Title of the PhD project: Cytoprotection induced by pharmacological modulation of reticular calcium leak channels in myocardial infarction.

Disciplines: Physiology
Laboratory INSERM U1060; Dir. H. Vidal. Team 5 Cardioprotection
Doctoral school: Interdisciplinary Doctoral program in health-sciences (EDISS) - ED 205

Scientific background and rationale:
Myocardial infarction is one of the leading causes of mortality. Ischemia-reperfusion in heart leads to a dysregulation of Ca2+ homeostasis. Calcium signaling is central for the heart function, through its physiological role in excitation-contraction coupling, and the detrimental impact of Ca2+ overload during heart failure and myocardial ischemia-reperfusion. During this latter condition, it is well accepted that the cytosolic accumulation of Ca2+ due to ER Ca2+ depletion via ER Ca2+ leak channels subsequently results in mitochondrial Ca2+ overload, which can trigger the opening of the permeability transition pore (PTP) leading to cell death. Although the role of ER calcium release and Ca2+ accumulation in cytosol and mitochondria has long been suspected as a major player of ischemia-reperfusion injury, little is known about the dynamic changes in sarcoplasmic reticulum (SR) Ca2+ handling at the critical moment of reperfusion.

Aim:
The working hypothesis is that ER calcium leak channels could be drug-targeted candidates allowing the modulation of Ca2+ disturbances and ER stress caused by ischemia-reperfusion. The general aim of the present study is, by using known agonists and antagonists of these channels, to modulate and quantify the effects of disturbances of the ER Ca2+ release on contraction, metabolism, ER stress and death of cardiomyocytes in control and ischemia-reperfusion conditions. Our previous works highlight the role of reticular calcium leak channels in skeletal muscle (Lotteau et al., 2013), in human cancerous prostatic cells (Hammadi et al., 2013) and in human beta cells (Cassel et al., 2016). In particular, we have shown that ER stress and apoptosis can be modulated via pharmacological activation (by puromycin) or inhibition (with anisomycin) of translocon, an ER calcium leak channel (Hammadi et al., 2013).

Description of the project methodology:
1-Expression, localization and functional study of translocon in cardiomyocytes.
2-Impact of translocon modulation in mitochondrial dynamics.
3-ER stress measurements in mouse hearts after I/R.
4-Cell survival and pharmaceutics-based cardioprotection in in vitro ischemia-reoxygenation protocol.
5-In vivo infarct size measurement in mice.
All systems and expertise are already available in the laboratory.

Perspectives: We hope that this study will reveal which ER stress pathways are potential therapeutic targets and whether the pharmacological modulation of ER calcium leak channels such as translocon is protective during an I/R episode. If our research are successful, we plan to develop clinical trials thanks to the “Centre d’Investigations Cliniques” of Lyon (Dir. Pr. M. Ovize).

Skills required: Cell culture; Fluorescence microscopy; Calcium imaging; Western blot; Statistic analysis.

Key-words: Heart ischemia-reperfusion; ion channels, reticulum, mitochondria, apoptosis.

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Application should include: CV, application letter, Names and addresses of two references.
The application file should be sent before May 14, 2017 to: (email of the supervisor).
The open competitive recruitment process is in two steps: 1. Internal laboratory procedure. 2. Interdisciplinary jury of EDISS.