PROJECT

Supervisor:	___Jean-Michel Cioni_____
Title:	___Endosomal control of translation in Alzheimer's disease. _____
Curriculum:	_____ Neurosciences and Experimental Neurology ___
Link to the personal page of the University or relevant hospital site website:	https://research.hsr.it/en/divisions/neuroscience/rna-biology-neuron.html

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

Background/gap of knowledge

Despite massive efforts, treatments for Alzheimer's disease (AD) are still very limited. Early diagnosis and intervention might be key for efficiently counteract the disease but the molecular processes that take place during the preclinical and prodromal phases of the disorder remain poorly understood. Endosomal dysfunction is one of the earliest pathological hallmarks common to sporadic and most of the familial form of Alzheimer's disease (AD). The presence of abnormal enlarged early endosomes (EEs) has been reported to occur before the accumulation of amyloid beta (Aβ) in the brain, and genetically mimicking these endosomal defects was found to drive an AD-related neurodegenerative cascade *in vivo*, supporting the possibility for a direct putative cause in AD pathogenesis and identifying endosomal dysfunction as a therapeutic target.

Rationale and hypothesis

We, and others, recently showed an endosomal function in controlling mRNA localization and translation in neurons. mRNAs and the translation machinery were found on EEs in axons and dendrites where they act as platforms to sustain subcellular translation. Based on these findings, our lab decided to characterize the EE-associated transcriptome in neurons and found a vast repertoire of mRNAs. Among them, our results revealed the presence of mRNAs that encode for proteins which dysregulation are associated with familial AD. Additionally, our findings showed an endosomal function in the localization of synaptic mRNAs, further opening the possibility that AD-related alterations of EEs might affect the trafficking of essential transcripts in neurons, a feature that have been understudied so far.

Objectives and specific aims

The main hypothesis driving this project is that AD-associated impairment of EEs could lead to detrimental changes in mRNA trafficking and translation, altering proteostasis and thus playing essential roles in neuronal degeneration. To test this idea, we have broken down the proposed research into two main objectives:

1) Determine how AD-related alterations of endosomal trafficking affect mRNA localization in neurons.

2) Define the molecular mechanisms driving endosome–mRNA dysregulation in AD-relevant cellular models.

Expected outcomes

This proposal will provide essential insights into the pathological mechanisms that might occur during early AD disease progression as well as a new view on the cascade of molecular events leading to AD-related neurodegeneration. Our results could lay the groundwork for future studies and generate knowledge that might become key for the development of new strategies to detect early neuronal dysfunctions and/or stopping the progression of AD and other neurodegenerative diseases associated with endosomal defects.

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

The student will acquire:

Technical skills: Primary culture of neuronal cells, iPSC cells, live-imaging approaches, immunocytochemistry, biochemical methods, genome-wide analysis, pharmacology treatments.

Image acquisition and analysis using specialized softwares (e.g. FIJI, NIS-Elements,...)

Data management and presentation (national and international meetings).

References (max. 15)

- Nixon, R.A., *Amyloid precursor protein and endosomal-lysosomal dysfunction in Alzheimer's disease: inseparable partners in a multifactorial disease.* FASEB J, 2017. **31**(7): p. 2729-2743.

- Pensalfini, A., et al., *Endosomal Dysfunction Induced by Directly Overactivating Rab5 Recapitulates Prodromal and Neurodegenerative Features of Alzheimer's Disease.* Cell Rep, 2020. **33**(8): p. 108420.

- Cioni, J.M., et al., *Late Endosomes Act as mRNA Translation Platforms and Sustain Mitochondria in Axons.* Cell, 2019. **176**(1-2): p. 56-72 e15.

- Schuhmacher, J.S., et al., *The Rab5 effector FERRY links early endosomes with mRNA localization.* Mol Cell, 2023. **83**(11): p. 1839-1855 e13.