ISSN 0006-2979, Biochemistry (Moscow), 2009, Vol. 74, No. 7, pp. 703-708. © Pleiades Publishing, Ltd., 2009.
Published in Russian in Biokhimiya, 2009, Vol. 74, No. 7, pp. 869-876.

REVIEW

Function of SIRT1 in Physiology

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Received September 17, 2008
Revision received January 16, 2009

Abstract—Sirtuins were originally defined as a family of oxidized nicotinamide adenine nucleotide (NAD^+)-dependent enzymes that deacetylate lysine residues on various proteins. The sirtuins are remarkably conserved throughout evolution from archae to eukaryotes. They were named after their homology to the *Saccharomyces cerevisiae* gene silent information regulator 2 (Sir2). The mammalian sirtuins, SIRT1-7, are implicated in a variety of cellular functions ranging from gene silencing, control of the cell cycle and apoptosis, and energy homeostasis. As SIRT1 is a nuclear protein and is the mammalian homolog most highly related to Sir2, it has been the focus of a large number of recent studies. Here we review some of the current data related to SIRT1 and discuss its mode of action and biological role in cellular and organismal models.

DOI: 10.1134/S0006297909070013

Key words: SIRT1, metabolism, calorie restriction, apoptosis

Sir2 was first identified as a gene that is required to maintain cell-mating type in *Saccharomyces cerevisiae* by repressing the transcription of mating-type genes. It leads to a decrease in histone acetylation [1] and an increase in lifespan in yeast [2], the nematode *Caenorhabditis elegans* [3], and metazoans [4]. Furthermore, it was reported that the Sir2 proteins are remarkably conserved throughout evolution from archae to eukaryotes. In *S. cerevisiae*, there are four sirtuins (Hst1-4) in addition to Sir2p, whereas in mammals seven homologs, named SIRT1-7, have been identified.

The seven founding members of sirtuin protein family display protein deacetylase and ADP-ribosyltransferase activities [5-7]. They belong to class III histone deacetylases (HDAC III), being different from class I and II enzymes in that their activity depends on NAD^+ and is not sensitive to the wide deacetylase inhibitor trichostatin A [7, 8] but is inhibited by nicotinamide. Thus, considering the importance of histone deacetylation in the regulation of gene expression, sirtuins have been proposed to provide a molecular link between cellular metabolic status, as expressed by the NAD^+/NADH levels, and adaptive transcriptional responses [9].

Among the seven members of the family, the nuclear SIRT1 is the closest homolog of yeast Sir2 [10] and is best characterized so far. Its substrates include not only histones. SIRT1 is also involved in transcriptional regulation, playing important roles in the regulation of apoptosis/cell survival, endocrine signaling, differentiation, metabolism, and chromatin remodeling. Furthermore, it is well known that caloric restriction (CR) can retard the aging process and delay the onset of numerous aging-related diseases. Interestingly, resveratrol (RSV) mimics the beneficial health outcomes of CR that are induced in a number of animal models, suggesting that the molecular pathways by which resveratrol acts are similar to those activated by CR. Recently, it was suggested that SIRT1 could be the common mediator that explains both the effects of resveratrol and CR pathways. In this review, we emphasize the role of SIRT1 in cellular and organismal models with the goal of elucidating potential sites of therapeutic intervention.

Abbreviations: ACS, acetyl-CoA synthase; AMPK, AMP-activated protein kinase; CR, caloric restriction; LXRs, liver X receptors; PGC-1α, coactivator-1α of peroxisome proliferator-activated receptor γ; PPARγ, peroxisome proliferator activated receptor γ; RSV, resveratrol.

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FUNCTIONS OF SIRT1 IN METABOLISM

Organismal glucose and lipid homeostasis is maintained by the coordination of central and peripheral sig-

nals that control appetite and dictate efficient nutrient distribution among tissues to sustain body functions [11]. Dysregulation of energy metabolism leads to associated pathological side effects, such as diabetes, and may even underlie key aspects of tumorogenesis [12, 13]. Recently, SIRT1 has been linked with metabolic control in several studies in mammals.

