Send Orders for Reprints to reprints@benthamscience.net

Current Stem Cell Research & Therapy, XXXX, *XX,* 1-12

REVIEW ARTICLE

Conditioned Media Therapy in Alzheimer's Disease: Current Findings and Future Challenges

Amin Firoozi[1], Mehri Shadi[1], Zohre Aghaei[2] and Mohammad Reza Namavar[1,3,4,*]

[1]*Department of Anatomical Sciences, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran;* [2]*Department of Physiology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran;* [3]*Histomorphometry and Stereology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran;* [4]*Clinical Neurology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran*

ARTICLE HISTORY

Received: January 11, 2023
Revised: April 05, 2023
Accepted: April 14, 2023

DOI:
10.2174/1574888X18666230523155659

Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder accompanied by a reduction in cognition and memory. Till now, there is no definite cure for AD, although, there are treatments available that may improve some symptoms. Currently, in regenerative medicine stem cells are widely used, mainly for treating neurodegenerative diseases. There are numerous forms of stem cells to treat AD aiming at the expansion of the treatment methods for this particular disease. Since 10 years ago, science has gained abundant knowledge to treat AD by understanding the sorts of stem cells, methods, and phasing of injection. Besides, due to the side effects of stem cell therapy like the potentiation for cancer, and as it is hard to follow the cells through the matrix of the brain, researchers have presented a new therapy for AD. They prefer to use conditioned media (CM) that are full of different growth factors, cytokines, chemokines, enzymes, *etc*. without tumorigenicity or immunogenicity such as stem cells. Another benefit of CM is that CM could be kept in the freezer, easily packaged, and transported, and doesn't need to fit with the donor. Due to the beneficial effects of CM, in this paper, we intend to evaluate the effects of various types of CM of stem cells on AD.

Keywords: Alzheimer's disease, Conditioned media, Stem cell, Neurodegenerative disease, cytokines, chemokines.

1. INTRODUCTION

Alzheimer's disease (AD) is the major reason for dementia and is quickly emerging as one of the most costly and fatal illnesses of this century [1]. It is estimated that about 50 million people worldwide are affected by AD [2] and this will increase to triple in 2050 in low-income countries. Age (older than 65) increases the risk factors of AD [3], and men are less affected than women, especially after the 80s. Most of the cases of AD are above 65, which is termed late-onset AD (LOAD), while about 5% of cases of AD are under 65 years old which is called early-onset AD (EOAD) [4]. About 1-2% of AD is hereditary and has symptoms like EOAD [5]. The most common symptom in the early phase of AD is a deficit in short-term memory, which affects daily activity [6]. Loss of neurons and synaptic dysfunction in the limbic system, archicortex, and neocortex can cause cognitive deficits [7].

Beta-amyloid (Aβ) is produced by sequential cleavage by proteases called secretase α, β, γ from the amyloid precursor protein (APP). Malformed APP produces extreme amounts of Aβ, which is poisonous to the neurons, and then finally induces neuronal apoptosis. Amyloid plaques are the accumulation of abnormally folded amyloid β- peptides in the extracellular matrix with 40 or 42 amino acids [8]. Insolubility and fibrillation of the plaques are because of Aβ42 which is more abundant than Aβ40 [7]. Tau is a protein that is bound to the microtubule to help axonal transport and alteration of signaling pathways [9]. Hyperphosphorylation of tau protein, which is called neurofibrillary tangles (NFT), can impair signaling cascades in pre-synaptic and post-synaptic compartments and then be associated with dementia by increasing in number [10-12]. Studies suggest that the balance of metal ions which include Cu^{2+}, Zn^{2+}, and Fe^{3+} might play a crucial function in determining the morphology of Aβ aggregation or its dissociation. Transition metals such as copper (Cu), iron (Fe), and zinc (Zn) were also identified at high concentrations in the Aβ plaques (~400 μM Cu, ~1 mM Zn, and ~1 mM Fe) and contributed to the neuropathology related to Aβ fibrils *via* affecting the rate of fibril formation, by modifying fibril morphology, and by direct chemical reaction with Aβ [13]. Silver ions by binding to Aβ peptides could decrease the fibrillation of Aβ [14]. Recent studies have proposed that one of the causes of AD and the accumulation of AB peptides may be due to high concentrations of metal ions like Fe^{+3}, Cu^{+2}, and Zn^{+2} [15, 16]. Ryu *et al* showed that Fe^{+3} could accelerate the Aβ peptide fibrillation more than the metal ions Zn^{+2}, and Cu^{+2} [13]. Studies

*Address correcpondence to this author at the Department of Anatomical Sciences, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran; E-mail: namavarm@sums.ac.ir

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors would like to thank Shiraz University of Medical Sciences, Shiraz, Iran, and also the Center for Development of Clinical Research of Nemazee Hospital and Dr. Nasrin Shokrpour for editorial assistance.

