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DisSIRTing on LXR and Cholesterol Metabolism

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The NAD-dependent deacetylase SIRT1 regulates lipid and carbohydrate metabolism and has been shown to extend life span in several species. In a recent issue of *Molecular Cell*, Li et al. (2007) demonstrate that SIRT1 deacetylates and activates the nuclear receptor LXR by favoring its ligand-dependent proteasomal degradation, thereby potentially regulating reverse cholesterol transport.

Sirtuins are NAD-dependent deacetylases that target histones, transcription factors, and coregulators to adapt gene expression to the cellular energetic state (Yamamoto et al., 2007). The founding member of the family, SIRT1, promotes longevity in species ranging from yeast to mammals, and it is believed that these protective actions may result at least in part from the beneficial regulation of energy and metabolic homeostasis. Despite the impact of high cholesterol levels on mortality, cholesterol has not been associated with the sirtuin gene family until recently. The concentration of cholesterol, a lipid that maintains cell membrane structure and is a precursor for the synthesis of bile acids, steroids, and vitamin D, is finely tuned. When the cholesterol concentration rises in the body, macrophages accumulate cholesterol, favoring the development of atherosclerosis, which negatively affects life span. Excess cholesterol can be removed from macrophages by high-density lipoprotein (HDL)-mediated reverse cholesterol transport (RCT), which redirects cholesterol to the liver for subsequent elimination via the bile. RCT is controlled by cholesterol transporters and metabolizing enzymes, which are transcriptionally regulated by the liver X receptors (LXRs) α and β, two nuclear receptors (NRs) that act as cholesterol sensors (Zelcer and Tontonoz, 2006).

Li et al. (2007) now report that SIRT1 deacetylates and induces LXRα and β activity. LXR is acetylated on lysine 432 (K432), located within helix 12 of the ligand-binding domain, whose repositioning upon ligand binding confers transcriptional activation. Interestingly, LXR agonists trigger deacetylation of the receptor, a process in which SIRT1 plays an important role, since it interacts with LXR and its absence blunts LXR deacetylation. However, it is not clear at present whether SIRT1 interacts with LXR in a ligand-dependent manner or whether the ligand-dependent deacetylation results from conformational changes of the receptor. In addition, further studies will be required to identify the acetyltransferases that promote LXR acetylation.

NRs associate with target promoters and induce transcriptional activation in a cyclical manner, which requires rounds of NR ubiquitination and proteasomal degradation (Reid et al., 2003). Li et al. (2007) demonstrate that LXR is hypo-ubiquitinated and therefore stabilized in the absence of SIRT1 and that mutation of K432 recapitulates this state, suggesting that acetylation of K432 prevents LXR ubiquitination and its subsequent degradation by the proteasome. Paradoxically, but as observed for other NRs, LXR stabilization by inhibition of its ubiquitination and proteasomal degradation reduces its transcriptional activity, explaining the lower LXR activity observed in the absence of SIRT1 or upon mutation of its target site K432. Interestingly, it seems that it is the availability of this key lysine residue more than the acetyl moiety itself that inhibits ubiquitination and limits LXR action. Indeed, the mutation of K432 to either arginine or glutamine, which mimic a constitutively deacetylated and acetylated lysine, respectively, but neither of which can be ubiquitinated, inhibits LXR activity.

The regulation of LXR activity by acetylation adds this NR to the growing list of transcriptional regulators whose activity is regulated by acetylation. Acetylation has been reported to regulate the activity of NRs such as the glucocorticoid and androgen receptors and steroidogenic factor 1 (SF-1/Ad4BP). SIRT1 also deacetylates other transcription factors and coregulators (Figure 1; Yamamoto et al., 2007), and acetylation of transcription factors synergizes or competes with other posttranslational modifications such

