# MASTER 2 BMC
# PARCOURS GENOPATH
# ANNÉE 2024-2025

## Exploring the role of nuclear receptor ERRα in MAMs alterations linked to insulin resistance in liver.

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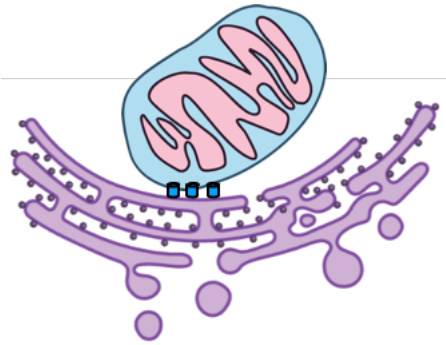
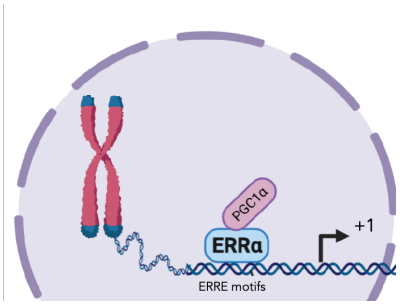
**Sujet de stage :**



Insulin resistance is a key factor in the development of metabolic diseases such as type 2 diabetes and non-alcoholic fatty liver disease. Independent dysfunction of the mitochondria and endoplasmic reticulum (ER) have both been widely implicated in hepatic insulin resistance and steatosis. These two organelles interact at contact sites called MAMs (mitochondria-associated ER membranes) to exchange phospholipids and calcium and regulate mitochondria bioenergetics. Therefore, MAMs play a crucial role in regulating cellular and metabolic homeostasis. Dr. Rieusset's laboratory has demonstrated in various mouse and human organs an alteration in MAMs involved in defects in insulin action and secretion in type 2 diabetes. Disruption of organelle interaction and calcium exchange is an early event in the liver, occurring as early as one week of overfeeding and preceding the development of hepatic insulin resistance and steatosis, suggesting a causal role in the development of metabolic disorders

associated with type 2 diabetes. However, the transcriptional regulation of MAMs has not yet been explored. A potential candidate could be the nuclear receptor ERRα, which plays an important role in the transcriptional regulation of metabolism, mitochondria and insulin resistance. We have demonstrated that ERRα binds to numerous genes already identified in the literature as playing a role in MAMs, using a ChIP-seq experiment in mouse liver. The aim of this internship will be to conduct a project to study and characterize the specific role of ERRα in the alterations of MAMs during insulin resistance. For this, Huh7 cells will be used with shRNAs or pharmacological inhibition of ERRα. Following these inhibitions, the mRNA and protein levels of MAM complexes will be assessed (RT-qPCR/WB), and the distance between mitochondria and ER will be measured by *in situ* PLA and electron microscopy. In addition, adenovirus transfections will enable us to use calcium sensors to monitor exchanges at MAM level. ERRα binding will be measured by ChIP-qPCR. The possibility of carrying out the same evaluations on mice receiving an ERRα inhibitor will be studied according to the *in vitro* results.




**Modèle et techniques utilisées :**

Cell culture, shRNAs, adenovirus, western-blot, RT-qPCR, ChIP-qPCR, electronic microscopy, in situ proximity ligation assay, calcium assay.

**Publications d'intérêt :**


1. Scholtes C. et al. (2024). Identification of novel hepatic ERRα transcriptional partners. **Molecular Metabolism**
2. Scholtes C. and V. Giguère. (2022). Transcriptional control of energy metabolism by nuclear receptors. **Nature Reviews Molecular Cell Biology**
3. Beaulant A. et al. (2022). Endoplasmic reticulum-mitochondria miscommunication is an early and causal trigger of hepatic insulin resistance and steatosis. **J. Hepatol**
4. Hui X. (2022) Insulin action and resistance are dependent on a GSK3β-FBXW7-ERRα transcriptional axis. **Nature Communications**
5. B'Chir W. (2018) Divergent Role of Estrogen-Related Receptor α in Lipid- and Fasting-Induced Hepatic Steatosis in Mice. **Endocrinology**
6. Rieusset J. (2018) The role of endoplasmic reticulum-mitochondria contact sites in the control of glucose homeostasis: an update. **Cell Death Dis**
7. Theurey P. et al. (2016). Mitochondria-associated endoplasmic reticulum membranes allow adaptation of mitochondrial metabolism to glucose availability in the liver. **J Mol Cell Biol**
8. Tubbs E. et al. (2014). Mitochondria-associated endoplasmic reticulum membrane (MAM) integrity is required for insulin signaling and is implicated in hepatic insulin resistance. **Diabetes**
9. Audet-Walsh E., Giguère V. (2014) The multiple universes of estrogen-related receptor α and γ in metabolic control and related diseases. **Acta Pharmacol Sin**