption.[19] Exosomes may cure AD in many ways (Figure 3 and 4) (Table 2).

Exosomes as a Drug Delivery Vehicle

Numerous benefits may be achieved by delivering APs via exosomes. In comparison to liposomes or polymeric nanoparticles, exosomes are superior because to their desirable properties, such as a prolonged half-life, the ability to target, biocompatibility, and almost non-immunogenicity.[234] Moreover, exosomes have the ability to enter tissues, spread throughout the circulation, and traverse the blood-brain barrier (BBB) in a specific way, which makes them ideal vectors for delivering genetic and medicinal components to treat neurological diseases.[235,236] Because exosomes mediate the transfer of foreign substances and cargo, including proteins, mRNAs, miRNAs, and lipids, from one cell to another, the idea of using them to transport drugs has evolved from their function as a mediator of intercellular communication.[237] It's possible that exosomes serve many purposes in the therapy of AD. Neuroprotective effects of extracellular elastin-rich oligosaccharides (exosomes) generated from mesenchymal stem cells (MSC-EXOs) include promoting functional recovery after traumatic brain injury (TBI) and neurodegenerative diseases (NDDs) by preventing cell death and inflammation in the brain.[75,238] Previous research has effectively reduced total Aβ1−42 levels, a key component of the amyloid plaque in AD pathogenesis, by engineering exosomes laden with siRNAs to target central nervous system cells and suppress BACE1 expression.[214] To boost Que bioavailability and brain targeting and potently enhance cognitive performance, Qi et al[239] produced exosomes loaded with Que (EXO-Que). They then used them to rats with okadaic acid-induced AD. EXO-Que reduced insoluble NFT formation and limited tau phosphorylation by cyclin-dependent kinase 5, indicating its therapeutic potential for the treatment of Alzheimer's disease, in comparison to free Que. However, there are still several unanswered questions, such as how to make exosomes correctly recognise target cells, how to load exosomes with medications, etc.

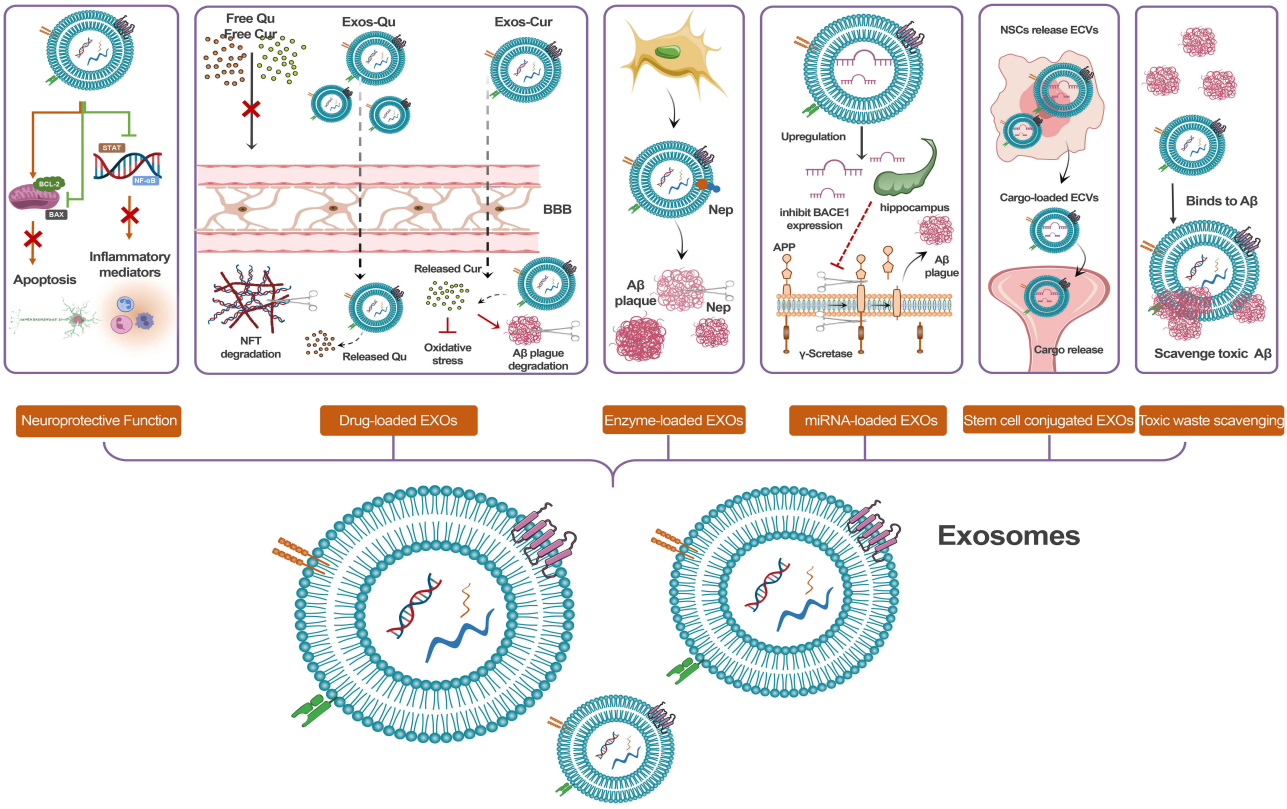

Figure 3 Role of exosomes in AD treatment.

Abbreviations: APP, amyloid precursor protein; Aβ, amyloid-beta; BCL2, B-cell lymphoma 2; BaX, BcL-2-associated X protein; BBB, blood–brain barrier; BACE-1, beta-site amyloid precursor protein cleaving enzyme 1; Cur, curcumin; ECVs, extracellular vesicles; MP-MSCs, multipotent mesenchymal stem cells; NEP, neprilysin; NSCs, neural stem cells; NF-κB, nuclear factor kappa-light-chain enhancer of activated B-cells; NFT, neurofibrillary tangles; QU, quercetin; STAT, signal transduction and activator of transcription protein.

Bioactive Substances Delivery

Exosomes are a type of stem cell secretome. Recent scientific discoveries have shown that exosomes derived from dental pulp stem cells (DPSCs),[216] bone marrow stromal cells (BMSCs),[217,240] and adipose-derived stem cells (ADSCs) contain neprilysin and an insulin-degrading enzyme, the roles of which are to break down Aβ.[52] The quantity of neprilysin in the extracellular matrix (ECM) components released by DPSCs was comparatively greater than that of BMSCs and ADSCs. Furthermore, these exosomes may degrade Aβ1–42 and reduce their neurotoxic effects in laboratory-grown SH-SY5Y neuroblastoma cells.[240] In another study, through electroporation, exogenous siRNA was loaded into purified exosomes that were targeted to the RVG. In these conditions, exosome-based gene therapy was shown to be effective in treating Alzheimer's disease (AD) by significantly lowering protein expression and reducing Aβ plaques in mice. A different study found that when miR-124a was delivered from neurons to glia through endothelial vesicles, it increased the surface expression of the excitatory amino acid transporter 2. This increased glutamate uptake is important for maintaining cognitive function in this situation.[241,242]

Toxic Waste Scavenging and Neuroprotective Effects

Exosomes have the ability to attach to Aβ via glycosphingolipids on the surface of the cell membrane, making them excellent Aβ scavengers. This indicates that exosomes may play a role in clearing Aβ from the central nervous system. A novel therapeutic pathway for AD may be opened up by enhancing Aβ clearance with the injection of exosome.[232] N2a cells, a neuronal genetically engineered neuroblastoma cell line, produces exosomes that may inhibit neuronal death and Aβ-induced alterations in synaptic plasticity.[135,164] In 2014, Yuyama et al found that exosomes scavenge Aβ via Aβ-glycan and exosome-glycosphingolipid attachment. This mechanism significantly reduces Aβ count, alleviating AD pathogenesis.[232] Transplantation of stem cells is

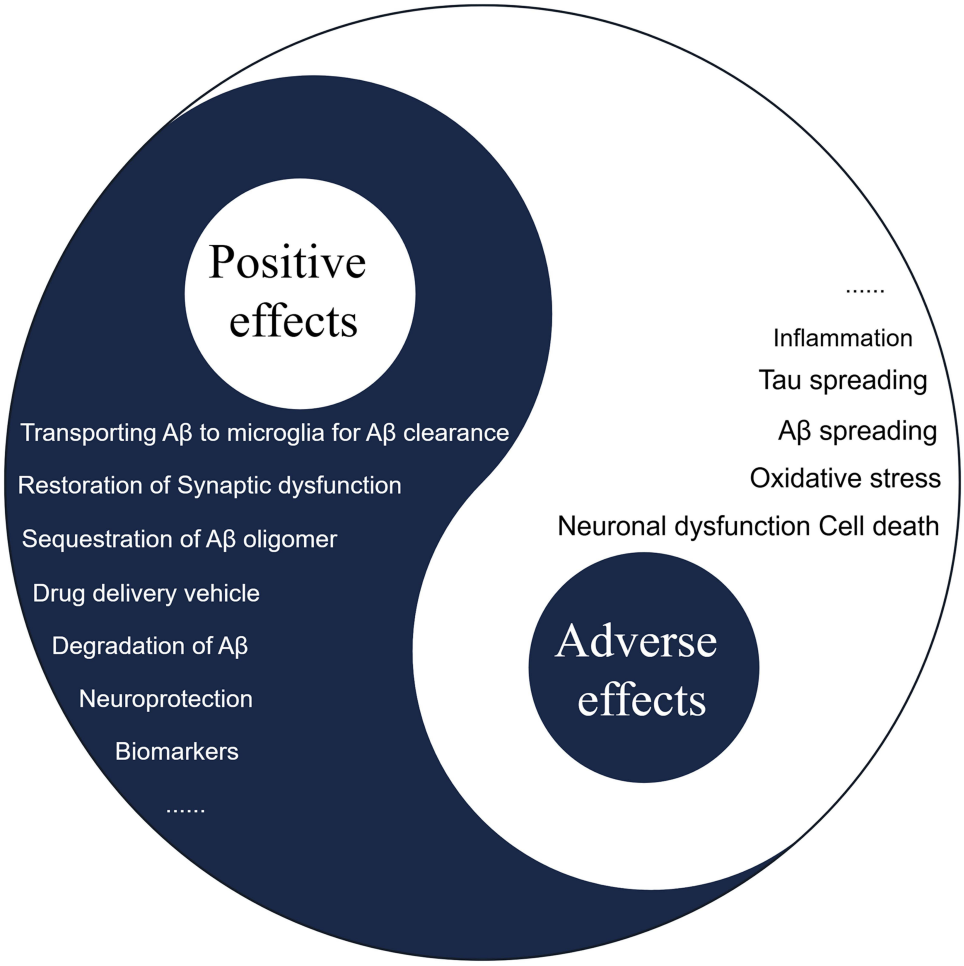

Figure 4 The dual role of exosomes in the pathogenesis of AD. By Figdraw.

