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Sirt1 as a New Therapeutic Target in Metabolic and Age-Related Diseases

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Sirt1 among the mammalian sirtuins has generated intense scientific interest in recent years, mainly because of its effects on longevity, metabolism, and other aging-related processes. Via nicotinamide adenine dinucleotide (NAD)-dependent protein deacetylation, Sirt1 can regulate important metabolic regulators. Sirt1 is involved in insulin secretion in the pancreas, fatty acid oxidation in liver and skeletal muscle, hepatic gluconeogenesis during fasting, the suppression of fat storage in white adipose tissue, and the enhancement of insulin sensitivity in skeletal muscle. It also communicates with AMP-activated protein kinase (AMPK). Resveratrol, a prototype of Sirt1 activator, can induce similar changes reminiscent of caloric restriction in insulin-resistant obese rodent models, although clinical studies are still limited. Intensive research efforts are now targeting Sirt1 for pharmacologic interventions in aging and age-related metabolic and degenerative disorders.

Key Words: *Sirt1; AMP-activated protein kinases; Caloric restriction; Longevity*

Introduction

The aging process, obesity, diabetes and metabolic diseases, cardiovascular diseases, inflammation, neurodegeneration, and carcinogenesis are the intensive themes of modern medical and biological sciences. To some extent, these processes are correlated with one another. Sirt1 has generated intense scientific interest in recent years, mainly because of its effects on longevity, metabolism, and other aging-related processes. Although further studies are required in humans, its activator resveratrol is already on the market. In this review, Sirt1 and its biology are discussed in relation to glucose and lipid metabolism.

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Sirtuins

Sirtuins in mammals were named after their homology to the *Saccharomyces cerevisiae* gene *silent information regulator 2* (*Sir2*). Sirtuins are a family of NAD-dependent protein deacetylases.[1] In an elegant experiment using *Saccharomyces cerevisiae*, over-expression of *Sir2* was shown to increase life span by 30%, whereas ablation of the *Sir2* gene had the opposite effect, reducing the life span of the yeast by 50%.[2] Sirtuins deacetylate lysine residues on histones and other proteins in a reaction that consumes NAD^+, releasing nicotinamide (NAM), O-acetyl ADP ribose, and the deacetylated substrate.[3,4] As such, sirtuin activity can be controlled by cellular [NAD^+]/[NADH] ratios and responds to changes in the metabolic state of the cell (Fig. 1).[5] NAM can noncompetitively bind to the sirtuins and play a role as a potent inhibitor of sirtuin activity.[5]

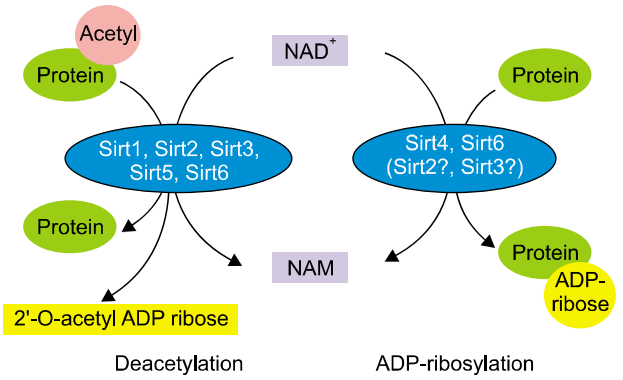

Fig. 1. The enzymatic activities of Sirtuins. Sirtuins have two different NAD^+-consuming activities. Sirt1, Sirt2, Sirt3, and Sirt5 act as deacetylase enzymes, using NAD^+ to cleave acetyl groups from ε-acetyl lysine residues of target proteins in a reaction that generates NAM and 2'-O-acetyl-ADP-ribose. Sirt4 acts as a mono-ADP-ribosyl transferase, in a reaction where the ADP-ribosyl moiety of NAD^+ is transferred to a substrate protein. Sirt6 has both enzymatic activities.

