Universidad de Navarra

Máster en Investigación Biomédica
Facultad de Ciencias

Research Project Proposal
Academic year 2016-2017

Project Nº 41

Title: How cells cope with stress: Study of the transport of XBP1 mRNA to ER stress response centers.

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Summary

Deficiencies in protein folding within the endoplasmic reticulum (ER) – the organelle where membrane and secreted proteins are folded – cause a dysfunctional situation known as ER stress that, if not corrected, is toxic for the cell. Diverse pathological conditions (i.e. inflammation, hypoxia, neurotoxic mutant proteins, metabolic stress) induce ER stress which, in turn, drives disease progression.
The unfolded protein response (UPR) comprises a set of intracellular signaling mechanisms to restore cellular homeostasis. Essentially, the UPR senses ER stress and promotes the activation of a gene expression program to 1) eliminate misfolded proteins and 2) adjust ER size and folding capacity to the cell needs.
We study the most core, conserved UPR mechanism, which is initiated by the ER stress transmembrane sensor IRE1. Under ER stress IRE1 concentrates in a few foci per cell, which are the sites where the response to ER stress initiates. A unique mRNA encoding the transcription factor XBP1 is recruited to these centers and undergoes a non-conventional splicing reaction. Splicing allows the expression of XBP1 protein, driving the response to stress.

Here, we propose to study the mechanism that brings XBP1 mRNA to the ER stress response centers. 1)We will visualize the movement of mRNA molecules towards ER stress response centers, 2) we will identify the factors that mediate such recruitment and we will try to understand 3) how these components work in the transport mechanism.
We will use advanced imaging techniques, molecular biology and biochemical methods including mass spectrometry, and visual/functional screens.

References

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

2. van Anken E, Pincus D, Coyle S, Aragón T, Osman C, Lari F, Gómez Puerta S, Korennykh AV, Walter P. Specificity in endoplasmic reticulum-stress signaling in yeast entails a step-wise engagement of HAC1 mRNA to clusters of the stress sensor Ire1. **Elife**. 2014 Dec 30;3:e05031.

POSSIBILITY OF PhD

YES*

* (PhD grant required)