SELECTION CRITERIA FOR INCLUDED STUDIES

For this review, we performed a search on PubMed and Scopus using the keywords condition medium AND Alzheimer's disease, human umbilical cord mesenchymal stem cells conditioned medium AND Alzheimer's disease, and Dental Pulp conditioned medium AND Alzheimer's disease. Articles published in English from 2011 to 2021 were considered in this review.

REFERENCES

[1] Lei P, Ayton S, Bush AI. The essential elements of Alzheimer's disease. J Biol Chem 2021; 296: 100105. http://dx.doi.org/10.1074/jbc.REV120.008207 PMID: 33219130

[2] Patterson C. World alzheimer report 2018. 2018.

[3] van der Lee SJ, Wolters FJ, Ikram MK, *et al*. The effect of APOE and other common genetic variants on the onset of Alzheimer's disease and dementia: A community-based cohort study. Lancet Neurol 2018; 17(5): 434-44. http://dx.doi.org/10.1016/S1474-4422(18)30053-X PMID: 29555425

[4] Association As. 2019 Alzheimer's disease facts and figures. Alzheimers Dement 2019; 15(3): 321-87. http://dx.doi.org/10.1016/j.jalz.2019.01.010

[5] Bateman RJ, Xiong C, Benzinger TLS, *et al*. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med 2012; 367(9): 795-804. http://dx.doi.org/10.1056/NEJMoa1202753 PMID: 22784036

[6] Lange KW, Lange KM, Makulska-Gertruda E, *et al*. Ketogenic diets and Alzheimer's disease. Food Sci Hum Wellness 2017; 6(1): 1-9. http://dx.doi.org/10.1016/j.fshw.2016.10.003

[7] Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Med 2011; 1(1): a006189. http://dx.doi.org/10.1101/cshperspect.a006189 PMID: 22229116

[8] Kelley BJ, Petersen RC. Alzheimer's disease and mild cognitive impairment. Neurol Clin 2007; 25(3): 577-609. http://dx.doi.org/10.1016/j.ncl.2007.03.008 PMID: 17659182

[9] Holtzman DM, Carrillo MC, Hendrix JA, *et al*. Tau: From research to clinical development. Alzheimers Dement 2016; 12(10): 1033-9. http://dx.doi.org/10.1016/j.jalz.2016.03.018 PMID: 27154059

[10] Gibbons GS, Lee VMY, Trojanowski JQ. Mechanisms of cell-to-cell transmission of pathological tau: A review. JAMA Neurol 2019; 76(1): 101-8. http://dx.doi.org/10.1001/jamaneurol.2018.2505 PMID: 30193298

[11] Ittner A, Ittner LM. Dendritic tau in Alzheimer's disease. Neuron 2018; 99(1): 13-27. http://dx.doi.org/10.1016/j.neuron.2018.06.003 PMID: 30001506

[12] Spires-Jones TL, Hyman BT. The intersection of amyloid beta and tau at synapses in Alzheimer's disease. Neuron 2014; 82(4): 756-71. http://dx.doi.org/10.1016/j.neuron.2014.05.004 PMID: 24853936

[13] Ryu J, Girigoswami K, Ha C, Ku SH, Park CB. Influence of multiple metal ions on β-amyloid aggregation and dissociation on a solid surface. Biochemistry 2008; 47(19): 5328-35. http://dx.doi.org/10.1021/bi800012e PMID: 18422346

[14] Wallin C, Jarvet J, Biverstål H, *et al*. Metal ion coordination delays amyloid-β peptide self-assembly by forming an aggregation–inert complex. J Biol Chem 2020; 295(21): 7224-34. http://dx.doi.org/10.1074/jbc.RA120.012738 PMID: 32241918

