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Sirtuins and Pyridine Nucleotides

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Abstract

The silencer information regulator (Sir) family of proteins has attracted much attention during the past decade due to their prominent role in metabolic homeostasis in mammals. The Sir1-4 proteins were first discovered in yeast as nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylases, which through a gene silencing effect promoted longevity. The subsequent discovery of a homologous sirtuin (Sirt) family of proteins in the mammalian systems soon led to the realization that these molecules have beneficial effects in metabolism- and aging-related diseases. Through their concerted functions in the central nervous system, liver, pancreas, skeletal muscle, and adipose tissue, they regulate the body's metabolism. Sirt1, -6, and -7 exert their functions, predominantly, through a direct effect on nuclear transcription of genes involved in metabolism, whereas Sirt3-5 reside in the mitochondrial matrix and regulate various enzymes involved in the tricarboxylic acid and urea cycles, oxidative phosphorylation, as well as reactive oxygen species production. An interesting aspect of sirtuin's functionality involves their regulation by the circadian rhythm, which impacts their function via cyclically regulating systemic NAD^+ availability, further establishing the link of these proteins to metabolism. In this review we will discuss the relation of sirtuins to NAD^+ metabolism, their mechanism of function, and their role in metabolism and mitochondrial functions. In addition, we will describe their effects in the cardiovascular and central nervous systems.

Keywords

Aging

Introduction

Silent information regulator 1-4 (Sir1-4) proteins were initially discovered in *Saccharomyces cerevisiae* as transcriptional repressors of the silent hidden *MAT* left (*HML*) and hidden *MAT* right (*HMR*) mating type loci [1–3] - which are suppressed copies of mating loci MATa and MATα for changing mating type in haploid cells - and of telomeres [4]. This effect is partly due to deacetylation of histones H3 and H4 and heterochromatin formation by Sir2 [5]. In addition, the Sir proteins are involved in double stranded DNA repair [6], as well as suppression of mitotic and meiotic intrachromosomal recombination of ribosomal DNA (rDNA) in the nucleolus [7, 8], which is responsible for extrachromosomal accumulation of the senescence-related rDNA circles [9]. This family of protein is mainly recognized for its role in longevity, as the phenotypes of the Sir2/3/4 mutants were characterized by a shortened

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lifespan [10, 11]. In the Sir3 and Sir4 mutants, this appears to be due to the concomitant expression of mating-type information a and α, while the Sir2 mutant failed to suppress rDNA recombination. Conversely, overexpression of Sir2 extended the lifespan of wild type yeast. It was later discovered that Sir2 is a nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylase enzyme [12–14], which is a unique feature among deacetylase, via which it deacetylates K9 and K14 of H3 and K16 of H4 [12]. The deacetylase activity is indeed responsible for Sir2-dependent gene silencing, suppression of rDNA recombination, and longevity in yeast [12]. In fact, the Sir family appears to be the main NAD^+-dependent histone deacetylase in yeast, as this activity is abrogated when Sir2 and its four homologues are deleted [14]. NAD^+ is not simply a regulator in this reaction but a substrate; it is hydrolyzed by Sir2 into nicotinamide and adenosine diphosphate (ADP)-ribose, which is an acceptor of the acetyl group hydrolyzed from an acetyl-lysine substrate, thus, forming 2'-*O*-acetyl-ADP-ribose [15], a reaction that is conserved from yeast to humans [16].

Yeast Sir2, in particular, is conserved from bacteria to humans [17]. There are currently 7 known isoforms of Sir2-like proteins in mammals (sirtuins 1-7). Frye et al cloned human SirT1-7, which are ubiquitously expressed and exhibit NAD^+-dependent deacetylase activity, and in the case of Sirt4 an ADP-ribosyltransferase activity, with Sirt1 being the most homologous to yeast Sir2 [18, 19]. Sirt1, Sirt6, and Sirt7 harbor a nuclear localization signal and, accordingly, are predominantly nuclear. However, Sirt1 is also present in the cytoplasm of various cell types under different developmental conditions [20]. For example, in E12.5 cardiac myocytes, Sirt1 is exclusively nuclear, whereas in the adult heart it is also found in the cytoplasm. This could be explained by the fact that in addition to its nuclear localization signals, Sirt1 harbors 2 nuclear export signals that allow for its nuclear-cytoplasmic shuttling [20]. On the other hand, Sirt2 is predominantly cytoplasmic [21], while Sirt3-5 are predominantly mitochondrial [22–23].

Like its yeast homolog, Sirt1 has also been implicated in the longevity of *C. elegans and D. melanogaster* by mimicking the effects of calorie restriction [24]. Similarly, Sirt1 mediates anti-apoptotic effects of calorie restriction in mammalian cells via deacetylating Ku70, which sequesters Bax [25]. Most significantly, it is required for the characteristic increase in physical activity [26] and enhanced sensitivity of muscle to insulin [27] that is associated with calorie restriction. Additionally, overexpression of Sirt1 was sufficient for preventing insulin resistance following a high-fat diet in mice [28]. Thus, it is not surprising that sirtuin mimics are being therapeutically exploited in an attempt to improve the quality and duration of life. Some of the main functions of sirtuins discovered to-date will be discussed below and their role in calorie restriction will be highlighted throughout.

Pyridine nucleotides and the regulation of sirtuins' activity

NAD^+ metabolism

The pyridine nucleotides NAD^+ and NADP are known for their roles in metabolism as hydride acceptors (forming NADH and NADPH), and subsequently donors, for oxidoreductases. On the other hand, NAD^+ also serves as a substrate for 4 classes of enzymes, mono-ADP-ribose transferases (MART), poly-ADP-ribose polymerases (PARP), cyclic-ADP-ribose synthases (cADP), and Sirtuin deacetylases, which accordingly couples them to the metabolic status of the cell. These enzymes utilize NAD^+ by hydrolyzing it into nicotinamide (NAM) and ADP-ribose that serves as the acceptor of the acetyl group, thus, forming 2'-O-acetyl-ADP-ribose [15]. NAD^+ levels are subsequently reconstituted through *de novo* or nicotinic acid/nicotinamide (vitamin D3 or niacin) salvage biosynthesis pathways (Fig.1). NAM, via a negative feedback loop, can inhibit the deacetylase activity [29], thus, underscoring the importance of the salvage pathways in eliminating this byproduct and restoring NAD^+ levels and sirtuins' activity.

NAD^+ can be replenished by *de novo* synthesis from L-tryptophan, particularly when nicotinic acid or nicotinamide are deficient. First, L-tryptophan is converted to quinolinic acid in the liver via 4 steps catalyzed by indolamine 2,3-dioxygenase, kynurenine formamidase, kynurenine 3-hydroxylase, kynureninase, 3-hydroxyanthranilate 3,4-dioxygenase, respectively (reviewed in detail in ref. [30]). Next, a phosphoribosyl group is added to quinolinic acid by quinolinate phosphoribosyltransferase to generate nicotinate mononucleotide (NaMN), which is then converted to nictoniate adenine dinucleotide (NaAD) via nicotinamide mononucleotide adenylyl transferase. The latter enzyme also catalyzes the conversion of nicotinamide mononucleotide (NMN) and NaMN into NAD^+ and NaAD, respectively, in the salvage pathways. Finally, NAD^+ synthase converts NaAD into NAD^+ [30] (Fig. 1).

A major salvage pathway for NAD^+ synthesis utilizes NAM, the byproduct of NAD^+ consumption by the various glycohydrolases. It was thus suggested that it is the main pathway responsible for reconstituting NAD^+ in mammalian cells [30]. It involves 2 steps, the conversion of NAM into NMN by NAM phosphoribosyl transferase (NAMPT), which is then converted to NAD^+ via NAM mononucleotide adenylyl transferases (NMNATs), NAMPT being the rate-limiting enzyme in this pathway [31]. Intracellular Nampt (iNampt) is particularly enriched in brown adipose tissue, heart, muscle, liver, and kidney, but is undetectable in the brain and pancreas [32]. It is worth noting that this enzyme is also secreted into the circulation by various tissues including visceral fat, liver, and leuckocytes where it is proposed to function as a pre-B-cell enhancing factor (PBEF) [33], also known as Visfatin, with mixed results regarding its role in diabetes and obesity [34–36]. In addition, it exhibits pro-inflammatory functions [37–39], thus linking NAD^+ metabolism to inflammation as well.

