Modeling and Therapeutic Strategies of Pluripotent Stem Cells for Alzheimer's Disease

Haigang Gu*
Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, TN 37232, USA

Alzheimer's disease (AD) is one of the most common neurodegenerative diseases, which is characterized by a progressive and age-related chronic loss of neurons in extensive brain areas, such as cerebral cortex and hippocampus, one of the most prominent being the basal forebrain cholinergic neurons (BFCN). In clinic, patients suffer from impairment of memory and cognitive function, language breakdown and eventually long-term memory loss. The burden of AD is heavy to patient's families and the whole society. The pathological findings of AD are senile plaques, neurofibrillary tangles and neuronal cell death. Senile plaques and neurofibrillary tangles are mainly consisted of β-amyloid (Aβ) peptides, which are formed by the cleavage of amyloid precursor protein (APP) by β- and γ-secretase. In the end, accumulation of Aβ peptides in neurons causes neuronal degeneration and cell death [1,2]. Although previous studies already showed the effects of Aβ peptides on cultured mammal neurons, how Aβ peptides affect human neurons, especially neurons from AD patients, are still not understood. On the other hand, although neurotrophic factors application, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), have showed functional recovery in animal model of AD and several drugs for the treatment of AD has been approved by FDA and have shown the improvement of cognitive function and memory of AD patient, it is still challenge to delay and reverse the neuronal degeneration and cell death [3-5].

Neural stem cells (NSCs) have been harvested from mammal brain and used for the therapeutic studies of AD [6,7]. But, it is difficult to transfer this strategy for clinical application due to limited resource. Recent progress in pluripotent stem cells biology makes it possible to generate patient-specific induced pluripotent stem cells (iPSCs) and induce pluripotent stem cells to differentiate into cholinergic neurons. In 2006, Dr Yamanaka's group developed a novel procedure to induce mouse embryonic and adult fibroblasts to dedifferentiate into iPSCs using 4 transcriptional factors, Oct4, Sox2, c-Myc, and Klf4 [8]. Later on, more and more groups use similar strategies to get iPSCs from somatic cells of normal people, even some patients [9-12]. This breakthrough makes Dr. Yamanaka to share the Nobel Prize in Physiology or Medicine in 2012 with Dr. Gurdon. Here, I will talk about the recent progress of modeling and therapeutic studies of AD using pluripotent stem cells, including iPSCs and embryonic stem cells (ESCs).

Modeling AD using Pluripotent Stem Cells

iPSCs derived from somatic cells of patients allow us to study the effects of genetic changes on the developmental and pathological changes of diseases. Yagi et al. [13] firstly generated iPSCs from familial AD (FAD) patients carrying PS1 and PS2 mutations and induced FAD-iPSCs to differentiate into neurons. In this study, they found that neurons derived from FAD-iPSCs carrying PS1 and PS2 mutations have increased amyloid β42 secretion. This phenomenon has been found in patients' brain with PS mutations. After applied γ-secretase inhibitor, Compound E, amyloid β42 secretion decreased [13]. In 2012, Israel et al. generated iPSCs from two AD patients carrying the duplication of the Aβ precursor protein gene (APP) [14]. They found that levels of Aβ40, phospho-tau and active glycogen synthase kinase-3β (aGSK-3β) were higher in iPSC-derived neurons from patients carrying APP mutation than that of controls. Interestingly, similar phenomena were observed in iPSC-derived neurons from sporadic AD patients. They also found that the genome of iPSC-derived neurons from one of sporadic AD patients had similar phenotypes with FAD samples [14]. Kondo et al. [15] generated iPSCs from FAD patients carrying E693A mutation and sporadic AD and induced iPSCs to differentiate into cortical neurons. The level of Aβ oligomers in iPSC-derived neurons and astrocytes carrying E693A mutation increased. The accumulated Aβ oligomers caused endoplasmic reticulum and oxidative stress, which could be reversed after applied docosahexaenoic acid (DHA) [15]. Cortical neurons were also generated from Down syndrome-iPSCs (DS-iPSCs) and ESCs (DS-ESCs). Cortical neurons derived from DS-iPSCs showed that extracellular accumulation of pathogenic Aβ42 in the culture of cortical neurons derived from DS-iPSCs is much higher than that of control in the late stage (after day 70). BTA1-labeled amyloid showed that intracellular and extracellular aggregates of amyloid in DS-iPSC-derived cortical neurons. To verify this observation, they generated cortical neurons from DS-ESCs. Extracellular and intracellular Aβ42 aggregation was observed in cortical neurons derived from DS-ESCs. Furthermore, the distribution of Aβ42 aggregation in cortical neurons derived from DS-ESCs was similar with that in cortical neurons derived from DS-iPSCs. These studies illustrated that iPSC-derived neurons from AD patients can be used to analyze pathological changes and screen the drugs for clinical applications [16].

