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Review Article

Unraveling the Potential of Mesenchymal Stem Cell-Derived Extracellular Vesicles in Combating Neuroinflammation and Mitochondrial Dysfunction in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) stands as a formidable, age-related neurodegenerative disorder that is marked by the relentless degeneration of diverse neuronal cell types. This degeneration leads to profound losses in neural tissue, disruption of synaptic networks, cerebral atrophy, and a debilitating decline in cognitive function. Accordingly, the multifaceted nature of AD necessitates a robust and comprehensive therapeutic approach. Although current pharmacological treatments mainly focus on modulating acetylcholine levels through the inhibition of acetylcholinesterase, they only provide symptomatic relief and fail to alter the disease's relentless progression. In this context, mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) emerge as a groundbreaking therapeutic strategy with remarkable potential. These vesicles can modulate neuroinflammation, influence immunological responses, orchestrate microglial activation, and reduce oxidative stress, thereby slowing AD progression. The inflammatory microenvironment plays a pivotal role in AD pathogenesis, with proinflammatory cytokines contributing to neurotoxicity and neuronal apoptosis. Moreover, due to their ability to cross the blood-brain barrier, MSC-EVs are considered key players in delivering therapeutic effects directly within the central nervous system. More precisely, they promote neural tissue regeneration, stimulate neurogenesis, enhance the reorganization of neuronal circuits, and improve synaptic plasticity, thereby fostering essential functional recovery. Therefore, this review highlights the transformative potential of MSCs-EVs in combating the progression of AD, presenting them as a vital pathway for the innovative treatment of neurodegenerative disorders.

Keywords: Alzheimer's disease, Pathophysiology, MSCs-EVs, Neuroinflammation, Mitochondrial conditions, Microglial activation

Introduction

Alzheimer's disease (AD) is regarded as the most prevalent neurodegenerative disorder, pathologically characterized by the extracellular aggregation of beta-amyloid (Aβ) plaques and the formation of intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein.[1] In addition, this disorder is associated with synaptic degeneration, neuronal loss, and gliosis.[2] Clinically, AD frequently begins with mild cognitive impairment, manifesting as early memory deficits and difficulties with short-term memory retention.[3] As the disease progresses, patients may exhibit increasingly severe impairments in complex attention, expressive language, visuospatial processing, and executive function. It should be noted that AD accounts for approximately 60–80% of all dementia cases.[4] While around 1% of cases are early-onset and exhibit an autosomal dominant inheritance pattern, typically manifesting symptoms before age 65, often in individuals' 40s or 50s, the vast majority (99%) are late-onset, sporadic cases.[5]

Pathophysiology of Alzheimer's Disease

AD pathophysiology is primarily driven by the accumulation of Aβ in the brain, which is linked to the amyloid precursor protein (APP) gene on chromosome 21.[6] APP exists in three isoforms, with APP695 being predominantly found in neurons. Moreover, it can be processed through the amyloidogenic pathway, which produces neurotoxic Aβ peptides, and the non-amyloidogenic pathway, which prevents Aβ formation. In the amyloidogenic pathway, APP is cleaved by β-secretase (beta-site amyloid precursor protein cleaving enzyme-1:

BACE1) and γ-secretase, generating Aβ40 and Aβ42, with Aβ42 being particularly harmful.[7] Furthermore, the non-amyloidogenic pathway yields protective fragments that facilitate synaptic plasticity. The amyloid cascade hypothesis proposes that Aβ accumulation triggers the formation of NFTs, ultimately leading to cognitive decline. Tau, essential for microtubule stability and neuronal transport, becomes dysfunctional in AD, disrupting these functions and causing cognitive deficits.[8] The pathological hyperphosphorylation of tau leads to the formation of NFTs, which begin in the entorhinal cortex and spread to other brain areas.[9] Additionally, dysfunctions in lysosomal pathways promote tau accumulation and spread, while Aβ deposition accelerates tau pathology. Overall, Aβ and tau contribute to synaptic dysfunction and neuronal death (Figure 1).[2]

Genetic Background and Relevant Risk Factors

Genetic predisposition is a critical component in AD pathophysiology, accounting for approximately 58–79% of cases. The autosomal dominant forms of AD are linked to rare mutations in the *APP*, *PSEN1*, and *PSEN2* genes.[10] Among genetic risk factors, the apolipoprotein E (APOE) gene is the most significant for sporadic AD.[11] The prevalence of the APOEε4 allele is reported to be around 66% in individuals diagnosed with AD and approximately 64% among those with mild cognitive impairments. The presence of a single APOE ε4 allele escalates the risk of developing AD by 3–4 times, while individuals carrying two alleles face a risk increase of 9–15 times.[12] Additionally, age remains the predominant risk factor, with an estimated prevalence of AD at 18.1% in individuals aged 65 and older, which surges to 33.2% for those aged 85 and above.[13]

Mitochondrial Dysfunction in Alzheimer's Disease Development

Mitochondrial abnormalities are increasingly recognized in the pathogenesis of neurodegenerative diseases, such as AD, Parkinson's, and Huntington's. Mitochondrial

