RESEARCH TOPIC MEM8

Investigating the role of Oligophrenin-1 SUMOylation in the etiology and treatment of X-Linked Intellectual Disability

Curriculum MEM

Laboratory name

Pharmacology and Brain Pathology Lab, Humanitas University Campus, Building E, Pieve Emanuele (MI)

Pre-clinical Supervisor

Michela Matteoli
michela.matteoli@hunimed.eu
Alessandra Folci
alessandra.folci@humanitasresearch.it

Abstract

SUMOylation is a post-translational modification essential for neuronal physiology. Alterations in SUMOylation are associated with neurodevelopmental disorders such as intellectual disability (ID). Oligophrenin-1 (OPHN1) is a novel SUMO target in the brain. Mutations in Ophn1 gene are associated with ID. Among them, a novel mutation identified in patients localizes near the SUMOylation site of OPHN1 raising hypotheses that this mutation may alter the sumoylation of OPHN1 and, thus, participates in the development of ID by altering the synaptic function of OPHN1. In this project, we will investigate the impact of SUMOylation on OPHN1-dependent neuronal processes such as dendritic spine maturation and AMPA receptor trafficking on primary neuronal cultures and neurons derived from human induced pluripotent stem cells (hIPSCs). We will also evaluate whether restoration of proper OPHN1 sumoylation can ameliorate the neuronal alterations associated with this mutation.

Main technical approaches

The project requires several techniques including:
- biochemistry;
- molecular biology;
- confocal imaging;
- live cell imaging;
-super resolution microscopy.

The ideal candidate will work on:
- Primary neuronal cultures derived from transgenic mouse models;
- neurons derived from human induced pluripotent stem cells (hIPSCs).

Scientific references

- Billuart, P. et al. Oligophrenin-1 encodes a rhoGAP protein involved in X-linked mental retardation. Nature 392, 923–926 (1998).

- Govek, E.-E. et al. The X-linked mental retardation protein oligophrenin-1 is required for dendritic spine morphogenesis. Nat. Neurosci. 7, 364–372 (2004).

- Nadif Kasri, N., Nakano-Kobayashi, A., Malinow, R., Li, B. & Van Aelst, L. The Rho-linked mental retardation protein oligophrenin-1 controls synapse maturation and plasticity by stabilizing AMPA receptors. Genes Dev. 23, 1289–1302 (2009)

- Folci, A., Mirabella, F. & Fossati, M. Ubiquitin and Ubiquitin-Like Proteins in the Critical Equilibrium between Synapse Physiology and Intellectual Disability. eNeuro 7, (2020).

- Henley, J. M. et al. SUMOylation of synaptic and synapse-associated proteins:

- An update. J. Neurochem. 156, 145–161 (2021)

Type of contract

Scholarship of € 21.000 gross per year awarded by Istituto Clinico Humanitas. This sum is subject to IRPEF income tax and exempt from social security contributions.

Borsa di studio pari a € 21.000 annui lordi erogata da Istituto Clinico Humanitas. Importo soggetto a tassazione IRPEF ed esente da contribuzione previdenziale.

Humanitas University
Via Rita Levi Montalcini, 4
20072 Pieve Emanuele (MI) Italy
Tel +39 0282241 - Fax +39 0282242394
info@hunimed.eu
hunimed.eu
CF 97692990159