G12/G13 biology in energy metabolism

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Skeletal muscle is a key organ in energy homeostasis owing to its high requirement for nutrients. Heterotrimeric G proteins converge with activated GPCRs to modulate cell-signaling pathways. Here, we report that muscle-specific ablation of $G\alpha 13$ in mice promotes reprogramming of myofibers to the oxidative type, with resultant increases in mitochondrial biogenesis. Mechanistically, $G\alpha 13$ and its downstream effector RhoA suppressed nuclear factor of activated T cells 1 (NFATc1), a chief regulator of myofiber conversion, by increasing Rock2-mediated phosphorylation at Ser243. Ser243 phosphorylation of NFATc1 was reduced after exercise, but was higher in obese animals. Consequently, $G\alpha 13$ ablation in muscles enhanced whole-body energy metabolism, thus affording protection from diet-induced obesity and hepatic steatosis. In the absence of $G\alpha 13$, $G\alpha 12$ plays a role in mitochondrial regulation. Mechanistically, $G\alpha 12$ stabilized SIRT1 protein through induction of USP22 via HIF-1 α . Consistently, $G\alpha 12$ -KO mice fed a high-fat diet displayed greater susceptibility to diet-induced liver steatosis and obesity due to decrease in energy expenditure. Thus, $G\alpha 12$ regulates SIRT1-dependent mitochondrial respiration through HIF-1 α -dependent USP22 induction, which contributes to the regulation of mitochondrial energy expenditure.