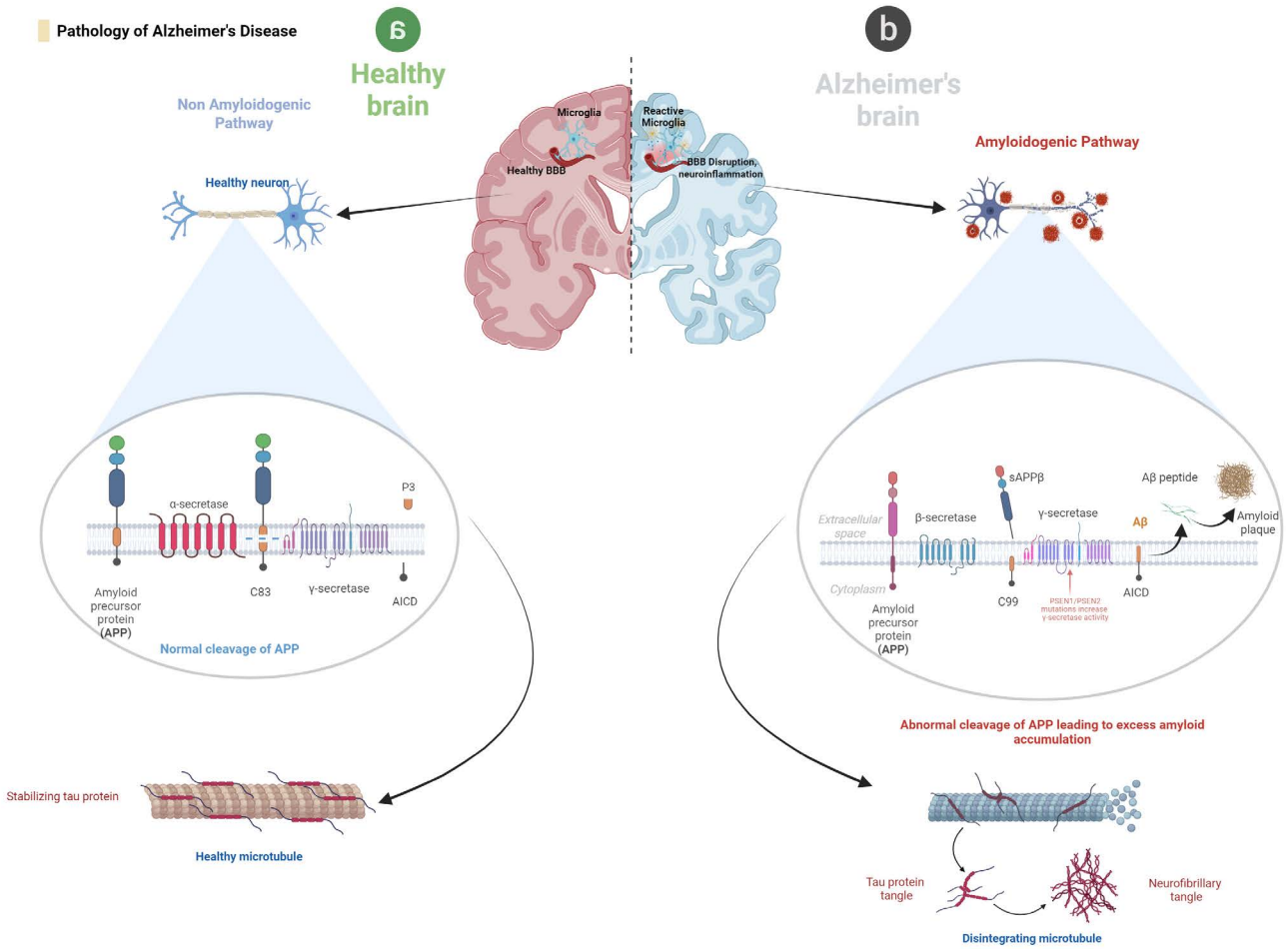

Figure 1. Pathophysiological Mechanisms Underlying Alzheimer's Disease

Note. APP: Amyloid-beta precursor protein; BBB: Blood–brain barrier; Aβ: Beta amyloid; AD: Alzheimer's disease. The left panel illustrates the healthy brain, in which the APP undergoes normal non-amyloidogenic cleavage by α-secretase and γ-secretase, generating non-pathogenic fragments and preventing formation. Aβ plays a major role in synaptic development, mineral transfer, neuronal plasticity, and regulation of cell signaling in neuronal tissues. Neurons retain stable microtubules supported by physiologic tau activity, and both the BBB and microglial populations remain in a resting, protective state. The right panel displays the amyloidogenic pathway of APP processing, which characterizes the general pathology of AD. The sequential cleavage of APP by β-secretase and γ-secretase produces Aβ peptides that aggregate and accumulate into amyloid plaques. Abnormal tau modification leads to tau tangles and microtubule disassembly, resulting in the instability of microtubules, which play a crucial role in neuronal cell structure. It should be noted that such molecular events promote neuroinflammation, reactive microglia, and BBB disruption characteristics of AD progression.

dysfunction, metabolic issues, increased reactive oxygen species (ROS), and impaired mitochondrial quality control (QC) are early indicators in AD and play a crucial role in disease progression.[14] In addition, genome-wide studies have linked variants in the *ABCA7* gene to late-onset AD. Research using cortical organoids derived from ABCA7-deficient-induced pluripotent stem cells (iPSCs) demonstrates serious neuronal damage, including disrupted mitochondrial lipid metabolism and excessive ROS production, both of which are critical for cognitive function. Mitochondrial QC involves dynamic processes, such as fission, fusion, and mitophagy, and impairments in these processes may contribute to neurodegenerative disorders (Figure 2).[15] Furthermore, mitochondrial fission and fusion processes are integral to mitochondrial dynamics and cellular homeostasis. Fission, the process of mitochondrial division, enables mitochondrial fragmentation, thereby facilitating the removal of damaged components and allowing for the effective distribution of mitochondria during cell division. Conversely, fusion involves the merging of mitochondria, promoting the mixing of mitochondrial contents and DNA, which is essential for maintaining healthy, functional organelles. In general, these dynamic processes are critical for regulating mitochondrial function, influencing adenosine triphosphate (ATP) production, metabolic efficiency, and the cellular stress response, and ultimately impacting overall cellular health and metabolic homeostasis (Figure 3).[16] Early Alzheimer's models show reduced mitophagy in iPSC-derived neurons. The accumulation of APP cleavage products at mitochondria can lead to mitophagy deficits. In familial Alzheimer's, iPSC-derived neurons frequently have defective mitochondria due to compromised autophagic degradation linked to lysosomal dysfunction.[17] Moreover, mutant PS1 M146L iPSC-derived cells exhibit defects in respiratory chain enzymes and autophagy-related proteins, influencing AD pathology. Further, both nuclear and mitochondrial DNA mutations play critical roles in the development of the disease and the aging process.[18]

Oxidative Stress and Alzheimer's Disease Development

An imbalance in ROS production and accumulation causes OS. ROS are essential signaling molecules in biological systems, but excess ROS can harm cells.[19,20] They include chemically reactive oxygen-free radicals and oxygen derivatives that are not radicals. A cell might enter an oxidative state if it produces more ROS or if its antioxidant system is not functioning well. The brain is susceptible to oxidative damage due to excessive oxygen consumption, elevated concentrations of polyunsaturated fatty acids, increased levels of redox-

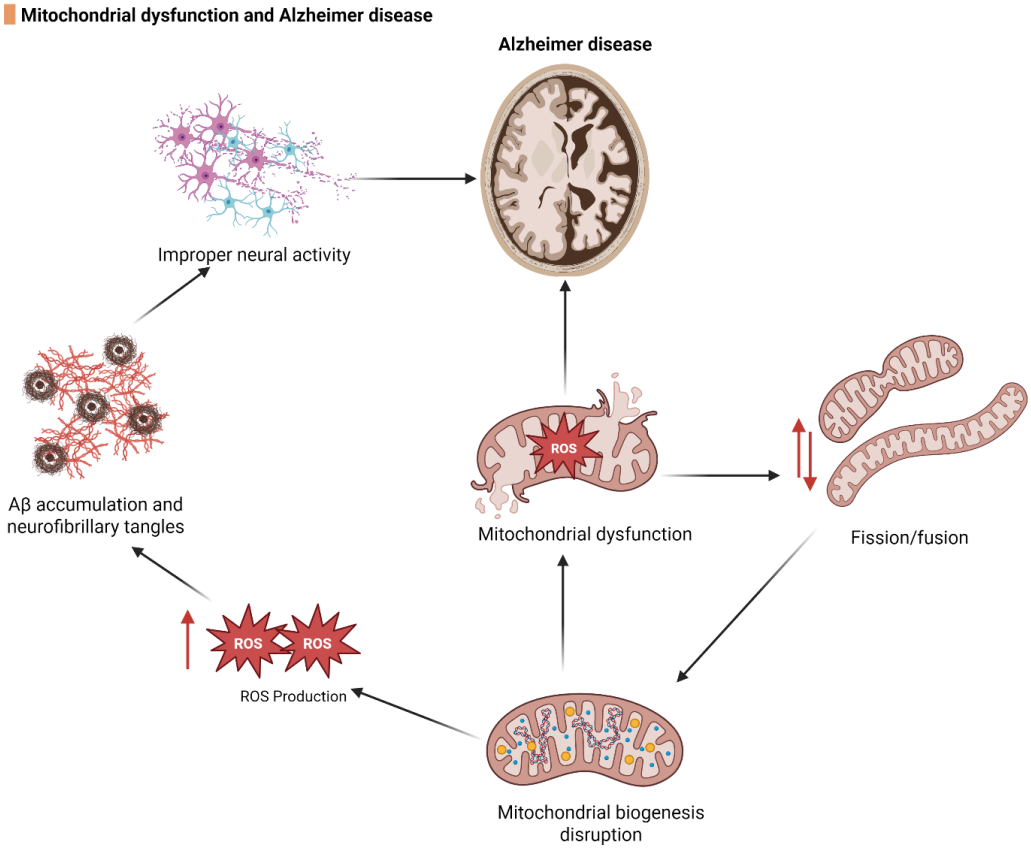

Figure 2. How Dysregulated Mitochondrial Dynamics Contribute to Alzheimer's Disease Pathology.
Note. Under normal conditions, there are no signs of abnormality; mitochondrial fusion and fission balance each other to maintain mitochondrial integrity and proper distribution, ensuring normal energy production. However, this balance shifts toward excessive mitochondrial fission in abnormal conditions. Increased mitochondrial fragmentation leads to abnormal intracellular distribution resulting from these defects, which disturb neuronal energy homeostasis, changes, and prompt neuronal apoptosis, thereby accelerating cognitive decline and showing primary signs of Alzheimer's disease.

