大学院特別講義

新潟脳神経研究会特別例会の御案内

日　　時：令和５年８月 25 日(金) 11:00～12:00

場　　所：中田記念ホール　脳研究所 統合脳機能研究センター６階

Mechanisms of glutamatergic synapse degeneration in brain aging

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Brain aging is a universal phenomenon in all mammalian species and has many manifestations, including structural changes and decline of functions. The synapses are the main computational unit of neural circuits. Reduction of synaptic numbers and decline of synaptic functions, which occur in healthy aging, are closely correlated with brain aging and may be the underlying mechanism of decline of brain function. Work from our lab showed that the planar cell polarity (PCP) signaling pathway plays an essential and direct role in glutamatergic synapses formation in development and glutamatergic synapse maintenance in adulthood (Thakar et al., 2017) (Zou, 2020) (Ban et al., 2021) (Feng et al., 2021) (Freitas et al., 2023). The PCP proteins are localized in the developing and adult synapses and interact with synaptic scaffold proteins and glutamate receptors and are responsible for the formation and stability of the vast majority of glutamatergic synapses in the brain. Neurodegenerative disorders, such as Alzheimer's disease (AD), are a form of accelerated aging and are thought to start with synapse degeneration. Our lab found that planar cell polarity is the key signaling mechanism for synapse maintenance and the direct target for amyloid β induced synapse degeneration (Feng et al., 2021). Oligomeric Aβ binds to Celsr3 and weakens the interaction between Celsr3 and Frizzled3 and assists Vangl2 in disassembling synapses. A regulator of PCP signaling, Ryk, is also required for Aβ-induced synapse loss functioning together with Vangl2. In the 5XFAD mouse model of Alzheimer's disease, Ryk conditional knockout in neurons or intracerebroventricular infusion of a function-blocking monoclonal Ryk antibody protected synapses and preserved cognitive function (Feng et al., 2021). In healthy humans, Frizzled3 express level declines with age whereas Vangl2 expression level increases, suggest that the PCP proteins may also mediate age-related synapse decline in healthy aging (Folke et al., 2019). Therefore, the PCP pathway has emerged as a key regulatory mechanism for synapse decline in both accelerated and heathy brain aging and provides novel target to understand and intervene brain aging.

References

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どうぞ奮ってご参加ください。　　（担当：脳研究所 細胞病態学分野）

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