now showing promise as a treatment for neurological diseases. Restoring the biomolecules required for non-functional cells, exosomes produced from MSCs when administered might alleviate a range of neurologic disorders. In order to restore bioenergy after depletion caused by glutamate excitotoxicity, MSCs generated from human adipose tissue released exosomes that had direct neuroprotective effects by avoiding neuronal apoptosis. This helped with central nervous system regeneration and repair.[243] There is evidence that changes in NF-κB are associated with cancer, inflammatory and autoimmune disorders, septic shock, viral infections, and the development of synaptic plasticity and memory.[244] Research has shown that glial cell control and reduction of inflammatory mediator levels controlling NF-kB pathways may be achieved with treatment with exosomes produced from MSCs.[245] Additionally, Past research has shown that when microglia consume exosomes, they may be able to lower brain Aβ-protein levels. Neuroprotective substances may also be transmitted across cells by these mechanisms.[246]

Numerous studies suggest that stem cell-derived exosomes may improve AD pathology. According to Lee et al, exosomes from ADSCs may decrease β-amyloidosis and neuronal death in AD transgenic mice models and improve axon development in AD patients' brains.[215] Mesenchymal stromal cells (MSCs) have a high in-vitro multiplicity, are abundant in many tissues, and are easy to separate, making them a promising potential source of exosomes.[247,248] Further research shows that MSC-derived exosomes may help enhance AD pathology and cognition.[218] By correcting BDNF-associated neuropathology, bone-MSC exosomes slow cognitive decline in AD-like mice.[224] Furthermore, bone-MSC injection in double transgenic APP/PS1 mice may activate the sphingosine kinase-1/sphingosine-1-phosphate signaling pathway, reducing Aβ accumulation and promoting cognitive performance in AD animals.[225] Many inflammation-related disorders may be treated using hucMSC exosomes. HucMSC-exosome injection reduces Aβ

Table 2 Role of Exosomes in AD Treatment

Source of Exosomes	Models	Outcomes	References
ADSC	NSCs from the brains of TG2576 AD mice	Decreasing Aβ42 and Aβ40 levels, AD neuronal cell death, and stimulating neurite development.	[215]
ADSC	N2a cell line	Decrease the levels of Aβ.	[216,217]
MSCs	Human neural cell culture model with FAD mutations and AD transgenic mice	Lowering Aβ levels, boosting brain glucose metabolism and cognitive performance in AD animals, and restoring the expression of genes linked to neuronal memory and synaptic plasticity in the cell model.	[218]
MSCs	5 × FAD mice	Diminish persistent inflammation and expedite the elimination of Aβ.	[219]
MSCs	C57BL/6 mice	Encourage neurogenesis and the restoration of cognitive function.	[220]
MSCs	APP/PS1 mice	Reduce the neurological deficit of CA1 synaptic transmission in an AD animal model by inhibiting the inducible nitric oxide synthase (iNOS) in cultured primary neurons.	[221]
MSCs	Aβ-treated SH-SY5Y cells	Reduce apoptosis in neural cells and promote cell migration.	[222]
MSCs	APP/PS1 mice	Reduce Aβ levels and plaque accumulation while restoring normal inflammatory cytokine levels to enhance learning and memory.	[223]
BMSCs	A sporadic AD mouse model	Enhancing AD-like behaviors, preventing astrocyte and microglia hyperactivation, and enhancing BDNF-related neuropathology.	[224]
BMSCs	APP/PS1 mice	APP/PS1 mice's capacity for spatial learning and memory is improved, and SphK1 and S1P expression is increased. Amyloid levels are lowered, and NeuN expression is encouraged.	[225]
BMSCs	APP/PS1 mice	Diminish the quantity of dystrophic neurites and the Aβ plaque burden in the hippocampus and cortex.	[226]
BMSCs	APP/PS1 mice	The hippocampus will express more microRNA-146a, and astrocytes' levels of nuclear factor kappa B (NF-κB) will drop. This will result in synaptogenesis and the improvement of cognitive impairment.	[227]
HucMSCs	APP/PS1 mice	Restore cognitive deficits and remove Aβ deposits.	[228]
HBMVECs	Aβ-induced AD mice model	Promoting the removal of Aβ from the brain and improving cognitive impairment.	[229]
M2 microglia	Neuronal HT-22 cells and APP/PS1 mice	Improving PINK1/Parkin-mediated mitophagy.	[230]
MExo-Gem	BV2 cells and Aβ1−42-induced AD mice	Binding with Aβ and preferentially targeting microglia, which encourages lysosome-mediated Aβ clearance and enhances AD mice's capacity for learning and memory.	[231]
Neuroblastoma	APP transgenic mice	Reduce amyloid buildup, Aβ-mediated synaptotoxicity, and Aβ levels in the hippocampal tissues.	[232]
Neuronal	APP transgenic mice	Reduce amyloid deposition and Aβ.	[233]
Dendritic cells	C57BL/6 mice	Reduce Aβ and BACE1.	[214]

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid beta; ADSC, adipose-derived stem cells; NSCs, neuronal stem cells; MSCs, mesenchymal stem cells; FAD, familial AD; BMSCs, bone-marrow mesenchymal stem cells, BDNF, brain-derived neurotrophic factor; SphK1, sphingosine kinase-1; S1P, sphingosine-1-phosphate; HucMSCs, human umbilical cord mesenchymal stem cells; HBMVECs, human brain microvascular endothelial cells, PINK1, PTEN-induced putative kinase1; MExo-Gem, mannose-modified exosomes laden with Gem; N2a cells, Mouse neuroblastoma Neuro-2a cells.

accumulation, improves cognitive performance in AD mice, and modulates microglia cell activation, reducing neuroinflammation.[228] Transfer of ADSCs-derived exosomes into N2a cells reduces intracellular Aβ levels.[216,217] In AD, stem cells and other cell-derived or bioengineered exosomes are useful. In a study, exosomes from human brain microvascular endothelial cells with p-glycoprotein were used to remove Aβ peptides from the brain. This was achieved through capture of p-glycoprotein and Aβ, resulting in improved cognitive function in AD mice.[229] By enhancing PINK1/Parkin-mediated mitophagy, M2 microglia-derived exosomes also protect against AD.[230] It is also necessary to use synthetic liposomes consisting of glycosphingolipids to collect Aβ and presenilin instead of natural exosomes. This would provide several advantages, such as consistent and contamination-free collection.[249] Bioengineering can create microglia-targeting exosomes and tailored medication delivery. Mannose-modified exosomes with gemfibrozil interact with Aβ and target microglia, boosting Aβ entrance, stimulating lysosome activity, and speeding Aβ clearance in microglia.[231]

Conclusions, Limitations and Future Perspectives

This review primarily discusses on the generation and functions of exosomes along with their complex role in the pathology, diagnosis, and treatment of Alzheimer's disease. Exosomes have attracted considerable interest due to their small size, important function in intercellular communication, biocompatibility, safety, and potential use as diagnostic and therapeutic tools in multiple brain disorders, such as AD. Exosomes seem to have a dual function in AD, being implicated in both the development of the disease and perhaps in its improvement. Exosomes may expedite the diseased process by facilitating the dissemination of disease-related proteins, triggering inflammation and oxidative stress, angiogenesis, or initiating cell death. Conversely, exosomes have been shown to slow down the disease progression by facilitating the clearance of Aβ and tau proteins.

However, the potential mechanisms by which exosomes exert these varying functions are still not clear enough, and further in-depth research is needed to investigate the mechanism of exosomes participating in AD and validate their potential as candidate drugs. Additional data is required to uncover the functions of exosomes in AD, particularly with advanced imaging labeling methods that provide real-time viewing of exosome interactions in cells or animals. Besides, collecting exosomes from certain cells is difficult, especially human cells. The absence of standard techniques for isolating and purifying exosomes is another primary barrier to effectively incorporating them into the translational clinical application, and thus practical and dependable exosome separation technologies require additional improvement. Moreover, exosomes function as promising diagnostic markers for AD are still in the infancy stage of development despite of their distinctive molecular traits. In future study, more clinical samples and data will be required to validate the postulated potential significance of exosomes in the diagnosis of AD. Furthermore, although a series of clinical trials have found the efficacy of exosomes in AD, there are some differences in data from different teams, and the metabolic process of exosomes in the human body and the specific process of their effects still need further investigation. With the appropriate combination of technological advancement and scientific understanding, the potential offered by exosomes could be fully realized.

Data Sharing Statement

The current study was based on the results of relevant published studies. Data is available from the corresponding author upon request.

Acknowledgments

We are grateful to the editors and reviewers for giving valuable advice and important comments in the review.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This review was funded by the Scientific Research Project of of Health Commission of Changzhou (No. ZD202019).

Disclosure

The authors declare no conflict of interest.

