알츠하이머치매와 파킨슨병의 병인과 유전자, 약물 및 줄기세포치료술 개발

서 유 헌
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Pathogenesis, Potential Gene, Drug and Stem cell Therapy for Alzheimer's and Parkinson's Disease

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Several lines of evidence suggest that some neurotoxicity in Alzheime's disease(AD) is caused by proteolytic fragments of amyloid precursor protein (APP), which generates amyloid beta (Aβ) by proteolysis. However, amyloid beta (Aβ) may not be the sole active component involved in the pathogenesis of AD. The CTFs, Carboxy-terminal fragments of APP, including AICD (Amyloid Intra Celluar Domain) have been found in AD patients' brain. We proposed the hypothesis that CTFs might importantly contribute to pathogenesis of AD by different mechanisms from Aβ.

To investigate the regulatory genes responsible for the neuropathology in AD, we performed microarray analysis in APPV717I-CT100 transgenic mice and isolated the

S100a9 gene. We also found that S100a9 expression was increased in the brains of Tg2576 mice, animal model of AD and AD patients. Silencing S100a9 gene decreased the production of inflammatory cytokines induced by Aβ or APP-CTs. In Tg2576 mice, knockdown and knockout of S100a9 gene significantly reduced the neuropathology and improved the learning ability. These results clearly show that the upregulation of S100a9 gene plays an important role in the neuropathology and memory impairment in AD, suggesting that the regulation of this gene has a therapeutic potential for AD.

14-3-3 proteins have recently been reported to be abundant in the neurofibrillary tangles (NFTs) observed inside the neurons of brains affected by Alzheimer's disease (AD).

These NFTs are mainly constituted of phosphorylated Tau protein to bind 14-3-3. Despite this indication of 14-3-3 protein involvement in the AD pathogenesis, the role of 14-3-3 proteins in the Tauopathy remains to be clarified. In the present study we elucidated the role of 14-3-3 proteins in the molecular pathways leading to Tauopathies. These data suggest a rationale for a possible pharmacologic intervention of the Tau/14-3-3 interaction.

We found that Dehydroevodiamine×HCI (DHED), carboxy DHED, Minocycline, BT11 and Methyl Paraben (MP) had neuro-protective, memory or motor enhancing activities using various in vitro and in vivo models, which might be beneficial in AD.

DHED might be one of the potential therapeutic candi-

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dates for AD, including other neurodegenerative diseases. We have completed the phase I clinical study for this agent and are now preparing its derivatives to increase the solubility of DHED. A DHED derivative greatly reduced the learning and memory deficit and neuropathology including neuritic plaques and Aβ load. Aβ lowering effect of a DHED derivative is more potent than that of Donepezil which is the most commonly used drug for AD at present. These results indicate that DHED and its derivatives might be very effective for Alzheimer's disease but also the vascular type of dementia.

BT-11 was extracted from the roots of the plant polygala tenuifolia willdenow and improved memory impairments in rats, the stress-induced memory impairments through increment of glucose utilization by 18FDG-PET and enhanced memory in normal and elderly humans. BT can be used as nutraceutical that provide heath benefits; including disease prevention and/or treatment.

We examined whether intracerebrally or intravenously transplanted human adipose-derived stem cells (hASCs) could have therapeutic or preventive effects in AD mouse model (Tg2576). We demonstrated that intracerebral or intravenous injection of hASCs rescued memory deficit and gave benefits of blocking the pathogenesis in the brain of Tg mice by reducing the number of plaques and neuropathology. Hence, we demonstrated that hASCs are expected to be preventive and therapeutic approach for AD.

PD is caused by the progressive degeneration of dopaminergic neurons and is characterized by cytoplasmic inclusions known as Lewy bodies in the substantia nigra. α -Synuclein is known to be the main component of Lewy body.

α-Synuclein (α-SN) has been postulated to play a central role in the pathogenesis of Parkinson's disease(PD), AD, and other neurodegenerative disorders. However, little is known about the neuronal functions and mechanisms underlying neuronal loss and immune abnormalities. Here, we show that α-SN plays dual roles of neuroprotection and neurotoxicity depending on its concentration and a-SN expression in peripheral immune system might be one of the primary causes of immune abnormalities in PD patients. Furthermore, we first demonstrated that microglial migration is up-regulated by α-SN-mediated induction of CD44 and MT1-MMP in Parkinson's disease. We also demonstrated that nuclear translocation of α–SN was mediated by the karyopherin α6 and regulated by the SUMO and α-SN might affect transcription of genes.

We isolated active constituent from indian plant(Neeli) against α-Synuclein toxicity and The active constituent was found to be methyl paraben (MP).

MP decreased ROS generation, rotational behavior increased by 6-OHDA and increased Rotarod performance and memory reduced by 6-OHDA.

In addition, MP increased TH immunoristochemical staining in the subsetantia Nigra of 6-OHDA-lesioned mice. MP might be a potential drug for PD. In many studies, it has been described that the stuctural and functional alteration of mitochondria were associated with neurodegenerative dieases including PD. Therefore, we investigated the effects of intra-venous injection of hASCs on mitochondrial functions in PD mouse model. Intravenous injection of hASCs greatly impoved behavior, pathology and mitochondrial dysfuction in PD mice model.

Intravenous personalized autologous hASC therapy might be revolutionary if the effects are confirmed in clinical study in future.