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Analysis of mesenchymal stem cells in Alzheimer's disease

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Abstract. The prevalence of Alzheimer's disease (AD) is increasing with the emerged of aging society. While there is no effective therapy to treat it, this review delves into the potential of mesenchymal stem cells (MSCs) in treating AD, a neurodegenerative disorder characterized by progressive memory loss and cognitive impairments. MSCs is a multipotent cell derived from various sources including bone marrow and adipose tissue, with low immunogenicity, ease of acquisition, and multifaceted therapeutic capabilities. MSCs can meliorate AD pathology in various aspects, including the reduction of amyloid-β (Aβ) plaques, enhancement of autophagy, and modulation of neuroinflammation. Therefore, this paper explores the use of mesenchymal stem cells (MSCs) in the clinical treatment of Alzheimer's disease based on a literature review, collating current research findings. Despite the promising preclinical outcomes, MSCs also need for further research and challenges related to effectiveness and the mechanism in human need to be further determine.

Keywords: mesenchymal stem cell, Alzheimer's disease, regenerative medicine.

1. Introduction

With significant improvements in medical care and quality of life, people around the world are living longer and longer. Today, the vast majority of people can hope to live into their 60s and beyond. The number of older people in most countries is increasing steadily. As a result, aging has become one of the most serious problems in the world. According to the World Health Organization (WHO), in 2020, there will be 1 billion people aged 60 and over, and that number is expected to rise to 1.4 billion. By 2050, the number of people aged 60 and over will have doubled to a staggering 2.1 billion. Between 2020 and 2050, the number of persons aged 80 and over is expected to more than triple to 426 million [1].

In addition, it is important to emphasize that aging is a key risk factor for most neurodegenerative diseases, including the most common ones, Alzheimer's disease (AD) and Parkinson's disease (PD). The risk of developing Alzheimer's disease increases exponentially with advancing age. More than 6 million Americans age 65 and older may be suffering from Alzheimer's disease. Even more people under the age of 65 are unfortunately suffering from the disease [2]. In 2018, as many as 5.7 million people in the United States were diagnosed with Alzheimer's disease, but unfortunately, there is still no proven cure for the disease, with some treatments only providing partial relief and limited ability to prevent the disease from progressing. Therefore, new AD-related therapies are essential for this situation [2]. Therefore, this paper analyzes one of the therapeutic modalities for Alzheimer's, stem cell therapy, based on the literature review at that time to understand the therapeutic principles and therapeutic effects of

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stem cell therapy. Alzheimer is considered as one of the untreatable diseases and as the frequency of the disease increases, more is known about the specific manifestations of the disease but not about its treatment options as the research in this paper can promote the popularization of Alzheimer's science.

2. Background

2.1. Alzheimer's Disease

Alzheimer's disease (AD) is a chronic neurodegenerative disease first discovered and described in 1906 by German psychiatrist and neuropathologist Eros Alzheimer. It manifests itself primarily as progressive dementia, resulting in memory loss and cognitive impairment. Patients usually experience mild memory problems in the early stages, such as forgetting recent events and having difficulty remembering new information. As the disease progresses, symptoms such as language impairment, disorientation (e.g., getting lost), changes in mood and personality, and decreased judgment may gradually appear. In the advanced stage, patients may completely lose the ability to take care of themselves and need round-the-clock care from others [3].

It is caused by synaptic loss, the presence of amyloid-β (Aβ) plaques and tau junctions. Amyloid-β (Aβ) plaques are produced by the breakdown of amyloid precursor proteins by β-secretase and γ-secretase. Amyloid-β is toxic to neurons and increases free radicals in neurons. As a result, it leads to impaired mitochondrial redox activity as well as neuronal dysfunction [4]. Current treatment options mainly include the use of cholinesterase inhibitors (e.g., donepezil, carboplatin, etc.) and NMDA receptor antagonists (e.g., memantine) to ameliorate cognitive symptoms; the use of antidepressants and antipsychotics to treat symptomatic emotional and psychiatric symptoms; and new treatment methods such as immunotherapy and gene therapy are also being actively explored, such as mesenchymal stem cell. In addition, non-pharmacological treatments such as cognitive training, social activities, and healthy lifestyles (including balanced diet, moderate exercise, and adequate sleep) also play a role in slowing down the progression of the disease.

