How do stem cell-derived cells slow down or reverse cognitive decline in Alzheimer's Disease patients?

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Abstract:

Alzheimer's Disease (AD) is one of the leading causes for dementia and has no standout treatment. Most therapies only address short term AD symptoms, and fail to cure it as a whole. They provide marginal assistance, necessitating for there to be methods addressing AD's multifaceted pathologies, like amyloid-beta plaque deposits and neuroinflammation. Stem cell therapies, particularly with mesenchymal stem cells (MSCs) and MSC-derived extracellular vesicles (EVs), hold promise for neuronal proliferation.

Objectives: The overview addresses MSC and EV therapy for AD, including the potential it has, its mechanisms, the advances made , and its limitations, with emphasis on how EV therapy overcomes the limitations of MSC therapy.

MSCs demonstrated efficacy in AD models through immunomodulation (e.g., NLRP3 inflammasome inhibition), enhancement of amyloid-beta clearance, promotion of synaptic repair, and neurogenesis via secreted neurotrophic factors. However, the process of getting MSC therapies standardized has been hampered by poor biodistribution, some risks of tumorigenesis and immunogenicity, and a lack of protocols. In contrast, MSC-derived EVs have the many therapeutic benefits of MSCs, like by delivering protective cargo (e.g., miR-21-5p) that modulates neuroinflammation and tau pathology, but with superior safety and biodistribution profiles. Their nanoscale size enables enhanced blood-brain barrier penetration, and they eliminate most of the risks associated with cell transplantation. Despite this promise, EV therapies face their own hurdles, including isolation and standardization complexities, limited

intrinsic amyloid clearance, and unanswered questions regarding optimal dosing and long-term efficacy. Conclusion: MSC treatment is effective but restricted. EV strategies provide targeted, safer alternatives. Standardization, better delivery through bioengineering, and investigating combination therapies are crucial to success in the future. EVs have the potential to transition AD treatment from symptom control to disease modification.

Introduction:

Alzheimer's Disease is the leading cause of dementia, and a significant contributor to elderly mortality rates. Over 57 million people worldwide have dementia with 70% of them having Alzheimer's as a precursor, and this number is also set to triple in the next 3 decades. It is also a huge socioeconomic burden on elderly people (Rather et al., 2023) Paying for the many treatments and drugs, as well as finding support systems in family, friends, relatives, is quite difficult.

Alzheimer's is a progressive neurodegenerative disorder that negatively affects the victim's cognitive function, severely impacting their ability to do even the most trivial tasks and leading to irreversible cognitive decline. It is characterized by synaptic dysfunction, neurofibrillary tangles caused by phosphorylated tau proteins, and the mass increase of extracellular amyloid-beta peptides between neurons, (Aβ plaques), (Liu et al., 2020). \The global rise in Alzheimer's Disease (AD) underscores the urgent need for effective treatments. However, current therapeutic approaches remain limited, partly because the underlying pathophysiology of AD is not yet fully understood. Current treatments like N-methyl-D-aspartate (NMDA) antagonists and acetylcholinesterase inhibitors only offer short-term symptom relief, not long-term cures that stop disease progression. (Reza-Zaldivar et al., 2023). Consequently, more and more of the scientific community have been looking towards the rapidly improving technology of stem cells and extracellular vesicles, as they can target many pathophysiological pathways simultaneously.

Despite promising preclinical results, the efficacy of stem cell therapies within human AD patients remains ambiguous. The objective of this study is to address the question: How do stem cell-derived therapies slow, or reverse cognitive decline within AD patients; and fill any gaps left by other papers.

Methodologies:

This report is founded on an integrated narrative review of published research relevant to stem cell and extracellular vesicle remediations for Alzheimer's disease. The general objective was to integrate understanding regarding mechanisms, efficacy, and constraints of mesenchymal stem cell (MSC) and MSC-derived extracellular vesicle (EV) therapy, calling special attention to how EV-centered methodologies may sidestep problems inherent to whole-cell therapy.

An extensive search of the published literature was accomplished through use of PubMed and Google Scholar databases to uncover appropriate peer-reviewed articles that appeared between the years 2015 and 2024. The years sought to point out recent findings in the area. Key search terms were: "Alzheimer's disease," "mesenchymal stem cells," "MSC," "extracellular vesicles," "exosomes," "EV," "cognitive decline," and "neurodegeneration." Boolean terms (AND, OR) were employed to successfully combine these terms.