A second salvage pathway utilizes nicotinic acid (Na). In fungi and bacteria, but not in mammalian cells, nictoinamidase converts NAM into NA. On the other hand, NA maybe supplied to mammalian cells in the form of niacin/vitamin B3, which can be converted into NAD^+ in 3 steps [40]. First, Na is converted to NaMN by Na phosphoribosyltransferase (NaPRT). Second, NaMN is converted to Na adenine dinucleotide (NaAD), which at this juncture converges on the de novo pathway. Yet a third pathway is activated during *H. influenzae* infections in humans, in which the hydrolysis of NMN to nicotinamide ribosde (NR) is reversed by nicotinamide riboside kinase [41].

NAD World

"NAD world" is a term introduced by Dr. Imai that describes the functional relation between the circadian cycle, extracellular Nampt (eNampt) levels and systemic NAD^+ biosynthesis, Sirt1, and metabolism [42]. Intriguingly, it was discovered that Nampt regulates the biosynthesis of NAD^+ in a circadian-dependent oscillatory fashion, which, accordingly, adjusts the activity of Sirt1 and the sensitivity of its response to nutritional stimuli [43, 44]. Sirt1, through a negative feedback loop, inhibits the circadian cycle by counteracting the acetyltransferase function of CLOCK:BMAL1 - a positive transcriptional regulator of Nampt. This NAD^+-driven CLOCK-Nampt-Sirt1 loop has been dubbed "NAD world" [45]. Since eNampt is secreted from adipose tissue into the plasma [34–36], the effect of this circadian loop would have a systemic influence. NAD^+ as well is found extracellularly, as it is released from cells through connexin43 hemi channels [46]. As expected, plasma eNampt converts NAM into NMN, which can be uploaded by cells and converted to NAD^+, thereby, regulating whole body NAD^+ availability [32].

Organs that are deficient in Nampt, such as neurons and the pancreas, rely on systemic NMN to replenish their NAD^+ supply [32], these are known as the frailty points in the NAD world. It has indeed been shown that the pancreas is dependent on eNampt and extracellular NMN for glucose-induced insulin secretion, which may partly explain why dysregulation of

the circadian cycle affects glucose metabolism [32]. Indeed, metabolism [47–49], as well as aging [50, 51], are known to be under the influence of the circadian rhythm, which further supports their connection to NAD^+ world and sirtuins. The brain, which centrally regulates metabolism via Sirt1, is also deficient in iNampt, however, there is no direct evidence yet of how essential circulating NMN is for it function.

Although the cardiovascular system has relatively high iNampt, it could potentially be indirectly impacted by eNampt and NAD^+ levels through their effect on pancreatic insulin secretion, or alternatively through circadian fluctuations in iNampt and intracellular NAD^+ and Sirt1 activity. Indeed, cardiovascular diseases including ischemia [52], infarction [53], stroke [53], and sudden cardiac arrest [54] have all been shown to have a circadian pattern in the frequency of their occurrence. Until it is verified, it is interesting to speculate that these events may coincide with the periods during which Nampt, NAD^+, and Sirt1 levels are at their lowest during the circadian cycle.

PARP and the consumption of NAD^+

Fluctuations in PARP activity alone can dramatically perturb the levels of intracellular NAD^+ and impact cell viability, as shown in a type I diabetes model [55]. In particular, that study shows that activation of PARP by streptozocin resulted in consumption of ~70% of intracellular NAD^+ and apoptosis of pancreatic islet cells, both of which were reversed by the knockout of PARP. From those data, one can predict that activation of PARP would compromise the activity of other NAD^+-consuming enzymes and vice versa. This was proven to be the case when Bai *et al* deleted PARP-1 in brown adipose tissue and found that NAD^+ availability and Sirt1 activity were increased [56]. A reciprocal relation between Sirt1 and PARP may also be true, as deletion of Sirt1 enhanced PARP activity [57].

Transcriptional and posttranscriptional regulation of Sirtuins' expression

In addition to their regulation by NAD^+, sirtuins' levels are also regulated at the transcriptional and posttranscriptional levels. For example, in nutrient-deprived PC12 rat cells, forkhead box O3a (FoxO3a) interacts with p53 to induce the transcription of the mouse Sirt1 gene via two p53-binding sites in its promoter [58]. Under normal conditions, however, p53 suppresses the mouse Sirt1 promoter. In addition to FoxO3, FoxO1 has also been reported to activate the Sirt1 promoter [59]. Likewise, the human Sirt1 promoter harbors a p53-binding site that is also required for its activation via a p53-FoxO3a-dependent mechanism during calorie restriction, but differs from the mouse promoter in that p53 has no impact on its activity under normal nutrient availability [60, 61]. Interestingly, the p53-binding site in the human Sirt1 promoter exhibits a C/T variation, wherein the C variant reduces p53 binding and, thereby, promoter activity during nutrient restriction [61]. In accordance, obese human subjects carrying at least one T allele have higher Sirt1 levels in their skeletal muscle after 3–6 months of calorie restriction. In addition to p53, human and mouse Sirt1 are induced by cAMP response-element-binding protein (CREB) during calorie restriction, which otherwise remains suppressed by carbohydrate response-element-binding protein [27]. Additionally, peroxisome proliferator-activated receptor (PPAR) beta/delta indirectly enhances transcription of human Sirt1 via an Sp1 binding-site in its promoter [62]. In contrast, to these activating factors, Sirt1 transcription is inhibited by PARP-2 in mice [63].

Sirt1 has the capacity to auto-regulate itself through its interaction with hypermethylated in cancer 1 (HIC1), a complex which inhibits Sirt1's transcription in both mouse and human fibroblast [64]. This effect is reversed when glycolysis is inhibited (for example during calorie restriction), as the redox sensor C-terminal-binding protein (CtBP) interacts with HIC1, thus, releasing Sirt1's promoter from its inhibitory effect and enhancing transcription [65]. The

human promoter contains two HIC1-binding sites in close proximity to the p53-binding site, to which HIC1 binding is also reduced during nutrient restriction and replaced by p53 [61].

Sirt1 is also differentially regulated under conditions that are unrelated to nutrient availability and in a cell type dependent manner. For instance, E2F1 regulates Sirt1 expression during DNA damage in human non-small cell lung cancer cells [66], while early growth response (Egr-1) is responsible for stretch-induced Sirt1 in skeletal muscle [67]. Overall, the data reveal the diversity of transcription factors and conditions that differentially regulate the transcription of Sirt1 and the high degree of their conservation between mice and humans.

Sirt1 is also regulated at the posttranscriptional level, mainly via miRNAs (Fig. 2). In general, these posttranscriptional regulators have a profound effect on gene expression during development and disease (reviewed in [68]). MiR-34a, which is a tumor suppressor and a transcriptional target of p53, directly binds the 3'UTR and suppresses translation of Sirt1 mRNA in human cell lines [69]. As a result, overexpression of miR-34a in human colon cancer cells induces downregulation of Sirt1, upregulation of acetylated p53, and, thereby, apoptosis. In endothelial cells, both miR-217 [70] and miR-34a [71] target and suppress Sirt1 and promote senescence of human umbilical vein, aortic, and coronary artery endothelial cells [70]. In human fibroblast, an increase in miR-22 also induces senescence by targeting Sirt1 [72]. MiR-132 also targets Sirt1 in human adipocytes, resulting in an increase in acetylated p65 and activation of NFκB [73]. In pancreatic β-cells, glucose-dependent insulin secretion is associated with an increase in miR-9, which target and suppresses Sirt1 [74]. In hippocampal cells, miR-9 and miR-181c target Sirt1 [75]. In mammary epithelial cells, miR-200a, whose downregulation is required for the upregulation zinc finger E-box binding homeobox proteins and the mediation of endothelial-to-mesenchymal transition [68], also targets Sirt1 [76]. In cardiac myocytes, miR-199a-5p is rapidly downregulated during hypoxia, which results in an increase both its targets, Sirt1 and Hif-1α [77]. However, this increase is reversed upon prolonged deleterious periods of hypoxia. In addition, miR-195 mediates palmitate-induced apoptosis in cardiac myocytes by targeting Sirt1 [78]. All the miRNAs except for miR-195, are predicted by the one or more of the miRNA target-prediction engines, miRanda, Pictar, or TargetScan, to have a conserved binding site in the 3'UTR of Sirt1 (Fig. 2). Thus, in addition to transcriptional regulation, a wide array of miRNAs regulate the translation of Sirt1 during cell survival, senescence and metabolism, plausibly in a cell type- and condition-specific fashion.

