

Sirtuin biology and relevance to diabetes treatment

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Practice Points

- Exercise and diet should always be considered when managing Type 2 diabetes.
- Sirtuins may be partly attributed to the beneficial effects of calorie restriction and exercise. Although the underlying mechanisms are not quite clear, SIRT1 and SIRT3 have been demonstrated to mediate some of the salutary effects of calorie restriction and exercise in animal models, including an increase in mitochondrial function and protection against oxidative stress.
- Resveratrol may act partly through SIRT1 to improve glucose and lipid metabolism in diabetics.
- Strategies to boost NAD biosynthesis may be beneficial for metabolic homeostasis.

SUMMARY Sirtuins are a group of NAD⁺-dependent enzymes that post-translationally modify histones and other proteins. Among seven mammalian sirtuins, SIRT1 has been the most extensively studied and has been demonstrated to play a critical role in all major metabolic organs and tissues. SIRT1 regulates glucose and lipid homeostasis in the liver, modulates insulin secretion in pancreatic islets, controls insulin sensitivity and glucose uptake in skeletal muscle, increases adiponectin expression in white adipose tissue and controls food intake and energy expenditure in the brain. Recently, SIRT3 has been demonstrated to modulate insulin sensitivity in skeletal muscle and systemic metabolism, and *Sirt3*-null mice manifest characteristics of metabolic syndrome on a high-fat diet. Thus, it is reasonable to believe that enhancing the activities of SIRT1 and SIRT3 may be beneficial for Type 2 diabetes. Although it is controversial, the SIRT1 activator SRT1720 has been reported to be effective in improving glucose metabolism and insulin sensitivity in animal models. More research needs to be conducted so that we can better understand the physiological functions and molecular mechanisms of sirtuins in order to therapeutically target these enzymes for diabetes treatment.

Sirtuins are evolutionarily conserved

Sirtuins are a family of proteins that are homologous to yeast Sir2. Sirtuins are evolutionarily conserved as they exist in a wide range of organisms, from bacteria to mammals. In humans, there are seven sirtuins (SIRT1–SIRT7). These sirtuins have different

subcellular localizations: SIRT1 (also found in the cytoplasm) and SIRT6 are found in the nucleus, SIRT2 is primarily found in the cytoplasm (but is also found in nucleus), SIRT3, SIRT4 and SIRT5 are present in mitochondria, and SIRT7 is found in the nucleolus [1–3]. All sirtuins share well-conserved domains for

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NAD⁺ and peptide binding, which are also called sirtuin domains (Figure 1) [4]. At least four distinct enzymatic activities have been characterized in sirtuin family members: deacetylation (the transfer of an acetyl group from the substrate to ADP-ribose moiety of NAD⁺ and the generation of *O*-acetyl-ADP-ribose and nicotinamide [NAM]), ADP-ribosylation (the transfer of ADP-ribose moiety of NAD⁺ to the substrate), desuccinylation (the transfer of a succinyl group from the substrate to the ADP-ribose moiety of NAD⁺) and demalonylation (the transfer of a malonyl group to the ADP-ribose moiety of NAD⁺) [5–12]. Since NAD⁺ is required for the enzymatic activities of sirtuins, it has been suggested that they may be important metabolic sensors [13]. Although it is not fully established how sirtuins respond to NAD⁺ flux in cells, changes in the NAD⁺/NADH ratio or the reaction product NAM have been demonstrated to be critical [14–19]. The NAD⁺ levels, at least in mouse livers, oscillate in a circadian manner that peaks both late in the day and also late in the night [20,21]. However, SIRT1 activity does not seem to follow exactly the same pattern because either SIRT1 protein levels or activities only peak at night in mice [22,23]. This apparent inconsistency between NAD⁺ levels and SIRT1 activity has not been resolved yet.

To date, the deacetylation function of sirtuins has been best characterized among all the sirtuin enzymatic activities. It is well documented

that acetylation/deacetylation play pleiotropic roles in all biological systems, including gene transcription, protein stability, signal transduction and metabolism [24–27]. Protein acetylation status and sirtuin activities are dynamic and change in response to different metabolic conditions [24–27]. Mammalian sirtuins, except SIRT4, have characterized deacetylation activities on a variety of protein substrates described in Table 1.