References

1. Gomes P, Tzouanou F, Skolariki K, et al. Extracellular vesicles and Alzheimer's disease in the novel era of precision medicine: implications for disease progression, diagnosis and treatment. *Exp Neurol*. 2022;358:114183. doi:10.1016/j.expneurol.2022.114183
2. Reisberg B, Borenstein J, Salob SP, Ferris SH, Franssen E, Georgotas A. Behavioral symptoms in Alzheimer's disease: phenomenology and treatment. *J Clini Psych*. 1987;48 Suppl:9–15.
3. Merriam AE, Aronson MK, Gaston P, Wey SL, Katz I. The psychiatric symptoms of Alzheimer's disease. *J Am Geriatr Soc*. 1988;36(1):7–12. doi:10.1111/j.1532-5415.1988.tb03427.x
4. Alzheimer's Association. 2016 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2016;12(4):459–509. doi:10.1016/j.jalz.2016.03.001
5. Kumar A, Singh A, Ekavali A. A review on Alzheimer's disease pathophysiology and its management: an update. *Pharmacol Rep*. 2015;67 (2):195–203. doi:10.1016/j.pharep.2014.09.004
6. Meraz-Ríos MA, Toral-Rios D, Franco-Bocanegra D, Villeda-Hernández J, Campos-Peña V. Inflammatory process in Alzheimer's Disease. *Front Integrative Neurosci*. 2013;7:59. doi:10.3389/fnint.2013.00059
7. Soares Martins T, Trindade D, Vaz M, et al. Diagnostic and therapeutic potential of exosomes in Alzheimer's disease. *J Neurochemistry*. 2021;156(2):162–181. doi:10.1111/jnc.15112
8. Farlow MR, Miller ML, Pejovic V. Treatment options in Alzheimer's disease: maximizing benefit, managing expectations. *Dementia Geriatric Cognit Disord*. 2008;25(5):408–422. doi:10.1159/000122962
9. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. *Science (New York, NY)*. 2020;367(6478):6977. doi:10.1126/science.aau6977
10. Caruso Bavisotto C, Scalia F, Marino Gammazza A, et al. Extracellular vesicle-mediated cell‐cell communication in the nervous system: focus on neurological diseases. *Int J Mol Sci*. 2019;20(2):434.
11. Zhang T, Ma S, Lv J, et al. The emerging role of exosomes in Alzheimer's disease. *Ageing Res Rev*. 2021;68:101321. doi:10.1016/j.arr.2021.101321
12. Kanninen KM, Bister N, Koistinaho J, Malm T. Exosomes as new diagnostic tools in CNS diseases. *BBA*. 2016;1862(3):403–410. doi:10.1016/j.bbadis.2015.09.020
13. Soliman HM, Ghonaim GA, Gharib SM, et al. Exosomes in Alzheimer's disease: from being pathological players to potential diagnostics and therapeutics. *Int J Mol Sci*. 2021;22(19):10794.
14. Takahashi RH, Milner TA, Li F, et al. Intraneuronal Alzheimer abeta42 accumulates in multivesicular bodies and is associated with synaptic pathology. *Am J Pathol*. 2002;161(5):1869–1879. doi:10.1016/s0002-9440(10)64463-x
15. Verbeek MM, Otte-Höller I, Fransen JA, de Waal RM. Accumulation of the amyloid-beta precursor protein in multivesicular body-like organelles. *j Histochemistry Cytochemistry*. 2002;50(5):681–690. doi:10.1177/002215540205000509
16. Rajendran L, Honsho M, Zahn TR, et al. Alzheimer's disease beta-amyloid peptides are released in association with exosomes. *Proc Natl Acad Sci USA*. 2006;103(30):11172–11177. doi:10.1073/pnas.0603838103
17. Perez-Gonzalez R, Gauthier SA, Kumar A, Levy E. The exosome secretory pathway transports amyloid precursor protein carboxyl-terminal fragments from the cell into the brain extracellular space. *J Biol Chem*. 2012;287(51):43108–43115. doi:10.1074/jbc.M112.404467
18. Sardar Sinha M, Ansell-Schultz A, Civitelli L, et al. Alzheimer's disease pathology propagation by exosomes containing toxic amyloid-beta oligomers. *Acta Neuropathol*. 2018;136(1):41–56. doi:10.1007/s00401-018-1868-1
19. Yuyama K, Sun H, Mitsutake S, Igarashi Y. Sphingolipid-modulated exosome secretion promotes clearance of amyloid-β by microglia. *J Biol Chem*. 2012;287(14):10977–10989. doi:10.1074/jbc.M111.324616
20. Raposo G, Stoorvogel W. Extracellular vesicles: exosomes, microvesicles, and friends. *J Cell Biol*. 2013;200(4):373–383. doi:10.1083/jcb.201211138
21. Yáñez-Mó M, Siljander PR, Andreu Z, et al. Biological properties of extracellular vesicles and their physiological functions. *J Extracell Vesicles*. 2015;4:27066. doi:10.3402/jev.v4.27066
22. Battistelli M, Falcieri E. Apoptotic Bodies: particular Extracellular Vesicles Involved in Intercellular Communication. *Biology*. 2020;9(1):21.
23. Ha D, Yang N, Nadithe V. Exosomes as therapeutic drug carriers and delivery vehicles across biological membranes: current perspectives and future challenges. *Acta pharmaceutica Sinica B*. 2016;6(4):287–296. doi:10.1016/j.apsb.2016.02.001
24. Hessvik NP, Llorente A. Current knowledge on exosome biogenesis and release. *Cell. Mol. Life Sci.* 2018;75(2):193–208. doi:10.1007/s00018-017-2595-9
25. Elkin SR, Lakoduk AM, Schmid SL. Endocytic pathways and endosomal trafficking: a primer. *Wiener medizinische Wochenschrift*. 2016;166 (7–8):196–204. doi:10.1007/s10354-016-0432-7
26. Malm T, Loppi S, Kanninen KM. Exosomes in Alzheimer's disease. *Neurochem Int*. 2016;97:193–199. doi:10.1016/j.neuint.2016.04.011
27. Huotari J, Helenius A. Endosome maturation. *EMBO J*. 2011;30(17):3481–3500. doi:10.1038/emboj.2011.286
28. van Niel G, D'Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles. *Nat Rev Mol Cell Biol*. 2018;19(4):213–228. doi:10.1038/nrm.2017.125
29. Janas AM, Sapoń K, Janas T, Stowell MH, Janas T. Exosomes and other extracellular vesicles in neural cells and neurodegenerative diseases. *BBA*. 2016;1858(6):1139–1151. doi:10.1016/j.bbamem.2016.02.011
30. Kandimalla R, Aqil F, Tyagi N, Gupta R. Milk exosomes: a biogenic nanocarrier for small molecules and macromolecules to combat cancer. *Am j Reproductive Immunol*. 2021;85(2):e13349. doi:10.1111/aji.13349

31. Munagala R, Aqil F, Jeyabalan J, Gupta RC. Bovine milk-derived exosomes for drug delivery. *Cancer Lett*. 2016;371(1):48–61. doi:10.1016/j.canlet.2015.10.020
32. Li P, Kaslan M, Lee SH, Yao J, Gao Z. Progress in exosome isolation techniques. *Theranostics*. 2017;7(3):789–804. doi:10.7150/thno.18133
33. Lobb RJ, Becker M, Wen SW, et al. Optimized exosome isolation protocol for cell culture supernatant and human plasma. *J Extracell Vesicles*. 2015;4:27031. doi:10.3402/jev.v4.27031
34. Lobb R, Möller A. Size exclusion chromatography: a simple and reliable method for exosome purification. *Methods Mol Biol*. 2017;1660:105–110. doi:10.1007/978-1-4939-7253-1_9
35. Chen BY, Sung CW, Chen C, et al. Advances in exosomes technology. *Int j Clin Chem*. 2019;493:14–19. doi:10.1016/j.cca.2019.02.021
36. Théry C, Amigorena S, Raposo G, Clayton A. Isolation and characterization of exosomes from cell culture supernatants and biological fluids. *Curr Protocols Cell Biol*. 2006. doi:10.1002/0471143030.cb0322s30
37. Hsu MY, Chiu CC, Wang JY, et al. Paper-based microfluidic platforms for understanding the role of exosomes in the pathogenesis of major blindness-threatening diseases. *Nanomaterials*. Basel, Switzerland 2018;8(5):310. doi:10.3390/nano8050310
38. Théry C, Witwer KW, Aikawa E, et al. Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the international society for extracellular vesicles and update of the MISEV2014 guidelines. *J Extracell Vesicles*. 2018;7(1):1535750. doi:10.1080/20013078.2018.1535750
39. Colombo M, Raposo G, Théry C. Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. *Annu. Rev. Cell Dev. Biol.* 2014;30:255–289. doi:10.1146/annurev-cellbio-101512-122326
40. Bobrie A, Colombo M, Krumeich S, Raposo G, Théry C. Diverse subpopulations of vesicles secreted by different intracellular mechanisms are present in exosome preparations obtained by differential ultracentrifugation. *J Extracell Vesicles*. 2012;18397. doi:10.3402/jev.v1i0.18397
41. Song Z, Xu Y, Deng W, et al. Brain derived exosomes are a double-edged sword in Alzheimer's disease. *Front Mol Neurosci*. 2020;13:79. doi:10.3389/fnmol.2020.00079
42. DeTure MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. *Mol Neurodegeneration*. 2019;14(1):32. doi:10.1186/s13024-019-0333-5
43. Chadha S, Behl T, Sehgal A, Kumar A, Bungau S. Exploring the role of mitochondrial proteins as molecular target in Alzheimer's disease. *Mitochondrion*. 2021;56:62–72. doi:10.1016/j.mito.2020.11.008
44. Kumari M, Anji A. Small but mighty-exosomes, novel intercellular messengers in neurodegeneration. *Biology*. 2022;11(3):413. doi:10.3390/biology11030413
45. Sadigh-Eteghad S, Sabermarouf B, Majdi A, Talebi M, Farhoudi M, Mahmoudi J. Amyloid-beta: a crucial factor in Alzheimer's disease. *Med Principles Practice*. 2015;24(1):1–10. doi:10.1159/000369101
46. Shankar GM, Li S, Mehta TH, et al. Amyloid-beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. *Nature Med*. 2008;14(8):837–842. doi:10.1038/nm1782
47. Zhao Z, Sagare AP, Ma Q, et al. Central role for PICALM in amyloid-β blood-brain barrier transcytosis and clearance. *Nat Neurosci*. 2015;18(7):978–987. doi:10.1038/nn.4025
48. Graykowski DR, Wang YZ, Upadhyay A, Savas JN. The dichotomous role of extracellular vesicles in the central nervous system. *iScience*. 2020;23(9):101456. doi:10.1016/j.isci.2020.101456
49. Baker S, Polanco JC, Götz J. Extracellular vesicles containing P301L mutant tau accelerate pathological tau phosphorylation and oligomer formation but do not seed mature neurofibrillary tangles in ALZ17 mice. *J Alzheimer's Dis*. 2016;54(3):1207–1217. doi:10.3233/jad-160371
50. Polanco JC, Scicluna BJ, Hill AF, Götz J. Extracellular vesicles isolated from the brains of rTg4510 mice seed tau protein aggregation in a threshold-dependent manner. *J Biol Chem*. 2016;291(24):12445–12466. doi:10.1074/jbc.M115.709485
51. Winston CN, Goetzl EJ, Akers JC, et al. Prediction of conversion from mild cognitive impairment to dementia with neuronally derived blood exosome protein profile. *Alzheimer's & Dementia*. 2016;3:63–72. doi:10.1016/j.dadm.2016.04.001
52. Bulloj A, Leal MC, Xu H, Castaño EM, Morelli L. Insulin-degrading enzyme sorting in exosomes: a secretory pathway for a key brain amyloid-beta degrading protease. *J Alzheimer's Dis*. 2010;19(1):79–95. doi:10.3233/jad-2010-1206
53. Glebov K, Walter J. Statins in unconventional secretion of insulin-degrading enzyme and degradation of the amyloid-β peptide. *Neuro-Degenerative Diseases*. 2012;10(1–4):309–312. doi:10.1159/000332595
54. Pacheco-Quinto J, Clausen D, Pérez-González R, et al. Intracellular metalloprotease activity controls intraneuronal Aβ aggregation and limits secretion of Aβ via exosomes. *FASEB j*. 2019;33(3):3758–3771. doi:10.1096/fj.201801319R
55. Tamboli IY, Barth E, Christian L, et al. Statins promote the degradation of extracellular amyloid {beta}-peptide by microglia via stimulation of exosome-associated insulin-degrading enzyme (IDE) secretion. *J Biol Chem*. 2010;285(48):37405–37414. doi:10.1074/jbc.M110.149468
56. Sharples RA, Vella LJ, Nisbet RM, et al. Inhibition of gamma-secretase causes increased secretion of amyloid precursor protein C-terminal fragments in association with exosomes. *FASEB j*. 2008;22(5):1469–1478. doi:10.1096/fj.07-9357com
57. Howitt J, Hill AF. Exosomes in the pathology of neurodegenerative diseases. *J Biol Chem*. 2016;291(52):26589–26597. doi:10.1074/jbc.R116.757955
58. Vingtdeux V, Hamdane M, Loyens A, et al. Alkalizing drugs induce accumulation of amyloid precursor protein by-products in luminal vesicles of multivesicular bodies. *J Biol Chem*. 2007;282(25):18197–18205. doi:10.1074/jbc.M609475200
59. Zheng T, Pu J, Chen Y, et al. Exosomes secreted from HEK293-APP swe/ind cells impair the hippocampal neurogenesis. *Neurotox Res*. 2017;32(1):82–93. doi:10.1007/s12640-017-9713-1
60. Ding L, Yang X, Xia X, et al. Exosomes mediate APP dysregulation via APP-miR-185-5p axis. *Front Cell Develop Biol*. 2022;10:793388. doi:10.3389/fcell.2022.793388
61. Yuyama K, Igarashi Y. Linking glycosphingolipids to Alzheimer's amyloid-ß: extracellular vesicles and functional plant materials. *Glycoconjugate j*. 2022;39(5):613–618. doi:10.1007/s10719-022-10066-8
62. Ariga T, Kobayashi K, Hasegawa A, Kiso M, Ishida H, Miyatake T. Characterization of high-affinity binding between gangliosides and amyloid beta-protein. *Arch. Biochem. Biophys.* 2001;388(2):225–230. doi:10.1006/abbi.2001.2304
63. Hayashi H, Kimura N, Yamaguchi H, et al. A seed for Alzheimer amyloid in the brain. *J Neuroscience*. 2004;24(20):4894–4902. doi:10.1523/jneurosci.0861-04.2004

