PGC-1/ERRα regulation of muscle growth

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The transcriptional coactivators peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α) and β (PGC-1β) are positive regulators of many functions important for maintaining skeletal muscle health including mitochondrial biogenesis, skeletal muscle fibre type, glucose transport, lipid oxidation and angiogenesis (Finck & Kelly, 2006). Many of their actions in skeletal muscle depend on the transcription factor, estrogen-related receptor-α (ERRα)(Finck & Kelly, 2006). The expression levels of PGC-1α and ERRα are positively regulated by endurance exercise (Cartoni *et al.*, 2005). PGC-1α mRNA is also increased in human skeletal muscle following resistance exercise (Deldicque *et al.*, 2008), while an isoform of PGC-1α, PGC-1α4, stimulates muscle hypertrophy via an IGF1-mediated mechanism (Ruas *et al.*, 2012). Diseases associated with attenuated muscle metabolism and muscle atrophy, including ageing, cancer cachexia (Sandri *et al.*, 2006) and amyotrophic lateral sclerosis (ALS) (Russell *et al.*, 2012) demonstrate reductions the PGC-1α and PGC-1β. Transgenic overexpression of PGC-1α or PGC-1β in mouse skeletal muscle prevents muscle atrophy following denervation, fasting and sarcopenia (Sandri *et al.*, 2006; Wenz *et al.*, 2009; Brault *et al.*, 2010). This protective action may due to a reduction in protein degradation via attenuated FOXO3a transcriptional activity (Sandri *et al.*, 2006; Brault *et al.*, 2010). The maintenance of muscle mass is also controlled by protein synthesis which is significantly reduced in many catabolic states. The role of PGC-1/ ERRα in regulating muscle cell protein synthesis has not been well investigated. We show that PGC-1α and PGC-1β increase protein synthesis and myotube diameter in C2C12 myotubes; an effect dependent on ERRα, but independent of Akt and mTOR activity. Global gene expression profiling followed by Gene-Set Enrichment Analysis (GSEA) as well as discriminant gene selection in C2C12 myotubes overexpressing PGC-1α or PGC-1β identified the regulation of molecular targets associated with protein synthesis and translation, supporting our finding of increased protein synthesis. To provide potential clinical relevance to these observations, several of these PGC-1α and PGC-1β gene targets were also regulated in human skeletal muscles following resistance exercise, a known activator of muscle protein synthesis, and in atrophied muscle samples of patients with amyotrophic lateral sclerosis (ALS). These novel findings provide insight into how PGC-1α and PGC-1β positively influence skeletal muscle growth.

Brault JJ, Jespersen JG & Goldberg AL. (2010) *Journal of Biological Chemistry* **285**, 19460-71.

Cartoni R, Leger B, Hock MB, Praz M, Crettenand A, Pich S, Ziltener JL, Luthi F, Deriaz O, Zorzano A, Gobelet C, Kralli A & Russell AP. (2005) *Journal of Physiology* **567**, 349-58.

Deldicque L, Atherton P, Patel R, Theisen D, Nielens H, Rennie MJ & Francaux M. (2008) *Journal of Applied Physiology* **104**, 371-78.

Finck BN & Kelly DP. (2006) *Journal of Clinical Investigation* **116**, 615-22.

Ruas JL, White JP, Rao RR, Kleiner S, Brannan KT, Harrison BC, Greene NP, Wu J, Estall JL, Irving BA, Lanza IR, Rasbach KA, Okutsu M, Nair KS, Yan Z, Leinwand LA & Spiegelman BM. (2012) *Cell* **151**, 1319-31.

Russell AP, Wada S, Vergani L, Hock MB, Lamon S, Leger B, Ushida T, Cartoni R, Wadley GD, Hespel P, Kralli A, Soraru G, Angelini C & Akimoto T. (2012) *Neurobiology of Disease* 49C, 107-17.

Sandri M, Lin J, Handschin C, Yang W, Arany ZP, Lecker SH, Goldberg AL & Spiegelman BM. (2006) *Proceedings National Academy Science USA* **103**, 16260-65.

Wenz T, Rossi SG, Rotundo RL, Spiegelman BM & Moraes CT. (2009) *Proceedings National Academy Science USA* **106**, 20405-10.