ISSN: 2538-5887; Pathobiology Research. 2025; 28 (3): 19-34
DOI: ----------

Exosome-Based Therapeutics for Alzheimer's Disease: Modulating Immune Dysregulation

Received: Apr 27, 2025
Accepted: May 12, 2025

Article Type:
Review

Authors:
Soheil Nouri
Masoud Soleimani*

Department of Hematology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran.

**** Corresponding author:***
Masoud Soleimani

E-mail: *soleim_m@modares.ac.ir*

ABSTRACT

Alzheimer's Disease stands as the common neurodegenerative and progressive ailment that leads to dementia. Its pathological manifestations include amyloid-beta (Aβ) plaques, tau neurofibrillary tangles, chronic inflammation, and oxidative stress. The paper reviews recent findings about AD pathogenesis by demonstrating how Aβ plaques link with immunological dysfunction and cellular stress events to drive dementia pathology. Aβ accumulation served initially as the primary therapeutic target. Still, scientists recognize it functions within a more complex sequence that includes glial activation, abnormal tau phosphorylation, and reciprocal neuroimmune processes. Research findings show that neuroinflammation exists in two opposing states because protective and pathological effects depend on disease progression and immune system conditions. The current therapeutic focus has shifted towards monoclonal antibodies, enzymatic modulators, and immunization methods for lowering Aβ burden during the early stages of the disease. These treatments demonstrate restricted effectiveness when applied during advanced stages; thus, researchers investigate multiple treatment approaches focused on simultaneously addressing Aβ and tau and inflammatory pathways. Their access across the blood-brain barrier to transfer therapeutic compounds enables them to be hopeful agents for modifying diseases and creating biomarkers. Preclinical models indicate that exosomes generated from stem cells and immune cells demonstrate a reduction of Aβ accumulation, neuroinflammation control, and cognitive ability maintenance. The paper shows an urgent necessity for customized multi-system treatment methods as it introduces exosome dynamics for modern translational AD investigation. These therapies, integrating three key components of targeted delivery with immune modulation and neuroprotection, offer an innovative solution for managing AD.

Keywords: Alzheimer's disease, Exosome, Exosome-Based therapy, Mesenchymal stem cell, Immune modulation

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia worldwide. It is pathologically characterized by the deposition of amyloid-beta (Aβ) plaques and the formation of neurofibrillary tangles, which initiate a cascade of neuronal dysfunction and eventual cell death. The pathological hallmarks of AD include extracellular Aβ plaques, intracellular aggregates of hyperphosphorylated tau protein, chronic neuroinflammation, and oxidative stress—each of which contributes to the complex, interrelated mechanisms driving disease progression (1,2).

Aβ plaques are primarily composed of insoluble peptides produced through sequential cleavage of the amyloid precursor protein (APP), with beta-secretase 1 (BACE1) playing a critical enzymatic role in this process. Although neurons are traditionally regarded as the primary source of Aβ, recent studies underscore the involvement of glial cells in synthesizing and depositing these toxic aggregates (3). Tau pathology further contributes to neurodegeneration. Under physiological conditions, tau stabilizes microtubules essential for axonal transport. However, in AD, tau becomes abnormally phosphorylated, dissociates from microtubules, and aggregates into tangles that disrupt intracellular transport and impair synaptic

communication (4).

Concurrently, neuroinflammation emerges as a central element in AD pathology. Microglia—the resident immune cells of the central nervous system—are activated in response to Aβ and tau accumulation, adopting a spectrum of phenotypes that may mitigate or exacerbate neuronal injury depending on disease stage and context. Inflammatory mediators, such as inducible nitric oxide synthase (iNOS/NOS2), can modify Aβ peptides, promoting aggregation and intensifying plaque burden, illustrating the bidirectional relationship between inflammation and amyloid pathology (5,6).

Oxidative stress is another critical factor implicated in AD. It arises from an imbalance between reactive oxygen species (ROS) production and the brain's antioxidant defenses. Elevated ROS levels lead to widespread molecular damage, including the oxidation of proteins, lipids, and nucleic acids (7). Additionally, advanced glycation end products (AGEs), which accumulate in amyloid plaques, further contribute to cellular toxicity. The interaction between oxidative stress, neuroinflammation, and protein aggregation establishes a self-perpetuating cycle that accelerates neuronal loss and cognitive deterioration (8). Collectively, these pathological processes culminate in synaptic failure, widespread neuronal death, and the progressive cognitive decline that defines Alzheimer's disease.

Immune dysregulation in AD represents a formidable challenge due to the intricate, dynamic, and often paradoxical interactions between the central and peripheral immune systems that contribute to neurodegeneration and cognitive decline. These interactions involve multiple communication pathways, including infiltrating peripheral immune cells into the central nervous system and modulating microglial activity by systemic inflammatory signals (9). As AD progresses, immune responses shift from predominantly innate—mediated by microglia—to increasingly adaptive, marked by the infiltration and activation of T lymphocytes, particularly $CD8^+$ tissue-resident memory T cells. This transition reflects a broader shift from early-stage inflammation, which may play a neuroprotective role, to chronic neuroinflammation that drives neuronal injury and accelerates disease pathology (10).

Neuroinflammation in AD functions as a double-edged sword. While acute immune responses may facilitate the clearance of amyloid-beta (Aβ) plaques and support neural homeostasis, prolonged or dysregulated inflammation contributes to synaptic dysfunction, neuronal loss, and tau pathology. The capacity of immune responses to oscillate between protective and harmful states presents a significant obstacle in developing targeted therapies (11). Epidemiological data further support the immunological underpinnings of AD, demonstrating an increased incidence of the disease among individuals with autoimmune conditions—suggesting that immune dysregulation and autoimmunity may be mechanistically intertwined with AD pathogenesis (12).

Therapeutic strategies targeting Aβ pathology in AD are primarily designed to mitigate disease progression by reducing cerebral Aβ burden, which is believed to be a critical upstream event in the cascade leading to neurodegeneration (13). These interventions encompass monoclonal antibodies to clear existing plaques, enzymatic modulators that suppress Aβ production, and emerging immunization strategies. Monoclonal antibodies such as *lecanemab* and *donanemab* are engineered to selectively bind aggregated Aβ, facilitating its clearance from the brain (14). Immunization strategies, including Aβ-directed vaccines, seek to harness the adaptive immune system to elicit endogenous antibody responses against Aβ, potentially offering a scalable and preventive approach to disease management. Although adverse neuroinflammatory events hampered initial vaccine trials, contemporary designs focus on refining immune targeting to avoid excessive inflammation (15).

Despite these advances, amyloid-targeted therapies offer only partial disease modification, as downstream tau pathology and neurodegeneration may continue to progress independently once initiated. As a result, there is growing interest in combination therapies that concurrently target Aβ deposition, tau aggregation, and neuroinflammatory cascades to achieve more robust and sustained clinical benefits (16).

Exosomes are nanoscale extracellular vesicles, typically measuring around 100 nanometers in

diameter, released by a wide range of cell types through a tightly regulated biogenetic process involving the endosomal system. Functionally, exosomes act as pivotal mediators of intercellular communication, influencing recipient cells' physiological and pathological behavior by transferring their molecular contents. Within the nervous system, they play a vital role in neuron-glia interactions and have been implicated in the propagation of neurodegenerative pathology by transporting disease-associated proteins such as amyloid-beta (Aβ) and tau. These pathogenic cargos contribute to the spread of molecular dysfunction in disorders like AD (17–19).

This review aims to explore the complex pathophysiology of Alzheimer's disease, focusing on the interplay between amyloid-beta, tau pathology, immune dysfunction, oxidative stress, and neuroinflammation. It seeks to evaluate current therapeutic limitations and the need for multi-targeted approaches. The paper highlights the dual role of the immune system and emphasizes the importance of timing and precision in intervention. Finally, it examines the potential of exosomes as innovative therapeutic and diagnostic tools in future AD management strategies.

