



## Mini Review

**Sirtuins: Novel targets for metabolic disease in drug development**

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## ABSTRACT

Calorie restriction extends lifespan and produces a metabolic profile desirable for treating diseases such as type 2 diabetes. SIRT1, an NAD<sup>+</sup>-dependent deacetylase, is a principal modulator of pathways downstream of calorie restriction that produces beneficial effects on glucose homeostasis and insulin sensitivity. Activation of SIRT1 leads to enhanced activity of multiple proteins, including peroxisome proliferator-activated receptor coactivator-1 $\alpha$  (PGC-1 $\alpha$ ) and FOXO which helps to mediate some of the in vitro and in vivo effects of sirtuins. Resveratrol, a polyphenolic SIRT1 activator, mimics the effects of calorie restriction in lower organisms and in mice fed a high-fat diet ameliorates insulin resistance. In this review, we summarize recent research advances in unveiling the molecular mechanisms that underpin sirtuin as therapeutic candidates and discuss the possibility of using resveratrol as potential drug for treatment of diabetes.

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As a consequence of the increased prevalence of obesity, type 2 diabetes mellitus (T2D) has become a global epidemic, with more than 300 million individuals worldwide projected to be afflicted with T2D by the year 2025 [1]. T2D is characterized by insulin resistance in the target tissues [2]. The peptide hormone insulin lowers blood glucose levels by facilitating glucose uptake, mainly into skeletal muscle and fat tissue, and by inhibiting endogenous glucose production in the liver [3]. However, insulin resistance occurs when a normal dose of the hormone is incapable of eliciting these metabolic responses [3]. Currently, alleviating insulin resistance is still one of the key avenues to treating type 2 diabetes [4].

It has been known since the 1930s that limiting the food consumed by laboratory rodents increases their lifespan [5]. Recent genetic and molecular studies in model organisms, in fact, suggest that low caloric intake might be a regulated process, with the silent information regulator 2 (Sir2) gene playing an important role. This gene was first identified because it mediates gene silencing in yeast [6]. The Sir2 ortholog, SIRT1, a member of the Sir2 family called sirtuins, might mediate a broad array of physiological effects that occur in age-related disease, diabetes, and tumorigenesis [7–9]. Resveratrol, a component in many red wines, has been demonstrated to activate SIRT1 and extends lifespan in multiple model organisms [10,11]. In mice, resveratrol has also displayed positive effects on outcomes in multiple disease states including cancer, ageing and metabolic diseases [12]. This review examines the experimental work implicating sirtuins, and SIRT1 in particular, as modulators of cellular metabolism in different physiological contexts and the potential therapeutic implications of sirtuins.

**Overview of sirtuins**

Sir2 is the founding member of a large and diverse family of protein-modifying enzymes known as sirtuins that regulate key pathways throughout biology, in eubacteria, archaea, eukaryotes, and even viruses [13]. Consistent with the role of yeast Sir2 in silencing transcription, this enzyme is a histone deacetylase [14–16]. Unlike previously characterized histone deacetylases, however, which catalyze the simple hydrolysis of acetyllysine [17,18], Sir2 was shown to deacetylate lysine residues in a novel chemical reaction that consumes nicotinamide adenine dinucleotide, releasing nicotinamide, O-acetyl ADP ribose, and the deacetylated substrate. In the mammalian system, sir2's mammalian counterpart SIRT1 has been shown to be involved in multiple metabolic including glucose homeostasis [19], insulin secretion [20,21], and lipid mobilization [22]. Studies continue to uncover the roles that members of the sirtuin family play in important biological processes, such as lifespan regulation and cellular response to stress [10,23].

