Review

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Posted Date: 6 August 2024

doi: 10.20944/preprints202408.0229.v1

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Review

Mesenchymal Stem Cell-Derived Exosomes as a Neuroregeneration Treatment for Alzheimer's Disease

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Abstract: Background: Neuroprotective and immunomodulatory microRNAs derived from mesenchymal stem cells (MSCs), neural growth factors, and anti-inflammatory cytokines are contained in nano-sized extracellular vesicles called mesenchymal stem cell-derived exosomes (MSC-Exo). These vesicles attenuate neuro-inflammation, promote neo-vascularization, induce neurogenesis, and decrease the apoptotic loss of neural cells. Methods: Systematic retrieval of information was performed on PubMed. 60 articles were found in a search on Mesenchymal Stem Cell, Exosomes, and Alzheimer's Disease. These 2 articles were Meta-analyses, Randomized Controlled Trials, clinical trials, and Systematic Reviews. The rest were Literature review articles. These articles were till the year 2024. Appropriate studies were isolated, and important information from each of them was understood and entered into a database from which the information was used in this article. The clinical trials on Mesenchymal Stem Cell Exosomes for Alzheimer's Disease were searched on clinicaltrials.gov. Results: Several experimental investigations have shown that MSC-Exo improves cognitive impairment in rats. In this review paper, we summarized existing understanding regarding the molecular and cellular pathways behind MSC-Exo-based cognitive function restoration, with a focus on MSC-Exos therapeutic potential in the treatment of Alzheimer's disease. Conclusion: AD is a significant health issue in our culture and is linked to several important neuropathological characteristics. Exosomes generated from stem cells, such as MSCs or NSCs, have been examined more and more in a variety of AD models, indicating that they may be viable therapeutic agents for the treatment of diverse disorders. Exosome yields may be increased and their therapeutic efficacy can be improved using a range of tailored techniques and culture conditions. It is necessary to provide standardized guidelines for exosome manufacture to carry out excellent preclinical and clinical research.

Keywords: Alzheimer's disease; mesenchymal stem cells; drug discovery and development; Neurosurgery; Neurology; Novel theapies

1. Introduction

Alzheimer's disease (AD) is the most common type of dementia and is a chronic progressive disease. With advanced age being the strongest risk factor, AD affects 1 in 9 people aged 65 or older, and over 6 million people currently suffer from AD in the US alone. Given the direct relation of Age to the disease, AD has rapidly become a major public health problem worldwide. The burden of AD is expected to increase with the aging population with an estimation of 152 million by 2050. Alzheimer's Disease causes neurodegeneration and loss of neurons in the brain which is irreversible and can eventually be life-threatening. AD is the sixth-leading cause of death[1]. As stated by the Alzheimer's Association, one in three older Americans dies with Alzheimer's every year, and the number of deaths has more than doubled between 2000 and 2021. AD is recognized clinically by the

 doi:10.20944/preprints202408.0229.v1

accumulation of β-a amyloid peptides and the formation of hyperphosphorylated tau aggregates in neurofibrillary tangles (NFT). As the disease progresses, it results in the death of brain neurons, including cholinergic neurons which are crucial for memory function and learning. Therefore, the patient will present with symptoms such as loss of memory and executive functions, lack of communication, and lack of object and place identification, known as aphasia and agnosia. AD risks include Aging, Diabetes, cardiovascular diseases, and genetics. B-amyloid peptides are usually on chromosome 21, therefore, Down's syndrome patients have a higher risk for developing early-onset AD as they have 3 copies of chromosome 21. With all the hazards caused by cholinergic neuron damage, three cholinesterase inhibitor drugs (eg: Donepezil, rivastigmine, and galantamine) approved by the FDA are currently being used as the main therapy for AD to block the breakdown of acetylcholine and to increase its availability at synapses, however, they only aim to improve cognitive function temporarily without altering the inevitable progression of the disease or reversing the neuronal damage. (NMDA and AMPA), not to mention their adverse effects on the elderly such as syncope, bradycardia, and reduced cardiac output[2,3].

As of this day, there is no definitive treatment for Alzheimer's, which has become an epidemic and will continue to increase globally with the aging population. For this reason, new effective clinical and medical approaches are urgently needed for this irreversible disease and there are no treatment options at this moment. Recent evidence has shown that mesenchymal stem cell-derived exosomes (MSCs) hold significant promise as a potential therapeutic agent for AD due to their ability to migrate and mediate damage repair, enhance neurogenesis, and replace lost neurons [4–6]. This study aims to explore the pathophysiology of AD and compiles recent preclinical and clinical findings on the use of stem cell-derived exosomes in its treatment.