SIRT1 in glucose homeostasis. In mammals, homeostatic mechanisms respond to hormones, such as the key hormones insulin, glucagons, and glucocorticoids, and to nutrients like pyruvate to maintain blood glucose levels within a narrow range. Among the hormones, we know insulin is secreted by the β-cells in the pancreatic islets of Langerhans to promote glucose uptake and catabolism in peripheral tissues in response to raised glucose levels. Thus, pancreatic β-cells play a central role in maintaining glucose homeostasis. And the fact that SIRT1 is a positive regulator of insulin may seem surprising in light of the fact that sir-2.1 in *C. elegans* appears to be a negative regulator of the insulin-like signaling pathway [3].

SIRT1 is expressed in pancreatic β-cell lines as well as mouse islets [14]. It has also been demonstrated to augment insulin secretion in response to glucose in pancreatic β-cells of β-cell-specific SIRT1-overexpressing (BESTO) transgenic mice. This response involves SIRT1-dependent suppression of expression of uncoupling protein 2 (UCP2), which uncouples respiration from ATP production in mitochondria [15]. Moreover, SIRT1 knockout mice had much lower blood levels of insulin compared with littermate control animals whenever the samples were collected under *ad libitum* or starved conditions, whereas, conversely, mice overexpressing SIRT1 in pancreatic β-cells exhibited an enhanced response to glucose challenge attributed to higher blood insulin [14, 15]. SIRT1 can also form a complex with the promyelocytic leukemia protein (PML) and FOXO1 to activate two insulin transcription factors, NeuroD and MafA, which may protect the pancreatic β-cell pathway from oxidative damage [16]. All these facts indicate that SIRT1 positively regulates insulin secretion in pancreatic β-cells.

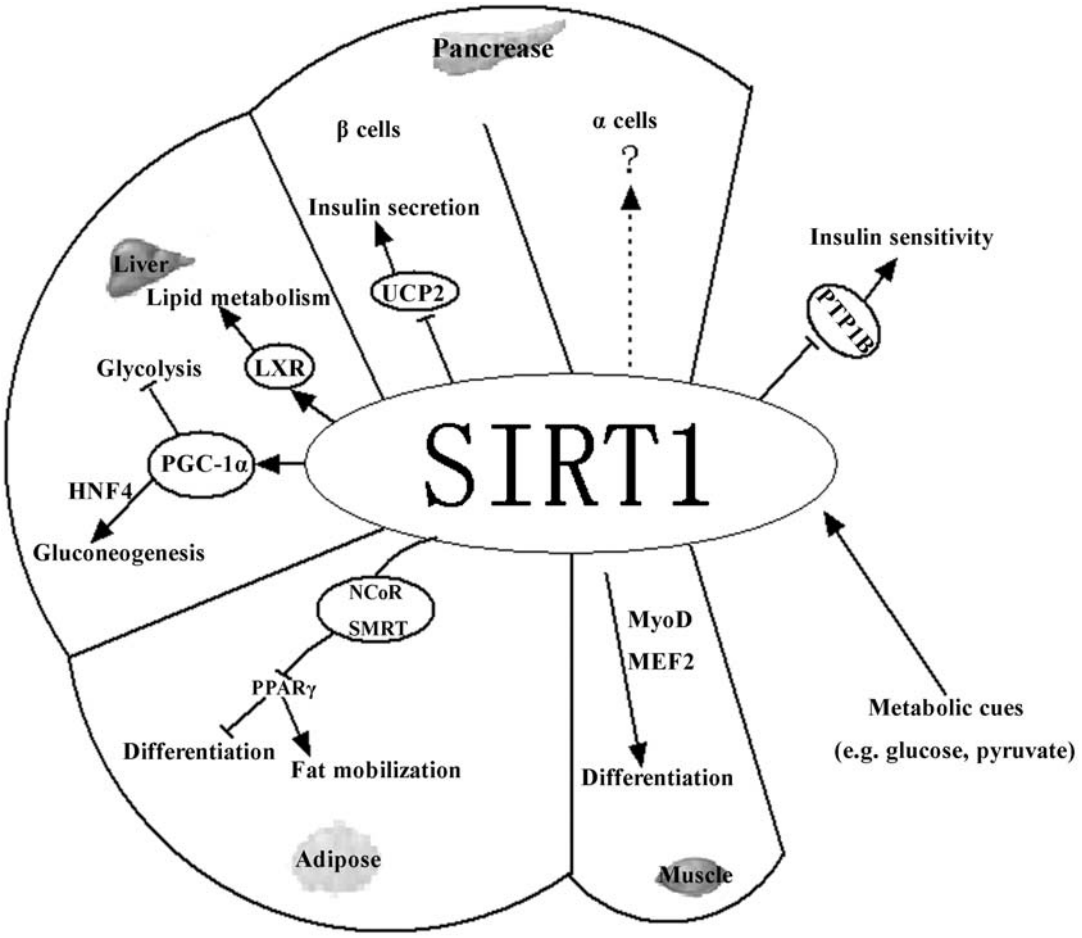
Furthermore, SIRT1 appears to have a positive role in insulin sensitivity, which is often characterized as the most critical factor contributing to the development of type 2 diabetes. SIRT1 is downregulated in insulin-resistant cells and tissues, and knockdown or inhibition of SIRT1 was shown to induce insulin resistance in a recently study. Moreover, increased expression of SIRT1 improved insulin sensitivity, especially under insulin-resistant conditions [17]. Further studies demonstrated that the effect of SIRT1 on insulin resistance is mediated by repressing PTP1B transcription at the chromatin level [17]. Similarly, resveratrol, which was shown to enhance SIRT1-dependent cellular processes, has been demonstrated to improve insulin sensitivity in a diet-induced obesity model [18]. Taken together, the findings that SIRT1 improves insulin sensitivity have implications toward resolving insulin resistance and type 2 diabetes.

