Formulaire de stage
Parcours M2 GGBS 2021-22

Laboratoire : L'Institut du thorax research unit Inserm UMR 1087 / CNRS UMR 6291
N° d'équipe : Équipe IV

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Titre du stage: Circadian metabolic regulation of the hepatic mitochondrial network

Résumé du projet proposé:

Circadian (*about a day*) rhythms are central in health and diseases. They originate from the circadian clock (CC) that anticipates daily environmental changes. In mammals, the CC is molecular and present in virtually all cells. Hence, peripheral organs like the liver, and hepatocytes have an intrinsic CC.

The liver CC fine-tunes metabolism by supporting metabolic flexibility, the capacity to adapt fuel oxidation to fuel availability. In fact, abnormal feeding schedules, such as those observed in high fat diet condition, impose a circadian misalignment contributing to metabolic diseases. However, the molecular mechanisms implicated remain elusive.

The goal of the project is to use a circadian approach to discover novel mechanisms constituting fertile ground for future therapeutic targets notably in metabolic diseases.

To date, it has been shown that to adjust metabolism across daily cycles of energy intake, the CC and feeding control the mitochondrial network and its quality control mechanisms (mitochondrial dynamics). A fused mitochondrial network enhances bioenergetic efficiency whereas fission limits the oxidative stress during nutrient overload. Of note, loss of this mechanism through genetic disruption of the hepatic CC triggers metabolic disease.

The project will analyze the role of a post-translational modification (PTM), lysine malonylation, (K-mal) which we recently identified as modulated by the molecular CC.

During this internship, using experimental and bioinformatics tools, we propose:

(1) To analyse and compare the effect of mitochondrial malonylation modulation on the mitochondrial network connectivity in cell culture experiment.
(2) To analyse these effects in experimental conditions mimicking a high fat diet.
(3) To validate the observed results *in vivo* using a mouse tissue bank available in the lab.

The team: the candidate will join an interdisciplinary team that uses innovative approaches to study diurnal metabolic regulation. The team is part of *l'institut du thorax*.

The candidate: The candidate will be highly motivated to explore **both** experimental (cell culture, microscopy) and (bio)informatic (e.g. R, ImageJ, statistical modelling of circadian rhythms) approaches.

Do not hesitate to contact Daniel Mauvoisin for more information about the internship.

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