PROJECT

DoS: Vania Broccoli

Title: **Dissecting the pathophysiological bases of the Wolfram syndrome neurological dysfunctions in patient iPSC-derived neuronal models**

Curriculum: Neuroscience and Experimental Neurology

Link to OSR/UniSR personal page: http://research.hsr.it/en/divisions/neuroscience/stem-cells-and-neurogenesis/vania-broccoli.html

Project description:

Wolfram syndrome type 1 (WS) is an autosomal recessive disorder mainly characterized by childhood-onset diabetes associated to severe and disabling neurological dysfunctions such as hearing loss, optic nerve atrophy and progressive neurodegeneration. This disease is caused by heterozygous or homozygous mutations in the WFS1 gene located on 4p16 and encoding for an ER membrane protein named Wolframin. It remains unknown to date the reasons and mechanisms by which WFS1 mutations are leading to retinal ganglion and brain neuronal cell death. The overarching goal of this project is to establish an iPS cell (iPSC) system for a superior in vitro modeling of the Wolfram syndrome in order to illuminate the molecular mechanisms leading to loss of retinal ganglion and brain neurons. By differentiating WS and isogenic control iPSCs into functional retinal and brain cells, we plan to unravel whether the ER stress or other novel candidate pathways are responsible, and through which mechanisms, for cell dysfunctions and subsequent cell death. By generating retinal organoids, ganglion neurons can be isolated to generate pure cultures of these neurons to assess their survival fitness and relative dysfunctions through video-imaging and genome-wide RNA sequencing. Moreover, WS and matched control iPSCs will be differentiated into brain cortical neurons to assess how WFS1 gene mutations affect their functional state. Finally, through a cross-referenced computational analysis of large databases of protein-protein interactions and gene expression profiling, we collected intriguing evidence pointing at novel candidate interacting proteins that are implicated in ER protein trafficking and cell survival. Thus, it will be tested whether these molecular pathways contribute to dysfunctions responsible for the neurological manifestations in WFS1. This experimental program will illuminate the molecular and cellular bases responsible for the WS neurological co-morbidities and lay the foundation for innovative rational therapeutic strategies.

Skills to be acquired by the student:
Culture and manipulation of human iPSC stem cells, retinal and neuronal differentiation, time-lapse video-recording, morphological analyses, gene expression studies.

References (max. 3):

Bueno GE, Ruiz-Castañeda D, Martínez JR, Muñoz MR, Alascio PC.
Natural history and clinical characteristics of 50 patients with Wolfram syndrome.
Endocrine. 2018 May 4. doi: 10.1007/s12020-018-1608-2.

Cagalinec M, Liiv M, Hodurova Z, Hickey MA, Vaarmann A, Mandel M, Zeb A, Choubey V, Kuum M, Safiulina D, Vasar E, Veksler V, Kaasik A.
Role of Mitochondrial Dynamics in Neuronal Development: Mechanism for Wolfram Syndrome.
PLoS Biol. 2016 Jul 19;14(7):e1002511.