Alzheimer’s Disease and Stem Cell Therapy

Sung S. Choi1#, Sang-Rae Lee2#, Seung U. Kim3 and Hong J. Lee1*

1Medical Research Institute, Chung-Ang University College of Medicine, Seoul 156-756,
2National Primate Research Center, Korea Research Institute of Bioscience and Biotechnology, Ochang 363-883, Korea,
3Division of Neurology, Department of Medicine, University of British Columbia, Vancouver 317-2194, Canada

http://dx.doi.org/10.5607/en.2014.23.1.45
Exp Neurobiol. 2014 Mar;23(1):45-52.
pISSN 1226-2560 • eISSN 2093-8144
Review Article

The loss of neuronal cells in the central nervous system may occur in many neurodegenerative diseases. Alzheimer’s disease is a common senile disease in people over 65 years, and it causes impairment characterized by the decline of mental function, including memory loss and cognitive impairment, and affects the quality of life of patients. However, the current therapeutic strategies against AD are only to relieve symptoms, but not to cure it. Because there are only a few therapeutic strategies against Alzheimer’s disease, we need to understand the pathogenesis of this disease. Cell therapy may be a powerful tool for the treatment of Alzheimer’s disease. This review will discuss the characteristics of Alzheimer’s disease and various available therapeutic strategies.

Key words: Alzheimer’s disease, stem cell-gene therapy, transplantation

PATHOGENESIS OF ALZHEIMER’S DISEASE

The exact causes of dementia are not yet known. By type, Alzheimer’s disease (AD), which is also known as (senile) dementia of the Alzheimer type (DAT), is caused by the aggregation of toxic proteins in the brain, and stroke-induced cerebrovascular dementia accounts for 80~90% of all dementia cases, with hydrocephalus or infectious diseases accounting for the rest. Dementia, which is a degenerative disease that is characterized by the general impairment of cognitive functions caused by temporary or lasting brain damage, is a serious “21st-Century disease.”

In the United States, as of 2012, 1 out of 8 senior citizens (13%) is suffering from AD, making it the sixth most common cause of death. Over 5.4 million Alzheimer’s patients are currently receiving medical care in the USA, and they incur care costs that are as high as $200 billion a year [1]. AD is a disease that is commonly characterized by a gradual decline of memory, language, and cognitive ability. It was first identified in 1907 by Alois Alzheimer, a German psychiatrist and neuropathologist, in his case report describing the pathological structure of senile plaques and neurofibrillary tangles in the brain of a 55-year-old woman who showed severe dementia symptoms with pathological features, such as a reduction of total brain volume, thinning of the cortical grey matter, ventricular enlargement, and deposits of amyloid, tau, and cerebrovascular amyloid proteins [2-5].

Senile plaques and neurofibrillary tangles are the hallmark pathological features that are observed in the brain of an Alzheimer’s patient. Senile plaques are deposits of a distinct protein fragment called beta-amyloid (Aβ), which induces neuronal cytotoxicity, and neurofibrillary tangles are abnormal structures that are formed by changes in the tau protein inside nerve cell bodies. The nerve cells in the brains of Alzheimer’s patients progressively shrink and die. Such neuronal cell death occurs first in the brain regions that are responsible for memory and language, but it ultimately spreads to the entire brain. The neural
networks of Alzheimer’s patients are impaired by the decreased brain concentrations of acetylcholine, which is a neurotransmitter that is involved in intercellular signaling, and deficiencies in the production of other neurotransmitters, such as somatostatin, serotonin, and norepinephrine [6]. Familial Alzheimer’s disease (FAD) is caused by gene mutations, and the aggregation of Aβ is observed in FAD as a result of a gene mutation of the Aβ precursor protein, which is the main component of senile plaques, one of the hallmark pathological features of AD. Such excessive Aβ aggregation destroys neurons. Furthermore, there have been reports on the possible link between the apolipoprotein E (APOE) gene and the incidence of AD. There are three types of APOE, of which E4 is associated with AD, and E2 and E3 are known to serve the function of providing protection against AD. Everyone carries APOE gene, and APOE epsilon 4 is the susceptible gene. About 40% of AD patients are associated with APOE epsilon 4 (e4), whereas the remaining 50% or more are known to be not associated with APOE genotype. There are three types of APOE, of which E4 is associated with AD, and E2 and E3 are known to serve the function of providing protection against AD [7].

Once AD develops due to the various causes described above, cholinergic neurons and synapses become affected and gradually degenerate or die. Many brain regions then display amyloid plaques and neurofibrillary tangles. Distribution of amyloid plaques can be classified into three stages (stage A, B, C). It is known that they form relatively constant patterns [8]. Neurofibrillary tangles show a regular pattern of aggregation [9]. The disease starts in the transentorhinal cortex and progressively spreads to the entorhinal cortex, the hippocampus, and the cerebral cortex. With the clear manifestation of neuronal cell death, memory and cognitive functions gradually decline along with the progression of dementia, while accelerating the patients’ death [10-12].