64. Falker C, Hartmann A, Guett I, et al. Exosomal cellular prion protein drives fibrillization of amyloid beta and counteracts amyloid beta-mediated neurotoxicity. *J Neurochemistry*. 2016;137(1):88–100. doi:10.1111/jnc.13514
65. Clavaguera F, Bolmont T, Crowther RA, et al. Transmission and spreading of tauopathy in transgenic mouse brain. *Nat Cell Biol*. 2009;11(7):909–913. doi:10.1038/ncb1901
66. Morales R, Duran-Aniotz C, Castilla J, Estrada LD, Soto C. De novo induction of amyloid-β deposition in vivo. *Mol Psychiatry*. 2012;17(12):1347–1353. doi:10.1038/mp.2011.120
67. Thompson AG, Gray E, Heman-Ackah SM, et al. Extracellular vesicles in neurodegenerative disease - pathogenesis to biomarkers. *Nat Rev Neurol*. 2016;12(6):346–357. doi:10.1038/nrneurol.2016.68
68. Jackson NA, Guerrero-Muñoz MJ, Castillo-Carranza DL. The prion-like transmission of tau oligomers via exosomes. *Front Aging Neurosci*. 2022;14:974414. doi:10.3389/fnagi.2022.974414
69. Polanco JC, Götz J. Exosomal and vesicle-free tau seeds-propagation and convergence in endolysosomal permeabilization. *FEBS J*. 2022;289(22):6891–6907. doi:10.1111/febs.16055
70. Miyoshi E, Bilousova T, Melnik M, et al. Exosomal tau with seeding activity is released from Alzheimer's disease synapses, and seeding potential is associated with amyloid beta. *Lab investigat*. 2021;101(12):1605–1617. doi:10.1038/s41374-021-00644-z
71. Wang Y, Balaji V, Kaniyappan S, et al. The release and trans-synaptic transmission of Tau via exosomes. *Mol Neurodegeneration*. 2017;12(1):5. doi:10.1186/s13024-016-0143-y
72. Van Acker ZP, Bretou M, Annaert W. Endo-lysosomal dysregulations and late-onset Alzheimer's disease: impact of genetic risk factors. *Mol Neurodegeneration*. 2019;14(1):20. doi:10.1186/s13024-019-0323-7
73. Crotti A, Sait HR, McAvoy KM, et al. BIN1 favors the spreading of Tau via extracellular vesicles. *Sci Rep*. 2019;9(1):9477. doi:10.1038/s41598-019-45676-0
74. Asai H, Ikezu S, Tsunoda S, et al. Depletion of microglia and inhibition of exosome synthesis halt tau propagation. *Nat Neurosci*. 2015;18(11):1584–1593. doi:10.1038/nn.4132
75. Cai ZY, Xiao M, Quazi SH, Ke ZY. Exosomes: a novel therapeutic target for Alzheimer's disease? *Neural Regeneration Res*. 2018;13(5):930–935. doi:10.4103/1673-5374.232490
76. Engel PA. Does metabolic failure at the synapse cause Alzheimer's disease? *Med Hypotheses*. 2014;83(6):802–808. doi:10.1016/j.mehy.2014.10.013
77. Chen JX, Yan SS. Role of mitochondrial amyloid-beta in Alzheimer's disease. *J Alzheimer's Dis*. 2010;20 Suppl 2:S569–78. doi:10.3233/jad-2010-100357
78. Crews L, Masliah E. Molecular mechanisms of neurodegeneration in Alzheimer's disease. *Human Molecular Genetics*. 2010;19(R1):R12–20. doi:10.1093/hmg/ddq160
79. Soria Lopez JA, González HM, Léger GC. Alzheimer's disease. *Handbook Clin Neurol*. 2019;167:231–255. doi:10.1016/b978-0-12-804766-8.00013-3
80. Goetzl EJ, Schwartz JB, Abner EL, Jicha GA, Kapogiannis D. High complement levels in astrocyte-derived exosomes of Alzheimer disease. *Ann. Neurol.* 2018;83(3):544–552. doi:10.1002/ana.25172
81. Marsh J, Alifragis P. Synaptic dysfunction in Alzheimer's disease: the effects of amyloid beta on synaptic vesicle dynamics as a novel target for therapeutic intervention. *Neural Regeneration Res*. 2018;13(4):616–623. doi:10.4103/1673-5374.230276
82. Overk CR, Masliah E. Pathogenesis of synaptic degeneration in Alzheimer's disease and *Lewy* body disease. *Biochem Pharmacol*. 2014;88(4):508–516. doi:10.1016/j.bcp.2014.01.015
83. Prada I, Gabrielli M, Turola E, et al. Glia-to-neuron transfer of miRNAs via extracellular vesicles: a new mechanism underlying inflammation-induced synaptic alterations. *Acta Neuropathol.* 2018;135(4):529–550. doi:10.1007/s00401-017-1803-x
84. Wang G, Dinkins M, He Q, et al. Astrocytes secrete exosomes enriched with proapoptotic ceramide and prostate apoptosis response 4 (PAR-4): potential mechanism of apoptosis induction in Alzheimer disease (AD). *J Biol Chem*. 2012;287(25):21384–21395. doi:10.1074/jbc.M112.340513
85. Elsherbini A, Kirov AS, Dinkins MB, et al. Association of Aβ with ceramide-enriched astrosomes mediates Aβ neurotoxicity. *Acta Neuropathologica Communications*. 2020;8(1):60. doi:10.1186/s40478-020-00931-8
86. Elsherbini A, Qin H, Zhu Z, Tripathi P, Crivelli SM, Bieberich E. In vivo evidence of exosome-mediated Aβ neurotoxicity. *Acta Neuropathologica Communications*. 2020;8(1):100. doi:10.1186/s40478-020-00981-y
87. Li JJ, Wang B, Kodali MC, et al. In vivo evidence for the contribution of peripheral circulating inflammatory exosomes to neuroinflammation. *J Neuroinflammation*. 2018;15(1):8. doi:10.1186/s12974-017-1038-8
88. Fricke F, Gebert J, Kopitz J, Plaschke K. Proinflammatory extracellular vesicle-mediated signaling contributes to the induction of neuroinflammation in animal models of endotoxemia and peripheral surgical stress. *Cell Mol Neurobiol*. 2021;41(6):1325–1336. doi:10.1007/s10571-020-00905-3
89. Banerjee A, Khemka VK, Roy D, et al. Role of pro-inflammatory cytokines and vitamin D in probable Alzheimer's disease with depression. *Aging Dis*. 2017;8(3):267–276. doi:10.14336/ad.2016.1017
90. Ly M, Yu GZ, Mian A, et al. Neuroinflammation: a modifiable pathway linking obesity, Alzheimer's disease, and depression. *Am J Geriatr Psychiatry*. 2023;31(10):853–866. doi:10.1016/j.jagp.2023.06.001
91. Kacířová M, Zmeškalová A, Kořínková L, Železná B, Kuneš J, Maletínská L. Inflammation: major denominator of obesity, Type 2 diabetes and Alzheimer's disease-like pathology? *Clin Sci (Lond)*. 2020;134(5):547–570. doi:10.1042/cs20191313
92. Zhu B, Liu Y, Hwang S, et al. Trem2 deletion enhances tau dispersion and pathology through microglia exosomes. *Mol Neurodegener*. 2022;17(1):58. doi:10.1186/s13024-022-00562-8
93. Weng S, Lai QL, Wang J, et al. The role of exosomes as mediators of neuroinflammation in the pathogenesis and treatment of Alzheimer's disease. *Front Aging Neurosci*. 2022;14:899944. doi:10.3389/fnagi.2022.899944
94. Novoa C, Salazar P, Cisternas P, et al. Inflammation context in Alzheimer's disease, a relationship intricate to define. *Biol. Res.* 2022;55(1):39. doi:10.1186/s40659-022-00404-3
95. Gupta A, Pulliam L. Exosomes as mediators of neuroinflammation. *J Neuroinflammation*. 2014;3(11):68. doi:10.1186/1742-2094-11-68

