10 Years of NAD-Dependent SIR2 Family Deacetylases–Implications for Metabolic Diseases

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Abstract

In the past decade since the discovery of NAD-dependent deacetylase activity of the SIR2 (silent information regulator 2) family, now called “sirtuins,” many exciting connections between protein deacetylation and energy metabolism have been revealed. The importance of sirtuins has been firmly established in the regulation of many fundamental biological responses to a variety of nutritional and environmental stimuli. Sirtuins have also emerged as critical regulators for aging and longevity in model organisms. Their absolute requirement of NAD has revived an enthusiasm in the study of mammalian NAD biosynthesis. Furthermore, sirtuin-targeted pharmaceutical and nutriceutical interventions against age-associated diseases are now on the horizon. This review will summarize the recent progress in sirtuin research, particularly in the field of mammalian sirtuin biology, and reevaluate the connection between sirtuins, metabolism, and age-associated diseases, such as type 2 diabetes, to set a milepost for the next 10 years of sirtuin research.

Introduction

We have arrived at the 10th anniversary of this discovery of NAD-dependent SIR2 family deacetylases. The sir2 gene was identified as mar1, a gene affecting yeast mating ability, in 1979. Over the past decade, more than 1,500 papers have been published on the SIR2 family, now called “sirtuins,” while there were less than 100 before this period. We believe this is a good opportunity to assess what has been done and what still needs to be achieved in this exciting field of sirtuin biology. Therefore, in this review, we will summarize the recent progress in sirtuin research, particularly in the field of mammalian sirtuin biology, and reevaluate the connection between sirtuins, metabolism, and age-associated diseases.
Chronology of sirtuin research over the past 10 years

A brief history

In 1998, Tsang and Escalante-Semerena reported that a protein called CobB in *Salmonella typhimurium* can substitute for the function of CobT, a protein that transfers phosphoribose from nicotinic acid mononucleotide to dimethylbenzimidazole in the cobalamin biosynthesis pathway. Intriguingly, CobB has signature motifs of the evolutionarily conserved SIR2 family, which turned to be the first important clue suggesting that SIR2 proteins might catalyze a related pyridine nucleotide transfer reaction. Following their paper, in 1999, Roy Frye showed that SIR2 proteins from *Escherichia coli* and humans were able to transfer $^{32}$P from $[^{32}P]$NAD to bovine serum albumin, albeit weakly. Subsequent to this study, Danesh Moazed’s group demonstrated that SIR2 was indeed able to transfer ADP-ribose from NAD to histones, leading them to the conclusion that the observed ADP-ribosyltransferase activity of SIR2 was involved in gene silencing in yeast.

Meanwhile, we noticed that peptides of the amino-terminal tails of histone H3 or H4 could accept $^{32}$P from $[^{32}P]$NAD in the reactions mediated by recombinant yeast SIR2 or mammalian SIRT1 proteins, but only if the peptides were acetylated. Like Frye’s findings, however, this transfer reaction was extremely weak even using the acetylated peptides as substrates. Believing the low concentrations of labeled NAD may be below the $K_m$ of the enzyme, we attempted to significantly increase the NAD concentration in the SIR2 enzymatic reaction (using unlabeled NAD), which necessitated analyzing the reaction products directly by mass spectrometry. Using this assay in October 1999, we found that the relative molecular weight of the reaction product was not larger but actually smaller than that of the acetylated peptide exactly by 42 Da. Moreover, both the yeast and mammalian sirtuin proteins robustly converted the substrate peptides to their smaller products. This serendipitous experiment was the first demonstration that the major enzymatic activity of SIR2 is NAD-dependent deacetylase. Importantly, yeast and mammalian SIRT2 proteins were able to specifically deacetylate lysine 16 of H4 in an NAD-dependent manner, strongly suggesting that the NAD-dependent deacetylase activity plays a critical role in establishing silenced chromatin structures *in vivo*. Sirtuins require NAD, but not NADH, NADP, and NADPH, for their enzymatic activity, immediately suggesting that sirtuins might function as sensors of the cellular energy status represented by NAD. Within months of the paper on these findings, reports appeared showing that SIR2 and HST2, a yeast SIR2 homolog, catalyze both NAD-nicotinamide exchange reaction and NAD-dependent deacetylation.