CHOLINERGIC HYPOTHESIS

In the latter half of the 1970s, neurochemical studies of post-mortem tissue specimens reported damage to the cholinergic system, resulting in decreased acetylcholine-producing choline acetyltransferase (ChAT) activity, decreased choline absorption, and decreased acetylcholine release [13-15], as well as decreased cortical acetylcholinesterase activity [16, 17]. Cholinergic basal forebrain nuclei (ChBF) are the major neural pathways over which cholinergic neurons enter the hippocampus and cerebral cortex, and these nuclei are crucial for memory, concentration, and other cognitive procedures [12, 18]. In many animal experiments, the removal of cholinergic neurons or treatment with cholinergic antagonists, such as scopolamine or hyoscine, has been shown to elicit impairments of memory and other cognitive functions [19-23].

The hypofunction of cholinergic neurons in the ChBF and cerebral cortex impairs Alzheimer’s patients’ cognitive functions [11]. The cholinesterase inhibitors (CEI) - rivastigmine, donepezil, and galantamine- suppress the acetylcholinesterase activity of decomposing acetylcholine, reducing cholinergic damage and leading to some improvements in behavior, concentration, and social involvement, as well as cognitive functions. However, they have the drawback of side effect and drug resistance [24] for long-term use. However, a glutamatergic N-methyl-D-aspartate receptor antagonist memantine, can also prevent amyloid-induced cholinergic neuron loss, and it is expected to bring about good results if used in combination with a CEI [25].

AMYLOID AND TAU HYPOTHESES

The suppression or removal of the formation of amyloid or neurofibrillary tangles is also crucial in the treatment of AD. Aβ is generated in normal people as well, however, unlike in Alzheimer’s patients, amyloid precursor protein (APP) undergoes a sequential cleavage first by α-secretase and then by γ-secretase, generating a water-soluble and nonpoisonous peptide different from Aβ [26]. In contrast, amyloid or Aβ in Alzheimer’s patients is a insoluble 4-kDa peptide that is generated when APP is cleaved by β- and γ-secretases [27]. γ-secretase is a multiprotein complex comprising presenilin (PSEN) 1 and PSEN 2, which generates Aβ by cleaving the transmembrane domain of APP after its cleavage by β-secretase [28, 29]. For the most part, Aβ generates Aβ1-40, which consists of 40 amino acids, but, due to a large number of cleavage sites, it occasionally generates a small amount of Aβ1-42, which is more likely to form fibrils more resistant to decomposition, making it more toxic to neurons compared to Aβ1-40.

While late-onset AD occurs in people aged 65 or older, FAD develops earlier because FAD is triggered by gene mutations of APP (chromosome 21). PSEN1 (chromosome 14), or PSEN2 (chromosome 1), whereby eliciting Aβ aggregation in earlier years [30, 31]. Of these 3 types, the PSEN1 mutation has a relatively high proportion of Aβ1-42. As Aβ1-42 is more toxic than Aβ1-40, FAD progresses more rapidly in this case, and the time of onset can come as early as 20–30 years of age.

The brain has a small quantity of antioxidant enzymes despite its high amount of oxygen consumption, which makes it susceptible to reactive oxygen species. Aβ causes damage to mitochondrial membranes and hence increases the amount of intracellular H2O2, thus affecting the genes downstream by interacting with numerous
receptors and damaging neurons, ultimately accelerating cell death [32].

Tau is a neuronal microtubule-associated protein that stabilizes axonal microtubules by binding with them. If tau proteins get phosphorylated, they are separated from microtubules, and they form paired helical filaments in the neuronal cytoplasm [33]. Neurofibrillary tangles are abnormal intracellular aggregates of bundles of 12-kDa protein consisting of the residual microtubule-binding sites of tau protein after the truncation of the N- and C-terminal domains. Although it is not clearly known whether Aβ plays a role in the formation of neurofibrillary tangles, a study has reported [34] that the injection of Aβ1-42 into the brain of a tau-transgenic mouse resulted in a 5-fold increase in the formation of neurofibrillary tangles that was elicited by an increase of tau phosphorylation.

Whereas Aβ triggers the formation of neurofibrillary tangles, it is the formation of neurofibrillary tangles rather than Aβ itself that aggravates Alzheimer’s symptoms. In fact, in the case of FTDP-17, which is a chromosome 17-type dementia involving mutations in the tau gene, the symptoms of dementia are manifested without any Aβ aggregation [35].

**Stem cell therapy for AD**

Stem cells have therapeutic effects using regeneration and substitution of cells and tissues themselves. The therapeutic strategy of stem cell has two directions. One is to induce the activation of endogenous stem cell and the other is to regenerate injured cell or tissues through stem cell transplantation (Table 1).