Therapeutic Studies of AD using Pluripotent Stem Cells

Previous studies showed that transplantation of embryonic BFCN to hippocampus could improve the ability of learning and memory in aged brains or animal models of AD [17]. To obtain large amount of cholinergic neurons, the scientists have made a lot of effort to generate cholinergic neurons from stem cells. Mouse ESCs were induced to differentiate into neurons when they were co-cultured with chick dorsal root ganglion (DRG) conditioned medium. Among these neurons, around 14% of neurons were cholinergic neurons, which were labeled with the anti-ChAT antibody [18]. Manabe et al. [19] reported that suppression of L3/Lhx8 in mouse ESCs by siRNA could dramatically decrease ChAT positive neuronal differentiation and overexpression of L3/Lhx8 could recover this suppression. Their studies showed that L3/Lhx8 is an important factor for cholinergic neuronal differentiation from ESCs [19]. Except of Lhx8, BFCN also express Gbx1. Bissonnette

*Corresponding author: Haigang Gu, Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, TN 37232, USA, Tel: 615-343-6890; Fax: 615-343-6532; E-mail: hg.gu@vanderbilt.edu

Received June 15, 2013; Accepted June 18, 2013; Published June 20, 2013

Citation: Gu H (2013) Modeling and Therapeutic Strategies of Pluripotent Stem Cells for Alzheimer’s Disease. J Stem Cell Res Ther 3: e115. doi:10.4172/2157-7633.1000e115

Copyright: © 2013 Gu H. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
et al. [20] generated cholinergic neurons from human ESCs by overexpression of Lhx8 and Gbx1. Cholinergic neurons derived from human ESCs showed functional electrophysiological properties and integrated with the neurons in ex vivo slice cultures.

Pluripotent stem cells have been used for the cell replacement therapy of AD. Before transplantation, neuronal precursor cells (NPCs) derived from mouse ESCs were treated with growth factors, which related to cholinergic neuronal differentiation, such as NGF, sonic hedgehog (SHH), retinoic acid (RA) and interleukin-6 (IL-6). Morris water-maze and spatial-probe testing showed a significant functional recovery in memory deficits of ibotenic acid-lesioned rat model of AD after ES-NPCs transplantation [21]. Dr. Zhang’s group developed a new protocol to induce human ESCs to efficiently differentiate into medial ganglionic eminence (MGE)-like cells after applied high concentration of SHH (1000 ng/ml) during neuroepithelia stage around 18 days. In the presence of NGF, BDNF, BMP9 and SHH, MGE progenitors could be further differentiated into cholinergic- and GABA-neurons. After transplantation, ESC-derived MGE could differentiate into cholinergic- and GABA-neurons and integrate with host tissue. Furthermore, ESC-derived MGE transplantation significantly increased the learning and memory of AD model [22].

Using reprogramming techniques, scientists generated induced neurons and induced NSCs (iNSCs) from mouse and human fibroblasts [23-26]. NSCs have been used to model neurological diseases 10 years ago. Induced cholinergic neurons and cholinergic neurons generated from iNSCs will be generated in the future, which will provide us a new platform for modeling and therapeutic studies of AD.

