Research Project Proposal
Academic year 2018-2019

Project Nº 41

Title: *New insights into the molecular pathogenesis of CALR-mutated myeloproliferative neoplasms using a Caenorhabditis elegans model*

Department/ Laboratory *Genetics, Department of Biochemistry & Genetics, School of Sciences.*

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Summary

20 and 25% of patients with essential thrombocythemia (ET) and primary myelofibrosis (PMF) show mutations in CALR. This gene encodes calreticulin, a chaperone in endoplasmic reticulum that binds calcium. The most frequent variants are a 52-bp deletion (type 1 mutation) and a 5-bp insertion (type 2 mutation) that cause phenotypes with subtle clinical differences. It has been described that mutant calreticulin can stimulate the thrombopoietin receptor (TPOR) activating the JAK/STAT pathway, but mutant calreticulin could also trigger additional TPOR-independent effects on gene expression. To identify them we are using Caenorhabditis elegans, a model organism with a CALR homolog (CRT-1) but not a TPOR homolog.

Previously, our group has obtained by CRISPR/Cas two C. elegans strains with homologous changes to type 1 and 2 mutations. Expression analyses by microarrays have shown several differential expressed genes. Some of them seem to be a consequence of a loss-of-function of calreticulin but we have also detected a differential expression of nhr-17 between both mutants that could explain the clinical differences in patients with myeloproliferative diseases. This gene encodes a nuclear receptor homolog to human RXR's.

In this project we want to validate these results in samples from patients and unravel the molecular mechanism of such aberrations by promoting expression of aberrant calreticulin in C. elegans and analyzing some phenotypic features in double mutant crt-1/nhr-17 worms.

yes	
no	**X**

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