Endogenous stem cells can be induced and show neuroprotective effects by Chemical compounds and factors stimulating stem cells such as allopregnanolone (Apa), fluoxetine, granulocyte colony stimulating factor (G-CSF), AMD3100 and stromal cell-derived factor-1a (SDF-1a). Apa induced endogenous neural precursor cells (NPCs) activation and promoted survival of newly generated cells showing significantly increasing BrdU+ cells as well as improvement of learning and memory in 3xTg-AD mice [36]. Another research group used three factors to stimulate endogenous hematopoietic progenitor cells (HPC). GCSF and AMD3100, CXCR4 antagonist, and SDF-1a facilitated the mobilization and migration of bone marrow derived hematopoietic progenitor cell (BM-HPCs) into brain. AD model mice were improved memory as well as hippocampal neurogenesis in AD animal models after treatment of three factors, whereas Aβ deposition was not changed. These factors may act synergistically to migrate HPC and to produce a therapeutic effect [37]. Fluoxetine treatment was shown the neuronal differentiation and protective effects of NSCs against Aβ induced cell death [38].

It has recently been reported [39-45] that Alzheimer’s symptoms could be alleviated by transplanting stem cells derived from human umbilical cord, amniotic membrane-derived epithelial cells and mesenchyme into the brains of Alzheimer's transgenic animals. The treatment led to improve cognitive and memory performances and increased neuronal survival as a result of the decrease in Aβ, APP generation, and microglia activation. Another study [46] has reported a therapeutic effect of decreasing the size and number of Aβ as a result of differentiating peripheral mononuclear cells into microglia by injecting stromal cell-derived factor 1 into Alzheimer’s transgenic animals.

Transplantation of stem cells has shown promise for improving functional recovery for Alzheimer’s disease. MSCs could promote survival, increased the metabolic activity and help to rescue the AD cell model in vitro [47]. The coculture of human MSCs and BV-2, mouse microglia, increased neprilysine expression, the Aβ-degrading enzyme, under the exposure of Aβ [48]. The transplantations of human and mouse MSC derived stem cells were shown to reduce Aβ deposition, to improved memory and to alleviate the AD pathology in AD mouse models [49-51]. Mouse NSCs were colonized around amyloid plaques and modified to express metalloproteinase 9 (MMP9), a secreted protease reported to degrade aggregated Ab peptides, whereas these NSCs didn’t migrate into other regions after transplantation in AD mouse brain [52]. ADSCs also improved AD pathology involving reduction of Aβ deposition and memory improvement due to decreasing of proinflammatory factors [53]. Human amniotic epithelial cells (HSECs) were observed their survivals and no any immune rejection for 8 weeks. HAEc transplantation significantly ameliorated spatial memory deficits in TG mice, as well as increased acetylcholine levels and the number of hippocampal cholinergic neuritis [39].

Stem cell itself has therapeutic effects however, further studies are needed to determine the appropriate conditions to improve the therapeutic effects for AD pathology.

**Gene therapy for AD**

For the development of new medical drugs, it is necessary to gain a deeper understanding of the genetic factors of AD, the roles of amyloid and tau protein, and the mechanisms involved in neuronal degeneration. The current therapeutic mechanism of Alzheimer’s is to provide maximum support for the functions of the neurons remaining in the patient’s brain. The latest research direction of DAT focuses on early diagnosis, given that the medication that is administered upon the initial manifestation of memory loss can help to maintain the quasi-normal state of cognitive functions longer.
### Table 1. Stem cell therapy for AD

| Cell                                                                 | Additional Treatment                                      | Model                                                                 |
|----------------------------------------------------------------------|-----------------------------------------------------------|----------------------------------------------------------------------|
| Endogeneous bone marrow derived hematopoietic progenitor cell (BM-HPCs) | GCSE, AMD3100 and SDF-1α                                  | APP/PS1 mice                                                          |
| Endogeneous NPCs                                                     | Subcutaneous inj. of Allopregnanolone (Apα)               | 3xTgAD mice                                                          |
| NSCs                                                                | Fluoxetine treatment                                      | In vitro                                                             |
| MSCs                                                                | Coculture with AD model cells                             | Truncated tau (151-391) expressing neuroblastoma cells               |
| HUMSCs                                                              | Coculture with BV2 and Aβ transplantation                 | APP/PS1 mice, Aβ exposure                                            |
| Bone marrow derived mesenchymal stem cells (BM-MSCs)                | Transplantation                                           | AD mice                                                              |
| Human umbilical cord mesenchymal stem cell (HUMSCs)                 | Transplantation                                           | APP/PS1 mice                                                          |
| Bone marrow derived monocytic cells (BMM)                           | Monocyte Differentiation                                   | Irradiated mice                                                      |
| NSCs                                                                | Transplantation                                           | APPswe/PS1dE9 Line 85 mice                                           |
| Adipose derived stem cells (ADSCs)                                  | Intracerebral transplantation                             | APP/PS1 mice                                                          |
| Human amniotic epithelial cells (HAECs)                             | Transplantation                                           | APP/PS1 mice                                                          |