In addition to these, the gluconeogenic/glycolytic pathways in liver are also very important for glucose levels. SIRT1, which is reported to form a complex including the hepatocyte nuclear factor-4 (HNF-4), deacetylates and activates coactivator-1α of peroxisome proliferator-activated receptor γ (PGC-1α), promoting gluconeogenesis following fasting [19]. PGC-1α is an important transcriptional coactivator that regulates multiple aspects of cellular energy metabolism including mitochondrial biogenesis, hepatic gluconeogenesis, and β-oxidation of fatty acids. In contrast to gluconeogenesis, the expression of glycolytic genes such as glucokinase and liver pyruvate kinase (LPK) are decreased on treatment with PGC-1α and pyruvate. And SIRT1 siRNA increased the expression of these genes under pyruvate treatment [20]. In a recent report [21], blood glucose levels were modestly but consistently lower in SIRT1 small hairpin RNA (shRNA)-infected mice compared with control shRNA mice, both in fed and fasted states. These results indicate that SIRT1 and PGC-1α co-modulate, in opposite directions, the patterns of gluconeogenic and glycolytic gene expression in response to pyruvate, reflecting a broader role for SIRT1 in balancing glucose homeostasis in the body.

From all the studies discussed above, it is suggested that SIRT1 could contribute to the glucose homeostasis through its role in insulin secretion and survival of pancreatic β-cell and gluconeogenesis in the liver. The function of SIRT1 in insulin sensitivity might have implications toward resolving insulin resistance and type 2 diabetes. It is also reported that hepatic knockdown of SIRT1 results in mild hypoglycemia, increased glucose tolerance, insulin sensitivity, and decreased hepatic glucose production [20] (Scheme 1).

SIRT1 function in regulating lipid metabolism. In addition to glucose metabolism, the liver has key roles in lipid homeostasis. Dysregulation of hepatic fatty acid β-oxidation and/or fatty acid synthesis enzymes leads to hepatic steatosis or fatty liver [21]. Moreover, cholesterol is synthesized and degraded in the liver according to the needs of other tissues [22].