2. Pathophysiology of AD

Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive memory loss and cognitive impairment. The pathophysiology of AD is primarily caused by three main hallmarks: the accumulation of amyloid-beta (Aβ) plaques, also known as senile plaques, the presence of neurofibrillary tangles of hyperphosphorylated tau protein, and the marked neuronal degeneration. Aβ proteins are chemically "sticky" and generally build up to plaques that if accumulated in the brain, can clump and block cell-to-cell signaling at synapses. [7] They also activate the brain's immune system which triggers inflammatory responses that further damage the disabled neuron cells. [8–10]. Neurofibrillary tangles are tangles of the protein called Tau, which is a microtubule-associated protein that stabilizes neuronal microtubules under normal physiological conditions; however, in AD, tau becomes phosphorylated causing toxic aggregates that deposit within the neuron. These pathological changes are associated with the loss of cholinergic neurons, synaptic dysfunction, and glial activation, contributing to widespread atrophy of the hippocampus and subsequently the cerebral cortex. While the exact pathophysiology of AD as well as its treatment remains a mystery, there are two proposed hypotheses based on these pathologic abnormalities.

The Cholinergic Hypothesis: states that reduced levels of acetylcholine caused by neuronal loss play a crucial role in the development of Alzheimer's disease. Acetylcholine is important for several physiological processes such as memory, attention, learning, and other critical cognitive functions hence why Beta-amyloid is believed to affect cholinergic function and impair acetylcholine release negatively.

The Amyloid Hypothesis: the widely accepted hypothesis suggests that Alzheimer's Disease (AD) is caused by the accumulation of amyloid beta (Aβ) peptides, particularly Aβ42, which are derived from the amyloid precursor protein (APP) through the actions of β- and γ-secretase enzymes. Elevated levels of Aβ42 lead to the formation of toxic amyloid aggregates that damage neurons[11,12].

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Braak and Braak Staging

A staging system introduced in the late 1980's by two scientists: T Heiko Braak and Eva Braak, categorizes the progression of neurofibrillary tangles into six stages. It's widely recognized diagnostic criteria provided by the National Institute on Aging and the Reagan Institute [13]. Neurofibrillary tangles have a stronger correlation with dementia severity in AD patients compared to amyloid plaques, although amyloid is still a major hallmark of the disease. The pathogenes of AD are often likened to a "trigger and bullet" scenario [14]. Amyloid is considered the trigger that initiates the disease. At the same time, tau, in the form of neurofibrillary tangles, acts as the bullet that leads to neurodegeneration and cognitive impairment. Moreover, the Accumulation of amyloid beta (Aβ) in cerebral blood vessels, termed cerebral amyloid angiopathy (CAA), can lead to faster deterioration, and cognitive, and memory decline in AD patients [15].

3. Neuroregeneration Therapy

Stem Cells

Are a unique type of cells with the ability to proliferate, self-renew, and differentiate into various mature cell types. Stem cells have been used for decades especially in Parkinson's Disease (PD), with significant success in numerous cell transplantation studies [16–18]. Therapeutic strategies involve direct cell replacement, secretion of neurotrophic and growth factors, and activation of endogenous neural precursor cells [19–21]. There are multiple types of stem cells including Embryonic stem cells (ESCs), induced pluripotent stem cells(IPSCs), Neural stem cells (NSCs), and Mesenchymal stem cells(MSCs). In our study, we focus on evaluating mesenchymal stem cell's proposed role in treating Alzheimer's disease. MSCs are adult multipotent cells that can be obtained from adult tissues such as (bone marrow, skin, umbilical cord, adipose tissue, spleen, etc.[22]) they can regenerate into different cell types such as bone, cartilage, fat, lung, liver, and muscle[23]. They possess remarkable therapeutic potential, particularly in orthopedic applications. They also play roles in regenerative medicine and cancer treatment as anti-inflammatories, immunosuppressives, and vehicles for gene/protein therapy. Mesenchymal stem cells (MSCs) have been shown to promote the expression of anti-inflammatory factors like interleukin-10 and prostaglandin: however, It is important to explore the underlying mechanisms to determine if MSC transplantation directly influences inflammation or if the effects are due to tissue damage. Understanding this distinction is critical for optimizing MSC-based therapies. Further research is needed to clarify these mechanisms and their implications for treating neurodegenerative diseases [24]. In vitro, human MSCs can significantly increase the number of neurons in the hippocampus and induce neural precursor cells (NPCs) to differentiate into neurons via the Wnt signaling pathway. Additionally, human MSCs can lower Aβ42 levels by stimulating autophagy both in vitro and in vivo[22]. Figure 1 compares neurons of the healthy cortex and diseased by Alzheimer's. Figure 2 depicts the main pathological markers in a diseased Alzheimer's.

