Exercise and regulation of metabolic function in human skeletal muscle
with special reference to PGC-1α and the mitochondria
ABSTRACT

Regular physical activity is highly associated with many health benefits and regular exercise training is used in the prevention and treatment of a large number of disease conditions, including type 2 diabetes, cardiovascular disease and cancer. One of the key adaptations to regular exercise training is mitochondrial biogenesis and improved oxidative capacity, particularly in skeletal muscle tissue. There is an inverse relationship between the dose of regular physical activity and the risk for premature death and this might in part be explained by the mitochondrially related improvement of metabolic health in trained skeletal muscle. In contrast, low whole body aerobic capacity and muscle mitochondrial content are characteristics of a sedentary lifestyle that contribute to the development of metabolic disease and other disorders. Most tissues adapt to exercise training, not least skeletal muscle, which is a highly plastic tissue. Cellular adaptations in skeletal muscle are driven by extra- and intracellular signals arising from the exercise stimulus, e.g. changes in shear stress, oxygen tension, energy levels, pH and temperature. Ultimately, these cellular perturbations lead to gene expression and protein alterations that improve skeletal muscle, e.g. through enhanced mitochondrial function.

The results in this thesis are based on skeletal muscle biopsies from the m.vastus lateralis, taken at rest (all studies) and at 30 min (study 2 and 3), 2hrs, 6hrs and 24 hrs (study 3) after an acute bout of exercise or after three months of training (study 4). The study subjects in Studies 1-3 were young healthy normally active individuals while in study 4 older men with impaired glucose regulation was recruited. Four different experimental models were used in this thesis: first, a one-legged knee extension exercise model with or without restricted blood flow in the leg; second, an acute bout of 60 min cycling; third, an acute bout of 60 min cycling (humans) or 36-40 min running on a treadmill (mice) or a 12-weeks high fat diet intervention (mice); and last a 12-week intervention in which resistance training or Nordic walking was performed. The main focus of this thesis was on the transcriptional coactivator PGC-1α and its upstream and downstream targets, coactivators and corepressors and how all these are affected by exercise.

In Paper I, we show for the first time that PGC-1α can be transcribed from an alternative promotor in human skeletal muscle and that the PGC-1α-ex1b transcript seems like the most avidly exercise-induced transcript. In brief, an acute exercise bout with restricted blood flow massively increased the mRNA levels of the human skeletal muscle PGC-1α splice variant 2 hours after exercise, most likely mediated through activation of an alternative promoter. Protein data supported previous studies demonstrating the importance of AMPK activation in exercise-induced expression of PGC-1α mRNA. In paper III, twenty-two mRNA transcripts and five proteins were measured over a 24 h time-course. Interestingly, as a response to exercise the protein levels of PGC-1α-ex1b increased before the elevation of the Total PGC-1α protein which might indicate its importance in the early adaptation processes. We also demonstrated for the first time the existence and post-exercise expression pattern of two LIPIN-1 (LIPIN-1α and LIPIN-1β) and three NCoR1 (NCoR1-1, NCoR1-2, and NCoR1-3) isoforms in human skeletal muscle. And just as in Paper I the data emphasized PGC-1α-ex1b as the most exercise-responsive PGC-1α isoform. In Paper II, the investigation aimed to define a functional role for BRCA1 in skeletal muscle using a translatonal approach. For the first time, BRCA1 and two shorter isoforms were identified in both humans and mouse skeletal muscle. In response to exercise, an increased interaction between BRCA1 and ACC-p was seen in both humans and mice. Decreasing the content of BRCA1 in primary human myotubes resulted in decreased oxygen consumption by the mitochondria and increased reactive oxygen species production. The decreased BRCA1 content also resulted in increased storage of intracellular lipids and reduced insulin signaling in human myotubes. These results indicate that BRCA1 might play a critical role in the regulation of metabolic function in skeletal muscle and address BRCA1 as a novel target to study further to pursue metabolic diseases.

Lastly, Paper IV shows for the first time that protein levels of the mitochondrially encoded and derived peptide humanin increases after 12-weeks of regular resistance exercise. This very small peptide has been implied to have multiple functions including neuroprotective effect and a positive effect on glucose metabolism and oxidative stress. Preliminary data from the same study material also revealed that MOTS-c, another small mitochondrially derived and encoded peptide, from the 12S rRNA gene, also seems to be affected by resistance training. These mitochondrially encoded peptides are interesting target to study further in the attempt to understand, and in the future to optimize, retrograde signaling and maybe use them to treat diseases in which mitochondrial function is impaired, e.g. type 2 diabetes, Alzheimer’s disease and cancer.

In conclusion, regular endurance training increases mitochondrial density through a complex network of transcriptional regulators that in an accumulated way are affected by each single exercise bout, and therefore is acute exercise also important to study in the endeavor to comprehend mitochondrial adaptations. Thus, it is important from a clinical, as well as basic science perspective to understand the regulation of skeletal muscle gene activity and the adaptation process at a molecular level in an attempt to recognize how it might contribute to the many health benefits seen with a physically active lifestyle.