Tata Institute of Fundamental Research
Survey No. 36/P, Gopanpally Village, Serilingampally, Ranga Reddy Dist., Hyderabad – 500 046

Seminar

Cellular and Developmental basis of neurodevelopmental defects In Lowe syndrome

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The activity of signalling 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 [PIP_2] 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 signalling. Treatment of iPSC derived brain organoids with an inhibitor of PIP5K, the lipid kinase that synthesises PIP_2, was able to restore neuronal excitability and rescue Notch signalling defects in LS patient derived organoid cultures. Overall, our results demonstrate a role for PIP_2 dependent regulation of Notch signalling, cell fate specification and development of neuronal excitability regulated by OCRL activity.

Tuesday, Aug 26th 2025

16:00 Hrs (Tea / Coffee 15:45 Hrs)

Auditorium, TIFRH