Major advances and questions in sirtuin research

The above findings set the stage for sirtuin biology, and in the past 10 years, significant progress has been made in this quickly evolving field. First, the catalytic mechanism of NAD-dependent deacetylase has been extensively studied. Importantly, the deacetylation reaction has been demonstrated to be tightly coupled with the cleavage of NAD into nicotinamide and ADP-ribose and the formation of a previously unidentified compound, O-acetyl-ADP-ribose. Crystal structures of yeast, mammalian, and archaeobacterial sirtuins have been determined, and the structure-based catalytic mechanism of this reaction have been proposed.

In mammals, there are seven sirtuin family members, named SIRT1 through SIRT7 (Table 1). Numerous target proteins have been identified for sirtuins, particularly for the mammalian SIR2 ortholog SIRT1, and it has been established that NAD-dependent deacetylation of those target factors by sirtuins plays a critical role in the regulation of fundamental biological responses to nutritional and environmental stimuli in each subcellular compartment. SIRT2 and its orthologs have also emerged as critical...
regulators for aging and longevity in model organisms, such as yeast, worms, and flies. In certain genetic backgrounds, they mediate anti-aging and life span-extending effects of caloric restriction, a dietary regimen low in calories without malnutrition that delays aging and extends life span in a wide variety of organisms.

These studies also potentiated screening for small molecule sirtuin activators. These screens initially identified a plant polyphenolic compound resveratrol, but more potent activators were identified later. These compounds have so far provided a hope of new therapeutic interventions against age-associated complications, such as type 2 diabetes and Alzheimer’s disease.

Lastly, the biological significance of NAD biosynthetic pathways for the regulation of sirtuin enzymatic activity has been brought front and center. In particular, nicotinamide phosphoribosyltransferase (NAMPT), the rate-limiting enzyme in a major NAD biosynthetic pathway from nicotinamide in mammals, has recently been shown to play important roles in a variety of biological events related to sirtuin biology, metabolism, cancer, and immune response. With all these great advances, there are currently two major questions in the field of sirtuin biology: 1) Do mammalian sirtuins play critical roles in the pathogenesis of major age-associated diseases, such as type 2 diabetes, neurodegenerative diseases, osteoporosis, and others? 2) Do mammalian sirtuins, particularly SIRT1, indeed function as a key regulator for aging and longevity in mammals? In the next two sections, we will address these questions and summarize our current knowledge on the diverse functions of mammalian sirtuins.

Mammalian sirtuins and age-associated metabolic complications

It is not yet clear whether mammalian sirtuins determine longevity, but they have been implicated in retarding aging, as defined by degenerative processes leading to diseases. For example, increasing lines of evidence have firmly established that mammalian sirtuins, particularly SIRT1, regulate metabolic responses to changes in nutritional availability in multiple tissues, implying that mammalian sirtuins play essential roles in the pathogenesis of age-associated metabolic diseases. In the pathogenesis of type 2 diabetes, a delicate balance between insulin sensitivity and secretion is compromised by both environmental and genetic factors, resulting in the development of insulin resistance and β cell dysfunction. SIRT1 contributes to both aspects of type 2 diabetes pathogenesis in liver, skeletal muscle, adipose tissue, and pancreatic β cells.