References

1. Hardy J (2004) Toward Alzheimer therapies based on genetic knowledge. Annu Rev Med 55: 15-25.
2. Perl DP (2010) Neuropathology of Alzheimer’s disease. Mt Sinai J Med 77: 32-42.
3. Xuan AG, Long DH, Gu HG, Yang DD, Hong LP et al. (2008) BDNF improves the effects of neural stem cells on the rat model of Alzheimer’s disease with unilateral lesion of fimbria-fornix. Neurosci Lett 440: 331-335.
4. Gu H, Long D, Song C, Li X (2009) Recombinant human NGF-loaded microspheres promote survival of basal forebrain cholinergic neurons and improve memory impairments of spatial learning in the rat model of Alzheimer’s disease with fimbria-fornix lesion. Neurosci Lett 453: 204-209.
5. Gandy S, DeKosky ST (2013) Toward the treatment and prevention of Alzheimer’s disease: rational strategies and recent progress. Annu Rev Med 64: 387-383.
6. Gu H, Long D, Song C, Li X (2009) The effects of neural stem cell transplantation on cholinergic neurons of the basal forebrain and abilities of learning and memory of the rat model of Alzheimer’s disease. Chin J Clin Anat 27: 85-89.
7. Gu H, Long D, Li X, Zhang G, Luo M et al. (2008) Proliferation and differentiation of neural stem cells from neonatal rat basal forebrain of newborn rats into neurons in different culture conditions. J Clin Rehabilit Tiss Eng Res 12: 1445-1448.
8. Takahashi K, Yamanaka S (2006) Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 126: 663-676.
9. Yu J, Vodyanik MA, Smuga-Otto K, Antosiewicz-Bourget J, Franke JL, et al. (2007) Induced pluripotent stem cell lines derived from human somatic cells. Science 318: 1917-1920.
10. Yamanaka S (2012) Induced pluripotent stem cells: past, present, and future. Cell Stem Cell 10: 678-684.
11. Takahashi K, Yamanaka S (2013) Induced pluripotent stem cells in medicine and biology. Development 140: 2457-2461.
12. Yamanaka S (2010) Patient-specific pluripotent stem cells become even more accessible. Cell Stem Cell 7: 1-2.
13. Yagi T, Ito D, Okada Y, Akamatsu W, Nihei Y, et al. (2011) Modeling familial Alzheimer’s disease with induced pluripotent stem cells. Hum Mol Genet 20: 4530-4539.
14. Israel MA, Yuan SH, Bardy C, Reyna SM, Mu Y et al. (2012) Probing sporadic and familial Alzheimer’s disease using induced pluripotent stem cells. Nature 482: 216-220.
15. Kondo T, Asai M, Tsukita K, Kotoiku Y, Ohsawa Y, et al. (2013) Modeling Alzheimer’s disease with iPSCs reveals stress phenotypes associated with intracellular Abeta and differential drug responsiveness. Cell Stem Cell 12: 487-496.
16. Shi Y, Kirwan P, Smith J, MacLean G, Orkin SH, et al. (2012) A human stem cell model of early Alzheimer’s disease pathology in Down syndrome. Sci Transl Med 4: 124ra129.
17. Gage FH, Bjorklund A, Stenevi U, Dunnett SB, Kelly PA (1984) Intrahippocampal septal grafts ameliorate learning impairments in aged rats. Science 225: 533-536.
18. Kitazawa A, Shimizu N (2007) Characterization of neurons differentiated from mouse embryonic stem cells using conditioned medium of dorsal root ganglia. J Biosci Bioeng 104: 257-262.
19. Manabe T, Tatsumi K, Inoue M, Makinodan M, Yamauchi T, et al. (2007) L3/ Lhx8 is a pivotal factor for cholinergic differentiation of murine embryonic stem cells. Cell Death Differ 14: 1080-1085.
20. Bissonnette CJ, Lyass L, Bhattacharyya BJ, Belmadani A, Miller RJ, et al. (2011) The controlled generation of functional basal forebrain cholinergic neurons from human embryonic stem cells. Stem Cells 29: 802-811.
21. Moghadam FH, Alaei H, Karbalai K, Tanhaei S, Nasr Esfahani MH, et al. (2009) Transplantation of primed or unprimed mouse embryonic stem cell-derived neural precursor cells improves cognitive function in Alzheimerian rats. Differentiation 78: 59-68.
22. Liu Y, Weick JP, Liu H, Krenick R, Zhang X, et al. (2013) Medial ganglionic eminence-like cells derived from human embryonic stem cells correct learning and memory deficits. Nat Biotechnol 31: 440-447.
23. Pang ZP, Yang N, Vierbuchen T, Ostermeier A, Fuentes DR, et al. (2011) Induction of human neuronal cells by defined transcription factors. Nature 478: 220-223.
24. Vierbuchen T, Ostermeier A, Pang ZP, Kokubu Y, Sudhof TC, et al. (2010) Direct conversion of fibroblasts to functional neurons by defined factors. Nature 463: 1035-1041.
25. Thier M, Worsdorfer P, Lakes YB, Gorris R, Herm S, et al. (2012) Direct conversion of fibroblasts into stably expandable neural stem cells. Cell Stem Cell 10: 473-479.
26. Han DW, Tapia N, Hermann A, Heimer K, Hoing S, et al. (2012) Direct reprogramming of fibroblasts into neural stem cells by defined factors. Cell Stem Cell 10: 465-472.