96. Yin Z, Han Z, Hu T, et al. Neuron-derived exosomes with high miR-21-5p expression promoted polarization of M1 microglia in culture. *Brain Behav Immun*. 2020;83:270–282. doi:10.1016/j.bbi.2019.11.004
97. Liang T, Zhang Y, Wu S, Chen Q, Wang L. The Role of NLRP3 inflammasome in Alzheimer's disease and potential therapeutic targets. *Front Pharmacol*. 2022;13:845185. doi:10.3389/fphar.2022.845185
98. Chen X, Zhou Y, Yu J. Exosome-like nanoparticles from ginger rhizomes inhibited NLRP3 inflammasome activation. *Mol Pharmaceut*. 2019;16 (6):2690–2699. doi:10.1021/acs.molpharmaceut.9b00246
99. Huang S, Ge X, Yu J, et al. Increased miR-124-3p in microglial exosomes following traumatic brain injury inhibits neuronal inflammation and contributes to neurite outgrowth via their transfer into neurons. *FASEB j*. 2018;32(1):512–528. doi:10.1096/fj.201700673R
100. Cai Z, Zhao B, Ratka A. Oxidative stress and β-amyloid protein in Alzheimer's disease. *Neuromolecular Med*. 2011;13(4):223–250. doi:10.1007/s12017-011-8155-9
101. Hajam YA, Rani R, Ganie SY, et al. Oxidative stress in human pathology and aging: molecular mechanisms and perspectives. *Cells*. 2022;11 (3):552. doi:10.3390/cells11030552
102. Wang X, Zhou Y, Gao Q, et al. The role of exosomal microRNAs and oxidative stress in neurodegenerative diseases. *Oxid Med Cell Longev*. 2020;2020:3232869. doi:10.1155/2020/3232869
103. Cai Z, Hussain MD, Yan LJ. Microglia, neuroinflammation, and beta-amyloid protein in Alzheimer's disease. *Int j Neurosci*. 2014;124 (5):307–321. doi:10.3109/00207454.2013.833510
104. Cai Z, Wan CQ, Liu Z. Astrocyte and Alzheimer's disease. *J Neurol*. 2017;264(10):2068–2074. doi:10.1007/s00415-017-8593-x
105. Bhat AH, Dar KB, Anees S, et al. Oxidative stress, mitochondrial dysfunction and neurodegenerative diseases; a mechanistic insight. *Biomed Pharmacothe*. 2015;74:101–110. doi:10.1016/j.biopha.2015.07.025
106. Khan A, Vaibhav K, Javed H, et al. Attenuation of Aβ-induced neurotoxicity by thymoquinone via inhibition of mitochondrial dysfunction and oxidative stress. *Mol Cell Biochem*. 2012;369(1–2):55–65. doi:10.1007/s11010-012-1368-x
107. Reddy PH, Beal MF. Amyloid beta, mitochondrial dysfunction and synaptic damage: implications for cognitive decline in aging and Alzheimer's disease. *Trends Mol Med*. 2008;14(2):45–53. doi:10.1016/j.molmed.2007.12.002
108. Atienzar-Aroca S, Flores-Bellver M, Serrano-Heras G, et al. Oxidative stress in retinal pigment epithelium cells increases exosome secretion and promotes angiogenesis in endothelial cells. *J Cell & Mol Med*. 2016;20(8):1457–1466. doi:10.1111/jcmm.12834
109. Yarana C, St Clair DK. Chemotherapy-induced tissue injury: an insight into the role of extracellular vesicles-mediated oxidative stress responses. *Antioxidants*. 2017;6(4):75. doi:10.3390/antiox6040075
110. Benedikter BJ, Weseler AR, Wouters EFM, Savelkoul PHM, Rohde GGU, Stassen FRM. Redox-dependent thiol modifications: implications for the release of extracellular vesicles. *Cell Mol Life Sci*. 2018;75(13):2321–2337. doi:10.1007/s00018-018-2806-z
111. Zhou Y, Xu H, Xu W, et al. Exosomes released by human umbilical cord mesenchymal stem cells protect against cisplatin-induced renal oxidative stress and apoptosis in vivo and in vitro. *Stem Cell Res Ther*. 2013;4(2):34. doi:10.1186/scrt194
112. Arslan F, Lai RC, Smeets MB, et al. Mesenchymal stem cell-derived exosomes increase ATP levels, decrease oxidative stress and activate PI3K/ Akt pathway to enhance myocardial viability and prevent adverse remodeling after myocardial ischemia/reperfusion injury. *Stem Cell Res*. 2013;10(3):301–312. doi:10.1016/j.scr.2013.01.002
113. Biasutto L, Chiechi A, Couch R, Liotta LA, Espina V. Retinal pigment epithelium (RPE) exosomes contain signaling phosphoproteins affected by oxidative stress. *Exp Cell Res*. 2013;319(13):2113–2123. doi:10.1016/j.yexcr.2013.05.005
114. Manček-Keber M, Frank-Bertoncelj M, Hafner-Bratkovič I, et al. Toll-like receptor 4 senses oxidative stress mediated by the oxidation of phospholipids in extracellular vesicles. *Sci Signal*. 2015;8(381):ra60. doi:10.1126/scisignal.2005860
115. Tancini B, Buratta S, Sagini K, et al. Insight into the role of extracellular vesicles in lysosomal storage disorders. *Genes (Basel)*. 2019;10 (7):510. doi:10.3390/genes10070510
116. Hessvik NP, Øverbye A, Brech A, et al. PIKfyve inhibition increases exosome release and induces secretory autophagy. *Cell Mol Life Sci*. 2016;73(24):4717–4737. doi:10.1007/s00018-016-2309-8
117. Fader CM, Sánchez D, Furlán M, Colombo MI. Induction of autophagy promotes fusion of multivesicular bodies with autophagic vacuoles in k562 cells. *Traffic*. 2008;9(2):230–250. doi:10.1111/j.1600-0854.2007.00677.x
118. Yang JS, Kim JY, Lee JC, Moon MH. Investigation of lipidomic perturbations in oxidatively stressed subcellular organelles and exosomes by asymmetrical flow field-flow fractionation and nanoflow ultrahigh performance liquid chromatography-tandem mass spectrometry. *Anal Chim Acta*. 2019;1073:79–89. doi:10.1016/j.aca.2019.04.069
119. Hedlund M, Nagaeva O, Kargl D, Baranov V, Mincheva-Nilsson L. Thermal- and oxidative stress causes enhanced release of NKG2D ligand-bearing immunosuppressive exosomes in leukemia/lymphoma T and B cells. *PLoS One*. 2011;6(2):e16899. doi:10.1371/journal.pone.0016899
120. Wang R, Li J, Zhang X, et al. Extracellular vesicles promote epithelial-to-mesenchymal transition of lens epithelial cells under oxidative stress. *Exp Cell Res*. 2021;398(1):112362. doi:10.1016/j.yexcr.2020.112362
121. Chiaradia E, Tancini B, Emiliani C, et al. Extracellular vesicles under oxidative stress conditions: biological properties and physiological roles. *Cells*. 2021;10(7):1763. doi:10.3390/cells10071763
122. López-Ortiz S, Pinto-Fraga J, Valenzuela PL, et al. Physical exercise and Alzheimer's disease: effects on pathophysiological molecular pathways of the disease. *Int J Mol Sci*. 2021;22(6):2897. doi:10.3390/ijms22062897
123. Chen Y, Qin C, Huang J, et al. The role of astrocytes in oxidative stress of central nervous system: a mixed blessing. *Cell proliferation*. 2020;53 (3):e12781. doi:10.1111/cpr.12781
124. Chen Z, Morales JE, Avci N, et al. The vascular endothelial cell-expressed prion protein doppel promotes angiogenesis and blood-brain barrier development. *Development*. 2020;147(18):94. doi:10.1242/dev.193094
125. Li S, Selkoe DJ. A mechanistic hypothesis for the impairment of synaptic plasticity by soluble Aβ oligomers from Alzheimer's brain. *J Neurochemistry*. 2020;154(6):583–597. doi:10.1111/jnc.15007
126. Bell RD, Zlokovic BV. Neurovascular mechanisms and blood-brain barrier disorder in Alzheimer's disease. *Acta Neuropathol*. 2009;118 (1):103–113. doi:10.1007/s00401-009-0522-3
127. Sagare AP, Bell RD, Zlokovic BV. Neurovascular defects and faulty amyloid-β vascular clearance in Alzheimer's disease. *J Alzheimer's Dis*. 2013;33 Suppl 1(0 1):S87–100. doi:10.3233/jad-2012-129037

