Universidad de Navarra

Máster en Investigación Biomédica
Facultad de Ciencias

Research Project Proposal
Academic year 2016-2017

Project Nº 26

Title: Molecular mechanisms of neurodegeneration; role of the unfolded protein response (UPR).

Department/ Laboratory Cellular Neurobiology laboratory (2.05), Neurosciences Department- Center for Applied Medical research, CIMA

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Summary

The molecular mechanisms underlying the main neurodegenerative disorders (Alzheimer's disease (AD), Parkinson's disease (PD)) are not fully understood. Analysis of post-mortem brains affected by these disorders identified changes in the accumulation/status of proteins, and cellular pathways alterations that tightly correlate with the neurodegenerative process. A fundamental question is whether these changes 1) contribute to neuronal death 2) are part of a coping response or 3) are just an epiphenomenon not related with neuronal death. Answering this key point will definitely help us to find targets for effective therapeutic intervention.

The unfolded protein response (UPR) is the intracellular mechanism activated by deficiencies in protein folding to restore homeostasis. Abnormal protein accumulation and UPR activation constitute a hallmark of neurodegenerative diseases. Being a coping response to stress, UPR activation should promote neuronal survival. However, when stress is excessive or chronic, UPR induces neuronal death. Therefore, it is key to understand how this pathway determines neuronal fate to design therapies these disorders.

We seek to identify molecular mechanisms of neurodegeneration. Specifically; we want to determine the role of UPR activation in neuronal survival in different neurodegeneration models.

Using a microscopy based-system we longitudinally track individual neurons over long periods of time. Simultaneously, we monitor and link events of interest (protein levels, activation of cellular pathways using visual reporters) with neuronal survival/death.

We will determine if/how activation of the UPR affects neuronal survival in the presence of neurotoxic proteins (tau (AD), alpha-synuclein (PD)).

The project involves molecular and cellular neurobiology, microscopy and statistics.

References

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2. Miller* J., **Arrasate* M.,** Brooks E., Peters-Libeu C., Legleiter J., Hatters D., Curtis J., Cheung K., Krishnan P., Mitra S., Widjaja K., Shaby B.A., Lotz G.P.Newhouse Y., Mitcell E., Osmand A., Gray M., Thulasiramin V., Saudou F, Muchowski P.J., Segal M., Yang W.X., Masliah E., Thompson L.M., Muchowski P.J., Weisgraber K. H., and Finkbeiner S. **(2011)** Identifying polyglutamine protein species in situ that best predict neurodegeneration. **Nature Chemical Biology**. **(*equal contribution)**
3. **Aragón T*.,** van Anken E., Pincus D., Serafimova IM., Korennykh AV., Rubio CA., and Walter P. (2009) Messenger RNA targeting to endoplasmic reticulum stress signalling sites. **Nature,** 457:736-39**(*corresponding author)**

POSSIBILITY OF PhD

YES*

* (PhD grant required)