MASTER 2 BMC
PARCOURS GENOPATH
ANNEE 2024-2025

Titre :

Investigation of common pathophysiological mechanisms and therapeutic opportunities for two lipid-related mitochondrial diseases using yeast models

Nom, adresse de l'unité d'accueil / Nom du responsable de l'unité :

Laboratoire de Biologie Moléculaire et Cellulaire des Eucaryotes (UMR8226) dirigé par Maria Teresa Teixeira
Institut de Biologie Physico-Chimique (IBPC) 13 rue Pierre et Marie Curie 75005 Paris France

Nom, adresse de l'équipe d'accueil / Nom du responsable d'équipe :

Equipe Dynamique Membranaire et Modifications Post-Traductionnelles dirigée par Mickaël Cohen

Nom, tel, adresse e-mail de l'encadrant de stage :

Dr Mickaël Cohen, 01 58 41 51 89, cohen@ibpc.fr

Sujet de stage :

This project aims to decipher the pathophysiological mechanisms of the Barth syndrome and HACD1 congenital myopathy using relevant yeast models. The Barth syndrome and HACD1 congenital myopathy are rare mitochondrial myopathies that affect young children and for which no treatment is available yet. In both cases, mitochondria dysfunction is due to an alteration in the lipid composition of mitochondrial membranes that prevents efficient respiratory function within the inner mitochondrial membrane (IMM). Indeed, the IMM contains a specific phospholipid, called cardiolipin, that plays a major role in mitochondrial respiratory efficiency. The Barth syndrome is caused by mutations in the *TAZ* gene, which encodes the Tafazzin enzyme that it is required for cardiolipin remodelling in the skeletal muscles and the heart. Recently, we have identified 2 new genes, *Hacd1* and *Hacd2*, involved in cardiolipin metabolism. In human patients and mouse models, HACD1 deficiency leads to a

congenital myopathy that shares many features with the Barth syndrome. Given the mechanistic and phenotypic proximity of the Barth syndrome and HACD1 myopathy, we hypothesized that common drugs could alleviate the mitochondrial dysfunction of these two lipid-related mitochondrial diseases and reveal the key pathophysiological mechanisms that underlie their mitochondrial dysfunction. For this, we decided to use the baker yeast *Saccharomyces cerevisiae* that constitutes a powerful model to study mitochondrial function and to perform large-scale drug screening. In parallel to the well-validated yeast model for the Barth syndrome (*taz1* mutant yeasts), we developed yeast strains harbouring loss-of-function mutations in *Phs1* gene, the yeast homolog of *HACD1*. We showed that *phs1* mutant yeasts display a reduced growth rate, which is severely exacerbated on a non-fermentable medium on which mitochondrial respiration is mandatory, which is a specific feature of mitochondrial dysfunction in yeast. Moreover, *phs1* mutant strains present a fragmentation of their mitochondrial network and alterations in their mitochondria phospholipid content, which are reminiscent of the alterations observed in mitochondria from *Hacd1* mutant mice. We then designed a mitochondria-targeted approach to screen a library of 1500 FDA-approved drugs in *phs1* mutant yeasts, and then *taz1* mutant yeasts. We sorted out 8 drugs able to rescue the respiratory defect of both strains, which validates our hypothesis and provides promising candidates for this project. Of note, all these drugs are inhibitors of the synthesis of ergosterol, a sterol lipid that modulates membrane fluidity.
During this M2 project, the selected trainee will use the rescuing drugs as well as genetic manipulations to investigate the precise pathophysiological mechanisms involved in the mitochondrial alterations of both *phs1* and *taz1* mutant yeasts and to identify the common levers by which these sterol-lowering strategies rescue mitochondria efficiency in these mutant yeasts. For this, we will study the organization of the mitochondrial network and quantify the respiratory parameters of *taz1* and *phs1* mutant yeasts in the presence or not of the rescuing drugs and in combination with mutations in key genes involved in mitochondrial dynamics or lipid synthesis pathways. Lipidomic analyses will complete these investigations and precise the exact molecular mechanisms allowing the rescue of the respiratory function in both mutant strains. In a long-term goal, this study will open the path for a transposition of this therapeutic strategy for the treatment of the corresponding diseases in mammals.

The internship will be performed in the team of Mickaël Cohen (team Membrane Dynamics and Post-Translational Modifications, IBPC, Paris), who studies mitochondrial dynamics in yeast and the trainee will be supervised by Mickaël Cohen and Fanny Pilot-Storck (team of Vincent Gache, Muscle Nuclear and Cytoskeleton architecture, Institut Neuromyogène, Université Claude Bernard Lyon 1 and VetAgro Sup, Lyon), who is involved in *Hacd1* characterization. The two teams benefit from a high technical and scientific level, with a very dynamic and young lab organization. Applicants will have experience in cell biology and genetics and will be highly motivated by molecular and cellular dissection of pathophysiological mechanisms. Skills in self-organization and communication will help benefit from the coupled interdisciplinary supervision.

This M2 project is a first step towards a PhD project.

Modèle et techniques utilisées :

Yeast models

Yeast genetics, respiration assays, drug assays, western blots, molecular biology, confocal microscopy

Publications d'intérêt :

A review on lipid-related mitochondrial diseases:

• Lu, Y.-W. & Claypool, S. M. Disorders of phospholipid metabolism: an emerging class of mitochondrial disease due to defects in nuclear genes. *Front. Genet.* **6**, 3 (2015). doi.org/10.3389/fgene.2015.00003

A review on mitochondrial dynamics:

• Cohen, M. M. & Tareste, D. Recent insights into the structure and function of Mitofusins in mitochondrial fusion. *F1000 Faculty* vol. 1983 (2018). doi.org/10.12688/f1000research.16629.1

First description of the Barth syndrome:

• Barth, P. G. *et al.* An X-linked mitochondrial disease affecting cardiac muscle, skeletal muscle and neutrophil leucocytes. *J. Neurol. Sci.* **62**, 327–355 (1983). doi.org/10.1016/0022-510x(83)90209-5

Review on the yeast model of the Barth syndrome:

• Ji, J. & Greenberg, M. L. Cardiolipin function in the yeast S. cerevisiae and the lessons learned for Barth syndrome. *J. Inherit. Metab. Dis.* **45**, 60–71 (2022). doi.org/10.1002/jimd.12447

Two descriptions of HACD1 congenital myopathy:

• Muhammad, E. *et al.* Congenital myopathy is caused by mutation of HACD1. *Hum. Mol. Genet.* **22**, 5229–5236 (2013). doi.org/10.1093/hmg/ddt380

• Abbasi-Moheb, L. *et al.* Biallelic loss-of-function HACD1 variants are a bona fide cause of congenital myopathy. *Clin. Genet.* **99**, 513–518 (2021). doi.org/10.1111/cge.13905

Characterization of Hacd1 roles in muscle development and mitochondrial function

• Blondelle, J. *et al.* HACD1, a regulator of membrane composition and fluidity, promotes myoblast fusion and skeletal muscle growth. *J. Mol. Cell Biol.* **7**, 429–440 (2015). doi.org/10.1093/jmcb/mjv049

• Prola, A. *et al.* Cardiolipin content controls mitochondrial coupling and energetic efficiency in muscle. *Sci. Adv.* **7**, eabd6322 (2021). doi.org/10.1126/sciadv.abd6322