

SIRT1 and insulin resistance

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Abstract | Sirtuin 1 (SIRT1), the mammalian homolog of SIR2, was originally identified as a NAD-dependent histone deacetylase, the activity of which is closely associated with lifespan under calorie restriction. Growing evidence suggests that SIRT1 regulates glucose or lipid metabolism through its deacetylase activity for over two dozen known substrates, and has a positive role in the metabolic pathway through its direct or indirect involvement in insulin signaling. SIRT1 stimulates a glucose-dependent insulin secretion from pancreatic β cells, and directly stimulates insulin signaling pathways in insulin-sensitive organs. Furthermore, SIRT1 regulates adiponectin secretion, inflammatory responses, gluconeogenesis, and levels of reactive oxygen species, which together contribute to the development of insulin resistance. Moreover, overexpression of SIRT1 and several SIRT1 activators has beneficial effects on glucose homeostasis and insulin sensitivity in obese mice models. These findings suggest that SIRT1 might be a new therapeutic target for the prevention of disease related to insulin resistance, such as metabolic syndrome and diabetes mellitus, although direct evidence from clinical studies in humans is needed to prove this possibility. In this Review, we discuss the potential role and therapeutic promise of SIRT1 in insulin resistance on the basis of the latest experimental studies.

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Introduction

Insulin resistance is the critical pathological feature of type 2 diabetes mellitus, obesity, metabolic syndrome, and aging.¹ Although the precise pathogenesis of insulin resistance remains ill-defined, several factors have been proposed to have a role in this process, such as adipokines, defects in the insulin signaling pathway,² mitochondrial dysfunction³ and inflammation.²

SIR2 proteins have been implicated in the regulation of lifespan under calorie restriction in multiple model organisms. So far, seven homologs of SIR2 have been identified in mammals (the sirtuins, SIRT1–SIRT7). SIRT1, the most extensively studied sirtuin, has roles in the DNA damage response, regulation of lifespan and carcinogenesis, which are mediated via its NAD-dependent deacetylase activity. SIRT1 also has a prominent role in metabolic tissues, such as the liver, skeletal muscle and adipose tissues, where it deacetylates a range of substrates, including PGC1 α , UCP2, NF κ B and FoxO1 proteins, which results in a pronounced effect on glucose homeostasis and insulin secretion.^{4–6} SIRT1 regulates the activity of the nuclear receptor PPAR γ and thus influences adipogenesis as well as fat storage in white adipose tissue,^{7,8} glucose and lipid metabolism in the liver^{4,9} and differentiation of muscle cells.¹⁰ Together, these roles suggest an association between SIRT1 and insulin action.

Moreover, increasing evidence suggests that decreased SIRT1 expression or activity might contribute to the pathogenesis of diseases related to insulin resistance. SIRT1 protein levels were reduced in mice fed a high-fat diet¹¹ and in two mice models of aging,¹² both of which

conditions are associated with insulin resistance. In addition, inhibition of SIRT1 induces insulin resistance in cultured insulin-sensitive cells and tissues.¹³ Thus, reduced SIRT1 levels might directly cause or at least substantially contribute to insulin resistance *in vivo* and *in vitro*. In support of this theory, activators of SIRT1 enhance insulin sensitivity *in vitro* in a SIRT1-dependent manner and ameliorate insulin resistance *in vivo*.^{13–15} Taken together, these findings suggest that SIRT1 activation is a potential therapeutic target to combat insulin resistance. Taking advantage of such a target requires a detailed understanding of the molecular mechanisms by which SIRT1 influences insulin action, and thereby the role of SIRT1 in insulin resistance and its related diseases.

This Review first discusses the relationships between SIRT1 and adiponectin and inflammation, both of which contribute to the development of insulin resistance. Second, we analyze the role of SIRT1 in insulin signaling within insulin-sensitive organs. Third, we discuss the relationship between SIRT1 and mitochondrial function, a novel potential link with insulin resistance.