Immune Dysregulation in Alzheimer's Disease

Microglial polarization plays a pivotal role in the immune dysregulation characteristic of AD, profoundly influencing both neuroinflammation and disease progression. The M1 phenotype, representing the classically activated state, is defined by the production of pro-inflammatory mediators—including cytokines, chemokines, and reactive oxygen species—which contribute to neuronal damage and exacerbate Aβ deposition (20). This inflammatory cascade not only heightens neurotoxicity but also impairs the clearance of Aβ plaques, thereby accelerating neurodegeneration and cognitive decline. Chronic activation of M1 microglia establishes a self-perpetuating cycle of inflammation and neuronal injury, a hallmark of AD pathology. Age-related changes and disease advancement further bias microglial populations toward this detrimental M1 state, amplifying the expression of pro-inflammatory markers and exacerbating neural dysfunction (5,21).

The interaction between microglia and Aβ plaques in AD is intricate and multifaceted, encompassing pathological and protective dimensions. Microglia are intimately involved in all stages of plaque dynamics, from initial seeding to subsequent compaction and containment. By encapsulating amyloid aggregates, microglia create a neuroprotective boundary that limits the diffusion of toxic species and shields surrounding neurons (22). Upon Aβ plaque emergence, microglia swiftly extend their processes and migrate toward the deposits, establishing long-term, stable associations. The density of microglial clustering correlates with plaque size, and these cells maintain high motility at the plaque periphery, suggesting sustained functional engagement. Although microglia attempt to clear Aβ through phagocytosis and enzymatic degradation, their efficacy diminishes as AD progresses (23,24).

The relationship between early-stage protective inflammation and late-stage harmful inflammation in Alzheimer's disease (AD) involves a dynamic shift in microglial activation and immune responses throughout the disease. In the early stages of AD, microglial cells become activated in a generally protective way. This early activation aims to clear Aβ plaques and release neurotrophic factors that support neuron survival and repair (25). This protective response includes the upregulation of inflammatory and regenerative pathways that precede more severe neurodegenerative changes, suggesting that inflammation initially participates in brain tissue repair and amyloid clearance. When amyloid accumulation and other toxic factors overwhelm the initial protective mechanisms, microglia shift toward a pro-inflammatory phenotype. This state releases pro-inflammatory cytokines and neurotoxins that exacerbate neuronal damage and perpetuate a cycle of neuroinflammation (26). In this chronic phase, microglia become less efficient at clearing Aβ plaques, even as they continue to produce inflammatory mediators that worsen pathology and neurodegeneration. Sustained inflammation promotes further Aβ and tau pathology.This late-stage inflammation is associated with increased oxidative stress, neuronal apoptosis, and failure of neuroprotective mechanisms, ultimately leading to worsening cognitive impairment (27).

In Alzheimer's disease, early-stage inflammation is predominantly protective, aimed at clearing amyloid and supporting neuronal

health. However, as the disease progresses, this response becomes dysregulated, shifting to a harmful, chronic pro-inflammatory state that contributes to neurodegeneration and cognitive decline. This dual role of inflammation suggests that therapeutic strategies might need to be stage-specific, supporting early protective inflammation while mitigating late-stage harmful inflammation.

Chronic neuroinflammation exerts a profound influence on the progression of AD, acting not only as a consequence of pathological changes but also as a key driver of neurodegeneration. Sustained activation of glial cells, particularly microglia and astrocytes, results in the persistent release of pro-inflammatory cytokines and neurotoxic substances that exacerbate hallmark features of AD, including Aβ plaque accumulation and tau hyperphosphorylation leading to neurofibrillary tangle (NFT) formation (23,26,27). This inflammatory milieu establishes a mechanistic bridge between early Aβ pathology and the subsequent emergence of tau pathology, thereby accelerating neuronal dysfunction and cognitive decline. Chronic neuroinflammation perpetuates a vicious cycle. Persistent immune activation impairs Aβ clearance, intensifies tau pathology, and fosters a neurotoxic environment that disrupts synaptic integrity and promotes neuronal death. Both central glial responses and peripheral immune infiltration converge to amplify this pathological feedback loop, hastening disease progression (28).

With prolonged activation, microglia exhibit diminished capacity to recognize, engulf, and degrade Aβ deposits despite continued secretion of pro-inflammatory mediators. This functional decline facilitates further plaque accumulation and propagates neuroinflammation (28). The ongoing production of cytokines, chemokines, reactive oxygen species (ROS), and nitric oxide (NO) contributes to a toxic extracellular environment that compromises synaptic plasticity, impairs neuronal communication, and ultimately triggers apoptotic pathways. As microglial inefficiency mounts, additional immune cells are recruited to the site of pathology, reinforcing the inflammatory cascade and perpetuating neuronal injury (29).

Beyond the central nervous system, peripheral immune cells—including B and T lymphocytes—cross AD's compromised blood-brain barrier (BBB), releasing cytokines that potentiate microglial and astrocytic activation. These infiltrating cells further exacerbate neuroinflammation and neuronal loss. Age-associated vascular deterioration and chronic inflammation compromise BBB integrity, facilitating the entry of peripheral immune factors and further exacerbating neurodegenerative processes (30).

Pro-inflammatory cytokines and chemokines act through diverse but interconnected mechanisms to intensify neurodegeneration. Activated glial cells release interleukins such as IL-1β, IL-6, and TNF-α in response to Aβ accumulation. IL-1β, notably, upregulates other inflammatory mediators like IL-6 and IL-17, establishing a self-reinforcing loop that exacerbates neuronal injury (31,32). These cytokines also regulate APP expression and processing, favoring amyloidogenic pathways and enhancing Aβ production. Simultaneously, they influence kinase activity involved in tau phosphorylation, contributing to tangle formation and functional neuronal impairment. Persistent exposure to such pro-inflammatory signals disrupts synaptic plasticity, induces excitotoxicity, and accelerates neuronal apoptosis (33,34).

Chemokines, including CCL2 (MCP-1), CCL5, and CXCL8 (IL-8), are markedly elevated in AD and facilitate the recruitment of peripheral immune cells—monocytes, macrophages, and lymphocytes—into the brain. This infiltration augments local inflammation and drives disease progression. Secreted primarily by activated microglia and astrocytes, chemokines promote persistent glial-neuron signaling and maintain inflammatory activity around Aβ plaques. Chronic chemotactic signaling sustains microglial activation, exacerbating neuronal damage (35,36).

Oxidative stress, primarily driven by excessive ROS, constitutes another critical axis of neurodegeneration in AD. ROS are predominantly generated by dysfunctional mitochondria and NADPH oxidases and are further amplified by interactions between Aβ peptides and redox-active metals such as iron and copper. This leads to widespread oxidative damage affecting nucleic acids, proteins, and lipids vital to neuronal health (37). ROS damages cellular components and activates signaling pathways—such as NF-κB and MAPK—that intensify cytokine production and glial activation,

reinforcing neuroinflammation. Mitochondrial dysfunction, impaired autophagy, and defective mitophagy contribute to the accumulation of damaged organelles, further escalating ROS generation (38).

Need for Immune Modulation in AD Therapy:

The need for immune modulation in AD therapy arises from the significant role that immune system dysfunction and neuroinflammation play in the pathogenesis and progression of AD. Microglia contribute to sustained neuroinflammation and impaired clearance of toxic protein aggregates. Modulating microglial activity to restore normal function can help reduce amyloid and tau pathology and protect neurons (39,40). Given AD's heterogeneity and complex immune landscape, immune-inflammation modulation is proposed as a therapeutic strategy, especially for subgroups of patients identified through biomarkers and genetic profiling. This approach aligns with personalized medicine, aiming to tailor immunotherapies to patients most likely to benefit.

Immunotherapeutic strategies targeting Aβ and tau proteins have become a central focus in treating AD. Active immunotherapy involves vaccinating patients with Aβ peptides or fragments to stimulate the patient's immune system to produce endogenous antibodies against Aβ or tau proteins. This elicits both humoral and cellular immune responses. It generally requires fewer injections and can induce long-lasting antibody production, potentially providing sustained protection after a limited number of doses. Risk of autoimmune reactions, such as T cell-mediated meningoencephalitis, as seen in the AN1792 vaccine trial where about 6% of patients developed brain inflammation, leading to trial termination (41,42).

Passive immunotherapy involves directly administering pre-formed monoclonal antibodies targeting specific forms or strains of Aβ or tau proteins. These antibodies facilitate the clearance of pathological aggregates through mechanisms like opsonization, phagocytosis, complement activation, and peripheral sink effects. Repeated and continuous antibody infusions are required because the antibodies have a limited half-life and do not induce endogenous antibody production. Repeated dosing increases treatment costs and patient burden. Side effects include amyloid-related imaging abnormalities (ARIA), such as vasogenic edema and microhemorrhages, which have been observed with some monoclonal antibodies like bapineuzumab. Limited penetration of antibodies across the blood-brain barrier (approximately 0.1–0.2%) is another disadvantage of this kind of therapy (43,44).

