PROJECT

Supervisor:	Luca Colnaghi
Title:	Protein quality control in NEDAMSS, a rare neurodevelopmental disorder
Curriculum:	Neuroscience and Experimental Neurology
Link to the personal page of the University or relevant hospital site website:	https://research.hsr.it/en/divisions/neuroscience/luca-colnaghi.html

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Recently identified as a novel regressive neurological disorder, Neurodevelopmental Disorder with Regression, Abnormal Movements, Loss of Speech, and Seizures (NEDAMSS) stems from mutations in the gene encoding the IRF2BPL protein (1-4). This gene encodes a protein poorly characterized with intrinsically disordered domains, ubiquitin ligase activity, and transcriptional regulation function. Due to this lack of knowledge, the mechanisms underlying its association with NEDAMSS, and potential therapeutic avenues for this condition remain unclear. Therefore, this Ph.D. project proposal seeks to elucidate the fundamental mechanisms of IRF2BPL function, and the dysfunction linked to NEDAMSS, to identify potential novel therapeutic targets, stemming from both published and unpublished results.

Rationale and hypothesis

We have recently showed that IRF2BPL can undergo liquid-liquid phase separation (LLPS) (5). Patient-derived mutations show an aberrant cytosolic LLPS. In preliminary experiments, we found that IRF2BPL is modified post-transcriptionally and can display specific biochemical behaviours that are altered by pathogenic mutations. All these are features that are shared by several other proteins involved in neurological disorders (6-7). Therefore, the aim of the project is to dissect all these preliminary findings to shed new light on the molecular mechanisms of NEDAMSS.

Objectives and specific aims

Leveraging the expertise of the lab and using multidisciplinary approaches including *in vitro* approaches, microscopy, and human neuron cultures starting from iPS cells, we will study:

i) How is the physiological activity of IRF2BPL regulated in human-derived neurons?

ii) Can pharmacological treatments targeting post-translational modifications of IRF2BPL alter its pathological behaviour in human-derived neurons?

Expected outcomes

This work will shed new light on the molecular pathogenesis of NEDAMSS uncovering how NEDAMSS-related mutations may cause disease by disrupting or altering the physiological roles of IRF2BPL. Moreover, it will identify regulatory mechanisms of IRF2BPL function (e.g.: post-translational modifications) that may represent attractive therapeutic targets for NEDAMSS, which is currently an untreatable disorder.

Skills that the student should acquire (max. 600 characters including spaces):

During the PhD, the student will be expected to progressively develop autonomy in designing, conducting, and interpreting experimental work and data. From a technical standpoint, the student will gain hands-on experience in culturing and manipulating mammalian cells, including the engineering and differentiation of induced pluripotent stem cells (iPSCs). In addition, the student will be trained in a range of core laboratory techniques such as protein analyses, advanced microscopy methods (CLEM, SIM, FRET etc), and standard molecular biology and biochemical assays.

References (max. 15)

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Robinet C, Vitobello A. De novo truncating variants in the intronless IRF2BPL are responsible for developmental epileptic encephalopathy. Genet Med. 2019 Apr;21(4):1008-1014. doi: 10.1038/s41436-018-0143-0. Epub 2018 Aug 31. PMID: 30166628.

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