RESEARCH TOPIC MEM23

Investigating UBE3A-dependent sumoylation imbalance in the pathogenesis of the Angelman syndrome and autism

Curriculum MEM

Laboratory name
Pharmacology and Brain Pathology Lab, IRCCS Humanitas Research Hospital

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Abstract
Neurodevelopmental disorders (NDD) affect millions of people in the world and are a major socio-economic burden. Given the complex multifactorial origin of these diseases, the pathogenetic mechanisms are poorly understood and no effective therapies are available. This research program focuses on two NDDs caused by genetic alterations of UBE3A gene. Loss of UBE3A causes the Angelman syndrome (AS), characterized by developmental delay, intellectual disability and epilepsy, while increased levels of UBE3A are associated with autism. This project combines in vivo genetic tools with proteomics and advanced imaging to dissect the pathogenesis of AS and autism. The relevance of our observations will be also validated in human neurons from differentiated induced pluripotent stem cells (iPSCs) obtained from AS patients. This project will uncover novel pathogenic insights into the development of AS and autism and hopefully offer new perspectives to treat these as yet incurable diseases.

Main technical approaches
Proteomics, biochemistry, molecular biology, in vivo manipulation of gene function, confocal and super-resolution microscopy.

Scientific references
Folci A., Mirabella F., Fossati M. Ubiquitin and ubiquitin-like proteins in the critical equilibrium between synapse physiology and intellectual disability. 2020 eNeuro 7 (4): ENEURO.0137-20.2020 Rotaru DC, Mientjes EJ, Elgersma Y. Angelman Syndrome: From Mouse Models to Therapy. 2020 Neuroscience 445:172-189. Vatsa N. and Jana NR. UBE3A and Its Link With Autism. 2019 Front Mol Neurosci. 11: 548 Flotho A. and Melchior F. Sumoylation: a regulatory protein modification in health and disease. 2013 Annu Rev Biochem 82: 357-85

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