128. Zhao Y, Forst CV, Sayegh CE, Wang IM, Yang X, Zhang B. Molecular and genetic inflammation networks in major human diseases. *Mol Biosyst*. 2016;12(8):2318–2341. doi:10.1039/c6mb00240d
129. Negri L, Ferrara N. The prokineticins: neuromodulators and mediators of inflammation and myeloid cell-dependent angiogenesis. *Physiol Rev*. 2018;98(2):1055–1082. doi:10.1152/physrev.00012.2017
130. Wang HL, Zhang CL, Qiu YM, Chen AQ, Li YN, Hu B. Dysfunction of the blood-brain barrier in cerebral microbleeds: from bedside to bench. *Aging and Disease*. 2021;12(8):1898–1919. doi:10.14336/ad.2021.0514
131. Harris R, Miners JS, Allen S, Love S. VEGFR1 and VEGFR2 in Alzheimer's disease. *J Alzheimer's Dis*. 2018;61(2):741–752. doi:10.3233/jad-170745
132. Estrada LD, Oliveira-Cruz L, Cabrera D. Transforming growth factor beta type i role in neurodegeneration: implications for Alzheimer´s disease. *Curr. Protein Pept. Sci.* 2018;19(12):1180–1188. doi:10.2174/1389203719666171129094937
133. Ghidoni R, Paterlini A, Albertini V, et al. Cystatin C is released in association with exosomes: a new tool of neuronal communication which is unbalanced in Alzheimer's disease. *Neurobiol Aging*. 2011;32(8):1435–1442. doi:10.1016/j.neurobiolaging.2009.08.013
134. Pérez-González R, Sahoo S, Gauthier SA, et al. Neuroprotection mediated by cystatin C-loaded extracellular vesicles. *Sci Rep*. 2019;9(1):11104. doi:10.1038/s41598-019-47524-7
135. An K, Klyubin I, Kim Y, et al. Exosomes neutralize synaptic-plasticity-disrupting activity of Aβ assemblies in vivo. *Molecular Brain*. 2013;6:47. doi:10.1186/1756-6606-6-47
136. Simón D, García-García E, Gómez-Ramos A, et al. Tau overexpression results in its secretion via membrane vesicles. *Neuro-Degenerative Diseases*. 2012;10(1–4):73–75. doi:10.1159/000334915
137. Peng C, Trojanowski JQ, Lee VM. Protein transmission in neurodegenerative disease. *Nat Rev Neurol*. 2020;16(4):199–212. doi:10.1038/s41582-020-0333-7
138. Huang S, Liao X, Wu J, et al. The Microglial membrane receptor TREM2 mediates exosome secretion to promote phagocytosis of amyloid-β by microglia. *FEBS Lett*. 2022;596(8):1059–1071. doi:10.1002/1873-3468.14336
139. Jain N, Ulrich JD. TREM2 and microglia exosomes: a potential highway for pathological tau. *Mol Neurodegeneration*. 2022;17(1):73. doi:10.1186/s13024-022-00581-5
140. Jiang T, Zhang YD, Gao Q, et al. TREM2 ameliorates neuronal tau pathology through suppression of microglial inflammatory response. *Inflammation*. 2018;41(3):811–823. doi:10.1007/s10753-018-0735-5
141. Ruan Z, Delpech JC, Venkatesan Kalavai S, et al. P2RX7 inhibitor suppresses exosome secretion and disease phenotype in P301S tau transgenic mice. *Mol Neurodegeneration*. 2020;15(1):47. doi:10.1186/s13024-020-00396-2
142. Coravos A, Khozin S, Mandl KD. Developing and adopting safe and effective digital biomarkers to improve patient outcomes. *Npj Digital Med*. 2019;2(1):90. doi:10.1038/s41746-019-0090-4
143. Kim S, Nam Y, Kim HS, et al. Alteration of neural pathways and its implications in Alzheimer's disease. *Biomedicines*. 2022;10(4):845. doi:10.3390/biomedicines10040845
144. Blennow K, Zetterberg H. Biomarkers for Alzheimer's disease: current status and prospects for the future. *J Internal Med*. 2018;284(6):643–663. doi:10.1111/joim.12816
145. Blennow K. Cerebrospinal fluid protein biomarkers for Alzheimer's disease. *NeuroRx*. 2004;1(2):213–225. doi:10.1602/neurorx.1.2.213
146. Tapiola T, Alafuzoff I, Herukka SK, et al. Cerebrospinal fluid {beta}-amyloid 42 and tau proteins as biomarkers of Alzheimer-type pathologic changes in the brain. *Arch. Neurol.* 2009;66(3):382–389. doi:10.1001/archneurol.2008.596
147. Counts SE, Ikonomovic MD, Mercado N, Vega IE, Mufson EJ. Biomarkers for the Early Detection and Progression of Alzheimer's Disease. *Neurotherapeutics*. 2017;14(1):35–53. doi:10.1007/s13311-016-0481-z
148. Zhuang X, Xiang X, Grizzle W, et al. Treatment of brain inflammatory diseases by delivering exosome encapsulated anti-inflammatory drugs from the nasal region to the brain. *Mol Therapy*. 2011;19(10):1769–1779. doi:10.1038/mt.2011.164
149. Li TR, Wang XN, Sheng C, et al. Extracellular vesicles as an emerging tool for the early detection of Alzheimer's disease. *Mechanisms Ageing Dev*. 2019;184:111175. doi:10.1016/j.mad.2019.111175
150. Winston CN, Romero HK, Ellisman M, et al. Assessing neuronal and astrocyte derived exosomes from individuals with mild traumatic brain injury for markers of neurodegeneration and cytotoxic activity. *Front Neurosci*. 2019;13:1005. doi:10.3389/fnins.2019.01005
151. Sun R, Wang H, Shi Y, et al. A pilot study of urinary exosomes in Alzheimer's disease. *Neuro-Degenerative Diseases*. 2019;19(5–6):184–191. doi:10.1159/000505851
152. Cheng L, Doecke JD, Sharples RA, et al. Prognostic serum miRNA biomarkers associated with Alzheimer's disease shows concordance with neuropsychological and neuroimaging assessment. *Mol Psychiatry*. 2015;20(10):1188–1196. doi:10.1038/mp.2014.127
153. Liu CG, Song J, Zhang YQ, Wang PC. MicroRNA-193b is a regulator of amyloid precursor protein in the blood and cerebrospinal fluid derived exosomal microRNA-193b is a biomarker of Alzheimer's disease. *Mol Med Rep*. 2014;10(5):2395–2400. doi:10.3892/mmr.2014.2484
154. Cogswell JP, Ward J, Taylor IA, et al. Identification of miRNA changes in Alzheimer's disease brain and CSF yields putative biomarkers and insights into disease pathways. *J Alzheimer's Dis*. 2008;14(1):27–41. doi:10.3233/jad-2008-14103
155. Gámez-Valero A, Campdelacreu J, Vilas D, et al. Exploratory study on microRNA profiles from plasma-derived extracellular vesicles in Alzheimer's disease and dementia with *Lewy* bodies. *Translational Neurodegeneration*. 2019;8:31. doi:10.1186/s40035-019-0169-5
156. McKeever PM, Schneider R, Taghdiri F, et al. MicroRNA expression levels are altered in the cerebrospinal fluid of patients with young-onset Alzheimer's disease. *Mol Neurobiol*. 2018;55(12):8826–8841. doi:10.1007/s12035-018-1032-x
157. Yang TT, Liu CG, Gao SC, Zhang Y, Wang PC. The serum exosome derived MicroRNA-135a, −193b, and −384 were potential Alzheimer's disease biomarkers. *Biomed Environ Sci*. 2018;31(2):87–96. doi:10.3967/bes2018.011
158. Dong H, Li J, Huang L, et al. Serum MicroRNA profiles serve as novel biomarkers for the diagnosis of Alzheimer's disease. *Dis Markers*. 2015;2015:625659. doi:10.1155/2015/625659
159. van den Berg MMJ, Krauskopf J, Ramaekers JG, Kleinjans JCS, Prickaerts J, Briedé JJ. Circulating microRNAs as potential biomarkers for psychiatric and neurodegenerative disorders. *Progress Neurobiol*. 2020;185:101732. doi:10.1016/j.pneurobio.2019.101732
160. Krishna G, Santhoshkumar R, Sivakumar PT, et al. Pathological (Dis)Similarities in neuronal exosome-derived synaptic and organellar marker levels between Alzheimer's disease and frontotemporal dementia. *J Alzheimers Dis*. 2023;94(s1):S387–s397. doi:10.3233/jad-220829