Emerging therapeutic strategies in AD increasingly focus on the precise modulation of immune cell behavior to mitigate chronic neuroinflammation and support neuroprotection. This includes regulating microglial phenotypes and fine-tuning T cell responses, particularly enhancing the activity of regulatory T cells (Tregs) to suppress aberrant immune activation (40,45). Nanomedicine-based immunotherapies, such as nanoparticle-mediated delivery of anti-inflammatory agents or immune modulators, are being explored to achieve targeted, controlled immune modulation with reduced systemic toxicity (46). Additionally, approaches leveraging Treg expansion, adoptive transfer, or enhancement of their immunosuppressive functions aim to restore immune homeostasis in the brain (47). These immune-directed strategies are gaining momentum as mounting evidence implicates dysregulated innate and adaptive immune responses in exacerbating amyloid and tau pathology, synaptic dysfunction, and neuronal loss. Therefore, immune modulation represents a promising avenue for developing disease-modifying therapies that address both upstream and downstream mechanisms of Alzheimer’s disease pathogenesis.

Exosome Biogenesis and Characterization

Exosomes are nanoscale extracellular vesicles generated through the endosomal pathway and released into the extracellular space following multivesicular bodies (MVBs) fusion with the plasma membrane. Their biogenesis involves a series of coordinated steps, beginning with the maturation of early endosomes into late endosomes or MVBs. Within these MVBs, intraluminal vesicles (ILVs)—exosome precursors—form via inward budding of the endosomal membrane. During this process, specific cargos, including proteins, lipids, and nucleic acids, are selectively incorporated into ILVs (48,49). This sorting is tightly regulated by the endosomal sorting complex required for

transport (ESCRT) and associated accessory proteins. MVBs face two primary cellular fates: fusion with lysosomes for degradation or fusion with the plasma membrane to release ILVs as exosomes (50). The decision between degradation and secretion is governed by molecular pathways that regulate endolysosomal trafficking; inhibition of MVB-lysosome fusion, for instance, promotes exosome release.

Structurally, exosomes are characterized by a lipid bilayer membrane enriched with specific lipids such as phosphatidylserine, phosphatidylcholine, sphingomyelin, ceramides, and cholesterol—components essential for their membrane integrity and functional versatility. Their protein cargo includes membrane trafficking proteins (e.g., Rab GTPases, annexins), biogenesis regulators (e.g., ALIX, TSG101), heat shock proteins (HSP70, HSP90), integrins, and the Tetraspanins CD9, CD63, and CD81. These tetraspanins, abundantly expressed on exosomal membranes, serve as canonical surface markers for exosome identification and isolation. Additionally, exosomes carry a broad spectrum of nucleic acids. These molecules can be transferred to recipient cells, thereby modulating gene expression and cellular behavior (51,52).

Exosome characterization involves confirming their size, morphology, and molecular markers using techniques such as Nanoparticle tracking analysis (NTA) or dynamic light scattering (DLS) for size distribution and concentration, transmission electron microscopy (TEM) for morphology visualization, Western blotting, or flow cytometry for detecting exosomal surface proteins (e.g., CD63, CD81), and Mass spectrometry for proteomic profiling (53).

Exosome isolation methods are based on physical properties (size, density) or biochemical affinity. Differential Ultracentrifugation is the gold standard method that separates exosomes by sequential centrifugation steps at increasing speeds to pellet particles based on size and density. It effectively isolates exosomes but can be time-consuming and may co-isolate contaminants like lipoproteins. Density Gradient Centrifugation uses a density medium (e.g., sucrose or iodixanol) to separate exosomes from other vesicles and protein aggregates by buoyant density. This method improves purity but is labor-intensive (54). Size-exclusion chromatography (SEC) separates particles based on size by passing samples through porous beads. It preserves exosome integrity and reduces protein contamination. Often combined with ultracentrifugation or ultrafiltration to enhance purity. Ultrafiltration uses membrane filters to isolate exosomes by size exclusion. It is simpler and faster than ultracentrifugation but may cause vesicle deformation or loss. Polymer Precipitation employs polymers like polyethylene glycol (PEG) to reduce exosome solubility, causing precipitation that can be collected by low-speed centrifugation. It is easy and scalable but prone to co-precipitating contaminants (55). Exosome isolation balances yield, purity, time, and cost. Ultracentrifugation remains the gold standard but is often combined with size-exclusion chromatography or ultrafiltration for improved purity. Polymer precipitation is widely used for convenience, while immunoaffinity and microfluidic approaches provide high specificity and efficiency for advanced applications.

In the brain, exosomes are secreted by various neural cell types—including neurons, astrocytes, microglia, and oligodendrocytes—and play critical roles in maintaining neural homeostasis and mediating intercellular communication. These vesicles carry molecular signatures reflective of neuronal status and regulate synaptic plasticity, neurotransmission, and neuronal viability (56). Significantly, they can propagate pathological proteins such as tau and Aβ, contributing to the pathogenesis of neurodegenerative diseases like AD. Neuronal exosomes are preferentially internalized by microglia, aiding in the clearance of damaged cellular components, but are less efficiently taken up by astrocytes. Microglia release exosomes that influence inflammatory signaling and immune responses. These exosomes can also be involved in neuron–microglia communication, enhancing the microglial capacity to remove degenerative neuronal elements and sustain tissue homeostasis (57,58).

Exosomes can traverse the blood-brain barrier in both directions, enabling systemic-to-brain and brain-to-systemic communication. This capability makes them attractive candidates for diagnostic biomarkers and vehicles for therapeutic delivery in neurological disorders. Exosomes from neurons, astrocytes, microglia, and oligodendrocytes orchestrate essential aspects of

brain health, and their dysregulation is intricately linked to the pathophysiology of neurodegenerative and psychiatric diseases (59).

Exosomes offer multiple advantages as vehicles for therapeutic delivery. As naturally secreted vesicles, they exhibit high biocompatibility and low immunogenicity, minimizing the risk of adverse immune responses in clinical applications (60). One of their key strengths lies in their ability to protect cargo molecules from enzymatic degradation in biological fluids, thereby enabling the stable and sustained delivery of therapeutic agents—including RNAs, proteins, and small-molecule drugs. Importantly, exosomes can traverse the (BBB) one of the most formidable challenges in treating central nervous system disorders (61). This unique capability allows for the targeted delivery of therapeutic payloads directly into brain tissue. Emerging evidence suggests that exosomes not only cross the BBB but may also actively modulate its permeability and facilitate trans-endothelial transport.

Building on these advantageous properties, exosomes have garnered significant attention in the context of neurodegenerative diseases—particularly Alzheimer's disease. Their ability to traverse the BBB and deliver functional biomolecules directly to affected brain regions underlies their potential as both therapeutic agents and delivery vehicles. In this regard, exosomes are increasingly recognized not only for their delivery capabilities but also for their intrinsic biological roles within AD pathology.

Therapeutic Roles of Exosomes in Alzheimer's Disease

Exosomes exhibit a dual or "double-edged sword" role in AD. Therapeutically, exosomes clear Aβ plaques via microglial uptake and enzymatic degradation, Deliver neuroprotective molecules and miRNAs to modulate inflammation and neuronal survival, Modulate tau pathology and neuroinflammation through microglia-derived exosomes, and Serve as promising, low-risk carriers for targeted drug delivery across the BBB (58). This multifaceted therapeutic potential positions exosomes as a novel and promising avenue for Alzheimer's disease treatment development. The therapeutic functions of exosomes in Alzheimer's disease encompass various methods.

Clearance of Aβ Peptides: Exosomes derived from mesenchymal stem cells (MSCs) or other sources can carry enzymes such as neprilysin that degrade Aβ peptides. This enzymatic activity helps reduce amyloid plaque burden in the brain. MSC-derived exosomes have been shown to decrease Aβ42 and Aβ40 levels, reduce neuroinflammation, and improve cognitive function in AD models (62,63). Neuron-derived exosomes (NDEs) can bind Aβ peptides and facilitate their transport to microglial lysosomes for degradation, thereby reducing the amyloid plaque burden in the brain. This process involves glycosphingolipids (GSLs) on the exosome surface that capture Aβ and promote its clearance by microglia (64). Microglia-derived exosomes also contribute to Aβ degradation by secreting insulin-degrading enzyme (IDE) and neprilysin (NEP), which break down extracellular Aβ. Exosomes from human brain microvascular endothelial cells carrying p-glycoprotein can precisely capture and clear Aβ, improving cognitive function in AD mouse models (64).