Mechanisms of gene regulation by sirtuins

The Sir2 family of proteins was first discovered in yeast as a gene silencer of the silent mating loci and teleomeres [1–4]. The underlying mechanism of its function was found to involve deacetylation of histones H3 and H4, which favors the formation of transcriptionally silent heterochromatin [5]. In particular, Sir2 deacetylates K9 and K14 of H3 and K16 of H4, which proved to be responsible for its gene silencing and prolongation of lifespan effects in yeast [12]. In mammalian cells, Sirt1 deacetylates K9 of H3 and K16 of H4, in addition to its interaction with, and deacetylation of, K26 of H1, also responsible for inducing gene silencing [79]. Moreover, Sirt1 deacetylates and induces degradation of the histone H2A variant H2A.z, which was shown to selectively activate gene transcription in cardiac myocyte [80]. In yeast, H2A.z prevents the spread of silent heterochromatin into euchromatin regions near telomeres [81]. Heterochromatin formation also relies on an increase in histone methylation. It was soon discovered that Sirt1 can promote this function through an interaction with the methyl transferase enzyme SUV39H1, activating it through deacetylation of lysine 266 [82]. Accordingly, during starvation in mammalian cells, an increase in the NAD^+/NADH ratio results in activating Sirt1, which then deacetylates H3

and SUV39H1 and induces silencing of rRNA transcription [83]. As a result, energy would be conserved due to the inhibition of the high energy-consuming ribosome biosynthesis. This mechanism potentially links Sirt1 to energy conservation during caloric restriction conditions. Collectively, these findings prove that one of the main mechanisms that are employed by Sirt1 in regulating gene expression involves differential gene silencing via promoting heterochromatin formation (Fig. 3).

Additionally, sirtuins are known to indirectly impact transcription by negatively regulating the function of histone acetylases. Indeed, Sirt1 regulates the circadian clock genes by interacting with the CLOCK histone acetyltransferase and inhibiting its function through deacetylating its partner BMAL1 [84]. It also deacetylates the CLOCK/BMAL1 regulatory partner Period and induces its degradation [85]. Likewise, Sirt1 interacts with deacetylates as it inhibits the histone acetyltransferase p300 [86]. Other mechanisms employed by Sirt1 in regulating transcription involve direct modulation of transcription factors' activities via deacetylation. In fact, Sirt1 is involved in a negative feedback loop with some of the factors that regulate its own expression. For example, while the p53/FoxO3a complex induces the expression of Sirt1, Sirt1 binds to, deacetylates, and deactivates, p53 [87]. It also associates with FoxO3a and inhibits its pro-apoptotic capacity [88, 89]. Similarly, Sirt1 deacetylates E2F1 in a negative feedback loop, and inhibits its activity [66], as well as its partner Rb protein [90]. Moreover, it inhibits NF-κB [91], myocyte enhancer factor 2 [92], myogenic differentiation [93], and ying yang 1 [73]. Thus, whether it is through epigenetic modifications and chromatin remodeling or through regulating the activity of transcription factors, Sirt1 appears to have a predominantly silencing effect on gene expression (Fig. 3).

Sirtuins in metabolism

Sirt1 in glucose metabolism

Sirt1 has been reported to regulate glucose metabolism at multiple levels, including insulin secretion and sensitivity, gluconeogenesis, and glycolysis. It regulates insulin secretion from pancreatic β-cells via directly inhibiting transcription of uncoupling protein 2 (UCP2) [94, 95]. The UCP family of proteins are transporters found in the inner membrane of mitochondria, where UCP2 is induced by dietary fat and reduces the production of mitochondrial ROS, which in-turn results in suppressing glucose-induced insulin secretion [96]. Consequently, the β-cell-specific Sirt1-overexpressing mice (BESTO) exhibit enhanced glucose-induced insulin secretion and better glucose tolerance [94]. Interestingly, though, these benefits of Sirt1 were lost in the aging mice [97]. Since the pancreas does not have detectable intracellular Nampt it relies on the circulating eNampt and NMN for producing NAD^+ (see above "NAD^+ world"), and because plasma levels of NMN were reduced in older mice, it could explain why Sirt1 became ineffective. Indeed, replenishing NMN restored Sirt1 activity and function in older mice, emphasizing the role of NAD world in age-associated insulin resistance. These results were confirmed by a general Sirt1 transgenic mouse reported to have phenotype that recapitulates that of calorie restriction, which exhibits lower plasma insulin and superior glucose tolerance [98]. In addition to regulating insulin secretion, Sirt1 regulates insulin sensitivity. It is reduced in insulin resistant cells and was found to be both necessary and sufficient for improving insulin sensitivity by directly repressing transcription of protein tyrosine phosphatase 1B (PTP1B) [99], which is responsible for dephosphorylation and deactivation of the insulin receptor [100]. While all of the above studies were in rodents, in humans, it was shown that Sirt1 levels positively correlated with insulin sensitivity in adipose cells [101].

During fasting, Sirt1 and peroxisome proliferative activated receptor, gamma, coactivator 1 alpha (PGC-1α) are upregulated in hepatocytes, which leads to their direct association and the deacetylation and activation of PGC-1α by Sirt1 [102]. This enables PGC-1α to promote

gluconeogenesis by enhancing the expression of the genes involved in this process, while inhibiting those involved in glycolysis [103]. As a consequence, knockdown of Sirt1 in the mouse liver results in reduced gluconeogenesis, mild hypoglycemia and an increase in insulin sensitivity, particularly during fasting [104]. In agreement, knockdown of Sirt1 in the liver of a rat model of type 2 diabetes inhibited gluconeogenesis, reduced fasting blood glucose levels, and increased insulin sensitivity, which was associated with increased acetylation of PGC-1α and reduced levels of phosphoenolpyruvate carboxylase kinase and glucose-6- phosphatase [105]. These results, have been challenged by Liu et al, who report that during the early phase of fasting, gluconeogenesis is induced by CREB-regulated transcription coactivator 2 (CRTC2) not Sirt1 [106]. However, during the later stage, Sirt1 suppresses CRTC2, while FoxO1 activates gluconeogenesis. Thus, according to this model, knockdown of Sirt1 in the liver increases CRTC2 activity and, thereby, gluconeogenesis.

Yet another study shows that calorie restriction decreases, not increases, NAD^+ and Sirt1 activity in the liver, which is contrary to what is observed in white adipose tissue and muscle [107]. According to this study, mice with liver-specific knockout of Sirt1 are normal when maintained on a regular or calorie-restricted diet, and did not differ in any aspect, including gluconeogenesis, from their wild-type counterpart. On the other hand, when fed a high fat diet they had less body and liver fat, hypoglycemia, low insulin, and better glucose tolerance v. wild type. This contrasts with another study that shows that the same mice displayed an increase in hepatic lipids and a decrease in fatty acid oxidation [108].