161. Jia L, Zhu M, Kong C, et al. Blood neuro-exosomal synaptic proteins predict Alzheimer's disease at the asymptomatic stage. *Alzheimers Dement*. 2021;17(1):49–60. doi:10.1002/alz.12166
162. Vella LJ, Hill AF, Cheng L. Focus on Extracellular vesicles: exosomes and their role in protein trafficking and biomarker potential in Alzheimer's and *Parkinson*'s Disease. *Int J Mol Sci*. 2016;17(2):173. doi:10.3390/ijms17020173
163. Xia X, Wang Y, Huang Y, Zhang H, Lu H, Zheng JC. Exosomal miRNAs in central nervous system diseases: biomarkers, pathological mediators, protective factors and therapeutic agents. *Progress Neurobiol*. 2019;183:101694. doi:10.1016/j.pneurobio.2019.101694
164. Yin Q, Ji X, Lv R, et al. Targeting exosomes as a new biomarker and therapeutic approach for Alzheimer's disease. *Clin Interventions Aging*. 2020;15:195–205. doi:10.2147/cia.S240400
165. Fiandaca MS, Kapogiannis D, Mapstone M, et al. Identification of preclinical Alzheimer's disease by a profile of pathogenic proteins in neurally derived blood exosomes: a case-control study. *Alzheimer's dementia*. 2015;11(6):600–7.e1. doi:10.1016/j.jalz.2014.06.008
166. Jia L, Qiu Q, Zhang H, et al. Concordance between the assessment of Aβ42, T-tau, and P-T181-tau in peripheral blood neuronal-derived exosomes and cerebrospinal fluid. *Alzheimer's Dementia*. 2019;15(8):1071–1080. doi:10.1016/j.jalz.2019.05.002
167. Lim CZJ, Zhang Y, Chen Y, et al. Subtyping of circulating exosome-bound amyloid β reflects brain plaque deposition. *Nat Commun*. 2019;10 (1):1144. doi:10.1038/s41467-019-09030-2
168. Jeyaraman M, Rajendran RL, Muthu S, et al. An update on stem cell and stem cell-derived extracellular vesicle-based therapy in the management of Alzheimer's disease. *Heliyon*. 2023;9(7):e17808. doi:10.1016/j.heliyon.2023.e17808
169. Giovannelli L, Bari E, Jommi C, et al. Mesenchymal stem cell secretome and extracellular vesicles for neurodegenerative diseases: risk-benefit profile and next steps for the market access. *Bioact Mater*. 2023;29:16–35. doi:10.1016/j.bioactmat.2023.06.013
170. Winston CN, Goetzl EJ, Schwartz JB, Elahi FM, Rissman RA. Complement protein levels in plasma astrocyte-derived exosomes are abnormal in conversion from mild cognitive impairment to Alzheimer's disease dementia. *Alzheimer's & Dementia*. 2019;11:61–66. doi:10.1016/j.dadm.2018.11.002
171. Gallart-Palau X, Guo X, Serra A, Sze SK. Alzheimer's disease progression characterized by alterations in the molecular profiles and biogenesis of brain extracellular vesicles. *Alzheimer's Res Ther*. 2020;12(1):54. doi:10.1186/s13195-020-00623-4
172. Chen JJ, Yang G, Yan QQ, Zhao J, Li S. Exosome-encapsulated microRNAs as promising biomarkers for Alzheimer's disease. *Rev Neurosci*. 2019;31(1):77–87. doi:10.1515/revneuro-2019-0001
173. Manna I, De Benedittis S, Quattrone A, Maisano D, Iaccino E, Quattrone A. Exosomal miRNAs as potential diagnostic biomarkers in Alzheimer's disease. *Pharmaceuticals*. 2020;13(9):243. doi:10.3390/ph13090243
174. Van Giau V, An SS. Emergence of exosomal miRNAs as a diagnostic biomarker for Alzheimer's disease. *J Neurol Sci*. 2016;360:141–152. doi:10.1016/j.jns.2015.12.005
175. Leidinger P, Backes C, Deutscher S, et al. A blood based 12-miRNA signature of Alzheimer disease patients. *Genome Biol*. 2013;14(7):R78. doi:10.1186/gb-2013-14-7-r78
176. Yılmaz SG, Erdal ME, Özge AA, Sungur MA. Can Peripheral MicroRNA expression data serve as epigenomic (upstream) biomarkers of Alzheimer's disease? *Omics*. 2016;20(8):456–461. doi:10.1089/omi.2016.0099
177. Lee BK, Kim MH, Lee SY, Son SJ, Hong CH, Jung YS. Downregulated Platelet miR-1233-5p in patients with Alzheimer's pathologic change with mild cognitive impairment is associated with Aβ-induced platelet activation via P-selectin. *J Clin Med*. 2020;9(6):1642. doi:10.3390/jcm9061642
178. Tan L, Yu JT, Tan MS, et al. Genome-wide serum microRNA expression profiling identifies serum biomarkers for Alzheimer's disease. *J Alzheimers Dis*. 2014;40(4):1017–1027. doi:10.3233/jad-132144
179. Hara N, Kikuchi M, Miyashita A, et al. Serum microRNA miR-501-3p as a potential biomarker related to the progression of Alzheimer's disease. *Acta Neuropathol Commun*. 2017;5(1):10. doi:10.1186/s40478-017-0414-z
180. Zhu Y, Li C, Sun A, Wang Y, Zhou S. Quantification of microRNA-210 in the cerebrospinal fluid and serum: implications for Alzheimer's disease. *Exp Ther Med*. 2015;9(3):1013–1017. doi:10.3892/etm.2015.2179
181. Jia LH, Liu YN. Downregulated serum miR-223 servers as biomarker in Alzheimer's disease. *Cell Biochem Funct*. 2016;34(4):233–237. doi:10.1002/cbf.3184
182. Tan L, Yu JT, Liu QY, et al. Circulating miR-125b as a biomarker of Alzheimer's disease. *J Neurol Sci*. 2014;336(1–2):52–56. doi:10.1016/j.jns.2013.10.002
183. Galimberti D, Villa C, Fenoglio C, et al. Circulating miRNAs as potential biomarkers in Alzheimer's disease. *J Alzheimers Dis*. 2014;42 (4):1261–1267. doi:10.3233/jad-140756
184. Li W, Li X, Xin X, Kan PC, Yan Y. MicroRNA-613 regulates the expression of brain-derived neurotrophic factor in Alzheimer's disease. *Biosci Trends*. 2016;10(5):372–377. doi:10.5582/bst.2016.01127
185. Kumar S, Vijayan M, Reddy PH. MicroRNA-455-3p as a potential peripheral biomarker for Alzheimer's disease. *Hum Mol Genet*. 2017;26 (19):3808–3822. doi:10.1093/hmg/ddx267
186. Wu Y, Xu J, Xu J, et al. Lower serum levels of miR-29c-3p and miR-19b-3p as biomarkers for Alzheimer's disease. *Tohoku J Exp Med*. 2017;242(2):129–136. doi:10.1620/tjem.242.129
187. Zhao X, Wang S, Sun W. Expression of miR-28-3p in patients with Alzheimer's disease before and after treatment and its clinical value. *Exp Ther Med*. 2020;20(3):2218–2226. doi:10.3892/etm.2020.8920
188. Liu Q, Lei C. Neuroprotective effects of miR-331-3p through improved cell viability and inflammatory marker expression: correlation of serum miR-331-3p levels with diagnosis and severity of Alzheimer's disease. *Exp Gerontol*. 2021;144:111187. doi:10.1016/j.exger.2020.111187
189. Lu L, Dai WZ, Zhu XC, Ma T. Analysis of Serum miRNAs in Alzheimer's Disease. *Am J Alzheimers Dis Other Demen*. 2021;36:15333175211021712. doi:10.1177/15333175211021712
190. Shigemizu D, Akiyama S, Asanomi Y, et al. Risk prediction models for dementia constructed by supervised principal component analysis using miRNA expression data. *Commun Biol*. 2019;2:77. doi:10.1038/s42003-019-0324-7
191. Zhang M, Han W, Xu Y, Li D, Xue Q. Serum miR-128 serves as a potential diagnostic biomarker for Alzheimer's disease. *Neuropsychiatr Dis Treat*. 2021;17:269–275. doi:10.2147/ndt.S290925
192. Kumar P, Dezso Z, MacKenzie C, et al. Circulating miRNA biomarkers for Alzheimer's disease. *PLoS One*. 2013;8(7):e69807. doi:10.1371/journal.pone.0069807

193. Bhatnagar S, Chertkow H, Schipper HM, et al. Increased microRNA-34c abundance in Alzheimer's disease circulating blood plasma. *Front Mol Neurosci*. 2014;7:2. doi:10.3389/fnmol.2014.00002
194. Siedlecki-Wullich D, Català-Solsona J, Fábregas C, et al. Altered microRNAs related to synaptic function as potential plasma biomarkers for Alzheimer's disease. *Alzheimers Res Ther*. 2019;11(1):46. doi:10.1186/s13195-019-0501-4
195. Cosín-Tomás M, Antonell A, Lladó A, et al. Plasma miR-34a-5p and miR-545-3p as early biomarkers of Alzheimer's disease: potential and limitations. *Mol Neurobiol*. 2017;54(7):5550–5562. doi:10.1007/s12035-016-0088-8
196. Kiko T, Nakagawa K, Tsuduki T, Furukawa K, Arai H, Miyazawa T. MicroRNAs in plasma and cerebrospinal fluid as potential markers for Alzheimer's disease. *J Alzheimers Dis*. 2014;39(2):253–259. doi:10.3233/jad-130932
197. Liu CG, Wang JL, Li L, Wang PC. MicroRNA-384 regulates both amyloid precursor protein and β-secretase expression and is a potential biomarker for Alzheimer's disease. *Int J Mol Med*. 2014;34(1):160–166. doi:10.3892/ijmm.2014.1780
198. Nagaraj S, Laskowska-Kaszub K, Dębski KJ, et al. Profile of 6 microRNA in blood plasma distinguish early stage Alzheimer's disease patients from non-demented subjects. *Oncotarget*. 2017;8(10):16122–16143. doi:10.18632/oncotarget.15109
199. Wang Z, Qin W, Wei CB, et al. The microRNA-1908 up-regulation in the peripheral blood cells impairs amyloid clearance by targeting ApoE. *Int J Geriatr Psychiatry*. 2018;33(7):980–986. doi:10.1002/gps.4881
200. Kenny A, McArdle H, Calero M, et al. Elevated plasma microRNA-206 levels predict cognitive decline and progression to dementia from mild cognitive impairment. *Biomolecules*. 2019;9(11):734. doi:10.3390/biom9110734
201. Wang J, Chen C, Zhang Y. An investigation of microRNA-103 and microRNA-107 as potential blood-based biomarkers for disease risk and progression of Alzheimer's disease. *J Clin Lab Anal*. 2020;34(1):e23006. doi:10.1002/jcla.23006
202. Dong Z, Gu H, Guo Q, et al. Profiling of serum exosome MiRNA reveals the potential of a MiRNA panel as diagnostic biomarker for Alzheimer's disease. *Mol Neurobiol*. 2021;58(7):3084–3094. doi:10.1007/s12035-021-02323-y
203. Dong Z, Gu H, Guo Q, et al. Circulating small extracellular vesicle-derived miR-342-5p ameliorates beta-amyloid formation via targeting beta-site APP Cleaving Enzyme 1 in Alzheimer's Disease. *Cells*. 2022;11(23):3830. doi:10.3390/cells11233830
204. Lugli G, Cohen AM, Bennett DA, et al. Plasma Exosomal miRNAs in persons with and without Alzheimer disease: altered expression and prospects for biomarkers. *PLoS One*. 2015;10(10):e0139233. doi:10.1371/journal.pone.0139233
205. Nie C, Sun Y, Zhen H, et al. Differential expression of plasma Exo-miRNA in neurodegenerative diseases by next-generation sequencing. *Front Neurosci*. 2020;14:438. doi:10.3389/fnins.2020.00438
206. Lehmann SM, Krüger C, Park B, et al. An unconventional role for miRNA: let-7 activates Toll-like receptor 7 and causes neurodegeneration. *Nat Neurosci*. 2012;15(6):827–835. doi:10.1038/nn.3113
207. Sala Frigerio C, Lau P, Salta E, et al. Reduced expression of HSA-miR-27a-3p in CSF of patients with Alzheimer disease. *Neurology*. 2013;81(24):2103–2106. doi:10.1212/01.wnl.0000437306.37850.22
208. Denk J, Boelmans K, Siegismund C, Lassner D, Arlt S, Jahn H. MicroRNA profiling of CSF reveals potential biomarkers to detect Alzheimer`s disease. *PLoS One*. 2015;10(5):e0126423. doi:10.1371/journal.pone.0126423
209. Müller M, Jäkel L, Bruinsma IB, Claassen JA, Kuiperij HB, Verbeek MM. MicroRNA-29a Is a candidate biomarker for Alzheimer's disease in cell-free cerebrospinal fluid. *Mol Neurobiol*. 2016;53(5):2894–2899. doi:10.1007/s12035-015-9156-8
210. Lusardi TA, Phillips JI, Wiedrick JT, et al. MicroRNAs in human cerebrospinal fluid as biomarkers for Alzheimer's disease. *J Alzheimers Dis*. 2017;55(3):1223–1233. doi:10.3233/jad-160835
211. Derkow K, Rössling R, Schipke C, et al. Distinct expression of the neurotoxic microRNA family let-7 in the cerebrospinal fluid of patients with Alzheimer's disease. *PLoS One*. 2018;13(7):e0200602. doi:10.1371/journal.pone.0200602
212. Kumar S, Reddy PH. Elevated levels of MicroRNA-455-3p in the cerebrospinal fluid of Alzheimer's patients: a potential biomarker for Alzheimer's disease. *Biochim Biophys Acta Mol Basis Dis*. 2021;1867(4):166052. doi:10.1016/j.bbadis.2020.166052
213. Sandau US, McFarland TJ, Smith SJ, Galasko DR, Quinn JF, Saugstad JA. Differential effects of APOE genotype on microRNA cargo of cerebrospinal fluid extracellular vesicles in females with Alzheimer's disease compared to males. *Front Cell Dev Biol*. 2022;10:864022. doi:10.3389/fcell.2022.864022
214. Alvarez-Erviti L, Seow Y, Yin H, Betts C, Lakhal S, Wood MJ. Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. *Nature Biotechnol*. 2011;29(4):341–345. doi:10.1038/nbt.1807
215. Lee M, Ban JJ, Yang S, Im W, Kim M. The exosome of adipose-derived stem cells reduces β-amyloid pathology and apoptosis of neuronal cells derived from the transgenic mouse model of Alzheimer's disease. *Brain Res*. 2018;1691:87–93. doi:10.1016/j.brainres.2018.03.034
216. Katsuda T, Tsuchiya R, Kosaka N, et al. Human adipose tissue-derived mesenchymal stem cells secrete functional neprilysin-bound exosomes. *Sci Rep*. 2013;3:1197. doi:10.1038/srep01197
217. Katsuda T, Oki K, Ochiya T. Potential application of extracellular vesicles of human adipose tissue-derived mesenchymal stem cells in Alzheimer's disease therapeutics. *Methods Mol Biol*. 2015;1212:171–181. doi:10.1007/7651_2014_98
218. Chen YA, Lu CH, Ke CC, et al. Mesenchymal stem cell-derived exosomes ameliorate Alzheimer's disease pathology and improve cognitive deficits. *Biomedicines*. 2021;9(6):594. doi:10.3390/biomedicines9060594
219. Cone AS, Yuan X, Sun L, et al. Mesenchymal stem cell-derived extracellular vesicles ameliorate Alzheimer's disease-like phenotypes in a preclinical mouse model. *Theranostics*. 2021;11(17):8129–8142. doi:10.7150/thno.62069
220. Reza-Zaldivar EE, Hernández-Sapiéns MA, Gutiérrez-Mercado YK, et al. Mesenchymal stem cell-derived exosomes promote neurogenesis and cognitive function recovery in a mouse model of Alzheimer's disease. *Neural Regen Res*. 2019;14(9):1626–1634. doi:10.4103/1673-5374.255978
221. Wang SS, Jia J, Wang Z. Mesenchymal stem cell-derived extracellular vesicles suppresses inos expression and ameliorates neural impairment in Alzheimer's disease mice. *J Alzheimers Dis*. 2018;61(3):1005–1013. doi:10.3233/jad-170848
222. Wei H, Xu Y, Chen Q, Chen H, Zhu X, Li Y. Mesenchymal stem cell-derived exosomal miR-223 regulates neuronal cell apoptosis. *Cell Death Dis*. 2020;11(4):290. doi:10.1038/s41419-020-2490-4
223. Cui GH, Guo HD, Li H, et al. RVG-modified exosomes derived from mesenchymal stem cells rescue memory deficits by regulating inflammatory responses in a mouse model of Alzheimer's disease. *Immun Ageing*. 2019;16:10. doi:10.1186/s12979-019-0150-2
224. Liu S, Fan M, Xu JX, et al. Exosomes derived from bone-marrow mesenchymal stem cells alleviate cognitive decline in AD-like mice by improving BDNF-related neuropathology. *J Neuroinflammation*. 2022;19(1):35. doi:10.1186/s12974-022-02393-2