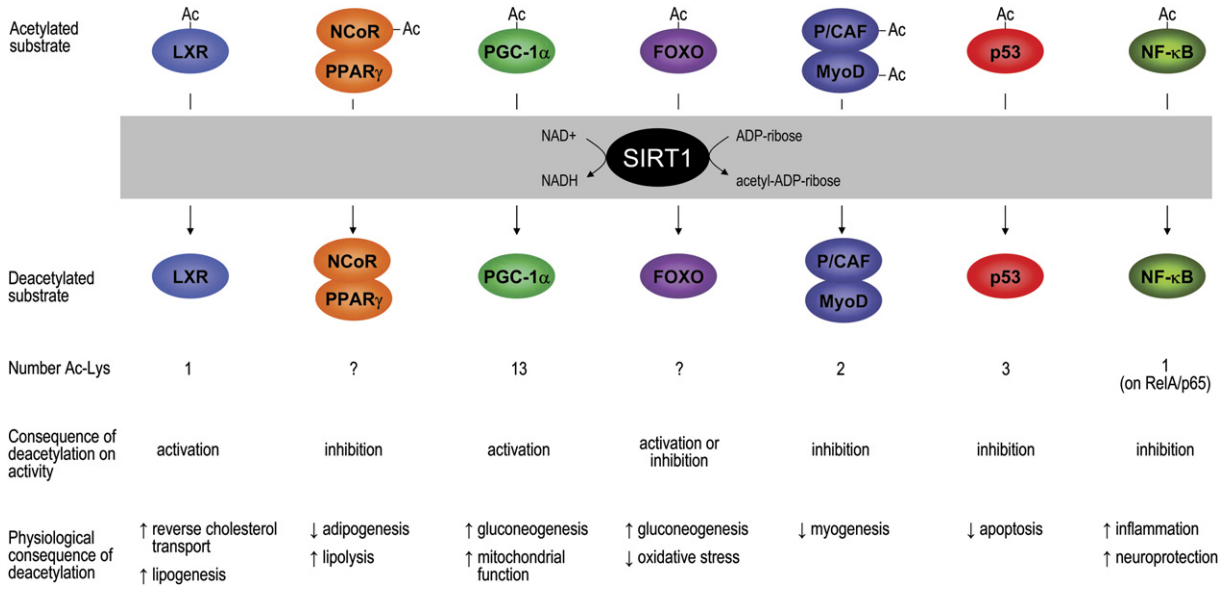

Figure 1. SIRT1 Regulates Homeostatic Gene Expression Programs by Deacetylating Key Transcription Factors and Coregulators
SIRT1 is a nuclear class III deacetylase that transfers the acetyl group of an acetylated substrate to ADP-ribose. The activity of SIRT1 is allosterically controlled by the levels of oxidized nicotinamide adenine dinucleotide (NAD^+), which increase when energy supplies are low. SIRT1 is therefore a sensor of energetic levels that regulates the activity of transcription factors and coregulators via deacetylation. The number of acetylated lysines and the main biological consequences of SIRT1-mediated deacetylation are indicated. Abbreviations: LXR, liver X receptor; NCoR, nuclear receptor corepressor; PPARγ, peroxisome proliferator-activated receptor γ; PGC-1α, PPARγ coactivator 1α; FOXO, forkhead box O; P/CAF, P300/CBP-associated factor; MyoD, myoblast determination protein 1; NF-κB, nuclear factor κB.

as phosphorylation, SUMOylation, and ubiquitination to regulate gene expression (Lonard and O'Malley, 2007). From all of these studies, a general picture emerges wherein the combination of distinct posttranslational modifications on many actors of a transcriptional network determines the final transcriptional output.

Li et al. (2007) also characterize the consequences of the regulation of LXR by SIRT1 on cholesterol homeostasis by showing that *Sirt1*$^{-/-}$ mice have lower levels of HDL cholesterol, while low-density lipoprotein (LDL) cholesterol is unaffected. Since cholesterol export is reduced in macrophages and liver from *Sirt1*$^{-/-}$ mice, it seems that SIRT1 may positively control LXR activity in vivo to stimulate RCT. Consistent with this hypothesis, *Sirt1*$^{-/-}$ mice accumulate hepatic cholesterol. However, it is unclear whether this accumulation of cholesterol stems solely from the inhibition of direct cholesterol excretion in bile or whether the LXR-dependent conversion of cholesterol to bile acids, catalyzed by the enzyme CYP7A1, is also inhibited. Although SIRT1 has been shown to occupy the *Cyp7a1* promoter in cellular models, thus suggesting that SIRT1 can promote bile acid synthesis, changes of CYP7A1 expression or bile acid pool were not investigated by Li et al. Puigserver's group, however, recently showed that CYP7A1 expression is reduced in the absence of SIRT1, suggesting that bile acid synthesis, in addition to macrophage cholesterol efflux, is enhanced by SIRT1. Interestingly, the regulation of CYP7A1 was also found to be dependent on the coregulator PGC-1α (Rodgers and Puigserver, 2007), but it remains unclear whether the direct deacetylation of PGC-1α by SIRT1 is involved (Rodgers et al., 2005).