SIRT1 in liver

SIRT1 regulates glucose production, fatty acid oxidation, and cholesterol flux in the liver. In response to fasting, SIRT1 enhances and represses gluconeogenesis and glycolysis, respectively, by interacting with and deacetylating peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α), FOXO1, CRTC2 (a.k.a. TORC2), and STAT3, in an NAD-dependent manner. SIRT1 also promotes fatty acid oxidation through PGC-1α and peroxisome proliferator-activated receptor α (PPARα), a nuclear receptor that controls physiological responses to fasting. Furthermore, SIRT1 regulates cholesterol flux by deacetylating and activating LXRα, a critical nuclear receptor that controls cholesterol and lipid homeostasis. As a total sum of these responses, SIRT1 appears to contribute to the negative regulation of insulin sensitivity in the liver because adenovirus-mediated hepatic SIRT1 knockdown results in improved glucose and insulin tolerance in mice, while hepatic SIRT1 overexpression causes moderate glucose intolerance. This notion is also consistent with a report that knockdown of SIRT1 in the liver decreases fasting plasma glucose and increases hepatic insulin sensitivity in a type 2 diabetes rat model. High fat diet (HFD)-fed liver-specific SIRT1 knockout (LKO) mice also show improved glucose tolerance.
tolerance and lower levels of blood glucose and insulin \(^66\). On the other hand, it is reported that HFD-fed SIRT1 LKO mice also develop hepatic steatosis, hepatic inflammation, and endoplasmic reticulum stress \(^64\). It is possible that differences in the cholesterol and fat content between the various HFDs exert subtly different effects on liver metabolism, and further investigation will be necessary to clarify the hepatic function of SIRT1 in diet-induced diabetes models.

**SIRT1 in skeletal muscle**

SIRT1 induces mitochondrial fatty acid oxidation in response to nutrient deprivation through deacetylation of PGC-1\(\alpha\) \(^67\). Given that intramyocellular fatty acid metabolism and the expression of PGC-1\(\alpha\) and mitochondrialOXPHOS genes are reduced in skeletal muscle of insulin-resistant or type 2 diabetes patients \(^68–70\), SIRT1 might contribute in this way to the improvement of insulin sensitivity in skeletal muscle (Figure 1). Consistent with this notion, SIRT1 improves insulin sensitivity through the transcriptional repression of the protein tyrosine phosphatase 1B (PTP1B) gene in skeletal myotube cells \(^71\). PTP1B is a key insulin receptor phosphatase, and PTP1B-deficient mice have been shown to be more insulinsensitive and more resistant to diet-induced obesity compared to controls \(^72\). Although these reported effects of SIRT1 should be validated in vivo, these findings indicate that SIRT1 might play an important role in improving insulin sensitivity in skeletal muscle.

**SIRT1 in white adipose tissue**

SIRT1 triggers lipolysis and promotes free fatty acid mobilization in response to fasting by repressing PPAR\(\gamma\), a nuclear receptor that promotes adipogenesis \(^73\). SIRT1 also regulates the production and/or the secretion of insulin sensitizing factors, such as adiponectin and FGF21, through the regulation of FOXO1 and PPAR\(\gamma\) \(^74–76\). Nonetheless, further investigation with in vivo models will be necessary to determine the actual effect of SIRT1 in adipose tissue on systemic insulin sensitivity (Figure 1).

**SIRT1 in pancreatic \(\beta\) cells**

SIRT1 positively regulates glucose-stimulated insulin secretion (GSIS) in part by repressing the expression of uncoupling protein 2 (Ucp2), a mitochondrial inner membrane proton pore that uncouples respiration from ATP production, and increasing cellular ATP levels \(^77, 78\). Indeed, pancreatic \(\beta\) cell-specific SIRT1-overexpressing (BESTO) transgenic mice show enhanced insulin secretion and improved glucose tolerance in response to glucose \(^78\). Furthermore, BESTO mice are still able to maintain significantly improved glucose tolerance with enhanced GSIS compared to controls under a HFD condition \(^79\). Consistent with this observation, SIRT1 also plays an important role in protecting pancreatic \(\beta\) cells from metabolic stress- and cytokine-induced \(\beta\) cell death by deacetylating FOXO1 and the p65 subunit of NF-\(\kappa\)B, respectively \(^80, 81\). Therefore, SIRT1 plays an important role in protecting pancreatic \(\beta\) cells from their dysfunction caused by increasing peripheral insulin resistance (Figure 1).

