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

Gaëlle Laurent[1], Natalie J German[1], Asish K Saha[2], Vincent CJ de Boer[1,3], Frank Fischer[4], Gina Boanca[4], Noah Dephoure[5], Bhavapriya Vaitheesvaran[6], Michael Davies[7], Steven P Gygi[5], Deborah M Muoio[7], Irwin J Kurland[6], Clemens Steegborn[4], Neil B Ruderman[2], Marcia C Haigis[1*]

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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.

Author details
[1]Department of Cell Biology, The Paul F. Glenn Labs for the Biological Mechanisms of Aging, Harvard Medical School, Boston, MA 02115, USA. [2]Diabetes Research Unit, Section of Endocrinology, Department of Medicine, Boston University Medical Center, Boston, MA 02118, USA. [3]Current address: Laboratory Genetic Metabolic Diseases, Academic Medical Center, Amsterdam, 1105AZ, The Netherlands. [4]Department of Biochemistry, University of Bayreuth, 95447 Bayreuth, Germany. [5]Department of Cell Biology, Harvard University Medical School, Boston, MA 02115, USA. [6]Department of Medicine, Diabetes Center, Stable Isotope and Metabolomics Core Facility, Albert Einstein College of Medicine, Bronx, New York 10461, USA. [7]Departments of Medicine and Pharmacology & Cancer Biology, Sarah W. Stedman Nutrition and Metabolism Center, Duke University Medical Center, Durham, NC27710, USA.

[1]Department of Cell Biology, The Paul F. Glenn Labs for the Biological Mechanisms of Aging, Harvard Medical School, Boston, MA 02115, USA
Full list of author information is available at the end of the article

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