Since glucose homeostasis is a concerted function of the whole body and not that of a single organ, it may be more relevant to examine the role of Sirt1 in a systemic fashion. There are two general Sirt1 transgenic models that were engineered for that purpose, one with a Sirt1 knock-in into the beta actin gene [98] and another Sirt1 bacterial artificial chromosome overexpressor (BACO) [28]. The first model is characterized by a leaner mouse that has lower levels of plasma fatty acids, leptin, and adiponectin, and improved glucose tolerance. Although the reduced levels of adiponectin here is hard to reconcile with its role in increasing insulin sensitivity [109]. The second model showed no difference in body weight, but conferred protection against type 2 diabetes during high fat intake and in the db/db mice due to increased hepatic insulin sensitivity, which may be an effect of hyperadiponectinemia secreted from white adipose tissue. Sirt1, plausibly via a decrease in acetyl-FoxO1 and an increase in adiponectin, also increased the levels of phospo-AMPK and PPARα. One major difference that could account for some of the discrepancies between the 2 models is the lack of an increase in hepatic Sirt1 in the first model. In agreement with these models, injecting mice with the Sirt1-specific activator SRT1720 reduced obesity and improved insulin sensitivity after being fed a high fat diet, with no change in gluconeogenesis [110].

Thus, while liver-specific knockout of Sirt1 improved insulin sensitivity in some reports, systemic overexpression of Sirt1 also had a similar effect, in seemingly inconsistent outcomes. Since glucose homeostasis is the net effect of its regulation by various organs, we may conclude that the systemic effects of Sirt1 may be a more faithful representation of its in vivo effect on glucose metabolism. In support, Sirt1 levels were lower than normal in humans exhibiting insulin resistance and metabolic syndrome, albeit that this study involved only 13 subjects [111]. Moreover, incubating human monocytes with high doses of glucose reduced Sirt1 and Nampt, and increased p53 [111]. The results also confirm the conservation of some of Sirt1's functionality between rodents and humans.

Sirt1 in lipid metabolism

Sirt1, like calorie restriction, functions to preserve body energy through increasing fatty acid oxidation. This effect is partly mediated through the deacetylation and activation of the transcriptional coactivator PGC-1α in skeletal muscle [112]. In addition to enhancing the

transcription of gluconeogenic genes, PGC-1α associates with PPARα and activates the transcription of genes involved in fatty acid oxidation [113]. Both Sirt1 transgenic models described above support a role for Sirt1 in promoting fatty acid oxidation. One model, where the body weight was normal when maintained on a regular diet, responded to food restriction by increasing fatty acid oxidation [98]. In the second model, the mice were leaner and exhibited lower circulating fatty acids, LDL, and HDL, in addition to higher O_2 consumption, plausibly also reflecting an increase in fatty acid oxidation [28]. More conclusively, specific activation of Sirt1 in vivo by SRT1720 results in an increase in fatty acid metabolism in the liver, muscle, and brown adipose tissue, with less accumulation of lipid in the liver and white adipose tissue [110]. This, however, was not associated with an increase in mitochondrial density or oxidative phosphorylation genes, but was associated with an increase in enzymes involved in fatty acid oxidation in all 3 organs. Notably, this phenotype was associated with reduced acetylation of the Sirt1 targets, PGC-1α, FoxO1, and p53. In addition, chronic treatment with SRT1720 resulted in activation of AMP-activated protein kinase AMPK, possibly as a result of reduced ATP levels [110].

Conversely, mice with a liver-specific deletion of Sirt1 exhibited lower fatty acid oxidation after fasting, while accumulating more lipid in the liver and white adipose tissue when fed a Western diet [108]. This was associated with reduced expression of genes involved in fatty acid oxidation. In addition, there was an increase in hepatic cholesterol due to a reduction in the enzymes that converts it into bile. In this model, PPARα, a known regulator of genes involved in fatty acid oxidation, was found to directly interact with Sirt1 in the liver, an association that was required for deacetylating its coactivator PGC-1α. Similarly, the $Sirt1^{+/-}$ mouse exhibited an increase in liver triglycerides, glycerol, cholesterol, and body fat, after a moderate fat diet, possibly as a result of increased lipogenesis [114]. Fatty acid oxidation remained unchanged under these conditions, but was unexamined during calorie restriction. In contrast to the above studies, another shows that $Sirt1^{-/-}$ mice have reduced plasma HDL-cholesterol and triglycerides when fed a normal diet, which has been attributed to Sirt1's requirement for the deacetylation and activation of the liver x receptor (LXR) that regulates both lipid and cholesterol homeostasis [115]. Overall, however, the consensus derived from these studies is that Sirt1 enhances fatty acid oxidation and reduces body fat.

Sirt6 in metabolism

Sirt1 is not the only sirtuin to regulate metabolism; it appears that nuclear Sirt6 is involved in mediating some of Sirt1's effects. Although $Sirt6^{-/-}$ mice have a phenotype that is mainly characterized by defects in the excision/repair system and genomic instability, it is also associated with extremely low levels of insulin-like growth factor-1 and serum glucose [116]. It was found that Sirt1/FoxO3a/nuclear respiratory factor 1 complex activates the expression of Sirt6 during caloric restriction. Sirt6 then through deacetylating H3K9, reduces the expression of genes involved in glycolysis and triglyceride synthesis, while increasing those required for fatty acid oxidation, as evidenced by a liver-specific knockout of Sirt6 [117]. This model also suffers from fatty liver. On the other hand, a transgenic mouse overexpressing Sirt6 has a phenotype that is reminiscent of Sirt1 transgenics when fed a high fat diet [118]. In specific, these mice accumulate less visceral fat, triglycerides, and LDL-cholesterol, in addition to improved glucose-induced insulin secretion and glucose tolerance. Thus, there appears to be redundancies in the functions of some sirtuin family members that may account for some of the variations observed between the different transgenic and knockout animal models.

Sirtuins in mitochondrial metabolism and biogenesis

From the discussion above it became evident that the nuclear sirtuins, Sirt1 and Sirt6, impact mitochondrial metabolism through upregulating the transcription of nuclear genes involved

in fatty acid oxidation via deacetylating and activating PGC-1α [112]. This protein has also been implicated in the biogenesis of mitochondria through inducing upregulation of mitochondrial transcription factor A [119]. Notably, though, a complementary role for PGC-1β is required for this process [120]. Although resveratrol [121], exercise [122], and calorie restriction [123] are associated with an increase in Sirt1 and mitochondrial biogenesis, it remains uncertain whether Sirt1 is sufficient or even required [124] for increasing mitochondrial biogenesis. On the other hand, Sirt1 may reduce mitochondrial numbers through a Bnip3-dependent protective mitophagy during calorie restriction, as seen in kidney cells [125].

In addition to the nuclear sirtuins, there are other family members that are localized to the mitochondria (Sirt3-5) that have been shown to directly regulate the activity of some of the genes involved in mitochondrial functions (Fig. 4). Sirt3 is characterized as a NAD^+-dependent histone deacetylase that is localized to the mitochondrial matrix [22, 126]. Mice deficient in Sirt3, but not Sirt4 or Sirt5, exhibited an increase in acetylated mitochondrial proteins, including glutamate dehydrogenase (GDH), but with no overt phenotype at basal or fasting conditions [23]. However, embryonic fibroblasts isolated from $Sirt3^{-/-}$ mice had a lower ATP content, which was attributed to the requirement of Sirt3 for the activation of Complex I through its interaction with, and deacetylation of, the NDUFA9 subunit [127]. Sirt3 also deacetylates and activates acyl-CoA synthetase 2, which catalyzes the synthesis of acetyl-CoA [128, 129].

Upon a closer look, it was noted that $Sirt3^{-/-}$ mice exhibited lower levels of fatty acid oxidation in the liver that was associated with reduced ATP and higher acetylated long-chain acyl-CoA synthetase levels [130]. In addition, the knockout mice exhibited a defect in the urea cycle due to hyperacetylation and deactivation of ornithine transcarbamoylase enzyme [131]. Ketogenesis was also impacted due to hyperacetylation and deactivation of the rate limiting mitochondrial 3-hydroxy-3methylglutaryl CoA synthase 2 [132]. In addition, Sirt3 deacetylates and activates manganese superoxide dismutase (MnSOD), thus, reducing mitochondrial superoxide, as evidenced by studies in the liver of $Sirt3^{-/-}$ mice[133, 134].