**SIRT1 and type 2 diabetes**

Does SIRT1 promote or prevent type 2 diabetes at a systemic level? Accumulating bodies of evidence have so far suggested that SIRT1 functions to provide overall protection against type 2 diabetes. SIRT1-overexpressing transgenic mice using large genomic fragments that contain the entire \(Sirt1\) gene locus show significant protection from the adverse effects of HFD or normal aging on metabolism, including hepatic inflammation and impaired insulin sensitivity \(^74, 82\). Additionally, resveratrol and new SIRT1-activating non-polyphenolic compounds are able to improve glucose homeostasis and insulin sensitivity in diet-induced and genetic type 2 diabetes animal models \(^37–40, 42\). In humans, it has recently been reported
that certain genetic variations of the SIRT1 gene influence survival of subjects with type 2 diabetes in interaction with dietary niacin and smoking and risk of obesity in Dutch populations. Taken together, all these findings strongly suggest that SIRT1 can protect animals and possibly humans from type 2 diabetes.

Other mammalian sirtuins and metabolic complications

The connection between other mammalian sirtuin members and age-associated metabolic complications is still unclear. Mitochondrial sirtuins SIRT3-5 might be the next targets for intensive studies on their potential connection to metabolic diseases. SIRT3 deacylates and activates the mitochondrial enzyme acetyl-CoA synthetase 2 (AceCS2). It has recently been reported that AceCS2-deficient mice exhibit a significant defect in acetate oxidation necessary for the generation of ATP and heat under low-glucose or ketogenic conditions. Consistent with this finding, SIRT3-deficient mice also show a significant reduction in basal ATP levels in multiple tissues. On the other hand, SIRT4 negatively regulates amino acid-stimulated insulin secretion by ADP-ribosylating and inhibiting glutamate dehydrogenase in pancreatic β cells. Finally, SIRT5 deacylates and activates CPS1, the first and committed step in the urea cycle for ammonia detoxification. This activity is particularly important when diets are limiting in energy, forcing the use of amino acids for energy and the generation of excess ammonia via their catabolism. Therefore, it will be of great interest to examine metabolic responses of SIRT3- and SIRT4-deficient mice to HFD conditions, which might provide critical insights into their connection to the pathogenesis of type 2 diabetes.

Mammalian sirtuins and their connection to the regulation of aging and longevity

SIRT1 and physiological aspects of aging

Recent studies have provided significant support for the importance of SIRT1 in the induction of age-associated physiological changes. Most recently, it has been demonstrated that oxidative stress-induced redistribution of SIRT1 causes the desilencing of SIRT1-bound target genes in mouse embryonic stem (ES) cells. This damage-induced SIRT1 redistribution requires DNA damage signaling through a mammalian PI3-kinase ATM and histone H2AX. Importantly, these SIRT1-bound target genes that are derepressed by oxidative stress in mouse ES cells are also derepressed in aged mouse brain, and SIRT1 overexpression is able to suppress these age-associated changes, suggesting that the damage-induced SIRT1 redistribution might trigger certain age-associated physiological changes in mouse brain.

Another line of evidence is that SIRT1 activity is significantly reduced in aged β cells, likely due to a significant decrease in NAMPT-mediated systemic NAD biosynthesis over age, resulting in the reduction in GSIS in aged β cells. Indeed, a progressive age-associated decline in β cell function has been suggested to be one of the major contributing factors to the pathogenesis of type 2 diabetes. Interestingly, administration of nicotinamide mononucleotide (NMN), a reaction product of NAMPT and a key NAD intermediate, restores higher GSIS in both aged wild-type and BESTO females. These findings suggest that the age-associated reduction in SIRT1 activity due to NAD insufficiency plays a critical role in inducing the age-associated decrease in GSIS in pancreatic β cells.

SIRT1 and caloric restriction (CR)

