Abstract

Worldwide, the level of physical inactivity is declining. This contributes to increased risk of type 2 diabetes, obesity, cardiovascular complications, cancer and age-related muscle wasting, sarcopenia, which all constitute an enormous socioeconomic burden. Skeletal muscle comprises ~40 % of the total body mass, making it indispensable for exercise performance and essential for sustaining whole-body metabolic homeostasis. Exercise and exercise-mimicking stimuli effectively counteract the detrimental phenotypic changes following physical inactivity, and may provide important countermeasures to the chronic conditions related to physical inactivity. However, exercise is a continuum of different modalities, with resistance and endurance exercise representing the extremes. The two exercise modalities result in distinct phenotypes elicited by diverse molecular adaptations controlled by a network of intertwined catabolic and anabolic signalling pathways.

In skeletal muscle, mTORC1 is a key regulator of anabolic signalling, modulating muscle size, autophagy and metabolism. mTORC1 is mainly activated by the availability of nutrients and growth factors, but also mechanical stress by resistance exercise can activate mTORC1 and increase muscle mass. On the contrary, endurance exercise and energy scarcity activates AMPK, resulting in enhanced substrate utilisation, autophagy and protein breakdown. Through a tightly balanced regulation, both signalling cascades impact positively on muscle function. Thus, understanding the underlying molecular mechanisms and cross-talk between the anabolic and catabolic signalling pathways are of great importance.

The aim of the present PhD thesis was to describe the regulation of downstream mTORC1 signalling events in response to different stimuli, especially mechanical stress in skeletal muscle. Furthermore, the aim was to identify unknown mechanical stress-regulated substrates of mTORC1, potentially important in the regulation of muscle mass and function. By applying different mTORC1-activating stimuli such as amino acids, insulin and stretch to isolated mouse muscles, we found that stretch did not phosphorylate ULK1 Ser757, opposite to amino acids and insulin, suggesting that mechanical stress did not inhibit autophagy. In addition, by using pharmacological inhibitors of ULK1 and VPS34 (ULK1 substrate) in mouse muscles, we found that the two autophagy-related proteins may be required for glucose transport independently of autophagy.

Phosphoproteomic analysis and kinase substrate predictions of mouse EDL muscles subjected to the AMPK activator AICAR, stretch or combined AICAR and stretch, revealed an extremely complex and intertwined signalling network. From this, we identified the muscle-specific protein PERM1 as a novel mTORC1 substrate that was phosphorylated in response to mechanical stress, presumably to modulate transcription of genes involved in mitochondrial biogenesis following exercise.

Altogether, these findings indicate that stretch-stimulated mTORC1 activation is unique from other mTORC1 stimuli, and that mTORC1 has several hitherto unidentified substrates in muscle. These results contribute to the understanding of the underlying molecular mechanisms activated by physical activity. Thus, they may provide basis for development of strategies or therapeutics to prevent loss of muscle mass and the associated complications.