 doi:10.20944/preprints202408.0229.v1

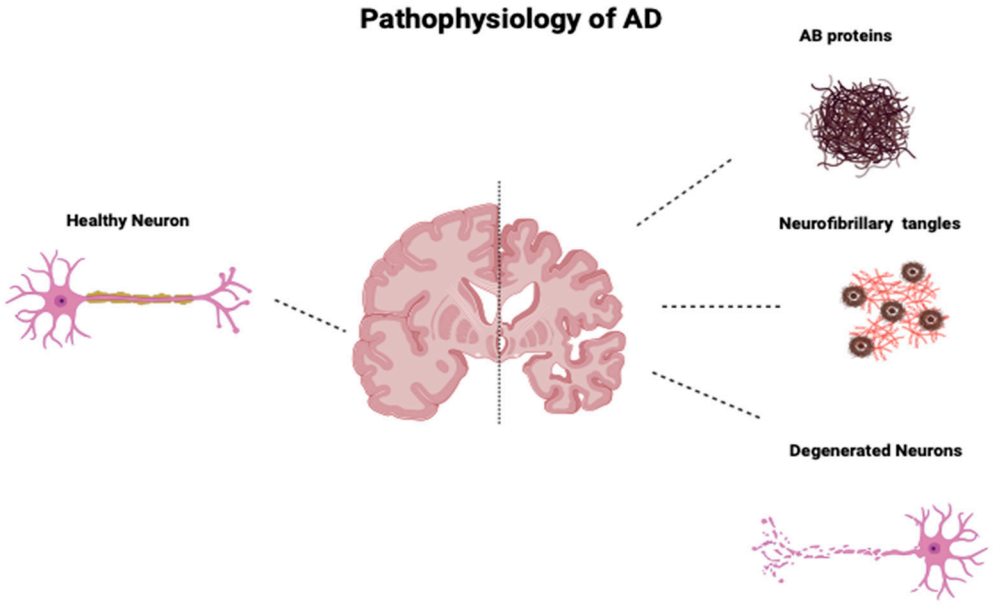

Figure 1. Comparison of Neurons of the healthy cortex and diseased by Alzheimer's. AD's main pathologic changes are an accumulation of AB proteins, neurofibrillary tangles of tau protein, and loss and degeneration of Neurons.

