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Exercise-induced mitochondrial biogenesis in human skeletal muscle

With special reference to mitochondrial transcription factors and lipin-1

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ABSTRACT

Mitochondrial biogenesis is one prominent adaptation to endurance training in skeletal muscle tissue. An increased mitochondrial density of the muscle fibres contributes to an enhanced aerobic capacity and thereby to improved fatigue-resistance. Multiple signalling pathways and transcriptional networks are involved in controlling mitochondrial biogenesis. The transcriptional co-regulator lipin-1 is one factor proposed to contribute, based on its ability to interact with PGC-1α and co-active transcription of metabolic genes. The mitochondrial transcription factors TFAM, TFB1M, TFB2M and mTERF have also been put forward as candidates. They are transcribed in the nucleus and post-translationally translocated to the mitochondria in order to govern the stability and use of the mitochondrial genome.

Firstly, this thesis explores the presence of lipin-1 splice variants in human skeletal muscle. Secondly, the importance of lipin-1 and mitochondrial transcription factors in exercise-induced mitochondrial biogenesis was assessed by investigating the influence of acute exercise and long term training on their expression in human skeletal muscle. Biopsies were obtained from the vastus lateralis of untrained healthy voluntary subjects before and after one bout of endurance exercise as well as after regular endurance training. In addition, biopsies were taken from well-adapted endurance athletes and moderately active individuals.

Two lipin-1 mRNA isoforms were identified in human skeletal muscle, corresponding to the previously described murine Lpin1α and Lpin1β. There were, however, no significant increases of total human LPIN1 or LPIN1α mRNA levels for up to 24 hours after a single bout of exercise or in response to 12 weeks of endurance training. This might imply LPIN1β to be more involved than LPIN1α in exercise-induced mitochondrial biogenesis in humans.

Furthermore, TFAM mRNA was more abundant after 10 days of training and elite athletes had higher levels of TFAM protein compared to moderately active. This indicates that TFAM may be important for maintenance of muscle mitochondrial mass and mainly regulated by protein stabilisation. The mRNA, but not protein, levels of TFB1M and TFB2M were higher in elite athletes compared to individuals with a moderate level of physical activity. Both factors were also elevated in response to 10 days of training with reduced blood flow to the working leg. This might suggest that TFB1M and TFB2M are altered pre-translationally in response to training.

The mitochondrial termination factor mTERF mRNA levels were higher in elite athletes with enhanced oxidative capacity, but did not change in response to endurance training. This implies that mTERF is not inhibitory for mitochondrial biogenesis, that long-term endurance adaptation increases its transcription and that it thus rather supports mitochondrial adaptations.

Further studies are needed to better understand the potential roles of lipin-1 isoforms and mitochondrial transcription factors in skeletal muscle adaptation to exercise training, and possibly also in some of the health benefits that accompanies an active lifestyle.

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