Sending the message: Training-nutrient interactions to stimulate mitochondrial biogenesis

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Endurance exercise induces an increase in muscle mitochondria (Holloszy, 1967). A single bout of exercise stimulates mitochondrial biogenesis, as evidenced by increases in the expression of mitochondrial proteins (Baar *et al.*, 2002; Wright *et al.*, 2007). Repeated bouts of exercise (*i.e.* training), maintain this effect. Recent advances in molecular biology and in understanding of the mechanisms that regulate mitochondrial biogenesis have made it possible to elucidate how exercise stimulates mitochondrial biogenesis. The initial breakthrough in elucidating how mitochondrial biogenesis is regulated was the discovery of the transcription factors that regulate expression of the nuclear genes that encode mitochondrial proteins (Scarpulla, 2006). These include nuclear-respiratory factor 1 (NRF-1) and nuclear-respiratory factor 2 (NRF-2) which bind to the promoters, and activate transcription of the genes that encode mitochondrial respiratory chain proteins (Kelly & Scarpulla, 2004). NRF-1 also activates expression of the nuclear gene that encodes mitochondrial transcription factor A, (TFAM) which moves to the mitochondria where it regulates transcription of the mitochondrial DNA (*i.e.* the mitochondrial genome). The second major breakthrough was the discovery of an inducible co-activator, the peroxisome proliferator-activated receptor-gamma coactivator (PGC-1α), that docks on and activates these transcription factors and, thus, activates and regulates the coordinated expression of mitochondrial proteins encoded in the nuclear and mitochondrial genomes (Lin, Handschin & Spiegelman, 2005). A single bout of exercise induces a rapid increase in PGC-1α in skeletal muscle (Baar *et al.*, 2002). The initial phase of the increase in mitochondrial biogenesis induced by exercise appears to be mediated by activation of PGC-1α, while the second phase is mediated by the increase in PGC-1α protein (Wright *et al.*, 2007). The p38 mitogen-activated protein kinase (p38 MAPK) phosphorylates and activates PGC-1α (Puigserver *et al.*, 2001). P38 MAPK also increases PGC-1α expression by phosphorylating the transcription factor ATF-2, which increases PGC-1 protein expression by binding to and activating the CREB site on the PGC-1α promoter (Akimoto *et al.*, 2005). Exercise results in rapid activation of p38 MAPK, which mediates both the activation and increased expression of PGC-1α (Akimoto *et al.*, 2005). Recent evidence reveals that nutrient availability serves as a potent modulator of many acute responses and chronic adaptations to both endurance and resistance exercise (Hawley *et al.*, 2011). Changes in macronutrient intake rapidly alter the concentration of blood-borne substrates and hormones, causing marked perturbations in the storage profile of skeletal muscle and other insulin-sensitive tissues. In turn, muscle energy status exerts profound effects on resting fuel metabolism and patterns of fuel utilization during exercise as well as acute regulatory processes underlying gene expression and cell signaling. Such nutrient-exercise interactions can activate or inhibit many biochemical pathways with putative roles in training adaptation. This is leading to an understanding of the molecular and cellular events that take place in skeletal muscle in response to both endurance and resistance exercise commenced after acute and/or chronic alterations in nutrient availability.

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