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## **Thyroid Hormone Regulates Glutamine Metabolism and Anaplerotic Fluxes by Inducing Mitochondrial Glutamate Aminotransferase GPT2**

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Thyroid hormones (THs) are key metabolic regulators coordinating short- and long-term energy needs. In skeletal muscle, THs modulate energy metabolism in pathophysiological conditions. Indeed, hypothyroidism and hyperthyroidism are leading causes of muscle weakness and strength; however, the metabolic pathways underlying these effects are still poorly understood. Using molecular, biochemical and isotope-tracing approaches combined with mass spectrometry and denervation experiments, we found that THs regulate glutamine metabolism and anaplerotic fluxes by up-regulating the Glutamate Pyruvate Transaminase 2 gene (GPT2). In humans, GPT2 autosomal recessive mutations cause a neurological syndrome characterized by intellectual disability, microcephaly, and progressive motor symptoms. Herein, we demonstrate a new role of TH/GPT2 axis in skeletal muscle, regulating muscle weight and fiber diameter in resting and atrophic conditions and resulting in protection from muscle loss during atrophy. These results describe a new anabolic route by which THs rewire glutamine metabolism towards the maintenance of muscle mass.

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