The title and abstract screens started with the first search results. Articles that would receive full-text evaluation had to be original research articles or systematic reviews published in English and directly relevant to MSC or EV usage in models or Alzheimer's disease patients. Articles studying other cells than MSCs or other neurodegenerative diseases than AD were not considered.

Data from articles chosen in this review were extracted and thematically synthesized to yield answers to the review's key questions: MSCs' and EVs' mechanisms of actions, proof of

efficacy from both clinical and preclinical studies, and overarching problems in both therapy approaches. Due to heterogeneity between and among studies in designs, models, and outputs, synthesis was carried out qualitatively through narrative evaluation instead of quantitative meta-analysis. Through this method, comprehensive explorations about the status quo on research in the topic could be conducted, identification of consensus findings achieved, and discussions about contradictory results and dominant knowledge gaps accomplished.**MSC Therapies: Clinical Progress and its Mechanisms**

A promising new pathway for treatment is the usage of mesenchymal stem cells, or MSCs. They help regulate neuroinflammation, improve synaptic repair and growth, reduce hyperphosphorylation of tau proteins, and reduce Aβ plaque by increasing their clearance through accelerating microglial growth around plaque deposits. (Hernández & García, 2021; Reza-Zaldivar et al., 2023). Additionally, MSCs hold strong anti-inflammatory properties through inhibiting the NRLP3 inflammasome in microglia, which reduce the amount of neurotoxic cytokines like interleukin-1 beta (IL-1β), (Wang et al., 2022). Furthermore, MSCs derived from human umbilical cord tissue have shown even more benefits, like stimulating neurogenesis within the hippocampus, and promoting synaptic repair with the help of neurotrophic factors such as the brain-derived neurotrophic factor (BDNF), (Kim et al., 2023). However, there is still controversy over MSC transplantation, with some reports highlighting paracrine effects and others suggesting that direct neuronal differentiation could make up for what MSC-derived therapy lacks. (Cao et al., 2024) This ambiguity poses a fundamental obstacle to standardizing MSC treatments for AD patients.

The clinical translation of these preclinical observations has had inconsistent success, but it points to both the potential as well as limitations of MSC therapy. Early-phase clinical studies have established the safety of MSC delivery in AD patients, with some reporting modest cognitive gains. For example, a phase I study (Kim et al., 2021) using intranasal MSC delivery reported better mini-mental state examination (MMSE) scores in patients with mild AD, without noticeable side effects (Gonçalves et al., 2023). However, these positive and hopeful results have not been universally reproduced, as seen in a phase II study (Baumel, 2025)that was unable to show significant cognitive improvement (Rather et al., 2023). Such disparity in clinical success may be due to numerous factors, ranging from MSC source (bone marrow vs. fat tissue), preparation, route of administration, and patient-related factors like disease stage and genetic background. Of particular concern is the low engraftment efficiency of intravenous delivery, while more direct intracranial injection methods pose increased risks of death. (Cao et al., 2024). These issues highlight the requirement for greater stringency in standardization of clinical trial design and conduct.

As promising as MSCs sound as a future treatment option for Alzheimer's, after conducting animal trials, errors were still being made regularly. The immune system sometimes rejected these stem cells, they were transplanted incorrectly, and the mass proliferation of cells even led to tumors growing. Furthermore, there continues to be a large number of controversies and unanswered questions regarding the usage of MSC therapy for AD. The debate for the perfect source of MSCs is contentious, with bone marrow-derived cells having possessed strong immunomodulatory effects but lacked the same level of neuronal proliferation as other MSC sources, whereas adipose-derived MSCs are more readily available, but their strength in curing AD is still questionable. (Karvelas et al., 2022). Another gap in existing research regards the

timing of intervention, as the majority of clinical trials have targeted mild-to-moderate AD patients, which did not address any potential benefit of MSCs in early or preclinical AD largely (Rather et al., 2023). In addition, the longevity of therapeutic benefits is a huge unknown, as long-term follow-up studies are noticeably lacking in the literature. Scientists are still uncertain whether or not MSC-induced benefits are short-lived or hold the potential to significantly impact AD's progression on the victim (Cao et al., 2024). These gaps in knowledge highlight the necessity for more extensive research aimed at developing standardized protocols and finding trustworthy biomarkers of response to treatment.

