MASTER 2 BMC
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Involvement of SH3KBP1 in the modulation of myofiber integrity via autophagy regulation

Unit:
Pathophysiology and genetics of neuron and muscle (PGNM)
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Research project:

Muscle dysfunction is implicated in a plethora of human diseases and in sarcopenia, i.e. muscle atrophy with age, which constitutes the leading cause of loss of ambulation and independence. This project aims at identifying important pathways for muscle intracellular organization, under physiological and pathological conditions. The function of the muscle fiber (myofiber) is supported by a precise positioning of its organelles and nuclei. Myofibrils generate contractile force under the control of the "excitation-contraction coupling" (ECC) process, based on the interplay between the sarcoplasmic reticulum (SR), a complex network of tubular endoplasmic reticulum (ER), and Transverse (T)-tubules formed by repeated radial invaginations of the plasma membrane. This interplay takes place at specific interactions sites called triads.

We identified SH3KBP1 (SH3 domain-containing kinase-binding protein 1) as a new factor controlling both myonuclear positioning and T-tubule organization. SH3KBP1 scaffolds perinuclear ER through calnexin binding, and contributes to the formation and maintenance of T-tubules. We also evidenced that this protein binds to DNM2. Thus, these two SH3KBP1 partners could contribute to the correct positioning of myonuclei, organization of triads and to proper function of ECC.

We aim at characterizing the pathways regulating the organization and functionality of myofibers, focusing on ER and T-tubule remodeling and on associated functions such as autophagy in physiological or pathological (CentroNucleoMyopathies) contexts.

The proposed internship will focus on ER remodeling and autophagy. The M2 student will be involved in the determination of the biological functions of SH3KBP1 and associated proteins in the formation/maintenance of ER,

and thus nuclear positioning, through regulation of the autophagic pathway with a focus on either autophagic initiation or autophagic lysosome reformation (ALR) steps.

Models and techniques:

- *in vitro* cellular assays (cultured myotubes and mature myofibers)
- *primary culture of mice myoblasts*
- *Differentiation*
- Immunofluorescence, western blots
- *Real-time imaging (by confocal microscopy)*

References:

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