In mammals, seven homologs of Sir2 have been described, namely Sirt1-7, which are ubiquitously expressed and share a conserved catalytic core comprising 275 amino acids.[6,7] Sirt1, Sirt6, and Sirt7 are loca- lized in the nucleus and are enriched in the nucleoplasm, in heterochromatin, and in nucleoli, respectively.[3] Sirt2 is usually localized in the cytoplasm, although it can also regulate gene expression by deacetylating transcription factors that shuttle from the cytoplasm to the nucleus. Finally, Sirt3, Sirt4, and Sirt5 are predominantly mitochondrial proteins.[3,8] In addition to their different subcellular localization, not all mammalian sirtuins have similar enzymatic activities. Indeed, Sirt1 and Sirt5 act as deacetylases, whereas Sirt4 and Sirt6 act as mono-ADP-ribosyl transferases, and Sirt2 and Sirt3 have both enzymatic activities. In the case of Sirt7, no clear activity has been reported as yet, although it has been proposed to act as a deacetylase.[5] Recently, there has been an increasing interest in Sirt1 among the sirtuins as a new therapeutic target for type 2 diabetes mellitus in the field of metabolism and aging.

Caloric restriction and longevity

Caloric restriction (CR) has been shown to enhance longevity of organisms ranging from yeast to mammals.[8] It has been reported that Sir2 is involved in the CR-related enhancement of longevity in yeast, although some studies suggest that other pathways in addition to Sir2 are involved.[8] Reducing glucose levels in yeast leads to elevated NAD levels, reduced NADH levels, and/or reduced nicotinamide levels, which in turn lead to Sir2 activation.[8,9]

Table 1. The diverse functions of Sirt1 in different metabolic tissues

Organ	Involved pathway	Physiologic effect
Liver	LXRs, FOXOs, and PGC1 α	Increase gluconeogenesis, fatty acid oxidation, and cholesterol scavenging
White adipose tissue	PPAR γ	Suppress adipogenesis and fat storage
Brown adipose tissue	PGC1 α	Increase mitochondrial activity and thermogenesis
Pancreas	UCP2	Increase insulin secretion
Skeletal muscle	PGC1 α, PTP1b, and MyoD	Increase mitochondrial activity, fatty acid oxidation, and insulin sensitivity suppress myogenesis

Sirt1 in mammals

Sirt1 is the mammalian ortholog of the founder protein Sir2 in yeast and is by far the best characterized. Because most mammalian sirtuin research has focused on the function of Sirt1, this manuscript discusses mainly Sirt1 among the mammalian sirtuins. Although it is not yet proven whether Sirt1 regulates aging and longevity in mammals, it has already been established that Sirt1 plays a critical role in the regulation of metabolism in response to nutrient availability and cell survival in response to stress.

Various energy stresses such as a low glucose state, fasting, and calorie restriction have been shown to activate Sirt1.[8] Sirt1 activity is closely related with metabolic homeostasis (Table 1). By deacetylating protein substrates including a number of transcription factors and cofactors, Sirt1 can regulate important metabolic regulators, for example, peroxisome proliferator-activated

receptor γ (PPAR γ), PPAR γ coactivator-1 α (PGC-1 α), p53, and FOXOs. Sirt1 can also directly regulate the activity of acetyl-CoA synthetase through deacetylation.[8,10] The relevance of Sirt1 in the control of whole-body glucose homeostasis is the result of the combined action on different tissues, and it has a critical role during fasting. In the fasted liver, NAD^+ levels are 50% higher than in control conditions, and the expression of the Sirt1 protein is induced.[5] Sirt1 interacts with and deacetylates PGC-1 α in liver. This deacetylation activates PGC-1 α function, consequently promoting PGC-1 α-mediated gluconeogenesis. Sirt1 has also been shown to deacetylate and activate the transcription factor FOXO1, leading to the subsequent enhanced expression of FOXO1 target genes that induce gluconeogenesis and glucose release from hepatocytes.[5,7] Hepatic cholesterol accumulation and decreased serum cholesterol levels were also observed upon hepatic knockdown of Sirt1 in $Sirt1^{+/-}$ mice.[11] Reduction of Sirt1 activity in the liver leads to the decreased expression of genes involved in cholesterol efflux and degradation. Because both LXR α and LXR β are deacetylated and activated by Sirt1, altered cholesterol metabolism in Sirt1 deficient mice might relate with the role of LXRs.[7,12] However, resveratrol, a Sirt1 activator, does not affect blood cholesterol levels,[13,14] which might be due to the potential Sirt1-independent effects of resveratrol. Whereas LXR α can positively affect insulin sensitivity, it is not clarified whether the activation of LXR α by Sirt1 is involved in the regulation of insulin sensitivity.[15] A specific Sirt1 activator was shown to increase fibroblast growth factor (FGF) 21 expression in the liver, probably as a consequence of increased PPAR α action.[16] FGF21 regulation could as such contribute to the positive metabolic effects of Sirt1 activation.

