Universität Basel

Research Project

Importance of the mTORC1 signaling in the maintenance and the plasticity of neuromuscular junctions

Third-party funded project

Project title Importance of the mTORC1 signaling in the maintenance and the plasticity of neuromuscular junctions
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Neuromuscular junctions (NMJ) transmit information from brain to muscle and thereby drive its contraction. It is known that a prolonged reduction in neuronal activity, caused by immobilization, degeneration of the motoneurons or alteration of the NMJs, leads to muscle atrophy. In this context, muscle wasting has been related to an increased catabolic activity relying on the proteasome system and on the autophagy flux, although the detailed molecular mechanisms at play in their induction remain to be elucidated. Histone deacetylases (HDAC) have been shown to participate in the response of muscle to changes in the neuronal activity, and to regulate in particular the expression of atrogenes, myogenic and synaptic genes. In parallel, we have recently demonstrated that mTORC1 inhibition is strictly required for the induction of constitutive and starvation-induced autophagy in skeletal muscle. In this project, we will further decipher the involvement of the mTORC1 pathway in muscle homeostasis by analyzing its role in the maintenance and the plasticity of NMJs. Specifically, we will analyze whether mTORC1 signaling regulates the autophagy flux and the activity of class II HDACs during a prolonged period of inactivity mimicked by denervation. We also aim to establish the consequences of mTORC1 deregulation on the innervation and thereby the properties of the muscle tissue during a period of activity recovery. Lastly, we will determine whether an impaired activity of the mTORC1 pathway is involved in pathological alterations of NMJs; to this purpose we will focus on CollagenVI-related myopathies and on aging, which are two conditions where a deregulation of mTORC1 is suggested to participate in the deteriorations of the muscle tissue. The project will bring new insights regarding the function of mTORC1 signaling and the importance of NMJ in the balance between muscle growth and wasting. This work may also open new avenues for therapeutic strategies that may counteract muscle atrophy occurring in a context of prolonged perturbation of the neuronal activity.

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