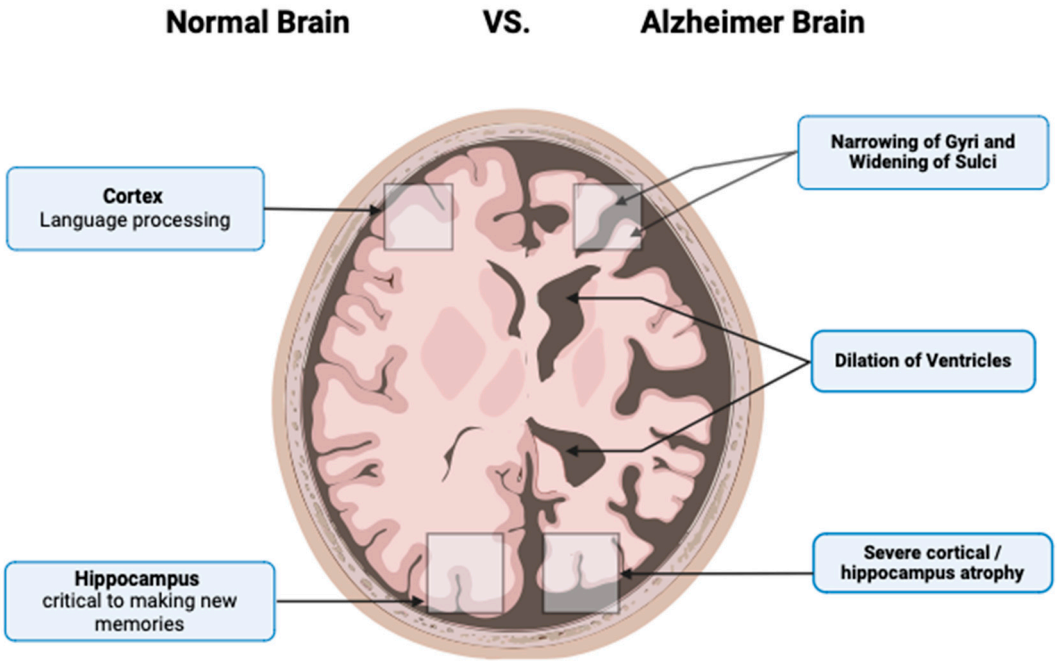

Figure 2. Main pathological markers in a diseased Alzheimer's cortex include the Narrowing of Gyri and sulcus, significant Dilation of ventricles, and severe cortical atrophy that involves important brain functions such as language processing and making new memories.

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3.2. Exosomes

3.2.1. Isolation of Exosomes

Ultracentrifugation - A conventional technique frequently employed to separate exosomes generated from stem cells is ultracentrifugation. Researchers can process a huge amount of samples with this technology. Large debris is first removed with low centrifugal force, then crude exosomal fractions are pelleted with high centrifugal force. Exosomes that have been identified and deemed crude are utilized in research without additional purification or are refined using density gradient ultracentrifugation [25].

Size-Based Filtration: To exclude any further extracellular vesicles that are bigger than 150 nm or less than 50 nm, biofluid samples can be run via size-exclusion chromatography or certain pore-sized filters. Exosome enrichment is not possible with this technique. After these filtering stages, ultracentrifugation might be utilized if exosome enrichment is required [26].

Precipitation of Polymers - To collect the vesicles with an exosomal size range (30–150 nm) and decrease exosomal solubility, which permits exosomes to precipitate, biofluid samples are mixed with a polymer, such as polyethylene glycol (PEG), to use polymer precipitation techniques for exosome purification. With standard laboratory equipment, this method is possible, but it depends on the polymer net size[27].

Immunoaffinity- The ability to withstand The particular proteins (antigens) found on exosomal membranes serves as the foundation for this technique. Particular antibodies coupled to a carrier, such as agarose or magnetic beads, can be used to extract a particular subtype of exosomes with great purity [62]. This approach is extensively employed in many applications, including fundamental research and clinical investigations, such as illness diagnosis and prognosis because it has no volume constraint and is easily carried out with ordinary laboratory instruments. However, the materials needed for this process are often pricey [28].

3.2.2. Cell Culture

Mesenchymal stem cells (MSCs) are grown under carefully controlled conditions to ensure they develop properly for research or therapeutic purposes. Usually, MSCs are cultured in a basic growth medium like Dulbecco's Modified Eagle Medium (DMEM), which is often enriched with fetal bovine serum (FBS). Fetal bovine serum (FBS) is used to provide the nutrients and growth factors needed for the cells to grow well. To keep the cultures free from contamination, a mix of antibiotics and antifungal agents is added. These cells are usually maintained in an environment with controlled humidity and 5% CO2 at a temperature of 37°C, which closely resembles their natural surroundings. In clinical applications, it's crucial to decrease or eliminate animal-derived components, so serum-free media is often used. The cells are then cultured until they reach a certain level of growth, which ensures they stay healthy and maintain their ability to develop into different types of cells[29].

3.2.3. Working Model Biogenesis, Secretion, and Uptake

To understand the process of exosome synthesis, secretion, and uptake, tremendous effort has been made. The early sorting endosomes (ESEs) are first formed by endocytosis of external components and cell surface proteins, together with the inward budding of the plasma membrane. Intraluminal vesicles (ILVs) are formed by the invagination of the limiting endosomal membrane during the maturation phase of endosomes[30]. Many molecular machinery components influence the production of ILVs, but the endosomal sorting complex needed for transport (ESCRT) machinery complex is the primary regulator of this process. About thirty proteins make up the ESCRT mechanism, which assembles into four complexes (ESCRT-0, ESCRT-I, ESCRT-II, and ESCRT-III) and related proteins (including Vps4, Alix, and Tsg101) that are involved in the production of ILVs[31]. The ESCRT-I/II/III complex induces membrane deformation, ESCRT-0 sequesters ubiquitinated cargo proteins, and the Vps4 complex facilitates vesicle scission and recycling of the ESCRT-III complex[32]. A different pathway of exosome biogenesis, including tetraspanins, ceramides, cholesterol,

