



July 29, 2019

We are pleased to submit our research article, Skeletal Muscle mTORC1 Activation Increases Energy Expenditure and Reduces Longevity in Mice for consideration for publication in Molecular Metabolism.

Our manuscript reports several novel research findings that advance our understanding of the mechanisms contributing to energy homeostasis. In particular, our work demonstrates an important role for skeletal muscle-specific mechanistic target of rapamycin complex 1 (mTORC1) activity in the regulation of energy expenditure and aging. We demonstrate that skeletal muscle mTORC1 activation increases energy expenditure and does so, we propose, in part, by a mechanism involving SR/ER uncoupling. We also report that chronic mTORC1 activation in skeletal muscle results in accelerated aging and early death. Our findings support the hypothesis that activation of mTORC1 and its downstream targets, specifically in skeletal muscle, are important regulators of thermogenesis, and point to a role for mTORC1 in stimulating mechanisms of energy expenditure in response to caloric overload. This is a novel way of thinking about mTORC1, but since it is activated by elevated nutrient status, it is reasonable that it may also respond to these stimuli by dissipating excess energy. Our manuscript also raises the important question of whether the positive effects of skeletal muscle mTORC1 activation (i.e., increased energy expenditure, reduced adiposity) can be separated from the negative effects of chronic mTORC1 activation (i.e., accelerated aging and early death) and leveraged in the fight against obesity.

We believe that the research findings we report are in line with the scientific mission of Molecular Metabolism. Our manuscript is not published elsewhere, nor is it under consideration for publication at any other journal. All authors contributed fairly to the finished body of work and all have approved the version of the manuscript we are submitting for your consideration.

Regards,

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