



PhD Research Proposal Form China Scholarship Council (CSC) - ENS Group

FIELD: Biology

(eg: Mathematics, Physics, Sociology,)

Thesis subject title: Understanding the role of lipid droplets in regulated cell death

Name of the French doctoral school : Biologie Moléculaire Intégrative et Cellulaire, ED 340

Name of the Research team : Regulated Cell Death and Genetics of Neurodegeneration Website : https://www.ens-lyon.fr/LBMC/equipes/ApoDroso

Name of the Supervisor : Professor Bertrand Mollereau

Email : bertrand.mollereau(at)ens-lyon.fr

Lab Language : English, French

Research Proposal Abstract :

The dogma that apoptosis is the sole form of cell death involved in eliminating supernumerary cells during development and pathology has been challenged by the discovery that necrotic cell death, previously considered accidental, can also be genetically controlled. It is now widely accepted that programmed necrosis plays a role in regulating cell homeostasis during differentiation. For instance, programmed necrosis is involved in the elimination of germ cells during Drosophila spermatogenesis (Napoletano, 2017). To study the kinetics of programmed necrosis, we identified novel testes-specific markers, including the release of nuclear proteins and lipid droplet (LD) accumulation in dying germ cells. We observed a significant accumulation of LDs in necrotic germ cells at the apical tip of the Drosophila testis, which may result from altered LD turnover during necrosis. LDs are dynamic and universal fat storage organelles conserved from yeast to human cells. LDs are composed of a neutral lipid core, surrounded by a phospholipid monolayer associated with a LD proteome. The homeostasis of LDs depends on the equilibrium between the mechanisms of lipid biogenesis and lipolysis, the latter being controlled by lipases (Figure). An increase in TG biogenesis or an inhibition of lipases can lead to the accumulation of LDs. In this thesis project, the candidate will determine in both Drosophila and human cultured cells: 1-if LD labelling is a cellular signature and even a biomarker of regulated necrosis. 2- the role of LDs in the execution of cell death. And 3- a direct regulation of lipid metabolism by the cell death machinery.



Figure: Lipid droplet turnover mediates cellular protection against lipotoxicity and ROS. **A** Schematic of biogenesis and degradation of TAG-containing LDs is shown. At the ER, DGAT1 (midway in flies) enzymes convert DAG into TAG, allowing LD biogenesis. This is followed by TAG degradation by the lipase ATGL (Brummer in flies), providing unsaturated and saturated FAs, which can enter the mitochondria. CPT1-mediates the conversion FAs into acyl carnitine for fatty acid oxidation (FAO) to produce ATP via the TCA cycle and oxidative phosphorylation (OXPHOS). By promoting FA storage, lipid droplet biogenesis inhibits lipotoxicity and protects lipid from ROS-mediated peroxidation. Adapted from Islimye, Girard and Gould. Front Cell Dev Biol 2022. Biorender was used to create this schematic.

References :

-Shan Y and Mollereau, B. Non-canonical functions of regulated cell death machinery regulate cellular growth, invasion and the interplay between cell death modalities. Frontiers in Cell Death. 2024. 3. 10.3389/fceld.2024.1423805

- Girard V, Jollivet F, Knittelfelder O, Arsac J-N, Chatelain G, Van den Brink DM, Baron T, Shevchenko A, Davoust N, Mollereau B. Alpha-synuclein enhances lipid droplet accumulation in neurons in a Drosophila model of Parkinson's disease. PLoS Genetics. 2021. 17 (11). e1009921. 10.1371/journal.pgen.1009921.

-Girard, V, Goubard V, <u>Querenet M</u>, Seugnet L, Pays L, Nataf S, Dufourd E, Cluet D, Mollereau B, Davoust N. Spen modulates lipid droplet content in adult *Drosophila* glia cells and protects against paraquat toxicity. Scientific Report 2020, 10(1):20023. doi: 10.1038/s41598-020-76891-9. * Corresponding authors.

-Napoletano F, Gibert B, Vincent S, Favrot C, Mehlen P, Girard V, Teil M, Chatelain G, Walter L, Arama E, Mollereau B. p53dependent programmed necrosis controls germ cell homeostasis during spermatogenesis. PLOS Genetics. 2017, Sept 25, 13(9), 1-21.

Type of PhD:

1.Full PhD

• Joint PhD/cotutelle (leading to a double diploma) :	NO
• Regular PhD (leading to a single French diploma) :	YES

2. Visiting PhD (for students enrolled at a Chinese institution who will be invited to a French institution to carry out a mobility period) : NO