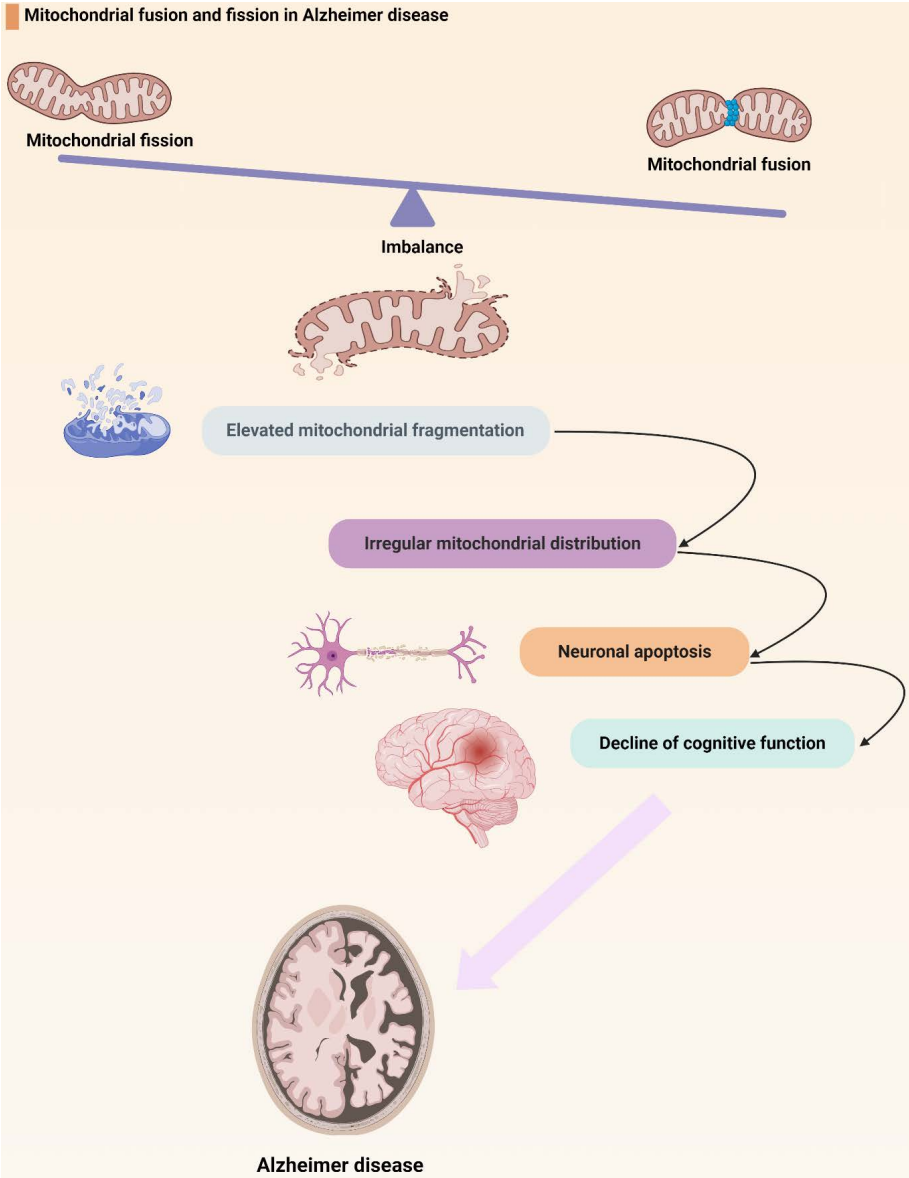

Figure 3. Physiological Associations Between Mitochondrial Dysfunction and the Initiation of Alzheimer's Disease
Note. Aβ: Beta-amyloid; ROS: Reactive oxygen species. Mitochondrial fission and fusion, along with affected mitochondrial biogenesis, lead to increased ROS production and mitochondrial damage. that an abnormal state, as well as mitochondrial biogenesis that does not work right, cause the mitochondria to make more ROS and get hurt. More ROS leads to more Aβ accumulation and the formation of neurofibrillary tangles, causing neurons to function less effectively and leading to abnormal behavior. The cycle of oxidative stress, mitochondrial damage, and protein aggregation causes severe neurodegeneration, which is a sign of Alzheimer's disease.

active transition metal ions, and decreased antioxidant levels.[21,22] According to research, ROS can damage cells in diseases that impair the brain's ability to function.[23] In AD, ROS causes the accumulation of Ab proteins, thereby disrupting lysosomal membrane integrity and killing neurons.[24] In AD, cytochrome c oxidase deficiency is the most common problem with the mitochondrial electron transport chain, leading to more ROS production, less energy storage, and problems with energy metabolism.[25] Additionally, ROS inhibits phosphatase 2A,[26] thereby facilitating the activation of glycogen synthase kinase 3β (GSK-3β), a kinase involved in the phosphorylation of tau. Increased GSK-3b activation may result in tau hyperphosphorylation and neurofibrillary lesions in AD.[27] Oxidized biomolecules from ROS (e.g., the phosphorylation of tau) are highly stable and are often used as ROS indicators. In addition, ROS can be indirectly measured by looking at the levels of antioxidants or the activity of enzymes. In AD, there is often an imbalance in the OS and an increase in by-products. Some studies indicate that AD markedly elevates lipid peroxidation, a process in which ROS target lipids, generating products via a free radical chain reaction.[28,29] It is also essential to monitor malondialdehyde, a key marker of OS and lipid peroxidation, at regular intervals. It is a straightforward and cost-effective method for tracking how AD is worsening and how well treatment is working. Protein carbonyls, 3-nitrotyrosine, TBARS, free fatty acid release, isoprostane and neuroprostane formation, 2-propen-1-al (acrolein), 4-hydroxy-2-trans-nonenal, advanced glycation end products, and 8-OH-2'-deoxyguanosine (8-OH-guanos) are a few common OS markers that

are found in biological samples. It should be noted that elevated levels of toxic carbonyls, 3-nitrotyrosine, and 4-hydroxy-2-trans-nonenal are initial alterations in AD following OS.[30,31] Based on reports, oxidative and nitrosative stress can alter key biological molecules, including proteins, lipids, and nucleic acids. When oxygen is only partially reduced, it generates ROS, including the superoxide radical anion (O_2-), hydrogen peroxide (H_2O_2), the hydroxyl radical (HO•), nitric oxide (NO), and peroxynitrite (ONOO-). Oxidative phosphorylation in mitochondria is a primary source of free radicals, as electron leakage from the mitochondrial electron transport chain results in O_2 production.[32] Moreover, progressive mitochondrial dysfunction is a principal catalyst of ROS generation in aging and AD, as well as a significant target of oxidative damage.[33] Some studies have linked mitochondrial dysfunction to altered ROS processing in AD.[34,35] In addition, adding Ab oligomers to the bilayer can generate ROS, which can then damage membrane lipids, proteins, and nucleic acids inside the cell.[36,37] OS is also associated with mitochondrial function, as ROS can impair mitochondrial function. Decreasing ROS through dietary modifications, physical activity, and antioxidant supplementation can safeguard mitochondrial function in the brain by mitigating oxidative stress and associated damage (Figure 3).