When hepatic SIRT1 expression was altered, defects in fatty acid and cholesterol metabolism in mice were seen. Hepatic knockdown of SIRT1 resulted in reduced systemic levels of total cholesterol in the fed and fasted state. Interestingly, SIRT1 overexpression reversed this effect, increasing systemic cholesterol most significantly in the fasted state. Furthermore, hepatic SIRT1 controls gene expression of enzymes involved in triglyceride, fatty acid, and cholesterol metabolism pathways, such as medium chain acyl-CoA dehydrogenase and carnitine palmitoyltransferase-1a [20]. Interestingly, liver X receptors (LXRs) also regulate reverse cholesterol transport, a process by which high-density lipoprotein (HDL) carries



Protective functions of SIRT1 in metabolism and differentiation. The role of SIRT1 in pancreatic β-cells, where it is highly expressed, is unknown. Activation of SIRT1 induces muscle differentiation and lipid homeostasis by deacetylating MEF2 and LXR/AMPK and favors insulin secretion by repressing the uncoupling protein 2 (UCP2). SIRT1 decreases white adipose tissue formation through repression of PPARγ and promotes gluconeogenesis and inhibits glycolysis in response to fasting through PGC-1α. SIRT1 increases insulin sensitivity by decreasing the expression of protein tyrosine phosphatase 1B (PTP1B)

Scheme 1

cholesterol from peripheral tissues to the liver, where it can be secreted into bile [23]. A recent study demonstrated that SIRT1 deacetylates and activates the nuclear receptor LXR by favoring its ligand-dependent proteasomal degradation, thereby potentially regulating reverse cholesterol transport [24] (Scheme 1).

Furthermore, some previous studies demonstrated that AMP-activated protein kinase (AMPK) is a key molecule for the beneficial effects of polyphenols on hepatic lipid accumulation, hyperlipidemia, and atherosclerosis in type 1 diabetic mice, and dysfunction of hepatic AMPK induced by hyperglycemia is a key mechanism for hepatic lipid accumulation and hyperlipidemia associated with diabetes [25, 26]. AMPK was originally identified through its phosphorylation and inactivation of acetyl-CoA carboxylase and fatty acid synthase in the liver [27, 28]. Hou et al. reported that SIRT1 is a critical regulator of AMPK signaling in controlling hepatocellular lipid metabolism in an LKB1-dependent mechanism [29]. These findings define a novel molecular mechanism by which SIRT1 regulates hepatic lipid metabolism through activation of AMPK and suppression of its downstream effectors—acetyl-CoA carboxylase and fatty acid synthase.

Acetate is also very important to metabolic homeostasis. Unlike prokaryotes, mammals have only the acetyl-CoA synthase (ACS) pathway to convert free acetate back to a useable metabolite, acetyl-CoA. In the last several years, some groups reported that a Sir2 homolog in *Salmonella enterica* could regulate the activity of ACS through deacetylation, permitting bacterial growth on acetate and propionate [30, 31]. Amazingly, this regulatory mechanism appears to be evolutionarily conserved, SIRT1 can deacetylate ACS1 in cells, and specific deacetylation leads to enhanced fatty acid synthesis through acetate incorporation.

Another tissue of interest in metabolic regulation is the adipose tissue. There are two specialized tissues: brown and white adipose tissues. White adipose tissue is able to store excess calories in the form of triglyceride. When cells require energy, such as during periods of fasting, these needs are largely met by fatty acids and glycerol formed from lipolysis of stored triglyceride. Peroxisome proliferator activated receptor γ (PPARγ) is a key regulator in adipogenesis and fat storage through the control of the expression of many adipocyte-specific genes [32]. In white adipose tissue, SIRT1 was shown to repress the key regulatory protein PPARγ, an effect that, in addition to SIRT1, also involved the nuclear receptor co-repressor (NcoR) and silencing mediator SMRT, resulting in fat mobilization in response to food limitation [33]. Moreover, in $SIRT1^{+/-}$ mice, the circulating free fatty acid levels in the blood after overnight food deprivation were lower compared with wild type.

In conclusion, the present studies establish a molecular cross-talk between SIRT1 and the regulation of metabolism. The findings have potential implications for protection by SIRT1 against hepatocellular lipid accumulation and acceleration of atherosclerosis associated with diabetes and metabolic disorders.