### Table 1. Continued

| Cell                                                                 | Results                                                                 | Ref. |
|----------------------------------------------------------------------|-------------------------------------------------------------------------|------|
| Endogeneous bone marrow derived hematopoietic progenitor cell (BM-HPCs) | *Induction of endogeneous BM-HPCs                                       | 37   |
| Endogeneous NPCs                                                     | *Improved memory                                                        | 36   |
| NSCs                                                                | *Enhance neuronal differentiation                                       | 38   |
| MSCs                                                                | *Protective effects against Aβ induced cell death                       | 47   |
| HUMSCs                                                              | *Promote survival                                                       | 48   |
| Bone marrow derived mesenchymal stem cells (BM-MSCs)                | *Increased the metabolic activity                                       | 49   |
| Human umbilical cord mesenchymal stem cell (HUMSCs)                 | *Rescue the AD cell model                                               | 50   |
| Bone marrow derived monocytic cells (BMM)                           | *Increase neprilysin expression                                          | 51   |
| NSCs                                                                | *Reduce Aβ burden                                                       | 51   |
| Adipose derived stem cells (ADSCs)                                  | *Colonization in white matter tracts                                   | 52   |
| Human amniotic epithelial cells (HAECs)                             | *High conc. Of MMP9 around amyloid plaques                              | 53   |
|                                                                      | *No migration                                                           | 53   |
|                                                                      | *Reduced Aβ deposition                                                  | 53   |
|                                                                      | *Improved memory                                                        | 53   |
|                                                                      | *Decreased proinflammatory factors                                     | 39   |
|                                                                      | *Survival of HAECs for 8 weeks                                          | 39   |
|                                                                      | *Migration without immune rejection                                     | 39   |
|                                                                      | *Ameliorated memory                                                     | 39   |
|                                                                      | *Increased acetylcholine levels                                         | 39   |
There have been recent encouraging results in animal studies with administration of Aβ antibodies to PDAPP mice in order decrease Aβ. They showed the recovery of acetylcholine release and choline absorption in the hippocampus. The learning capacity was also improved [54]. The results have led to related clinical trials in humans [55, 56]. Continuous reduction of Aβ might be another method of addressing Alzheimer's. This can be done with proteases such as neprilysin [57], insulin-degrading enzyme [58, 59], plasmin [60], and cathepsin B [61]. The intraventricular injection of the human neprilysin gene expressing viruses into amyloid transgenic mouse models has contributed to a decrease in Aβ aggregation and neuronal degradation in the frontal cortex and hippocampus [62]. According to a report [63], intraventricular injections of the human neprilysin gene expressing fibroblasts into Aβ-aggregation transgenic mouse models have resulted in a considerable decrease of amyloid plaques. These studies have provided the evidence that proteases can be used as Aβ-reducing therapeutic agents on account of their function of decomposing Aβ and paved the way for cure-oriented studies that focus on protease-expressing neural stem cells.

In an effort to overcome this drawback, the Tuszynski research team has recently conducted a study of ex vivo gene therapy with NGF (Table 2) [64]. Similarly, in clinical trials where human NGF genes were grafted into the fibroblasts harvested from each patient and that were transplanted back into the basal forebrain area of the patient, 6 patients were confirmed to show improvements of cognitive functions and increases of cerebral cortex metabolism in positron emission tomography after 22 months of the intervention without any side effects or toxicity, with 2 of them showing improvements in cognitive performances, electroencephalography, and nicotinic receptor binding [65].

ChAT-overexpressing human neural stem cells (HB1.F3.ChAT) were transplanted into Alzheimer's animal models [40, 66]. As a result, it was confirmed that learning and memory functions were restored, the volume of acetylcholine in the cerebrospinal fluid was increased, and the transplanted cells were successfully migrated to several brain regions [40, 66]. According to a report, it was observed that transplantation of nerve growth factor (NGF) expressing human NSCs into hippocampus region of ibotenic acid-injected mice (one of the cognitive dysfunction models) could be improved the learning and memory as well as differentiated into neuron and astrocytes. These NGF carrying hNSCs showed the further neuro-protective effects than parental hNSCs against cytotoxic agents [67].

Among the cells expressing foreign genes that are used for Alzheimer's therapy, HB1.F3.ChAT has proved its effectiveness. When these cells were applied to animal models with cognitive defects induced by AF64A and kainic acid, similarly safe and effective results were obtained [66]. Taken together, it can be expected that therapies with cells that simultaneously express neurotransmitters and growth factors could achieve better results.