 doi:10.20944/preprints202408.0229.v1

phosphatidic acids, and heat-shock proteins (HSPs), is produced apart from the processes of the ESCRT machinery[33]. RNA loading into exosomes via lipid mediation relies on cargo domains and self-organizing lipids. Then, cytoplasmic substances including RNA, proteins, and lipids are encased in the lumen and gathered inside the late endosome to form multivesicular bodies (MVBs)[34]. The Golgi complex and endoplasmic reticulum play a role in the process. Some MVBs are carried to lysosomes for disintegration by fusing with autophagosomes or not, while other MVBs fuse with the plasma membrane through the cytoskeletal and microtubule network of the cell, eventually releasing their vesicles into the extracellular environment as exosomes[35]. Ceramides are more abundant in secreted MVBs than in degradative MVBs. It has been suggested that the distinct outcomes experienced by MVBs might be connected to the coexistence of subpopulations inside cells. Exosomal markers include proteins including flotillin, Alix, TSG101, tetraspanins (CD9, CD63, and CD81), and the endosome pathway, which is involved in exosome creation and release [36]. Furthermore, ceramide and sphingomyelin, two components of the lipid raft, are highly concentrated in exosomes [37].

4. Exosomes as AD Biomarkers

Currently, biomarkers of AD pathology (Aβ1-42/1-40, T-Tau, p-Tau), cognitive behavioral syndrome (CBS), and positron emission tomography (PET)/CT are the major methods used to diagnose AD. However, because AD has a latent onset, bioimaging (PET/CT) and CBS-based diagnosis are frequently delayed. Biomarkers for monitoring, particularly with CSF, were intrusive and caused harm to patients. Currently, there are no reliable techniques for diagnosing or predicting AD [38]. AD is diagnosed in the clinic using a variety of methods, such as bioimaging, biochemical analysis, and questionnaires. The results of bioimaging, such as PET or CT, might be influenced by other dementia disorders, and the procedure is expensive. Surveys are prone to subjectivity and are often influenced by the survey taker [38]. Neuron adhesion molecules and neurotransmitter receptors are two examples of the distinctive receptors found in nervous tissues present in exosomes generated from neurons. The mediating function of those receptors is essential for the interactions that exosomes have with target cells. They make it easier for exosomes to bind and be taken up selectively, which allows their "cargo" to be delivered to certain cellular targets [39]. These receptors' presence on exosomes makes it easier to use them for diagnostic purposes in neurodevelopmental disorders (NDDS). Blood, urine, and saliva are just a few of the bodily fluids from which exosomes from AD patients may be separated. Therefore, the ease of collection and non-invasiveness of exosomes, in addition to their stability following sample capture, further validate their usefulness in the field of AD and associated illnesses diagnoses. Ruihua Sun et al. showed that exosomes obtained from the blood of AD patients were reduced in size and number compared to those from healthy controls using transmission electron microscopy (TEM) and nanoparticle tracking analysis (NTA) [40]. Antonio Longobardi et al. discovered that AD patients' blood had 40% fewer exosomes than that of healthy controls, which is in line with that conclusion [41]. Exosomes from AD patients, according to different research, were bigger than those from healthy controls. At the moment, there is insufficient evidence to substantiate the precise variations in exosome size between AD patients and healthy controls. Exosome size variation may be influenced by several variables, such as sample origins, methods of collection, and procedures of analysis. To confirm these variations, learn more about their significance in the pathophysiology of AD, and assess their potential diagnostic use, more research is required[42]. Exosome morphology may be one factor in the diagnosis of AD, however, standardizing the methods for extracting and examining exosomes is necessary. An essential part of exosomes is proteins. β-site APP cleaving enzyme 1 (BACE-1), soluble peptide APP beta (sAPPβ), soluble peptide APP alpha (sAPPα), γ-secretase, and Aβ1-42 were detected in the exosomes obtained from AD patients [43]. These findings are strongly associated with the etiology and development of AD. Exosome lipids have the potential to be useful biomarkers for the diagnosis of AD. Su et al. discovered using semi-quantitative mass spectrometry that the brain-derived exosomes from AD patients had considerably higher levels of lipids and plasmalogen glycerophosphoethanolamine (PE) molecules (p-36:2, p-38:4) on their membranes than in the control groups [44]. Another type of "cargo"