As a founding member, SIRT1 can deacetylate histone (H1K26, H3K9 and H4K16) and non-histone substrates (e.g., FOXO1/3, PGC-1 α , p53, NF- κ B, CREB, TORC2, LXR, MyoD, MEF2, SREBP-1 and BMAL1; see Table 1). Thus, SIRT1 has pleiotropic cellular functions including cell proliferation, survival, anti-inflammation, antistress and metabolism [28,29]. SIRT2 deacetylates α -tubulin, PEPCK, FOXO3 and others for the regulation of mitosis, chromatin remodeling, gene transcription, autophagy and metabolism [3,30–37]. SIRT3 is a predominant mitochondrial sirtuin that deacetylates numerous proteins or enzymes, such as ACCS2, ALDH2, LCAD and SOD2, which are involved in diverse metabolic functions and antioxidative stress [38–56]. SIRT4 can inhibit glutamate dehydrogenase (GDH) activity and amino acid-stimulated insulin secretion in pancreatic β cells through NAD⁺-dependent ADP-ribosylation [8,9,57]. SIRT5 can deacetylate and desuccinylate CPS1 to promote ammonia detoxification through the urea cycle [11,58,59]. SIRT6 is involved in glucose homeostasis, chromatin remodeling and DNA repair through deacetylation of histone 3, lysines 9 and 56, CtIP and PARP1, respectively [60–70]. With regard to SIRT7, only p53 has been reported to be a substrate in the regulation of cell survival and cardiac function [71–74]. Since the scope of this review focuses on diabetes, here I mainly summarize the metabolic functions of sirtuins in Table 2 and discuss them as follows.

Sirtuin functions in pancreatic β cells

SIRT1 and SIRT4 have been reported to play roles in pancreatic β cells. SIRT1 can increase insulin gene transcription and glucose-stimulated insulin secretion (GSIS). This has been confirmed in *Sirt1*-knockout and β -cell-specific overexpression transgenic mice (BESTO) [75–78]. GSIS was blunted in the knockout mice and elevated in the BESTO mice. One potential mechanism may be the repression of the *UCP2* gene expression

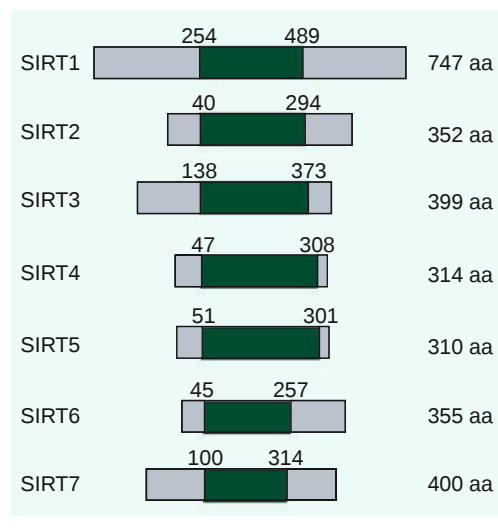


Figure 1. Human sirtuin proteins and their domain structure. The conserved sirtuin domain is shaded. The protein sequences and annotations are based on the NCBI Gene data set.

Table 1. The identified substrates of sirtuins.