SIRT1 and adiponectin

Adipocytes are critical factors in the development of insulin resistance, mainly because they can store excess saturated lipids and produce adipokines (a group of hormones and cytokines that regulate insulin actions and insulin sensitivity). One of these molecules, adiponectin, has a direct role in insulin sensitivity in both the liver and muscle tissue, and protects against the development of insulin resistance and type 2 diabetes mellitus.^{16,17}

Several studies suggest that SIRT1 regulates adiponectin secretion from adipocytes. By deacetylating FoxO1, SIRT1

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Competing interests

The authors declare no competing interests.

Key points

- SIRT1 upregulates adiponectin expression by deacetylating FoxO1, and thus protects against insulin resistance
- SIRT1 attenuates tumor-necrosis-factor-induced inflammation, potentially by deacetylating NFκB
- SIRT1 has a largely positive role in the insulin-signaling pathway by inducing insulin secretion, repressing Ptpn1, and by regulating insulin-receptor substrates (IRS) 1 and 2 and Akt activation
- SIRT1 mediates mitochondrial biogenesis by deacetylating PGC1α, upregulates antioxidant enzyme expression by deacetylating FoxO3a and thereby reduces the levels of reactive oxygen species

enhances not only the interaction between FoxO1 and C/EBPα, but also the formation of a complex of these two transcription factors at the adiponectin promoter, which results in enhanced transcription of the gene that encodes adiponectin in adipocytes.¹⁸ SIRT1-mediated translocation of FoxO1 from the cytoplasm to the nucleus might be involved in this process, as the SIRT1 activator resveratrol promotes the nuclear retention of FoxO1 through its tight association with a nuclear subdomain.¹⁹ This finding is corroborated by the observation that calorie restriction, which upregulates SIRT1 expression, also induces high levels of plasma adiponectin in rats.²⁰ Although an *in vitro* study showed that SIRT1 suppresses adiponectin secretion by downregulating the PPARγ-responsive gene, *EroIL*,²¹ transgenic mice with moderate overexpression of SIRT1 had increased levels of adiponectin—mediated by FoxO1—in models of insulin resistance and diabetes.²² Hence, SIRT1 is likely to improve insulin resistance by upregulating adiponectin.

SIRT1 and inflammation

Growing evidence links a chronic and/or subacute inflammatory state to the development of type 2 diabetes mellitus, obesity, metabolic syndrome, and other conditions related to insulin resistance. In fact, inflammation is one of the most important factors that underlie the pathogenesis of insulin resistance, as proinflammatory cytokines and other mediators of inflammation have been suggested to contribute directly to this condition.²³

SIRT1 can participate in the inflammatory process by deacetylating NFκB, in particular its subunit, transcription factor p65.²⁴ Increased acetylation of transcription factor p65 is closely correlated with a decrease in SIRT1 level.²⁵ Furthermore, inflammatory markers, such as intercellular adhesion molecule 1 and tumor necrosis factor (TNF) are upregulated during inflammation, which can in turn be inhibited by the SIRT1 activator, resveratrol.²⁶ Interestingly, calorie restriction, in which upregulated SIRT1 expression seems to have a critical role, exerts a powerful anti-inflammatory effect in rodents, nonhuman primates, and humans.²⁷ These data provide a useful insight into the role of SIRT1 in inflammatory pathways.

A recent report provides direct evidence that SIRT1 activation reduces TNF-induced inflammatory response, potentially via deacetylation of NFκB in insulin-resistant

adipocytes.²⁸ Consistent with previous studies,^{24,25} this report showed that SIRT1 knockdown (experimentally reduced protein expression) in cultured 3T3-L1 adipocytes increases acetylation of NFκB and its binding to target gene promoters, which results in increased expression of NFκB-regulated inflammatory genes. By contrast, both SIRT1 activation and NFκB knockdown lead to decreased expression of these inflammatory genes. These findings suggest that increased expression of proinflammatory genes mediated by hyperacetylated NFκB contributes to the increased inflammatory responses and decreased insulin action induced by SIRT1 depletion. SIRT1 activators, such as SRT2530 and SRT1720, inhibit inflammatory responses and increase cellular insulin sensitivity via decreasing TNF-stimulated NFκB acetylation. Further studies on this particular function of SIRT1 might offer novel and promising targets for anti-inflammatory therapy in insulin-resistance-related disease.