225. Wang X, Yang G. Bone marrow mesenchymal stem cells-derived exosomes reduce Aβ deposition and improve cognitive function recovery in mice with Alzheimer's disease by activating sphingosine kinase/sphingosine-1-phosphate signaling pathway. *Cell Biol Int*. 2021;45(4):775–784. doi:10.1002/cbin.11522
226. Elia CA, Tamborini M, Rasile M, et al. Intracerebral injection of extracellular vesicles from mesenchymal stem cells exerts reduced aβ plaque burden in early stages of a preclinical model of Alzheimer's disease. *Cells*. 2019;8(9):1059. doi:10.3390/cells8091059
227. Nakano M, Kubota K, Kobayashi E, et al. Bone marrow-derived mesenchymal stem cells improve cognitive impairment in an Alzheimer's disease model by increasing the expression of microRNA-146a in hippocampus. *Sci Rep*. 2020;10(1):10772. doi:10.1038/s41598-020-67460-1
228. Ding M, Shen Y, Wang P, et al. Exosomes isolated from human umbilical cord mesenchymal stem cells alleviate neuroinflammation and reduce amyloid-beta deposition by modulating microglial activation in Alzheimer's disease. *Neurochem Res*. 2018;43(11):2165–2177. doi:10.1007/s11064-018-2641-5
229. Pan J, He R, Huo Q, Shi Y, Zhao L. Brain microvascular endothelial cell derived exosomes potently ameliorate cognitive dysfunction by enhancing the clearance of aβ through up-regulation of P-gp in mouse model of AD. *Neurochem Res*. 2020;45(9):2161–2172. doi:10.1007/s11064-020-03076-1
230. Li Y, Meng S, Di W, et al. Amyloid-β protein and MicroRNA-384 in NCAM-Labeled exosomes from peripheral blood are potential diagnostic markers for Alzheimer's disease. *CNS Neurosci Ther*. 2022;28(7):1093–1107. doi:10.1111/cns.13846
231. Hao Y, Su C, Liu X, Sui H, Shi Y, Zhao L. Bioengineered microglia-targeted exosomes facilitate Aβ clearance via enhancing activity of microglial lysosome for promoting cognitive recovery in Alzheimer's disease. *Biomater Adv*. 2022;136:212770. doi:10.1016/j.bioadv.2022.212770
232. Yuyama K, Sun H, Sakai S, et al. Decreased amyloid-β pathologies by intracerebral loading of glycosphingolipid-enriched exosomes in Alzheimer model mice. *J Biol Chem*. 2014;289(35):24488–24498. doi:10.1074/jbc.M114.577213
233. Yuyama K, Sun H, Usuki S, et al. A potential function for neuronal exosomes: sequestering intracerebral amyloid-β peptide. *FEBS Lett*. 2015;589(1):84–88. doi:10.1016/j.febslet.2014.11.027
234. Hantak MP, Qing E, Earnest JT, Gallagher T. Tetraspanins: architects of viral entry and exit platforms. *J Virol*. 2019;93(6):17. doi:10.1128/jvi.01429-17
235. Yuyama K, Igarashi Y. Exosomes as Carriers of Alzheimer's amyloid-ß. *Front Neurosci*. 2017;11:229. doi:10.3389/fnins.2017.00229
236. Li D, Zhang P, Yao X, et al. Exosomes Derived From miR-133b-modified mesenchymal stem cells promote recovery after spinal cord injury. *Front Neurosci*. 2018;12:845. doi:10.3389/fnins.2018.00845
237. Li SP, Lin ZX, Jiang XY, Yu XY. Exosomal cargo-loading and synthetic exosome-mimics as potential therapeutic tools. *Acta Pharmacol. Sin.* 2018;39(4):542–551. doi:10.1038/aps.2017.178
238. Xin H, Li Y, Chopp M. Exosomes/miRNAs as mediating cell-based therapy of stroke. *Front Cell Neurosci*. 2014;8:377. doi:10.3389/fncel.2014.00377
239. Qi Y, Guo L, Jiang Y, Shi Y, Sui H, Zhao L. Brain delivery of quercetin-loaded exosomes improved cognitive function in AD mice by inhibiting phosphorylated tau-mediated neurofibrillary tangles. *Drug Delivery*. 2020;27(1):745–755. doi:10.1080/10717544.2020.1762262
240. Ahmed Nel M, Murakami M, Hirose Y, Nakashima M. Therapeutic potential of dental pulp stem cell secretome for Alzheimer's disease treatment: an in vitro study. *Stem Cells Int*. 2016;2016:8102478. doi:10.1155/2016/8102478
241. Morel L, Regan M, Higashimori H, et al. Neuronal exosomal miRNA-dependent translational regulation of astroglial glutamate transporter GLT1. *J Biol Chem*. 2013;288(10):7105–7116. doi:10.1074/jbc.M112.410944
242. Peterson AR, Binder DK. Post-translational regulation of GLT-1 in neurological diseases and its potential as an effective therapeutic target. *Front Mol Neurosci*. 2019;12:164. doi:10.3389/fnmol.2019.00164
243. Hao P, Liang Z, Piao H, et al. Conditioned medium of human adipose-derived mesenchymal stem cells mediates protection in neurons following glutamate excitotoxicity by regulating energy metabolism and GAP-43 expression. *Metab Brain Dis*. 2014;29(1):193–205. doi:10.1007/s11011-014-9490-y
244. Meffert MK, Chang JM, Wiltgen BJ, Fanselow MS, Baltimore D. NF-kappa B functions in synaptic signaling and behavior. *Nat Neurosci*. 2003;6(10):1072–1078. doi:10.1038/nn1110
245. Cui GH, Wu J, Mou FF, et al. Exosomes derived from hypoxia-preconditioned mesenchymal stromal cells ameliorate cognitive decline by rescuing synaptic dysfunction and regulating inflammatory responses in APP/PS1 mice. *FASEB j*. 2018;32(2):654–668. doi:10.1096/fj.201700600R
246. Liu W, Bai X, Zhang A, Huang J, Xu S, Zhang J. Role of exosomes in central nervous system diseases. *Front Mol Neurosci*. 2019;12:240. doi:10.3389/fnmol.2019.00240
247. Mastrolia I, Foppiani EM, Murgia A, et al. Challenges in clinical development of mesenchymal stromal/stem cells: concise review. *Stem Cells Translational Med*. 2019;8(11):1135–1148. doi:10.1002/sctm.19-0044
248. Perets N, Betzer O, Shapira R, et al. Golden exosomes selectively target brain pathologies in neurodegenerative and neurodevelopmental disorders. *Nano Lett*. 2019;19(6):3422–3431. doi:10.1021/acs.nanolett.8b04148
249. Iranifar E, Seresht BM, Momeni F, et al. Exosomes and microRNAs: new potential therapeutic candidates in Alzheimer disease therapy. *J Cell Physiol*. 2019;234(3):2296–2305. doi:10.1002/jcp.27214