



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
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Lab Language : English, French

Research Proposal Abstract :

Lipid droplets (LDs) are small, dynamic organelles found in almost all cells. LDs maintain their balance through a careful interplay between their creation (biogenesis) and breakdown (lipolysis), processes that are closely tied to how mitochondria handle energy. Beyond their role as fat reservoirs, LDs are deeply involved in how cells respond to stress. In studies using *Drosophila* fruit fly models alongside human cell cultures, our laboratory observed that LDs tend to build up in dying cells, pointing to a key role in controlling death-related pathways.

This project tackles the unknowns surrounding how LD build-up influences regulated forms of cell death (RCD), such as apoptosis, and seeks to identify subsets of LDs that can protect cells. We will work across species, combining *Drosophila* genetics with mammalian cancer cell models, unraveling the molecular mechanisms involving LD proteins, and decipher the functional effects of LD changes during RCD.

The research of the PhD candidate is organized into three main packages. In WP1, we will chart the interactions between LDs and death-related proteins, measure LD-mitochondria contact points, and test how altering LD content affects apoptosis. WP2 will pinpoint and study LD subsets that help cells survive, using imaging, proteomics, lipidomics, and rescue assays. WP3 will map the protein profiles of LDs during apoptosis in both models and confirm whether conserved regulators influence cell death outcomes.

This project integrates multi-omic analyses with high-resolution imaging. The goal is to shed light on how LDs govern life-and-death decisions at both the cellular and organism level, in line with broader research priorities on organelle dynamics and RCD.

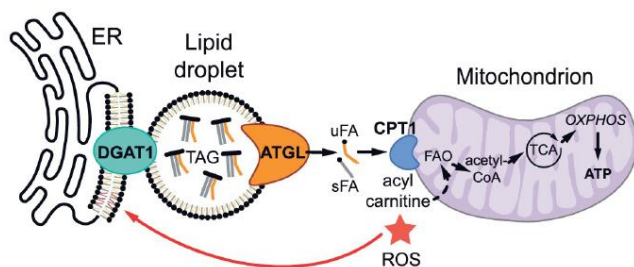


Figure: Lipid droplet turnover mediates cellular protection against lipotoxicity and ROS. **A** Schematic of biogenesis and degradation of TAG-containing LDs is shown. At the ER, DGAT1 (midway in flies) enzymes convert DAG into TAG, allowing LD biogenesis. This is followed by TAG degradation by the lipase 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 Islimy, 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, Querenet M, 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. p53-dependent programmed necrosis controls germ cell homeostasis during spermatogenesis. *PLOS Genetics*. 2017, Sept 25, 13(9), 1-21.

Type of PhD :

1.Full PhD

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| • 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