SIRT1 and insulin signaling pathways**Insulin secretion**

A number of studies suggest that SIRT1 has a role in the regulation of insulin secretion from pancreatic β cells. Overexpression of SIRT1 in β cells enhances ATP production by repressing UCP2,²⁹ which mediates the uncoupling of ATP synthesis from glucose, and an elevated ATP level leads to cell membrane depolarization and Ca²⁺-dependent exocytosis. β cells in SIRT1-deficient mice, however, produce less ATP in response to glucose than those in normal mice do. By deacetylating FoxO1, SIRT1 also promotes the activation and transcription of *NeuroD* and *MafA*, which preserve insulin secretion and promote β-cell survival *in vivo*.⁵

In β-cell-specific, SIRT1-overexpressing (BESTO) mice, the increased level of SIRT1 in pancreatic β cells improves glucose tolerance and enhances insulin secretion in response to glucose.⁶ In addition, SIRT1 activity decreases with age owing to decreased systemic NAD biosynthesis, which results in failure of glucose-sensitive insulin secretion in β cells. Administration of nicotinamide mononucleotide, a metabolite that is important for the maintenance of normal NAD biosynthesis, restores glucose-sensitive insulin secretion levels and improves glucose tolerance in aged BESTO mice.³⁰

These findings indicate that SIRT1 modulates glucose-ATP signaling and insulin secretion from pancreatic β cells, mainly via UCP2, FoxO1, and NAD metabolism. The established importance of SIRT1 in β-cell function *in vivo* may uncover new therapeutic tools for insulin resistance and type 2 diabetes mellitus.

Postreceptor insulin signaling

SIRT1 is also involved—directly or indirectly—in the insulin signaling pathway. Firstly, it represses the transcription of *Ptpn1*,¹³ which acts as a negative regulator of insulin signaling, mainly through dephosphorylation of the insulin receptor and insulin-receptor substrate (IRS) 1 (Figure 1).^{31,32} Moreover, SIRT1 also regulates

insulin-induced tyrosine phosphorylation of IRS-2 through deacetylation of this substrate, which affects a crucial step in the insulin signaling pathway. Inhibition of SIRT1 activity also directly interferes with insulin signaling at both the protein and mRNA levels (Figure 1).³³ SIRT1 knockdown reduces the activation of Akt by insulin, which correlates with markedly decreased *SIRT1* mRNA levels.³³ Whereas tyrosine residues in insulin receptors and IRS-1 remain highly phosphorylated in these cells, tyrosine phosphorylation of IRS-2 is substantially reduced, which results in markedly decreased Akt activation.³³ These findings support the importance of SIRT1 in insulin-induced Akt activation. Furthermore, a new study demonstrates the positive effect of SIRT1 on insulin signaling.²⁸ SIRT1 knockdown in adipocytes inhibits insulin-stimulated glucose uptake and GLUT4 translocation, accompanied by increased phosphorylation of JNK and serine phosphorylation of IRS-1, along with inhibition of insulin-signaling steps, such as tyrosine phosphorylation of IRS-1, and phosphorylation of Akt and ERKs. By contrast, SIRT1 activation increases glucose uptake and insulin signaling and decreases serine phosphorylation of IRS-1 (Figure 1).²⁸

Our understanding of the role of SIRT1 in the post-receptor insulin signaling pathway is based on *in vitro* experiments only. Nevertheless, such studies provide crucial evidence of SIRT1's roles in insulin signaling and will ultimately improve our understanding of the protein's activity in insulin resistance. SIRT1 protein was detected in both nuclear and cytosolic fractions by cell fractionation,³³ and was localized in the cytoplasm of murine pancreatic β cells and neonatal rat cardiomyocytes.^{6,34} Interestingly, nuclear-associated SIRT1 interacts with cytoplasmic proteins, such as IRS-2.³⁵ Localization of SIRT1 within the cell is partly regulated by PI3K–Akt signaling.³⁶ A PI3K inhibitor, LY294002, mediates transfer of SIRT1 from the nucleus to the cytoplasm in C2C12 cells, and the effect of LY294002 is attenuated by insulin-like growth factor I (IGF-I).