Sirtuin	Known substrates	Process involved	Ref.
SIRT1	ACSS1: K661	Conversion of acetate to acetyl-CoA	[169]
	AR: K630	Androgen receptor signaling	[170]
	BMAL1: K537	Circadian rhythms	[23]
	β -catenin	Suppression of tumorigenesis	[171]
	Cortactin	Cell migration	[172]
	CREB: K136	Glucose and lipid metabolism	[81]
	CRTC2: K628	Gluconeogenesis	[87]
	DNMT1: K1349, 1415	DNA methylation	[173]
	eNOS: K496, K506	Endothelium vasodilation	[174]
	FOXO1: K242, K245, K262, K274, K294, K559	Transcription, autophagy, among others	[175–177]
	FOXO3: K242, K245, K259, K271, K290, K569	Transcription	[177,178]
	FOXO4: K186, K189, K215, K237, K407	Transcription	[177]
	Histone H1: K26	Heterochromatin formation	[179]
	H2A.x	DNA damage response	[180]
	H2A.z: K15	Cardiac hypertrophy	[181]
	Histone H3: K9	Chromatin remodeling	[179]
	Histone H3: K56	Chromatin remodeling	[182]
	Histone H4: K16	Chromatin remodeling	[179]
	HIV Tat: K50	HIV transcription	[183]
	HNF4 α	Transcription	[184]
	Ku70: K539, K542	DNA repair	[148]
	LKB1: K48	Cell proliferation and metabolism	[130]
	LXR α : K432	Lipid metabolism	[97]
	c-Myc: K323	Cell proliferation	[185]
	MyoD: K99, K102, K104	Muscle differentiation	[186]
	p53: K317, K370, K382	Cell survival and stress response	[187,188]
	p300: K102, K1024	Protein acetylation	[189]
	PARP1	Cell survival	[190]
	PCAF	DNA damage response	[186]
	PER2	Circadian rhythms	[22]
	PGC-1 α : K77, K144, K183, K253, K270, K277, K320, K412, K441, K450, K757, K778	Mitochondrial biogenesis and metabolism	[84]
	PGC-1 β	Glucose and lipid metabolism	[191]
	NF- κ BRelA/p65: K310	Transcription	[192]
	Rb: K873, 874	Cell cycle control	[193]
	Smad7: K64, K70	Apoptosis	[194]
	SREBP-1c: K289, K309	Lipid metabolism	[95]
	SUV39H1: K266	Heterochromatin formation	[195]
	TAF(I)68	rDNA transcription	[196]
	Zyxin	Cytoskeletal dynamics	[197]
SIRT2	CDC20	Mitosis	[31]
	CDH1	Mitosis	[31]
	FOXO1: K262, K265, K274	Adipogenesis and autophagy	[33,35]
	FOXO3: K242, K259, K290, K569	Oxidative stress and ubiquitination	[30,116]
	Histone H3: K56	DNA damage response	[198]
	Histone H4: K16	Mitosis	[3]
	NF- κ BRelA/p65: K310	Transcription	[34]
	p53	Cell survival and stress response	[199]
	p300: K418, K423, K1542, K1546, K1549, K1699, K1704, K1707	Chromatin remodeling	[200]
	Par3: K831, K848, K881, K1327	Myelination	[201]
	PEPCK: K70, K71, K594	Gluconeogenesis	[32]
	PRLR	Prolactin receptor dimerization	[202]
	α -tubulin: K40	Mitosis	[36]

ETC: Electron transport chain; PTP: Permeability transition pore; Rb: Retinoblastoma.

Table 1. The identified substrates of sirtuins (cont.).

Sirtuin	Known substrates	Process involved	Ref.
SIRT3	ACSS2: K635	Conversion of acetate to acetyl-CoA	[169,203]
	ALDH2: K377	Alcohol metabolism	[38]
	CYPD: K166	Mitochondrial PTP control	[204]
	GDH	Glutamate oxidation and insulin secretion	[56]
	HMGCS2: K310, K447, K473	Ketogenesis	[50]
	IDH2	Anti-oxidative stress	[48]
	LCAD: K42	Fatty acid oxidation	[53]
	MRPL10: K124, K162, K196	Mitochondrial protein synthesis	[47]
	NDUF9A	Mitochondrial ETC	[54]
	OTC: K88	Urea cycle	[43]
	SDH	Mitochondrial ETC	[205]
	SOD2: K53, K68, K89, K122	Anti-oxidative stress	[51]
SIRT4	GDH	Glutamate oxidation and insulin secretion	[8,9]
SIRT5	CPS1	Urea cycle	[59]
	CS	Citric acid cycle	[11]
	GDH	Amino acid-induced insulin secretion	[11]
	GOT2	Amino acid metabolism	[11]
	HMGCS2	Ketogenesis	[11]
	MDH	Citric acid cycle	[11]
	TST	Cyanide detoxification	[11]
SIRT6	CtIP: K432, K526, K604	DNA repair	[66]
	H3K9	Chromatin remodeling	[69]
	H3K56	Chromatin remodeling	[67,206]
	PARP1: K521 (mono-ADP-ribosylation)	DNA repair	[60]
SIRT7	p53	Cell survival	[72]

ETC: Electron transport chain; PTP: Permeability transition pore; Rb: Retinoblastoma.

by SIRT1. Moreover, SIRT1 also protects β cells against inflammation-induced apoptosis [79]. By contrast, SIRT4 inhibits amino acid-induced insulin secretion through the ADP-ribosylation of GDH [8,9].

Sirtuin functions in the liver

■ Glucose metabolism

Several sirtuins have been found to play important roles in the liver. SIRT1 has been reported to regulate hepatic gluconeogenesis. However, reports are still conflicting with regard to either activation or inhibition of this process. Motta *et al.* reported that SIRT1 might inhibit gluconeogenesis through suppression of *PEPCK* gene expression, which is one of the key enzymes in the gluconeogenic process [80]. Qiang *et al.* suggest that SIRT1 suppresses hepatic gluconeogenesis via direct deacetylation and inhibition of CREB, a critical transcription factor for *PEPCK* [81]. Recently, Wang *et al.* have found that SIRT1 also suppresses the hepatic expression of *PEPCK* and glucose 6-phosphatase genes via upregulation of *Rictor*, a unique component of the mTORC2 complex, and subsequent inhibition of FOXO1 activity [82]. Several other reports

suggest that SIRT1 might upregulate gluconeogenic genes through the activation of FOXO1 and PGC-1 α via direct deacetylation [83–86]. A study has indicated a time-dependent switch from early CRT2 to late FOXO1 activation; however, SIRT1 plays dual roles by not only inhibiting CRT2 but also promoting FOXO1 activity [87]. SIRT1 can also activate gluconeogenesis via inhibition of STAT3 [88]. Moreover, there is also a feedback mechanism in which the SIRT1/FOXO1 pathway induces the expression of *SHP* and subsequently, SHP inhibits FOXO1 transcriptional activity [83]. Apparently the regulation of hepatic gluconeogenesis by SIRT1 is quite complex and dynamic under different conditions [81–88]. It requires more systemic study to pinpoint how SIRT1 is involved in gluconeogenesis in a time course. SIRT2 also regulates hepatic gluconeogenesis through direct deacetylation of *PEPCK* [32]. Additionally, SIRT1 and SIRT6 regulate glycolysis through distinct mechanisms. SIRT1 may repress the expression of glucokinase and pyruvate kinase genes through deacetylation of PGC-1 α and FOXO1 [84,89,90], whereas SIRT6 suppresses these two genes via deacetylation of H3K9 [64].

Table 2. Sirtuin metabolic functions.

