KGRI Lecture Series

2022年5月9日（月） 11:30-12:30

場所：慶應義塾大学信濃町キャンパス 総合医科学研究棟 1階ラウンジ
開催方法：ハイブリッド形式
参加申込：https://keio-univ.zoom.us/webinar/register/WN_pzD-oQ1KQdSIh2CaGaEHPA
言語：英語（同時通訳なし）
その他：どなたでもご参加可、参加費無料

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Characterizing roles of Palmitoyl-protein Thioesterase 1 in Developmental Plasticity and CLN1 disease

Infantile neuronal ceroid lipofuscinosis (CLN1) is a devastating neurodegenerative disease that affects children. CLN1 is cause by mutations in the depalmitoylating enzyme palmitoyl-protein thioesterase 1 (PPT1). Protein palmitoylation and depalmitoylation are critical for synaptic function. However, the role of Ppt1-mediated depalmitoylation in neurodevelopmental plasticity and how loss of Ppt1 drives neurodegeneration in CLN1 is unclear. To address these questions, we studied plasticity mechanisms that underlie neural circuit development in the visual cortex of the *Ppt1*$^{-/-}$ mouse model of CLN1.

In a first set of experiments, the role of Ppt1 in the regulation of N-methyl-D-aspartate (NMDA) receptors was examined. The composition of NMDA receptors shifts during neurodevelopment coincident with the maturation of the visual cortical circuit. We found that loss of Ppt1 leads to a stagnation of this developmental molecular pattern. Specifically, dysregulated synaptic calcium dynamics and left *Ppt1*$^{-/-}$ neurons vulnerable to excitotoxicity, partly due to hyperpalmitoylation of the immature NMDA receptor subunit GluN2B.

In a second line of experimentation, the role of Ppt1 in the synaptic scaling of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors was examined. *Ppt1*$^{-/-}$ neurons demonstrated exaggerated synaptic upscaling of calcium-permeable AMPA receptors *in vitro* and *in vivo*. A postsynaptic scaffold implicated in synaptic scaling, A-kinase anchor protein 5 (Akap5), was over-palmitoylated in *Ppt1*$^{-/-}$ neurons. Further, this pathway linked for the first time dysregulated synaptic calcium to a neuroinflammatory cascade in CLN1.

Together, these findings emphasize a vital role for PPT1-mediated depalmitoylation in synaptic plasticity that underlies circuit formation and function in the developing nervous system.

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