

【Grant-in-Aid for Scientific Research(S)】
Biological Sciences (Agricultural sciences)



Title of Project : Physiological actions and pathological relevance of growth factors in the brain

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Research Area : Agricultural sciences

Keyword : Physiology, Pathological condition

【Purpose and Background of the Research】

Progranulin is a growth factor that has gained attention with recent discoveries of its multifunctional roles in normal brain development and neurodegenerative disorders. We have demonstrated that progranulin is a sex steroid-inducible gene that is involved in masculinization of the perinatal rodent brain. We have also found that gene expression of progranulin, as well as neurogenesis, is enhanced by estrogen in the hippocampus in adult rats, suggesting that progranulin mediates the mitogenic effects of estrogen on neural progenitor cells. Since it has been recently reported that mutations in progranulin gene are responsible for a type of frontotemporal lobar degeneration in humans, progranulin appears to be also involved in protecting neurons from degeneration. The research group of this study has identified abnormally phosphorylated TAR DNA-binding protein of 43 kDa (TDP-43) as a component of inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. The aim of this study is to elucidate the molecular mechanisms regulating neural cell fate by growth factors in the brain under both physiological and pathological conditions, and the relevance of growth factor insufficiency to the deposition of abnormal proteins that lead neurodegenerative diseases.

【Research Methods】

By means of progranulin-deficient mice and other animal models we have generated, physiological functions of progranulin and other growth factors in the brain in regulating neurogenesis, cell differentiation, cell death, neurodegeneration and behaviors will be studied *in vivo*. The actions of growth factors at cellular levels and their signal transduction mechanisms will be also analyzed *in vitro* using neural progenitor cell culture derived from various animal models.

To explore the molecular mechanisms of the deposition of abnormally phosphorylated TDP-43 in neurons, pathological and biochemical analyses will be performed on

brain specimens suffering from various neurodegenerative diseases. Using animal and cellular models, including progranulin-deficient mice and TDP-43 transgenic mice, the mechanisms underlying TDP-43 deposition and resultant neurodegeneration under the condition of growth factor insufficiency will be also studied.

【Expected Research Achievements and Scientific Significance】

This study aims to explore physiological significance of growth factors in normal development and maintenance of brain functions. The underlying mechanisms for growth factor actions will be also clarified at cellular and molecular levels, which lead us to a better understanding of the biological roles of growth factors in the brain. This study will provide molecular basis of neurodegeneration due to growth factor insufficiency followed by deposition of abnormal proteins and contribute to develop new insights for prevention and cure of neurodegenerative diseases.

【Publications Relevant to the Project】

Nedachi T, Nishihara M et al. Progranulin enhances neural progenitor cell proliferation through glycogen synthase kinase 3 β phosphorylation. *Neuroscience* 185, 106-115, 2011.

Ahmed Z, Nishihara M et al. Accelerated lipofuscinosis and ubiquitination in granulin knockout mice suggests a role for progranulin in successful aging. *Am J Pathol* 177, 311-324, 2010.

【Term of Project】 FY2011-2015

【Budget Allocation】 155,800 Thousand Yen

【Homepage Address and Other Contact Information】

<http://www.vm.a.u-tokyo.ac.jp/seiri/>