SIRT1 IN DIFFERENTIATION

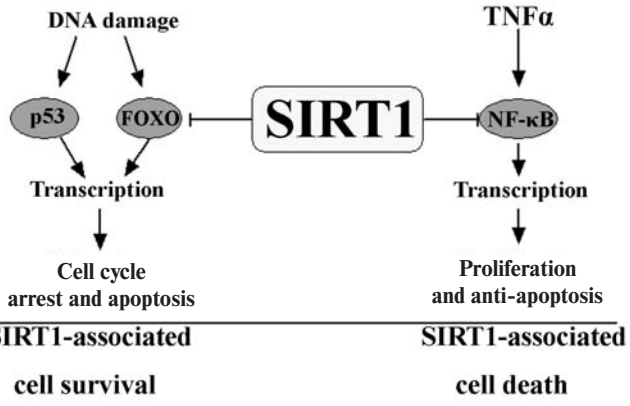
In view of the prevalence of obesity and obesity-related diseases, such as type 2 diabetes, it is important to understand how white and brown adipose tissues develop and how the activities of these tissues are regulated. Many factors are involved in the differentiation of adipose tissues [34]. SIRT1, one of these factors, inhibits fat cell differentiation in white adipose tissue via a mechanism involving interaction of SIRT1 with PPARγ and suppression of the transcriptional activity of PPARγ [28].

SIRT1 is also reported to play an important role during myocyte differentiation. The levels of SIRT1 and the $[NAD^+]/[NADH]$ ratio decrease during muscle differentiation. Overexpression of SIRT1 retards muscle differentiation via formation of a complex with the acetyltransferase PCAF and MyoD, while in cells with reduced SIRT1 expression muscle gene expression and differentiation is enhanced [30]. Nicotinamide, a noncompetitive NAD^+ antagonist that acts as an inhibitor of Sir2, can maintain PCAF and MyoD in an acetylated state, and when applied to Sir2-overexpressing muscle cells it can simulate muscle gene expression and differentiation. Moreover, reducing the levels of endogenous Sir2 augments muscle gene expression and causes increased cell differentiation. Importantly, modulation of the cytosolic $[NAD^+]/[NADH]$ ratio influences muscle gene expression in a Sir2-dependent manner [35]. In addition, the muscle cell transcription factor MEF2 is inactivated through deacetylation by SIRT1 [36] (Scheme 1). Together these data suggest that the effect of SIRT1 in differentiation is important.

SIRT1 AND CONTROL OF CELL SURVIVAL, STRESS RESISTANCE, AND APOPTOSIS

SIRT1 homologs have been previously shown to extend life span in response to calorie restriction (CR) in lower eukaryotes including yeast [37], worms [3], and flies [4]. In the last few years, mouse models have linked SIRT1 to CR, the only regimen that slows aging and extends lifespan of most classes of organism including mammals. CR did not extend lifespan of SIRT1-null mice, and SIRT1 is required for *in vivo* response to CR [38].

Many factors that control cell proliferation and apoptosis are identified as sirtuin substrates. The most widely known is p53 [39-41]. SIRT1 binds to and deacetylates p53 *in vivo* and *in vitro*, thereby negatively regulating p53-mediated transcriptional activation [39]. Deacetylation of p53 prevents cellular senescence and apoptosis caused by DNA damage and stress. In thymocytes from SIRT1-deficient mice, the levels of p53 acetylation were significantly upregulated after exposure to ionizing radiation [42], indicating that SIRT1 has a role in increasing the stress resistance of cells. Recently, SIRT1 was shown to control Bax-induced apoptosis by deacetylating Ku70, which is essential for the repair of DNA double-strand breaks and has important roles in



Differential SIRT1-mediated repression of p53, FOXO, and NF-κB controls life and death signals. In response to DNA damage, SIRT1-mediated deacetylation of p53 and FOXO inhibits the expression of gene products that are associated with cell cycle arrest and apoptosis. The overall effect under these conditions is SIRT1-mediated cell survival. The reverse is true for TNFα signaling, where SIRT1-induced deacetylation on RelA/p65 results in diminished NF-κB transcription and a decrease in pro-survival gene products that are responsible for overcoming TNF-induced apoptosis. The net effect under these conditions is SIRT1-associated cell death

Scheme 2

telomere maintenance [43]. Sir2 and the forkhead transcription factor DAF-16 regulate lifespan in organisms such as yeast and *C. elegans*. The mammalian Sir2 ortholog SIRT1 also inhibits forkhead-mediated cell death in mammals [44].