Current and Conventional Therapeutic Interventions

Current therapeutic interventions in AD encompass several approaches, reflecting ongoing trends, challenges, and emerging prospects. Despite significant advances in understanding the pathophysiology of the disease, a definitive cure remains unavailable.[38]

Approved and Traditional Drugs

Cholinesterase inhibitors, including donepezil, rivastigmine, and galantamine, function by inhibiting the breakdown of acetylcholine, thereby enhancing cognitive performance in patients with mild-to-moderate AD.[39] Meanwhile, the N-methyl-D-aspartate receptor antagonist memantine modulates glutamate transmission, helping mitigate excitotoxicity in individuals with moderate to severe disease.[40] Although these pharmacological agents offer symptomatic management, they do not alter the underlying trajectory of disease progression. Recent advancements in formulation, such as Namzaric (a combination of memantine and donepezil) and transdermal donepezil patches, strive to promote patient adherence while minimizing the adverse effects.[41]

Targeted and Next-Generation Drugs

Recent research is increasingly focused on targeted interventions for amyloid and tau pathologies. Monoclonal Abs, including aducanumab, lecanemab, and donanemab, are designed to facilitate the clearance of Aβ plaques and thereby decelerate AD progression. However, the clinical efficacy of these therapies remains contentious within the scientific community.[42] Sodium oligomannate (GV-971) modulates the gut microbiome, thereby reducing neuroinflammation, a factor increasingly recognized as a key driver of neurodegenerative disease pathology.[43] In addition, selective inhibitors of molecular pathways (e.g., GSK-3β, DYRK1A, and HDAC6) and dual-target compounds (e.g., ladostigil) are being used to enhance specificity while decreasing toxicity.[44] Moreover, innovative therapeutic strategies are emerging, such as proteolysis-targeting chimeras and protein-protein interaction inhibitors. These strategies are under investigation for their potential to selectively degrade pathogenic proteins associated with neurodegeneration. It is noteworthy that these advancements signal a promising horizon for addressing the underlying mechanisms of AD and related disorders.[45]

Combination and Multifactorial Therapies

Given the multifactorial etiology of AD, there is a trend toward employing combination therapies to enhance treatment efficacy. Notable pairings (e.g., Varoglutamstat with Aducanumab—which specifically target neurotoxic N3pE peptides) are yielding promising preliminary results.[46] Additionally, the integration of radiotherapy, histone deacetylase inhibitors, and nutritional supplements, along with neuroprotective agents, appears to confer a synergistic advantage. These multitarget approaches not only aim to boost therapeutic outcomes but also may mitigate adverse effects and help prevent the development of drug resistance.[47]

Complementary and Alternative Medicine

Both Mediterranean and ketogenic dietary patterns have been shown to inhibit amyloidosis and tau phosphorylation processes, which are pivotal in neurodegenerative diseases.[48] Acupuncture has been demonstrated to modulate synaptic protein expression and enhance neural plasticity, potentially offering therapeutic benefits for cognitive function.[49] Further, some practices, such as Kirtan Kriya yoga, have been linked to reductions in OS, subsequently improving both mental performance and mood regulation. Furthermore, herbal extracts from Ginkgo biloba, Bacopa monnieri, and Curcuma longa, as well as other plants rich in polyphenolic compounds, exhibit essential anti-amyloidogenic and anti-inflammatory properties.[50] Finally, routine physical exercise is associated with increased cerebral blood flow and neuroprotection, contributing to overall cognitive resilience.[51]

Stem Cell Therapy

It represents an innovative and promising intervention in the regenerative medicine landscape, particularly in addressing neurodegenerative disorders, such as AD. Various stem cell types, including pluripotent, mesenchymal, and neural stem cells, have demonstrated significant potential for repairing and replacing damaged

neuronal tissue. Key characteristics of stem cells drive their therapeutic application, notably their capacity for self-renewal and differentiation into diverse specialized cell types. They are classified into totipotent, pluripotent, multipotent, and unipotent types.[52] In neurodegeneration, this type of therapy aims to utilize stem cells and their derivatives to restore neuronal function. Mesenchymal stem cells (MSCs), which are multipotent and can be sourced from various tissues (e.g., bone marrow, adipose tissue, umbilical cord, placenta, amniotic fluid, and dental pulp) have garnered particular interest.[53] These cells secrete a range of anti-inflammatory and neurotrophic factors, as well as exosomes (EXOs) that facilitate nervous system repair. In preclinical AD models, MSC transplantation has been shown to reduce amyloid plaques while improving cognitive function. Clinical trials have begun to reveal modest cognitive stabilization and improvements in patients treated with MSCs. The evidence suggests efficacy in other neurodegenerative conditions, such as Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis, through different mechanisms, including neuroprotection, reduced inflammation, remyelination, and enhanced neural function.[54] Likewise, some studies have explored the genetic modification of MSCs to promote differentiation into cholinergic neurons, with subsequent transplantation into cortical regions leading to synaptic reconstruction and improvements in memory processes. Establishing standardized protocols for the extraction, cultivation, transplantation, and long-term safety assessment of MSCs is crucial to exptending these therapeutic strategies.[55] Nevertheless, several challenges must be addressed before implementing stem cell therapies, notably concerns about safety, tumorigenesis, and effective penetration into brain tissue.[56] Despite advancements, hurdles persist in achieving targeted differentiation and functional integration within host neural networks and ensuring the long-term safety of the interventions. Progress in imaging techniques, cellular engineering, and clinical trial methodologies may ultimately facilitate the development of safe and effective stem cell therapies for AD and other neurodegenerative conditions.[57]

Extracellular Vesicles as an Innovative and Cell-Free Therapy

Research indicates that intercellular communication predominantly occurs through paracrine signaling, in which cells release EVs into the extracellular matrix. These EVs play a critical role in mediating signaling cascades and modulating cellular responses within the local microenvironment.[58] Molecular and ultrastructural analyses categorize these vesicles into three primary subtypes: apoptotic bodies, EXOs, and macrovesicles. Apoptotic bodies range from 1,000 nm to 5,000 nm in diameter. In addition, macrovesicles are approximately 100 nm to 1,000 nm, and EXOs are smaller, measuring between 50 nm and 200 nm.[59] Among them, EXOs are of particular interest in the context of EV research due to their significant role in advancing cell-based therapies and drug-delivery systems. These nanoscale EVs exhibit intricate genomic, proteomic, and lipidomic profiles and can be isolated from various biofluids, thereby enhancing their utility as targeted delivery vesicles in regenerative medicine applications.[60-62] Moreover, their intrinsic biocompatibility and capacity to facilitate intercellular communication render them exceptionally valuable in therapeutic settings.[63,64] Importantly, nearly all cell types can synthesize and secrete EVs in both physiological and pathological contexts.[65,66] Further, EVs have nanoscale dimensions and a lipid bilayer, enabling them to cross the blood-brain barrier (BBB) and deliver biomolecules (e.g., proteins and nucleic acids) directly to neuronal cells.[67] This makes EVs efficient drug-delivery systems in AD, reducing side effects and targeting damaged areas. Although altered EV function can contribute to AD progression, modifying their cargo can transform them into therapeutic carriers that reduce inflammation and protein accumulation, thereby enhancing cognitive functions. Likewise, EVs loaded with micro ribonucleic acids (miRNAs) and short interfering RNAs targeting genes (e.g., *BACE1* and *tau*) demonstrate promise for treating AD by silencing harmful genes.[68] Preclinical studies have successfully engineered EVs for targeted brain delivery of small RNAs, mitigating pathological protein aggregation. Additionally, EVs derived from mesenchymal and neuronal stem cells provide neurotrophic and anti-inflammatory benefits, making this cell-free strategy safer than traditional cell transplants. Furthermore, these vesicles serve as biomarkers for early AD diagnosis and disease monitoring, encapsulating pathogenic molecules detectable in biofluids.[69] Research highlights the role of MSC-derived EVs, particularly those overexpressing miR-146a, in reducing inflammation while improving cognitive function in murine models.[70] As AD progresses, amyloid-beta (Aβ) and tau aggregates accumulate in predictable patterns, with EVs mediating intercellular communication and the transmission of disease factors. Inhibiting EV release has shown potential to alleviate AD symptoms, emphasizing their key role in the development of the disease.[67] Similarly, emerging data suggest that MSC-derived EVs can clear pathological proteins (e.g., Aβ plaques and hyperphosphorylated tau), activate autophagic pathways, and modulate proteins and microRNAs (miRNAs) essential for neuronal viability. In addition, these vesicles enhance autophagy, regulate neuroprotective proteins, such as sphingosine 1-phosphate (S1P) and neprilysin (NEP), and promote anti-inflammatory responses. S1P signaling enhances cognitive function and reduces Aβ deposition, while NEP facilitates amyloid degradation. Additionally, EVs transfer miRNAs that mitigate neuroinflammation and support neuronal health. They also alleviate OS by delivering antioxidative enzymes and activating the nuclear factor erythroid 2–related factor 2 pathway, promoting a

reparative microglial state. Further, mesenchymal EVs prevent neuronal apoptosis, promote neurogenesis, and enhance synaptic function, thereby improving cognitive outcomes. Overall, MSC-derived EVs represent a promising therapeutic approach for AD, as they reduce neuroinflammation and protect neurons.[71]

