DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO

41° Cycle

Project proposal for a PhD scholarship

Main research line

Title of the research: In *vivo* models applicability for investigation of mitochondrial dysfunctions

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Summary

This project proposes to characterize the pathogenetic effects of several mutations which compromise the mitochondrial function and are responsible for severe pathologies in humans. By now a large number of mutations in nuclear or mitochondrial genes are identified to alter the mitochondrial functionality and this number is constantly increasing. By Next-Generation Sequencing technology new potential pathogenetic mutation can be rapidly identified in patients. The use of simple models is validated for molecular and biochemical analysis of detrimental effects of a lot of these isolated mutations. The project aims to characterize the mutations in yeast *Saccharomyces cerevisiae* or in the pluricellular model *Caenorhabditis elegans* to validate their pathologic effects on mitochondrial functionality. The project starts with the fine-tuning of different genetic strategies to delete the endogenous genes and to introduce their mutated versions into the mitochondria of the host organisms. The molecular, phenotypic and physiologic effects of the knock-out and the gene mutations will be investigated. The yeast and nematode models also offer the possibility to generate platforms for multi-drugs screening by which testing different therapeutic molecules. The rescuing effects of these molecules will be tested on the capacity to ameliorate the mitochondrial defects of the mutants.

Pertinent Publications of the proponent (last 5 years)

1. Ficociello G, Schifano E, Di Nottia M, Torraco A, Carrozzo R, Uccelletti D, Montanari A (2023) Silencing of the mitochondrial ribosomal protein L-24 gene activates the oxidative stress response in Caenorhabditis elegans, Biochim Biophys Acta Gen Subj 1867, 130255. doi: 10.1016/j.bbagen.2022.130255

2. Torraco A, Morlino S, Rizza T, Di Nottia M, Bottaro G, Bisceglia L, Montanari A, Cappa M, Castori M, Bertini E, Carrozzo R (2022) A novel homozygous variant in COX5A causes an attenuated phenotype with failure to thrive, lactic acidosis, hypoglycemia, and short stature, Clin Genet 102, 56-60. doi: 10.1111/cge.14127

3. Montanari A (2022) In Vivo Analysis of Mitochondrial Protein Synthesis in Saccharomyces cerevisiae Mitochondrial tRNA Mutants, Methods Mol Biol 2497, 243-254. doi: 10.1007/978-1-0716-2309-1_15

4. De Luca V, Leo M, Cretella E, Montanari A, Saliola M, Ciaffi G, Vecchione A, Stoppacciaro A, Filetici P (2022) Role of yUbp8 in Mitochondria and Hypoxia Entangles the Finding of Human

Ortholog Usp22 in the Glioblastoma Pseudo-Palisade Microlayer, Cells 11, 1682. doi: 10.3390/cells11101682

5. Montanari A, Leo M, De Luca V, Filetici P, Francisci S (2019) Gcn5 histone acetyltransferase is present in the mitoplasts, Biol Open 8, bio041244. doi: 10.1242/bio.041244