The inhibition of RCT in SIRT1-deficient mice suggests that the pharmacological modulation of SIRT1 could be of interest to curb atherosclerosis. However, it is currently unclear whether this conclusion, based on loss-of-function studies in mice, will extend to conditions of SIRT1 activation in humans, which regulate cholesterol differently from mice. Several studies in mice also challenge this conclusion and suggest that the actions of SIRT1 on cholesterol homeostasis may be complex. Activation of SIRT1 by resveratrol administration, for instance, does not impact cholesterol levels (Baur et al., 2006; Lagouge et al., 2006). Strikingly, cholesterol levels are reduced both in *Sirt1*$^{-/-}$ mice and in mice overexpressing SIRT1 (Li et al., 2007; Bordone et al., 2007). The fact that calorie restriction, which is known to activate SIRT1, improves atherosclerosis and cholesterol homeostasis in humans, however, agrees with the hypothesis of Li et al. (Fontana et al., 2004). To address the complex impact of the SIRT1-mediated regulation of LXR and cholesterol homeostasis, studies in mice that are either challenged by a hypercholesterolemic diet or genetically predisposed to atherosclerosis will be required. Furthermore, tissue-specific contribution of SIRT1 to RCT will only be elucidated by the future study of mice with specific inactivation of SIRT1 in macrophages, liver, and intestine.

Activation of LXR is beneficial in that it not only inhibits intestinal cholesterol uptake and promotes RCT but also exerts potent anti-inflammatory effects that involve transrepression (Zelcer and Tontonoz, 2006). It will therefore

be important to dissect to what extent the SIRT1-mediated deacetylation of LXR can affect these anti-inflammatory effects. In that respect, it is worth noting that transrepression by LXR requires its SUMOylation (Ghisletti et al., 2007), again underscoring the potential impact of various posttranslational modifications on transcriptional regulation. Finally, a major adverse effect of LXR activation is hepatic steatosis as a consequence of lipogenesis (Zelcer and Tontonoz, 2006). SIRT1-mediated activation of LXR could here have an edge over LXR ligands, since SIRT1 agonists may limit hepatic lipid accumulation because of the concomitant induction of oxidative metabolism through AMPK and PGC-1α activation (Baur et al., 2006; Lagouge et al., 2006).

Altogether, recent studies extend the role of SIRT1 in metabolic homeostasis to the regulation of cholesterol metabolism (Li et al., 2007; Rodgers and Puigserver, 2007). Although further studies will be required, these results also suggest potential new pharmacological strategies to combat age-related diseases resulting from hypercholesterolemia.

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More Than Satiety: Central Serotonin Signaling and Glucose Homeostasis

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Serotonergic agents have been used in the past for reduction of appetite and body weight. As reported by Zhou et al. (2007) in this issue of *Cell Metabolism*, they also have unexpected effects on peripheral glucose homeostasis independent of food intake and body weight.

Previous research on appetite suppression by serotonin has centered on the role of serotonin signaling in the brain's "appetite center," the hypothalamus. Effective weight loss has been achieved via fenfluramine and dexfenfluramine, which increase brain serotonin by interfering with its uptake and causing a reverse release of serotonin through the serotonin transporter. Of the many subtypes of serotonin (5-HT) receptors, the 5-HT_{2C} receptor (5-HT_{2C}R) is the proposed target mediating the anorectic effects of fenfluramine. Unfortunately, use of fenfluramine was associated with pulmonary hypertension through action on peripheral 5-HT_{2B} receptors, leading to proscription of its use. Today, the only antiobesity drug with serotonergic action is sibutramine (Meridia), which inhibits serotonin reuptake but is not very effective. Despite these problems, the search for selective 5-HT_{2C}R agonists devoid of 5-HT_{2A} and 5-HT_{2B} activity has continued, and some agents have progressed to phase III clinical trials (e.g., lorcaserin) (Halford et al., 2007). Most studies have focused on the weight-reducing properties of serotonergic agents; their role in peripheral metabolism has not been previously explored. In this issue, Zhou et al. (2007) show that subanorectic doses of mCPP, a classical 5-HT_{2C}R agonist, also affect glucose homeostasis independent of food intake and weight loss.

Zhou et al. (2007) present convincing evidence for improved glucose and insulin tolerance in genetic and diet-induced models of obesity after both acute injections and long-term infusion