COLLEGE ED BIOLOGIE DOCTORAL SANTE PAYS DE LA LOIRE

Year 2024/2027

THESIS TOPIC

Subject N° (to be completed by the ED):	**FUNDING:** ☒ **Requested** ☐ **Acquired**	**Funding origin: C-UA**
Thesis title: **C-UA-Exploring the protective role of mitochondrial fusion on cardiac pathologies linked to mitochondrial DNA instability during aging**		3 keywords: Genome instability, Mitochondria, Cardiac pathologies
Unit / team: **UMR 6015 CNRS / 1083 INSERM, Mitovasc, Mitolab Team**		
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Socio-economic and scientific context (approximately 10 lines):
Cardiovascular disease is a major public health issue. They are one of the main causes of mortality in the world, and aging is one of the main risk factors. Thus, as people age, they experience a high incidence of cardiac dysfunction and a worsening of ischemic heart diseases (Lesfnesky et al. 2001; Shih et al. 2011). Although these pathologies are certainly driven by multiple factors, several studies suggest the involvement of mitochondrial dysfunction. These cellular organelles are at the heart of metabolic pathways and have their own multi-copy DNA (mtDNA), which is unstable during aging and accumulates mutations. At critical levels of heteroplasmy (% of mutated vs. wild mtDNA copies), they lead to severe impairment of mitochondrial activity in the cell. Using the mouse model K320E-Twinkle^{Myo}, which recapitulates this phenomenon in the heart, we have shown that this genomic instability is involved in the pathogenesis of cardiac arrhythmias (Baris et al. 2015) and facilitates the occurrence of post-infarction arrhythmias (Stockigt et al. 2017). Thus, developing approaches aimed at slowing down the accumulation of mtDNA mutations during aging could lead to concrete therapeutic approaches for humans.

Working hypothesis and aims (approximately 8 lines):
Several studies in the literature show that the ability of mitochondria to fuse together is important for mtDNA stability and maintenance (Amati-Bonneau et al., 2008; Chen et al., 2010). In the laboratory, our current work shows that when mitochondrial fusion is systemically impaired (by haploinsufficiency in OPA1 fusion protein) in the K320E-TwinkleMyo model, the proportion of cells with impaired mitochondrial activity in the heart doubles in aged mice, without increasing the overall proportion of mtDNA molecules harbouring deletions. The aim of this thesis work will be to understand this phenomenon, to determine how mitochondrial fusion plays a protective role in the heart during aging, and whether pharmacological approaches aimed at stimulating fusion are conceivable for delaying the development of heart diseases. Our main hypothesis is that fusion influences the pathological threshold of mtDNA heteroplasmy in the cells, by a mechanism that still has to be identified.

Main milestones of the thesis (approximately 12 lines):
The candidate will be integrated into the Mitolab team, which is very involved in the training of PhD students, and which will offer him/her the human and technological environment needed to carry out his/her project, from the design of experiments to the valorisation of the results obtained through publication and dissemination at conferences. For this project, the candidate will use K320E-TwinkleMyo mice with altered mitochondrial fusion or subjected to pharmacological treatments aimed at modulating mitochondrial dynamics. He/she will verify the impact of these interventions on mitochondrial DNA deletions in cardiomyocytes (heteroplasmy rates, distribution of mutated molecules in mitochondria), as well as the physiological consequences and the evolution of heart diseases in these animals (arrhythmias, ischemia/reperfusion lesions). These steps will call on the tools available at the UMR for mitochondrial labeling and morphology analysis (high-resolution microscopy), determination of the spectrum of mitochondrial DNA deletions (Next generation sequencing) and their localization in the cell (Two-color FISH), as well as exploration of heart disease (telemetry, echocardiography). The candidate will also develop cell models derived from K320E-TwinkleMyo mice (fibroblasts, isolated cardiomyocytes), showing increased susceptibility to mitochondrial genome instability, which will enable him/her to determine the molecular pathways responding to fusion modulations and influencing the development of cells with impaired mitochondrial activity, in order to discover new therapeutic targets, which should ultimately stimulate the development of treatments for humans.

Scientific and technical skills required by the candidate (2 lines):
Good knowledge of biochemistry and molecular biology; ability to handle laboratory animals (mice); fluency in English (written/oral).

3 publications from the team related to the topic (last 5 years):

Kimoloi S, Sen A, Guenther S, Braun T, Brügmann T, Sasse P, Wiesner RJ, Pla-Martín D, **Baris OR**. (2022) Combined fibre atrophy and decreased muscle regeneration capacity driven by mitochondrial DNA alterations underlie the development of sarcopenia. J. Cachexia Sarcopenia Muscle, 13(4):2132-2145.

Urbanczyk S, **Baris OR**, Hofmann J, Taudte RV, Guegen N, Golombek F, Castiglione K, Meng X, Bozec A, Thomas J, Weckwerth L, Mougiakakos D, Schulz SR, Schuh W, Schlötzer-Schrehardt U, Steinmetz TD, Brodesser S, Wiesner RJ, Mielenz D. (2022) Mitochondrial respiration in B lymphocytes is essential for humoral immunity by controlling the flux of the TCA cycle. Cell Rep., 39(10):110912.

Basu S, Xie X, Uhler JP, Hedberg-Oldfors C, Milenkovic D, **Baris OR**, Kimoloi S, Matic S, Stewart JB, Larsson NG, Wiesner RJ, Oldfors A, Gustafsson CM, Falkenberg M, Larsson E. (2020) Accurate mapping of mitochondrial DNA deletions and duplications using deep sequencing. PLoS Genetics 16(12):e1009242.

National and international collaborations:

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