Internship offer
M2 Musculo-Skeletal system, Locomotion, Exercise (MuSkLE)

Title of the Internship: Role of PHF2 lysine demethylase in the lipid metabolism regulation of Muscle stem cell fate.

Laboratory (name, n°, website): Institut NeuroMyoGène-Pathophysiology and genetics of Neuron and Muscle (INMG-PGNM), Faculté de Médecine, 8 Avenue Rockefeller, 69008 Lyon. https://pgnm.inmg.fr/en/

Research team (name, website): NERVE-MUSCLE INTERACTIONS, https://pgnm.inmg.fr/en/schaeffer/

Supervisor to contact (name, email address): Isabella Scionti, isabella.scionti@inserm.fr

Project description including a short introduction, aim/objectives and methods/approach to be used

Lipid metabolism is a key process required for the maintenance and the differentiation capacity of pluripotent and adult stem cells. ***Muscle stem cells (MuSC)*** **are a unique model of stem cell fate, as their fate transition can be followed *in vivo* after muscle injury, in a well-characterized process called regenerative myogenesis.** In the last decade an increasing number of studies have pointed out on the importance of the MuSCs metabolic status. MuSCs, like all other cells, require energy to carry out the reactions necessary for life. However, the metabolic demands (supported by fatty acids, carbohydrates and aminoacids) required by quiescent MuSC, activated/proliferating myoblasts and differentiating myocytes differ. Indeed, it was reported that MuSC fate transition is supported by a profound alteration in metabolic pathways, called *metabolic reprogramming* that are coordinated by metabolic sensors such as the energy sensor AMPK. In particular, it has been described that lipid droplet (LD) abundance and turnover influence MuSC fate. In adult skeletal muscle, quiescent and self-renewed MuSCs are characterized by low LD content, since their metabolism mostly relies on fatty acids oxidation. Upon MuSC activation LDs accumulate and reach their highest concentration in committed myocytes. Later, LDs need to be catabolized to allow the fusion of committed myocytes into multinucleated myotubes. However, while it is clear that any perturbation of LD dynamics impairs MuSC homeostasis, **the molecular regulators coordinating LD turnover during MuSC fate transition remain unknown.**

The project focuses on the study of the role of the lysine demethylase, **PHF2**. PHF2 stands out among lysine demethylases enzymes as it requires post-translational phosphorylation by cAMP-dependent protein kinase A (PKA) and/or the AMP-activated protein kinase (AMPK) for its functional activation. This unique mode of activation suggests a specific regulatory mechanism for PHF2 upon energy stress. Our preliminary results provide compelling evidence supporting the hypothesis that PHF2, as a component of the AMPKα2 metabolic signaling pathway, plays a crucial role in maintaining energy homeostasis in MuSCs during regenerative myogenesis, particularly by modulating lipid droplet homeostasis.

The internship has the objectives:

- to assess the role of AMPKα2/PHF2 axis in lipid droplet metabolism-regulated fate transition,
- to identify PHF2-dependent changes at proteomic level required for MuSC metabolic reprogramming during MuSC fate transition.

This subject is of particular interest for candidates that would like to apply to doctoral school.

Techniques: flow cytometry, Fluorescence-Activated Cell Sorting (FACS), Primary muscle stem cell isolation from mouse model and cell culture, molecular biology, histology, immunofluorescence, imaging, proteomic approaches, seahorse/SCENITH (to measure cellular metabolism).

References of the group:

- Mouradian, S., et al (2024). LSD1 controls a nuclear checkpoint in Wnt/β-Catenin signaling to regulate muscle stem cell self-renewal. Nucleic Acids Res, gkae060. https://doi.org/10.1093/nar/gkae060.
- Cicciarello, D., and Scionti, I. (2023). [The unexpected role of lipid droplets in the regulation of muscle stem cells fate]. Med Sci (Paris) *39 Hors série n° 1*, 28–31. https://doi.org/10.1051/medsci/2023144.

Skills required: experience with cell culture, willingness to work with mouse model, scientific curiosity, capacity to work in a team.