Universidad de Navarra

Máster en Investigación Biomédica
Facultad de Ciencias

Research Project Proposal
Academic year 2015-2016

Project Nº 21

Title: How cells respond to (endoplasmic reticulum) stress: Study of the transport of XBP1 mRNA

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Summary

The endoplasmic reticulum (ER) is the site where most membrane proteins are folded. Deficiencies in this folding process cause the accumulation of misfolded proteins and the establishment of ER stress which, if not corrected, triggers cell death. To restore ER homeostasis, eukaryotic cells have developed an intracellular signalling pathway, the unfolded protein response (UPR).

Our group tries to understand a key, conserved mechanism that controls the expression of the essential UPR transcription factor, XBP1. ER stress causes the activation of a transmembrane ER stress sensor, IRE1, turning on its endonuclease domain at the cytosolic surface of the ER. Then, IRE1 excises a non-canonical intron from the XBP1 mRNA, and the resulting exons are joined by the tRNA ligase. The spliced XBP1 mRNA encodes for a transcription factor, XBP1s, which will initiate a complex transcription program to adjust ER function and size to need.

Our earlier work demonstrated that specific mRNA transport mechanisms are necessary to facilitate the encounter between XBP1 mRNA and IRE1. We have identified sequence elements whithin XBP1 mRNA that engage this mRNA into RNA transport; also, our initial results suggest that XBP1 mRNA uses cytoskeletal fibers to reach IRE1 at the ER surface.

In this master project, we propose to 1) Identify by affinity purification/mass spectrometry the proteins bound to XBP1 targeting elements to then establish their role in mRNA transport 2) Visualize the movement of individual XBP1 mRNA molecules towards IRE1 foci, and 3) Explore the role of intermediate filaments on mRNA transport.

References

Messenger RNA targeting to endoplasmic reticulum stress signalling sites. Aragón T, van Anken E, Pincus D, Serafimova IM, Korennykh AV, Rubio CA, Walter P. Nature. 2009 Feb 5;457(7230):736-40.

1. Specificity in endoplasmic reticulum-stress signaling in yeast entails a step-wise engagement of HAC1 mRNA to clusters of the stress sensor Ire1.van Anken E, Pincus D, Coyle S, Aragón T, Osman C, Lari F, Gómez Puerta S, Korennykh AV, Walter P.Elife. 2014 Dec 30;3:e05031.
2. XBP1 uses a new mechanism to reach IRE1 centers under acute endoplasmic reticulum stress. Gómez-Puerta S, Argemí JM, Ferrero R, Martínez-Salas E, Aragón T. (in preparation)

POSSIBILITY OF PhD

YES* The decision to continue the project with a PhD thesis will depend on the evaluation of the student's performance and the availability of funding resources to support the student

* (PhD grant required)