CONCLUSION

Alzheimer's therapies so far have revolved around retarding the progression of the disease rather than restoring the damaged neurons. However, the recent trend is to focus on removing the causes of the disease with stem cell-based therapies. If the causes of AD are understood more deeply and safer cell therapies are developed, AD could be conquered in the not too distant future.

ACKNOWLEDGEMENTS

This study was supported by grants from National Research Foundation of Korea funded by the Korean Ministry of Education, Science and Technology (No. 2010-0023426) and KRIBB Research.
Initiative Program (KGM4241433).

REFERENCES

1. Alzheimer’s association (us) (2012) 2012 Alzheimer’s disease facts and figures. Alzheimer’s association. Washington, DC.
2. Alzheimer A (1907) Übereine eigenartigeErkrankung der Hirnrinde. AllgemeineZeitschriftfürPsychiatriePsychisch-GerichtlichMedizin46:146-148.
3. Williams S, Chalmers K, Wilcock GK, Love S (2005) Relationship of neurofibrillary pathology to cerebral amyloid angiopathy in Alzheimer’s disease. Neuropathology and Applied Neurobiology31:414-421.
4. Liu YH, Zeng F, Wang YR, Zhou HD, Giunta B, Tan J, Wang YJ (2013) Immunity and Alzheimer’s disease: immunological perspectives on the development of novel therapies. Drug Discov Today18:1212-1220.
5. Poduslo JF, Hultman KL, Curran GL, Preboske GM, Chamberlain R, Marjańska M, Garwood M, Jack CR Jr, Wengenack TM (2011) Targeting vascular amyloid in arterioles of Alzheimer disease transgenic mice with amyloid β protein antibody-coated nanoparticles. J NeuropatholExpNeurol70:653-661.
6. Feldman H, Gracon S (1996) Alzheimer’s disease: symptomatic drugs under development. In: Clinical Diagnosis and Management of Alzheimer’s Disease (Gauthier S, ed), pp239-259. Martin Dunitz Ltd, London.
7. Rebeck GW, Kindy M, LaDu MJ (2002) Apolipoprotein E and Alzheimer’s disease: the protective effects of ApoE2 and E3. J Alzheimers Dis4:145-154.
8. Braak H, Braak E (1997) Diagnostic criteria for neuropathologic assessment of Alzheimer’s disease. Neurobiol Aging18:S85-S88.
9. Braak H, Braak E (1991) Neuropathologicalstaging of Alzheimer-related changes. ActaNeuropathol82:239-259.
10. Whitehouse PJ, Price DL, Clark AW, Coyle JT, DeLong MR (1981) Alzheimer disease: evidence for selective loss of cholinergic neurons in the nucleus basalis. Ann Neurol10:122-126.
11. Bartus R, Dean RL, Beer B, Lippa AS (1982) The cholinergic hypothesis of geriatric memory dysfunction. Science217:408-411.
12. Coyle JT, Price DL, DeLong MR (1983) Alzheimer’s disease: a disorder of cortical cholinergic innervation. Science219:1184-1190.
13. Davies P, Maloney AJ (1976) Selective loss of central cholinergic neurons in Alzheimer’s disease. Lancet2:1403.
14. Perry EK, Perry RH, Gibson PH, Blessed G, Tomlinson BE (1977) A cholinergic connection between normal aging and senile dementia in the human hippocampus. NeurosciLett685-89.
15. Sims NR, Bowen DM, Allen SJ, Smith CC, Neary D, Thomas DJ, Davison AN (1983) Presynaptic cholinergic dysfunction in patients with dementia. J Neurochem40:503-509.
16. Dekosky ST, Harbaugh RE, Schmitt FA, Bakay RA, Chui HC, Knoopman DS, Reeder TM, Shetter AG, Senter HJ, Marksbery WR (1992) Cortical biopsy in Alzheimer’s disease: diagnostic accuracy and neurochemical, neuropathological, and cognitive correlations. IntraventricularBethanecol Study Group. Ann Neurol32:625-632.
17. Rinne JO, Kaasinen V, Jarvenpaa T, Nagren K, Roivainen A, Yu M, Oikonen V, Kurki T (2003) Brain acetylcholinesterase activity in mild cognitive impairment and early Alzheimer’s disease. J NeurolNeurosurg Psychiatry74:113-115.
18. Sarter M, Bruno JP (2004) Developmental origins of the age-related decline in cortical cholinergic function and associated cognitive abilities. Neurobiol Aging25:1127-1139.