Mesenchymal Stem Cell-Derived Extracellular Vesicles and Neuroinflammation

Neuroinflammation plays a crucial role in AD development and progression, mainly due to the dysregulated activation of microglia. In a healthy brain, microglia remain quiescent, but in AD, they are activated by damage-associated and pathogen-associated molecular patterns via pattern recognition receptors. The nucleotide oligomerization domain-like receptor protein 3 (NLRP3) inflammasome is particularly important, as its activation in microglia leads to increased interleukin (IL)-1β levels. Inhibiting NLRP3 can reduce Aβ accumulation, lower levels of inflammatory cytokines, and improve cognitive deficits while also decreasing tau hyperphosphorylation (Figure 4).[72,73] Research has shown that MSC-EVs enhance the expression of genes involved in synaptic plasticity and memory, thereby contributing to neuroprotection. Furthermore, they improve calcium homeostasis and neuronal function while reducing neuronal apoptosis through the phosphatase and tensin homologue-phosphatidylinositol 3-kinase/protein kinase B pathway.[74] The anti-inflammatory cytokine IL-10 in MSC-EVs helps shift macrophage polarization from a pro-inflammatory to an anti-inflammatory phenotype, thereby improving immune responses in the central nervous system (CNS). Moreover, MSC-EVs alleviate OS by reducing inducible NO synthase expression and delivering catalase, thereby enhancing neuronal survival. Additionally, the activation of the nuclear factor erythroid 2–related factor 2 signaling pathway by MSC-EVs is vital for maintaining redox balance and reducing inflammation, further supporting neuronal function. Likewise, MSC-EVs effectively target neuroinflammation, modulate immune responses and microglial function, and attenuate OS. These mechanisms collectively facilitate neural regeneration, underscoring

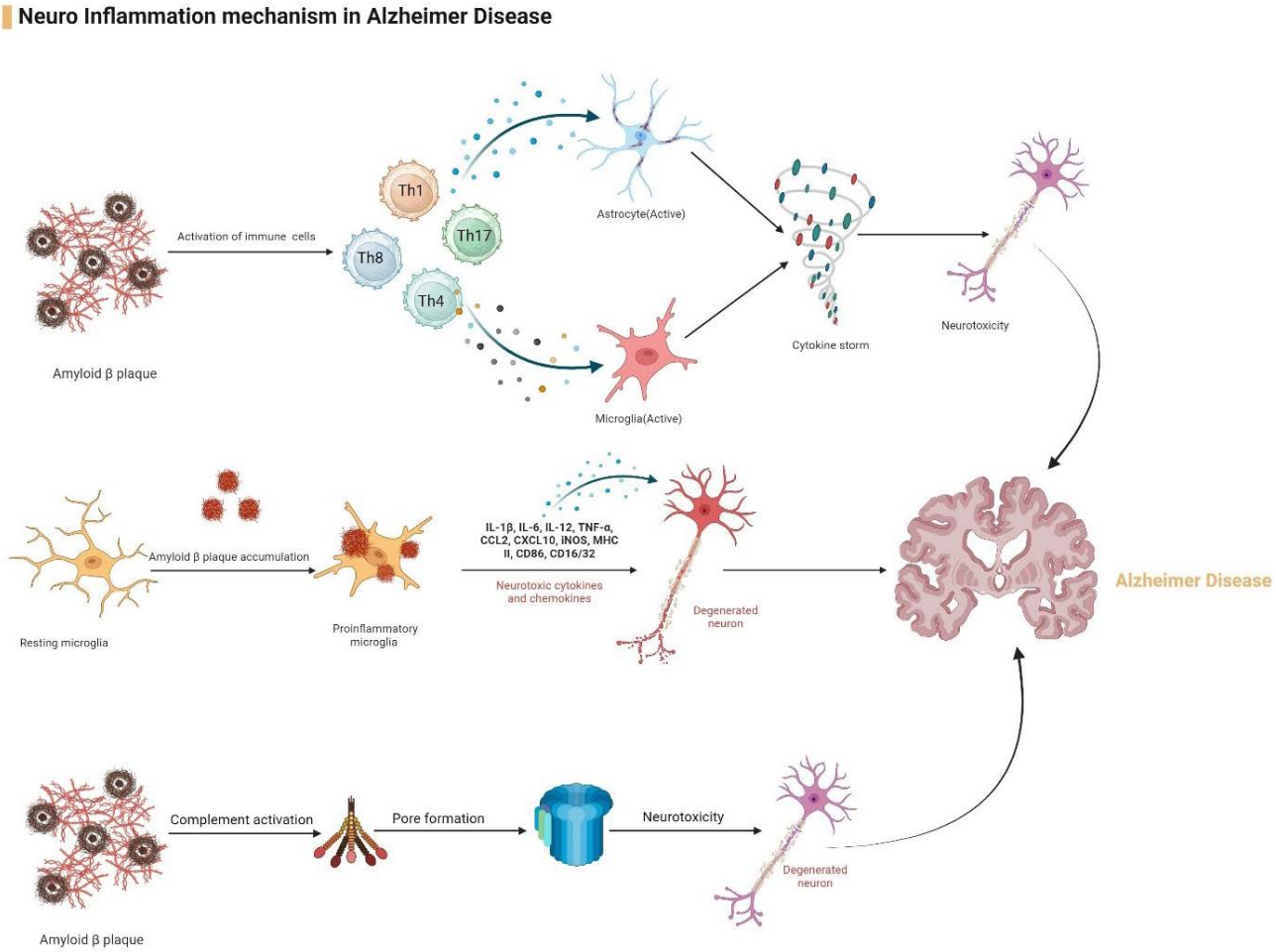

Figure 4. Different Ways of Showing That Neuroinflammation Happens in Alzheimer's Disease

Note. Th: T helper; IL: Interleukin; TNF-α: Tumor necrosis factor-alpha; Aβ: Beta-amyloid. The diagram illustrates three primary mechanisms by which the accumulation of Aβ plaques leads to neurotoxicity and ultimately contributes to the development of Alzheimer's disease: Activation of immune cells. Aβ plaques stimulate various types of Th cells (including Th1, Th4, Th8, and Th17) to become active, thereby triggering astrocytes and microglia, leading to a cytokine storm and neurotoxicity. Microglial transition: Resting microglia collect Aβ plaques and transition into proinflammatory microglia that release neurotoxic cytokines and chemokines (e.g., IL-1β, IL-6, IL-12, TNF-α, CCL12, and the like), causing the neuron to degenerate. Activation of the complement system: Aβ plaques cause the complement system to become active, leading to the formation of pores and neurotoxicity and neuronal death.

the potential of MSC-EVs to advance AD therapies.[71]

Mesenchymal Stem Cell-Derived Extracellular Vesicles and Immunological Responses

MSCs are particularly essential for their potent immunomodulatory properties,[74,75] making them promising therapeutic candidates for immune homeostasis and regenerative medicine,[75,76] They efficiently modulate innate and adaptive immunity[77,78] via the secretion of bioactive molecules and direct cell-to-cell interactions with immune cells,[77,78] Similarly, MSCs and EVs derived from them are highly suitable for treating certain inflammatory and autoimmune disorders due to their distinctive characteristics, which enable them to reduce inflammation, regenerate tissue, and maintain immunological homeostasis.[79,80] As an alternative to MSCs, MSC-EV offers numerous benefits, including reduced immunogenicity and an enhanced safety profile,[82,83] as well as the capacity to cross biological barriers.[81] Additionally, the MSC-EV application circumvents immunological rejection, entrapment of the lung microvasculature, and ectopic tumor formation associated with stem cells.[82,83] The creation of EV as therapeutic regimens is amply justified, if not called for, by these benefits and mounting evidence for the therapeutic effects of MSC-EV.[83] According to recent research, treatment with MSCs applied in neurodegenerative illnesses such as AD is safe and efficient, even when more invasive delivery methods are utilized, such as intracerebral injection.[84] It is challenging to make apples-to-apples comparisons of clinical trial results, as serious heterogeneity remains in the sources, doses, and modes of administration of MSCs. Autologous bone marrow-derived MSCs and adipose tissue-derived MSCs are the most frequently examined cells for neurological therapy. However, over recent years, more attention has been paid to the umbilical cord as a promising source of MSCs.[84] Umbilical cord-derived MSCs possess similar characteristics (e.g., low immunogenicity) and certain benefits over other sources; the primary benefit is that they can be obtained in bulk quantities from a disposable source (the post-birth umbilical cord) without discomfort or harm to mother or child.[85] It should be noted that MSCs come from diverse sources, can be easily isolated and amplified, have low immunogenicity, have low teratoma formation potential, have high migratory and interactive potential, modulate diverse biological processes, and are, therefore, a promising option for autologous and allogeneic cell therapies in neurological disease based on preclinical studies.[86] Nonetheless, the QC and reproducibility of MSC therapy in clinical trials are more contentious.