 doi:10.20944/preprints202408.0229.v1

from exosomes, miRNAs, has drawn more attention because of their function in regulating gene expression. It was established that exosomes from AD patients have significantly different miRNAs than exosomes from healthy controls [45]. According to Liu et al., in the exosomes from the serum of AD patients, 19 miRNAs (such as miR-15a-5p) were elevated while 5 other miRNAs (such as miR-15b-3p) were downregulated. By using microarray analysis to examine the expression levels of miRNA in the CSF of AD patients[46]. Gamez-Valero et al. discovered that the expression of miR-132-5p, miR-485-5p, and miR-125b-5p was up while that of miR-16-2, miR-29c, and miR-331-5p was lowered [47]. The "cargo" and amounts of biomarkers formed from exosomes have changed, indicating their great potential for use in the diagnosis of AD. Exosomes obtained from diverse bodily fluids guarantee their accessibility and availability for diagnosis purposes. Moreover, exosomes obtained from neurons and blood exhibit superior creditability in comparison to CSF biomarkers or PET/CT. Table no– summarizes the biomarkers in diagnosing AD. Table 1 summarizes the use of biomarkers in the diagnosis of AD

Table 1. Summary of biomarkers in diagnosis of AD and their source.

Source	Sample	Biomarker Protein Change
Neural	Plasma	P-T181-tau, P-S396-tau, and Aβ1–42 ↑, NRGN, REST ↓ compared to CNC and stable MCI patients [48].
Neural	Plasma or serum	Total Tau, P-T181-tau, P-S396-tau and Aβ1–42 ↑compared to controls[49]
Neural	Plasma	cathepsin D, LAMP-1, ubiquitinylated proteins ↑, and HSP70 ↓ compared to controls and FTD[50]
Neuronal	Plasma or serum	Aβ42, T-tau, and P-T181-tau ↑ compared to aMCI and control groups[51]
Neuronal	Plasma	synaptophysin, synaptopodin, synaptotagmin-2, and neurogranin ↓ compared to controls[52]
Neuronal	Plasma	NPTX2, NRXN2α, AMPA4, NLGN1 ↓[53]
Astrocyte	Plasma	complement proteins, IL-6, TNF-α, IL-1β ↑; complement regulatory proteins (CD59, CD46, DAF), complement receptor type 1 ↓ compared to controls[54]
Astrocyte	Plasma	BACE-1, (s)APPβ ↑, GDNF ↓ compared to controls[55]

5. Therapeutic Properties of Exosomes and Application in Alzheimer's Disease

Mesenchymal stem cells (MSCs) are shown as a potential treatment and promise for AD for their regenerative properties such as secretion of growth factors, anti-inflammatory proteins, membrane receptors, and microRNAs (miRNAs) that can block apoptosis, decrease neuronal loss, and stimulate neurogenesis, synaptogenesis, and angiogenesis. [56,57]Their anti-apoptotic and antioxidant qualities aid in preventing Neuronal cell death. Furthermore, MSCs secrete growth factors that encourage neural progenitor cells to improve neurogenesis, such as glial cell line-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF). MSCs produce neurotrophins including VEGF, HGF, NGF, BDNF, and neurotrophin-3 after they migrate to injured brain regions and interact with brain cells. [58–60] These neurotrophins support neuritic formation and neurorestoration, which helps with neurological recovery.

Moreover, MSCs regulate the immune response by suppressing inflammatory microglia (M1) and activating anti-inflammatory microglia (M2), which helps in preventing tissue damage caused by chronic neuroinflammation. They also promote the accumulation of microglia around Aβ deposits to increase Aβ clearance and to stimulate autophagy that aids in the lysosomal removal of Aβ

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plaques. These actions contribute to the therapeutic potential of MSCs in neurodegenerative disease treatment[61,62]

Numerous studies reveal that soluble factors produced from MSCs can alter the neuroprotective characteristics of Alzheimer's disease (AD) models. For instance, Kim et al., report that MSCs derived from human umbilical cord blood have a neuroprotective effect against Aβ toxicity in vitro by secreting galectin-3. Moreover, transplanting these MSCs into mice with AD transgenics causes microglia to produce MME/neprilysin, which improves Aβ clearance through soluble ICAM-1 secretion [63].