The apparent shuttling of SIRT1 between the cytoplasm and nucleus seems to have a crucial role in its regulatory function.³³ Future studies should establish how the subcellular localization of SIRT1 correlates with its involvement in insulin signaling. Also, we do not know yet whether the insulin-activated PI3K–Akt pathway affects SIRT1 function or whether SIRT1 regulates the insulin signaling pathway directly.

SIRT1 and insulin-sensitive organs

The ubiquitous expression of SIRT1 in the body means that it potentially affects insulin-sensitive cells, such as adipocytes, hepatocytes and skeletal muscle cells.

Adipose tissue

In white adipose tissue, SIRT1 binds to PPAR γ through two PPAR γ cofactors: a nuclear receptor corepressor and a thyroid-hormone receptor, both of which repress the transcription-activating effects of PPAR γ . The

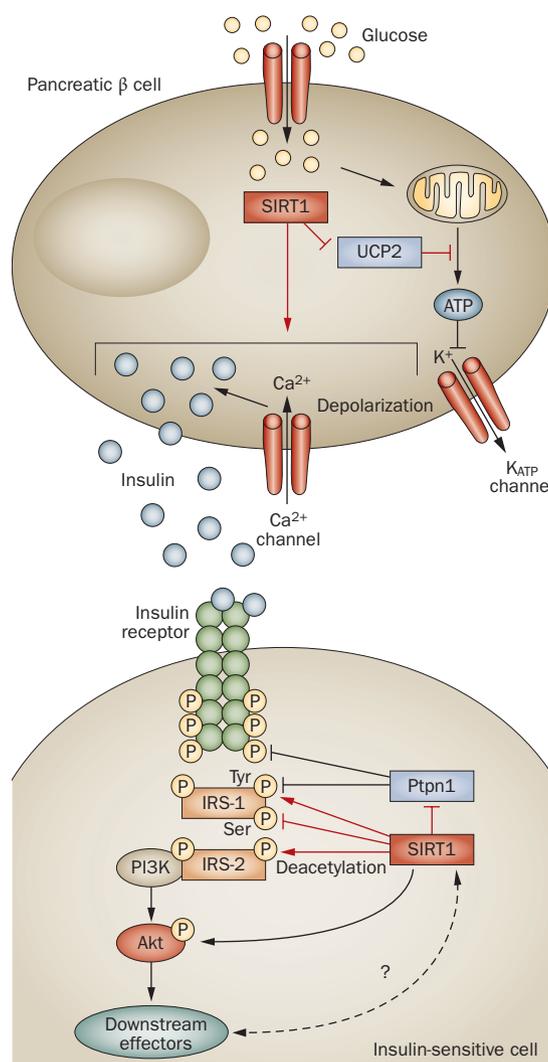


Figure 1 | SIRT1-mediated regulation of insulin secretion and insulin signaling. SIRT1 induces insulin secretion through the reduction of UCP2 expression and the enhancement of depolarization in pancreatic β cells. Furthermore, SIRT1 positively regulates insulin signaling through repression of Ptpn1 expression, deacetylation of IRS-2, regulation of IRS-1 phosphorylation and activation of Akt in insulin-sensitive cells.

binding of SIRT1, therefore, suppresses adipogenesis and fat retention in adipose tissue by inhibition of the metabolic effects of PPAR γ , which are crucial for adipocyte differentiation and fat storage;⁷ this action results in fat mobilization in response to food limitation.^{7,8} These effects could also involve increased interaction between SIRT1 and FoxO1, which also represses PPAR γ activity.³⁷ In fact, low levels of FoxO1 are a hallmark of insulin-resistant adipocytes, the formation of which is induced by a high-fat diet.³⁸ In addition, the adipocytes of *db/db* mice, which develop type 2 diabetes mellitus and obesity, have markedly lower levels of FoxO1 and SIRT1 proteins than nondiabetic control mice do.^{38,18} The SIRT1 activator resveratrol increased

induces mitochondrial biogenesis and respiration.⁴⁷ SIRT1 can deacetylate PGC1 α at several lysine residues and thereby increase its ability to activate transcription of target genes involved in mitochondrial biogenesis.⁴⁸ This ability suggests that modulation of SIRT1 activity contributes to maintenance of the number of mitochondria in a cell. Indeed, feeding mice with resveratrol to activate SIRT1 upregulates the number of mitochondria in their muscle cells.⁴⁹

