Alterations to mTORC1 signaling in the skeletal muscle differentially affect whole-body metabolism

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The mammalian target of rapamycin complex 1 (mTORC1) is a central node in a network of signaling pathways controlling cell growth and survival. This multiprotein complex integrates external signals and affects different nutrient pathways in various organs. However, it is not clear how alterations of mTORC1 signaling in skeletal muscle affect whole-body metabolism.; We characterized the metabolic phenotype of young and old raptor muscle knock-out (RAmKO) and TSC1 muscle knock-out (TSCmKO) mice, where mTORC1 activity in skeletal muscle is inhibited or constitutively activated, respectively. Ten-week-old RAmKO mice are lean and insulin resistant with increased energy expenditure, and they are resistant to a high-fat diet (HFD). This correlates with an increased expression of histone deacetylases (HDACs) and a downregulation of genes involved in glucose and fatty acid metabolism. Ten-week-old TSCmKO mice are also lean, glucose intolerant with a decreased activation of protein kinase B (Akt/PKB) targets that regulate glucose transporters in the muscle. The mice are resistant to a HFD and show reduced accumulation of glycogen and lipids in the liver. Both mouse models suffer from a myopathy with age, with reduced fat and lean mass, and both RAmKO and TSCmKO mice develop insulin resistance and increased intramyocellular lipid content.; Our study shows that alterations of mTORC1 signaling in the skeletal muscle differentially affect whole-body metabolism. While both inhibition and constitutive activation of mTORC1 induce leanness and resistance to obesity, changes in the metabolism of muscle and peripheral organs are distinct. These results indicate that a balanced mTORC1 signaling in the muscle is required for proper metabolic homeostasis.
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