Universidad de Navarra
Facultad de Ciencias

MASTER'S DEGREE IN BIOMEDICAL RESEARCH
Research Project Proposal
Academic year 2023-2024

Project Nº 50 ASIGNADO

Título: Deciphering the molecular mechanisms involved in copper toxicity

Department/ Laboratory
Gene therapy for rare diseases

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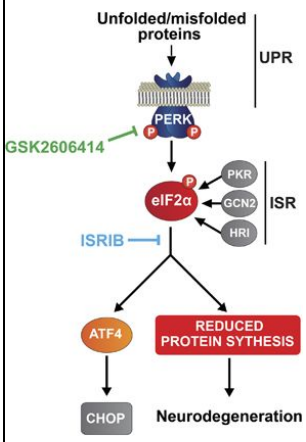
Summary

Analysis of the molecular mechanism involved in Cu-mediated ATF4 induction in vitro and in vivo, evaluation of the role of ATF4 in copper toxicity (beneficial or detrimental) and identification of potential targets to modulate Cu toxicity.

- Task 2.1. Characterization of the induction of ATF4 and ATF4-induced genes expression in HepG2 ATP7B+/+ and HepG2 ATP7B-/-. Analysis of the effect of copper concentration and the kinetic of induction.
- Task 2.2. Analysis of the pathways involved in the induction of ATF4 expression by Cu in HepG2 ATP7B+/+ and HepG2 ATP7B-/-. Study the role of ER stress, ISR and mTOR pathways.
- Task 2.3. Validation of the cellular findings in the animal model of Wilson disease.



The expression of ATF4 and ATF4-induced genes will be analysed in in both cell lines. In order to determine the mechamism of ATF4 induction, the involvement of ER stress (PERK), the integrated stress response (ISR) and mTOR patway will be determined. For that purpose first the phosphorylation status of PERK, PKR, GCN2 and HRi and eIF2a will be determined and in parallel inhibitory studies of the different kinases will be performed.
On the other hand, the role of mTOR pahtway will be determined, the activation of this pathway will be determined by the analysis of P-4EBP1 and P-PS6K and mTOR pathway will be inhibited using rapamycin, torin 1 and MLN0128. CRISPR-Cas9 editing experiments will be performed to corroborate the data.

yes	x
no	

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