Research Project Proposal

Academic year 2020-2021

Máster en Investigación Biomédica

Project Nº 56 ASIGNADO

Title: *From single molecule mRNA visualization in living cells to genetic and proteomic screens: Discovering the composition of transport of the XBP1 ribonucleoprotein*

Department/ Laboratory *Department of Gene Therapy and Regulation of Gene Expression. Laboratory of Tomás Aragón: The response to protein misfolding in neurodegenerative diseases.*

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Summary

Deficiencies in protein folding at the endoplasmic reticulum (ER) trigger an intracellular signalling pathway, the unfolded protein response (UPR) that builds a gene expression program to adjust the size and folding capacity of the ER to the cell needs. From a biomedical perspective, UPR activation plays a key role in a wide set of pathologies including diverse types of cancer, metabolic disorders and neurodegenerative diseases.

The most conserved, core process of the UPR is the non-canonical splicing of the mRNA encoding the transcription factor XBP1. In response to ER stress, the ER stress sensor IRE1 clusters into discrete foci at the ER, recruits XBP1 mRNA to these foci, and excises a 26-nucleotide intron from this mRNA; the resulting exons are ligated by the RTCB ligase, yielding the spliced XBP1 mRNA. XBP1 splicing enables the expression of XBP1s protein, a potent transcription factor that drives the efficient response to ER stress.

In spite of its relevance for biomedicine we know very little about the mechanism by which XBP1 mRNA is targeted to IRE1. This project aims to use multiple advanced approaches to identify the factors associated to XBP1 mRNA throughout its life (we will purify the XBP1 ribonucleoprotein), to elucidate which ones are important for its regulation (we will perform CRISPR screens to identify genes required for XBP1 splicing), and the path that XBP1 mRNA follows towards IRE1 (we will visualize single XBP1 mRNA molecules in living cells). In summary, we will have fun understanding how this relevant, unique mRNA works.

yes	
no	**X**

Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator?