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The Role of Mammalian Sirtuins in the Regulation of Metabolism, Aging, and Longevity

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Abstract

Ever since the discovery of sirtuins a decade ago, interest in this family of NAD-dependent deacetylases has exploded, generating multiple lines of evidence implicating sirtuins as evolutionarily conserved regulators of lifespan. In mammals, it has been established that sirtuins regulate physiological responses to metabolism and stress, two key factors that affect the process of aging. Further investigation into the intimate connection among sirtuins, metabolism, and aging has implicated the activation of SIRT1 as both preventative and therapeutic measures against multiple age-associated disorders including type 2 diabetes and Alzheimer's disease. SIRT1 activation has clear potential to not only prevent age-associated diseases but also to extend healthspan and perhaps lifespan. Sirtuin activating compounds and NAD intermediates are two promising ways to achieve these elusive goals.

Keywords

Age-associated disorders; Aging; Lifespan; NAD intermediates; NAD world; Nicotinamide adenine dinucleotide; Nicotinamide mononucleotide; SIRT1; Sirtuins; Sirtuin activating compounds

1 Introduction

The *s*ilent *i*nformation *r*egulator *2*(SIR2) family of proteins, also called sirtuins, are evolutionarily conserved nicotinamide adenine dinucleotide (NAD)-dependent protein deacetylases/ADP-ribosyltransferases. Now classified as class III histone deacetylases (HDACs), the founder *SIR2* gene was originally identified as one of the genes that regulate the mating types of budding yeast, *Saccharomyces cerevisiae* (Klar and Fogel 1979). The biochemical function of SIR2 proteins had been a mystery for 20 years when the *Salmonella typhimurium* SIR2-like protein, CobB, was found to catalyze the reaction in the late step of cobalamin biosynthesis, transferring phosphoribose from nicotinic acid mononucleotide to dimethylbenzimidazole (Tsang and Escalante-Semerena 1998). This first important clue for the enzymatic activity of SIR2 proteins suggested that they might catalyze a related pyridine nucleotide transfer reaction. Indeed, both bacterial and mammalian SIR2 proteins were reported to transfer ^{32}P from [^{32}P]NAD to bovine serum albumin (Frye 1999). Subsequently, it was proposed that the ADP-ribosyltransferase activity of SIR2 was essential for gene silencing in budding yeast (Tanny et al. 1999). Furthermore, it was found

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that acetylated amino-terminal tails of histone H3 or H4 could specifically accept ^{32}P from [^{32}P]NAD in the reactions mediated by recombinant yeast and mammalian SIR2 proteins (Imai et al. 2000). Surprisingly, analysis of the reaction products by mass spectrometry revealed that SIR2 proteins across evolution could specifically deacetylate lysine 16 of H4 in an NAD-dependent manner, strongly indicating that this novel and unique deacetylase activity of SIR2 proteins plays a critical role in establishing silenced chromatin structures in vivo (Imai et al. 2000). The absolute requirement of NAD for the SIR2 deacetylase activity suggested that SIR2 and its closely related homologs function as sensors of the cellular energy status represented by NAD. Following this breakthrough, reports appeared showing that both SIR2 and a yeast SIR2 homolog, HST2, catalyze the NAD-nicotinamide exchange reaction and NAD-dependent deacetylation (Landry et al. 2000; Smith et al. 2000).

Further studies have demonstrated that sirtuins play an important role in the regulation of lifespan. For example, in yeast, an extra copy of the *SIR2* gene increases replicative lifespan up to 30%, while its deletion or mutation shortens lifespan to ~50% (Kaeberlein et al. 1999). In *C. elegans*, increasing the dosage of *sir-2.1*, the ortholog of yeast SIR2, extends lifespan by up to 50% (Tissenbaum and Guarente 2001). An increase in the dosage of *Drosophila Sir2* (*dSir2*) also extends lifespan, whereas a decrease in the dosage of *dSir2* shortens lifespan and blocks the lifespan extension by caloric restriction (CR) (Rogina and Helfand 2004). CR extends lifespan in diverse organisms, from yeast (Lin et al. 2000), worms (Lakowski and Hekimi 1998), and flies (Chapman and Partridge 1996) to rodents (McCay et al. 1989; Weindruch and Walford 1982) and primates (Colman et al. 2009). In certain genetic backgrounds, sirtuins are also required for CR-induced lifespan extension (Anderson et al. 2003; Boily et al. 2008; Lin et al. 2000, 2002; Rogina and Helfand 2004; Wang and Tissenbaum 2006). Collectively, these findings implicate sirtuins as evolutionary conserved regulators of lifespan. In mammals, it has been established that sirtuins regulate metabolic and stress responses, two important components that affect the process of aging. In this chapter, we will focus on the metabolic functions of mammalian sirtuins as well as mechanisms regulating their activity. We will further discuss the potential connections among sirtuin biology, age-associated diseases, and the aging process, and finally introduce the manipulation of sirtuin function as a pharmacological approach to remedy and prevent age-associated pathophysiological changes.

2 The Catalytic Reaction of Sirtuins

The principal factor distinguishing sirtuins from other HDACs is that sirtuins require the cosubstrate NAD to perform their lysine deacetylase reaction (Fig. 1) (Imai et al. 2000; Landry et al. 2000; Smith et al. 2000). In addition to this dependency on NAD, sirtuin activity can be pharmacologically separated from that of other HDACs by their insensitivity to a potent HDAC inhibitor, Trichostatin A (Dali-Youcef et al. 2007). All sirtuin family members contain a highly conserved, 250- to 270-residue catalytic domain consisting of a large domain containing a reverse Rossmann fold and a smaller domain composed of a zinc ribbon and a flexible helical subdomain (Finnin et al. 2001; Min et al. 2001). The cleft between these two domains forms a tunnel lined with hydrophobic residues in which catalysis occurs. The Rossmann fold contains a Gly–X–Gly sequence important for binding of the phosphate of NAD as well as a small pocket and charged residues to bind the two ribose groups of NAD. The zinc ribbon is composed of a three-stranded antiparallel β sheet, an α helix, and a zinc atom bound and stabilized by two pairs of cysteine residues. To commence catalysis, sirtuins require both the acetylated lysine substrate and NAD to respectively bind the cleft and the Rossmann fold, forming a ternary complex (Borra et al. 2005). Substrate binding triggers a conformational change that buries the acetyl-lysine of the substrate in the hydrophobic tunnel (Avalos et al. 2002). This conformational change also forms an enzyme-substrate β sheet as well as generates a charge destabilization that

promotes productive binding of NAD (Avalos et al. 2002, 2004). Subsequent to these events, sirtuins cleave the glycosidic bond separating nicotinamide and ribose moieties of NAD, forming nicotinamide and an enzyme–ADP–ribose intermediate (Landry et al. 2000). Sirtuins then transfer the acetyl group from the acetylated substrate to the ADP–ribose portion of NAD, generating 2′-*O*-acetyl-ADP-ribose (Borra et al. 2005; Zhao et al. 2004). Next, nicotinamide is released, followed by the 2′-*O*-acetyl-ADP-ribose and the deacetylated lysine.

In contrast to the high degree of structural conservation across family members in this catalytic domain (Finnin et al. 2001; Min et al. 2001), the N- and C-terminal regions flanking it are highly divergent (Zhao et al. 2003). Interestingly, the X-ray crystal structure of a yeast sirtuin family member, HST2, provides evidence for the involvement of the N- and C-terminal regions in catalysis, potentially indicating that the sequence divergence in the regions among family members may play a role in their substrate binding differences and/or biological activities. The number of sirtuin family members tends to increase with organismal complexity (except for budding yeast having five): prokaryotes express one to two family members, fission yeast expresses three, worms express four, flies express five, and mammals express seven (Blander and Guarente 2004). The seven mammalian family members, SIRT1 through SIRT7, have slightly different enzymatic activities, localizations, and functions (Table 1). Among them, all except SIRT4 exhibit deacetylase activity (Imai and Guarente 2010). For SIRT4, only ADP-ribosyltransferase activity has been reported (Imai and Guarente 2010). SIRT1 and SIRT2 can be cytoplasmic or nuclear proteins, while SIRT3, SIRT4, and SIRT5 are localized to the mitochondria, and SIRT6 and SIRT7 reside in the nucleus or nucleolus, respectively (Finkel et al. 2009; Imai and Guarente 2010). Of these seven members, SIRT1 is the ortholog of yeast SIR2 (Finkel et al. 2009), and its function has been characterized most extensively. Therefore, the following sections will mainly focus on SIRT1 function.

3 Metabolic Regulations by Mammalian Sirtuins

Numerous studies now show an intricate connection exists between metabolism and aging (Conti et al. 2006; Hakimi et al. 2007; Harrison et al. 2009; Pawlikowska et al. 2009; Selman et al. 2009; Tatar et al. 2003). It has been well established that mammalian sirtuins regulate metabolic responses to nutritional input in multiple tissues/organs. In this section, we will outline the functions of SIRT1 in the liver, skeletal muscle, adipose tissue, pancreatic β-cells, and hypothalamus (Fig. 2).

3.1 Liver

The liver plays an important role in the regulation of glycolysis, gluconeogenesis, and lipid metabolism, such as fatty acid oxidation. Under nutrient deprivation, gluconeogenesis increases while glycolysis decreases in the liver in order to maintain plasma glucose levels. Meanwhile, fatty acid oxidation is enhanced in response to pancreatic glucagon and adrenal cortisol, promoting gluconeogenesis (Bhathena 2000; McGarry and Foster 1980). The liver also plays a vital role in the excretion of ammonia through the urea cycle (Haussinger 1990).

SIRT1 is important for the positive regulation of gluconeogenesis and fatty acid oxidation under nutrient deprivation. In the case of gluconeogenesis, SIRT1 deacetylates and activates peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) (Rodgers et al. 2005), stimulating hepatic gluconeogenic gene expression while inhibiting glycolytic genes, as well as multiple targets including CREB-regulated transcription coactivator 2 (CRTC2, also known as TORC2), forkhead transcription factor O1 (FOXO1), and signal transducer and activator of transcription 3 (STAT3) (Frescas et al. 2005; Liu et al. 2008b; Nie et al. 2009). To up-regulate fatty acid oxidation, SIRT1 deacetylates PGC-1α, promoting an

interaction between SIRT1 and peroxisome proliferator-activated receptor α (PPARα). This complex transcriptionally induces PPARα target genes, which in turn enhances fatty acid oxidation (Purushotham et al. 2009).

It has also been reported that SIRT1 positively regulates the function of liver X receptor α (LXRα), a nuclear receptor that functions as cholesterol sensor and regulates cholesterol and lipid homeostasis (Zelcer and Tontonoz 2006). SIRT1 interacts with and deacetylates LXRα, activating the transcription of the LXRα target gene ABCA1, a transporter that mediates HDL synthesis and HDL-mediated reverse cholesterol transport (RCT) (Li et al. 2007). Consistent with this finding, *Sirt1*-deficient mice display lower levels of HDL cholesterol in plasma and accumulate hepatic cholesterol (Li et al. 2007). However, total plasma cholesterol levels are reduced in both *Sirt1*-deficient mice (Li et al. 2007) and *Sirt1*-overexpressing transgenic mice (Bordone et al. 2007). Thus, further study is required to fully understand the function of SIRT1 in cholesterol homeostasis.

Similar to SIRT1, two other sirtuin family members, SIRT5 and SIRT6, also play important roles in metabolic regulation in the liver. SIRT5 regulates urea cycle by deacetylating carbamoyl phosphate synthase1 (CPS1), an enzyme that catalyzes the initial step of the urea cycle for ammonia detoxification and disposal, and up-regulating its activity (Nakagawa et al. 2009; Schapira 2011). On the other hand, SIRT6 down-regulates glycolysis by interacting with and deacetylating/inactivating hypoxia-inducible factor-1α (HIF1α), a transcription factor that modulates multiple genes to activate glycolysis (Zhong et al. 2010; Mahajan et al. 2011). The evidence that liver-specific *Sirt6*-deficient mice results in hepatic steatosis suggests that increasing SIRT6 activity in the liver would, at least in part, prevent the liver dysfunction caused by hepatic steatosis (Kim et al. 2010).

3.2 Skeletal Muscle

In skeletal muscle, mitochondrial fatty acid oxidation is vital for preserving glycogen stores and blood glucose levels upon nutrient deprivation and after exercise. SIRT1 enhances mitochondrial fatty acid oxidation by binding to and deacetylating PGC-1α, which increases its activity on its promoter through an interaction with myogenic determining factor (MyoD) (Amat et al. 2009; Canto et al. 2010). Given that dysregulation of skeletal muscle fatty acid oxidation is associated with insulin resistance and obesity (Kelley et al. 1999; Newgard et al. 2009), SIRT1 might also improve the insulin sensitivity of skeletal muscle. Indeed, in myotube cells, SIRT1 also inhibits the transcription of protein tyrosine phosphatase 1B (PTP1B). PTP1B dephosphorylates the insulin receptor and negatively regulates insulin signaling (Sun et al. 2007). In fact, *Ptp1b*-deficient mice display higher susceptibility to insulin when fed a high-fat diet (HFD) and resistance to diet-induced obesity (Elchebly et al. 1999). Moreover, a decrease in SIRT1 protein levels in the gastrocnemius muscle under HFD is accompanied by an increase in PTP1B levels (Sun et al. 2007). On the other hand, during fasting, SIRT1 protein levels increase while PTP1B protein levels decrease (Sun et al. 2007). Together, these findings suggest that SIRT1 plays an important role in the maintenance of skeletal muscle insulin sensitivity.

3.3 Adipose Tissue

A primary function of white adipose tissue (WAT) is to produce and store fatty acids as an energy reserve to allow their mobilization into the blood upon nutrient deprivation. WAT also plays an important role as an endocrine organ for adipokines, including leptin, adiponectin, and tumor necrosis factor-α (TNF-α) that modulate insulin resistance, hepatic lipoprotein production, and vascular inflammation (Mohamed-Ali et al. 1998).

SIRT1 can enhance fatty acid mobilization from WAT. Upon fasting, SIRT1 is recruited by PPARγ to DNA-binding sites in the aP2 promoter, promoting adipogenesis and fat storage (Lehrke and Lazar 2005). SIRT1 binds to PPARγ and represses the transcriptional activation of PPARγ by binding to nuclear receptor coreceptor/silencing mediator of retinoid and thyroid hormone receptor (NCoR/SMRT) complex, resulting in the reduction of fat accumulation in WAT and higher level of free fatty acids in blood (Picard et al. 2004).

On the other hand, whether or not SIRT1 regulates adipokine secretion from WAT is still debatable. Whole-body bacterial artificial chromosome (BAC)-driven *Sirt1*-overexpressing transgenic mice have increased levels of plasma adiponectin (Banks et al. 2008). Adiponectin is known as antidiabetic and antiatherogenic adipokine by exerting a potent insulin sensitizing effect (Kadowaki et al. 2006). In contrast, suppression of SIRT1 enhances the expression of endoplasmic reticulum oxidoreductase Ero1-Lα, a membrane-associated oxidoreductase that generates disulfide bonds (Frand and Kaiser 1998), and stimulates adiponectin secretion in adipocytes (Qiang et al. 2007). By binding to and deacetylating FOXO1, SIRT1 enhances the formation of FOXO1-CCAAT/enhancer-binding protein α (C/EBPα) transcription complex in the adipocytes, increasing the transcription of adiponectin (Qiao and Shao 2006). However, it has also been reported that SIRT1 suppresses the expression of adiponectin and fibroblast growth factor 21 (FGF21, an activator of glucose uptake in adipocytes), possibly by inhibiting of PPARγ in adipocytes (Qiang et al. 2007; Wang et al. 2008). Since it has been reported that SIRT1 upregulates the expression of adiponectin in adipocytes (Qiang et al. 2007; Qiao and Shao 2006; Wang et al. 2008), and the direction of the adiponectin secretion is not conclusive between in vivo and in vitro (Banks et al. 2008; Qiang et al. 2007), further work is required to understand adiponectin secretion.

While SIRT1 is predominantly a nuclear protein, SIRT2 is predominantly a cytoplasmic one (Michishita et al. 2005; North et al. 2003). In fact, SIRT2 is the most abundant sirtuin in adipocytes, where it plays an important role for adipocyte differentiation by deacetylating FOXO1 (Jing et al. 2007). Thus, it is possible that SIRT2 targets FOXO1 in the cytoplasm, while SIRT1 catalyzes FOXO1 deacetylation in the nucleus. It is also possible that SIRT1 and SIRT2 target different molecules, giving them different physiological or pathological functions in WAT. Further in vivo studies using genetically modified SIRT2 mice are required to address this possibility.

Brown adipose tissue (BAT) is a crucial regulator of energy expenditure through mitochondrial uncoupling protein-1 (UCP-1), thus protecting against obesity and diet-induced insulin resistance in mammals (Cederberg et al. 2001; Kopecky et al. 1995; Nedergaard et al. 2007; Seale et al. 2008). Although it has been reported that SIRT3 is highly expressed in BAT and plays an important role in adaptive thermo-genesis by activating mitochondrial function (Scher et al. 2007; Schapira 2011), the metabolic regulatory function of SIRT1 in BAT is still unknown. It is reported that SIRT1 might regulate brown adipocyte differentiation based on microarray gene expression study (Timmons et al. 2007). Since adult humans have morphologically distinguishable BAT and increasing brown adipocyte differentiation may offer a new therapeutic treatment for obesity and type 2 diabetes (Cypess et al. 2009; Kajimura et al. 2010; Lidell and Enerback 2010; Virtanen et al. 2009), it will be of great interest to further investigate the role of SIRT1 in the brown adipocyte differentiation.

3.4 Pancreatic β-Cells

Pancreatic β-cells play a major role in the regulation of glucose homeostasis by secreting insulin in response to elevated blood glucose. In pancreatic β-cells, SIRT1 enhances glucose-stimulated insulin secretion and improves glucose tolerance, at least in part, by

repressing the expression of uncoupling protein 2 (UCP-2), an inner mitochondrial membrane protein (Bordone et al. 2006; Moynihan et al. 2005). UCP-2 functions as a proton transporter, whose activity has the effect of uncoupling the electron transport chain and ATP biosynthesis. Suppression of UCP-2 by SIRT1 increases ATP production, inducing glucose-stimulated insulin secretion. Indeed, islets isolated from beta cell-specific *Sirt1*-overexpressing (BESTO) transgenic mice exhibit increased ATP production in response to glucose. Interestingly, both pancreata and islets of BESTO mice show the enhancement of insulin secretion not only by glucose, but also by KCl-induced depolarization, suggesting that SIRT1 might also regulate insulin secretion downstream of β-cell depolarization, independently of UCP-2 (Moynihan et al. 2005).

β-cell dysfunction can be caused by a variety of cellular injuries, including glucolipotoxicity (Fontes et al. 2010). SIRT1 is able to prevent β-cell dysfunction against cellular injury. BESTO mice maintain glucose tolerance under a long-term HFD by increasing glucose-stimulated insulin secretion (Ramsey et al. 2008). The finding that BESTO mice exposed to HFD-induced stress display better β-cell functionality than wildtype littermates suggests that increasing SIRT1 activity in pancreatic β-cells might be able to sustain β-cell function under hyperlipidemic, diabetogenic conditions. Indeed, by deacetylating FOXO1, SIRT1 induces the expression of *NeuroD* and *MafA*, which are both transcriptional regulators of insulin 2 (*Ins2*) gene expression and protect β-cells under conditions that could cause apoptosis and promote β-cell senescence (Kitamura et al. 2005). Furthermore, SIRT1 overexpression completely prevents IL-1β and/or IFNγ-mediated cellular injury by inhibiting NF-κB signaling and subsequently repressing the expression of inducible nitric oxide synthase (iNOS) (Lee et al. 2009). Together, these findings strongly suggest that SIRT1 activity can prevent pancreatic β-cell dysfunction and thus type 2 diabetes.

Contrary to the function of SIRT1 in pancreatic β-cells, SIRT4 suppresses insulin secretion in response to amino acids and glucose (Schapira 2011). SIRT4 ADP-ribosylates and represses the activity of glutamate dehydrogenase (GDH), an enzyme that converts glutamate to α-ketoglutamate in mitochondria, thereby decreasing amino acid-stimulated insulin secretion (Haigis et al. 2006). Furthermore, depletion of SIRT4 increases glucose-stimulated insulin secretion through with the effects on ATP/ADP translocase (ANT), an ADP/ATP carrier protein, and insulin-degrading enzyme (IDE) (Ahuja et al. 2007). It is of great interest to investigate how SIRT1 and SIRT4 work together to regulate insulin secretion under various metabolic conditions such as HFD.

3.5 Hypothalamus

The hypothalamus regulates feeding behaviors in response to metabolic signals from peripheral tissues by way of hormones such as insulin, leptin, and ghrelin (Elmquist 2001). Neurons in diverse nuclei of the hypothalamus including arcuate and paraventricular nuclei (Arc and PVN, respectively) and the ventromedial, dorsomedial, and lateral hypothalamic nuclei (VMH, DMH, and LH, respectively) produce and secrete multiple neuropeptides and neurohormones that play important roles in the regulation of metabolism, body temperature, food intake, arousal, circadian rhythm, and the secretion of pituitary hormones (Cone 2005; Elmquist 2001; Green et al. 2008; Morrison et al. 2008; Morton et al. 2006; Sakurai 2007).

Hypothalamic SIRT1 appears to regulate food intake and feeding behavior, but the direction of regulation currently remains controversial. Intracerebroventricular administration of EX527, a selective inhibitor of SIRT1, or siRNA-mediated knockdown of *Sirt1* in the Arc inhibits feeding behavior in rats through decrease in augouti-related protein (AgRP) and increase in pro-opiomelanocortin (POMC) protein (Cakir et al. 2009). In contrast, it has been reported that intracerebroventricular administration of adenovirus expressing *Sirt1* in the mediobasal hypothalamus suppresses food intake (Sasaki et al. 2010). Since each

hypothalamic nucleus has a distinct role in systemic metabolic regulation, neuron-specific or nuclei-specific modification of *Sirt1* by genetic or stereotactic manipulation is necessary to elucidate the function of SIRT1 in the hypothalamus.

Numerous experimental and clinical findings suggest that hypothalamic dysfunction might be one of the underlying causes of abnormal glucose and lipid metabolism that occurs in type 2 diabetes and diet-induced obesity (Rosmond and Bjorntorp 2000; Schwartz and Porte 2005). Hypothalamic SIRT1 is reported to prevent the pathology of diet-induced obesity. Deletion of SIRT1 in POMC neurons results in weight gain and reduced energy expenditure by reducing sympathetic nerve activity and BAT-like remodeling of perigonadal WAT under HFD (Ramadori et al. 2010). BAT-like remodeling of perigonadal WAT increases mitochondrial content and UCP-1 expression under HFD, resulting in increased energy expenditure against obesity and insulin resistance (Plum et al. 2007). These results suggest that SIRT1 in POMC neurons is required for normal autonomic adaptation to diet-induced obesity and possibly insulin resistance.

4 The Regulation of Sirtuin Function

Given the importance and widespread effects of SIRT1 activity, it is important to understand factors that regulate its activity and expression. These regulatory factors can be broken down into four categories: NAD, protein regulators of SIRT1 activity, nucleocytoplasmic shuttling of SIRT1, and regulators of SIRT1 expression (Fig. 3).

4.1 NAD

Perhaps the most important regulator of sirtuin activity is cellular NAD (Imai 2009). NAD is specifically required for the sirtuin deacetylase reaction and cannot be substituted by NADH, NADP, and NADPH (Imai et al. 2000). However, NAD is required for many vital cellular processes besides the sirtuin reaction. For example, it acts as a cofactor in redox reactions of glycolysis, the trichloroacetic acid cycle, and the catabolism of carbohydrates, fats, proteins, and alcohols and also participates in DNA repair, G-protein coupled signaling, intracellular calcium signaling, and transcription (Bogan and Brenner 2008; Garten et al. 2009). As a result, the pool of intracellular NAD is limiting for sirtuin activity despite its seemingly adequate concentration of 300–400 μM (Bogan and Brenner 2008; Canto et al. 2010; Houtkooper et al. 2010; Koltai et al. 2010; Penberthy and Tsunoda 2009; Rodgers et al. 2005; Sauve 2008; Yang et al. 2007a). In addition to affecting SIRT1 activity, high levels of NAD can augment SIRT1 expression over twofold in multiple tissues (Hayashida et al. 2010; Hwang et al. 2009; Qin et al. 2006; Rodgers et al. 2005), whereas depletion of NAD had the reverse effect (Borradaile and Pickering 2009; de Kreutzenberg et al. 2010; Liu et al. 2008a). Since high concentrations of NADH inhibit sirtuin activity, there is some debate as to whether absolute NAD levels or the NAD/NADH ratio is more important to sirtuin function (Bogan and Brenner 2008; Lin et al. 2004). With the IC50 for NADH at 11–28 mM and the amount of NADH in the cytosol less than 1% of total free NAD and NADH, it is unlikely for NADH levels to become high enough to inhibit SIRT1 activity (Schmidt et al. 2004). Thus, NAD levels are expected to be a more critical indicator of SIRT1 activity.

Four different substrates can be used to generate NAD: tryptophan (Trp), nicotinamide (NAM), nicotinic acid (NA), and nicotinamide riboside (NR) (Fig. 4) (Bogan and Brenner 2008). Of these substrates, the pathway starting from nicotinamide is the predominant source of NAD in mammals (Houtkooper et al. 2010). In this pathway, homodimeric nicotinamide phosphoribosyltransferase (NAMPT) converts NAM to nicotinamide mononucleotide (NMN), and nicotinamide/nicotinic acid mononucleotide adenylyltransferase (NMNAT) converts NMN to NAD (Houtkooper et al. 2010; Revollo et al. 2004, 2007). Because NAMPT functions as the rate-limiting enzyme in this NAD

biosynthetic pathway, NAMPT is perhaps the most important component for the regulation of mammalian NAD biosynthesis. Expression levels of NAMPT are varied throughout the body: high in the liver, kidney, and BAT; intermediate in the heart; and low in the skeletal muscle, brain, pancreas, WAT, lung, spleen, and testis in mice (Revollo et al. 2007). Overexpression of NAMPT increases NAD levels, while overexpression of NMNAT has no effect (Araki et al. 2004; Revollo et al. 2004). The fact that intracellular NAD levels increase with NAMPT overexpression in multiple, diverse cell types (Borradaile and Pickering 2009; Fulco et al. 2008; Hsu et al. 2009; Pillai et al. 2005; Revollo et al. 2004; Rongvaux et al. 2008; Song et al. 2008; van der Veer et al. 2005) suggests that NAMPT expression is sufficient to induce NAD biosynthesis. As pharmacological inhibition of NAMPT activity by the highly specific inhibitor FK866 reduces NAD levels 50–95% (Billington et al. 2008; Bruzzone et al. 2009; Hasmann and Schemainda 2003; Revollo et al. 2007; Rongvaux et al. 2008), indicating that NAMPT is necessary for NAD biosynthesis. NAMPT is required for survival, with lack of NAMPT causing embryonic lethality prior to day 10.5 (Revollo et al. 2007). In fact, NAMPT function is so vital that reducing NAMPT activity hampers cellular viability up to 90% (Billington et al. 2008; Dahl et al. 2010; Jia et al. 2004; Rongvaux et al. 2008; van der Veer et al. 2005). Thus, the factors that regulate NAMPT activity and expression should also be potent regulators of mammalian sirtuins.

One of these factors is AMP-activated protein kinase (AMPK). As knockdown of SIRT1 in myocytes impairs the ability of AMPK to regulate the expression of genes related to mitochondrial metabolism and fatty acid oxidation and to increase lipid oxidation-driven O_2 consumption (Canto et al. 2009), SIRT1 is clearly a primary downstream component of AMPK signaling. AMPK activates SIRT1 to deacetylate FOXO1, FOXO3a, and PGC-1α by increasing cellular NAD levels with no effect on SIRT1 protein levels, its protein–protein interactions, or its phosphorylation status (Canto et al. 2009; Chau et al. 2010). Thus, conditions that activate AMPK, such as nutrient deprivation and exercise, are associated with higher NAD levels and SIRT1 activity (Canto et al. 2010; Fulco et al. 2008). While the mechanism by which AMPK increases NAD levels is not fully elucidated, it appears to be, at least in part, by up-regulating expression of NAMPT (Canto et al. 2010; Costford et al. 2010; Fulco et al. 2008). Interestingly, an increase in mitochondrial β-oxidation appears to be required for AMPK to increase NAD levels and PGC-1α deacetylation. FGF21 and adiponectin have been reported to modulate SIRT1 activity by activating AMPK. FGF21 regulates energy homeostasis in adipocytes by inducing LKB1 that phosphorylates AMPK (Chau et al. 2010). Indeed, an increase in levels of phosphorylated AMPK by FGF21 triggers SIRT1 to deacetylate PGC-1α in *ob/ob* mice, resulting in enhanced mitochondrial function and reduced body weight (Chau et al. 2010). In myocytes, adiponectin has a similar effect. Adiponectin induces calcium influx through its receptor adiponectin receptor 1 (adipoR1), and this calcium activates the other major AMPK kinase, calcium/calmodulin-dependent protein kinase kinase β (CaMKKβ) (Iwabu et al. 2010). CaMKKβ-mediated activation of AMPK increased SIRT1-mediated deacetylation of PGC-1α and increased mitochondrial biogenesis. Accordingly, skeletal muscle-specific AdipoR1 knockout mice exhibited decreased SIRT1 activity, PGC-1α expression, PGC-1α deacetylation, and mitochondrial biogenesis. Supporting the notions that FGF21 and adiponectin act upstream of AMPK, both factors also increase NAD levels (Chau et al. 2010; Iwabu et al. 2010).

4.2 Protein Regulators of SIRT1 Activity

Two proteins have been identified that regulate SIRT1 activity via a direct interaction: active regulator of SIRT1 (AROS) and deleted in breast cancer 1 (DBC1). Binding of the nuclear protein AROS to SIRT1 enhanced SIRT1-mediated p53 deacetylation, thus inhibiting the transcriptional activity of p53 and preventing p53-induced cell cycle arrest and apoptosis in response to DNA damage (Kim et al. 2007b). Opposite to AROS, binding of DBC1 to the

catalytic domain of SIRT1 inhibits its activity, preventing SIRT1 from deacetylating p53 and FOXO3 following cellular stress, with the result of up-regulating p53 and FOXO-mediated apoptosis (Kim et al. 2008, 2009; Zhao et al. 2008). The activity of SIRT1 has been shown to be regulated by posttranslational modifications: phosphorylation and sumoylation (Yang et al. 2007b). At least 14 residues in SIRT1 are phosphorylated in vivo, with phosphorylation increasing the activity of SIRT1 (Guo et al. 2010; Nasrin et al. 2009; Sasaki et al. 2008). The kinases responsible for this phosphorylation are known to include CyclinB/Cdk1, cJun N-terminal kinase (JNK1), and two dual specificity tyrosine phosphorylation-regulated kinases, DYRK1A and DYRK3. It will be interesting to determine what other SIRT1 kinases exist. Sumoylation of human SIRT1 has also been reported to enhance its ability to deacetylate p53 sufficiently to prevent stress-induced apoptosis, although the sumoylation site is not evolutionarily conserved. Thirdly, two proteins have been identified which enhance the activity of SIRT1 by binding SIRT1 substrates. Four-and-a-half LIM2 (FHL2) enhances SIRT1-mediated deacetylation of FOXO1 in prostate cancer cells by binding FOXO1 in a manner that promotes the interaction between SIRT1 and FOXO1 (Yang et al. 2005). Since deacetylation inactivates FOXO1, FHL2 activity decreases the levels of FOXO target genes and FOXO1-induced apoptosis. Similarly, in postmitotic neurons, necdin, a melanoma antigen family protein, interacts with SIRT1 and p53, potentiating SIRT1-mediated deacetylation of p53, and thus, protecting neurons from DNA damage-induced apoptosis (Hasegawa and Yoshikawa 2008).

4.3 Nucleocytoplasmic Shuttling of SIRT1

Finally, nucleocytoplasmic shuttling may modulate SIRT1 activity. Cytoplasmic localization of SIRT1 is higher in adulthood than during embryonic development in the heart (Tanno et al. 2007) and during postnatal development in brain (Li et al. 2008). The cellular localization of SIRT1 is also affected by differentiation and apoptosis. In myoblasts, SIRT1 is a nuclear protein until differentiation, at which point SIRT1 translocates to the cytoplasm (Tanno et al. 2007). In neural precursor cells, SIRT1 translocates from the cytoplasm into the nucleus for differentiation and then returns to the cytoplasm (Hisahara et al. 2008). SIRT1 also translocates from the nucleus to the cytoplasm during apoptosis (Jin et al. 2007; Ohsawa and Miura 2006). Despite these events, the significance of cytoplasmic SIRT1 remains unclear. As only nuclearly localized SIRT1 can engender direct transcriptional events (Tanno et al. 2007), cytoplasmic shuttling may be a way to down-regulate SIRT1 activity. However, SIRT1 deacetylase activity could still be highly relevant in the cytoplasm, as many substrates of SIRT1, such as p53, FOXOs, and NF-κB, also shuttle between compartments (Kwon and Ott 2008). Some evidence even suggests that cytoplasmically localized SIRT1 may promote apoptosis (Cohen et al. 2004; Jin et al. 2007; Tanno et al. 2007; Zhang 2007).

4.4 Regulators of SIRT1 Expression

Four transcriptional regulators have been reported to modulate of SIRT1 expression: p53, hypermethylated in cancer 1 (HIC1), C/EBPα, and E2F1. The first three may play a role in up-regulating SIRT1 expression under CR. Under basal nutritional conditions, p53 binds the SIRT1 promoter with the effect of repressing transcription of SIRT1 (Nemoto et al. 2004). However, upon starvation, the association of p53 with the SIRT1 promoter is prevented by the binding of FOXO3α to p53, thus up-regulating SIRT1 expression. HIC1 forms a transcriptional repression complex with SIRT1, the transcriptional corepressors CtBP, and class I HDACs that binds to the 5′ end of the SIRT1 promoter CpG island (Chen et al. 2005b). The association of CtBP with HIC1 is reduced upon glycolytic blockade, thus increasing SIRT1 expression in response to nutrient deprivation (Jin et al. 2010; Zhang 2007). SIRT1 expression is also enhanced upon nutrient deprivation by increased binding of C/EBPα to the SIRT1 promoter (Jin et al. 2010). While not linked to metabolic state, the

cell-cycle regulator E2F1 may connect SIRT1 expression with replicative aging, as it activates SIRT1 transcription when cells begin to enter S phase (Wang et al. 2006).

Translationally, at least one protein and three microRNAs have been shown to regulate SIRT1 protein levels by binding the 3′ untranslated region of SIRT1's mRNA: Hu antigen R (HuR), miR-34a, miR-132, and miR-217. HuR is an mRNA-binding protein whose binding increases the half-life of SIRT1 mRNA from 1.2 to 8 hours (Abdelmohsen et al. 2007). miR-34a decreases SIRT1 protein levels in multiple, diverse cell types, with the effect of increasing acetylation levels of p53 and FOXO (Lee et al. 2010; Tarantino et al. 2010; Yamakuchi et al. 2008; Zhao et al. 2010). miR-132 decreased SIRT1-mediated deacetylation of p65 in adipocytes, leading to activation of NF-κB (Strum et al. 2009). In endothelial cells, inhibition of SIRT1 by miR-217 induced premature senescence due to high levels of FOXO1 and nitric oxide synthase acetylation (Menghini et al. 2009). It will be interesting to see future work delineating the relevance of these molecular mechanisms to SIRT1 activity in vivo.

5 Sirtuin in Age-Associated Disorders

To achieve healthy aging, it is important to decrease the incidence and delay the onset of age-associated disorders. Accumulating bodies of evidence indicate that SIRT1 prevents age-associated disorders including type-2 diabetes (T2D) and Alzheimer's disease (AD) (Imai and Guarente 2010; Wang et al. 2010). Therefore, SIRT1 is an important therapeutic target to prevent age-associated diseases and extend healthspan (Fig. 5).

5.1 SIRT1 and T2D

T2D has a complex pathology consisting of defects in insulin secretion and action that together result in hyperglycemia (Bell and Polonsky 2001; Cavaghan et al. 2000). SIRT1 plays an important role in promoting insulin secretion by pancreatic β-cells and protecting against insulin resistance in the liver, skeletal muscle, and adipose tissue. These findings support the notion that SIRT1 is important for the maintenance of glucose homeostasis and the prevention of T2D. Indeed, under diabetogenic HFD conditions (Kraegen et al. 1991; Kubota et al. 1999; Surwit et al. 1988), the activity and/or protein expression of SIRT1 are reduced in several tissues (Deng et al. 2007; Escande et al. 2010; Qiao and Shao 2006). Moreover, increasing SIRT1 by genetic manipulation prevents metabolic disorders induced by HFD feeding. It has been reported that whole-body *Sirt1*-overexpressing transgenic mice improves glucose tolerance by decreasing hepatic glucose production without changes in body weight or fat composition in mice on a HFD (Banks et al. 2008). Similarly, another line of whole-body *Sirt1*-overexpressing transgenic mice show improvement of glucose tolerance, reduced lipid-induced inflammation, and protection against HFD-induced hepatic steatosis (Pfluger et al. 2008). In the kidney, which is highly susceptible to diabetic nephropathy, SIRT1 inhibits oxidative stress by inducing cyclooxygenase-2 (COX-2) expression (He et al. 2010b). It has also been reported that kidney-specific overexpression of SIRT1 protects cisplatin-induced acute kidney injury, likely by maintaining peroxisome number, upregulating catalase, and reducing renal reactive oxygen species (Hasegawa et al. 2010). Furthermore, SIRT1 genetic variation influences survival in the subjects with T2D (Zillikens et al. 2009a, b). These findings strongly suggest that SIRT1 could be a potential therapeutic target to improve insulin resistance and to protect against cell damage due to T2D.

Supporting the idea that SIRT1 could be a potential therapeutic target to combat metabolic disorders, SIRT1 also plays an important role in circadian rhythm. SIRT1 regulates CLOCK/BMAL1, the key transcription factor complex that controls the expression of clock genes (Nakahata et al. 2009). It has also been reported that SIRT1 directly regulates PER2

(Asher et al. 2008). The facts that *Clock* mutant mice and *Bmal1* mutant mice display metabolic disorders (Oishi et al. 2006; Turek et al. 2005) and that diet-induced obesity disrupts circadian behavior and circadian clock genes (Kohsaka et al. 2007) suggest that the maintenance of circadian rhythm is vital to prevent metabolic disorders. Interestingly, it has also been demonstrated that CLOCK:BMAL1 complex produces the circadian oscillation of NAMPT and NAD levels in vivo, comprising a novel circadian clock feedback loop involving NAMPT/NAD and SIRT1/CLOCK:BMAL1 (Nakahata et al. 2009; Ramsey et al. 2009). These findings strongly suggest that up-regulation of SIRT1 activity by NAMPT-mediated NAD biosynthesis could maintain proper circadian rhythm and prevent metabolic disorders.

5.2 SIRT1, AD, and Other Age-Associated Neurological Disorders

AD is chronic neurodegenerative disorder leading to synaptic dysfunction and neuronal cell loss (Haass and Selkoe 2007). Increasing lines of evidence suggest that SIRT1 provides protection from AD. Injection of lentivirus carrying *Sirt1*in the CA1 region of the hippocampus protects against neurodegeneration in the *p*25 transgenic mouse model of AD (Cruz et al. 2006; Kim et al. 2007a). In an AD mouse model encoding the human APPswe and PSEN1 dE9 alleles, which exhibits strong β-amyloid (Aβ) plaque formation, SIRT1 suppresses the production of Aβ and plaques by deacetylating retinoic acid receptor β (RARβ) and thereby activating the transcription of ADAM10 encoding α-secretase (Donmez et al. 2010). α-secretases cleave amyloid precursor protein (APP), a type I transmembrane glycoprotein and the precursor of Aβ, preventing Aβ formation (He et al. 2010a). As a result, the overexpression of ADAM10 prevents amyloid plaque formation and hippocampal behavioral defects in AD mice (Postina et al. 2004). These findings potentially indicate that increasing SIRT1 dosage can prevent AD. Interestingly, NAD treatment attenuates Aβ generation, by activating SIRT1 in primary hippocampal neuronal cultures (Qin et al. 2006). Epidemiological studies have shown a strong association between diabetes and AD (Biessels and Kappelle 2005; Janson et al. 2004), and risk of AD is increased with development of T2D (Leibson et al. 1997; Ott et al. 1999; Takeda et al. 2010). Although it is still uncertain whether or not SIRT1 has a unifying pathophysiological role in T2D and AD, it is of great interest to investigate whether NAMPT-mediated systemic NAD biosynthesis plays an important role in AD pathophysiology as well as T2D.

SIRT1 has also been shown to be required for basal neural functions such as synaptic plasticity, cognition, and memory. In the hippocampus, SIRT1 modulates synaptic plasticity and memory formation by miR-134, a brain-specific microRNA, through the up-regulation of the expression of cAMP response element binding protein (CREB) and brain-delivered neurotrophic factor (BDNF) (Gao et al. 2010), which have critical roles in synaptic plasticity and synapse formation (Frank and Greenberg 1994; Kang and Schuman 1995). Moreover, *Sirt1*-deficient mice have impaired cognitive abilities such as deficits in immediate memory, classical conditioning, and spatial learning due to defects in synaptic plasticity (Michan et al. 2010). These findings highlight the benefits of increasing SIRT1 activity in preserving brain function and preventing age-associated neurological disorders.

6 Sirtuins in the Aging Process

Although it is still unclear whether sirtuins also play an important role in the regulation of mammalian lifespan, as it does in lower eukaryotes, recent results suggest that SIRT1 is important in the regulation of age-induced physiological changes (Fig. 5). For example, SIRT1 is involved in DNA damage-induced chromatin reorganization that promotes genome stability and causes the reduction in silencing of SIRT1 target genes in mouse embryonic stem (ES) cells (Oberdoerffer et al. 2008; Oberdoerffer and Sinclair 2007). This damage-induced SIRT1 redistribution requires DNA damage signaling through a mammalian PI3-

kinase ATM and histone H2AX, one of the targets of ATM. 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 can suppress these age-associated changes (Oberdoerffer et al. 2008), suggesting that the damage-induced SIRT1 redistribution might trigger certain age-associated physiological changes in the brain.

The activity and expression of SIRT1 declines with age in several tissues. For example, in the kidney, mRNA and protein levels of SIRT1 significantly decline with age. Aged mice show the reduction of the interaction between SIRT1 and FOXO3, its transcriptional activity is regulated by SIRT1. Thus, SIRT1 activity is decreased in the aged kidney (Kume et al. 2010). In pancreatic β cells, SIRT1 activity appears to be reduced in aged mice due to a decline in systemic NAD biosynthesis. Aged BESTO mice lose the phenotype (see Sect. 3.4) that was shown in young BESTO mice, displays reduced level of *Ucp2* consistent with the lack of a difference in ATP content (Ramsey et al. 2008). Furthermore, the protein levels of SIRT1 are declined in several murine disease or accelerated aging models. (Pallas et al. 2008; Sommer et al. 2006), as well as during replicative senescence in normal human fibroblasts (Michishita et al. 2005). These findings strongly suggest that the maintenance of expression and/or activity of SIRT1 during senescence prevents against age-associated disorders.

Investigation into the intimate connection among sirtuins, metabolism, and aging has implicated that SIRT1 as a key mediator for physiological responses to CR in mammals. CR has been employed in aging research as an antiaging dietary intervention that shows protective effects on age-associated pathology of metabolic disorders and lifespan extension (Bronson and Lipman 1991; Colman et al. 2009; Fontana et al. 2004; Weindruch et al. 1986). Interestingly, CR-induced elevation of physical activity is abrogated in *Sirt1*-deficient mice (Chen et al. 2005a). *Sirt1*-deficient mice also exhibit dramatically reduced oxygen consumption under CR (Boily et al. 2008) and are resistant to CR-mediated improvement in the accumulation of damaged mitochondria under hypoxia in the kidney (Kume et al. 2010). Additionally, *Sirt1*-overexpressing transgenic mice display phenotypes similar to CR mice, including reduced body weight, improved glucose tolerance, reduced blood cholesterol, insulin, and fasted glucose levels, increased oxygen consumption, better performance on a rotarod challenge, and a delay in reproduction (Bordone et al. 2007). Additionally, two other systemic *Sirt1*-overexpressing transgenic mice have delayed the onset of age-associated disorder including obesity and T2D (Banks et al. 2008; Pfluger et al. 2008). Furthermore, SIRT1 functions as a key regulator of cell defenses and survival in response to stress, promoting CR-induced cell survival (Cohen et al. 2004). These findings suggest that manipulation of SIRT1 activity might mimic beneficial effects of CR on reducing age-associated disorders and possibly increasing longevity in mammals.

However, because SIRT1 has a divergent role in the regulation of metabolism in multiple tissues in mammals, it is conceivable that simply increasing SIRT1 activity systemically might not retard aging and show lifespan extension as well as CR. Indeed, it has recently been reported that whole-body SIRT1-overexpressing transgenic mice do not show lifespan extension (Herranz et al. 2010). Additionally, while most tissues show increases in SIRT1 protein levels under CR (Cohen et al. 2004; Qin et al. 2006), some other tissues show decreases or no change (Chen et al. 2008a; Cohen et al. 2009). In the brain, the effects of CR on SIRT1 expression are highly regional (Chen et al. 2008b). Therefore, increasing SIRT1 in a tissue/organ-specific manner by genetic manipulation might be important to retard aging and extend lifespan.

In this regard, the function of SIRT1 in the brain is interesting. In the hypothalamus, SIRT1 protein levels increase in the DMH, LH, and SCN (Satoh et al. 2010) under CR. Increasing

SIRT1 in the brain of transgenic mice (brain-specific *Sirt1*-overexpressing transgenic mice: BRASTO mice) enhances neural activity in the DMH and LH, maintains body temperature, and promotes physical activity by increasing the expression of orexin type-2 receptor, a G protein-coupled receptor that binds to the neuropeptide hormone orexin. Moreover, BRASTO mice are more responsive to ghrelin, a gut hormone whose plasma level is increased under CR, than wildtype littermate, suggesting the function of SIRT1 in the hypothalamus, particularly in the DMH and LH, as a key mediator of the central adaptive response to CR (Satoh et al. 2010). These results support the idea that increasing hypothalamic SIRT1 activity mediates neurobehavioral adaptation to CR. Additionally, it has been reported that SIRT1 in the brain is a link between somatotropic signaling and CR in mammals (Cohen et al. 2009). Brain-specific *Sirt1* knockout (BSKO) mice induce dwarfism, reduce somatotropic signaling such as levels of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) in plasma, displaying similar phenotypes to those in long-lived mutant mice (Chen et al. 2010), while BSKO mice do not increase their physical activity in response to CR as well as whole-body *Sirt1*-deficient mice (Chen et al. 2005a) and develop severe glucose intolerance with age (Cohen et al. 2009).

Other sirtuins might also play an important role for the regulation of aging and longevity. For example, SIRT3 has been linked to human longevity (Rose et al. 2003; Schapira 2011). *Sirt6*-deficient mice display the phenotype of premature senescence such as severe lymphopenia, loss of subcutaneous fat, osteopenia, and metabolic disorders, dying at around 4 weeks of age (Mostoslavsky et al. 2006). SIRT6 modulates telomeric chromatin by deacetylating lysine 9 of histone H3, preventing telomere dysfunction and cellular senescence (Michishita et al. 2008). Moreover, SIRT6 attenuates NF-κB signaling by deacetylating lysine 9 of histone H3 at chromatin, inhibiting apoptosis and cellular senescence (Kawahara et al. 2009; Mahajan et al. 2011). These findings provide the idea that increasing SIRT6 might prevent against age-induced physiological changes, thus possibly extend lifespan. It has been recently reported that SIRT1 is involved in maintaining SIRT6 expression under nutrient deprivation in both in vivo and in vitro (Kim et al. 2010). It should be addressed whether SIRT6 and other mammalian sirtuins serve to maintain physiological responses to CR.

7 Therapeutic Manipulation of Sirtuin Function

Considering the physiological effects of SIRT1 activity, SIRT1 activation has clear potential to combat numerous age-associated diseases, including metabolic syndrome, type 2 diabetes, cardiovascular disease, and neurodegenerative diseases (Borradaile and Pickering 2009; Ginsberg and MacCallum 2009; Hwang et al. 2009; Liu et al. 2008b; Milne et al. 2007; Picard et al. 2004; Qin et al. 2006; Ramsey et al. 2008; Sun et al. 2007). Augmentation of SIRT1 activity may also combat functional declines that occur with normal aging (Marton et al. 2010; Revollo et al. 2007). With this degree of potential, small-molecule sirtuin activating compounds (STACs) have been searched for and developed.

The STAC that coined the phrase is the polyphenolic compound, resveratrol, naturally found in grape skins (Howitz et al. 2003). First identified in a screen of small molecule libraries for hits which enhanced the deacetylase activity of human SIRT1 towards a synthetic, fluorophore-conjugated p53 peptide substrate, resveratrol increases deacetylation 2.0- to 2.6-fold, with 35- and 5-fold decreases in the Km of SIRT1 towards its substrate and NAD, respectively (Feige et al. 2008; Howitz et al. 2003; Milne et al. 2007; Pacholec et al. 2010). Supporting these biochemical assays, resveratrol can only convey its effects in cells expressing SIRT1 (Howitz et al. 2003; Lagouge et al. 2006). In mice, resveratrol (22 mg/kg/day) can significantly ameliorate or prevent HFD-induced impairments in insulin sensitivity, glucose tolerance, and motor function (Baur et al. 2006; Lagouge et al. 2006; Smith et al.

2009; Um et al. 2010). At higher doses (400 mg/kg/day), resveratrol can also protect HFD-fed mice against diet-induced weight gain. Furthermore, it has been reported that resveratrol prevents the HFD-induced decrease in lifespan (25–31%) (Baur et al. 2006; Pearson et al. 2008).

However, use of resveratrol is limited by two significant confounding factors. Firstly, resveratrol has many off-target effects (Baur 2010). Besides SIRT1, it can modulate AMPK, the estrogen receptor, the aryl hydrocarbon receptor, a cannabinoid receptor, and quinine reductase 2. Secondly, resveratrol has such low bioavailability that it is difficult to achieve serum levels in vivo high enough to activate SIRT1. For example, long-term administration of resveratrol (200 or 400 mg/kg/day) in rodents only generated nanomolar plasma concentrations (Lagouge et al. 2006). Furthermore, a volunteer trial in healthy humans found that even high doses of resveratrol could not elicit systemic levels high enough to be beneficial (Chaudhary and Pfluger 2009). To find compounds with higher potency and systemic retention, another small molecule screen was conducted, also using deacetylation of the fluorophore-conjugated p53 substrate to assess SIRT1 activity (Milne et al. 2007). The most potent molecule identified by this screen was SRT1720, which activates SIRT1 7.4-to 8.7-fold (Feige et al. 2008; Milne et al. 2007; Pacholec et al. 2010). Similar to resveratrol, treating HFD-fed mice or rodent models of diabetes with SRT1720 (100 mg/kg/day) improved glucose tolerance and insulin sensitivity in the liver, adipose tissue, and skeletal muscle as well as increased mitochondrial biogenesis (Feige et al. 2008; Milne et al. 2007; Smith et al. 2009). A higher dosage of SRT1720 (500 mg/kg/day) prevented diet-induced weight gain and reduced triglyceride and cholesterol levels in HFD-fed mice (Feige et al. 2008). It also strongly promoted fatty acid oxidation and fat consumption in the skeletal muscle, liver, and BAT. Both molecules appear to induce these physiological effects by stimulating the transcription of genes involved in oxidative phosphorylation and mitochondrial biogenesis while decreasing those involved in inflammatory NF-κB signaling (Baur et al. 2006; Lagouge et al. 2006; Smith et al. 2009).

Even though these molecules were shown to activate SIRT1 in vitro (Baur et al. 2006; Feige et al. 2008; Howitz et al. 2003; Lagouge et al. 2006; Milne et al. 2007), recent work has cast doubt on the notion that resveratrol, SRT1720, and other STACs are direct activators of SIRT1 (Borra et al. 2005; Kaeberlein et al. 2005; Pacholec et al. 2010). The in vitro assays originally used to identify all of these compounds were shown to be dependent upon the fluorophore placed on the substrate peptide. One explanation for the fluorophore dependency of SIRT1 activity is that the fluorophore mimics a hydrophobic residue or pocket found on the native, full-length substrate and/or endogenous regulators that promote a higher affinity for SIRT1. Another potentially reconciling explanation is that these compounds do affect SIRT1 in vitro but indirectly do so through AMPK-mediated increases in cellular NAD levels in vivo. Both resveratrol and SRT1720 have been shown to activate AMPK in multiple organs, and resveratrol almost doubles NAD levels in myotubes in an AMPK-dependent manner (Baur et al. 2006; Dasgupta and Milbrandt 2007; Feige et al. 2008; Um et al. 2010). In fact, resveratrol (400 mg/kg/day) cannot affect any of the aforementioned physiological processes in mice lacking functional AMPK (Um et al. 2010). In other words, while the downstream effects of STACs show clear promise, further enhancement of their specificity and bioavailability are required.

While these STACs currently provide hope for sirtuin-targeted pharmaceutical interventions, several potential problems exist. Firstly, as SIRT1 activity is limited by NAD availability and as NAD levels decline with age, attempts to increase SIRT1 activity long term may prove difficult. Increasing SIRT1 activity without increasing the NAD pool may even be deleterious, as unnaturally high and/or prolonged SIRT1 activity can deplete NAD levels (Liu et al. 2008a). Secondly, attempts to generate highly specific sirtuin activators may

prevent concurrent, beneficial activation of other sirtuin family members. Finally, although STACs can protect against or ameliorate disease pathology, they have minimal effects on metabolism and aging in regular chow fed rodents (Barger et al. 2008; Baur et al. 2006; Feige et al. 2008; Milne et al. 2007; Pearson et al. 2008).

One approach that may solve all these problems is to augment NAD levels through dietary supplementation of NAD substrates and intermediates. As these compounds are natural biological entities, they could be taken in the absence of disease pathology, potentially enhancing normal bodily functions throughout life. As evidence for this idea, pharmacologically increasing NADH oxidation in vivo increases SIRT1 activity with the effect of dramatically ameliorating all aspects of metabolic syndrome in a rodent model of the condition (Hwang et al. 2009). Systemic administration of NAD intermediates has further benefits of supplying NAD to the tissues/organs in which NAMPT expression is low, such as pancreatic β-cells and neurons (Imai 2009). These cell types likely depend upon extracellular NAD intermediates. Indeed, the existence of an extracellular form of NAMPT (eNAMPT) has led us to generate the concept of the NAD World, in which systemic NAD biosynthesis mediated by intra- and extracellular NAMPT intricately links metabolic status throughout the body. Based on this concept, systemic administration of NAD intermediates would result in a coordinated adjustment of a variety of metabolic functions.

Interestingly, multiple studies have shown that SIRT1 activity directly depends upon that of NAMPT. For example, NAMPT activity augments SIRT1-mediated transcriptional effects (Revollo et al. 2004; Zhang et al. 2009) and cellular survival upon insult (Araki et al. 2004; Pillai et al. 2005). NAMPT has also been shown to activate SIRT1 to lengthen replicative lifespan, delay senescence (Ho et al. 2009), promote cellular maturation (van der Veer et al. 2007), and induce differentiation (Skokowa et al. 2009). NAMPT can also stimulate SIRT1 to enhance the ability of smooth muscle cells to develop blood vessels (van der Veer et al. 2005), chrondrocytes to produce cartilage (Dvir-Ginzberg et al. 2008), osteoblasts to produce type I collagen (Xie et al. 2007), THP-1 monocytes to induce matrix metalloproteinase-9 activity, peripheral blood mononuclear cells to relate IL-8 and TNF-α (Dahl et al. 2007), and aortic endothelial cells to form endothelial tube networks (Borradaile and Pickering 2009). Since NAMPT produces NMN, administration of NMN should have similar effects. As increased dosage of NAMPT has similar effects on gene expression profiles as increasing the dosage of SIRT1 (Revollo et al. 2004), it appears that SIRT1 is the main transcription factor downstream of NAMPT, and thus the primary target of NMN. Consistent with this idea, systemic administration of NMN can correct defects in insulin secretion and glucose tolerance caused by aging (Ramsey et al. 2008). NMN may even be able to reduce plasma cholesterol and increase insulin sensitivity in the liver and WAT, effects were seen upon injection of a NAMPT expression vector into HFD rats (Sun et al. 2009). Thus far, no side effects of NMN administration have been reported, making NMN supplementation an ideal way to optimize SIRT1 function through the enhancement of NAD biosynthesis. NR is another therapeutic possibility as it can maintain NAD levels and improves SIR2-dependent functions in yeast (Belenky et al. 2007; Bieganowski and Brenner 2004). In mammals, NR generates NAD by way of nicotinamide riboside kinase (Nrk) or purine nucleoside phosphorylase (Pnp) and nicotinamide salvage (Belenky et al. 2009; Bieganowski and Brenner 2004). However, this newly discovered compound has yet to be applied therapeutically in mammalian studies (Houtkooper et al. 2010; Sauve 2008). Thus, more studies will be required to understand the effects of NR.

8 Conclusions

In the past 10 years, interest in the field of sirtuin biology has exploded, generating countless investigations into the functions of mammalian sirtuins. These findings have clearly

established that sirtuins are critical mediators of physiological responses to nutritional availability and also that SIRT1 activity has beneficial effects against numerous age-associated disorders, especially those accompanied by metabolic complications. As SIRT1 functionality declines in metabolic syndrome, age-associated disorders, and the aging process, we hypothesize that augmentation of SIRT1 activity will positively affect mammalian metabolism, aging, and longevity. This notion also gives clear therapeutic appeal to long-term augmentation of SIRT1 activity. Currently, using STACs and NAD intermediates are two promising ways to achieve this potentially valuable goal. Nevertheless, the path before us is still long. Answering the following critical questions in the near future will greatly further our progress:

1. Which tissue(s)/organ(s) play the most critical roles in, and thus are the most relevant therapeutic targets for sirtuin-mediated physiological responses to metabolic state and aging?
2. How is the activity and/or expression of SIRT1 regulated in each tissue in response to metabolic state and aging?
3. How is NAD biosynthesis regulated in each subcellular compartment, and how does that regulation impact on each sirtuin?
4. Which NAD intermediates most effectively increase SIRT1 activity in each tissue/organ, and what are the pharmacokinetics of each NAD intermediate?
5. Can chronic supplementation of STACs or NAD intermediates augment SIRT1 activity and combat the symptoms of metabolic syndrome and the aging process in humans?

Future work addressing these questions will greatly enrich our understanding of how sirtuin function can be fine-tuned throughout our body and surely provide insights into pharmaceutical and nutriceutical interventions that will promote healthy aging for mankind.

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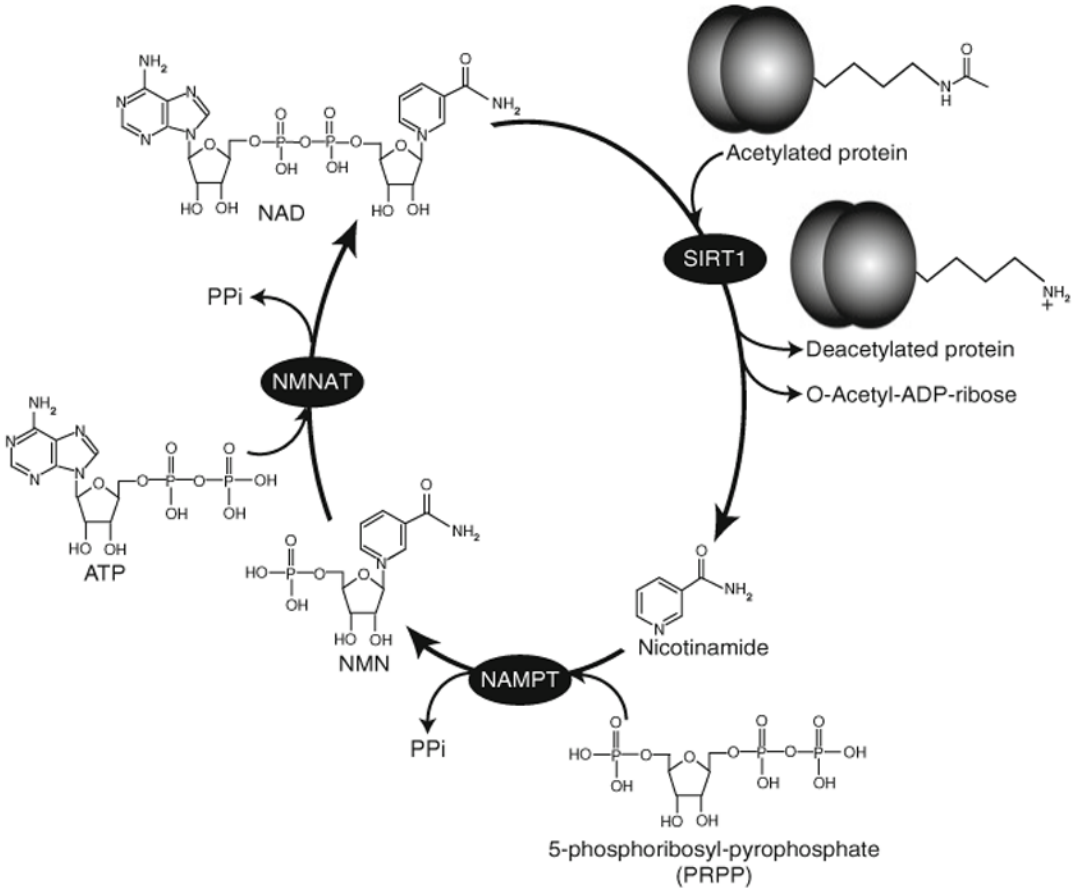

Fig. 1.

The deacetylation reaction of sirtuins. Upon the binding of both an acetylated lysine substrate and NAD, sirtuins cleave the glycosidic bond separating NAD into its nicotinamide and ribose moieties, producing nicotinamide, 2′-*O*-acetyl-ADP-ribose, and a deacetylated substrate

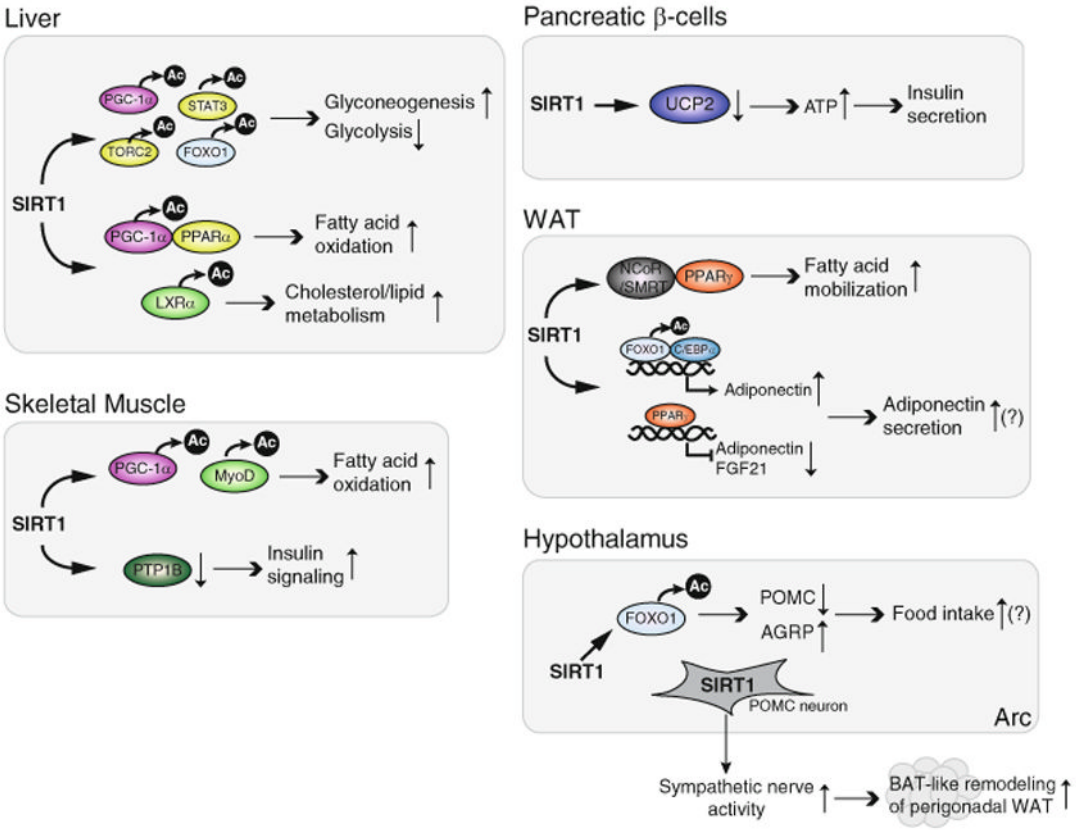

Fig. 2.

The metabolic regulation of SIRT1 in the liver, skeletal muscle, white adipose tissue (WAT), and hypothalamus. In the liver, SIRT1 regulates gluconeogenesis by deacetylating PGC-1α, TORC2, FOXO1, and STAT3. SIRT1 promotes fatty acid oxidation by deacetylating PGC-1α, promoting an interaction between SIRT1 and PPARα. SIRT1 also regulates cholesterol homeostasis by positively regulating the function of LXRα. In skeletal muscle, SIRT1 enhances mitochondrial fatty acid oxidation by deacetylating PGC-1α and MyoD. SIRT1 also improves insulin sensitivity by inhibiting the transcription of PTP1B. In WAT, SIRT1 enhances fatty acid mobilization by repressing the transcriptional activation of PPARγ by binding to NCoR/SMRT complex. SIRT1 regulates the production/secretion of adiponectin by deacetylating FOXO1, and possibly by inhibiting PPARγ. In pancreatic β-cells, SIRT1 enhances glucose-stimulated insulin secretion and improves glucose tolerance, at least in part, by repressing the expression of UCP-2. In the hypothalamus, SIRT1 in POMC neurons prevents the pathology of diet-induced obesity by reducing sympathetic nerve activity and BAT-like remodeling of perigonadal WAT. SIRT1 also regulates food intake and feeding behavior by decreasing and increasing the protein levels of AgRP and POMC, respectively

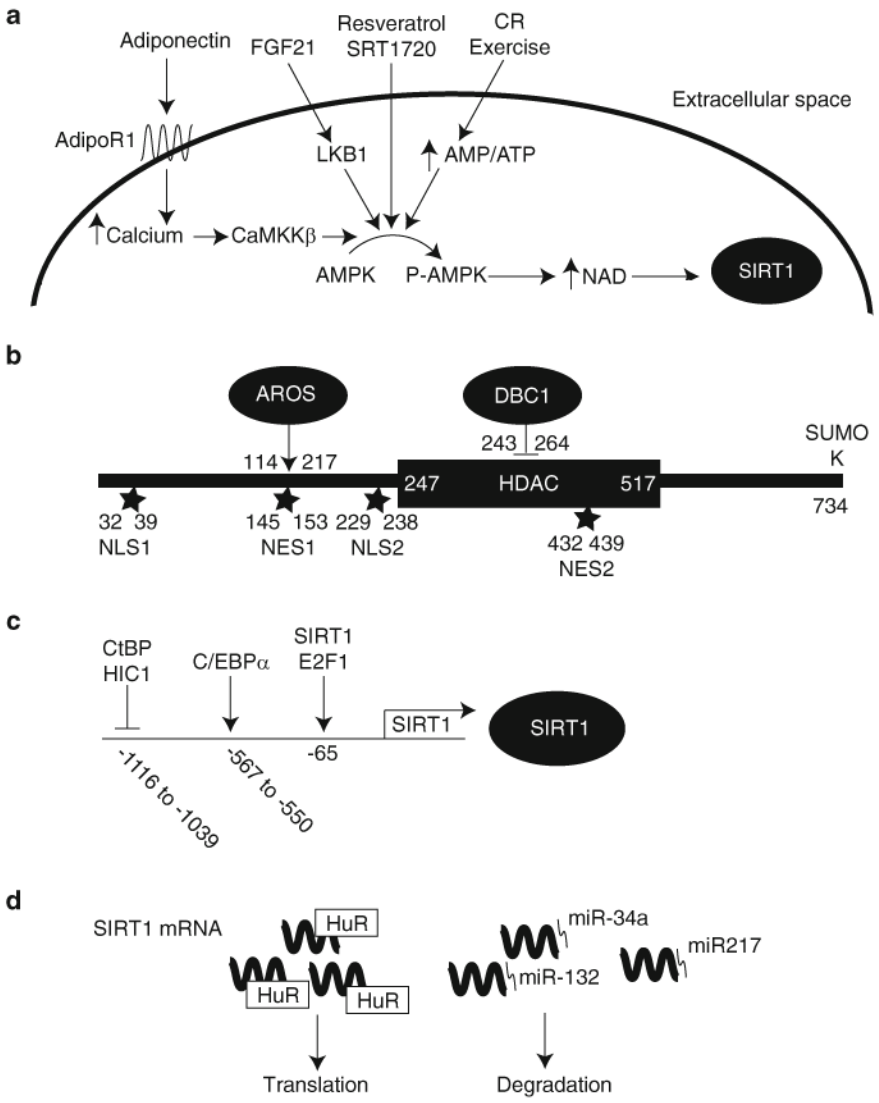

Fig. 3.

Regulation of SIRT1. SIRT1 activity is regulated by (A) NAD levels, (B) protein–protein interactions and posttranslational modifications, (C) factors that modulate its transcription, and (D) factors that modulate its translation. (A) SIRT1 activity is primarily regulated by NAD levels. NAD levels are regulated by AMPK-mediated up-regulation of NAMPT expression. AMPK can be activated by FGF21 and adiponectin. FGF21 induces LKB1, one of two major AMPK activators, to phosphorylate AMPK. Adiponectin induces calcium influx through its receptor adiponectin receptor 1 (adipoR1) and this calcium activates the other major AMPK kinase, calcium/calmodulin-dependent protein kinase kinase β (CaMKK β). (B) SIRT1 is activated by direct binding of AROS and sumoylation at Lysine734. Conversely, SIRT1 is inhibited by direct binding of DBC1. (C) p53 and HIC1 repress transcription of SIRT1 while C/EBPα and E2F1 enhance it. (D) Binding of HuR to SIRT1 mRNA increases its half-life. In contrast, binding of miR-34a, miR-132, or miR-217 results in translational repression of SIRT1 mRNA

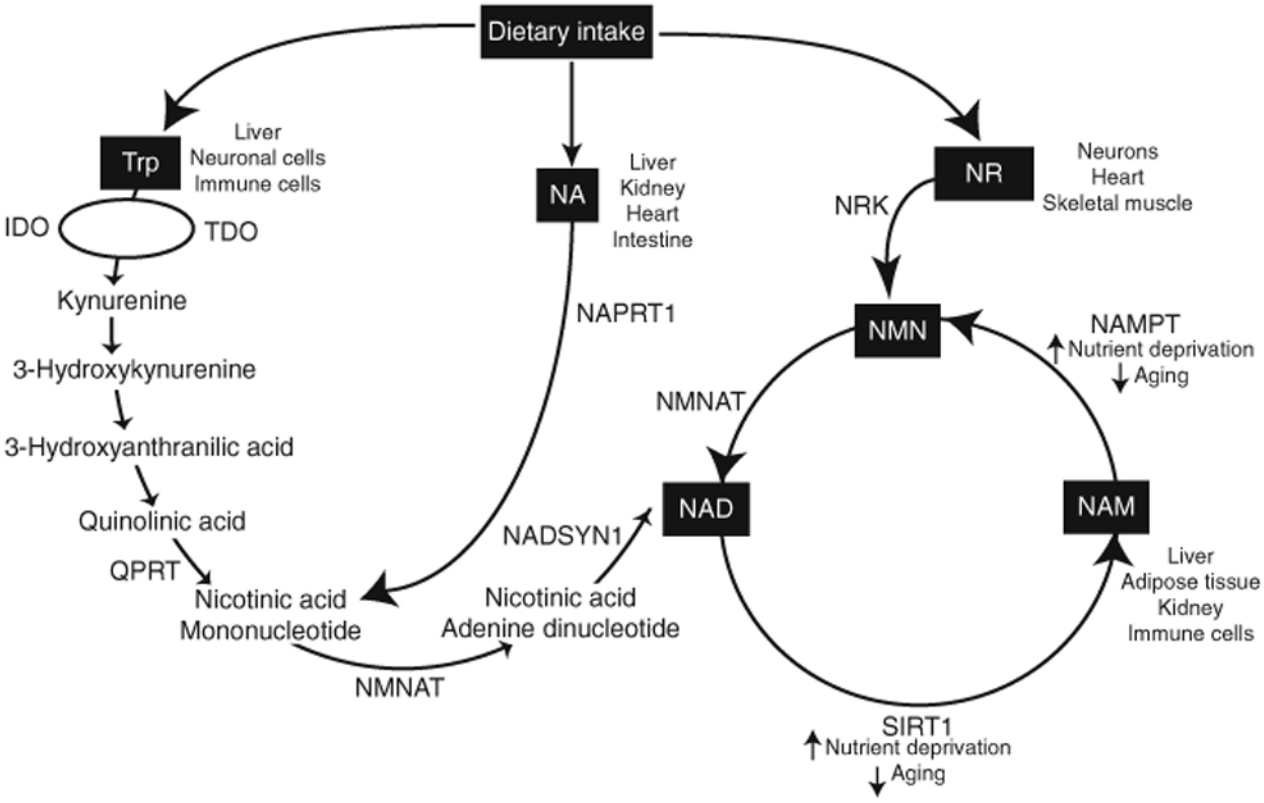

Fig. 4.

Pathways of mammalian NAD biosynthesis. Four dietary metabolites can be used to generate NAD: tryptophan (Trp), nicotinamide (NAM), nicotinic acid (NA), and nicotinamide riboside (NR). De novo NAD biosynthesis occurs from Trp via the eight-step Kynurenine pathway. The first and rate-limiting step in this pathway is shared by tryptophan dioxygenase (TDO) and indoleamine-2,3-dioxygenase (IDO), with TDO acting in the liver and the brain and IDO acting in the immune system. NA generates NAD through the Preiss–Handler pathway (PHP). In this pathway, nicotinic acid phosphoribosyltransferase (NAPRT1) forms nicotinic acid mononucleotide (NaMN), which is converted to NAD by the sequential actions of glutamine-dependent NAD synthetase (NADSYN1) and Nmnat. In the salvage pathway, homodimeric nicotinamide phosphoribosyltransferase (NAMPT) converts NAM to nicotinamide mononucleotide (NMN) and nicotinamide nucleotide adenylyltransferase (Nmnat) converts NMN to NAD. NR generates NAD by way of nicotinamide riboside kinase (Nrk) or purine nucleoside phosphorylase (Pnp) and nicotinamide salvage

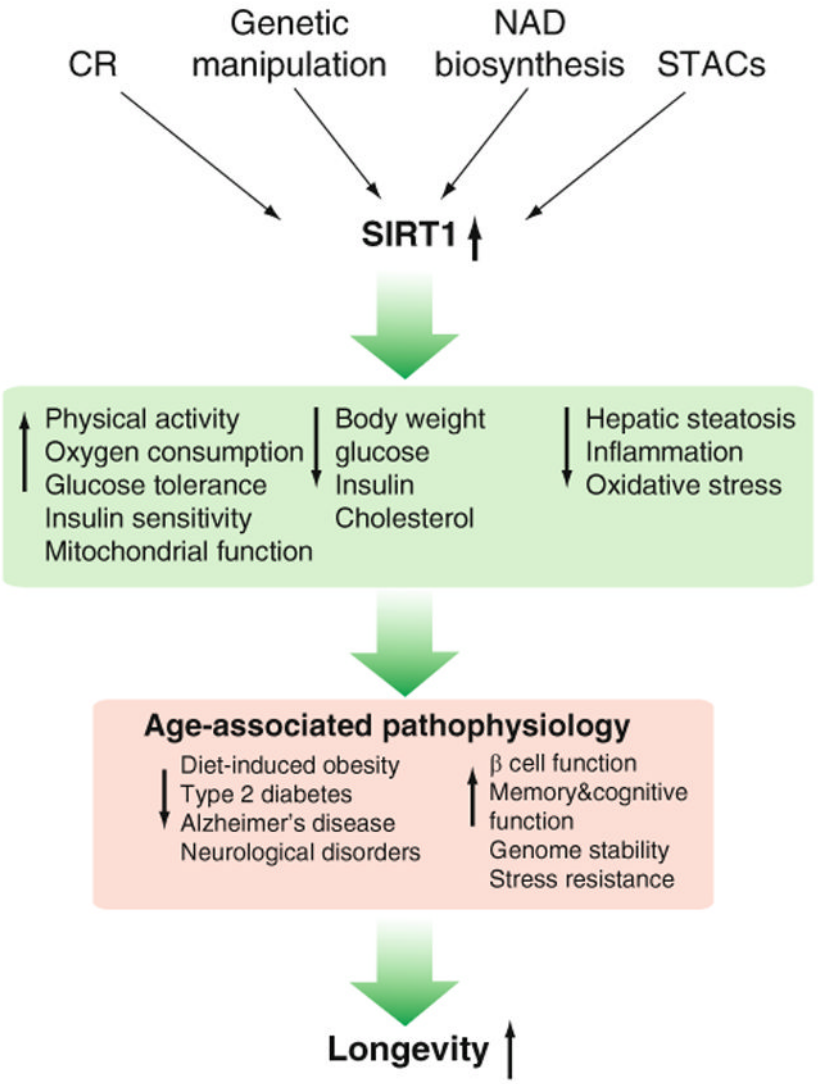

Fig. 5.

Manipulation of SIRT1 function. Caloric restriction (CR), genetic manipulation, NAD biosynthesis, and sirtuin activating compounds (STACs) increase the dosage/activity of SIRT1, providing beneficial metabolic responses against numerous age-associated physiology and thereby promoting longevity

Table 1

The enzymatic activity and localization of mammalian sirtuins

	Enzymatic activity		
	Deacetylase	**ADP-ribosyltransferase**	**Localization**
Sirt1	✓		Nucleus, cytoplasm
Sirt2	✓		Cytoplasm, nucleus
Sirt3	✓		Mitochondria
Sirt4		✓	Mitochondria
Sirt5	✓		Mitochondria
Sirt6	✓	✓	Nucleus
Sirt7	✓		Nucleolus