**Sirtuins and insulin signal pathway**

Insulin signaling pathway is initiated by auto tyrosine phosphorylation of insulin receptor upon insulin binding, and subsequently tyrosine phosphorylations of several key adaptor proteins including insulin receptor substrate 1 (IRS-1) and IRS-2. The phosphorylated IRS proteins further transmit insulin signaling to downstream events, mainly through two kinase cascades, the mitogen-activated protein kinase cascade (MAPK) and phosphatidylinositol 3-kinase-Akt cascades. The liver plays an important role in glucose and lipid homeostasis. Among its many functions, production of glucose by the liver is an essential process that

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contributes to normalization of systemic glucose levels [24,25]. A recent study demonstrated that suppression of SIRT1 activity selectively inhibited insulin-induced tyrosine phosphorylation of insulin receptor substrate-2 (IRS-2) and suggests a possible regulatory effect of SIRT1 on insulin signaling pathway, through deacetylation of IRS-2 protein [26].

It is well established that reduced intake of dietary energy results in metabolic changes similar to fasting [27,28]. It is reported that SIRT1 is up-regulated by fasting in the fat, muscle, and liver [23]. The majority of rate-limiting enzymes in key pathways involved in glucose and lipid homeostasis are controlled at the transcriptional level [29]. In the last several years, the peroxisome proliferator-activated receptor coactivator (PGC)-1 $\alpha$ / $\beta$  and liver X receptor (LXR)/sterol response element-binding protein (SREBP) have been identified as key transcriptional regulators of many metabolic enzymes and pathways [30–32]. SIRT1 has also been suggested to be involved in the processes of glucose homeostasis and insulin secretion. Rodgers et al. showed that SIRT1 controls hepatic glucose metabolism by interacting with and deacetylating PGC-1 $\alpha$ , a key transcriptional coactivator that controls glucose metabolism in the liver at the level of gene transcription. Concomitant with this effect is a repression of glycolytic genes [19]. Thus, SIRT1 stimulation of gluconeogenesis operates against the hepatic insulin response pathway that stores glucose and represses gluconeogenesis. Other groups have shown that SIRT1 represses peroxisome proliferator-activated receptor- $\gamma$  (PPAR $\gamma$ ) function, increasing lipolysis in white adipose tissue and insulin secretion in pancreatic  $\beta$  cells [20–22]. For example, Bordone et al. reported that a short interfering RNA-enforced reduction of SIRT1 expression in  $\beta$  cell lines leads to an increase in the expression of uncoupling protein 2 (UCP2) and a reduction in insulin secretion [20]. This finding might phenocopy food deprivation, known to induce UCP2 expression and reduce insulin secretion. In a second study, SIRT1 expression was elevated specifically in the mouse pancreas, leading to reduced UCP2 expression and enhanced insulin secretion during glucose stimulation [21]. SIRT1 also induces gluconeogenic genes and hepatic glucose output through the transcriptional coactivator PGC-1 $\alpha$  [19]. It is the storage and not the mobilization of fat that has been consistently associated with longevity extension in worms, flies, and mice, apparently as part of a program aimed at surviving long periods of starvation [33]. Elevated SIRT1 expression might extend lifespan by decreasing fat storage. Thus, sirtuins also have functions in adipose tissue. For instance, Picard et al. show that SIRT1 promotes fat mobilization in mammalian adipocytes by repressing peroxisome proliferator-activated receptor- $\gamma$  [22].

### Sirtuins and its substrates

Sirtuins comprise a large gene family of ancient origins, with homologs present from yeast to humans [34]. SIRT1, currently the best studied sirtuin homolog, is expressed in metabolic tissues including liver, skeletal muscle, adipose tissue, pancreas, and brain, where it regulates  $\beta$  cell and neuron survival, hepatic gluconeogenesis, insulin secretion, and adiposity [35]. To date, SIRT1 deacetylates approximately a dozen known substrates, including the transcription factors forkhead box O (FOXO) 1, 3, and 4; nuclear factor  $\kappa$ B (NF- $\kappa$ B) subunit p65; and peroxisome proliferator-activated receptor- $\gamma$  (PPAR $\gamma$ ) coactivator-1 $\alpha$  (PGC-1 $\alpha$ ). Other important substrates of SIRT1 include histones H1, H3, and H4, with histone deacetylation causing gene silencing. It is conceivable that SIRT1 gene silencing maybe mediated by deacetylation of multiple substrates involved in transcription [36].

Recently, Sun et al. demonstrated a direct regulation of insulin action by SIRT1 through its actions to control PTP1B gene expres-

sion. In insulin resistant cultured cells and mice, SIRT1 expression is downregulated. SIRT1 knockdown or inhibition impairs insulin signaling and insulin-stimulated glycogen synthesis, whereas SIRT1 overexpression ameliorates existing insulin resistance and impaired glucose transport in cultured cells. It was showed that these effects are mediated in part by silencing PTP1B expression through histone H3 deacetylation. Interestingly, SIRT1 overexpression in non-insulin-resistant cells does not affect insulin signaling or glucose transport or markedly affect PTP1B expression, suggesting that SIRT1's action on insulin signaling and PTP1B is minimal in insulin-sensitive states. Previous studies have shown that shown that PGC-1 $\alpha$ 's ability to induce gluconeogenesis is largely regulated by acetylation [19,37]. Recently, Rodgers et al. showed that in vivo knockdown and overexpression of SIRT1 is sufficient to alter endogenous acetylation of PGC-1 $\alpha$  [38]. The study showed that in the fasted liver the acetylation state of PGC-1 $\alpha$  strongly correlates with repression/induction of gluconeogenic genes. Importantly, when PGC-1 $\alpha$  levels are reduced by shRNA knockdown, SIRT1 overexpression no longer reduces glucose tolerance or up-regulates gluconeogenic genes, suggesting that SIRT1 requires PGC-1 $\alpha$  for these effects. Conversely, it seems that to a large extent that PGC-1 $\alpha$  requires SIRT1 to stimulate glucose production. SIRT1 knockdown reduces the effect of PGC-1 $\alpha$  overexpression in a PTT (pyruvate-tolerance test) and on gluconeogenic gene expression. Thus, they suggested that the fasting induction, interaction, and deacetylation of PGC-1 $\alpha$  by SIRT1 are an important regulatory component in the fasting induction of gluconeogenesis.

FoxO proteins are phylogenetically conserved and regulate key physiological functions, including cell proliferation, cell differentiation, and survival [39–42]. In addition, FoxO functions in complex ways to regulate insulin signaling and glucose and lipid metabolism [40,43]. In *Drosophila*, activation of dFoxO in fat body represses insulin-dependent signaling and increases life span [44]. Similarly in mammals, FoxO1 regulates multiple metabolic pathways in liver and pancreatic  $\beta$  cells [45], and transgenic expression of FoxO1 in various tissues leads to impaired insulin sensitivity and glucose intolerance [45–47]. On the other hand, both dFoxO and the mammalian equivalent FoxO1 activate transcription of the insulin receptor and insulin receptor substrate-2 (IRS-2) in *Drosophila* S2 cells and mouse C2C12 cells, which sensitizes the cellular response to insulin [48]. Also, whereas transgenic overexpression of constitutively active FoxO1 (caFoxO1) in liver triggers impaired fasting glucose and hyperinsulinemia [45,48], acute overexpression of caFoxO1 in liver reduces plasma insulin, glucose, and triglycerides [49]. And paradoxically, FoxO3-deficient mice exhibit impaired insulin sensitivity [50]. SIRT1 and the FOXO transcription factor FOXO3 formed a complex in cells in response to oxidative stress, and SIRT1 deacetylated FOXO3 in vitro and within cells. Commit with this finding, Lemieux et al. demonstrated that SIRT1 modulate the activity of FoxO in vivo [51]. In different tissues, FoxO transcriptional activity is capable of either sensitizing or inhibiting insulin responsiveness. For example, in both *Drosophila* and mammals, FoxO1 triggers insulin sensitization because of its actions to upregulate expression of the insulin receptor [12]. Interestingly, in *db/db* mice, hepatic FoxO is nuclear-localized and Akt is hyperphosphorylated in concert with dysregulated expression of genes controlling gluconeogenesis, a finding that suggests that FoxO-dependent mechanisms contribute to insulin resistance in this model of type 2 diabetes [52].