Gene	Functions	Ref.
<i>SIRT1</i>	Pancreatic β cells	
	▪ Increases insulin gene transcription	[75–79]
	▪ Decreases <i>UCP2</i> gene transcription	[75,76,78,207]
	▪ Increases glucose-stimulated insulin secretion	[75–79]
	▪ Protects against cytokine toxicity via NF- κ B downregulation	[79]
	▪ Protects against oxidative stress via upregulation of NeuroD and MafA	[175]
	Liver	
	▪ Regulates gluconeogenesis	[32,80,82–88]
	▪ Inhibits glycolysis	[84,89,90]
	▪ Inhibits lipogenesis	[91,95,96]
	▪ Increases fatty acid oxidation	[92]
	▪ Inhibits cholesterol biosynthesis	[96–98]
	▪ Improves hepatic insulin sensitivity	[82]
	▪ Inhibits oxidative stress, inflammation and ER stress	[82,92,94,208]
	▪ Regulates circadian rhythms	[22,23]
	▪ Modulates NAD biosynthesis	[20,21]
	Brain	
	▪ Mediobasal hypothalamic SIRT1 inhibits hepatic glucose production	[117]
	▪ Central SIRT1 positively regulates food intake and energy expenditure	[118–124]
	▪ Regulates physical activities	[123]
	Skeletal muscle	
	▪ Increases insulin sensitivity	[99,103]
	▪ Increases mitochondrial biogenesis	[100–102]
	▪ Increases fatty acid oxidation	[100,104]
<i>SIRT2</i>	Adipose tissue	
	▪ Increases adiponectin biosynthesis and secretion	[109–111]
	▪ Increases lipolysis	[112,113]
	▪ Inhibits adipogenesis	[112]
	Liver	
	▪ Increases hepatic gluconeogenesis via deacetylation of PEPCK	[32]
<i>SIRT2</i>	Adipose tissue	
	▪ Decreases oxidative stress via deacetylation of FOXO3	[116]
	▪ Inhibits adipocyte differentiation via deacetylation of FOXO1	[35,115]
<i>SIRT3</i>	Liver	
	▪ Regulates energy homeostasis via control of ETC complexes I and II	[54]
	▪ Reduces oxidative stress via deacetylation of SOD2	[51]
	▪ Increases fatty acid oxidation via deacetylation of LCAD and others	[39,43,50,53]
	▪ Increases ketone body production via deacetylation of HMGCS2	[50]
	▪ Promotes the urea cycle via deacetylation of OTC	[43]
	Skeletal muscle	
	▪ Induced by fasting, caloric restriction and exercise	[105–107]
	▪ Decreased by high-fat diet	[40,41,107]
	▪ Inhibits mitochondrial protein synthesis via deacetylation of MRPL10	[47]
	▪ Increases mitochondrial oxidation	[39,40]
	▪ Decreases ROS and insulin resistance	[40,108]
	▪ Increases mitochondrial biogenesis	[108]
	Brain	
	▪ Protects against age-related hearing loss by reducing oxidative damage	[48]
<i>SIRT4</i>	Pancreatic β cells	
	▪ Decreases insulin secretion via inhibition of GDH	[8,9]

ETC: Electron transport chain; GDH: Glutamate dehydrogenase; ROS: Reactive oxygen species.

Table 2. Sirtuin metabolic functions (cont.).		
Gene	Functions	Ref.
SIRT5	Liver	
	▪ Regulates the urea cycle via deacetylation of CPS1	[58,59]
SIRT6	Liver	
	▪ Inhibits glycolysis and lipogenesis via deacetylation of H3K9	[64]
	▪ Increases fatty acid oxidation via deacetylation of H3K9	[64]
	Brain	
	▪ Regulates somatic growth and adiposity via deacetylation of H3K9 and H3K56 in the brain	[63]
	Skeletal muscle	
	▪ Inhibits basal- and insulin-stimulated glucose uptake	[61,62]
	Adipose tissue	
	▪ Decreases triglyceride synthesis via downregulation of DGAT1	[65]
	▪ Inhibits glucose uptake	[61]
SIRT7	Regulates Pol I transcription and p53 function, particularly protects against stress, apoptosis and inflammation in the heart	[72,74]

ETC: Electron transport chain; GDH: Glutamate dehydrogenase; ROS: Reactive oxygen species.

■ Lipid metabolism

In addition to the regulation of glucose metabolism, SIRT1 also modulates hepatic lipid homeostasis. This function has been demonstrated by *Sirt1* knockout and transgenic mouse models. The liver-specific *Sirt1* knockout mice develop hepatic steatosis on a high-fat diet [91,92], whereas the overexpression of *Sirt1* specifically in the liver or globally, protects mice from developing fatty liver disease [93,94]. Several potential mechanisms may contribute to the beneficial effects of SIRT1 in triglyceride metabolism. First, SIRT1 increases hepatic fatty acid oxidation, possibly through the activation of PGC-1 α /PPAR α [92]. Second, SIRT1 improves cellular functions by reducing oxidative and endoplasmic reticulum (ER) stress [94]. Third, SIRT1 can inhibit lipogenesis through deacetylation-induced SREBP-1c degradation and downregulation of *ChREBP* gene expression [91,95,96]. However, constitutive systemic overexpression of *Sirt1* in mice also causes elevated hepatic and circulating levels of triglycerides and the inhibition of CREB by *Sirt1*-mediated deacetylation may play a critical role in this dysregulation [81]. SIRT1 has also been reported to control cholesterol homeostasis. Knockdown or knockout of *Sirt1* in mouse livers leads to an elevated level of total hepatic cholesterol. This may be attributed to the dysregulation of SREBP-2 and LXR protein stability and activities [96–98]. SIRT3 also plays an important role in lipid metabolism through deacetylation of some key enzymes including long chain acyl-CoA dehydrogenase for fatty acid oxidation and

