A Review of Neurobiological Advancements in Understanding Alzheimer's Disease

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Abstract: In this paper, I delve into the neurobiology of Alzheimer's disease, aiming to understand how it starts and progresses. I investigate potential ways to make the effects of this disease less visible. By keeping up with the latest in Alzheimer's research, I hope to raise awareness about promising and effective treatments to improve the lives of those grappling with this challenging brain condition. Stem cell therapy is emerging as a potential solution for Alzheimer's treatment. Overall, through my review of the published literature, I found that different types of stem cells, such as Ad-MSC, BM-MSC, hESC, iPSC, MGE progenitor cells, MSC, NSC, NPC, OEC, and UC-MSC, are being explored for their therapeutic effects. These stem cells offer benefits, including anti-inflammatory properties and regenerative capabilities. While the field is still in its early stages, the hope is that stem cell therapies could address the challenges posed by Alzheimer's. Ongoing research enhances living conditions for those who have this disease, and determines the most effective methods to administer these therapies. The exploration of stem cells for Alzheimer's reflects an area of study that may contribute to future advancements in managing this challenging neurodegenerative disease and the destructive effects for those who suffer.

Keywords: Alzheimer’s Disease, Stem Cells, Degenerative Diseases, Amyloid Beta

Lay Summary

1. Alzheimer's is a brain disorder that makes people forget things and have trouble thinking clearly. It gets worse over time, affecting memory and how the mind works.
2. It is the most common cause of dementia among older adults.
3. As Alzheimer's gets worse, people may find it hard to do everyday tasks, act differently, and have trouble talking to others.
4. We do not know exactly what causes Alzheimer's, but it has something to do with unusual protein build up in the brain.
5. There is no cure for Alzheimer's right now, but scientists are studying it to find better treatments for the symptoms.

Introduction

Alzheimer's Disease (AD) is a progressive neurological disorder that primarily affects cognitive and executive functions such as memory, attention, and behavior. It is the most common cause of dementia, slowly impairing an individual's ability to carry out daily tasks and after some time, leading to a decline in overall functioning, or death (Alipour et al., 2019). The prevalence of AD is significant and continues to rise globally as populations age. Total payments in 2016 for all individuals with AD and other dementias were estimated at $236 billion (Alzheimer's Association, 2016). As of now, millions of people worldwide are affected by this condition, and the numbers are expected to grow exponentially in the coming decades (McKhann et al., 2011). This not only poses immense challenges for healthcare systems but also emphasizes the urgency to try and understand, diagnose, and effectively treat this debilitating disease (Alipour et al., 2019).

The exact cause of AD is being constantly researched, but it is believed to involve a complex interplay of genetic, environmental, and lifestyle factors (Kyeong-Ah et al., 2018). The accumulation of abnormal protein deposits in the brain, namely beta-amyloid plaques and tau tangles, which we will further explore in this research paper, contributes to the degeneration and eventual death of nerve cells, disrupting communication between brain cells and leading to their gradual deterioration (Kyeong-Ah et al., 2018). This review is going to delve into the current understanding of AD, exploring its pathophysiology, risk factors, diagnostic approaches, ongoing research, and potential treatment strategies through different animal models (Alipour et al., 2019). By examining the multifaceted aspects of AD, this review seeks to contribute to the collective efforts aimed at tackling this devastating condition and integrating various perspectives into a cohesive framework that strives to make this condition more easily understandable for the general public (Elovsson et al., 2024).

Pathological hallmarks; formation of AB plaques, APP, abnormal proteins agitate and cause cell death

One of the putative causes of AD is the interplay of amyloid beta plaques (AB) which are extracellular deposits of the amyloid beta (Aβ) protein mainly in the gray matter of the brain and tau-related neurofibrillary tangles (NFT) (Elovsson et al., 2024). This significantly impacts neural cell survival and function, leading to the degeneration observed in affected brain regions (Elovsson et al., 2024). Degeneration refers to the major loss of neurons, synapses, and brain atrophy in Alzheimer’s disease (Alipour et al., 2019). Understanding the role of amyloid precursor protein (APP) in essential neural processes highlights its relevance in disease progression. Experimental models (discussed later) have explained early AB deposition and its potential implications, shedding light on disease mechanisms (Han & Lu, 2020). Efforts to target AB plaque formation through enzyme inhibitors offer promise in disease intervention (Alipour et al., 2019). Additionally, transplantation studies involving neural stem cells (NSCs) have shown encouraging results by promoting neurogenesis and synaptogenesis, potentially supporting neural cell survival and differentiation via growth factor secretion, notably brain-derived neurotrophic factor (BDNF) (Han & Lu, 2020).