Mesenchymal Stem Cell-Derived Extracellular Vesicles and Inflammatory Cytokines and Chemokines

MSC-derived EVs express diverse adhesion molecules (CD29, CD44, and CD73), enabling them to target inflamed and damaged tissues. In the mouse intracerebral hemorrhage model, MSC-EVs were accumulated in the damaged brains.[87] Likewise, EVs tagged with the RVG protein targeted neuronal cells more specifically and showed better therapeutic effects, with greater attenuation of AD, compared to naïve EVs.[88] Kooijman et al used glycosylphosphatidylinositol. This glycolipid is incorporated into the EV's membrane during biogenesis to deliver chemokine receptors, enzymes, Abs, and signaling molecules, thereby enhancing tropism and therapeutic effect.[89] MSC-EV membranes contain high levels of cholesterol, sphingomyelin, ceramide, and lipid raft proteins.[90] that enables membrane fusion with target cells and tracking of MSC-EVs through the body, regardless of biological barriers.[91] It was suggested that MSC-EVs, like tumor-derived EVs, cross the BBB and that transcytosis is the primary underlying mechanism.[92] The endothelial recycling endocytic pathway is involved in the transcellular transport of EVs.[93] After MSC-EVs have arrived at their target cells, they can communicate with each other via receptor-ligand interactions or be endocytosed to deliver their contents.[94] All MSC-EVs contain MSC-derived bioactive molecules (messenger RNA [mRNA], miRNAs, enzymes, cytokines, chemokines, immunomodulatory factors, and growth factors) that regulate immune cell phenotype, function, survival, and homing.[95] The immunosuppressive action of MSC-EVs was comparable to that of MSC transplantation.[91] It is noteworthy that MSC-derived EVs, a cell-free product, circumvent safety concerns associated with the long-term survival of MSCs, including uncontrollable differentiation, malignancy, and allogeneic immune response-induced rejection in MHC-mismatched patients.[95] The in vitro preconditioning of MSCs can modulate the content of MSC-EVs, thereby producing a disease-specific immunosuppressive product for cell-free therapy of inflammatory and autoimmune diseases.[95] MSCs contain catalase, an active enzyme that helps protect cells against OS. Catalase is crucial for MSC-EV anti-ROS-induced damage, as inactive catalase is incapable of suppressing ROS production in hippocampus neurons.[96] MSCs can also switch macrophages from M1 to M2, which are the primary sources of immunomodulatory cytokines, including arginase-1, A-degrading enzymes (NEP and insulin-degrading enzyme), transforming growth factor beta (TGF-β), IL-10, and TGF-α. In addition, MSC-EVs play a crucial role in treating AD by targeting Aβ pathology through distinct mechanisms. Adipose-derived MSC-EVs reduce Aβ42 and Aβ40 in the neural stem cells of AD mice, as well as both secreted and intracellular Aβ in human APP-expressing cells, potentially via NEP delivery.[97,98] Bone-marrow MSC-EVs reduced Aβ plaques and dystrophic neurites in APP/PS1 mice, a model of AD, through NEP.[99] Additionally, the miRNA contents of MSC-EVs influence inflammation, synaptic density, and cognitive function. In animal models of AD, miR-146a reduces proinflammatory microglial activation by inhibiting nuclear factor kappa B in astrocytes,[100] whereas

miR-21-5p improves synaptic function while decreasing Aβ plaques.[101,102]

Mesenchymal Stem Cell-Derived Extracellular Vesicles and Microglial Activation

A neurodegenerative disease causes progressive neuron degeneration and death, leading to cognitive and behavioral dysfunction.[103] Glial cells, or neuroglia, are non-neuronal CNS cells. These cells can be divided into four types: astrocytes, microglia, oligodendrocytes, and NG2a-glia. They regulate brain plasticity, protect neurons, and maintain homeostasis.[104] Microglia, the immune cells of the CNS, maintain tissue homeostasis under physiological conditions.[105] Furthermore, activated microglia release pro-inflammatory cytokines after neuronal damage. These cytokines can result in neurotoxicity or induce neutrophil migration into the inflamed tissue.[105] Additionally, hyperactivated microglia harm healthy neural tissue and cause dying neurons to release alarmins and DAMPs, creating a "positive inflammatory loop" in the CNS that leads to ongoing neuron death.[105] Recent research by Ding et al indicates that the therapeutic effects of MSC-EVs on AD primarily result from the modulation of microglial function.[106] The cerebral accumulation of excessive Aβ is a prevalent pathogenic characteristic of AD, leading to cognitive impairment.[107] The intravenous infusion of EXOs from human umbilical cord-derived MSCs could diminish Aβ deposition and enhance spatial learning and memory performance in APP/PS1 transgenic mice, a model of AD.[62] In their recent study, Bodart-Santos et al discovered that MSC-EVs mitigated neuronal damage in AD by alleviating OS-induced injury in hippocampal neurons.[96] Interactions among neurons, microglia, astrocytes, and oligodendrocytes can injure the CNS, leading to neuronal death and myelin damage.[108] Inflammation-activated astrocytes are being increasingly investigated for their role in contributing to neurodegenerative diseases.[109,110] Several studies also reported that type 1 astrocytes (neurotoxic phenotype) and proinflammatory cytokines had a role in neurodegenerative diseases.[111,112] Impaired astrocytes and activated microglia cooperated to reduce neuron survival in AD animal models.[113] Impaired microglia have been shown to significantly contribute to neurodegeneration. The BBB prevents peripheral immune cells from entering the brain, making it an "immunologically privileged" organ. Microglial activation triggers neuroinflammation by releasing ROS, NO, and the inflammatory cytokines IL-1β, IL-6, and tumor necrosis factor (TNF).[114] Likewise, activated microglia, proinflammatory mediators, and increased OS, and nitrosative stress are associated with chronic inflammation and neurodegenerative diseases.[115] Specific signaling molecules, including nucleotides, cytokines, and chemokines, are released by neurons undergoing apoptosis.[116] Astrocytes also control neuroinflammatory events.[117] Inflammatory stimuli appear to be mostly passive for microglia. In addition, microglial activation drives the transformation of astrocytes into toxic A1 cells. A1 astrocytes are abundant in neurodegenerative diseases, especially AD.[118] Although overactivated macrophages and microglia can cause immunotoxicity, they play a crucial role in the process. Microglia and macrophages can remove myelin debris from lesions, thereby inhibiting the development of oligodendrocyte precursor cells.[119] MSC-EXO skewed microglia to the M2 immunosuppressive phenotype. In A/PP/PS1 mice treated with MSC-Exos, M2 microglial cells expressing chitinase 3-like 3, arginase-1, and MRC1 were increased in the brains.[106] In M2 cells, A-degrading enzymes (NEP and IDE) and anti-inflammatory cytokines (IL-10 and TGF-β) could reduce A deposition and inflammation [61]. Moreover, MSC-Exo treatment of APP/PS1 mice resulted in increased NEP, IDE, IL-10, and TGF-α and decreased inflammatory cytokines (TNF-α and IL-1β) in the brain, reflecting a shift from inflammatory M1 to anti-inflammatory M2 microglia.[106] Myelin basic protein is a myelin protein present in macrophages and microglia.[120] Damaged axons do not provide the requisite structure and physiology for remyelination by CNS precursor cells.[121] Neurodegenerative disorders (e.g., AD) have shown MSC-EVs to have powerful therapeutic potential for treating various diseases by delivering therapeutic cargo, decreasing inflammation, enhancing tissue repair, and improving neuronal survival and function.[122]