According to Lee et al., bone marrow-derived MSCs exert neuroprotective effects on AD models that are underpinned by cellular and molecular mechanisms, and CCL5, which is secreted from blood-derived MSCs, recruits alternative microglia to the AD brain, thereby reducing Aβ deposition and memory impairment through the production of IL-4 and MME[64]. These data indicate that MSC treatment in Aβ-treated cells remarkably boosts autolysosome formation and autolysosomal catabolic function, which contribute to enhanced neuronal survival. Figure 3 depicts different sources of Mesenchymal stem cells and its properties of importance in AD.

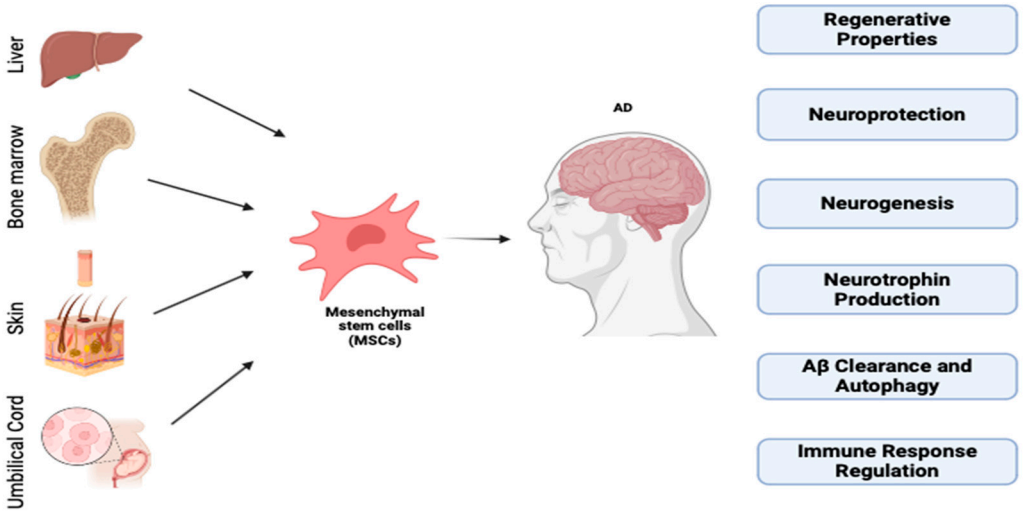

Figure 3. Different sources of Mesenchymal stem cells and their properties of importance in AD Treatment.

Therapeutic Mechanisms of Mesenchymal Stem Cells (MSCs) in Alzheimer's Disease (AD). MSCs derived from various sources, such as bone marrow, adipose tissue, umbilical cord blood skin, liver, and others, exhibit regenerative properties by secreting growth factors, anti-inflammatory proteins, membrane receptors, and miRNAs that block apoptosis, decrease neuronal loss, and stimulate neurogenesis, synaptogenesis, and angiogenesis. They provide neuroprotection through their anti-apoptotic and antioxidant effects and promote neurogenesis by releasing growth factors like GDNF and BDNF. Additionally, MSCs produce neurotrophins such as VEGF, HGF, NGF, BDNF, and neurotrophin-3, supporting neuritic formation and neurorestoration, and regulating the immune response by suppressing inflammatory microglia (M1) and activating anti-inflammatory microglia (M2), preventing tissue damage and enhancing Aβ clearance through microglial accumulation and autophagy stimulation.

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6. Clinical Trials

	Number	Therapy	Source	Status	Pathway	N=	Study location
1	NCT02600130	Cells	Bone marrow	Completed	Intravenous	33	USA
2	NCT03117738	Cells	Adipose tissue	Completed	Intravenous	21	USA
3	NCT02054208; NCT03172117 (Kim et al., 2021)	Cells	UCB	Completed; Unknown	Intracerebroventricular	45	South Korea
4	NCT01297218	Cells	UCB	Completed	Intracerebral	9	South Korea
5	NCT02833792	Cells	Bone marrow	Recruiting	Intravenous	40	USA
6	NCT04040348	Cells	Umbilical cord	Active, not recruiting	Intravenous	6	USA
7	NCT04482413	Cells	Adipose tissue	Not yet recruiting	Intravenous	80	USA
8	NCT04954534	Cells	UCB	Not yet recruiting	Intracerebroventricular	9	South Korea
9	NCT02672306	Cells	Umbilical cord	Unknown	Intravenous	16	China
10	NCT01547689	Cells	UCB	Unknown	Intravenous	30	China
11	NCT01696591	Cells	UCB	Unknown	Intracerebroventricular	9	South Korea
12	NCT04228666 [65,66]	Cells	Adipose tissue	Withdrawn Due to covid-19 pandemic	iv	24	USA
13	NCT04855955	Cells	Adipose tissue	completed	N/A	1	USA
14	NCT04388982	Cells	Adipose tissue	recruiting	Nasal drip	9	China
15	NCT02899091	Cells	N/A	recruiting	iv	24	South Korea
16	NCT04684602	Cells	N/A	recruiting	N/A	5000	USA