However, further investigations are crucial, particularly in assessing the safety and efficacy of NSC transplantation, including concerns about tumorigenesis and the potential for functional recovery in Alzheimer's patients (Alipour et al., 2019). The new discovery of induced neural stem cells (iNSCs) from various cell types opens new roads for personalized therapeutic approaches, but their full potential and safety profiles require deep exploration, particularly in the context of AD and how effective it will be (Yang et al., 2016).

Animal models of Alzheimer's genially or chemically induced models

The utilization of animal models, both genetically and chemically induced, has been fundamental in exploring potential therapeutic routes for AD (Scheltens et al., 2021). Embryonic stem cells (ESCs) have emerged as promising candidates for cell replacement therapy (Yang et al., 2016). Factors like sonic hedgehog (Shh), retinoic acid (RA), and leukemia inhibitory factors play pivotal roles in directing ESC differentiation (Kwak et al., 2018). Studies employing ESC-derived medial ganglionic eminence MGE-like progenitor cells have shown promising outcomes, where these cells generated functional basal forebrain cholinergic neurons (BFCNs), successfully restoring cholinergic innervation and cognitive function in AD mouse models (Alipour et al., 2019). Similarly, ESC-derived BFCNs, from both mouse and human origins, have demonstrated their potential to differentiate into mature cholinergic neurons and restore cognitive abilities, emphasizing their therapeutic promise (Scheltens et al. 2021).

Another area of research has directly been in human induced pluripotent stem cell iPSC-derived cholinergic neuronal precursors that stimulated neurogenesis and reversed spatial memory impairment in transgenic mouse models (Yang et al. 2016). Moreover, iPSC-derived macrophage-like cells modified to express Aβ-degrading protease showcased decreased plaque deposits and cognitive improvement upon transplantation into AD mice brains (Elovsson et al., 2024).

Furthermore, the transplantation of fetal human neural stem cells (hNSCs) into specific transgenic mice models not only yielded diverse neural cell types, enhanced spatial memory and can be better fitting for humans (Elovsson et al., 2022). These findings collectively highlight the immense potential of stem cell-based therapies in mitigating Alzheimer's pathology and restoring cognitive function, thereby needing continued exploration and refinement in the pursuit of effective treatments (Alipour et al., 2019).

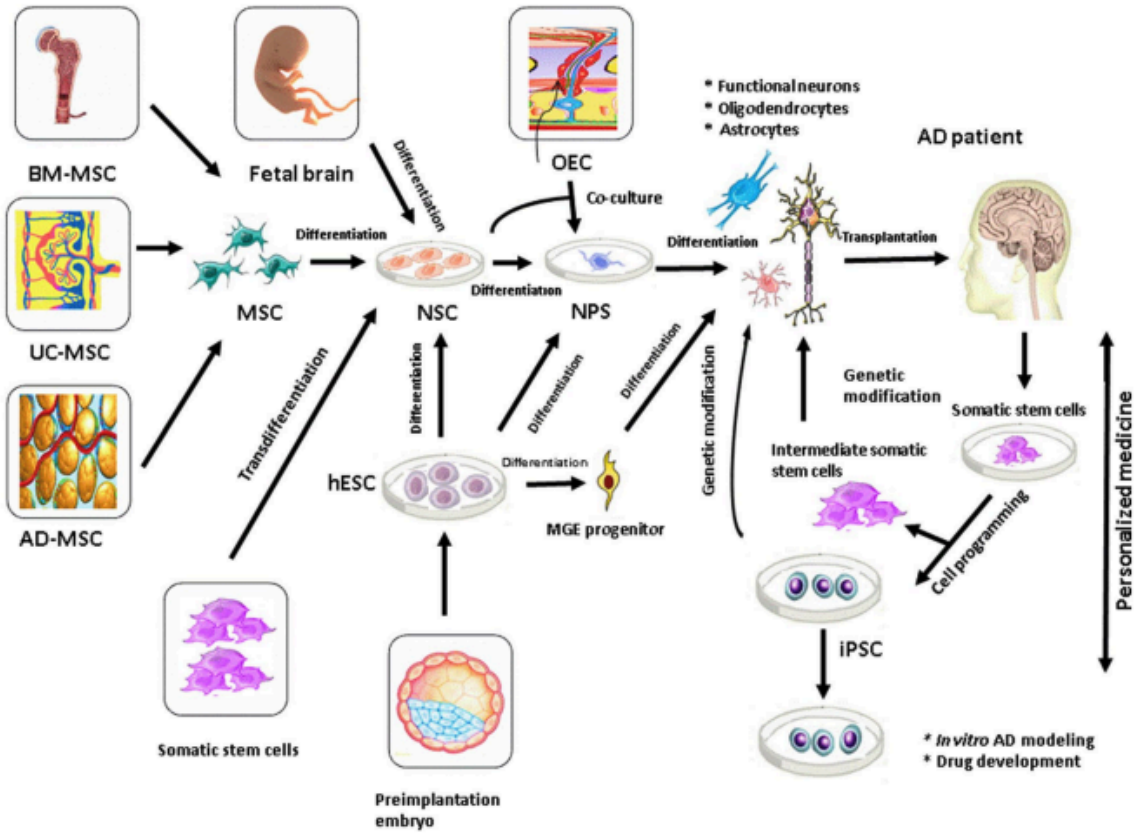
Therapeutic approaches; the immunotherapies that try to reduce the AB plaques