Mesenchymal Stem Cell-Derived Extracellular Vesicles and Mitochondrial Condition

Mesenchymal Stem Cell-Derived Extracellular Vesicles and Mitochondrial Fusion and Fission

Mitochondrial dysfunction is a hallmark of AD. However, current mitophagy inducers are toxic and do not effectively accumulate in the brain.[123] Numerous studies have shown that this type of dysfunction plays a crucial role in AD initiation and progression, occurring prior to the formation of amyloid plaques and NFTs.[124] Zhang et al investigated protective effects using human umbilical cord-derived MC-EVs in an in vitro model of AD and analyzed the associated mitochondrial mechanisms. Xu et al also generated nanosized MSC-derived EVs (MSC-EV-SHP2) that expressed high amounts of tyrosine phosphatase-2 (SHP2). Due to the excellent BBB penetration potential, MSC-EV-SHP2 could effectively deliver SHP2 to AD mice. Furthermore, it significantly reduced NLRP3-activated inflammasomes and apoptosis associated with mitochondrial damage in neural cells. Mitophagy further decreased inflammation and neuronal death in AD mouse models. Accordingly, it is an efficient EV-engineering strategy to promote mitophagy as a therapy in AD patients.[125] Dynamin-related protein 1 (Drp1) is one essential protein that is involved in mitochondrial fission. It is found in all living things, from yeast to mammals. It should be noted that this protein is vital for mitochondrial fission.[126,127] Loson et al reported that

resident protein receptors (e.g., Mff, Fis1, and MiD49/51) recruit Drp1 to the outer mitochondrial membrane in order to facilitate mitochondrial fission. Drp1 is essential for mitochondrial division, size, shape, and distribution in neurons, from the cell body to axons, dendrites, and nerve terminals. Furthermore, the Drp1 protein has a significant effect on mitochondrial movement, fusion, and the engulfment of other mitochondria. More precisely, it is a mitochondrial fission factor that breaks up mitochondria and makes fusion easier when it is turned down.[128] Drp1 imbalance can lead to mitochondrial dysfunction, which is a problem in AD and other neurodegenerative diseases.[129,130] Moreover, diseases that cause excessive mitochondrial fragmentation can raise Drp1 levels, leading to mitochondrial and nerve damage. In vitro AD models demonstrate that mitochondrial fission persists longer and has detrimental effects. When overexpressed or treated with Abs, APP can cause mitochondria to break apart and alter their distribution, resulting in problems with synapses in neuronal cultures.[129,131] Fission and fusion processes are linked to mitochondrial metabolism.[16] Mitochondrial fission is increased, thereby reducing mitochondrial oxidative phosphorylation (OXPHOS), and cell homeostasis requires a balance between fission and fusion.[132,133] Although mitochondrial fusion is not required for cell viability, it is necessary for normal growth. MSCs can rescue OXPHOS and alter morphology by promoting metabolic activities and ROS production.[16] Mitochondrial fusion genes (*mfn1* and *mfn2*) and optic atrophy 1 can be induced to protect cells from extracellular damage by enhancing respiration characteristics.[134] Additionally, MSCs can suppress mitochondrial apoptosis and oxidative damage in damaged cells by inhibiting the release of cytochrome into the cytoplasm. The cells secrete cytokines and growth factors that enhance anti-apoptotic proteins (BCL-XL and BCL-2) while decreasing pro-apoptotic proteins (BAX, BAK, and BAD) and cytochrome, thereby minimizing mitochondrial injury.[135]

Mesenchymal Stem Cell-Derived Extracellular Vesicles and Mitochondrial Quality Control

Mitochondrial quality management necessitates monitoring and preventive measures at multiple levels in order to ensure safety and optimal function. QC happens at the molecular, organelle, and cellular levels. At the molecular level, a proteolytic mechanism in the mitochondrial matrix and inner membrane breaks down damaged and misfolded proteins and disassembles protein aggregates for proteolysis.[136] In addition, the ubiquitin-proteasome system in the cytosol controls the quality of mitochondrial proteins.[137] Further, mitochondrial fusion and fission provide additional protection against mitochondrial damage at the organellar level. The combination of dysfunctional mitochondria and healthy mitochondria results in a mixture of healthy and defective mitochondria.[138,139] Severely damaged mitochondria are occasionally split apart by fission, leading to their removal from the autophagy-lysosomal system via mitophagy.[140] If the QC processes at the molecular and organellar levels are not up to par, or if the damage is too severe for them to handle, damaged mitochondria can rupture and release pro-apoptotic proteins, causing apoptosis and cell death. To maintain the health and proper functioning of mitochondria at the molecular, organellar, and cellular levels, it is essential to perform QC on them. QC that is not good enough at every step causes mitochondria to malfunction and damaged mitochondria to accumulate in unexpected ways. An imbalance in mitochondrial dynamics, diminished axonal transport, and insufficient mitochondrial phagocytosis have been identified in AD neurons, potentially hindering the effective elimination of dysfunctional mitochondria. Thus, bad QC could lead to mitochondrial disease in AD.[141] In AD, mitochondrial QC is impaired at the molecular level. The mitochondrial sequence protease presequence protease (PreP) degrades Ab within mitochondria, thereby diminishing its toxic impact on mitochondrial function.[142,143] Studies on the brains of AD patients and mice support the idea that enhanced ROS production impairs PreP proteolytic activity, leading to Ab accumulation and mitochondrial toxicity. Additionally, a decline in proteasome activity would affect the QC of other peptides and mitochondrial proteins.[144,145] It should be noted that the mitochondrial dysfunction detected in AD can be exacerbated by the toxic impact of the damaged peptides and mitochondrial proteins that accumulate accordingly.[146]

Mesenchymal Stem Cell-Derived Extracellular Vesicles and Mitochondria and Beta-Amyloid

AD brains demonstrate problems with their mitochondria, including reduced function, changes in dynamics and transport, increased mitochondrial DNA mutations, altered enzyme activity, and abnormal gene expression.[147] Reports indicate that the accumulation of APP and Aβ peptides is a significant contributor to mitochondrial toxicity. Purified mitochondria from patient brains and AD mouse models contain APP and Aβ.[148,149] According to research, Aβ interacts with mitochondrial matrix proteins ABAD and cyclophilin D, which have harmful effects.[150,151] Research further represents that the abnormal accumulation of Aβ in synaptic mitochondria may lead to early synaptic dysfunction in AD.[152] Moreover, mitochondrial dysfunction and Ab accumulation in the brains of people with AD are linked to cognitive decline.[153] Mitochondria are accessed via the mitochondria-associated membranes[87] or the translocase of the outer membrane complex. Hansson Petersen et al found that mitochondria internalize and absorb extracellular Aβ.[154] The findings of a recent study revealed that only the proximity of Aβ plaques in a living AD mouse model reduced mitochondrial membrane potential and led to the emergence of dystrophic and fragmented mitochondria, suggesting that Aβ plaques may serve as the focal sources

