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SIRT4 controls the balance between lipid synthesis and catabolism by repressing malonyl-CoA decarboxylase

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Lipid metabolism is highly controlled by the nutritional state of the organism. In this study, we identify the mitochondrial sirtuin, SIRT4, as a critical regulator of lipid homeostasis. We find that SIRT4 represses fatty acid oxidation while promoting lipid anabolism. Mechanistically, SIRT4 regulates this balance by inhibiting malonyl-CoA decarboxylase (MCD), an enzyme that produces acetyl-CoA from malonyl-CoA, a precursor for lipogenesis that also inhibits mitochondrial fat oxidation. We find that SIRT4 is active in nutrient-rich conditions, such as in the fed state. As a consequence, SIRT4 null mice display reduced levels of malonyl-CoA in skeletal muscle and white adipose tissue in the fed state and fail to further lower malonyl-CoA levels during fasting. SIRT4 null mice possess a catabolic signature of lipid metabolism and demonstrate decreased de novo lipogenesis. These studies highlight SIRT4 as a novel regulator of MCD activity and malonyl-CoA levels, providing new insight into the regulation of lipid homeostasis.

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