Sirt1 over-expression in pancreatic β cells leads to reduced UCP2 expression and enhanced insulin secretion during glucose stimulation.[17] In adipocytes, resveratrol, a Sirt1 activator, suppresses fat accumulation. After resveratrol treatment, the acetylated PPAR γ recruits the corepressors NCoR (nuclear receptor corepressor) and SMRT (silencing mediator of retinoid and thyroid hormone receptors) rather than coactivators.[18] Also, over-expression of Sirt1 attenuated the adipocyte differentiation and reduced the expression of fat storage-related genes in mature adipocytes.[7] Mice treated with resveratrol showed a lower white adipose tissue mass, a decrease in fat storage, and smaller adipocytes.[14] Mice treated with resveratrol exhibited enhanced thermogenesis, accompanied by an increase in the size of mitochondria and PGC1 α deacetylation in brown adipose tissue (BAT).[14] The enhanced mitochondrial activity in resveratrol-treated mice was also shown in skeletal muscle as reflected in the fact that these mice contained myofibers enriched in mitochondria.[14] Sirt1 also has an insulin-sensitizing effect.[19] Over-expression of Sirt1 in C2C12 myotubes improves insulin sensitivity under insulin-resistant conditions. The insulin-sensitizing effect of Sirt1 in the skeletal myotube cells is likely mediated by repressing the expression of protein tyrosine phosphatase (PTP)1B,[20] a negative regulator of the insulin signal pathways. Sirt1 transgenic mice show phenotypes resembling calorie restriction, and insulin sensitivity is improved in these transgenic mice.[21]

Other sirtuins

Although less is known about the cellular roles of the other sirtuins, recent excellent reviews are available.[7,10] Sirt2, a cytoplasmic sirtuin, can bind to chromatin in the nucleus during the G2/M phase of the cell cycle. Sirt2 also inhibits pre-adipocyte differentiation.[7] Sirt3 is involved especially in adaptive thermogenesis and mitochondrial function. Sirt3 expression was shown to be decreased in skeletal muscle of diabetic animals and in BAT of obese mice. The mitochondrial enzyme acetyl-CoA synthetase 2 (AceCS2) has been shown to be deacetylated and activated by Sirt3.[7,10] AceCS2 converts acetate to acetyl-CoA. As mentioned above, Sirt1 deacetylates and activates the cytoplasmic

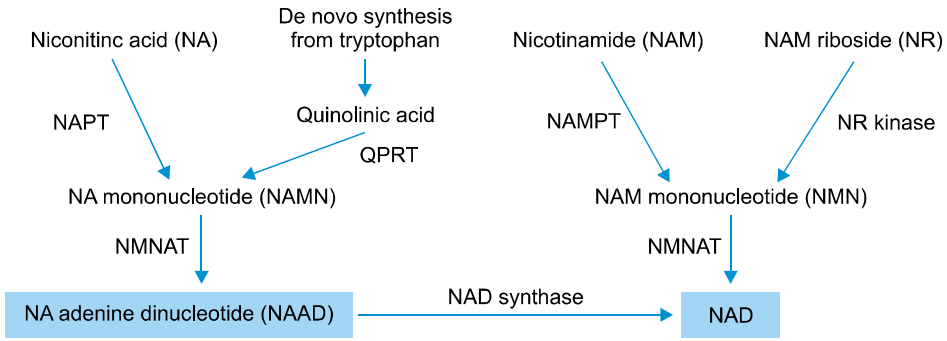

Fig. 2. NAD synthesis and salvage pathway. NAD is synthesized from tryptophan via a de novo pathway or in the NAD salvage pathway from its precursors NA, NAM, or NR. NAPT, NA phosphoribosyltransferase; NAMPT, NAM phosphoribosyltransferase; NMNAT, NMN adenylyltransferase; QPRT, quinolinate phosphoribosyltransferase.

