Boehringer Ingelheim Veterinary Scholars Program – France

Vet school: Ecole Nationale Vétérinaire d'Alfort

Yin and yang of mitochondria efficiency in muscles

Laboratory: Biology of the NeuroMuscular System, Team 3 (UPEC-EnvA; Head: Pr Frédéric RELAIX)
http://www.imrb.inserm.fr/en/teams/f-relaix-j-authier-2/

Principal investigator: Fanny PILOT-STORCK and Laurent TIRET

Scientific background

In humans, dogs and mice, loss-of-function mutations in the *HACD1* gene result in similar congenital myopathies combining generalized hypotrophy and muscle weakness. *HACD1* expression, restricted to striated muscles, is induced during myoblast differentiation and maintained in the adult skeletal muscle. It encodes an endoplasmic reticulum-resident enzyme and we showed that in the developing or regenerating muscle, it modulates myoblast membrane phospholipid content, thereby triggering a physical switch towards facilitated fusion. Accordingly, *Hacd1*-deficient animal models have a reduced muscle mass.

Besides, locomotor activity of *Hacd1*-deficient mice and muscle ATP content were reduced, which contrasted with an increased food intake and an increased energy expenditure at the whole-body level. Analysis of skeletal muscle mitochondria in *Hacd1*-deficient animals revealed that their cristae, shaped from the invaginating inner mitochondrial membrane, were dilated and associated with a less efficient phosphorylating oxidation of ADP. The mitochondrial network was also more fragmented, highlighting altered physical properties of mitochondria membranes which phospholipid content, including cardiolipin, was globally reduced. At the systemic level, the quantified mitochondrial uncoupling produced increased lipid and carbohydrate catabolism, which unexpectedly induced an increased tolerance to glucose overload, despite the decreased muscle mass and locomotor activity. Eventually, the muscle-specific poor respiratory efficiency also protected mice against diet-induced obesity.

We thus demonstrated that skeletal muscle performance, through muscle growth and mitochondrial coupling, is dependent upon the active remodeling of mitochondrial membrane composition. Whereas its perturbation is associated with poor muscle performance, it increases energy expenditure and protects against diet-induced obesity, which could open new paths for therapeutic strategies in metabolic diseases.

Ongoing experiments aim at exploring mitochondrial dynamics in Hacd1-deficient mice as well as testing rescuing strategies for defective myoblast fusion and mitochondrial efficiency.

Examples of references from the laboratory

- **Characterization of *Hacd1* deficiency**

Blondelle, J., Ohno, Y., Gache, V., Guyot, S., Storck, S., Blanchard-Gutton, N., Barthélémy, I., Walmsley, G., Rahier, A., Gadin, S., Maurer, M., Guillaud, L., Prola, A., Ferry, A., Aubin-Houzelstein, G., Demarquoy, J., Relaix, F., Piercy, R.J., Blot, S., Kihara, A., Tiret, L., Pilot-Storck, F., 2015. HACD1, a regulator of membrane composition and fluidity, promotes myoblast fusion and skeletal muscle growth***. J Mol Cell Biol*** 7, 429–440. https://doi.org/10.1093/jmcb/mjv049

Blondelle, J., Pais de Barros, J.-P., Pilot-Storck, F., Tiret, L., 2017. Targeted lipidomic analysis of myoblasts by GC-MS and LC-MS/MS***, in: Skeletal Muscle Development, Methods in Molecular Biology***. James Ryall, pp. 39–60.

Maurer, M., Mary, J., Guillaud, L., Fender, M., Pelé, M., Bilzer, T., Olby, N., Penderis, J., Shelton, G.D., Panthier, J.-J., Thibaud, J.-L., Barthélémy, I., Aubin-Houzelstein, G., Blot, S., Hitte, C., Tiret, L., 2012. Centronuclear myopathy in Labrador retrievers: a recent founder futation in the PTPLA Gene has rapidly disseminated worldwide***. PLoS ONE*** 7, e46408. https://doi.org/10.1371/journal.pone.0046408

Pelé, M., Tiret, L., Kessler, J.-L., Blot, S., Panthier, J.-J., 2005. SINE exonic insertion in the PTPLA gene leads to multiple splicing defects and segregates with the autosomal recessive centronuclear myopathy in dogs***. Hum. Mol. Genet.*** 14, 1417–1427. https://doi.org/10.1093/hmg/ddi151

Tiret, L., Blot, S., Kessler, J.-L., Gaillot, H., Breen, M., Panthier, J.-J., 2003. The cnm locus, a canine homologue of human autosomal forms of centronuclear myopathy, maps to chromosome 2***. Hum. Genet.*** 113, 297–306. https://doi.org/10.1007/s00439-003-0984-7

Walmsley, G.L., Blot, S., Venner, K., Sewry, C., Laporte, J., Blondelle, J., Barthélémy, I., Maurer, M., Blanchard-Gutton, N., Pilot-Storck, F., Tiret, L., Piercy, R.J., 2017. Progressive Structural Defects in Canine Centronuclear Myopathy Indicate a Role for HACD1 in Maintaining Skeletal Muscle Membrane Systems***. The American Journal of Pathology*** 187, 441–456. https://doi.org/10.1016/j.ajpath.2016.10.002

- **Canine and feline genetics**

Abitbol, M., Hitte, C., Bossé, P., Blanchard-Gutton, N., Thomas, A., Martignat, L., Blot, S., Tiret, L., 2015. A COLQ Missense Mutation in Sphynx and Devon Rex Cats with Congenital Myasthenic Syndrome***. PLoS ONE*** 10, e0137019.

Abitbol, M., Thibaud, J.-L., Olby, N.J., Hitte, C., Puech, J.-P., Maurer, M., Pilot-Storck, F., Hédan, B., Dréano, S., Brahimi, S., Delattre, D., André, C., Gray, F., Delisle, F., Caillaud, C., Bernex, F., Panthier, J.-J., Aubin-Houzelstein, G., Blot, S., Tiret, L., 2010. A canine Arylsulfatase G (ARSG) mutation leading to a sulfatase deficiency is associated with neuronal ceroid lipofuscinosis***. Proc. Natl. Acad. Sci. U.S.A.*** 107, 14775–14780. https://doi.org/10.1073/pnas.0914206107

Böhm, J., Vasli, N., Maurer, M., Cowling, B.S., Cowling, B., Shelton, G.D., Kress, W., Toussaint, A., Prokic, I., Schara, U., Anderson, T.J., Weis, J., Tiret, L., Laporte, J., 2013b. Altered splicing of the BIN1 muscle-specific exon in humans and dogs with highly progressive centronuclear myopathy***. PLoS Genet.*** 9, e1003430. https://doi.org/10.1371/journal.pgen.1003430

Beggs, A.H., Böhm, J., Snead, E., Kozlowski, M., Maurer, M., Minor, K., Childers, M.K., Taylor, S.M., Hitte, C., Mickelson, J.R., Guo, L.T., Mizisin, A.P., Buj-Bello, A., Tiret, L., Laporte, J., Shelton, G.D., 2010. MTM1 mutation associated with X-linked myotubular myopathy in Labrador Retrievers***. Proc. Natl. Acad. Sci. U.S.A.*** 107, 14697–14702. https://doi.org/10.1073/pnas.1003677107