19. Crow TJ, Grove-White IG (1973) An analysis of the learning deficit following hyoscine administration to man. Br J Pharmacol49:322-327.
20. Ridley RM, Barratt NG, Baker HF (1984) Cholinergic learning deficits in the marmoset produced by scopolamine and ICV hemicholinium. Psychopharmacology (Berl)83:340-345.
21. Ridley RM, Murray TK, Johnson JA, Baker HF (1986) Learning impairment following lesion of the basal nucleus of Meynert in the marmoset: modification by cholinergic drugs. Brain Res376:108-116.
22. Mandel RJ, Thal LJ (1988) Physostigmine improves water maze performance following nucleus basalis magnocellularis lesions in rats. Psychopharmacology (Berl)96:421-425.
23. Dekker AJ, Connor DJ, Thal LJ (1991) The role of cholinergic projections from the nucleus basalis in memory. NeurosciBiobehav Rev15:299-317.
24. Hake AM (2001) Use of cholinesterase inhibitors for treatment of Alzheimer disease. Cleve Clin J Med68:608-616.
25. Nyakas C, Granic I, Halmy LG, Banerjee P, Luiten PG (2011) The Basal Forebrain Cholinergic System in Ageing and Dementia. Rescuing cholinergic neurons from Neurotoxic Amyloid-beta42 with Memantine. Behav Brain Res221:594-603.
26. Esch FS, Keim PS, Beattie EC, Blacher RW, Culwell AR, Oltersdorf T, McClure D, Ward PJ (1990) Cleavage of amyloid beta peptide during constitutive processing of its precursor.
Science 248:1122-1124.
27. Vassar R, Bennett BD, Babu-Khan S, Kahn S, MendiMex EA, Denis P, Teplow DB, Ross S, Amarante P, LocellR, Luo Y, Fisher S, Fuller J, Edenson S, Lile J, Jarosinski MA, Biere AL, Curran E, Burgess T, Louis JC, Collins F, Treaker J, Rogers G, Citron M (1999) Beta-secretase cleavage of Alzheimer’s amyloid precursor protein by the transmembrane aspartic protease BACE. Science 265:735-741.
28. Wolfe MS, Xia W, Ostaszewski BL, Diehl TS, Kimberly WT, Selkoe DJ (1999) Two transmembrane aspartates in presenilin-1 required for presenilin-endoproteolysis and gamma-secretase activity. Nature 398:513-517.
29. Francis R, McGrath G, Zhang J, Ruddy DA, Sym M, Apfeld J, Nicoll M, Maxwell M, Hai B, Ellis MC, Parks AL, Xu W, Li J, Gurney M, Myers RL, Himes CS, Hiesch R, Ruble C, Nye JS, Curtis D (2002) aphi-1 and pen-2 are required for Notch pathway signaling, gamma-secretase cleavage of betaAPP, and presenilin protein accumulation. Dev Cell 3:85-97.
30. Muirhead KE, Borger E, Atikien L, Conway SJ, Gunn-Moore FJ (2010) The consequences of mitochondrial amyloid beta peptide in Alzheimer's disease. Biochem J 426:255-270.
31. Su B, Wang X, Nunomura A, Moreira PI, Lee HG, Perry G, Smith MA, Zhu X (2008) Oxidative stress signaling in Alzheimer’s disease. Curr Alzheimer Res 5:525-532.
32. Cappai R, Barnham KJ (2008) Delineating the mechanism of Alzheimer’s disease A beta peptide neurotoxicity. Neurochem Res 33:526-532.
33. Iqbal K, Alonso AC, Gong CX, Khatoun S, Pei JJ, Wang JZ, Grundke-Iqbal I (1998) Mechanisms of neurofibrillary degeneration and the formation of neurofibrillary tangles. J Neural TransmSuppl 53:169-180.
34. Gotz J, Chen F, van Dorpe J, Nitsch RM (2001) Formation of neurofibrillary tangles in P301I tau transgenic mice induced by Abeta 42 fibrils. Science 293:1491-1495.
35. Wilcock GK, Esiri MM (1982) Plaques, tangles and dementia. A quantitative study. J NeurolSci 56:343-356.
36. Shin J-W, Lee JK, Lee JE, Min W-K, Schuchman EH, Jin HK, Bae J (2011) Combined Effects of Hematopoietic Progenitor Cell Mobilization from Bone Marrow by Granulocyte Colony Stimulating Factor and AMD3100 and Chemotaxis into the Brain Using Stromal Cell-Derived Factor-1α in an Alzheimer’s Disease Mouse Model. Stem cells 29:1075-1089.