### Sirtuins and its activator

Resveratrol (RSV; 3,5,4-trihydroxystilbene) a naturally occurring phytoalexin found in juice and red wines, has been reported to activate SIRT1 and extends life span in multiple model

organisms [10,11]. Recently, RSV was reported to improve health and survival of mice on a high-calorie diet by reducing IGF-1 levels and increasing PGC-1 $\alpha$  activity [12]. Furthermore, it was reported that RSV ameliorates common diabetes mellitus symptoms [53], such as body weight loss, polyphagia, and polydipsia in streptozotocin-induced diabetes mellitus (DM) rats [54]. As discussed, SIRT1 is inducibly transcribed in response to CR or fasting, suggesting a broad role in mammalian physiology as a mediator of adaptation to nutrient deprivation. These functions imply that pharmacological modulation of SIRT1 activity is likely to have wide-reaching and not necessarily specific effects on human physiology. In diabetic conditions, both activation and inhibition of SIRT1 are worth considering as pharmacological approaches. Activation might reduce adipogenesis by repressing the fat regulator peroxisome proliferator-activated receptor- $\gamma$  [22] and possibly increase insulin release in the pancreas [20,21]. Recently, it was reported that activation of SIRT1 decreases adipocyte formation during osteoblast differentiation of mesenchymal stem cells [55]. Conversely, inhibition of SIRT1 could decrease glucose signaling in the pancreas, as indicated by the SIRT1 knockout mouse [20]. The balance of effects on insulin signaling pathways from pharmacological SIRT1 activation or inhibition needs to be experimentally addressed.

Resveratrol has been shown to significantly increase SIRT1 activity through an allosteric interaction, resulting in the increase of SIRT1 affinity for both nicotinamide adenine dinucleotide and the acetylated substrate [10]. Animal study found that RSV possessed an insulin-like effect in streptozotocin-induced diabetic rats. In a diet-induced obesity (DIO) model in mouse, oral daily dosing of resveratrol was demonstrated to significantly reduce glucose levels and improve insulin sensitivity [56]. Additional analysis has demonstrated that activity of the transcription factor, PGC-1 $\alpha$ , which drives mitochondrial biogenesis, was higher in these mice, thereby providing a mechanism through which SIRT1 activation leads to such diverse physiological changes. Moreover, mice treated with resveratrol had improved exercise tolerance such that they could run twice as far (almost 2 km) as those treated with vehicle. The positive metabolic results in the DIO model have also been confirmed in the leptin-deficient murine model and in the Zucker (fa/fa) rat [57]. Further proof that SIRT1 activation leads to improved metabolic control is provided in studies where small-molecule SIRT1 activators, unrelated to resveratrol, elicit similar changes [57]. With multiple and structurally different molecules activating SIRT1 in vitro and driving positive outcomes in vivo, these data strongly suggest that this mechanism is safe and may be of great therapeutic benefit. In light of these findings, RSV has the potential to be an antidiabetic drug.

## Summary

SIRT1 is widely distributed in mammalian tissues and has broad roles in regulating multiple transcriptional activities in a tissue-specific manner. Accumulating evidence suggests that activation of SIRT1 leads to multiple metabolic improvements including enhanced glucose utilization, improved insulin sensitivity and increased exercise tolerance. Resveratrol represents the first in a novel class of SIRT1 activators that has proven to be safe and well tolerated in humans. In summary, the development of therapeutics that target SIRT1 might provide novel approaches to the treatment of endocrine-related clinical conditions such as obesity, insulin resistance syndromes, and diabetes in the future. In this respect, RSV might be a good candidate for drug development.

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