In skeletal muscle cells, SIRT1-mediated deacetylation of PGC1 α is also required to activate genes that are associated with mitochondrial fatty-acid oxidation in response to energy demands.⁵⁰ The resultant increase in expression of mitochondrial genes, including regulatory genes (such as *ERR α*), as well as genes that regulate the citric acid cycle (for example, *Idh3 α*), respiratory chain (*Cyts*, *Cox5V α*), and fatty-acid metabolism (*Acadm*, *Cpt1b*, and *PDK4*) could exert positive effects on insulin signaling.⁴⁶ Remarkably, PGC1 α -induced upregulation of the expression of genes that regulate mitochondrial fatty-acid use is largely prevented by knockdown of SIRT1.⁴⁶

Furthermore, mitochondrial function is regulated in response to oxidative stress and calorie restriction through a shared mechanism that involves PGC1 α . During this process, the transcriptional activity of PGC1 α depends on its SIRT1-mediated nuclear accumulation.⁵¹ In human, insulin-resistant skeletal muscle cells, low levels of nuclear-encoded PGC1 α and mitochondrial-encoded COX1 are associated with impaired mitochondrial function that leads to development of insulin resistance.⁵² In addition, insulin resistance induced by a high-fat diet in rodents occurs in association with reduced expression of PGC1 α in muscle cells, and persistent elevations in intramuscular acylcarnitines, which are metabolic by-products of incomplete fatty-acid oxidation, whereas increased PGC1 α activity and/or enhanced mitochondrial efficiency may protect against lipid-induced insulin resistance.⁵³

Surprisingly, hepatic insulin sensitivity is enhanced in PGC1 α -deficient mice.⁵⁴ Hepatic glucose output is reduced in fasted *db/db* mice after silencing of hepatic SIRT1,⁹ whereas mice with hepatic overexpression of SIRT1 have decreased glucose tolerance.⁹ A reasonable interpretation for this finding might lie in the effect of PGC1 α on hepatic glucose production, in which SIRT1 is also involved. In this respect, the tissue-specific effects of SIRT1 might become a relevant target for combating insulin resistance.

SIRT1 and reactive oxygen species

Further molecular insights into the relationship between SIRT1 and mitochondrial function may be suggested by reactive oxygen species (ROS), which are thought to be causally involved in various forms of insulin resistance. ROS in insulin-secreting pancreatic β cells and in the target cells of insulin action are probably derived from the mitochondrial electron transport chain.¹ ROS can inactivate the signaling pathway between insulin

