Title of Project : Development of Molecular Targeted Disease Modifying Therapy for Polyglutamine Diseases

Gen Sobue
(Nagoya University, Graduate School of Medicine, Professor)

Research Area : Medicine, dentistry, and pharmacy

Keyword : Molecular pathophysiology

【Purpose and Background of the Research】

Neurodegenerative diseases are a group of devastating disorders which enfeeble movement and/or cognitive functions by affecting a certain population of neurons within the central nervous system. Although recent advances in molecular biology have identified the accumulation of abnormal proteins as the molecular basis for various neurodegenerative diseases, development of therapies is now challenged by drawbacks in clinical trials for neurodegenerative diseases: limited pools of potential participants, insensitive outcome measures and the slow progression of disease. The aims of this study are to develop model neurons derived from iPS cells from polyglutamine disease patients, to identify disease-related molecules, and to develop molecular-targeted therapies.

【Research Methods】

1) Development of model neurons derived from iPS cells from polyglutamine disease patients

Fibroblasts obtained from patients with polyglutamine disease, such as spinal and bulbar muscular atrophy (SBMA), will be differentiated to motor neurons, and will be used as a model for the screening of therapies.

2) Identification of low-molecular compounds activating ubiquitin-proteasome system (UPS)

Using iPS-derived motor neurons, we will identify low-molecular compounds that increase UPS activity and thereby selectively facilitate degradation of abnormal polyglutamine proteins. The selected compounds will be tested in animal models of polyglutamine diseases. Natural ingredients that activates UPS will also examined in the animal models of polyglutamine-mediated neurodegeneration.

3) Development of inducers of heat shock proteins (HSPs)

We have shown that 17-DMAG, an oral inhibitor of Hsp90, and paeoniflorin, a monoterpen-glucosid, potently induce the expression of Hsp70 and HSPs. The therapeutic effects, safety, and pharmacokinetics of these compounds will be evaluated in the animal models of polyglutamine diseases.

4) Identification of pathogenesis-related molecules and molecular-targeted therapies

Using a differential gene expression profile, we showed that a neuropeptide CGRP1 is prominently up-regulated in spinal motor neurons in an SBMA mouse model. In the present study, we will examine the effects of CGRP1 in cellular and animal models of polyglutamine diseases. Low-molecular compounds that inhibit CGRP1 expression will also be screened, and tested in the iPS-derived model neurons and animal models.

【Expected Research Achievements and Scientific Significance】

Neurons will be derived from iPS cells from polyglutamine disease patients, and used a cellular model for development of molecular target therapies. Low-molecular compounds that reinforce UPS and HSPs will also be identified and tested in the cellular and animal models of polyglutamine diseases.

【Publications Relevant to the Project】

・Banno H, Katsuno M, Suzuki K, et al. Phase 2 trial of leuprorelin in patients with spinal and bulbar muscular atrophy. Ann Neurol. 65: 140-150, 2009.
・Tokui K, Adachi H, Waza M, et al. 17-DMAG ameliorates polyglutamine-mediated motor neuron degeneration through well-preserved proteasome function in a SBMA model mouse. Hum Mol Genet. 18: 898-910, 2009.

【Term of Project】　　　FY2009-2013

【Budget Allocation】　　122,100 Thousand Yen

【 Homepage Address and Other Contact Information】
　　http://www.med.nagoya-u.ac.jp/medical/102/p10224.html