LaPEC
Laboratoire Pharm-Ecologie Cardiovasculaire UR4278, Sports and Research Center, Avignon Université.

NO-Stress group

PRINCIPAL INVESTIGATOR
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Title:
Modulation of mitochondrial oxidative stress by natural antioxidants: impact on mitochondrial dynamics during cardiac ischemia-reperfusion.

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Context:

Acute myocardial infarction (AMI) is a leading cause of morbidity and mortality worldwide, accounting for 9 million deaths each year [1]. To date, timely reperfusion of the ischemic myocardium is the only therapeutic solution to reduce cardiomyocytes death and limit infarct size. However, restoration of blood flow result paradoxically in additional and irreversible cardiac damages, termed « reperfusion injuries ». While molecular mechanisms proposed to explain this phenomenon are still debated, mitochondria have been recognized as key triggers of cell death during AMI. Indeed, the first few minutes of reperfusion leads to mitochondria-driven injuries explained by excessive reactive oxygen species (ROS) release and mitochondrial calcium overload which trigger opening of the mitochondrial permeability transition pore (mPTP). Long-lasting pore opening results in mitochondrial permeability, matrix swelling, rupture of mitochondrial membranes and subsequent release of cytochrome c and other pro-apoptotic factors which initiate cardiomyocyte death.

Besides the classical understanding of the vicious circle between Ca^{2+} and ROS during ischemia-reperfusion (IR), recent studies have highlighted that changes in the mitochondrial network may be relevant to explain the severity of IR injuries. Mitochondria are highly dynamic organelles constantly undergoing cycles of fission and fusion, referred as « mitochondrial dynamics ». Fusion is regulated by mitochondrial GTPases including optic atrophy 1 protein (OPA1) and mitofusin 1 and 2 (Mfn1 and Mfn2), while fission is mediated by the translocation of the cytosolic GTPase dynamin-related protein 1 (Drp1) to the outer mitochondrial membrane and its binding on Fis-1 receptor. Such changes in mitochondrial shape impact organelles Ca^{2+} homeostasis and calcium retention capacity (Kowaltowski et al 2019 Fasebj). In addition, during IR, excessive mitochondrial fission contributes to ROS production and subsequent increased infarct size. In line with this, the use of the Drp1 inhibitor Mdivi-1 during ischemia reperfusion on isolated neonatal murine cardiomyocytes (Sharp et al), isolated rat hearts and in a murine coronary artery ligation model (Hausenloy et al), preserved mitochondrial morphology, reduced ROS production and cytosolic calcium, prevented opening of the mPTP and reduced infarct size. These results strongly suggest that dysregulation of mitochondrial dynamics during IR constitute a key trigger of myocardial injuries.

Recently, we reported the identification of sinapine as a natural antioxidant with a mitochondrial tropism (Boulghobra et al., Redox Biol 2020). This compound is present in substantial amounts in the Brassicaceae family, most especially in rapeseed and mustard. As a choline ester of the sinapic acid, the sinapine contains a quaternary amine that is permanently and positively charged that might confer to the sinapine a significant mitochondrial tropism. In-vivo, on isolated heart and on primary isolated rat cardiomyocytes, we found that the sinapine (i) enters within the mitochondria, (ii) decreases the levels mitochondrial oxidative stress, and (iii) prevents the overproduction of ROS when under stress.

Objectives:

The aim of this project will be to evaluate whether sinapine is able to modulate cardiac mitochondrial fission during ischemia-reperfusion. The interplay between mtROS production, mitochondrial fission and mPTP activation during ischemia reperfusion will be evaluated both on isolated cardiomyocytes using specific fluorescent probes (mitoSoxRed; TMRM; mitotracker) treated or not with an inhibitor of mitochondrial fission (Mdivi-1) and on isolated heart.

Activities:
This work will require specific skills in experimental physiology. The trainee should also be able to develop skills in experimental physiology, animal physiology, biochemistry and cellular biology. Finally, the trainee will be involved in data analysis and interpretation.

Lab description:
The work carried out by the group "NO-Stress" of the Laboratory of Cardiovascular Physiology (LaPEC) aim to better understand the complex interplay between reactive oxygen species production and nitric oxide (NO) bioavailability and its role in the pathogenesis of common cardiovascular and metabolic disorders (i.e, obesity, diabetes,…). To decipher how non-pharmacological approaches, such as physical activity and/or nutrition, are able to impact the nitro-oxidative pathway, we also use acute or chronic physiological stressors: strenuous acute exercise, hyperglycemia or ischemia-reperfusion. We propose a translational research approach with interconnected studies in both rodents and humans.

Prerequisite skills and main competence acquired:
Skills: basic biochemistry lab skills, knowledge in animal physiology. Skills to be acquired: critical analysis of the bibliography, design and implementation of isolated organs and cellular physiology experiments, statistics, scientific writing methods in English.

Application form:
Please send a CV and a letter of motivation to Cyril.reboul@univ-avignon.fr