acetyl-CoA synthetase, AceCS1.[7,10] Because AceCS1 and AceCS2 are the only two known mammalian AceCSs to scavenge excessive acetate under ketogenic conditions such as prolonged fasting or diabetic ketoacidosis, Sirt1 and Sirt3 seem to be involved in acetate metabolism under stress. Sirt4 can affect insulin secretion by interacting with glutamate dehydrogenase and insulin-degrading enzyme.[7] Sirt5 can deacetylate and activate hepatic carbamoyl phosphate synthetase 1 and is involved in the metabolism of excess ammonia produced as a result of amino acid usage as an energy source during the fasting period. Sirt6 regulates genomic DNA stability and DNA repair and may play an essential role in maintaining organ integrity as animals age. Sirt7 has been shown to have anti-apoptotic and anti-proliferative actions.

Intrinsic and extrinsic regulators of Sirt1

1. NAD^+

Generally, NAD-linked dehydrogenase catalyzes oxidoreduction reactions in the oxidative pathways of metabolism, particularly in glycolysis, in the citric acid cycle, and in the respiratory chain of mitochondria. NAD^+ not only acts as a coenzyme for oxidoreductases, but also as a donator of ADP-ribose in some specific reactions. Three major families of enzymes can cleave NAD^+ in mammals: sirtuins; ADP-ribose transferases, including poly(ADP-ribose) polymerases (PARPs); and cyclic ADP (cADP)-ribose synthases.[15] In addition to *de novo* synthesis from tryptophan, the major pool of NAD^+ is from salvage pathways, which require the uptake of other NAD^+ precursors. Dietary niacin, consisting of nicotinic acid (NA), nicotinamide (NAM), and NAM riboside (NR), can serve as an NAD^+ precursor by means of the salvage pathways (Fig. 2).[5] In mammals, NAM phosphoribosyltransferase (NAMPT) converts NAM to NAM mononucleotide (NMN), an enzymatic activity that has not been described for lower organisms.[5] There are two isoforms of NAMPT, intracellular and extracellular forms (iNAMPT and eNAMPT, respectively). NAMPT, which is the rate-limiting step of this part of the pathway, is highly expressed in brown adipose tissue and liver and is undetectable in brain and pancreas.[22] By virtue of its function in the conversion of NAM to NAD^+, hence lowering NAM levels and increasing NAD^+, NAMPT is considered an important regulatory enzyme with respect to the NAD^+ consumers, notably the aging-associated histone deacetylase Sirt1. In human vascular smooth muscle cells, reduced NAMPT expression resulted in premature senescence, whereas a significant delay in senescence was observed upon overexpression of NAMPT.[22,23] NAMPT, also known as visfatin, has been reported to have an insulin mimetic effect.[15] However, further studies are required to verify this insulin mimetic effect. Among *de novo* biosynthetic pathway and salvage pathways, it is yet to be determined which pathway is more important for the cellular concentration of NAD and Sirt1 activation.

2. Other intrinsic regulators

A protein called DBC1 (deleted in breast cancer 1)

has been shown to inhibit Sirt1 deacetylation of its well-established substrate, p53.[24] Stress-inducing agents such as UV radiation and hydrogen peroxide induce the desumoylase SENP1 to interact with Sirt1. This association caused the desumoylation and consequent inactivation of Sirt1.[25] A nuclear protein, formerly identified as a ribosomal S19-binding protein with unknown function, was shown to enhance Sirt1 activity and was thereby named active regulator of Sirt1 (AROS). The expression profile of AROS is remarkably similar to that of Sirt1 in multiple cell lines. AROS specifically interacts with Sirt1 but not with other sirtuins, and its binding promoted Sirt1 to deacetylate p53.[26]