Calorie restriction induces Sirt3-dependent deacetylation of MnSOD as a means of reducing oxidative stress [134]. In contrast, high-fat diet results in downregulation of Sirt3 and hyperacetylation of liver mitochondrial protein [135]. Further reduction in Sirt3 levels by genomic deletion enhanced the development of obesity, insulin resistance, hyperlipidemia, and hepatic steatosis in these mice. This phenotype is partly attributed to an increase in stearoyl-CoA desaturase 1. There is evidence to suggest that Sirt3 may have a similar function in humans, where a single nucleotide polymorphism that reduced the activity of Sirt3 was found associated the metabolic syndrome [135].

While mitochondrial protein deacetylation is beneficial during calorie restriction and in metabolic syndrome, it should be noted that this effect might enhance hepatotoxicity by drugs that bind to lysine residues made accessible by deacetylation. Indeed, it was recently shown that fasting exacerbates, while Sirt3 knockout ameliorates, acetaminophine-induced liver injury in mice [136]. One of the major targets of Sirt3 deacetylase activity that seems responsible for this function is aldehyde dehydrogenase 2 (ALDH2), which is known to oxidize and, thereby, detoxify aldehydes including the acetaminophine metabolite *N*-acetyl-*p*-benzoquinoneimine. This is an example of why precaution should be exercised when considering the benefits of calorie restriction if combined with any drugs, even common analgesics.

As Sirt3 takes center stage in mitochondrial metabolism, little is known about the functions of mitochondrial Sirt4 and Sirt5. Unlike the rest of the family members, Sirt4 is mainly an

ADP-ribosyltransferase that is ubiquitously expressed. It ADP-ribosylates glutamate dehydrogenase (GDH), leading to its inhibition [137]. A Sirt4$^{-/-}$ mouse does not have any overt defects, but does exhibit an increase in GHD activity, but not protein, that is a result of a reduction in its ADP-ribosylation [137]. GDH is the enzyme involved in the reversible reaction involving synthesis of glutamate from ammonia and α-ketoglutarate. It was expected and subsequently proven that Sirt4 inhibits this function and, thus, indirectly inhibits amino acid-induced insulin release. Sirt5, on the other hand, regulates the urea cycle by deacetylating and activating carbamoyl phosphate synthetase 1 [138], which is the enzyme involved converting ammonia into carbamoyl phosphate. As a result, Sirt5$^{-/-}$ mice develop hyperammonemia during fasting or a high protein diet [138]. Notably, a recent finding shows that Sirt5 is also a NAD^{+}-dependent protein lysine demalonylase and desuccinylase, which in addition to deacetylating can desuccinylate carbamoyl phosphate [139].

Sirtuins in the heart

Sirtuins in myocardial ischemia and infarction

Sirt1, Sirt3, and Sirt7 have beneficial roles in the heart that can retard the damaging effects of aging and disease (Fig. 5). It was first noted that NAM-induced inhibition of Sirt1 in cardiac myocytes leads to p53-dependent programmed cell death and, conversely, forced expression of Sirt1 rescues the cells from starvation-induced apoptosis [140]. A role for Sirt1 in myocyte survival became evident during cardiac ischemia/reperfusion (I/R) when Sirt1 was downregulated, whereupon further reduction of the protein by cardiac-specific deletion led to aggravating the damage [141]. This function was confirmed with replenishment of Sirt1 by a cardiac-specific transgene, which reduced the size of the infarct and enhanced functional recovery. The effects of Sirt1 here are at least partly mediated through activation of FoxO1 and its downstream target, manganese superoxide dismutase. Similarly, Sirt1 reduced paraquat-induced oxidative stress in the heart [142] and mediated the cardioprotective effect of mIGF [143]. The role of Sirt1 in cardioprotection was further substantiated by data that showed that reconstituting Nampt levels in the heart during I/R restored NAD+ content and reduced injury [144].

Calorie restriction and sirtuins in the heart

Several reports show that calorie restriction can confer cardioprotection during aging, myocardial ischemia, or hypertrophy [145–148], however, the exact mechanism has not been fully elucidated. Although, we have learned that sirtuins play a major role in mediating the beneficial metabolic effects of calorie restriction, there is limited direct evidence that they mediate its cardioprotective effects. For example, one study shows that long-term calorie restriction, which is associated with increased Sirt1 and reduced H3 acetylation, reduced infarct size and improved recovery after I/R in a Sirt1-dependent fashion [149]. Another reports that caloric restriction protected the mitochondria from I/R-induced reduction in respiration, which was associated with increased deacetylation of mitochondrial proteins, including the Sirt3 substrate NDUFS1 [150]. More recently, it was reported that ischemia preconditioning shares a common feature with caloric restriction in the form of a reduction in acetylated proteins and enhanced Sirt1 activity/expression in the heart [77, 151].

Calorie restriction activates AMPK, which, like Sirt1, mediates some of its metabolic effects [152]. On the other hand, AMPK activates Sirt1, which has also been shown to mediate its effects [153]. Like calorie restriction, AMPK and Sirt1 have been independently shown to have cardioprotective effects. Thus, we may extrapolate from this that the cardioprotective effects of calorie restriction are at least in part mediated by AMPK via Sirt1.

Sirtuins in cardiac hypertrophy

Sirt1 exerts anti-hypertrophic effects in the heart, as it reduces aging-related cardiac hypertrophy, fibrosis, and contractile dysfunction, in cardiac-specific Sirt1 transgenic mice expressing 2.5–7.5 fold higher levels of Sirt1 [142]. Also, forced expression of Sirt1 in cardiac myocytes inhibits endothelin-1 [80] and phenylephrine-induced cardiac hypertrophy [154]. This is mediated in part by deacetylation and degradation of the histone variant H2A.z [80] and the deacetylation and activation of peroxisome proliferator-activated receptor-α (PPARα) [154]. It should be noted, that Sirt1 increases during pressure overload-induced hypertrophy up to 4–8 fold, possibly as an adaptive mechanism, which, in addition to curbing hypertrophy, reduces myocyte apoptosis [80, 155]. In contrast, however, 12.5-fold higher Sirt1 in the heart exacerbates age-induced cardiac hypertrophy and dysfunction [142]. In concordance with this latter observation, $Sirt1^{+/-}$ mice reduced the extent of pressure overload-induced hypertrophy and normalized ejection fraction [156]. This effect of Sirt1 was mediated through its interaction with PPARα, as the complex inhibited targets of estrogen-related receptor, which include genes regulating mitochondrial metabolism and cardiac contraction [156]. Thus, it would appear that moderate levels of Sirt1 that accumulate during the early stage of hypertrophy exert an anti-hypertrophic effect, but a spike in Sirt1 concentration during the later stages of hypertrophy and failure contributes to cardiac dysfunction.

In contrast to nuclear Sirt1 and Sirt6, little is known about the third nuclear family member Sirt7, apart from the fact that it associates with rDNA and RNA polymerase I and enhances transcription of ribosomal RNA [157]. In the heart, deletion of Sirt7 in mice induced cardiac hypertrophy and inflammation, and reduced life span [158]. Similar to Sirt1, Sirt7 deacetylates and inactivates p53 as a plausible mechanism for the observed phenotype. Mitochondrial Sirt3 also plays a role in the development of cardiac hypertrophy. $Sirt3^{-/-}$ mice exhibit exaggerated cardiac hypertrophy after transverse aortic banding [159, 160], as well as accelerated age-related cardiac hypertrophy and fibrosis that is manifest at 13 months of age [160]. Conversely, overexpression of Sirt3 attenuated angiotensin II- and isoproterenol-induced hypertrophy [160]. The mechanisms underlying its function involves the inhibition of mitochondrial permeability transition pore (mPTP) opening, since it was noted that the $Sirt3^{-/-}$ mouse is associated with hyperacetylation of cyclophilin D and mitochondrial swelling [160], in addition to deacetylation and activation of FoxO3a and its downstream targets, manganese superoxide dismutase and catalase [159]. Thus, both nuclear Sirt1 and Sirt7, and mitochondrial Sirt3 all have anti-hypertrophic functions, albeit through different mechanisms. Additionally, Sirt1 also exhibits pro-hypertrophic functions that may be dependent on a higher dosage.