Delivery Vehicles for Therapeutic Molecules: Exosomes are natural, biocompatible vesicles capable of transporting diverse molecular cargo, including proteins, enzymes, RNAs, and drugs, across the BBB to the brain. This makes them promising carriers for delivering therapeutic agents directly to affected brain regions in AD (65). For example, exosome-associated adeno-associated virus (exo-AAV) vectors improve gene delivery efficiency to the central nervous system at low doses and evade neutralizing antibodies, enhancing targeted therapy (66).

Modulation of Neuroinflammation and Tau Pathology: Exosomes expressing microglial surface receptors such as TREM2 can modulate inflammatory responses around Aβ plaques, enhancing microglial phagocytosis and reducing neuroinflammation (67). Upregulation of TREM2 in microglia-derived exosomes has been shown to ameliorate tau hyperphosphorylation and pathological spread, suggesting a protective role against tau pathology. Inhibition of specific exosome secretion pathways (e.g., P2RX7 receptor) reduces tau accumulation and improves cognitive functions in AD models (68). Exosomes can regulate inflammatory responses and promote synaptic plasticity. MSC-derived exosomes, for example, contain microRNAs (miRNAs) such as miR-21 and miR-133b that

modulate neuroinflammation, inhibit neuronal apoptosis, and enhance neurite outgrowth, contributing to cognitive improvement. These exosomes reduced TNF-α and IL-6 levels by 50–65%, inhibited apoptosis (Bax/Bcl-2 ratio normalization), and enhanced neurite outgrowth by up to 70%, significantly improving learning and memory in treated mice (69). They also help create a neuroprotective environment by delivering immunomodulatory cytokines and growth factors.

Gene Silencing and Molecular Therapy: Exosomes can be engineered to carry small interfering RNA (siRNA) or other nucleic acids to silence genes involved in AD pathology. For instance, dendritic cell-derived exosomes loaded with siRNA targeting BACE1, an enzyme involved in Aβ production, successfully reduced BACE1 expression in the brain, demonstrating a potential gene therapy approach (70).

Repair and Regeneration: Exosomes from stem cells promote neurogenesis, neural plasticity, and tissue repair, which is crucial for restoring cognitive function in AD. They also transfer functional molecules that stimulate neuronal survival and synaptic remodeling (71).

Exosomes derived from different cellular sources play distinct and complementary roles in treating AD, offering diverse therapeutic mechanisms based on their origin and cargo (As shown in Table1.)

Neuronal-derived exosomes (NDEs) mainly contribute to direct Aβ clearance and modulation of amyloid pathology. NDEs are rich in glycosphingolipids on their surface, which can bind Aβ peptides and promote their clearance by microglia through endocytosis and lysosomal degradation. Infusion of NDEs into AD mouse models reduces Aβ levels and amyloid plaque deposition, improving Aβ-related pathology. They also influence Aβ conformational changes that facilitate its clearance. Sphingomyelin metabolic enzymes regulate their secretion, and modulation of these enzymes can affect exosome release and Aβ uptake by microglia (72,73).

Mesenchymal Stem Cell-Derived Exosomes (MSC-Exos) carry enzymes like neprilysin (NEP) that degrade extracellular Aβ, neurotrophic factors, anti-inflammatory cytokines, and miRNAs (e.g., miR-21) that modulate neuroinflammation and synaptic plasticity. MSC-exos reduce Aβ plaque load, neuronal apoptosis, and neuroinflammation but enhance axon elongation, neurogenesis, and cognitive improvement in AD models (74). In a mouse model of AD (APP/PS1), intravenous administration of MSC-exosomes led to a 40% reduction in Aβ42 levels in the hippocampus and cortex and a 30% decrease in amyloid plaque density. These changes correlated with improved cognitive performance in the Morris water maze test, showing a 35% reduction in escape latency compared to untreated AD mice (62,74). Exosomes derived from different MSC sources (bone marrow, adipose tissue, umbilical cord) have reported similar advantages. Hypoxia-preconditioned MSC-exos exhibit enhanced therapeutic efficacy (75). (See Table1.)

MSC-exos carry enzymes such as neprilysin that degrade Aβ peptides, suppress neuroinflammation by modulating pro- and anti-inflammatory cytokines, promote neurogenesis, and improve cognitive function in AD model animals. Surface modification of MSC-exos (e.g., with RVG peptide) improves brain targeting and therapeutic efficacy, suppresses Aβ plaque formation, and improves memory in AD mice (76,77). MSC-exos reduce neuroinflammation by inhibiting pro-inflammatory signaling pathways such as NF-κB and MAPK and promoting microglial polarization towards anti-inflammatory phenotype (e.g., via miR-181b targeting IL-10/STAT3 pathway). MSC-exos carry antioxidant enzymes and miRNAs that reverse oxidative stress in neural tissues (78,79). MSC-exos can stimulate endogenous Neural Stem Cells (NSCs) towards brain repair and functional recovery. Exosomes from bone marrow MSCs alleviate cognitive decline in AD-like mice by improving neurotrophic factors such as BDNF and activating signaling pathways that reduce Aβ deposition (80).

Neural Stem Cell-Derived Exosomes (NSC-Exos) downregulate inflammatory signaling pathways (NF-κB/ERK/JNK), reduce pro-inflammatory mediators (iNOS, IL-1β, TNF-α, IL-6), and modulate Aβ and tau pathology. They enhance neuronal viability, reduce neurodegeneration, and improve cognitive functions in AD models. NSC-exos mainly act by modulating neuroinflammation and protecting neurons from degeneration. NSC-exosomes improve neuronal viability and alleviate neurodegeneration in AD models (81).

NSC-exos reduce the expression and activity of β-secretase (BACE1) and γ-secretase (PSEN1), key enzymes in the amyloidogenic pathway responsible for generating Aβ peptides. This leads to decreased Aβ production and plaque formation (82). NSC-exos increase the expression of ADAM10, an α-secretase involved in the non-amyloidogenic processing of APP, thereby reducing Aβ synthesis and favoring the production of non-toxic APP fragments (83). NSC-exos downregulate the expression and activity of kinases such as GSK-3β and CDK5, which are involved in tau hyperphosphorylation. This reduces phosphorylated tau (p-tau) levels and neurofibrillary tangle formation (84). NSC-Exosomes downregulated NF-κB, ERK, and JNK pathways, resulting in a 60% reduction in iNOS and IL-1β expression, and decreased tau phosphorylation by 55%, which was associated with restored long-term potentiation (LTP) and ~35% increase in synaptic density (84).NSC-exos also decrease acetylcholinesterase activity, which may further support neuronal health. NSC-exos suppress the NF-κB, ERK, and JNK signaling pathways in activated glial cells, reducing the production of inflammatory mediators. By modulating these pathways, NSC-exos decrease neuroinflammation, a major driver of neurodegeneration in AD (81,85). NSC-exos deliver regulatory microRNAs and proteins that protect synapses from Aβ and tau oligomer-induced toxicity, preserve long-term potentiation, and prevent synaptic loss. NSC-exos enhance the survival and viability of neurons exposed to AD-related stressors (86). (See Table 1.)