2.2. Mesenchymal Stem Cell

Neural stem cells (NSCs) are an approach that has received much attention and has significant research value today. NSCs are a class of cells with self-renewal ability and multidirectional differentiation potential, and they are capable of differentiating into various neuronal cell types such as neurons, astrocytes and oligodendrocytes. However, at present, neural stem cells mainly play the role of immunomodulators rather than direct neuronal replacement in practical applications. By immunomodulators, we mean drug therapies that can alter the body's immune response. In addition, Mesenchymal stem cells (MSCs) have an important role in therapy, but they do not integrate perfectly with host tissues and their therapeutic effect depends mainly on paracrine activity, which makes it necessary to explore new stem cells for the treatment of neurodegenerative diseases.

Mesenchymal stem cells (MSCs) are pluripotent stem cells found in adult bone marrow with strong differentiation ability, and their use in the treatment of AD and many central nervous system diseases is due to some of their own characteristics. MSCs have a wide range of origins, and they were initially isolated from the bone marrow and were thought to be bone marrow stromal cells. In subsequent studies, it was found that MSCs can also be derived from other tissues and can differentiate into various cell types such as osteoblasts, chondrocytes, adipocytes, muscle cells and neural cells under appropriate conditions [4]. MSCs have several significant advantages. First, MSCs are relatively easy to obtain and can be obtained from a variety of sources such as adipose tissue, bone marrow, umbilical cord blood and placenta [5]. In addition, MSCs have low expression of major histocompatibility complex (MHC) class I and class II molecules, which makes them less immunogenic and facilitates cell transplantation. While embryonic stem cells may trigger a strong immune response after transplantation and even risk tumor formation, MSCs are much less immunogenic and potentially risky, which improves safety to a certain extent. Meanwhile, MSCs also have neuroprotective effects, such as regulating ubiquitinated

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proteins and neuroinflammation, thus promoting neurogenesis and effectively improving neurological functional status.

3. Role of MSCs in Treating AD

According to the preclinical research. MSCs can improve several parts of the AD model. First, by reducing Aβ deposition and provoking its clearance in AD-treated animal models, the memory deficits can be alleviated. Similarly, MSCs can trigger autophagy which can decrease the levels of Aβ of pathological neurons in an AD mice model. In addition, MSCs can increase the level of acetylcholine which are essential neurotransmitter by regulating the expression of choline acetyltransferase and acetylcholinesterase. Microglial activation is a key element of neuroinflammation, it also plays a role in neuroinflammation which is the key pathogenesis of AD [6]. To be more specific, microglial processes have connections with neuronal synapses, prolonged activation of microglia related to AD induce synaptic toxicity, and accelerates neuronal loss. However, MSCs can reduce microglial activation by changing M1 phenotype, which will produce proinflammatory cytokine to M2 phenotype, which have an anti-inflammatory effect. This is proved in mouse mice cortexes. Finally, MSCs can upregulate the levels of neurotrophic factors, like the vascular endothelial growth factor (VEGF). When the brains of AD "patient" received MSCs, their neurons and neuronal integrity is improved.

Figure 1 shows in graphic form the steps of a multifunctional neural stem cell therapy for Alzheimer's disease. First, NSCs need to be genetically modified to stably express the key Aβ degrading protease NEP, which improves clearance and resistance. expression of NEP at the cell membrane consistently degrades Aβ in the brain, which improves the survival of NSCs in the AD microenvironment (blue arrows). Nanopreparations were then used to increase the efficiency of neuronal differentiation of NSC (red arrows) and to guide cell transplantation in vivo (black arrows). The use of SOX9 siRNA expression plasmid and retinoic acid (RA) enhances the efficiency of neuronal differentiation of NSC in pathological AD microenvironment by synergistically regulating Wnt/β-catenin and RA signaling pathways [7].