While SIRT1 is capable of protecting cells from p53-induced apoptosis, some other work provides evidence that SIRT1 activity augments apoptosis in response to TNFα by the ability of the deacetylase to inhibit the transactivation potential of NF-κB protein. SIRT1 physically interacts with the RelA/p65 subunit of NF-κB and inhibits transcription by deacetylating RelA/p65 at lysine 310 [45] (Scheme 2). Whether these apparently opposing functions reflect a broader role for SIRT1 in cell survival by coordinating multiple tissue responses to a common stimulus is a notion worth investigating.

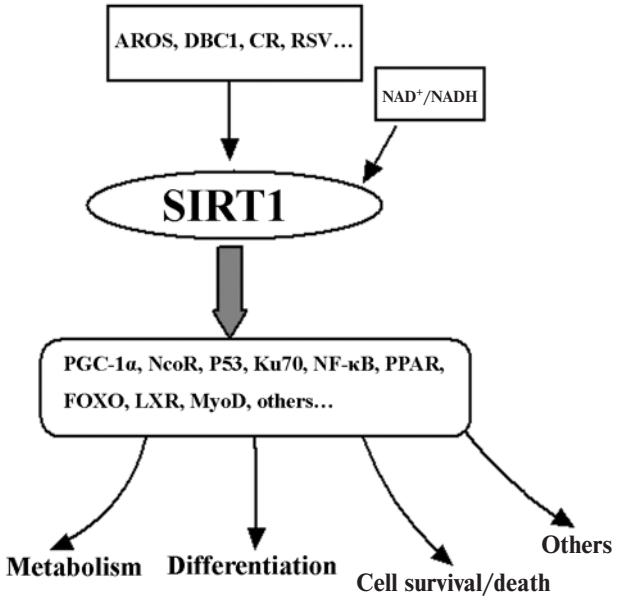
SIRT1 AND ITS REGULATORS

Together these data suggest that the effect of SIRT1 is pleiotropic. Because of its important role in mammals, some of its regulators have been studied, such as the active regulator of SIRT1 (AROS), which directly regulates SIRT1 function [46]. AROS can enhance SIRT1-mediated deacetylation of p53 both *in vitro* and *in vivo*, and it inhibited p53-mediated transcriptional activity. Furthermore, sumoylation identifies a novel post-translational modification of SIRT1 and regulates its deacetylase activity and cellular response to genotoxic stress [47]. Sumoylation of SIRT1 increased its deacetylase activity, and conversely SENP1, a nuclear desumoylase, reduced its deacetylase activity. There are some other inhibitors, such as DBC1 (deleted in breast cancer 1), acting as a native inhibitor of SIRT1 in human cells. DBC1-mediated repression of SIRT1 leads to increasing levels of p53 acetylation and upregulation of p53-mediated function [48].

SUMMARY AND PERSPECTIVE

Sirtuin proteins were shown to regulate lifespan in several model organisms, and its NAD-dependence quality links them unavoidably to the metabolic activity of cells. SIRT1, the mammalian Sir2 homolog, has been implicated in stress resistance and numerous metabolic pathways, including adipogenesis, gluconeogenesis, and insulin secretion and glucose homeostasis (Scheme 3). The modulation of SIRT1 has also been studied recently.

Although there are many functions of SIRT1, the actual molecular mechanisms are not very clear. Similarly, given that there are over 30 SIRT1 substrates so far [49], it is remarkable that SIRT1 knockout mice are viable and can sometimes reach two years of age. At this point, it is not yet clear which of the many SIRT1 substrate(s) is(are) responsible for the phenotype or which tissue(s) share(s) the metabolic defect. In the next few years, the answers to these and other questions will auger how well pharmacological agents that target SIRT1 will serve as CR mimetics. For its role in glucose levels and insulin sensitivity, drugs including resveratrol that enhance SIRT1 function and/or expression might provide a valuable new strategy for treating insulin resistance and type 2 diabetes.



SIRT1 is a potential physiological switch

Scheme 3

We can hope that new classes of drugs are on the horizon to deliver broad benefits for these diseases and longevity in humans.

This work was sponsored by the National High Technology Research and Development Program (No. 2006AA02Z192) and the National Natural Sciences Foundation of China (30700386).

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