Situins in the vascular system

Steady laminar flow, such as that observed in the thoracic aorta, is responsible for higher levels of Sirt1 in the endothelial lining, which account for lower levels of acetylated eNos through a direct association and deacetylation reaction [161]. This leads to activation of eNos, which promotes vasodilatation [162] and alleviates vasoconstriction after a high fat diet [163]. In contrast, oscillatory flow such as that seen in the atherosclerotic prone aortic arch, does not induce an increase in Sirt1, but does increase the expression of PARP-1 [161]. As discussed above, PARP-1 is a NAD^+ consumer that could deplete the substrate pool and reduce Sirt1's activity, which could promote atherogenesis, as described below. It should be noted though, that the effect of Sirt1 on vascular tone was challenged by another study, in which no significant differences were detected in vascular relaxation between $ApoE^{-/-}/SIRT1^{+/-}$ and $ApoE^{-/-}/SIRT1^{+/+}$ mice [164].

Sirt1 is also required for the budding and migration of endothelial cells, as well as, ischemia-induced neovascularization after hind limb ischemia [165]. This function appears to be

mediated through its interaction with FoxO1 and the regulation of an array of genes that are involved in vascular growth including fms-related tyrosine kinase 1, chemokine (C-X-C motif) receptor 4, platelet-derived growth factor receptor β, angiopoietin- like 2, matrix metallopeptidase 14, and EPH receptor B2. More recently, it was discovered that Sirt1 regulates endothelial cell budding via deacetylating Notch's intracellular domain [166]. Sirt1 also promotes the longevity of endothelial cells, as Nampt, which is the rate-limiting enzyme in the conversion of NAM to NAD^+, was shown to retard senescence that is precipitated by high glucose levels via activation of Sirt1 [167]. Conversely, in senescent endothelial cells, miR-34a [168] and miR-217 [70] are upregulated, both of which directly target and suppress the expression of Sirt1 mRNA. Moreover, overexpression of either miRNA accelerated senescence and reduced angiogenesis via suppressing Sirt1 and increasing acetylated FoxO1.

There have been conflicting reports on the role of Sirt1 in atherogenesis. Some studies suggest that Sirt1 has an anti-atherogenic effect since it is reduced in human [70] and in $ApoE^{-/-}$ mice [163] atherosclerotic plaques. Its anti-atherogenic effect may be partly mediated via inhibiting NFκB signaling in endothelial cells and reducing inflammation [164]. Additionally, Sirt1 has been shown to reduce neointimal hyperplasia via inhibiting vascular smooth muscle proliferation and migration [169]. A contrasting study, however, shows that Sirt1-overexpressing mice have higher levels of triglycerides and cholesterol, and accordingly larger atherosclerotic plaques [170]. It is plausible that the extent of Sirt1 overexpression dictates the nature of its effects, as was observed in the heart, where higher levels of the overexpressed Sirt1 had an adverse effect. Thus, it remains to be seen if precise normalization of endogenous Sirt1 levels during atherogenesis would affect the outcome.

Sirtuins in the central nervous system

As discussed earlier, sirtuins regulate metabolism through their local effects in the liver, pancreas, skeletal muscle, and adipose tissue. However, they also have the capacity to centrally regulate metabolism via regulating functions in the pituitary gland and hypothalamus. It was found that deletion of Sirt1 in neurons, astrocytes and glial cells resulted in dwarfism, associated with smaller pituitary gland / body weight ratio that produced lower levels of growth hormone, in addition to glucose intolerance that was manifest in older mice only [171]. More significantly, calorie restriction-enhanced insulin sensitivity and physical activity were abolished in these mice, suggesting that the beneficial effects of calorie restriction are mainly regulated by the central activity of Sirt1 in the brain. In specific, it was discovered that chronic diet restriction induces upregulation of Sirt1 in the dorsomedial and lateral hypothalamic nuclei and increases their activity, as well as increase thermogenesis and physical activity [172]. Gain- and loss-of-Sirt1 function in vivo proved that under these conditions Sirt1 induces the expression of orexin type 2 receptor in the dorsomedial and lateral hypothalamic nuclei, which in-turn increases their sensitivity to the stomach-released hormone gherlin. However, it isn't clear how this phenotype reconciles with the known role of gherlin in increasing food intake. Gherlin, which is involved in various eating disorders, also regulates appetite and food intake via inhibiting the activity of proopiomelanocortin (POMC) neurons in the hypothalamic arcuate nuclei (reviewed in [173]). These neurons secret α-melanocyte stimulating hormone, which suppresses appetite and increases thermogenesis. Sirt1 is also expressed in POMC neurons, where its deletion results in a significant increase in body weight (females more than males) versus wild type when the mice are maintained on high fat diet [174]. The main cause of obesity in these Sirt1 mutant mice appears to be a result of reduced O_2 consumption and thermogenesis, which ensued before weight gain. It is important to note that food intake, ambulation, and energy source, were unchanged in these mice. The phenotype may be attributed to noted defects in leptin signaling or reduced sympathetic nerve activity in the perigonadal white adipose tissue. This

contrasts with the phenotype of a mouse in which Sirt1 was deleted in Agrp neurons [175]. In this model, the Agrp neurons, which stimulate PMOC, were less sensitive to gherlin, resulting in reduced food intake and reduced body fat. Thus, Sirt1 has neuron-specific functions, however, the outcome of its combined effects in the brain may be best gauged in the model in which Sirt1 was deleted in all neurons [171].

Sirt1's function in the brain extends beyond the regulation of metabolism through the hypothalamus. Recent studies suggest that it plays a role in cognition [176, 177] via regulating miR-134 [177]. MiR-134 is a brain-restricted miRNA, increasing gradually in the hippocampus where it plateaus at P13 after synaptic maturation and then becomes localized to dendrites near synaptic sites [178]. Overexpressing it in hippocampal cells decreases the volume of dendritic spines and vice versa, an effect that is mediated by Lim domain-containing kinase-1 (LIMK-1). In agreement, a knockout model of this protein exhibits a similar phenotype [179]. The dendritic spines are known to increase in size during synaptic excitation and, thereby, establish sites of synaptic contact. It was recently found that a Sirt1-YY1 complex suppresses miR-134 [177]. In this study, miR-134 was shown to suppress the expression of cAMP responsive element binding protein (CREB) and brain-derived neurotrophic factor (BDNF). In accordance, knockout of Sirt1 in the brain reduced synaptic plasticity and impaired memory in mice [176, 177]. Another characteristic of advanced age that is regulated by Sirt1 includes reduced wakefulness [180]. Accordingly, Sirt1-deficient mice exhibit reduced spontaneous wake time that is associated with reduced wake-active neuron neurotransmitters or the rate limiting enzymes that are involved in their synthesis.

A protective effect of Sirt1 against neurodegeneration was first recognized upon discovering that the protein Wld^S, which is a fusion between ubiquitin assembly protein Ufd2a and Nmnat1, confers a delay of axonal degeneration in the Wallerian degeneration slow mice [181]. In addition, Sirt1-induced α-secretase activity and reduction of Aβ peptides in cultured neurons from a mouse model of amyloid neuropathy, suggested that it might have a beneficial effect in Alzheimer's disease (AD) [182]. This was indeed confirmed in vivo in a mouse model of AD, in which injection of a Sirt1-expressing vector into the hippocampus, ameliorated neuronal degeneration [183]. Likewise, overexpressing of Sirt1 in the brain reduced β-amyloid plaque formation in an AD mouse model by enhancing the expression of α-secretase gene (ADAM10) via deacetylating and activating its regulator, the retinoic acid receptor [184]. Thus, increasing Sirt1 in the brain can potentially retard some of the aging-related pathologies.