Table 1: Exosome-Based Therapies in Alzheimer's Disease

Exosome Source	Therapeutic Mechanisms	Key Molecules/Cargo	Outcomes in AD Models	Delivery Potential (BBB Penetration)	Limitations / Challenges
Neuronal-Derived Exosomes (NDEs)	Facilitate Aβ clearance via microglial uptake - Modulate Aβ conformations	Glycosphingolipids (GSLs)	↓ Aβ levels, ↓ plaques, ↑ microglial phagocytosis	Moderate; endogenous to CNS, limited modification potential	Limited yield, modest therapeutic cargo loading
Mesenchymal Stem Cell Exosomes (MSCs)	- Degrade Aβ plaques - Modulate inflammation - Promote neurogenesis and survival	Neprilysin, miR-21, miR-181b, cytokines, growth factors	↓ Aβ burden, ↓ neuroinflammation, ↑ cognitive function, ↑ neuronal survival	High; can be surface-modified (e.g., RVG peptide) for enhanced targeting	Variability across sources (bone marrow, adipose, umbilical), scalability challenges
Neural Stem Cell Exosomes (NSCs)	- Downregulate inflammation - Modulate APP processing - Reduce tau phosphorylation	miRNAs, ADAM10 ↑, BACE1 ↓, PSEN1 ↓, GSK-3β ↓, CDK5 ↓	↓ Aβ & tau pathology, ↑ synaptic protection, ↑ neuronal viability	High cross BBB and naturally target neural tissue	Lower yield, less studied clinically, standardization needed
M2 Microglia-Derived Exosomes	- Reduce inflammation - Promote mitophagy - Attenuate apoptosis	PINK1/Parkin pathway components	↓ mitochondrial dysfunction, ↓ neuroinflammation, ↑ neuroprotection	Moderate; naturally active in CNS	Hard to isolate pure M2 phenotype; unclear long-term effects
Endothelial Cell Exosomes	- Facilitate Aβ clearance through BBB transport	P-glycoprotein	↓ Aβ burden, ↑ cognitive performance in models	Very High; already engaged in BBB regulation and Aβ transport	Limited data on targeting specificity; potential off-target effects
Adipose-derived MSC Exosomes (ADSCs)	- Degrade Aβ (high NEP activity) - Reduce oxidative stress - Protect synapses	NEP (high), anti-apoptotic proteins (Bcl-2), miRNAs	↓ Aβ42/Aβ40 ratio, ↓ apoptosis, ↑ synaptic repair, ↑ neuronal resilience	High enriched cargo and BBB penetration potential	Needs more head-to-head comparison with other MSC sources; safety profiling is ongoing

Exosomes derived from adipose-derived stem cells (ADSCs) combat Aβ pathology through enzymatic degradation (NEP), modulation of Aβ aggregation, and neuroprotection, addressing both amyloid accumulation and downstream neuronal damage (87). A (DSC exosomes contribute to Aβ clearance in AD through multiple mechanisms. ADSC-derived exosomes carry functional NEP, which transfers NEP to neuronal cells, directly breaking down Aβ peptides and reducing extracellular and intracellular Aβ levels. The NEP activity in ADSC exosomes is significantly higher compared to exosomes from other sources like bone marrow-derived stem cells. ADSC exosomes decrease Aβ42 and Aβ40 levels in AD neuronal cells and normalize the Aβ42/40 ratio, a critical marker of amyloid toxicity. This reduction correlates with improved neuronal viability and reduced apoptosis, as evidenced by normalized levels of pro-apoptotic proteins (p53, Bax, caspase-3) and increased anti-apoptotic Bcl-2. ADSC-exos carrying high neprilysin levels reduced extracellular Aβ42 and Aβ40 by 50–60%, normalized the Aβ42/40 ratio, and enhanced neuronal viability by >70%. Apoptotic markers (p53, Bax, caspase-3) were reduced by 40–60%, and Bcl-2 was upregulated by 3-fold (81,87).

Furthermore, M2 Microglia-Derived Exosomes (M2-EXOs) carry cargo that attenuates neuronal apoptosis and modulates mitophagy pathways (PINK1/Parkin). M2-EXOs reduce mitochondrial dysfunction, neuronal death, and neuroinflammation in AD models, exerting neuroprotective effects (88). Endothelial Cell-Derived Exosomes can carry p-glycoprotein, which explicitly captures and facilitates Aβ peptides' clearance. These exosomes help reduce Aβ burden and improve cognitive dysfunction in AD models (89).

Exosomes are emerging as promising biomarkers for monitoring therapeutic response in Alzheimer's disease (AD) due to their unique biological properties and accessibility in peripheral biofluids such as blood. Exosomes can be isolated from blood plasma or serum, offering a minimally invasive alternative to cerebrospinal fluid (CSF) sampling or expensive neuroimaging techniques. This makes them suitable for repeated monitoring during therapy. Neuron-derived exosomes in blood carry AD-related molecules such as amyloid-β (Aβ) peptides and phosphorylated tau (p-tau), which correlate with brain pathology and CSF biomarkers, enabling peripheral tracking of disease processes (59). Proteomic analyses of blood-derived exosomes have identified specific proteins differentially abundant in AD patients versus controls, including Aβ-binding proteins like alpha-1-antichymotrypsin (AACT) and complement component C4-binding protein alpha (C4BPα), which can serve as novel biomarker candidates (90). Blood exosome levels of Aβ1–42, Aβ1–40, total tau, and various phosphorylated tau isoforms (e.g., p-tau181, p-tau217) have been shown to change with disease progression. They can be used to monitor biochemical responses to anti-amyloid or tau-targeting therapies (91). Changes in exosomal biomarker profiles may precede clinical improvement, allowing earlier assessment of therapeutic efficacy and adjustment of treatment regimens. Biomarker patterns in plasma exosomes can distinguish between mild cognitive impairment (MCI) patients who will progress to AD dementia and those who will not, aiding in patient stratification and evaluation of disease-modifying therapies.

Future Perspectives and Challenges

Despite exosomes' promising therapeutic potential in Alzheimer's disease, several significant challenges and limitations must be addressed to advance these therapies toward routine clinical use.

Therapeutic Risks and Biological Limitations: A critical limitation in exosome-based therapy is the potential for off-target effects. Because exosomes naturally facilitate intercellular communication, their biodistribution following systemic administration is not fully controllable, raising concerns about unintended interactions with healthy tissues. Furthermore, while exosomes are generally considered low-immunogenic, there is growing evidence that exogenous exosomes—especially those derived from allogeneic sources or modified exogenously—can provoke immune responses or inflammation, particularly upon repeated dosing. Another key issue is the potential tumorigenic risk. Depending on their cellular origin, exosomes can carry oncogenic microRNAs or proteins, posing a risk of promoting malignancy or facilitating tumor microenvironment modulation if not rigorously screened and purified. The lack

of long-term safety data from human trials adds to these concerns, mainly when applied chronically in neurodegenerative conditions like AD (92).

Scalability and Manufacturing Considerations: The successful clinical translation of exosome-based therapies hinges on solving primary production and quality control hurdles. Current isolation techniques—such as ultracentrifugation, size-exclusion chromatography, and polymer precipitation—often struggle to yield pure and homogeneous exosome populations at a scale suitable for clinical use. Variability in source cells, culture conditions, and purification methods can result in significant batch-to-batch inconsistencies, affecting therapeutic efficacy and reproducibility (93). Moreover, there is a lack of standardized protocols for exosome characterization, including defining acceptable thresholds for protein, RNA, and lipid content. The stability of exosome preparations during storage and transportation also poses a logistical challenge, especially if they are to be used globally. Meeting Good Manufacturing Practice (GMP) standards requires optimized protocols that balance purity, yield, and bioactivity—an area still under rapid development (94).

Delivery Efficiency and Targeting Challenges: Exosomes naturally cross the BBB, but their ability to home selectively to diseased brain regions remains limited. Passive targeting through systemic delivery often results in non-specific liver, spleen, and kidney tissue uptake. Efforts to engineer exosomes with targeting ligands, such as peptides or antibodies, have shown promise but add complexity to the manufacturing pipeline and raise regulatory scrutiny. Precise control over dosage, targeting, and biodistribution enhances safety and therapeutic index (95).

Regulatory and Ethical Considerations: The rapid development of exosome therapeutics has outpaced the establishment of clear regulatory frameworks. There is ongoing debate over whether exosomes should be classified as biologics, drugs, or advanced therapy medicinal products (ATMPs). These distinctions affect approval pathways, quality assurance requirements, and market access. Additionally, using stem cell-derived exosomes, especially from embryonic or genetically modified sources, raises ethical considerations that must be carefully addressed in clinical protocols and patient consent procedures (96).

To overcome these challenges, future research should prioritize engineering exosomes with enhanced targeting and immune evasion capabilities (e.g., surface modifications, ligand-conjugation). It should also develop scalable bioreactor-based production systems for high-yield exosome generation under GMP conditions. It should also establish robust quality control benchmarks, including potency assays and cargo profiling, to ensure clinical-grade consistency. To achieve synergistic disease-modifying effects, exosome therapy should be combined with other modalities, such as immunotherapy or gene editing. Exploring personalized exosome therapies derived from autologous cells to minimize immune rejection and maximize compatibility.

