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Development of therapeutic agents for neurodegenerative diseases targeting ubiquitinated protein aggregates
ユビキチン化蛋白質の凝集体を標的とした神経変性疾患に共通な治療薬の開発

【Keywords】

Parkinson's disease	Alzheimer's disease	Cancer	Autoimmune disease	Aging

■Summary

・Parkinson's disease (PD) is an intractable neurodegenerative disease characterized by dysfunction and cell death (loss) of neurons that control motor and cognitive functions. The major causative molecule of PD is α-synuclein. Ubiquitinated α-synuclein oligomers (multimers) are highly toxic to neurons and cause PD.
・**We have identified three proteins that control α-synuclein cytotoxicity**. Intriguingly, these three were found to control the neurotoxicity in Alzheimer's disease (AD), another neurodegenerative disease. Based on these findings, we aim to develop the common therapeutic agents for these neurodegenerative diseases.

- Neurodegeneration
  - Parkinson's disease
  - Alzheimer's disease
  - Amyotropic lateral sclerosis
  - Huntington chorea
  - etc
- Cancer
- Autoimmune disease
- Infectious disease
- Aging disease

Fig.1: Diseases associated with protein aggregates.

■Subject Details/Topic

・Ubiquitinated protein aggregates are involved in various diseases including Parkinson's disease (PD). PD is a progressive and refractory neurodegenerative disease that affects both motor and cognitive brain functions. α-synuclein is the main causative protein of PD. Ubiquitinated α-synuclein oligomers (multimers) are highly toxic to neurons and cause PD.
・**We have identified three proteins that control the neurotoxicity of α-synuclein**. USP10 and p62 reduced the toxicity of ubiquitinated α-synuclein oligomers by incorporating them into large aggregates called aggresomes. On the other hand, G3BP1 promoted degradation of ubiquitinated α-synuclein and suppressed oligomer formation. Interestingly, these three molecules were suggested to play a similar role in AD, another common neurodegenerative disease. Based on these backgrounds**, we will develop the common therapeutic agents for neurodegenerative diseases targeting these three molecules and their functions**.

○Advantages
・Our group first reported that USP10 and G3BP1 are involved in neurodegenerative diseases (iScience, 2018, Scientific Reports, 2019a, Scientific Reports, 2019b). We have accumulated information and research materials in the study of these molecules.

○Applications
・Neurodegenerative diseases (PD, AD, etc), Cancer, autoimmune diseases, and aging-associated diseases.

○Plans
・We are establishing the screening system for drugs to reduce the toxicity of ubiquitinated proteins targeting these molecules.

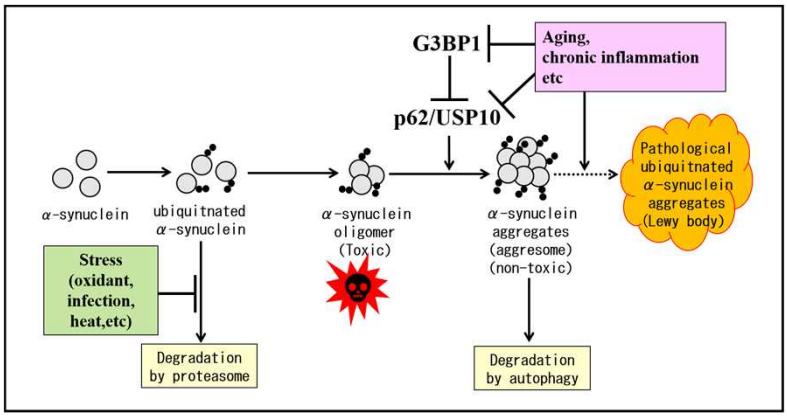

Fig.2: Control mechanism of α-synuclein toxicity.

■We hope to collaborate with…

・a drug screening targeting USP10, p62 and G3BP1 to develop the new therapeutics to several neurodegenerative diseases, cancer and autoimmune diseases.

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