

A metabolic role for the Hippo signalling pathway effector Yap in adult skeletal muscle fibres

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The Hippo signalling pathway effector protein Yap enhances adult skeletal muscle mass and limits skeletal muscle atrophy in settings of neuromuscular disease. However, the mechanisms that lead to changes in muscle attributes following alterations in Yap activity remain unclear. Here, we show in the limb musculature of adult mice that Yap regulates the expression of genes associated with metabolic capacity, prior to the onset of myopathy. Consistent with this finding, we demonstrate that the myofibre atrophy observed following sustained inhibition of Yap is more pronounced in muscles composed predominately of oxidative fibres. Silencing Yap results in altered fatty acid metabolism, reductions in skeletal muscle oxidative potential and activation of the unfolded protein response. In line with these findings, we demonstrate that Yap levels in skeletal muscle fibres are lower in the glycolytic muscles of db/db mice, and in the muscles of Insulin resistant, obese humans. Restoring Yap levels in the striated muscles of db/db mice was associated with an increase in skeletal muscle oxidative capacity and limited adiposity and hepatic lipid accumulation, independent of changes in lean mass or food intake. Our findings provide the first evidence for a functional metabolic role for the Hippo pathway effector Yap in a post-mitotic cell and suggest that modulating Yap activity may be an approach to promote skeletal muscle metabolic attributes.