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Evidence for a common mechanism of SIRT1 regulation by allosteric activators.

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Abstract

A molecule that treats multiple age-related diseases would have a major impact on global health and economics. The SIRT1 deacetylase has drawn attention in this regard as a target for drug design. Yet controversy exists around the mechanism of sirtuin-activating compounds (STACs). We found that specific hydrophobic motifs found in SIRT1 substrates such as PGC-1α and FOXO3a facilitate SIRT1 activation by STACs. A single amino acid in SIRT1, Glu(230), located in a structured N-terminal domain, was critical for activation by all previously reported STAC scaffolds and a new class of chemically distinct activators. In primary cells reconstituted with activation-defective SIRT1, the metabolic effects of STACs were blocked. Thus, SIRT1 can be directly activated through an allosteric mechanism common to chemically diverse STACs.