3-hydroxy-3-methylglutaryl-CoA synthase 2 for ketogenesis [39,43,50,53]. SIRT6 can improve lipid homeostasis through inhibition of lipogenesis and activation of fatty acid oxidation by modulating the expression of numerous genes such as *FASN*, *ACCI*, *ELOVL6*, *SCD1*, *CPT1* and *ACOX1* [64]. By contrast, SIRT4 has been shown to inhibit fatty acid oxidation in the liver and skeletal muscle [57].

Sirtuin functions in skeletal muscle

Sirtuins also play critical roles in skeletal muscle physiology. SIRT1 has been demonstrated to increase insulin sensitivity and insulin-stimulated glucose uptake in skeletal muscle or myotubes by downregulating *PTP1B* [99]. Mitochondrial quality and quantity are critical for skeletal muscle function. Significantly, SIRT1 can enhance mitochondrial biogenesis, and thus increases muscle function, partly through the activation of PGC-1 α [100–102]. SIRT1 also mediates calorie restriction (CR)-enhanced insulin sensitivity via the inhibition of STAT3-induced *p55 α /p50 α* of PI3K [103]. SIRT1 also boosts fatty acid oxidation in the skeletal muscle [100,104]. As a mitochondrial sirtuin, SIRT3 can be induced by fasting, caloric restriction and exercise [105–107]. SIRT3 activation can lead to increased mitochondrial biogenesis and function and can decrease oxidative stress [40,105–108]. By contrast, SIRT6 inhibits basal- and insulin-stimulated glucose uptake in the skeletal muscle by the inhibition of Akt phosphorylation and the suppression of recruitment of the glucose transporters, GLUT1 and GLUT4, to plasma membrane [62].

Sirtuin functions in adipose tissue

Adipose tissue has been increasingly appreciated to play a critical role in energy homeostasis. At least three sirtuins (SIRT1, 2 and 6) have been implicated in adipose functions. SIRT1 can increase the expression of adiponectin, an important adipokine for energy metabolism, in part through deacetylation of FOXO1 [109–111]. SIRT1 also inhibits adipogenesis and activates lipolysis through repression of PPAR γ , a key adipose regulator [112]. Through deacetylation and activation of FOXO1, SIRT1 induces the transcription of adipose triglyceride lipase and promotes lipolysis in adipose tissue [113]. In 3T3-L1 adipocytes, *SIRT1* knockdown decreases insulin signaling and insulin-stimulated glucose uptake [114]. SIRT2 can also inhibit adipocyte differentiation, partly through FOXO1 deacetylation [35,115]. In addition, SIRT2 activates FOXO3 in adipocytes to reduce oxidative stress [116]. SIRT6 has been reported to downregulate the expression of the *DGAT1* gene and decrease triglyceride biosynthesis [65].

Sirtuin functions in the brain

The brain plays a key role in the integration of systemic energy homeostasis. Interestingly, mediobasal hypothalamic SIRT1 has been implicated in the suppression of hepatic glucose production by resveratrol [117]. Moreover, CNS SIRT1 positively regulates food intake and energy expenditure [118–124]. Inhibition of central Sirt1 blocks ghrelin-induced food intake in rodents partly through regulation of p53 and melanocortin 4 receptor pathways [118,119,124]. Hypothalamic SIRT1 also mediates dietary restriction-induced neural adaption by increasing physical activity and body temperature [123]. Through chromatin remodeling, particularly deacetylation of H3K9 and H3K56, neural SIRT6 regulates normal somatic growth and adiposity and protects against obesity [63].

An integrative view of sirtuins in metabolism

As described above, sirtuins play distinct roles in different tissues, which are consistent with the tissue-specific functions. In general, each sirtuin has unique functions in a given tissue. For example, SIRT1 promotes mitochondrial biogenesis in skeletal muscle and SIRT5 detoxifies ammonia in the liver [58,59,101,125]. Our current understanding is that sirtuins also functionally cooperate to achieve systemic homeostasis. For example,

SIRT1 and SIRT3 both control fatty acid oxidation; however, SIRT1 does so at the gene transcription level mostly through PGC-1 α , whereas SIRT3 directly controls the activity of metabolic enzymes involved in the fatty acid oxidation (FAO) process [126]. Another example is that although both SIRT1 and SIRT2 regulate hepatic gluconeogenesis, again, SIRT1 acts via the control of *PEPCK* and *G6pc* gene expression (up or down) while SIRT2 directly deacetylates *PEPCK* and increases its stability [32,80,82–88]. Regarding SIRT4, only a few studies have been carried out but they mostly reveal an inhibitory effect on metabolism – inhibition of amino acid-stimulated insulin secretion in pancreatic β cells as well as inhibition of fatty acid oxidation in the liver and skeletal muscle [8,9,57].

Targeting sirtuins for diabetes therapeutics

As summarized above, most, if not all, sirtuins have been implicated in metabolism and energy homeostasis. Therefore, they may become useful therapeutic targets for diabetes and the metabolic syndrome. Although there are conflicting reports in the literature, resveratrol has been directly or indirectly linked to SIRT1 for metabolic functions, possibly involving AMPK and other pathways [14,93,127–135]. Indeed, resveratrol and SIRT1 share numerous similar effects. For example, resveratrol has been shown to improve insulin sensitivity in obese animals and humans, increase mitochondrial biogenesis and function and protect against inflammation (Table 3) [101,136–140]. A recent report has shown that 30-day resveratrol supplementation increases activated AMPK and protein levels of SIRT1 and PGC-1 α in skeletal muscle of obese subjects, decreases triglycerides in the liver and improves the homeostatic model assessment index and inflammatory markers [141]. Resveratrol can also improve dyslipidemia, ketoacidosis and inflammation in Type 1 diabetic rats [136,142]. Resveratrol is also found to increase GSIS in pancreatic β cells [77]. In most cases, the processes that resveratrol is involved in are also partially related to SIRT1 functions. However, it should be pointed out that it is still controversial as to whether resveratrol directly acts on SIRT1, since AMPK deficiency blunts resveratrol effects in mice [128]. Additionally, some reports suggest that SIRT1 overexpression may also cause increased lipogenesis [81,143,144]. More mechanistic studies are needed to clarify

Table 3. Sirtuin activators and metabolic effects.

Compound name	Metabolic effects	Ref.
Resveratrol	Improves insulin sensitivity	[99,117,140,141,209]
	Improves hyperglycemia	[140,141]
	Increases mitochondrial biogenesis	[101,137]
	Increases glucose uptake	[210–214]
	Increases lipid transport and β -oxidation in skeletal muscle	[137,141]
	Regulates hepatic gluconeogenesis	[117,140]
	Improves ketoacidosis and muscle protein degradation in T1DM	[136]
	Increases insulin secretion in pancreatic β cells	[77,215]
	Improves hepatic steatosis and hepatocyte ballooning	[208,216,217]
	Improves dyslipidemia	[93,218–220]
	Inhibits adipogenesis	[112,114,221,222]
	Protects against inflammation	[139,141,223,224]
	Protects against oxidative stress	[138,209,223,225]
SRT1720	Improves glucose homeostasis	[104,155]
	Increases insulin sensitivity	[104,155]
	Increases mitochondrial function	[104,155]
	Reduces lipogenic gene expression	[96,155,226]
NMN	Protects against inflammation in pancreatic islets	[227]
	Increases glucose-stimulated insulin secretion	[160,162,207]
	Improves glucose tolerance in obesity	[162]
	Improves glucose and lipid homeostasis in age-induced diabetes	[162,207]

T1DM: Type 1 diabetes mellitus.

how and when SIRT1 contributes to beneficial or adverse effects on lipid metabolism.