Future directions for research should attempt to resolve these limitations with a multi-faceted strategy. Furthermore, the implementation of consensus protocols for MSC isolation, expansion, and quality control is needed to minimize inter-study and inter-clinical variability (Karvelas et al., 2022). Combination therapies like the combination of MSCs with established anti-amyloid medications such as lecanemab or other tau-targeting drugs, could lead to great results and are another promising treatment. (Gonçalves et al., 2023). Vigorous biomarkers, and their neuroimaging processes or cerebrospinal fluid analysis hold the possibility to fundamentally change patient selection and treatment monitoring, not just for AD patients, but for many other neurological diseases as well. (Rather et al., 2023). Most importantly, large phase III trials with long-term follow-up are necessary to conclusively determine the success and safety profile of MSC therapies in heterogeneous AD populations (Cao et al., 2024). It is incredibly important that researchers work to eliminate the variability in MSC procedures, as a solid base understanding and a need for reliability will help create new, more accurate, and effective therapeutic avenues.

EV-Based Strategies: Advantages

Considering the flaws that MSC treatments have, scientists are attempting to replicate the benefits without the high margin of error that comes with it. They have been working on MSC-derived extracellular vesicles, which have replicated the benefits without the risks of incorrect cell transplantation and other negative implications. (Qin et al., 2022; Duan et al., 2023). Additionally, MSC-EVs can cross the blood-brain-barrier (BBB) without much risk, and restore synaptic plasticity. Focus has also shifted towards extracellular vesicle (EV) mediated-therapies. These extracellular vesicles, especially those secreted by MSCs, provided the same benefits as a MSCs, with a much lower immunogenicity, while also transporting neuroprotective microRNA (miRNA). Studies indicate EVs safeguard central nervous system cells through the delivery of proteins, lipid rafts, mRNAs, and microRNAs. This therapy takes advantage of whole cells' neuroprotection with fewer side effects. Preclinical models describe MSC-derived EVs as crossing the blood-brain barrier (BBB) more successfully than whole cells and transporting things vital for stopping AD progression such as miR-21-5p, that suppresses tau hyperphosphorylation and improves plasticity in AD models (Liu et al., 2020), (Reza-Zaldivar et al., 2022). EVs' nanosize offers pharmacokinetic benefits through low immunogenicity and risk of pulmonary entrapment upon delivery. Furthermore, since EVs do not possess the same replicative ability that MSCs have (Karvelas et al., 2022), tumorigenesis is less likely to occur.. EVs also stabilized well on cold chain logistics, and stored stably (Zizhen, Xidi, 2021), increasing their ability to be applied both clinically and commercially. Thanks to its stability, lyophilization (freeze-drying) capabilities, and low reconstitution with minimized loss of function, EVs hold an ideal niche for a variety of therapies. Moreover, EV production faces fewer ethical issues than stem cell therapies as it involves neither destruction of embryos or bulk

cell cultures.

EV Strategies: Where it Lacks

There are still many vulnerabilities that restrict interest in EV-based treatments. Although EVs hold promise for synapse functions and neuroinflammation, they lack the phagocytes present in whole MSCs, leading to less Aβ plaques being cleared (Gonçalves et al., 2023). That implies EV treatments might perform best in early-stage Alzheimer's or as an accompaniment to other amyloid-targeted therapy. This nature of EVs represents a significant setback, impacting efficiency and successfulness depending on cell source, cell culture, and method of separation (Qin et al., 2022). Such variety makes standardization of products and therapy protocols challenging. Prevalent separation methods like differential ultracentrifugation, size-exclusion chromatography, and polymer precipitation—are of varied purity and biological activity and thus make comparability studies complicated (Zizhen, Xidi, 2021).

Furthermore, while the translational clinical translation of extracellular vesicle (EV) therapy holds promise, they are still currently in the early stages. Recently, a 2022 pilot study established that intranasal MSC-derived EV therapy enhanced mild Alzheimer's patients' cognitive markers and showed no side effects, (Qin et al., 2022). These outcomes supported the preclinical data of decreased neuroinflammation and amyloid pathology induced by EVs. However, there are still some issues that must be solved prior to wider clinical deployment. The most critical amongst these issues is EV biodistribution, since intravenous EV delivery at concentrations of <5% resulted in central nervous system delivery (delivering therapeutic agents across the blood-brain-barrier). This delivery problem necessitates higher dosing or new delivery approaches for enhanced uptake into the brain. In contrast with live cells that have the ability to engraft and stay within damaged tissues, repeated EV therapy will be necessary as a result of low

therapeutic dosing of EVs on their own, leaving questions regarding ongoing therapy's feasibility and expense (Karvelas et al., 2022).