While exosome-based therapies represent a transformative innovation for AD treatment, their full clinical realization depends on overcoming current scientific, technical, and regulatory obstacles. Targeted investment in scalable production technologies, regulatory clarity, and safety validation will be essential to translate preclinical promise into real-world clinical success.

Conclusion

Alzheimer's disease is arguably the most daunting neurodegenerative disorder, with multi-domain pathologies encompassing amyloid-beta plaque formation, tau hyperphosphorylation, oxidative stress, and chronic neuroinflammation. Although conventional therapies have targeted individual entities with mostly modest clinical efficacy, the intricacy of AD pathology calls for an integrative therapeutic strategy. Exosomes in this scenario have surfaced as a game-changing platform, providing unprecedented versatility in diagnosis, immune modulation, and targeted therapy.

Exosomes' unique ability to traverse the BBB, deliver functional biomolecules, and mediate intercellular communication renders them ideal vectors for simultaneously targeting multiple aspects of AD. From a therapeutic perspective, exosomes derived from various cellular sources—mesenchymal and neural stem cells, microglia, and endothelial cells—have demonstrated potential in degrading amyloid-

beta, suppressing neuroinflammation, modulating tau pathology, and promoting neuroregeneration. Their natural biocompatibility and low immunogenicity enhance their appeal as a safe and scalable therapeutic platform.

However, despite this encouraging progress, there are still many challenges. They range from standardizing exosome isolation and characterization to improving therapeutic consistency and targeting specificity to establishing long-term safety. Surmounting these challenges will require interdisciplinary collaboration and robust translational platforms.

In conclusion, exosome therapy is a paradigm shift in treating AD. It is an attractive way forward to more effective, multimodal treatments by incorporating precision targeting, immune modulation, and regenerative potential. Ongoing studies to refine delivery platforms, advance molecular engineering, and offer individualized exosome therapy can create a new frontier in the clinical care of AD and make the disorder more amenable to treatment, with better patient outcomes.

Acknowledgments

Tarbiat Modares University, Tehran, Iran, supported this study.

Conflict of interests

The authors declare no conflict of interest.

References

1. Zhang J, Zhang Y, Wang J, Xia Y, Zhang J, Chen L. Recent advances in Alzheimer's disease: mechanisms, clinical trials and new drug development strategies. Signal Transduct Target Ther [Internet]. 2024;9(1):211. Available from: https://doi.org/10.1038/s41392-024-01911-3
2. Long JM, Holtzman DM. Alzheimer Disease: An Update on Pathobiology and Treatment Strategies. Cell [Internet]. 2019;179(2):312–39. Available from: https://www.sciencedirect.com/science/article/pii/S0092867419310074
3. O'Brien RJ, Wong PC. Amyloid precursor protein processing and Alzheimer's disease. Annu Rev Neurosci. 2011;34:185–204.
4. Wolfe MS. The role of tau in neurodegenerative diseases and its potential as a therapeutic target. Scientifica (Cairo). 2012;2012:796024.
5. Gao C, Jiang J, Tan Y, Chen S. Microglia in neurodegenerative diseases: mechanism and potential therapeutic targets. Signal Transduct Target Ther [Internet]. 2023;8(1):359. Available from: https://doi.org/10.1038/s41392-023-01588-0
6. Cai Y, Liu J, Wang B, Sun M, Yang H. Microglia in the Neuroinflammatory Pathogenesis of Alzheimer's Disease and Related Therapeutic Targets. Front Immunol. 2022;13:856376.
7. Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, et al. Oxidative Stress: Harms and Benefits for Human Health. Oxid Med Cell Longev. 2017;2017:8416763.
8. D'Alessandro MCB, Kanaan S, Geller M, Praticò D, Daher JPL. Mitochondrial dysfunction in Alzheimer's disease. Ageing Res Rev [Internet]. 2025;107:102713. Available from: https://www.sciencedirect.com/science/article/pii/S1568163725000595
9. Bettcher BM, Tansey MG, Dorothée G, Heneka MT. Peripheral and central immune system crosstalk in Alzheimer disease - a research prospectus. Nat Rev Neurol. 2021 Nov;17(11):689–701.
10. Chen X, Holtzman DM. Emerging roles of innate and adaptive immunity in Alzheimer's disease. Immunity. 2022 Dec;55(12):2236–54.
11. Zhang F, Jiang L. Neuroinflammation in Alzheimer's disease. Neuropsychiatr Dis Treat. 2015;11:243–56.
12. Ramey GD, Tang A, Phongpreecha T, Yang MM, Woldemariam SR, Oskotsky TT, et al. Exposure to autoimmune disorders is associated with increased Alzheimer's disease risk in a multi-site electronic health record analysis. Cell reports Med. 2025 Mar;6(3):101980.
13. Gulisano W, Maugeri D, Baltrons MA, Fà M, Amato A, Palmeri A, et al. Role of Amyloid-β and Tau Proteins in Alzheimer's Disease: Confuting the Amyloid Cascade. J Alzheimers Dis. 2018;64(s1):S611–31.
14. Zhao Z, Liu Y, Ruan S, Hu Y. Current Anti-Amyloid-β Therapy for Alzheimer's Disease Treatment: From Clinical Research to Nanomedicine. Int J Nanomedicine. 2023;18:7825–45.
15. Wisniewski T, Konietzko U. Amyloid-beta immunisation for Alzheimer's disease. Lancet Neurol. 2008 Sep;7(9):805–11.
16. Salloway SP, Sevingy J, Budur K, Pederson JT, DeMattos RB, Von Rosenstiel P, et al. Advancing combination therapy for Alzheimer's disease. Alzheimer's Dement (New York, N Y). 2020;6(1):e12073.
17. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science. 2020 Feb;367(6478).
18. Uddin MJ, Mohite P, Munde S, Ade N, Oladosu TA, Chidrawar VR, et al. Extracellular vesicles: The future of therapeutics and drug delivery systems. Intell Pharm [Internet]. 2024;2(3):312–28. Available from: https://www.sciencedirect.com/science/article/pii/S2949866X24000273

19. Chavda VP, Pandya A, Kumar L, Raval N, Vora LK, Pulakkat S, et al. Exosome nanovesicles: A potential carrier for therapeutic delivery. Nano Today [Internet]. 2023;49:101771. Available from: https://www.sciencedirect.com/science/article/pii/S1748013223000208

20. Qin J, Ma Z, Chen X, Shu S. Microglia activation in central nervous system disorders: A review of recent mechanistic investigations and development efforts. Front Neurol. 2023;14:1103416.

21. Nasb M, Tao W, Chen N. Alzheimer's Disease Puzzle: Delving into Pathogenesis Hypotheses. Aging Dis. 2024 Feb;15(1):43–73.

22. Miao J, Ma H, Yang Y, Liao Y, Lin C, Zheng J, et al. Microglia in Alzheimer's disease: pathogenesis, mechanisms, and therapeutic potentials. Front Aging Neurosci. 2023;15:1201982.

23. Lee CYD, Landreth GE. The role of microglia in amyloid clearance from the AD brain. J Neural Transm. 2010 Aug;117(8):949–60.

24. Zhang W, Xiao D, Mao Q, Xia H. Role of neuroinflammation in neurodegeneration development. Signal Transduct Target Ther [Internet]. 2023;8(1):267. Available from: https://doi.org/10.1038/s41392-023-01486-5

25. Long HZ, Zhou ZW, Cheng Y, Luo HY, Li FJ, Xu SG, et al. The Role of Microglia in Alzheimer's Disease From the Perspective of Immune Inflammation and Iron Metabolism. Front Aging Neurosci. 2022;14:888989.

26. Valiukas Z, Tangalakis K, Apostolopoulos V, Feehan J. Microglial activation states and their implications for Alzheimer's Disease. J Prev Alzheimer's Dis [Internet]. 2025;12(1):100013. Available from: https://www.sciencedirect.com/science/article/pii/S2274580724006058

27. Kinney JW, Bemiller SM, Murtishaw AS, Leisgang AM, Salazar AM, Lamb BT. Inflammation as a central mechanism in Alzheimer's disease. Alzheimer's Dement (New York, N Y). 2018;4:575–90.

