BDR SEMINAR (Kobe & online hybrid)

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Thursday, June 26, 2025

16:00-17:00

1F Auditorium, DB Building C, Kobe / Broadcast online via Zoom

Zoom meeting URL will be announced on the event day by e-mail.

※This seminar is open only to BDR Members.

Cellular and Developmental origin of Neurological Defects In Lowe's syndrome

Summary

The activity of signaling pathways is required for coordinated cellular and physiological processes leading to normal development of brain structure and function. Mutations in OCRL, a phosphatidylinositol 4,5 bisphosphate [PIP2] 5-phosphatase leads to the neurodevelopmental disorder, Lowe Syndrome (LS). However, the mechanism by which mutations in OCRL leads to the brain phenotypes of LS is not understood. We find that on differentiation of LS patient derived iPSC, developing neural cultures show reduced excitability along with enhanced P levels of Glial Fibrillary Acidic Protein. Multiomic single-nucleus RNA and ATAC seq analysis of neural stem cells generated from LS patient iPSC revealed an enhanced number of cells with a gliogenic cell state. RNA seq analysis also revealed increased levels of DLK1, a non-canonical Notch ligand in LS patient NSC associated increased levels of cleaved Notch protein and elevation of its transcriptional target HES5, indicating upregulated Notch signaling. Treatment of iPSC derived brain organoids with an inhibitor of PIP5K, the lipid kinase that synthesizes PIP2, was able to restore neuronal excitability and rescue Notch signaling defects in LS patient derived organoid cultures. Overall, our results demonstrate a role for PIP2 dependent regulation of Notch signaling, cell fate specification and development of neuronal excitability regulated by OCRL activity.

2-3 major papers:

1. Enhanced Notch dependent gliogenesis and delayed physiological maturation underlie neurodevelopmental defects in Lowe syndrome. Yojet Sharma, Priyanka Bhatia, Gagana Rangappa, Sankhanil Saha, Raghu P@ bioRxiv 2024.11.25.625332; doi: https://doi.org/10.1101/2024.11.25.625332

2. Saha S, H Krishnan H, Raghu P*. IMPA1 dependent regulation of phosphatidylinositol 4,5-bisphosphate and calcium signalling by lithium. Life Sci Alliance 2023 Dec 6;7(2):e202302425. doi: 10.26508/lsa.202302425. Print 2024 Feb.

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