3. Convergent role of Sirt1 and AMPK

Mammalian AMPK is a Ser/Thr kinase that is activated upon alterations in the cellular AMP/ATP ratio. Hence, perturbations in this ratio due to either defects in energy production or increased energy consumption will lead to the activation of AMPK.[27] AMPK as a metabolic switch activates catabolic pathways to produce ATP while simultaneously shutting down ATP-consuming anabolic processes. AMPK mediates these effects through the rapid phosphorylation of metabolic enzymes, such as acetyl CoA carboxylase and hydroxymethylglutaryl-CoA reductase, two rate-limiting enzymes for fatty acid oxidation and cholesterol synthesis, respectively.[28] If ATP stores remain depleted, AMPK can induce the phosphorylation of transcription factors and co-activators that regulate gene expression, including FOXO3, PGC1α, and HNF4. Interestingly, many of these transcription factors are also regulated by Sirt1.[29] In addition to having common activation events (glucose restriction, fasting, chronic calorie restriction, oxidative stress, and exercise), the AMPK and Sirt1 signaling pathways have similar effects on life span, aging, and metabolism.[29] Like Sirt1, AMPK has been proposed to be one of several molecules involved in regulating mammalian longevity. Chronic activation of AMPK occurs on a calorically restricted diet and has been proposed as a longevity strategy for mammals. Consistent with this idea, additional copies of the AMPK gene are sufficient to extend lifespan in C. *elegans*.[30] The aging process itself has been described to be associated with a decline in the activity of both Sirt1 and AMPK.

AMPK can phosphorylate PGC-1α directly,[31] whereas Sirt1 deacetylates and activates PGC-1α.[29] The connection between the two pathways was revealed in a recent excellent study.[32] AMPK regulates the expression of mitochondrial and lipid metabolism genes through the modulation of PGC-1α activity. This activation of PGC-1α involves both direct phosphorylation of PGC-1α by AMPK and deacetylation of PGC-1α by Sirt1.

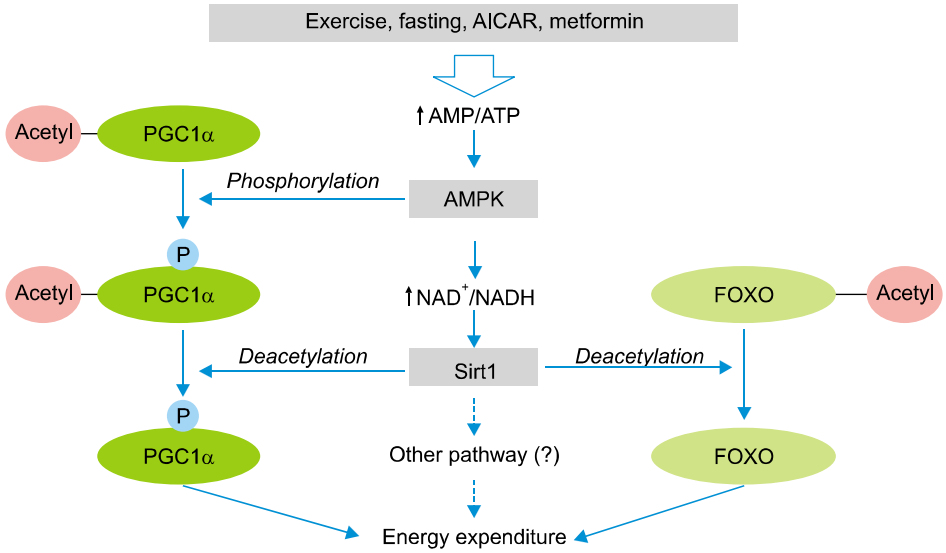

Fig. 3. The convergent actions of AMPK and Sirt1 on PGC-1α. Pharmacological (AICAR, metformin) and physiological (fasting or exercise) activation of AMPK in muscle increases the NAD^+/NADH ratio, leading to the activation of Sirt1. AMPK can phosphorylate PGC-1α directly, priming it for subse-quent deacetylation by Sirt1. The impact of AMPK and Sirt1 on the acetylation status of PGC-1α and other transcriptional regulators, such as the FOXO family of transcription factors, will then modulate mitochondrial function and lipid metabolism.