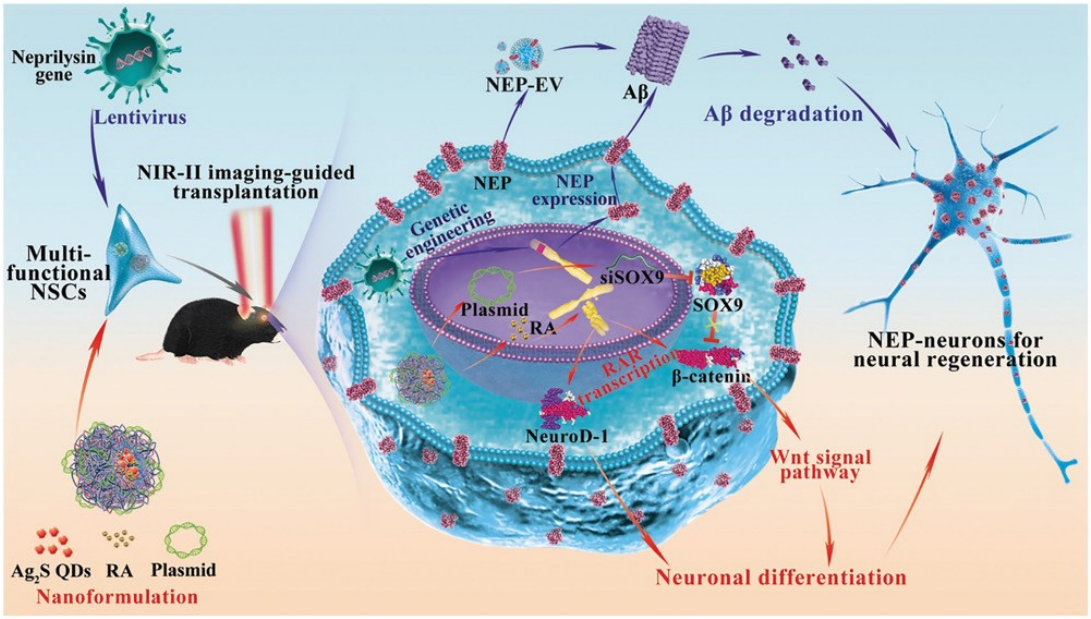

Figure 1. Multifunctional neural stem cell therapy for Alzheimer's disease [7]

3.1. Role of MSCs in Neuron Autophagy

By increasing the autophagy activity in neuron to increase the Aβ clearance is an indirect way to treat the AD, but that is what make it special. Autophagy is the main cellular mechanism for degrading and recycling intracellular proteins and organelles under different physiological and pathological conditions

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[8]. BECN1 and LC3-II play a key role in autophagy. It regulates the autophagy-promoting activity of PIK3C3/VPS34,16, but the level of this is reduced in AD patient. According to in vitro and in vivo model, fortunately, MSCs can upregulate the expression of LC3-II (By monitoring LC3 expression) and exert neuroprotective effects through enhancement of autophagy pathway-dependent Aβ clearance. Additionally, MSCs regulates BECN1 expression to regulate neuronal survival against Aβ toxicity [9].

3.2. Role of MSC-derived secretome and extracellular vehicles (EVs) in AD

MSC-derived secretome refers to the whole range of bioactive molecules secreted by MSCs, including proteins, growth factors, cytokines, chemokines, microRNAs (miRNAs), etc. These molcules can be encapsulated into EVs, which are small membrane structures secreted by cells, including exosomes and microvesicles. In this case MSCs act as “drug stores” that secrete neuroprotective agents which are the actual effectors of the therapeutic effects observed. EVs can deliver beneficial molecules directly to recipient cells to regulate cellular functions. Thus, researchers explored the amelioration in cognitive decline by observing the animal model through intracerebral, intravenous, or intranasal administration. Many studies reported reduced plaque deposition and Aβ levels. It can also regulate the inflammatory response which has discussed above.

4. Conclusion

In summary, there are plenty of in vitro and in vivo researches shows that MSCs is a potential therapy for AD, but it also faces some challenges. Although MSCs shows a clear influence on animal model, according to clinical experiment, there is no obvious improvement on the AD patient. However, these experiments indicated that MSCs are safe and feasible in clinical trials which is also an important factor in new therapy. For MSCs use as modulating the neural autophagy, the challenges may be to Develop drugs that specifically modulate autophagy. Since, it is various in different individuals, also the regulatory mechanism of autophagy is complex, it involved multiple signaling pathways. For the MSC-derived secretome and EVs, Standardized processes for MSC culture and EVs extraction need to be established to ensure consistency and reproducibility of therapeutic products. Also, the further clinical experiment needs to be carried to examine the effectiveness and safety of this therapy.

While MSCs present a safe and feasible treatment for AD, further investigation is required to optimize their therapeutic potential. The development of targeted drugs, standardized MSCs culture methods, and extensive clinical trials will be essential in harnessing the full therapeutic potential of MSCs in combating this debilitating disease.

However, the research in this paper has certain shortcomings, including the number of references cited, and the related experimental studies need to be further enhanced and optimized.

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