28. Dias D, Socodato R. Beyond Amyloid and Tau: The Critical Role of Microglia in Alzheimer's Disease Therapeutics. Biomedicines [Internet]. 2025;13(2). Available from: https://www.mdpi.com/2227-9059/13/2/279

29. Adamu A, Li S, Gao F, Xue G. The role of neuroinflammation in neurodegenerative diseases: current understanding and future therapeutic targets. Front Aging Neurosci [Internet]. 2024;Volume 16. Available from: https://www.frontiersin.org/journals/aging-neuroscience/articles/10.3389/fnagi.2024.1347987

30. Chen T, Dai Y, Hu C, Lin Z, Wang S, Yang J, et al. Cellular and molecular mechanisms of the blood-brain barrier dysfunction in neurodegenerative diseases. Fluids Barriers CNS. 2024 Jul;21(1):60.

31. Chen Z, Balachandran YL, Chong WP, Chan KWY. Roles of Cytokines in Alzheimer's Disease. Int J Mol Sci [Internet]. 2024;25(11). Available from: https://www.mdpi.com/1422-0067/25/11/5803

32. Bhol NK, Bhanjadeo MM, Singh AK, Dash UC, Ojha RR, Majhi S, et al. The interplay between cytokines, inflammation, and antioxidants: mechanistic insights and therapeutic potentials of various antioxidants and anti-cytokine compounds. Biomed Pharmacother [Internet]. 2024;178:117177. Available from: https://www.sciencedirect.com/science/article/pii/S0753332224010618

33. Domingues C, da Cruz E Silva OAB, Henriques AG. Impact of Cytokines and Chemokines on Alzheimer's Disease Neuropathological Hallmarks. Curr Alzheimer Res. 2017;14(8):870–82.

34. Hampel H, Hardy J, Blennow K, Chen C, Perry G, Kim SH, et al. The Amyloid-β Pathway in Alzheimer's Disease. Mol Psychiatry. 2021 Oct;26(10):5481–503.

35. Li H, Wu M, Zhao X. Role of chemokine systems in cancer and inflammatory diseases. MedComm. 2022 Jun;3(2):e147.

36. Zhao H, Wu L, Yan G, Chen Y, Zhou M, Wu Y, et al. Inflammation and tumor progression: signaling pathways and targeted intervention. Signal Transduct Target Ther. 2021 Jul;6(1):263.

37. Sharma C, Kim SR. Linking Oxidative Stress and Proteinopathy in Alzheimer's Disease. Antioxidants (Basel, Switzerland). 2021 Jul;10(8).

38. Dash UC, Bhol NK, Swain SK, Samal RR, Nayak PK, Raina V, et al. Oxidative stress and inflammation in the pathogenesis of neurological disorders: Mechanisms and implications. Acta Pharm Sin B [Internet]. 2025;15(1):15–34. Available from: https://www.sciencedirect.com/science/article/pii/S2211383524004040

39. Ghimire A, Rehman SA, Subhani A, Khan MA, Rahman Z, Iqubal MK, et al. Mechanism of microglia-mediated neuroinflammation, associated cognitive dysfunction, and therapeutic updates in Alzheimer's disease. hLife [Internet]. 2025;3(2):64–81. Available from: https://www.sciencedirect.com/science/article/pii/S2949928324000968

40. Balkhi S, Di Spirito A, Poggi A, Mortara L. Immune Modulation in Alzheimer's Disease: From Pathogenesis to Immunotherapy. Cells. 2025 Feb;14(4).

41. Bhadane P, Roul K, Belemkar S, Kumar D. Immunotherapeutic approaches for Alzheimer's disease: Exploring active and passive vaccine progress. Brain Res [Internet]. 2024;1840:149018. Available from: https://www.sciencedirect.com/science/article/pii/S0006899324002725

42. Song C, Shi J, Zhang P, Zhang Y, Xu J, Zhao L, et al.

Immunotherapy for Alzheimer's disease: targeting β-amyloid and beyond. Transl Neurodegener. 2022 Mar;11(1):18.

43. Alshamrani M. Recent Trends in Active and Passive Immunotherapies of Alzheimer's Disease. Antibodies (Basel, Switzerland). 2023 Jun;12(2).

44. Mavoungou C, Schindowski K. Immunotherapy with Anti-Aβ Monoclonal Antibodies in Alzheimer's Disease: A Critical Review on the Molecules in the Pipelines with Regulatory Considerations. In: Frontiers in Clinical Drug Research - Alzheimer Disorders. 2013. p. 3–85.

45. Müller L, Di Benedetto S. Neuroimmune crosstalk in chronic neuroinflammation: microglial interactions and immune modulation. Front Cell Neurosci. 2025;19:1575022.

46. Elumalai K, Srinivasan S, Shanmugam A. Review of the efficacy of nanoparticle-based drug delivery systems for cancer treatment. Biomed Technol [Internet]. 2024;5:109–22. Available from: https://www.sciencedirect.com/science/article/pii/S2949723X23000533

47. Wang M, Thomson AW, Yu F, Hazra R, Junagade A, Hu X. Regulatory T lymphocytes as a therapy for ischemic stroke. Semin Immunopathol. 2023 May;45(3):329–46.

48. Di Bella MA. Overview and Update on Extracellular Vesicles: Considerations on Exosomes and Their Application in Modern Medicine. Biology (Basel). 2022 May;11(6).

49. Krylova S V, Feng D. The Machinery of Exosomes: Biogenesis, Release, and Uptake. Int J Mol Sci. 2023 Jan;24(2).

50. Yang Y, Wang M, Zhang YY, Zhao SZ, Gu S. The endosomal sorting complex required for transport repairs the membrane to delay cell death. Front Oncol. 2022;12:1007446.

51. Ghadami S, Dellinger K. The lipid composition of extracellular vesicles: applications in diagnostics and therapeutic delivery. Front Mol Biosci [Internet]. 2023;Volume 10. Available from: https://www.frontiersin.org/journals/molecular-biosciences/articles/10.3389/fmolb.2023.1198044

52. Lee YJ, Shin KJ, Chae YC. Regulation of cargo selection in exosome biogenesis and its biomedical applications in cancer. Exp Mol Med. 2024 Apr;56(4):877–89.

53. Bağcı C, Sever-Bahcekapili M, Belder N, Bennett APS, Erdener ŞE, Dalkara T. Overview of extracellular vesicle characterization techniques and introduction to combined reflectance and fluorescence confocal microscopy to distinguish extracellular vesicle subpopulations. Neurophotonics. 2022 Apr;9(2):21903.

54. Yakubovich EI, Polischouk AG, Evtushenko VI. Principles and Problems of Exosome Isolation from Biological Fluids. Biochem (Mosc) Suppl Ser A Membr Cell Biol. 2022;16(2):115–26.

55. Jia Y, Yu L, Ma T, Xu W, Qian H, Sun Y, et al. Small extracellular vesicles isolation and separation: Current techniques, pending questions and clinical applications. Theranostics. 2022;12(15):6548–75.

56. Schnatz A, Müller C, Brahmer A, Krämer-Albers EM. Extracellular Vesicles in neural cell interaction and CNS homeostasis. FASEB bioAdvances. 2021 Aug;3(8):577–92.

57. You Y, Ikezu T. Emerging roles of extracellular vesicles in neurodegenerative disorders. Neurobiol Dis. 2019 Oct;130:104512.

58. Sun M, Chen Z. Unveiling the Complex Role of Exosomes in Alzheimer's Disease. J Inflamm Res. 2024;17:3921–48.

59. Dehghani S, Ocakcı O, Hatipoglu PT, Özalp VC, Tevlek A. Exosomes as Biomarkers and Therapeutic Agents in Neurodegenerative Diseases: Current Insights and Future Directions. Mol Neurobiol [Internet]. 2025; Available from: https://doi.org/10.1007/s12035-025-04825-5

60. Shen H, Li S, Lin L, Wu Q, Dong Z, Xu W. Advancements in plant-derived exosome-like vesicles: Versatile bioactive carriers for targeted drug delivery systems. J Pharm Anal [Internet]. 2025;101300. Available from: https://www.sciencedirect.com/science/article/pii/S2095177925001170

61. Fu S, Wang Y, Xia X, Zheng JC. Exosome engineering: Current progress in cargo loading and targeted delivery. NanoImpact [Internet]. 2020;20:100261. Available from: https://www.sciencedirect.com/science/article/pii/S2452074820300550

62. Jeong H, Kim OJ, Oh SH, Lee S, Reum Lee HA, Lee KO, et al. Extracellular Vesicles Released from Neprilysin Gene-Modified Human Umbilical Cord-Derived Mesenchymal Stem Cell Enhance Therapeutic Effects in an Alzheimer's Disease Animal Model. Stem Cells Int. 2021;2021:5548630.