[15] Lovell MA, Robertson JD, Teesdale WJ, Campbell JL, Markesbery WR. Copper, iron and zinc in Alzheimer's disease senile plaques. J Neurol Sci 1998; 158(1): 47-52. http://dx.doi.org/10.1016/S0022-510X(98)00092-6 PMID: 9667777

[16] Bush AI. The metallobiology of Alzheimer's disease. Trends Neurosci 2003; 26(4): 207-14. http://dx.doi.org/10.1016/S0166-2236(03)00067-5 PMID: 12689772

[17] House E, Collingwood J, Khan A, Korchazkina O, Berthon G, Exley C. Aluminium, iron, zinc and copper influence the *in vitro* formation of amyloid fibrils of Aβ42 in a manner which may have consequences for metal chelation therapy in Alzheimer's disease. J Alzheimers Dis 2004; 6(3): 291-301. http://dx.doi.org/10.3233/JAD-2004-6310 PMID: 15201484

[18] Garai K, Sengupta P, Sahoo B, Maiti S. Selective destabilization of soluble amyloid β oligomers by divalent metal ions. Biochem Biophys Res Commun 2006; 345(1): 210-5. http://dx.doi.org/10.1016/j.bbrc.2006.04.056 PMID: 16678130

[19] Vermunt L, Sikkes SAM, Hout A, *et al*. Duration of preclinical, prodromal, and dementia stages of Alzheimer's disease in relation to age, sex, and *APOE* genotype. Alzheimers Dement 2019; 15(7): 888-98. http://dx.doi.org/10.1016/j.jalz.2019.04.001 PMID: 31164314

[20] McKhann GM, Knopman DS, Chertkow H, *et al*. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7(3): 263-9. http://dx.doi.org/10.1016/j.jalz.2011.03.005 PMID: 21514250

[21] Farlow MR, Cummings JL. Effective pharmacologic management of Alzheimer's disease. Am J Med 2007; 120(5): 388-97. http://dx.doi.org/10.1016/j.amjmed.2006.08.036 PMID: 17466645

[22] Howard R, McShane R, Lindesay J, *et al*. Donepezil and memantine for moderate-to-severe Alzheimer's disease. N Engl J Med 2012; 366(10): 893-903. http://dx.doi.org/10.1056/NEJMoa1106668 PMID: 22397651

[23] Grossberg GT, Manes F, Allegri RF, *et al*. The safety, tolerability, and efficacy of once-daily memantine (28 mg): A multinational, randomized, double-blind, placebo-controlled trial in patients with moderate-to-severe Alzheimer's disease taking cholinesterase inhibitors. CNS Drugs 2013; 27(6): 469-78. http://dx.doi.org/10.1007/s40263-013-0077-7 PMID: 23733403

[24] Cummings JL, Tong G, Ballard C. Treatment combinations for Alzheimer's disease: Current and future pharmacotherapy options. J Alzheimers Dis 2019; 67(3): 779-94. http://dx.doi.org/10.3233/JAD-180766 PMID: 30689575

[25] Pooler AM, Polydoro M, Wegmann S, Nicholls SB, Spires-Jones TL, Hyman BT. Propagation of tau pathology in Alzheimer's disease: Identification of novel therapeutic targets. Alzheimers Res Ther 2013; 5(5): 49. http://dx.doi.org/10.1186/alzrt214 PMID: 24152385

[26] Rosenmann H. Immunotherapy for targeting tau pathology in Alzheimer's disease and tauopathies. Curr Alzheimer Res 2013; 10(3): 217-28. http://dx.doi.org/10.2174/1567205011310030001 PMID: 23534533

[27] Novak P, Schmidt R, Kontsekova E, *et al*. Safety and immunogenicity of the tau vaccine AADvac1 in patients with Alzheimer's disease: A randomised, double-blind, placebo-controlled, phase 1 trial. Lancet Neurol 2017; 16(2): 123-34. http://dx.doi.org/10.1016/S1474-4422(16)30331-3 PMID: 27955995

[28] Ding L, Meng Y, Zhang HY, Yin WC, Yan Y, Cao YP. Active immunization with the peptide epitope vaccine Aβ3-10-KLH induces a Th2-polarized anti-Aβ antibody response and decreases