International Journal of Humanities and Social Science Invention (IJHSSI)
ISSN (Online): 2319 – 7722, ISSN (Print): 2319 – 7714
www.ijhssi.org ||Volume 7 Issue 10 Ver. III||October 2018 || PP05-07

Current Standing On Mesenchymal Stem Cells In Alzheimer's Disease

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ABSTRACT:*Alzheimer's disease（AD）is a globally prevalent neurodegenerative disease.It brings physical and mental suffering to patients. Alzheimer's disease also brings heavy financial burden to social and family. Currently, there are no approved disease-modifying treatments which are available for AD treatment. The transplantation of mesenchymal stem cells may have a therapeutic effect on the pathogenesis and progression of Alzheimer's disease. This articlemainly discusses recent pre-clinical and clinical advances in MSC-based treatments of AD and introduces sRAGE as a tool to improve the modification of mesenchymal stem cells.*

KEY WORDS：*Mesenchymal Stem Cells, Alzheimer's Disease，Gene Regulation*

Date of Submission: 12-10-2018 Date of acceptance:27-10-2018

I. INTRODUCTION

Alzheimer's diseaseis a globally prevalent neurodegenerative disease. There is no effective treatment yet. Alzheimer's disease is characterized by progressive loss of memory in addition to cortical atrophy(Du Yi-feng, 2016). More than 50 million people in the world with dementia, and about two thirds have Alzheimer's. All of them have damage to the brain cells that can't be reversed. That community is likely to rise to about 152 million people by 2050. The current cost of the disease is about a trillion US dollars a year, and that's forecast to double by 2030(international A.s.d., 2018). Alzheimer's disease brings not only physical and mental suffering to the patients, but also a kind of heavy financial burden to social and family.

The pathogenesis and pathological changes of AD are not clear. The pathological features of AD include amyloid-beta (Aβ) plaque formation and tau hyperphosphorylation. AD's drug therapy can only relieve symptoms, and cannot control and reverse the condition.

Mesenchymal stem cells (MSCs) are multipotent stem cells that are capable of self-renewal and differentiation into various cell types when cultured under appropriate conditions. MSCs have the functions of nerve regeneration, immune regulation, nerve nutrition and protection, as well as promoting endogenous neuron regeneration. MSCs have emerged as promising tools for the treatment of AD, The transplantation of mesenchymal stem cells is one of the hotspots in the field of medicine. In this review, we will focus onrecent pre-clinical and clinical advances in MSC-based treatment of AD and introduces sRAGE as a tool to improve the modification of mesenchymal stem cells.

II. DEFINITION OF MSCs

Since the discovery of mesenchymal stem cells by professor Caplan in 1995, its research has become increasingly mature. MSCs can be isolated from many adult tissues, Such as bone marrow, umbilical cord, umbilical cord blood, amniotic membrane, adipose tissue, dental tissue, placenta. They are self-renewable, multipotent, easily accessible and culturally expandable in vitro and few ethical issues, markingits importance in cell therapy, regenerative medicine and tissuerepairmen. According to the sources, MSCs can be divided into bone marrow-derived mesenchymal stem cells, umbilical cord-derived mesenchymal stem cells, umbilical cord blood-derived mesenchymal stem cells, adipose-derived stem cells, amniotic membrane--derived mesenchymal stem cells, and placenta chorionic villi-derived mesenchymal stem cells.The following five sources of MSCs were used in clinical trials of AD In recent years. BM-MSCs、UC-MSCs、UCB-MSCs、AD-MSCs and PL-MSCs. Some of reports have highlighted PL-MSCs display potent pro-angiogenic activity in the therapy of AD.

III. FUNCTIONAL MECHANISM OF MSCs

Various of reports indicated that MSC-based treatment significantly improved the learning ability and memory. ameliorated the cognitive impairments in AD mice models(Ge et al., 2018). many studieshave shown that MSCs can treat AD through a variety of mechanisms. First, MSCs can affect AD pathology by neural differentiation. Second, MSCs secrete various trophic and growth factors which, in mouse models of AD, have

benefits that include reducing amyloid burden and tauhyperphosphorylation, modulating inflammation, oxidative stress, and Enhanced endogenous neurogenesis(Park et al., 2018). Third, Autophagy plays a key role in the transplantation of MSCs. They can improve the living environment of brain cells byinduced Aβ clearance(Li et al., 2018). Finally, MCSs and cell-derived extracellular vesicles protect neurons from oxidative stress and synapse damage induced by amyloid-β oligomers(de Godoy et al., 2018).

IV. GENE REGULATION

Studies show sRAGE（a soluble form of Receptor for Advanced Glycation End-products）secreting mesenchymal stem cells (sRAGE-MSCs) can prolong the survival time of MSC transplantation, Oh , et al found transplanted sRAGE-MSCs survived longer than control MSCs(Oh et al., 2018). This may be associated with reduced CD4 and CD3d and increased microglia.It will be beneficial to Aβ42 clearance.

V. MSCs INCLINICAL TRIALS

Clinical trials of MSCs（Ⅰ-Ⅲ）have reached dozens of species，such as degenerative arthritis, spinal cord injuries and acute myocardial infarction. Many of MSCs preparations have been approved in five countries, including Canada, South Korea, New Zealand, Japan and Switzerland.

The route of administration is an important factor to enhance MSC based treatment effects for AD. According torecent studies, the route of administration in MSC-based treatment of AD include intravenously, intra-ventricularly, intra-arterially, via the spinal cord and intra-cerebral. During the 2011-2017 period, In phase I/II clinical trial studies conducted in the United States, China and Korea. MSCs were given intra-ventricularly, intra-cerebral, or intravenously routes in subjects with AD(Park et al., 2018).

The blood–brain barrier is a major obstacle for the effective delivery of therapeutic compounds in central nervous system disease. Magnetic resonance-guided focused ultrasound in combination with intravenously injectedmicrobubbles has been shown to transiently open the blood–brain barrier, researchers used focusedultrasound to open the blood–brain barrier in five patients with Alzheimer'sdisease. This method can reduce beta-amyloid in animal models of Alzheimer's disease, but the clinical efficacy remains to be seen(Lipsman et al., 2018).

The oncogenicity of MSCs is waiting for further solving. Qiuwei Pan and his colleagues found the spontaneous tumorigenic transformation during culture expansion of MSCs. Although the spontaneous transformation of MSCs resulting in tumorigenesis is rare(Pan et al., 2014). Furthermore, MSCs could promote cancer metastasis. The possible mechanism is that TNFα-activated MSCs promote tumor metastasis via CXCR2+ neutrophil recruitment(Yu et al., 2016).

VI. CONCLUSION

Alzheimer's disease brings not only physical and mental suffering to the patients, but also a kind of heavy financial burden to social and family.This papermainly discusses recent pre-clinical and clinical advances in MSC-based treatments of AD and introduces sRAGE as a tool to improve the modification of mesenchymal stem cells.Recent exhilarating discoveries in engineering MSCs have made it a good source for stem cell therapy in AD. The human clinical trials of MSCs have been successfully carried out in the United States, China and Korea. However, many questions related to MSCs transplant are not resolved .This includes how to transfer MSCs to the appropriate site, and how to make MSCs to differentiate into nerve cells. And how to solve the oncogenic and safety problems of MSCs.

ACKNOWLEDGMENTS

This study was supported by the Natural Science Foundation of Zhejiang Province of China (No.LQ17C190002)

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Ji Chao"Current Standing On Mesenchymal Stem Cells In Alzheimer's Disease "International Journal of Humanities and Social Science Invention(IJHSSI), vol. 07, no. 10, 2018, pp. 05-07