63. Katsuda T, Tsuchiya R, Kosaka N, Yoshioka Y, Takagaki K, Oki K, et al. Human adipose tissue-derived mesenchymal stem cells secrete functional neprilysin-bound exosomes. Sci Rep [Internet]. 2013;3(1):1197. Available from: https://doi.org/10.1038/srep01197

64. Liang T, Wu Z, Li J, Wu S, Shi W, Wang L. The emerging double-edged sword role of exosomes in Alzheimer's disease. Front Aging Neurosci. 2023;15:1209115.

65. Sharma V, Mukhopadhyay C Das. Exosome as drug delivery system: Current advancements. Extracell Vesicle [Internet]. 2024;3:100032. Available from: https://www.sciencedirect.com/science/article/pii/S2773041723000112

66. Hudry E, Martin C, Gandhi S, György B, Scheffer DI, Mu D, et al. Exosome-associated AAV vector as a

robust and convenient neuroscience tool. Gene Ther. 2016 Apr;23(4):380–92.

67. Yassaghi Y, Nazerian Y, Ghasemi M, Nazerian A, Sayehmiri F, Perry G, et al. Microglial modulation as a therapeutic strategy in Alzheimer's disease: Focus on microglial preconditioning approaches. J Cell Mol Med. 2024 Aug;28(15):e18554.

68. Jain N, Ulrich JD. TREM2 and microglia exosomes: a potential highway for pathological tau. Vol. 17, Molecular neurodegeneration. England; 2022. p. 73.

69. Chen L, Xiong Y, Chopp M, Zhang Y. Engineered exosomes enriched with select microRNAs amplify their therapeutic efficacy for traumatic brain injury and stroke. Front Cell Neurosci. 2024;18:1376601.

70. Fu W, Li T, Chen H, Zhu S, Zhou C. Research Progress in Exosome-Based Nanoscale Drug Carriers in Tumor Therapies. Front Oncol. 2022;12:919279.

71. Zhong L, Wang J, Wang P, Liu X, Liu P, Cheng X, et al. Neural stem cell-derived exosomes and regeneration: cell-free therapeutic strategies for traumatic brain injury. Stem Cell Res Ther. 2023 Aug;14(1):198.

72. Soares Martins T, Trindade D, Vaz M, Campelo I, Almeida M, Trigo G, et al. Diagnostic and therapeutic potential of exosomes in Alzheimer's disease. J Neurochem [Internet]. 2021;156(2):162–81. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/jnc.15112

73. Yuyama K, Sun H, Usuki S, Sakai S, Hanamatsu H, Mioka T, et al. A potential function for neuronal exosomes: Sequestering intracerebral amyloid-β peptide. FEBS Lett. 2014;589.

74. Guo M, Yin Z, Chen F, Lei P. Mesenchymal stem cell-derived exosome: a promising alternative in the therapy of Alzheimer's disease. Alzheimers Res Ther. 2020 Sep;12(1):109.

75. Long R, Wang S. Exosomes from preconditioned mesenchymal stem cells: Tissue repair and regeneration. Regen Ther [Internet]. 2024;25:355–66. Available from: https://www.sciencedirect.com/science/article/pii/S2352320424000099

76. Yin T, Liu Y, Ji W, Zhuang J, Chen X, Gong B, et al. Engineered mesenchymal stem cell-derived extracellular vesicles: A state-of-the-art multifunctional weapon against Alzheimer's disease. Theranostics. 2023;13(4):1264–85.

77. Tan F, Li X, Wang Z, Li J, Shahzad K, Zheng J. Clinical applications of stem cell-derived exosomes. Signal Transduct Target Ther [Internet]. 2024;9(1):17. Available from: https://doi.org/10.1038/s41392-023-01704-0

78. Ma ZJ, Yang JJ, Lu YB, Liu ZY, Wang XX. Mesenchymal stem cell-derived exosomes: Toward cell-free therapeutic strategies in regenerative medicine. World J Stem Cells. 2020 Aug;12(8):814–40.

79. Liu MW, Li H, Xiong GF, Zhang BR, Zhang QJ, Gao SJ, et al. Mesenchymal stem cell exosomes therapy for the treatment of traumatic brain injury: mechanism, progress, challenges and prospects. J Transl Med. 2025 Apr;23(1):427.

80. Liu S, Fan M, Xu JX, Yang LJ, Qi CC, Xia QR, 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 Feb;19(1):35.

81. Khan MI, Jeong E, Khan MZ, Shin J, Kim JD. Stem cells-derived exosomes alleviate neurodegeneration and Alzheimer's pathogenesis by ameliorating neuroinflamation, and regulating the associated molecular pathways. Sci Rep. 2023;13.

82. Cole SL, Vassar R. The Alzheimer's disease beta-secretase enzyme, BACE1. Mol Neurodegener. 2007 Nov;2:22.

83. Nigam SM, Xu S, Kritikou JS, Marosi K, Brodin L, Mattson MP. Exercise and BDNF reduce Aβ production by enhancing α-secretase processing of APP. J Neurochem. 2017 Jul;142(2):286–96.

84. Engmann O, Giese KP. Crosstalk between Cdk5 and GSK3beta: Implications for Alzheimer's Disease. Front Mol Neurosci. 2009;2:2.

85. Daksh R, Mathew M, Bosco A, Sojan C, Tom A, Bojja S, et al. The role of exosomes in diagnosis, pathophysiology, and management of Alzheimer's Disease. Biochem Biophys Res Commun. 2025;754:151526.

86. Rao S, Madhu LN, Babu RS, Shankar G, Kotian S, Nagarajan A, et al. Extracellular vesicles from hiPSC-derived NSCs protect human neurons against Aβ-42 oligomers induced neurodegeneration, mitochondrial dysfunction and tau phosphorylation. Stem Cell Res Ther. 2025 Apr;16(1):191.

87. 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 Jul;1691:87–93.

88. Li N, Shu J, Yang X, Wei W, Yan A. Exosomes Derived From M2 Microglia Cells Attenuates Neuronal Impairment and Mitochondrial Dysfunction in Alzheimer's Disease Through the PINK1/Parkin Pathway. Front Cell Neurosci. 2022;16:874102.

89. 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 Sep;45(9):2161–72.

90. Soares Martins T, Marçalo R, Ferreira M, Vaz M, Silva RM, Martins Rosa I, et al. Exosomal Aβ-Binding Proteins Identified by "In Silico" Analysis Represent Putative Blood-Derived Biomarker

Candidates for Alzheimer´s Disease. Int J Mol Sci. 2021 Apr;22(8).

91. Lai R, Li B, Bishnoi R. P-tau217 as a Reliable Blood-Based Marker of Alzheimer's Disease. Biomedicines. 2024 Aug;12(8).

92. Ranjan P, Colin K, Dutta RK, Verma SK. Challenges and future scope of exosomes in the treatment of cardiovascular diseases. J Physiol. 2023 Nov;601(22):4873–93.

93. Dilsiz N. A comprehensive review on recent advances in exosome isolation and characterization: Toward clinical applications. Transl Oncol [Internet]. 2024;50:102121. Available from: https://www.sciencedirect.com/science/article/pii/S1936523324002481

94. Mateescu B, Kowal EJK, van Balkom BWM, Bartel S, Bhattacharyya SN, Buzás EI, et al. Obstacles and opportunities in the functional analysis of extracellular vesicle RNA - an ISEV position paper. J Extracell vesicles. 2017;6(1):1286095.

95. Xu M, Feng T, Liu B, Qiu F, Xu Y, Zhao Y, et al. Engineered exosomes: desirable target-tracking characteristics for cerebrovascular and neurodegenerative disease therapies. Theranostics. 2021;11(18):8926–44.

96. Wang CK, Tsai TH, Lee CH. Regulation of exosomes as biologic medicines: Regulatory challenges faced in exosome development and manufacturing processes. Clin Transl Sci. 2024 Aug;17(8):e13904.