of mitochondrial Aβ accumulation and toxicity.[155] These results suggest that APP and Aβ accumulation in the mitochondrial compartment may cause mitochondrial dysfunction by changing mitochondrial dynamics and transport. Hence, removing pathological proteins (e.g., Aβ plaques and hyperphosphorylated tau), which induce synaptic disruption and neuronal degeneration, is crucial for treating AD.[156] Research also indicates that natural MSC-EVs may help clear pathogenic proteins by modulating autophagy and regulating key protein levels in AD development, including those of hereditary proteins and miRNAs. miR, a 22-24 nucleotide non-coding RNA present in EVs, silences mRNA transcripts by attaching to the 3′ untranslated region.[157] Decreased v-ATPase activity and selective accumulation of Aβ/Aβ precursor protein (APP) in larger de-acidified autolysosomes.[158] Additionally, autophagy activation effectively scavenges Aβ plaques, suggesting that it is a promising method for preventing AD by removing aberrant protein buildup.[158] MSCs and MSC-EVs can activate autophagy, thereby reducing aberrant protein levels while improving AD.[159,160] In addition to activating autophagy, MSC-EVs can regulate the production of a critical protein that can eliminate aberrant proteins. Some researchers concluded that MSC-EVs can treat AD by regulating S1P expression, which promotes autophagy, protects neurons, modulates glial cell inflammatory responses, and inhibits apoptosis, thereby preventing the pathological changes associated with AD.[161] Cui et al used EXOs from hypoxia-preconditioned mesenchymal stromal cells to test cognitive rehabilitation in an APP/PS1 model of AD. MSCs and hypoxia-preconditioned MSC-derived EXOs reduced intracellular and extracellular Aβ oligomer deposits; however, MSCs were more effective at reversing learning and memory impairments.[101,162] This was achieved by minimizing pro-inflammatory cytokines (IL-1β and TNF-α) while maximizing anti-inflammatory cytokines (IL-4 and IL-10). Furthermore, EXOs minimized inflammation by inhibiting the activity of astrocytes and microglia. The obtained data confirmed that MSC-EVs enhance the memory of AD mice by activating the SphK/S1P signaling pathway and reducing Aβ deposition through the modulation of autophagy. In addition, NEP is a membrane-bound metallopeptidase that cleaves neuropeptides and amyloid proteins, making it a possible target for AD therapy.[163] Studies on living and nonliving cells have shown that NEP, present on MSC-EVs, can reduce Aβ accumulation.[98,99] Research reported that MSC-EVs might be able to get rid of harmful proteins using their inherited miRs. BACE1 or BACE1 inhibitors could be used to treat AD because β-secretase cleavage starts the breakdown of APP.[164] According to recent studies, BACE1 controls AD progression through miRs.[165] Sha et al[166] found that BMSC-EVs deliver miR-29c-3p to neurons, thereby suppressing BACE1 expression and activating the Wnt/β-catenin pathway, which has a positive effect on AD.[167] Likewise, Jeong et al observed that human umbilical cord MSC groups had significantly fewer amyloid plaques and lower BACE1 levels, as well as considerably more neurogenesis, compared to Aβ-injection groups.[168]

Mesenchymal Stem Cell-Derived Extracellular Vesicles and Mitochondria and Tau Protein

Tau is an essential protein that is linked to microtubules and has a significant impact on neuronal function. This protein has six isoforms in adult human brains, all derived from the same gene via alternative mRNA splicing.[169] A proline-rich region exists between the microtubule-binding domain and the projection domain, containing several phosphorylation sites.[170,171] The proline-rich tau region interacts with the microtubule surface, thereby stabilizing it.[172] As the principal posttranslational modification of tau, phosphorylation profoundly influences its dynamic equilibrium with microtubules.[173,174] Moreover, the phosphorylation of tau directed at serine and threonine has a direct effect on how well it binds to microtubules.[174] When tau does not bind to microtubules properly, it clumps, forms fibrils, and stops working properly.[175] It should be noted that the microtubule network is vital for the movement of materials along axons. Microtubule dysfunction can lead to abnormal axonal transport and synaptic impairment. Tau alters the microtubule network, thereby affecting the movement of signaling molecules, trophic factors, and essential organelles (e.g., mitochondria) along axons. Additionally, Tau plays a role in critical cellular processes, including structural and regulatory functions.[176] Mitochondrial dysfunction is also essential in AD pathogenesis.[177] Reduced ATP production, elevated ROS levels, and dysfunctional OXPHOS complexes and antioxidant enzymes demonstrate that mitochondria are not functioning properly.[178] In cell culture and transgenic mouse studies, tau overexpression diminishes mitochondrial function by decreasing the activity of mitochondrial complexes and antioxidant enzymes while enhancing ATP synthesis and synaptic function.[179,180] Furthermore, perinuclear mitochondrial distribution results in ATP depletion, OS, and synaptic dysfunction.[34,181] The findings of a study revealed that hypo-phosphorylated tau directly interacts with Drp1, leading to mitochondrial fission and excessive fragmentation in postmortem brain tissues from AD patients and mice.[182] Phosphorylated tau affects fission and interacts with voltage-dependent anion channel (VDAC) in AD brains, closing mitochondrial pores and preventing mitochondria from functioning properly.[182] Research has shown that pathogenic Tau variants affect mitochondrial function by either interacting with VDAC or blocking Drp1-mediated fission. Tau is a microtubule-associated protein that keeps axonal microtubules stable. In addition, it controls the movement of membrane organelles along axons, such as mitochondria.[183] The overexpression of tau selectively blocks kinesin in neuroblastoma cell lines, primary cortical neurons, and retinal ganglion neurons.[183,184] These

results indicate that tau and kinesin motors compete for binding to microtubules. Further, binding tau to microtubules can reverse the direction of dynein-motor movement, and the same process can cause kinesin to dissociate from microtubules, ultimately interrupting axonal transportation and neural connectivity.[185]

AD is characterized by several key features, including hyperphosphorylation of the tau protein, which leads to the formation of NFTs, a buildup of Aβ, and mitochondrial dysfunction.[186] A key player in this intricate pathology is miR-132-3p, which is a miRNA that is highly expressed in brain tissue. Notably, diminished levels of miR-132-3p in the hippocampus correlate with impaired synaptogenesis and increased Aβ production, highlighting its vital role in neuronal health.[187] MSC-EVs emerge as powerful carriers of miRNAs, proteins, and metabolites that can effectively modulate tau and mitochondrial pathways in neurons affected by AD. Research reveals that miR-132-3p in MSC-EVs inhibits RAS P21 protein activator 1, thereby enhancing Ras signaling and activating the protein kinase B pathway. This cascade of events regulates GSK-3β, which is crucial for controlling amyloid production and tau phosphorylation.[162] Tau hyperphosphorylation is noticeably reduced by enriching MSC-EVs with miR-132-3p, thereby positively influencing mitochondrial dynamics and promoting neuronal survival against OS.[188] In the context of AD, mitochondrial dysfunction intensifies ROS production and disrupts axonal transport, leading to further neuronal degeneration. However, MSC-EVs can counteract these detrimental effects by releasing antioxidants and modulating the activity of GSK-3β. Furthermore, MSC-EVs are strategically designed to target Aβ production by delivering short interfering RNAs against β-secretase and γ-secretase, alleviating mitochondrial stress, and preventing the progression of tau phosphorylation.[189] Most notably, MSC-EVs have the remarkable ability to cross the BBB while releasing anti-inflammatory factors, such as vascular endothelial growth factor and IL-10. This action not only supports mitochondrial function but also transforms the neuronal environment into a more anti-inflammatory state.[190] Therefore, MSC-EVs represent a groundbreaking, multi-target therapeutic strategy for AD, addressing its core pathological components and holding the potential to significantly alter the course of this devastating illness.[162]

Conclusion and Forward-Looking Remarks

Given the complex and multifaceted nature of AD, it is crucial to develop innovative therapeutic strategies that effectively target its primary contributing factors and underlying mechanisms. MSC-EVs present a groundbreaking opportunity to modulate neuroinflammation, shifting the microglial response toward a protective anti-inflammatory state. Furthermore, these vesicles can help mitigate OS and restore mitochondrial function, including vital processes such as fusion, fission, and QC, thereby effectively addressing the pathological hallmarks of AD. It is noteworthy that this cutting-edge, cell-free therapeutic platform not only promises to enhance immune response modulation but also holds the potential to reduce graft rejection and tackle tumorigenesis. While this approach is still in its initial stages, its development requires integrating advanced methodologies, robust foundational research, and rigorous preclinical trials in order to maximize its effectiveness and pave the way for clinical implementation. Overall, the future of AD treatment can lie within this innovative paradigm, opening new avenues for hope and healing in the fight against this devastating disease.

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Competing Interests

The authors declare no competing interests.

Ethical Approval

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