**Abstract**

New structured abstract for Mol Metab formatting

Objective

The mechanistic target of rapamycin (mTORC1) is a nutrient responsive protein kinase complex that helps co-ordinate anabolic processes across all tissues. There is evidence that signaling through mTORC1 in skeletal muscle may be a determinant of energy expenditure and aging and therefore components downstream of mTORC1 signaling may be potential targets for treating obesity and age-associated metabolic disease. This study aimed to identify mTORC1-dependent mechanisms in skeletal muscle that regulate energy balance and aging.

Methods

We generated mice with *Ckmm-Cre* driven ablation of *Tsc1,* which confers constitutive activation of mTORC1 in skeletal muscle and performed unbiased transcriptional analyses to identify pathways and candidate genes that may explain how skeletal muscle mTORC1 activity regulates energy balance and aging.

Results

Activation of skeletal muscle mTORC1 produced a striking resistance to diet- and age-induced obesity without inducing systemic insulin resistance. We found that increases in energy expenditure following a high fat diet were mTORC1-dependent and that elevated energy expenditure caused by ablation of *Tsc1* coincided with the upregulation of skeletal muscle-specific thermogenic mechanisms that involve sarcolipin-driven futile cycling of Ca2+ through SERCA2. Additionally, we report that constitutive activation of mTORC1 in skeletal muscle reduces lifespan.

Conclusions

These findings support the hypothesis that activation of mTORC1 and its downstream targets, specifically in skeletal muscle, may play a role in nutrient-dependent thermogenesis and aging.

Original (unstructured abstract)

The mechanistic target of rapamycin (mTORC1) is a nutrient responsive protein kinase complex that helps co-ordinate anabolic processes across all tissues. There is evidence that signaling through mTORC1 in skeletal muscle may be a determinant of energy expenditure and aging and therefore components downstream of mTORC1 signaling may be potential targets for treating obesity and age-associated metabolic disease. Here, we have generated mice with *Ckmm-Cre* driven ablation of *Tsc1,* which confers constitutive activation of mTORC1 in skeletal muscle. While we did not observe systemic insulin resistance in these mice, we detected a striking resistance to diet- and age-induced obesity. Unbiased transcriptional analysis identifies pathways and candidate genes that may explain how skeletal muscle mTORC1 activity regulates energy balance and aging. We show that increases in energy expenditure following a high fat diet are mTORC1-dependent and that elevated energy expenditure caused by ablation of *Tsc1* coincides with the upregulation of skeletal muscle-specific thermogenic mechanisms that involve sarcolipin-driven futile cycling of Ca2+ through SERCA2. Additionally, we show that constitutive activation of mTORC1 in skeletal muscle reduces lifespan. These findings support the hypothesis that activation of mTORC1 and its downstream targets, specifically in skeletal muscle, may play a role in nutrient-dependent thermogenesis and aging.