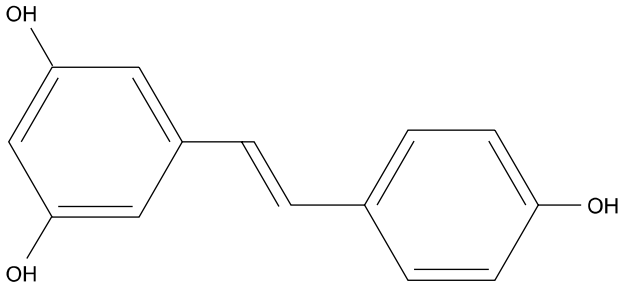

Fig. 4. The chemical structure of *trans*-resveratrol.

It seems that AMPK indirectly activates Sirt1 by altering the intracellular NAD^+/NADH ratio through an increase in mitochondrial fatty acid oxidation (Fig. 3).[32]

4. Resveratrol and other Sirt1 activators

Resveratrol (3, 5, 4'-trihydroxystilbene) (Fig. 4) belongs to the large group of polyphenols found in different plant species. Recently, resveratrol has been in the center of the Sirt1 research field after becoming known as a Sirt1 activator. Although the richest natural source of resveratrol is *Polygonum cuspidatum*, a plant root extract that has been used in Oriental folk medicine, grapes, grape juice, and red wine are more well-known sources because of the "French paradox," i.e., low mortality due to coronary heart disease as a result of moderate consumption of red wine.[1] There is an enormous amount of data about resveratrol and Sirt1. However, data concerning the potential beneficial effects of resveratrol in humans are still very limited.

Long-term rodent studies provided relatively convincing evidence that resveratrol exerts favorable effects in high-fat-fed animals. Resveratrol (22.4 mg/kg/day) treatment of 1-year-old middle-aged mice on a high-fat diet extends their life span, enhances insulin sensitivity, and increases hepatic mitochondrial content similar to calorie-restricted animals with greater Sirt1 expression.[13] The other important issue is that in contrast to the effect in high-fat-fed mice, mice consuming a standard diet did not live longer when treated with resveratrol.[13] A high dose of resveratrol (400 mg/kg/day) significantly increases the aerobic capacity and the endurance during exercise test by promoting oxidative phosphorylation and mitochondrial biogenesis of skeletal muscle in high-fat-fed or control mice and decreases total body fat content in high-fat-fed mice.[14] However, a lower dose of resveratrol (10 mg/kg body weight; admi-nistered for 8 weeks) was shown to be ineffective in reducing body weight gain in obese Zucker rats, although a slight decrease in body fat content was found.[33] I also observed that resveratrol therapy (30 mg/kg daily for 3 weeks) did not decrease body weight significantly in mice on a high-fat diet (manuscript in preparation). Even a smaller dose of resveratrol (4.9 mg/kg daily) in aging mice was reported to be effective in preventing cardiac and skeletal muscle dysfunctions induced by ageing and attenuating age-related changes in gene expressions.[34] Effects caused by resveratrol paralleled those found in mice on a calorie-restricted diet or evoked by every-other-day feeding.[35] It is also known that CR increases the expression of Sirt1, which provided further evidence supporting the importance of Sirt1 activation in the mechanism of resveratrol's action.[35] Interestingly, AMPK activity is also increased by resveratrol therapy in rats fed a high-fat diet.[13] Intensive research is ongoing to identify more potent, and more bioavailable, activators of Sirt1 than resveratrol. Recently, several small molecule activators of Sirt1 have been developed. They are structurally unrelated to and 1000-fold more potent than resveratrol and were shown to improve insulin sensitivity, lower plasma glucose, and increase mitochondrial function in insulin-resistant obese mice models.[36]

Perspectives

For the past several years, it has been demonstrated that Sirt1 plays a critical role in the regulation of metabolism and possibly aging in mammals. However, as summarized above, some of the effects of Sirt1 are tissue-dependent. Therefore, more studies are required in relation to glucose homeostasis, especially in humans. In addition to Sirt1, there are other sirtuins whose

functions are also very important. NAMPT-mediated NAD biosynthesis and AMPK are also important modulators of Sirt1 function. In the next few years, this new NAD-dependent metabolic network will be further explored, and therapeutic interventions based on research on Sirt1 and other sirtuins will be a new choice among various known and evolving ways to control metabolic and age-related diseases.

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