Epigenetyczny mechanizm deregulacji szlaku sygnałowego mTOR i procesu autofagii w nowych mysich modelach choroby Alzheimera

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Absrtact

Accumulation of homocysteine in our body is known as hyperhomocysteinemia. It results from insufficient dietary intake of vitamin B_6, B_{12}, folic acid or mutations in homocysteine metabolism related genes. Accumulated homocysteine is metabolized to thioester homocysteine thiolactone. Homocysteine thiolactone is highly reactive and modifies ε-amino group of a protein Lys residue in a reaction known as *N*-homocysteinylation. Protein *N*-homocysteinylation can affect protein structure and impair protein function.

Hyperhomocysteinemia is a risk factor for many diseases, including neurodegenerative diseases such as Alzheimer's disease, the leading cause of dementia in the elderly. Alzheimer's disease is caused by accumulation of amyloid beta and phosphorylated tau proteins and is characterized by upregulation of the mTOR signaling pathway, which leads to autophagy inhibition. Autophagy is a multi-step process in which damaged organelles and proteins, including amyloid beta and phosphorylated tau, are removed. Molecular mechanisms of mTOR activation and autophagy inhibition remain to be fully elucidated.

Homocysteine level is elevated while the activity of homocysteine metabolism related enzymes such as paraoxonase 1 and bleomycin hydrolase are lowered in brains of Alzheimer's disease patients. In addition, hyperhomocysteinemia leads to mTOR activation and autophagy inhibition. The mechanism by which hyperhomocysteinemia leads to Alzheimer's disease is still not fully understood.

The overall goal of the present thesis was to examine mechanisms by which genetic deficiencies in homocysteine thiolactone metabolism can lead to Alzheimer's disease, focusing on an epigenetic mechanism of mTOR activation and autophagy inhibition in novel mouse models of Alzheimer's disease.