Universität Basel

Research Project

Unravelling the molecular mechanisms leading to muscle wasting: Role(s) of mTORC1 and FoxO3 pathways in autophagy in skeletal muscle

Third-party funded project

Project title Unravelling the molecular mechanisms leading to muscle wasting: Role(s) of mTORC1 and FoxO3 pathways in autophagy in skeletal muscle
Principal Investigator(s) Castets, Perrine ;
Organisation / **Research unit**
Departement Biomedizin / Neuromuscular Research (Sinnreich)
Departement Biozentrum / Pharmacology/Neurobiology (Rüegg)
Department
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Autophagy is a major catabolic process, essential for cell homeostasis. Defects in autophagy have recently been associated with different pathologies, including muscle diseases, and are suggested to play a role in aging dysfunctions. In most tissues, the mTORC1 pathway is the central inhibitor of autophagy induction. However, in skeletal muscles, it was proposed that autophagy is activated by FoxO signaling and is independent from mTORC1.

The overall aim of the project is to further clarify **the respective roles of mTORC1 and FoxO pathways in autophagy in skeletal muscle** and **their importance in the balance between protein synthesis and degradation.** Using recently generated mice in which the mTORC1 pathway is specifically hyperactivated (TSCmKO mice) or inhibited (RAmKO mice) in skeletal muscle, we recently showed that constitutive and starvation-induced autophagy is blocked in TSCmKO muscles despite FoxO activation, and established that mTORC1 inactivation is sufficient and strictly required for autophagy induction. Complementary experiments need to be done to identify the **molecular mechanisms underlying mTORC1-dependent regulation of autophagy** in muscle and to further **unravel the function(s) of the pathway in muscle wasting**.

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The first, fundamental project will focus on **the molecular function of mTORC1 in the recruitment of the autophagy machinery and the induction of the process in muscle cells upon different stimuli.** We will first analyze the response of TSCmKO muscles to denervation, another paradigm modifying autophagy, which appears to accelerate the development of muscle alterations in mutant mice. We will then carry out *in vitro* studies on isolated muscle fibers to investigate the consequences of mTORC1 imbalance and the underlying molecular mechanisms in greater details. These experiments will combine biochemical and histological tools against autophagy markers, such as the LC3 and p62 proteins. To get further insight into the defects, modulation of the pathways will be conducted with pharmacological drugs (i.e. chloroquine, rapamycin) or transfection of muscle fibers with specific constructs (targeting the FoxO signaling pathway or mTORC1 effectors).

In parallel, a second, clinical project will seek to identify **the involvement of mTORC1 in the pathophysiology of a specific muscle wasting disorder, the myotonic dystrophy type 1 (DM1).** Indeed, previous, incomplete data from other labs suggested that DM1 pathophysiology could be partly caused by abnormal autophagy flux that may be related to changes in the Akt signaling. I will first determine if the mTORC1/FoxO signaling pathways are perturbed in DM1 muscles and then, in turn, test whether

the autophagy process is impaired. I will lastly try to rescue DM1 muscle alterations, including muscle atrophy, by modulating either the mTORC1 pathway or the autophagy process. This part of the project will benefit from international collaborations allowing a combined analysis of a DM1 mouse model and muscle biopsies and cells from DM1 patients.

These two projects will yield essential insights into the molecular mechanisms underlying muscle homeostasis, an essential step in identifying treatment options for DM1 and the numerous other pathological conditions leading to muscle wasting.

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