The skinny on SIRT1 regulation

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SIRT1 (sirtuin 1), the mammalian orthologue of yeast Sir2, is a highly conserved NAD+-dependant deacetylase that is emerging as an important regulator of aging and metabolic disease. SIRT1 and its family members promote longevity in different model organisms, including yeast, worms, flies and mice. SIRT1 deacetylates a diverse list of substrates including p53, NF-κB and histones (Haigis and Sinclair, 2009), thereby influencing gene silencing, apoptosis, stress resistance, and fat and glucose metabolism. The combination of these effects contributes to an anti-aging effect in mammals. SIRT1 activity can be modulated by the metabolic state of the organism, with increased activity during energy deficiency and decreased activity during energy surplus (Lagouge et al., 2006). However, how changes in SIRT1 activity are achieved during different metabolic conditions remains unclear.

Much attention has been given to the anti-aging and metabolic disease-curing potential that might be found through activation of SIRT1. The SIRT1 activator resveratrol, a small polyphenolic compound, shows therapeutic promise for the treatment of metabolic diseases (Baur et al., 2006; Lagouge et al., 2006). Mice fed a high-fat diet (HFD) along with resveratrol remain lean and healthy compared with overweight control animals (Lagouge et al., 2006). Additionally, resveratrol significantly increases aerobic capacity, as shown by increases in the physical stamina of animals and elevated oxygen consumption by their muscle fibers. Resveratrol treatment also protects mice against diet-induced obesity and insulin resistance (Baur et al., 2006). Groups are now focusing on the development of high affinity small molecule activators of SIRT1 as a therapeutic approach for treating diseases of aging such as type 2 diabetes. But whether resveratrol acts directly or indirectly through SIRT1 remains a subject of debate.

Despite creating numerous mouse models, establishing the mechanisms of tissue-specific regulation of SIRT1 has proved difficult for researchers. The full-body SIRT1 knockout mouse displays severe developmental abnormalities and high mortality rates, which makes it difficult to study SIRT1 physiology in the few resulting adult animals (McBurney et al., 2003). However, conditional knockout, transgenic overexpression or viral modulation of Sir1 gene dosage shows that FOXO3a, p53 or E2F1 may regulate SIRT1 at the transcription level (Chen et al., 2005; Nemoto et al., 2005; Wang et al., 2006). SIRT1 may also be regulated post-transcriptionally by mRNA stabilization, and post-translationally by sumoylation and phosphorylation (Sasaki et al., 2008; Yang et al., 2007). SIRT1 activity is further regulated by changes in cellular redox levels, which are controlled by a series of nicotinamide-converting enzymes. Recently, several groups have demonstrated that SIRT1 activity may also be negatively modulated by protein-protein interaction through the association of SIRT1 with the NAD+/NADH ratio increases in the liver upon starvation (Rodgers et al., 2005), whereas others show a decrease in the NAD+/NADH ratio under calorie restriction (Chen et al., 2008). Also, what drives cellular NAD+/NADH levels and SIRT1 activity under different metabolic conditions, and in different tissues such as muscle and adipose, remains unclear. Escande et al. analyzed the levels of both SIRT1 protein and NAD+ concentration in the liver following a standard diet, starvation and HFD feeding. Their data show that neither NAD+ levels nor SIRT1

![Fig. 1. Model depicting SIRT1-DBC1 interactions under different metabolic conditions in the liver.](image)

The development of SIRT1 activators such as resveratrol or other calorie restriction mimetic drugs may provide protection from age-associated diseases.
protein levels fluctuate in the liver regardless of feeding patterns (see fig. 1 in Escande et al.), which suggests that factors other than NAD⁺ changes, such as post-translational modifications or protein-protein interactions, regulate SIRT1 activity.

To examine the role of DBC1 in SIRT1 activity in vivo, the group generated a Dbc1 KO mouse model using a gene trap embryonic cell line. They measured acetylation status in cell extracts using a lysine-acylated p53 peptide substrate. The tumor suppressor p53 was the first non-histone substrate identified that is functionally regulated by SIRT1 (Vaziri et al., 2001). Mouse embryonic fibroblasts (MEFs) from Dbc1 KO mice demonstrated significantly more deacetylase activity than controls [see fig. 2 in Escande et al. (Escande et al., 2010)]. The increased SIRT1 activity in Dbc1 KO MEFs prompted the group to compare protein distribution patterns between SIRT1 and DBC1. Western blot analysis showed a remarkable correlation between SIRT1 and DBC1 protein levels in multiple tissues. Immunofluorescence of liver cells confirmed that SIRT1 and DBC1 colocalize within the nucleus (see fig. 4 in Escande et al.).

The liver is a central metabolic organ in charge of regulating nutrient homeostasis in fed and fasting conditions. SIRT1 is crucial in regulating hepatic fatty acid metabolism and inflammation, and it protects the liver from steatosis (Purushotham et al., 2008). Escande et al. demonstrate that Dbc1 KO mice are immune to the development of HFD-induced liver steatosis and inflammation (see figs 6, 7 in Escande et al.). They propose that, during HFD feeding, the inhibition of SIRT1 activity by Dbc1 induces hepatic inflammation and lipid accumulation, which contribute to liver disease. Constitutive activation of NF-κB and increased expression of proinflammatory cytokines in Dbc1 KO mice support this notion.

The Dbc1 KO mouse model provides a tractable model to study sirtuin regulation by removing a crucial SIRT1 interacting partner rather than the protein itself. It is interesting that, in the liver, the Dbc1 KO mouse phenocopies the SIRT1 LKO (liverspecific knockout) mouse under multiple feeding conditions. This evidence shows that DBC1 plays a role in the energy-dependent regulation of SIRT1 activity. Further research examining different tissues using multiple dietary regimes may help determine the tissue-specific metabolic role of SIRT1. Moreover, crossing the Dbc1 KO mouse with SIRT1 conditional knockout (Dbc1 KO mouse) revealed that DBC1 plays a role in the energy-dependent regulation of SIRT1 activity. Further research examining different tissues using multiple dietary regimes may help determine the tissue-specific metabolic role of SIRT1. Moreover, crossing the Dbc1 KO mouse with SIRT1 conditional knockout models may provide further mechanistic insight into SIRT1 regulation. Hopefully, the insight gained from these models will provide direction for new approaches for treating non-alcoholic liver steatosis, type 2 diabetes, and other components of the metabolic syndrome (Fig. 1).

REFERENCES


