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Understanding the role of mtDNA variation in oncogenesis and drug resistance.

Our lab studies nuclear-mitochondrial crosstalk using functional genomics approaches. Our recent data has shown that mtDNA variants induce different cellular responses involving key pathways involved in the mitochondrial stress responses (mtSR), such as mTORC1, HIF1a and ISR while modifying the risk of several cancers. Mechanistic analysis confirmed that these pathways act as a rheostat regulating mitochondrial biogenesis, function and dynamics, cytoplasmic ROS as well as carcinogenesis and metastasis capacity “in vivo” and cell migration “in vitro”. This can potentially explain the variability of response to anti-cancer drugs acting on these pathways between individuals. Thus, we aim carry a comprehensive analysis to understand how mtDNA population variants impact oncogenesis and drug sensitivity, which is sorely lacking from our current body of knowledge.

We will study whether the mtDNA background regulates tumorigenic capacity in a mtSR mediated manner, which can potentially explain the variability of response to mtSR inhibitors/Activators between individuals. We will use an in vitro model under metabolic, chemical and genetic manipulation systems.

Expected impact: This work will lead to a comprehensive understanding of how mtDNA variants impact oncogenesis and its interaction with treatment effectivity, which is sorely lacking from our current body of knowledge.

Methodology: We will use a combination of genomic (NGS, pyrosequencing and single cell), cell biology (cell culture, migration, invasion, cell growth, qPCR, WB, microscopy), as well as bioinformatic analysis on cancer tissues and cell models. In addition to their own research, there will be opportunities for training and career development.

Thus, training will be acquired in:

1. Cell biology: Microscopy, cell culture, FACs, siRNAs
2. Mitochondrial analysis: Seahorse, bioenergetics, enzymatic studies.
3. Molecular studies: Western blot, quantitative PCR, DNA sequencing.
4. Genomic studies: Basic bioinformatic analysis
5. Data analysis: Genetic analysis, statistical (Prism), cytometry analysis (FlowJo), Western blots analysis and microscopy, data presentation
6. Application to PhD fellowships and career planning.

Bibliography:

1. Gomez-Duran A*, et al. Common disease-associated mtDNA variants modulate proteostasis through N-formylmethionine. Nature Medicine. 2021
2. Gomez-Duran A*, et al. Effects of bezafibrate in mitochondrial disease. Embo Mol. Med. 2020, 12(3), e11589
3. Gomez-Duran A, et al. Oxidative phosphorylation differences between mitochondrial DNA haplogroups modify the risk of Leber's hereditary optic neuropathy. Biochimica et Biophysa Acta 2012, 1822(8), 1216-122
4. Gomez-Duran A, et al. Unmasking the causes of multifactorial disorders: OXPHOS differences between mitochondrial haplogroups. Hum Mol Genet. 2010, 19(17), 3343-3353.