CR is well known to retard aging and extend life span in many organisms, and recent studies have strongly suggested that SIRT1 mediates adaptive responses to CR in mammals. For
example, whereas wild-type CR mice show a significant increase in physical activity compared to ad libitum-fed controls, SIRT1-deficient mice do not exhibit such an increase. The CR-induced enhancement of mitochondrial biogenesis by nitric oxide-induced up-regulation of SIRT1 is also blunted in endothelial nitric oxide synthase (eNOS)-deficient mice. Furthermore, it has recently been reported that SIRT1-deficient mice are metabolically inefficient and unable to adapt to CR normally. SIRT1-overexpressing transgenic (SIRT1-KI) mice in which the SIRT1 cDNA is knocked into the β-actin locus display phenotypes that mimic some of the physiological changes in response to CR, including decreased blood insulin and glucose levels, improved glucose tolerance, reduced fat mass and circulating free fatty acid and leptin levels, reduced total blood cholesterol levels, enhanced oxygen consumption, improved activity in rotarod tests, and delayed reproductive timing. Two other independent lines of SIRT1 whole-body transgenic mice also show significant protection from the adverse effects of HFD or normal aging on metabolism, which CR has also been reported to convey. Given that CR delays the onset of and decreases the incidence of age-associated pathophysiological changes, these findings support the notion that SIRT1 counteracts the detrimental effects of aging in mammals.

**Does SIRT1 promote mammalian longevity?**

Based on these findings, one could expect that increasing SIRT1 dosage or activity throughout a body might extend life span in mammals. Unfortunately, life span results of currently existing SIRT1 transgenic mice have not yet been reported. However, an extra caution might be necessary because the roles of SIRT1 in each organ and tissue are significantly diverged so that beneficial effects of enhanced SIRT1 activity on life span in some organs/tissues might be balanced out with its unfavorable effects in others. Thus, SIRT1 whole-body transgenic mice might not show a significant extension of life span. Indeed, it has been reported that long-term treatment of regular chow-fed mice with resveratrol fails to extend life span, even though it recapitulates transcriptional profiles induced by CR in some organs/tissues. It is possible that SIRT1 dosage or activity is down-regulated in certain tissues by CR, as has been reported in the liver. Moreover, recent findings indicated that SIRT1 levels could be both up- and down-regulated locally within the same tissues, such as brain. Therefore, the idea that global activation of SIRT1 could extend the life span might be too simplistic. It will be of great importance to examine the effects of SIRT1 enhancement on pathophysiological aging of tissues and their propensity for diseases as well as longevity.

**Sirtuin-targeted anti-aging interventions**

**Sirtuin activator compounds (STACs)**

For the past decade, the developments summarized above have raised a broad interest in sirtuin-targeted anti-aging interventions with a hope to mimic beneficial effects of CR (Figure 3). The first case of the concept was the finding that a group of polyphenolic compounds, such as resveratrol, fisetin, and butein, was able to activate SIR2 and its orthologs in vitro and extend the life spans of yeast, worms, and flies. Following these findings, it has been reported that different doses of resveratrol counteract detrimental effects of HFD on metabolism and other physiological parameters and increase survival. Resveratrol also induces gene expression profiles similar to those induced by every-other-day feeding, which is known to convey physiological effects similar to those in CR, particularly in liver and skeletal muscle. Furthermore, new non-polyphenolic STACs have recently been shown to improve glucose homeostasis and insulin sensitivity in diet-induced and genetically obese rodent models, implicating a novel therapeutic
intervention for the treatment of type 2 diabetes. In particular, SRT1720, one of those new STACs, has been further examined and shown to mediate beneficial effects on energy metabolism in obese, insulin-resistant mice. These findings indicate that STACs might function as potential CR mimetics, at least in part, through the activation of SIRT1 and be effective to treat age-associated metabolic complications, such as type 2 diabetes (Figure 3). However, whether STACs directly activate SIRT1 in vivo is still controversial. Recent studies have shown that AMP-activated protein kinase (AMPK) plays a critical role in mediating the effect of resveratrol. Concern has also been raised by studies on the substrate specificity of SIRT1-activating effects in vitro. Therefore, careful assessments will be necessary to clarify the mechanism of action of STACs.