Concluding remarks

Overall, the experimental evidence is quite compelling regarding the beneficial effects of sirtuins on metabolic homeostasis in both rodents and humans. This is particularly evident during calorie restriction, which elicits upregulation of Sirt1 and Sirt3. Sirt1 exerts its effects on metabolism both locally in the liver, pancreas, skeletal muscle, and adipose tissue, and centrally through regulating functions of the pituitary gland and hypothalamus. The results of Sirt1 knockout in the mouse brain, would argue that the effects of calorie restriction are mainly governed by neuronal Sirt1. Since neurons are deficient in Nampt, neuronal Sirt1 activity is expected to be sensitive to circulating levels of eNampt and NMN, and thereby, the general metabolic status of the whole body. The findings to-date show that the mechanisms underlying the metabolic effects of Sirt1 are mainly mediated through regulating the activity of several key nuclear transcription factors involved in the transcription of metabolic genes via its deacetylase activity. An equally critical and complementary role for Sirt3 in metabolism has also been described, which involves direct regulation of mitochondrial enzymes via its deacetylase activity. One should recall, though, that sirtuins are also histone deacetylases, with the potential for inducing heterochromatin

formation and gene silencing. Until know we have little if any knowledge of whether this mechanism plays a major role are during calorie restriction in mammalian cells. Current state-of-the-art technologies, including high resolution profiling of histone modifications and chromatin remodeling, can be expected to help address this question.

The effects of Sirt1, in particular, extend beyond metabolism in various organs and cell types. For example, in the heart it protects it against ischemia/reperfusion damage, potentially by preventing p53-mediated apoptosis, although an equally beneficial metabolic effect as well has not been ruled out. Additionally, during cardiac hypertrophy and failure, Sirt1 regulates the transcription of contractile proteins, as well as, transcriptional regulators of metabolism. Sirt1 also impacts the vasculature, as it regulates vascular tone via deacetylating eNos and enhances endothelial cell migration and budding, while inhibiting smooth muscle cell proliferation. These are just a few examples that were described in this review, but the array of its functionality in other organs and cell types is vast and includes both metabolic and non-metabolic roles. However, since the activity of sirtuins is closely linked to the metabolic status of the body through the availability of NAD^+, the function of this NAD^+-dependent deacetylase family during metabolism remains a central focus.

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List of non-standard abbreviations

NAD^+	nicotinamide adenine dinucleotide
Sirt	sirtuin
PARP	poly-ADP-ribose polymerases
NAM	nictinamide
ADP	adenosine diphosphate
MNM	nicotinamide mononucleotide
Nampt	phosphoribosyl transferase
eNampt	extracellular Nampt
FoxO	forkhead box O
PPAR	peroxisome proliferator-activated receptor
PGC-1α	peroxisome proliferative activated receptor, gamma, coactivator 1 alpha
I/R	ischemia/reperfusion

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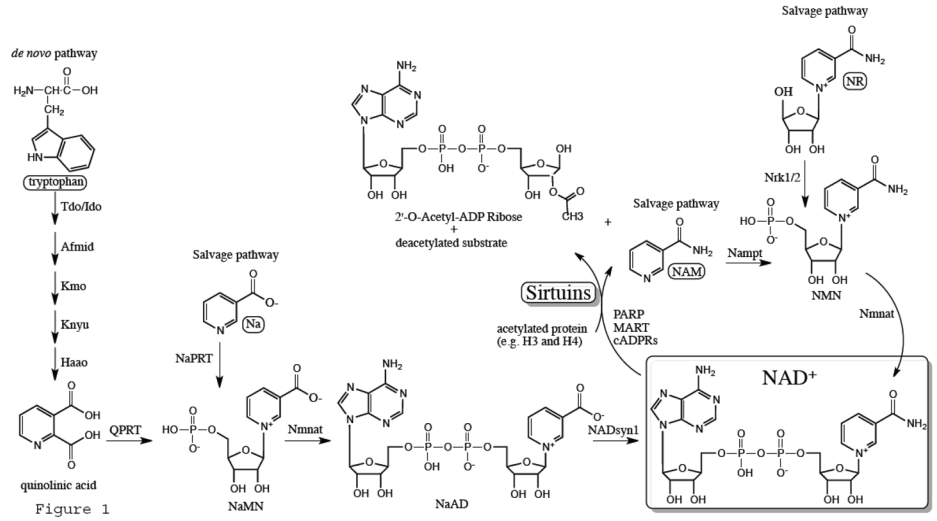

Figure 1.

An illustration of the reactions involved in NAD^+ biosynthesis and its consumption by sirtuins. Abbreviation include: mono-ADP-ribose transferases (MART), poly-ADP-ribose polymerases (PARP), cyclic-ADP-ribose synthases (cADP), nicotinamide (NAM), indolamine 2,3-dioxygenase (Ido), kynurenine formamidase (Afmid), kynurenine 3-hydroxylase (Kmo), kynureninase (Knyu), 3-hydroxyanthranilate 3,4-dioxygenase (Haao), nicotinate mononucleotide (NaMN), nictoniate adenine dinucleotide (NaAD), nicotinamide mononucleotide adenylyl transferase (Nmnat), nicotinamide mononucleotide (NMN), phosphoribosyl transferase (NAMPT), nicotinic acid (Na), Na phosphoribosyltransferase (NaPRT), nicotinamide ribosde (NR), nicotinamide riboside kinase (Nrk).

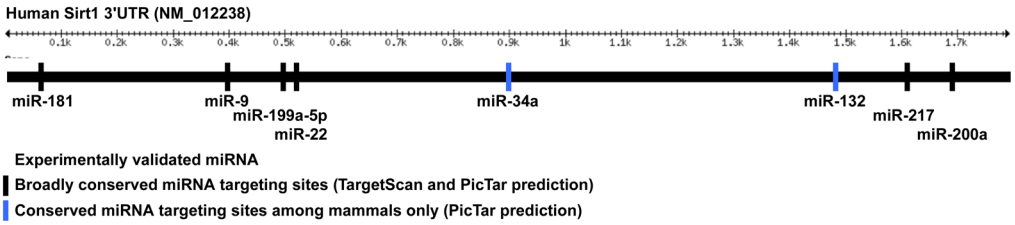

Figure 2.

MicroRNAs that target the 3'UTR of Sirt1. The illustration shows the various miRNAs that are predicted by TargetSan and PicTar applications that target Sirt1 through broadly conserved (black bars) or conserved (excludes chicken, blue bars) sites in its 3'UTR. The ones listed are only those that have been experimentally validated.

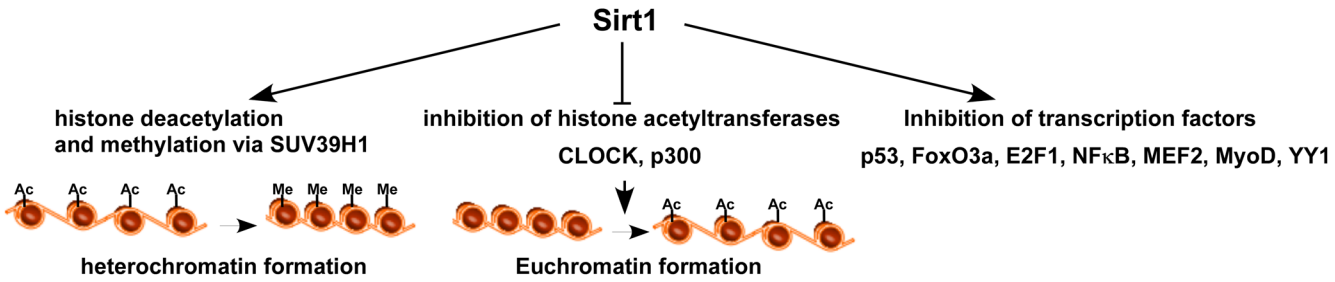

Figure 3.

