IS02-4 **Disease-Modifying Therapeutics for Parkinson's Disease and Amyotrophic Lateral Sclerosis**

○Kohji FUKUNAGA[1]
[1]Tohoku University Graduate School of Pharmaceutical Sciences

Development of disease-modifying therapeutics has been expected in treat neurodegenerative disorders such Parkinson's disease and amyotrophic lateral sclerosis (ALS). Like tau in the Alzheimer's disease, proteinopathy through aggregation of α-synuclein and TDP-43 is causative for neurodegenerative process. We recently found a novel mechanism of aggregation of α-synuclein in Parkinson's disease model. Fatty acid binding protein 3 (FABP3) overexpression aggravates arachidonic acid-induced α-synuclein oligomerization and promotes cell death in PC12 cells compared with mock cells. Indeed, FABP3 null mice were resistant to MPTP-induced dopaminergic neurodegeneration and motor deficits. We next observed that formation of TDP-43 inclusion in neuro2A cells is aggravated by overexpression of sigma-1 receptor (Sig-1R) mutation associated ALS. The TDP-43 aggregation in the cytosol under ER stress condition was associated with decreased proteasome activity induced by Sig-1R mutation. It is well known that Sig-1R is localized in the mitochondria-associated ER membrane and its stimulation promotes calcium transport to mitochondria, thereby elevating ATP production. The treatment with methyl pyruvate totally inhibited TDP-43 accumulation by Sig-1R mutation. Taken together, these findings provide novel strategy to modify the proteinopathy induced by α-synuclein and TDP-43 in the neurodegenerative disorders.