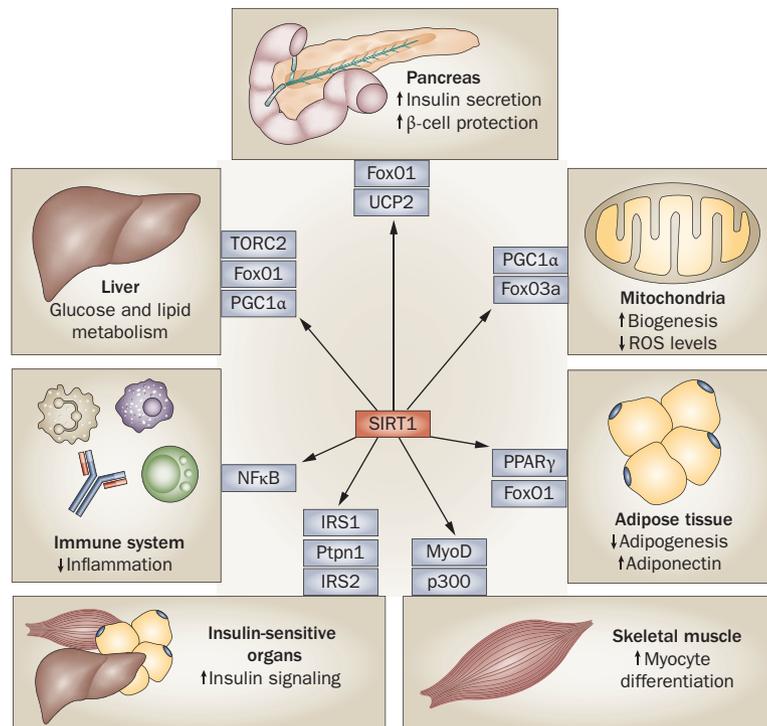


Figure 3 | Proposed roles and targets of SIRT1 in insulin resistance. By its deacetylase activity, SIRT1 represses the inflammatory response, and regulates insulin secretion from β cells, hepatic metabolism of glucose and lipids, mitochondrial homeostasis and ROS levels, adipogenesis and adiponectin secretion, the insulin signaling pathway, and myogenesis. Abbreviation: ROS, reactive oxygen species.

receptor and the glucose transporter system, which leads to the onset of insulin resistance in type 2 diabetes mellitus. In liver cells, similarly to hyperglycemic cells, TNF increases mitochondrial levels of ROS, which in turn activates the kinases ASK1 and JNK, increases serine phosphorylation of IRS-1, and decreases insulin-stimulated tyrosine phosphorylation of IRS-1; these actions ultimately lead to insulin resistance.⁵⁵ Lipid-induced insulin resistance could result from elevated levels of free fatty acids, which increase ROS production by enhancing reducing conditions in the electron transport chain. Subsequently, elevated production of ROS at the plasma membrane could inhibit signaling at the level of IRS phosphorylation (Figure 2).⁵⁶

Overexpression of SIRT1 reduces the level of oxygen consumption, which is linked with generation of ROS.⁴⁸ Consistent with this finding, SIRT1 activators decrease ROS generation.³⁸ Some experts posit that SIRT1-mediated mitochondrial biogenesis may reduce the production of ROS.⁵⁷ In addition, a recent study showed that if cells are stimulated with excess amounts of H₂O₂ (a reagent that increases intracellular concentrations of ROS and is commonly employed to induce oxidative stress), FoxO3a is translocated to the nucleus and deacetylated by SIRT1, which results in overexpression of catalase, the enzyme that converts H₂O₂ to H₂O and O₂.⁵⁸ By reducing ROS levels, SIRT1 protects against

oxidative stress and the ROS-related insulin resistance associated with aging and various diseases.

As mitochondrial dysfunction is strongly linked to insulin resistance,³ the close relationship between SIRT1 and mitochondrial function provides a new angle from which to explore the mechanisms that underlie the development of insulin resistance.

Perspectives

Recent studies demonstrated that some therapies regulate SIRT1 activity, such as calorie restriction,⁴⁰ exercise,⁵⁹ and treatment with SIRT1 activators.^{14,15} These interventions can be viewed as potential therapies for insulin-resistance-related conditions, such as type 2 diabetes mellitus, metabolic syndrome and aging. In fact, clinical trials of SRT-501, a novel SIRT1 activator that has proven to be safe and well tolerated in humans, are currently underway in patients with type 2 diabetes mellitus.⁶⁰ Further *in vitro* and animal studies that use tissue-specific SIRT1 knockout or overexpression or human clinical studies of SIRT1 activators are required to reveal the exact molecular mechanisms that underlie the effects of SIRT1 and its possible therapeutic roles in insulin-resistance-related diseases.

Conclusions

SIRT1 is likely to contribute to the development of insulin resistance through its regulatory effect on adipokines and insulin signaling (Figure 3). Studies on the anti-inflammatory effects of SIRT1 have focused mainly on NF κ B deacetylation, and provided direct evidence for SIRT1-related attenuation of inflammation during insulin resistance. SIRT1 seems to have a largely positive role in insulin action by inducing insulin secretion from β cells, repressing negative regulators of insulin signaling, and regulating IRS-2, IRS-1 and Akt activation. Moreover, SIRT1 is closely linked to mitochondrial function; this relationship should be explored to assess the role of SIRT1 in insulin resistance.

Review criteria

A search for English-language articles published between 2001 and 2008 that focused on SIRT1 and the insulin signaling pathway in association with insulin resistance was performed using PubMed. The search terms used were "insulin resistance", "SIRT1", "inflammation", "insulin signaling" and "mitochondria". The reference lists of identified articles were also searched for further papers.

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