Modes of transcriptional regulation by Sirt1. Sirt1 regulates transcription via 3 different mechanisms. The first involves histone deacetylation and heterochromatin formation, which results in gene silencing. This is complemented with a hypermethylation effect that is mediated by suppressor of variegation 3–9 homolog 1 (SUV39H1) methylase. The second involves inhibition of histone acetylases p300 and CLOCK, that also contributes to chromatin condensation. The third involves the deacetylation and inhibition or activation of specific transcription factors that include: p53, forkhead box O3a (FoxO3a), E2F transcription factor 1 (E2F), nuclear factor of kappa light polypeptide gene enhancer in B-cells (NFκB), myocyte enhancer factor 2 (MEF2), myogenic differentiation (MyoD), and ying yang 1 (YY1).

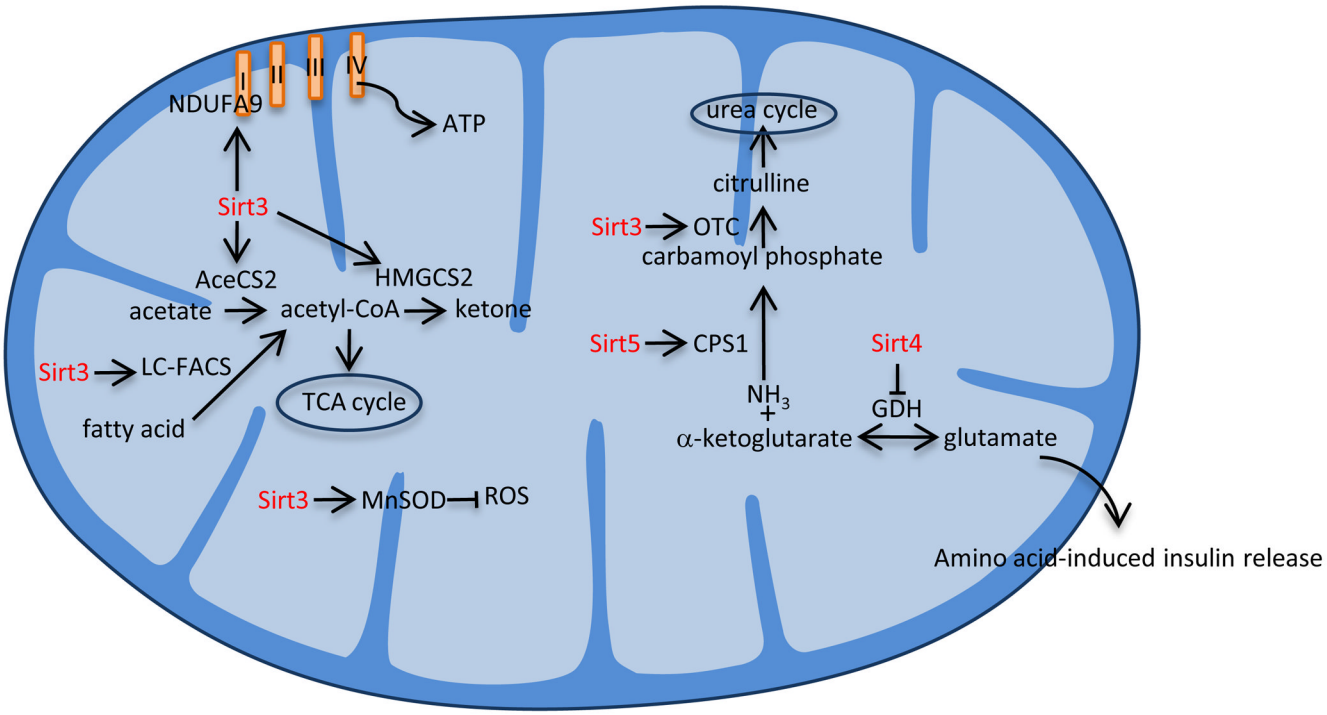

Figure 4.

Mitochondrial function of sirtuins. Sirt3 deacetylates and activates acetyl-CoA synthetase 2 (AceCS2) and long chain fatty acyl-CoA (LC-FACS), which convert acetate and fatty acid, respectively, into acetyl-CoA. It also activates 3-hydroxy-3methylglutaryl CoA synthase 2 (HMGCS2), which is involved in ketogenesis; ornithine transcarbamoylase (OTC), which is involved in the urea cycle; manganese superoxide dismutase (MnSOD), which inhibits reactive oxygen species (ROS) production; and NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 9 (NDUFA9), which a subunit of complex I in the electron transport chain. Sirt4 inhibits glutamate dehydrogenase (GDH), which is involved in the synthesis of glutamate and amino acid-induced insulin release, while Sirt5 is also involved in the urea cycle through activating carbamoyl-phosphate synthase 1 (CPS1).

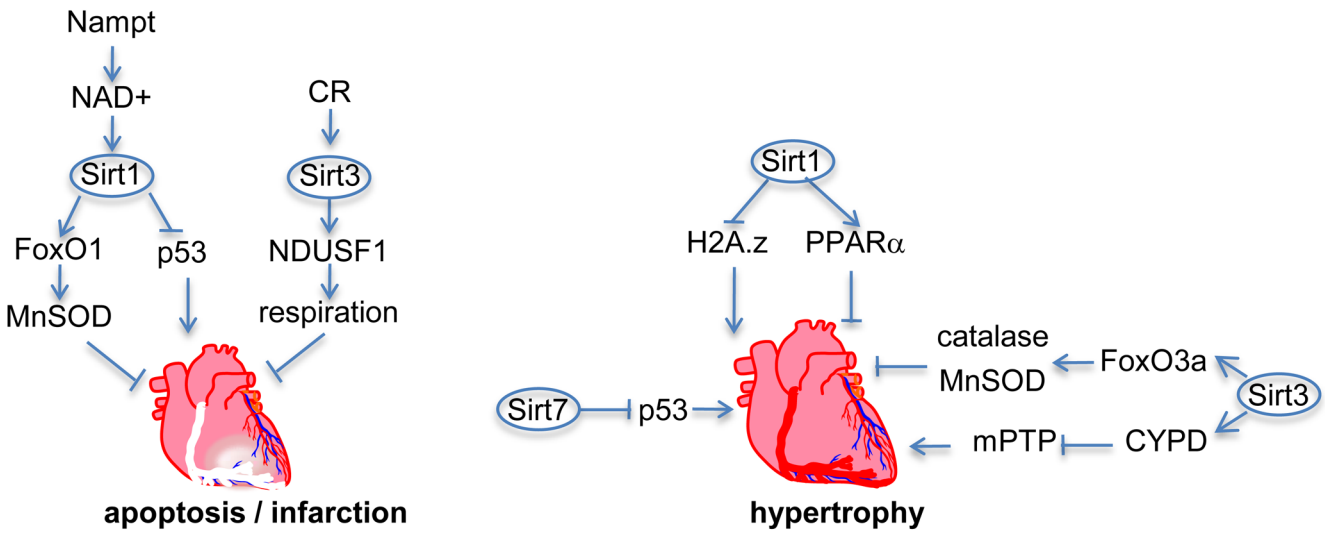

Figure 5.

Sirtuins inhibit cardiac ischemic injury and hypertrophy. Overexpression of phosphoribosyl transferase (NAMPT) in the heart increases NAD+ biosynthesis through the salvage pathway, which activates Sirt1. Sirt1 through inhibition of p53 and activation of forkhead O1 (FoxO1) and its downstream target manganese superoxide dismutase (MnSOD) reduces infarct size after ischemia/reperfusion. On the other hand, calories restriction (CR) activates Sirt3, which protects the heart through activation of the mitochondrial protein NADH dehydrogenase (ubiquinone) Fe-S protein 1 (NDUSF1), a subunit of complex I in the electron transport chain. Sirt1 inhibits hypertrophy by deacetylating and inducing degradation of histone 2A.z (H2A.z), as well as activating peroxisome proliferator-activated receptor alpha (PPARα). Sirt3 inhibits hypertrophy via activating forkhead O3a (FoxO3a) and cyclophilin D (CYPD), which inhibit the mitochondrial permeability transition pore (mPTP). Sirt 7 inhibits hypertrophy via deacetylating and inhibiting p53.