DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO

40th CYCLE
Project proposal for a Sapienza PhD scholarship

Main research line

Title: 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 [1]. 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. The use of simple models is validated for molecular and biochemical analysis of detrimental effects of a lot of these isolated mutations [2-6]. By Next-Generation Sequencing technology new potential pathogenetic mutation can be rapidly identified in patients [7,8]. The project aims to characterize the mutations in yeast Saccharomyces cerevisiae or in the pluricellular model Caenorhabditis elegans to validate their pathologic effects. 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. Furthermore, the yeast and nematode models offer the possibility to generate platforms for multi-drugs screening with which to test therapeutic molecules [9,10]. The mitochondrial mutants will be treated with a commercial library of natural compounds or different suppressive sequences isolated from the carboxy-terminal domain of human mitochondrial Leucyl-tRNA synthetase [11]. The rescuing effects of these molecules will be tested on the capacity to ameliorate the mitochondrial defects of the mutants. The most promising isolated compounds will subsequently be utilized to treat human cells in culture.

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Pertinent Publications of the proponent (last 5 years) (besides those indicated above)

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

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