NAD biosynthesis and sirtuins

Accumulating bodies of evidence have demonstrated that NAMPT-mediated NAD biosynthesis plays an important role in the regulation of SIRT1 activity in a number of cell types, such as pancreatic β cells, vascular smooth muscle cells, skeletal myoblasts, cardiac myocytes, and others. Most recently, SIRT1 has been connected to the circadian transcriptional regulation mediated by key circadian transcription factors CLOCK and BMAL1. Furthermore, the CLOCK:BMAL1 complex produces the circadian oscillation of NAMPT and NAD levels in vivo, thus comprising a novel circadian clock feedback loop involving NAMPT/NAD and SIRT1/CLOCK:BMAL1. Because the core molecular clock machinery is one of the most powerful modifiers of metabolism, it is conceivable that enhancing NAD biosynthesis at a systemic level by administering key NAD intermediates, such as NMN, might be able to activate SIRT1 and convey beneficial effects on metabolism and other physiological processes (Figure 3). Indeed, this idea has been demonstrated at least in Nampt-heterozygous mice and aged BESTO mice, in both of which NMN significantly improves GSIS and glucose tolerance. The mitochondrial sirtuins SIRT3-5 can also be activated by increasing NAMPT-mediated NAD biosynthesis. Therefore, it will be of great importance to examine whether intermediates in NAD biosynthesis can be used as an effective anti-aging nutriceutical intervention to ameliorate age-associated metabolic complications and thus improve the quality of life.

Concluding remarks

The past 10 years have been exciting and innovative for sirtuin-related research. Sirtuins have created a new arena where we can further investigate an intimate connection between NAD biology, metabolism, and aging. Many novel NAD-dependent biological processes have been revealed, and our knowledge on the dynamic interaction between protein acetylation and energy metabolism has been revolutionized. In this respect, it is striking that acetyl-CoA is both the product of carbohydrate and fat metabolism and the substrate for protein acetylation. Yet several important questions remain: What are the functions of other mammalian sirtuin family members in each subcellular compartment? How is the connection between sirtuins and NAD biosynthesis regulated in each subcellular compartment and through the whole body? Are there any other known or even unknown NAD intermediates and metabolites that are involved in the regulation of sirtuin activities? Can we really develop an effective sirtuin-targeted intervention to improve the quality of life in our aging society? Those questions will hopefully be addressed in the next 10 years, and we may be able to enjoy our lives with anti-aging pharmaceutical and nutriceutical interventions that target sirtuins.
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The tissue-specific metabolic functions of SIRT1 in the regulation of insulin sensitivity and secretion. SIRT1 plays a critical role in maintaining a delicate balance between insulin sensitivity and secretion in major metabolic tissues, such as liver, skeletal muscle, white adipose tissue (WAT), and pancreatic β cells. In the liver, SIRT1 regulates glucose production through PGC-1α, FOXO1, CRTC2, and STAT3 and appears to repress insulin sensitivity. SIRT1 also regulates LXRα and PPARα for cholesterol and fatty acid metabolism. In skeletal muscle, SIRT1 improves insulin sensitivity by increasing fatty acid oxidation through PGC-1α and repressing the expression of PTB1B. In WAT, SIRT1 promotes fatty acid mobilization by repressing PPARγ function and also regulates the production/secretion of adiponectin and FGF21 through FOXO1 and/or PPARγ. In pancreatic β cells, SIRT1 promotes glucose-stimulated insulin secretion and likely contributes to β cell adaptation in response to insulin resistance.
Figure 2.
The role of SIRT1 in the induction of age-associated physiological changes. A variety of environmental and nutritional perturbations likely induce DNA damage and a reduction in NAD biosynthesis over time, resulting in the redistribution of SIRT1 and the reduction in SIRT1 activity in many different tissues. These events might affect SIRT1-mediated biological processes in tissues, causing the reduction in physiological robustness and aging.
Figure 3.
SIRT1 as a molecular target for pharmaceutical and nutriceutical anti-aging interventions. Small molecule SIRT1-activating compounds (STACs) and the enhancement of NAD biosynthesis could mimic metabolic responses to caloric restriction (CR) through SIRT1 activation, leading to a possible extension of health span in mammals.
### Table 1

Mammalian sirtuins

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<th>SIRT</th>
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<td>Sir2p (<em>S. cerevisiae</em>)&lt;br&gt;Hst1p (<em>S. cerevisiae</em>)&lt;br&gt;SIR-2.1 (<em>C. elegans</em>)&lt;br&gt;dSIR2 (<em>D. melanogaster</em>)</td>
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WAT, white adipose tissue; BAT, brown adipose tissue
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