37. Singh C, Liu L, Wang JM, Irwin RW, Yao J, Chen S, Henry S, Thompsons RF, Brinton RD (2012) Allopregnanolone restores hippocampal-dependent learning and memory and neural progenitor survival in aging 3xTgAD and nonTg mice. Neurobiol Aging 33:1493-1506.
38. Chang K-A, Kim J, Kim S, Joo Y, Shin KY, Kim S, Kim H-S, Suh Y-H (2012) Therapeutic potentials of neural stem cells treated with fluoxetine in Alzheimer’s disease. Neurochem Int 61:885-891.
39. Zilka N, Zilkova M, Kazmerova Z, Sarissdy M, Gignkova V, Novak M (2011) Mesenchymal stem cells rescue the Alzheimer’s disease cell model from cell death induced by misfolded truncated tau. Neurosci 193:330-337.
40. Kim J-Y, Kim DH, Kim JH, Lee D, Jeon HB, Kwon S-J, Kim SM, Yoo YJ, Lee EH, Choi SJ, Sce SW, Lee JI, Na DL, Yang SY, Oh W, Champ JW (2012) Soluble intracellular adhesion molecule-1 secreted by human umbilical cord blood-derived mesenchymal stem cell reduces amyloid-b plaques. Cell Death Differ 19:680-691.
41. Bae JS, Jin HK, Lee JK, Richardson JC, Carter JE (2013) Bone marrow-derived mesenchymal stem cells contribute to the reduction of amyloid-β deposits and the improvement of synaptic transmission in a mouse model of pre-dementia Alzheimer’s disease. Curr Alzheimer Res 10:524-531.
42. Yang H, Xie Z, Wei L, Yang H, Yang S, Zhu Z, Wang P, Zhao C, Bi J (2013) Human umbilical cord mesenchymal stem cell-derived neuron-like cells rescue memory deficits and reduce amyloid-beta deposition in an AβPP/PS1 transgenic mouse model. Stem Cell Res Ther 4:76.
43. Magga G, Savchenko E, Malm T, Rolova T, Pollari E, Valonen P, Lehtonen S, Jantunen E, Aarnio J, Lehenkari P, Koistinaho M, Muona A, Koistinaho J (2012) Production of monocytes cells from bone marrow stem cells: therapeutic usage in Alzheimer’s disease. J Cell Mol Med 16:1060-1073.
44. Njiee G, Kantorovich S, Astary GW, Green C, Zheng T, Sempel-Rowland SL, Steindler DA, Sarntinoranont M, Streit WJ, Borchelt DR (2012) A Preclinical Assessment of Neural Stem Cells as Delivery Vehicles for Anti-Amyloid Therapeutics. PLoS ONE 7:e34097.
45. Ma T, Gong K, Ao Q, Yan Y, Song B, Huang H, Zhang X, Gong Y (2013) Intracerebral transplantation of adipose-derived mesenchymal stem cells alternatively activates microglia and ameliorates neuropathological deficits in Alzheimer’s disease mice. Cell Transpl 22:S113-126.
46. Xue SR, Chen CF, Dong WL, Hui GZ, Liu TJ, Guo LH (2012) Therapeutic effects of human amniotic epithelial cell transplantation on double-transgenic mice co-expressing APPsw and PS1ΔE9-deleted genes. Sci China Life Sci 55:132-140.
47. Bales KR, Tzavara ET, Wu S, Wade MR, Bymaster FP, Paul SM, Nomikos GG (2006) Cholinergic dysfunction in a mouse model of Alzheimer disease is reversed by an anti-Ab
antibody J Clin Invest 116:825-832.
48. Szabo P, Relkin N, Weksler ME (2008) Natural human antibodies to amyloid β peptide. Autoimmun Rev 7:415-420.
49. Relkin NR, Szabo P, Adamiak B, Burgut T, Monthe C, Lent RW, Younkin S, Younkin L, Schiff R, Weksler ME (2009) 18-Month study of intravenous immunoglobulin for treatment of mild Alzheimer disease. Neurobiol Aging 30:1728-1736.
50. Iwata N, Tsubuki S, Takaki Y, Shirotani K, Lu B, Gerard NP, Hama E, Lee HJ, Saito TC (2001) Metabolic regulation of brain Abeta by neprilysin. Science 292:1550-1562.
51. Farris W, Mansourian S, Chang Y, Lindley L, Eckman EA, Frosch MP, Eckman CB, Tanzi RE, Selkoe DJ, Guenette S (2003) Insulin-degrading enzyme regulates the levels of insulin, amyloid beta protein and the beta-amyloid precursor protein intracellular domain in vivo. Proc Natl Acad Sci USA 100:4162-4167.
52. Miller BC, Eckman EA, Sambamurti K, Dobbs N, Chow KM, Eckman CB, Hersh LB, Thiele DL (2003) Amyloid-beta peptide levels in brain are inversely correlated with insulin activity levels in vivo. Proc Natl Acad Sci USA 100:6221-6226.