Therapeutic approaches in AD have centered around immunotherapies aimed at reducing AB plaques, distinguishing it from conditions like Parkinson's Disease characterized by the demise of specific nerve cell types (Scheltens et al. 2016). The diverse cell death patterns observed in AD present challenges for targeted cell replacement strategies (Kwak et al., 2018). Hence, there's a growing interest in stimulating repair mechanisms through paracrine effects rather than focusing solely on cell replacement methods.

However, the decreased potential for neurogenesis in older individuals, coinciding with the start of AD, poses a challenge for such approaches (McKhann et al., 2011). In figure one, we can see the numerous different types of stem cells discussed previously in the paper. These could include anything from AD MSC, taken from fat cells, to NSC, which is rooted from stem cells from nervous systems (Figure 1). Modulating inflammation has emerged as another potential mechanism for intervention as well, which is still being worked on to this day (Han & Lu, 2020). Efforts using induced pluripotent stem cells (iPSCs) to generate AB-degrading protease-expressing macrophages hold promise, as mentioned before, but they do pose unresolved issues such as teratoma formation, tumorigenicity, and immunogenicity (Han & Lu, 2020). Concerns regarding patient-derived genetic defects and optimal reprogramming further complicate their use. (Alipour et al., 2019).

Similarly, while neural stem cell (NSC) transplantation shows promise, unwanted differentiation into non-neuronal glial cell types remains a challenge (Kwak et al., 2018). The extent to which neuronal replacement contributes to the observed benefits of NSC transplantation remains ambiguous. Paracrine effects following NSC transplantation have garnered more attention, suggesting that these indirect mechanisms might play a more significant role than direct cell replacement, similar to other stem cell transplantations (McKhann et al., 2011).

Figure 1.
Different Types of Stem Cells



Note. Figure was copied from Alipour et al. (2019).

Different types of stem cells are used to treat Alzheimer's disease (AD). These include Ad-MSC (stem cells from fat tissue), BM-MSC (stem cells from bone marrow), hESC (stem cells from embryos), iPSC (reprogrammed adult cells), MGE progenitor cells (similar to cells in the developing brain), MSC (general mesenchymal stem cells), NSC (stem cells in the nervous system), NPC (cells that develop into nerve cells), OEC (cells related to the sense of smell), and UC-MSC (stem cells from the umbilical cord).

Conclusion

The evolution of therapeutic strategies in Alzheimer's Disease is steering towards harnessing endogenous repair mechanisms and emphasizing paracrine effects, deviating from exclusive reliance on cell replacement therapies (Kwak et al., 2018). To advance these approaches, addressing challenges inherent in stem cell-based methodologies, deciphering their nuanced mechanisms, and simplifying patient-care protocols are pivotal (Alipour et al., 2019). Future research endeavors should center on refining these strategies, identifying key molecular components, and elucidating the intricate interplay between endogenous repair mechanisms and therapeutic interventions (Elovsson et al., 2024). In navigating these transformative breakthroughs in Alzheimer's treatment, it offers patients a renewed optimism and an enhanced quality of life (Kwak et al., 2018).

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