CR has been demonstrated to be effective for extending lifespan and improving age-related abnormalities [145–147]. Although it is still controversial whether sirtuins may increase lifespan, the current literature tends to suggest that there is some connection between sirtuin functions and CR effects. First, it has been reported that *SIRT1* gene expression is induced in fasting and CR-treated mice, rats and human subjects [84,148–150]. Second, transgenic and knockout mouse models indicate that SIRT1 may mediate some of the CR effects. For instance, *Sirt1* knockout mice are unresponsive to CR in activity changes [151]. Mice carrying the *Sirt1* transgene in the β -actin locus also manifest numerous characteristics of CR, including increased physical activity, decreased blood cholesterol, insulin and glucose as well as delayed reproduction [152]. Third, the metabolic functions of SIRT1, particularly in glucose, lipid and mitochondrial biogenesis, implicate its role in CR [84,96,97,112]. However, whether SIRT1 mediates CR-induced longevity is debatable because some yeast strains are still long-lived in the absence of Sir2 (yeast homolog of SIRT1) and overexpression or activation of SIRT1 in mice does not increase lifespan on a regular diet [133,152–155]. Additionally, SIRT1 is likely to function differently in a tissue-specific

manner. Chen *et al.* have reported that Sirt1 activities increase in skeletal muscle and white adipose tissue but decrease in the liver on a CR regimen [156]. More intriguingly, different regions of the brain respond differently to CR in the expression of *Sirt1* gene in mice – an increase in the cortex and hippocampus and a decrease in the midbrain and cerebellum [157]. In addition to SIRT1, other sirtuins may be also implicated in CR. For instance, SIRT3 has been shown to mediate some of the anti-oxidative stress effects by CR in the liver and in the brain, including cochlear neurons [48,51].

In pursuit of the development of small-molecule activators of sirtuins, several compounds including SRT1720 have been reported to specifically activate SIRT1 and manifest pharmacological efficacy on Type 2 diabetes in rodents [155]. However, whether those small molecules directly bind to SIRT1 is still debatable [158,159]. Another approach involving an increase in cellular NAD⁺ levels has been also tested in mouse models. NAD⁺ biosynthesis comprises of at least four pathways according to substrates: tryptophan (*de novo* synthesis), nicotinic acid, nicotinamide and nicotinamide riboside. It has been reported that the rate-limiting enzyme for the salvage biosynthesis of NAD⁺ – nicotinamide phosphoribosyltransferase (NAMPT) – plays a critical role in NAD⁺ homeostasis and insulin secretion in

mice [15,160,161]. As one of the key intermediates of NAD⁺ biosynthesis, nicotinamide mononucleotide (NMN; a product of the NAMPT enzyme) has been shown to have protective effects against obesity- and aging-induced diabetes [162]. Daily injections of 500 mg/kg body weight of NMN for 5–7 days improves glucose intolerance and insulin resistance in high-fat-induced diabetic mice. Similar treatment in old diabetic mice also demonstrated an improvement in glucose and lipid homeostasis [162].

Since no drug targeting sirtuins has yet been approved for clinical use and only limited animal studies have been performed, the advantages and disadvantages of sirtuin activators compared to current diabetes drugs are not clear. Some reports suggest that SIRT1 might mediate part of the metformin effects in the suppression of hepatic gluconeogenesis, the activation of fatty acid oxidation in skeletal muscle and protection against hyperglycemia-induced retina damage [14,163,164]. It is possible that AMPK activation by metformin may also stimulate SIRT1 activity [14]. Interestingly, it is hypothalamic SIRT1 but not AMPK that mediates resveratrol-suppressed hepatic glucose production [117]. Moreover, SIRT1 might also activate AMPK according to several lines of evidence [93,127,130,164–167]. Since sirtuins can be modulated by increasing cellular NAD⁺ levels, nutraceutical approaches by providing NAD⁺ biosynthesis substrates or

intermediate metabolites, such as NMN, may be also useful in the prevention or treatment of Type 2 diabetes [160,162,168].

Conclusion & future perspective

Sirtuins have pleiotropic functions in metabolism including glucose and lipid metabolism, energy expenditure and insulin secretion. Certainly, we still have many unanswered questions with respect to sirtuin biology and their therapeutic potentials. For example, what determines sirtuin activities? Why do *Sirt2/3/4/5* deficient mice have mild phenotype? How do we design specific assays for each sirtuin? How can we target sirtuins for specific diseases such as diabetes without complications? Through future investigation, we should be able to address those questions and choose the best available approach for drug development.

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