Regulation of Mitochondrial Redox Status by Calorie-restriction Protein SIRT3

SIRT3 Protein Deacetylates Isocitrate Dehydrogenase 2 (IDH2) and Regulates Mitochondrial Redox Status

Isocitrate dehydrogenase 2 (IDH2) is a critical part of the mitochondrial machinery that keeps cellular oxidative damage in check by producing NADPH. Malfunctions in IDH2 have been recently observed in cancer cells. In this Paper of the Week, John M. Denu and colleagues at the University of Wisconsin-Madison revealed how the activity of IDH2 is regulated by SIRT3, an NAD+-dependent protein deacetylase that regulates crucial metabolic pathways during nutrient deprivation and caloric restriction. Denu and colleagues demonstrated both in vivo and in vitro that, under conditions of caloric restriction, SIRT3 targeted a particular modified lysine on IDH2 and removed its acetyl moiety. The deacetylation by SIRT3 increased IDH2 activity by as much as 44-fold and produced more NADPH to protect against oxidative stress. The authors note, “In addition to regulation of mitochondrial redox status, these results implicate SIRT3 as a general regulator of IDH2 functions, particularly in cancer cell metabolism.”

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IDH2 is active when Lys-413 is deacetylated. Wild-type IDH2 and mutants K413R, K413Q, K272Q, K256Q, and K263Q were purified from HEK293 cells and tested for activity.

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