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Regulation of mTOR signaling in skeletal muscle hypertrophy

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Growth and maintenance of skeletal muscle mass is critical for long-term health and quality of life. Studies of exercise *in vivo* and stretch *in vitro* have established that mechanical loading of muscle cells induces growth[1-3]. This growth is characterized by increases in fiber cross-sectional area, total protein content and total RNA content. One cellular response that has been studied in both systems is the rate of protein synthesis[3-5]. These studies have shown that following one bout of exercise/stretch, rates of protein synthesis are elevated for hours after the bout. Previous studies have demonstrated that signaling through mTOR in skeletal muscle is critical for regulation of protein synthesis and is necessary for growth both *in vivo* and *in vitro*[6-9]. While this observation is well accepted, there is still very little understood about the specific upstream signaling mechanisms regulating mTOR activity required for growth.

mTOR is a serine/threonine kinase of the phosphatidylinositol kinase-related kinase family, it is highly conserved from yeast to mammals and is expressed in all cell types[10,11]. Studies have established that mTOR functions as a central integrator of growth and differentiation in muscle cells, osteoblasts and chondrocytes. Regulation of mTOR is most well defined in response to nutrients, such as amino acids, and growth factors such as IGF1[10,11]. In skeletal muscle, activation of mTOR signaling is also induced by mechanical strain via an intracellular pathway different to growth factors[12-14]. While the mTOR pathway has been demonstrated to be a critical mediator of muscle hypertrophy there is still little known about the intracellular mechanisms regulating its activity.

Upstream of mTOR is the TSC complex (tuberous sclerosis complex) which is a heterodimeric complex of the TSC1 and TSC2 gene products, hamartin and tuberin, respectively. Studies have shown that the TSC1/TSC2 heterodimer regulates cell growth and cell proliferation as a downstream component of the PI3K (phosphoinositide 3-kinase)-Akt signaling, which modulates signal transduction through mTOR. Cells null for TSC1 or TSC2, cells depleted of TSC1 or TSC2 by RNA interference, and human and mouse tissues deficient in TSC1 or TSC2, all have high mTOR activity, as measured by S6K1 phosphorylation[15]. Together with its partner TSC1, TSC2 functions as a GAP (GTPase activating protein) for a small G protein named Rheb (Ras homolog enriched in brain).

Phosphorylation of TSC2 is thought to inhibit its GAP activity, allowing Rheb to accumulate in its active GTP-bound form. GTP-bound Rheb strongly stimulates mTOR activity and TSC2 functions to inactivate Rheb by increasing the intrinsic rate of GTP hydrolysis on Rheb[10,11,15].

Recently, two hypoxia-induced genes, termed *Scylla* and *Charybdis*, were identified in *Drosophila* from a genetic screen for negative regulators of the dTOR pathway[16]. In mammals, these genes are named REDD1 and REDD2 (mammalian orthologs of *Scylla* and *Charybdis*, also called RTP801/DDIT4 and RTP801L/DDIT4L, respectively) and have been shown to inhibit mTOR kinase activity. Previous studies have indicated that REDD1 is ubiquitously expressed and is essential for the down-regulation of mTOR activity by hypoxia, dexamethasone treatment and/or cellular energy stress[17-19]. The regulation and function of REDD2 is less well known but of interest because REDD2 has previously been shown to be highly induced in response to skeletal muscle unloading, a model of muscle atrophy, and associated with diminished mTOR activity.

The goal of this talk will be to present research highlighting the specificity of mechanical signaling of mTOR signaling in skeletal muscle, to evaluate the contribution of the TSC1:TSC2 complex in mediating mTOR activity and present evidence demonstrating the role of REDD2 in negatively regulating mTOR signaling in mammalian skeletal muscle.

The author has no conflict of interest.

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