7. Advantages and *Challenges*

Mesenchymal stem cells (MSCs) ability to differentiate into various cell types, including those involved in the production of bone, cartilage, and adipose tissue, makes them highly advantageous

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for use in neurodegenerative diseases. Some studies have shown their anti-tumorigenic effects such as Clarke et al., who stated that breast cancer cells cultured in an MSC-conditioned medium exhibit significant migratory inhibition compared with cells cultured in a standard medium[67,68]. Similarly, Bruno et al. showed tumor cell growth inhibition by MSCs. A human hepatocellular carcinoma cell line (HepG2), a human ovarian cancer cell line (Skov-3), and Kaposi's sarcoma cell lines co-cultured in the presence of BM-MSCs exhibited reduced in vitro growth[69,70]. MSCs can also be obtained using minimally invasive means, such as bone marrow, adipose tissue, and umbilical cord blood. They can affect immune system function and reduce inflammation, which is very helpful for treating inflammatory and autoimmune diseases. Their therapeutic value is increased by the minimal risk of immunological rejection in transplant recipients.

While SCs have the potential to repair and regenerate damaged cells, the precise ways in which they might work are still not fully understood. Most of the studies show that a single transplantation of MSCs is safe and does not induce an immune response. However, repeated administration of MSCs may result in the production of allo-antibodies. So far, there have been only a few clinical trials where SCs were transplanted into AD patients, and the results from animal studies haven't provided solid proof that these therapies are either safe or effective. Andrzejewska et al also reported Antibacterial activities and interactions of the MSC secretome with cancer cells[71]. Additionally, there are a lot of social, ethical, and regulatory issues that make research difficult and limit federal funding. In the U.S., the FDA has only approved stem cells from cord blood, but many clinics are offering various unregulated treatments, often charging a lot of money. To make sure these treatments are safe and effective, especially for complicated diseases like Alzheimer's, it's really important to have ongoing patient monitoring and clearer regulatory guidelines.

8. Conclusion

MSC-Exos plays a crucial role as a mediator in the information transfer between MSCs and recipient cells, such as microglia and neurons. Improvements in cognitive function are brought about by MSC-Exo-derived miRNAs, trophic factors, enzymes, immunomodulatory, and pro-angiogenic chemicals, which stimulate neurogenesis and inhibit inflammation-induced damage to hippocampus neurons. Crucially, MSC-Exos generated immunomodulation and neuroprotection that was either identical to or superior to that of their parent MSCs in terms of immunomodulation. The effects of MSC-Exos are independent of the local tissue microenvironment. MSC-Exos are immune-modulatory and neuroprotective cells that do not change in response to various stimuli, unlike MSCs, which change in phenotype and function upon engraftment in different tissue microenvironments. This suggests that MSC-Exos may find clinical application in treating neurocognitive diseases. MSC-expos is a unique cell-free therapeutic agent, that offers incomparable benefits over cell-based therapy, which is thought to be a potential substitute in the treatment of AD.

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, S.S. and H.M.; methodology, S.S.; software, S.S.; validation, S.S., H.M. and B.L.; formal analysis, T.A.; investigation, T.A.; resources, B.L.; data curation, S.S.; writing—original draft preparation, S.S., H.M., T.A., B.L.; writing—review and editing, S.S., H.M., T.A., B.L.; visualization, S.S., H.M., T.A., B.L.; supervision, S.S.; project administration, B.L.; funding acquisition, B.L.

Funding: This research received no external funding

Institutional Review Board Statement: Not applicable

Informed Consent Statement: Not applicable

Data Availability Statement: We encourage all authors of articles published in MDPI journals to share their research data. In this section, please provide details regarding where data supporting reported results can be found, including links to publicly archived datasets analyzed or generated during the study. Where no new data were created, or where data is unavailable due to privacy or ethical restrictions, a statement is still required. Suggested Data Availability Statements are available in section "MDPI Research Data Policies" at https://www.mdpi.com/ethics.

Acknowledgments: NONE.

 doi:10.20944/preprints202408.0229.v1

Conflicts of Interest: The authors declare no conflicts of interest.

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