53. Melchior JP, Pawlak R, Strickland S (2003) The tissue plasminogen activator-plasminogen proteolytic cascade accelerates amyloid-beta degradation and inhibit Abeta-induced neurodegeneration. J Neurosci 23:8867-8871.
54. Mueller-Steiner S, Zhou Y, Arai H, Roberson ED, Sun B, Chen J, Wang X, Yu G, Esposito L, Mucke L, Gan L (2006) Antiamyloidogenic and neuroprotective functions of cathepsin B: implications for Alzheimer's disease. Neuron 51:703-714.
55. Marr RA, Rockenstein E, Mukherjee A, Kindy MS, Hersh LB, Gage FH, Verma IM, Masliah E (2003) Neprilysin gene transfer reduces human amyloid pathology in transgenic mice. J Neurosci 23:1992-1996.
56. Hemming ML, Patterson M, Reske-Nielsen C, Lin L, Isaacson O, Selkoe DJ (2007) Reducing amyloid plaque burden via ex vivo gene delivery of an Ab-degrading protease: a novel therapeutic approach to Alzheimer disease. PLoS Med 4:e262.
57. Lee HJ, Lim IJ, Park SW, Ko YB, Kim SU (2012) Human neural stem cells genetically modified to express human nerve growth factor gene restore cognition in mouse with ibotenic acid-induced cognitive dysfunction. Cell Transplant 21:2487-2496.
58. Tuszyński MH, Thal L, Pay M, Salmon DP, U HS, Bakay R, Patel P, Blesch A, Vahlsing HL, Ho G, Tong G, Potkin SG, Fallon J, Hansen L, Mufson EJ, Kordower JH, Gall C, Conner J (2005) A phase 1 clinical trial of nerve growth factor gene therapy for Alzheimer disease. Nat Med 11:551-555.
59. Eriksson-Jönhagen M, Linderoth B, Lind G, Aladellie L, Almkvist O, Andreasen N, Blennow K, Bogdanovic N, Jelic V, Kadir A, Nordberg A, Sundström E, Wahlund LO, Wall A, Wiberg M, Winblad B, Seiger A, Almqvist P, Wahlberg L (2012) Encapsulated cell biodelivery of nerve growth factor to the Basal forebrain in patients with Alzheimer's disease. Dement Geriatr Cogn Disord 33:18-28.
60. Park D, Lee HJ, Joo SS, Bae DK, Yang G, Yang YH, Lim I, Matsuo A, Tooyama I, Kim YB, Kim SU (2012) Human neural stem cells over-expressing choline acetyltransferase restore cognition in rat model of cognitive dysfunction. Exp Neurol 234:521-526.
61. Park D, Joo SS, Kim TK, Lee SH, Kang H, Lee HJ, Lim I, Matsuo A, Tooyama I, Kim YB, Kim SU (2012) Human neural stem cells overexpressing choline acetyltransferase restore cognitive function of kainic acid-induced learning and memory deficit animals. Cell Transplant 21(1):365-371.
62. Wen SR, Qi HP, Ren YJ, Liu GJ, Gong FC, Zhong H, Bi S (2011) Expression of δNp73 in hippocampus of APP/PS1 transgenic mice following GFP-BMSCs transplantation. Neuroil Res 33:1109-1114.
63. Chen SQ, Cai Q, Shen YY, Wang PJ, Teng GJ, Li MH, Zhang W, Zang FC (2012) (1)H-MRS evaluation of therapeutic effect of neural stem cell transplantation on Alzheimer's disease in AβPP/PS1 double transgenic mice. J Alzheimers Dis 28:71-80.
64. Darlington D, Deng J, Giunta B, Hou H, Sanberg CD, Kuzmin-Nichols N, Zhou HD, Mori T, Ehrhart J, Sanberg PR, Tan J (2013) Multiple Low-Dose Infusions of Human Umbilical Cord Blood Cells Improve Cognitive Impairments and Reduce Amyloid-β-Associated Neuropathology in Alzheimer Mice. Stem Cells Dev 22:412-421.
65. Esmaeilzade B, Nobakht M, Joghataei MT, RahbarRoshandel N, Rasouli H, SamadiKuchaksaraei A, Hosseini SM, Najafzade N, Asalgoo S, HejazianLB, MoghaniGhoroghi F (2012) Delivery of epidermal neural crest stem cells over-expressing choline acetyltransferase to hippocamp in Alzheimer's disease rat model. Iran Biomed J 16:1-9.
66. Naert G, Rivest S (2012) Hematopoietic CC-chemokine receptor 2 (CCR2) competent cells are protective for the cognitive impairments and amyloid pathology in a transgenic mouse model of Alzheimer's disease. Mol Med 18:297-313.
67. Wang Q, Xu Y, Chen JC, Qin YY, Liu M, Liu Y, Xie MJ, Yu ZY, Zhu Z, Wang W (2012) Stromal cell-derived factor 1a decreases β-amyloid deposition in Alzheimer's disease mouse model. Brain Res 1459:15-26.