Another controversy involves the source of therapeutic effect from EVs: molecular cargo like microRNAs and proteins or membrane constituents like tetraspanins (Liu et al., 2020). This influences therapy design and gives scientists the option between natural and engineered EVs. Another one involves the utilization of autologous versus allogeneic EV sources. Allogeneic cell-line-derived sources provide an option of scalability and quality control but risk eliciting an immune response in chronic diseases like Alzheimer's (Karvelas et al., 2022). Bioengineered EVs with therapeutic cargo like BACE1-targeted siRNA enhance complexity and prospective efficacy but pose safety issues(Zizhen, Xidi, 2021). Engineered siRNA have the potential to unintentionally silence non-target genes because of similarities in their sequences, potentially disrupting normal cellular functions. This is especially concerning in chronic conditions like AD where long-term treatment, care and reports are required.:Exogenous RNA can trigger pattern recognition receptors (Toll-like receptors), potentially causing inflammatory responses. This risk starts to increase when it is repeated many times. Consequently, artificial loading of high siRNA concentrations could disrupt the integrity of the EV membrane, leading to unpredictable biodistribution or cytotoxicity. Furthermore, they could induce adverse effects in the immune system, which is particularly problematic for allogeneic EVs that need repeated dosing to treat AD (Karvelas et al., 2022). Engineered EVs with enhanced BBB penetration could potentially accumulate in non-target organs, though this remains poorly characterized in clinical settings.The additional engineering steps introduce new variables that may affect EV consistency, complicating GMP compliance and safety standardization. The persistence and clearance

mechanisms of bioengineered EVs are not fully understood, raising questions about potential accumulation with chronic use.

Research in EV medicine must be centered on AD therapies. Potency assays and GMP production are crucial (Zizhen, Xidi, 2021). Techniques of bioengineering such as brain-targeting peptides or antibodies can enhance delivery and reduce mis-targeting (Qin et al., 2022). Combining EV and conventional immunotherapy might improve EV's poor capacity to clear amyloids (Rather, et al., 2023). Blood EV profiles and neuroimaging biomarkers are essential to follow up on therapy and classify patients(Liu et al., 2020). Comparative studies of EVs and whole MSCs in AD models need to weigh benefits. EV therapies are promising for AD with advantages over whole-cell therapies regarding safety, delivery, and scalability. Targeted research, however, is required due to challenges in standardization and production. Preclinical evidence suggests these issues need to be addressed and EV biology well understood for successful clinical application. Industry-academic collaboration might alleviate production issues and move therapies forward. Future treatment might be a combination of EV-based strategies as technologies improve for treating complex AD cases. Research should target finding best candidates for EV therapy and defining best protocols to ensure the maximum benefit at the minimum risk.

Scientists should now aim to prioritize key areas like enhancing brain targeting, establishing a proper standard to these therapies, and confirm reliable biomarkers to monitor treatment. (Liu et al., 2020). As more knowledge is gained, and as treatment advances, foundations in EV therapies will become vital for AD treatment strategies, particularly for early intervention. Their unique combination of safety, deliverability, and multifactorial mechanisms

of action positions EVs as a promising next-generation therapeutic platform for neurodegenerative diseases.

Conclusion:

Creating effective solutions to Alzheimer's continues to be an incredibly pressing problem in medicine. Stem cell-based treatment plans, and more specifically those involving MSCs (mesenchymal stem cells) and their derived EVs, have the possibility to be the most effective AD treatment, with the potential to target several facets of AD pathology simultaneously. Although MSC therapies have shown promise in preclinical and early-stage clinical trials it still has some controversies surrounding its safety, and widespread standardization, which have hindered their progress to become used worldwide. EV-based treatments present a hopeful solution to AD, while maintaining many of the therapeutic advantages of MSCs while overcoming a lot of its limitations. EV-based treatments boast an improved safety profile, easier to ship, and possible standardized manufacturing, making them hopeful prospects for efficacious AD therapies. However, more effort is still needed when it comes to EV production and demonstrating its clinical effectiveness. Looking ahead, the best treatment for AD might be a combination strategy - possibly utilizing EVs for neuroprotection and inflammation management in combination with other strategies for amyloid clearance. As the research evolves, collaboration between researchers looking for better solutions, and those working in the industry to implement those solutions, will be necessary to develop these promising therapies effectively. With ongoing innovation and investment, stem cell-derived therapies can potentially bring hope for changing the trajectory of this debilitating disease.

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