Molecular regulation of skeletal muscle mass

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Skeletal muscle mass is increased in response to increases in functional demand as seen with resistance training (Fry, 2004). In contrast, skeletal muscle mass is dramatically reduced in diseases and conditions such as cancer, diabetes, sepsis, AIDS, denervation, ageing and muscular dystrophies (Lynch, 2001). The control of skeletal muscle mass is tightly regulated by the synergy between anabolic pathways controlling protein synthesis and catabolic pathways regulating protein degradation. These pathways are not necessarily independent of each other (Bodine *et al.,* 2001).

Advances have been made in understanding the factors controlling skeletal muscle hypertrophy and atrophy using pharmacological and genetic manipulation in cellular and rodent models. Akt (also called PKB; Protein Kinase B) has been identified as a pivotal point in the hypertrophy and atrophy signalling pathways (Bodine *et al.,* 2001). Akt phosphorylates several downstream targets including glycogen synthase kinase-3β (GSK3β) and the mammalian target of rapamycin (mTOR), promoting increases in protein synthesis and translation initiation (Rhoads, 1999) and muscle hypertrophy (Bodine *et al.,* 2001). Chronic resistance exercise results in muscle hypertrophy which is associated with increased levels of Akt and its downstream targets (Bodine *et al.,* 2001; Leger *et al.,* 2006). In contrast, acute resistance exercise is able to stimulate protein synthesis, independently of Akt phosphorylation, but in parallel with increases in mTOR and its downstream target p70s6K (Dreyer *et al.,* 2008).

Skeletal muscle atrophy is characterized by an up-regulation of the muscle specific E3-ligases, atrogin-1 and MuRF1, in numerous models of muscle wasting (Glass, 2005). Atrogin-1 and MuRF1 are often increased by Forkhead (FoXO) transcription factors (Sandri *et al.,* 2004) with a concomitant increase in proteasomal and lysosomal protein degradation (Zhao *et al.,* 2007). Over-expressing Akt (Sandri *et al.,* 2004) or peroxisome proliferator-activator receptor co-activator gamma-1α (PGC-1α) (Sandri *et al.,* 2006) can inhibit the FoXO dependent increase in atrogin-1 and MuRF1 and attenuate muscle wasting.

Akt and PGC-1α signalling appear to be key elements regulating skeletal muscle mass. Determining how these proteins can be therapeutically manipulated in skeletal muscle *in vivo* may help with attenuating skeletal muscle wasting.

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