Evaluation of the Role of Endoplasmic Reticulum Stress and Novel Neurodegeneration Inducing Factor PRMT8 in the Pathogenesis of Alzheimer's Disease Model Mouse

Abstract of Doctoral Thesis

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Neurodegenerative diseases such as Alzheimer's disease (AD) were refractory disease, thus finding methods for diagnosis and treatment are crucial. It is proposed the 'amyloid cascade hypothesis' that deposition of amyloid-β (Aβ) (amyloid pathology) is the initial pathological event in AD, followed by hyperphosphorylation of tau (tau pathology), and finally neurodegeneration and cell death. However, the mechanistic link(s) between these AD pathological features remains unclear. Familial AD is caused by mutations in *APP*, *PSEN1* and *PSEN2* genes, which encode amyloid precursor protein (APP), presenilin 1 (PS1) and presenilin 2 (PS2), respectively. Several AD model mice containing gene mutations associated with familial AD; these APP and/or PS1-overexpressing Transgenic (Tg) mice have been used widely as AD mouse models. However, there is concern that the elevated ER stress phenotype might be an artifact of overexpression of APP and PS1. Based on these research background, this research have 2 project for the aim of “Re-examining the relationship between AD pathophysiology and endoplasmic reticulum stress”, and “Examination of the effect of PRMT 8 on neuropathology”.

In project 1, to determine whether the ER stress response is heightened because of Aβ pathology, PS1 mutation, several ER stress markers expression levels were investigated in mouse models of several amyloidosis and tauopathy. In result, no difference in any of the stress markers was observed between wild-type (WT) mouse, *App* knock-in mouse, the model shows Aβ deposition except overexpression of APP, APP-Tg mouse, and Tau-Tg mouse. On the other hand, the mouse of models express genetic modification of PS1 showed upregulation of some ER stress markers. These results indicate that “neither Aβ deposition, APP overexpression, nor tau pathology result in detectable ER stress”. It is assumed that the genetic modification of PS1 induces ER stress through a mechanism that is not related to the Aβ pathology.

In project 2, I focused on Protein Arginine Methyltransferase 8 (PRMT 8) that was identified as protein which tau interaction altered by amyloid pathology. To investigate the role of PRMT8 in AD pathogenesis, *PRMT8* gene was deleted or overexpressed in $App^{NL\text{-}G\text{-}F}$ mouse x *MAPT* KI mouse; double KI (dKI) as AD model mouse and pathological features were investigated by biochemical and histological analysis. In result, introducing PRMT8 into dKI mouse via the AAV vector resulted in upregulated phosphorylated tau level, inducted brain inflammation, apoptotic cell-death pathways, and severe vacuole-like structure. However, these pathological phenotypes were observed in PRMT8 introduced Tau-KO and WT mouse. Contrary to expectations, this suggests “PRMT8 is a factor that induces neurodegeneration independent of tau pathology”.

This research provides new information on the study of neurodegenerative diseases including AD.