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CELL SIGNALLING

Building strong muscles

The mass and energy status of skeletal muscle are dynamically regulated in response to nutrient availability, growth and exercise. Two recent studies unravel some of the underlying mechanisms of skeletal muscle control.

Skeletal muscle mass increases in response to nutrient availability through protein synthesis. The translation initiation complex eIF4F, which contains the phosphoprotein eIF4G, promotes protein synthesis under nutrient-rich conditions. Mitogen-activated protein kinase-interacting kinase 1 (MNK1) and MNK2 are known to interact with eIF4F and to promote its function. Unexpectedly, however, Hu *et al.* reveal that MNK2 also contributes to muscle atrophy by downregulating eIF4G phosphorylation at Ser1108, leading to reduced protein synthesis.

> “new aspects of the role of mTOR and other signalling pathways in the dynamic function of skeletal muscle”

Phosphorylation of eIF4G at Ser1108 was found to decrease in muscle cells following nutrient deprivation *in vitro*. Interestingly, overexpression of MNK2, but not MNK1, had a similar effect, whereas the addition of insulin-like growth factor 1 (IGF1) or deletion of MNK2 increased the levels of eIF4G phosphorylation at Ser1108. Similarly, the levels of eIF4G phosphorylation at Ser1108 in skeletal muscle of MNK2-deficient (but not MNK1-deficient) mice increased, indicating that MNK2 is a negative regulator of eIF4G activity and thus of protein synthesis.

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Further analysis revealed that MNK2 acts downstream of the nutrient sensor mammalian target of rapamycin (mTOR; which is known to promote protein synthesis), as mTOR inhibitors required MNK2 expression to reduce eIF4G phosphorylation at Ser1108. MNK2 was found to directly interact with mTOR complex 1 (mTORC1) and to compete with Pro-rich AKT substrate (PRAS40) for binding to regulatory-associated protein of mTOR (RAPTOR), an mTORC1 component. Moreover, overexpression of Ser/Arg-rich protein kinase 1 (SRPK1) enhanced basal eIF4G phosphorylation at Ser1108, and this effect was abolished by MNK2 overexpression. Therefore, MNK2 negatively regulates eIF4G by acting downstream of mTOR inhibition and upstream of SRPK1.

Energy metabolism in differentiated skeletal muscle depends on mitochondrial biogenesis, which enables a metabolic switch from glycolysis to oxidative phosphorylation, thereby supporting the increased energy requirements of differentiated myotubes. In their study, Bakkar *et al.* identify an essential role for the non-canonical nuclear factor-κB (NF-κB) signalling pathway in mitochondrial biogenesis in skeletal muscle.

The formation of the RelB–p52 heterodimer, which activates non-canonical NF-κB-mediated transcription, is promoted by inhibitor of NF-κB kinase-α (IKKα). Interestingly, IKKα overexpression in mouse skeletal muscle increased the levels of mitochondrial DNA and proteins, the number and elongation of mitochondria as well as their oxidative activity, whereas genetic deletion of IKKα or RelB had the opposite effects. In addition, activation of the non-canonical NF-κB pathway was implicated in the specification of muscle fibre types, as IKKα overexpression increased the levels of slow twitch oxidative fibres whereas RelB deficiency resulted in increased levels of fast twitch glycolytic myofibres.

Further analysis revealed that the transcriptional co-activator PPARα co-activator-1β (PGC1β) is specifically and directly induced by the RelB–p52 heterodimer (which binds on two sites of the *Pgc1β* locus) in skeletal muscle and orchestrates mitochondrial biogenesis-related gene expression. Moreover, mTOR was found to interact with IKKα, and mTOR inhibition was sufficient to abolish IKKα activity and PGC1β expression. Thus, energy flux in differentiated myotubes appears to be regulated by the mTOR-induced activation of non-canonical NF-κB signalling, which activates a mitochondrial biogenesis transcriptional programme through PGC1β.

Taken together, the two studies reveal new aspects of the role of mTOR and other signalling pathways in the dynamic function of skeletal muscle.

Maria Papatriantafyllou

ORIGINAL RESEARCH PAPERS Hu, S. I. *et al.* MNK2 inhibits eIF4G activation through a pathway involving serine-arginine-rich protein kinase in skeletal muscle. *Science Signal.* **5**, ra14 (2012) | Bakkar, N. *et al.* IKKα and alternative NF-κB regulate PGC1-β to promote oxidative muscle metabolism. *J. Cell Biol.* **196**, 497–511 (2012)