

TARGETING SIRTUIN 1 IN TYPE 2 DIABETES MELLITUS: A NOVEL APPROACH

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Abstract

Background: Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disease defined by insulin resistance, hyperglycemia, and chronic inflammation. Sirtuin-1 (SIRT1), an NAD⁺-dependent acetylase, regulates the metabolism of glucose, lipids, mitochondrial function, and inflammatory processes. Activating SIRT1 strengthens the sensitivity of the body to insulin, accelerates the oxidation of fatty acids, and decreases hepatic steatosis. Both natural products like resveratrol, quercetin, and synthetic activators like SRT2104 effectively regulate the activity of SIRT1, although bioavailability and safety limitations exist. Circulating concentrations of SIRT1 are inversely correlated to glycemic and inflammatory indices, suggesting the latter as an acceptable indirect biomarker. Furthermore, the activation of pancreatic β -cells by SIRT1 shields these cells from oxidant and inflammatory injury, supporting the preservation of the secretion. **Conclusion:** SIRT1 represents a tri-functional target that integrates metabolic control, biomarker value, and therapeutic strategy in T2DM. Treatments that enhance SIRT1 activity by pharmacological, nutraceutical, or lifestyle interventions can maximize glycemic control, minimize complications, and allow precision medicine.

Keywords: Sirtuin-1, Type 2 Diabetes Mellitus, Insulin Resistance, Biomarker, Therapeutic Target.

1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic, progressive metabolic disorder that is marked by hyperglycemia, insulin resistance, and failure of the β -cells (1). Its prevalence continues to grow unchecked due to sedentary lifestyle, obesity, and genetics (1,2). Despite various therapies, its multifactorial pathogenesis must be explored for novel molecular targets (3). Sirtuin-1 (SIRT1), a nicotinamide adenine dinucleotide (NAD^+)-dependent histone deacetylase, is an emerging modulator of glucose homeostasis, lipid metabolism, mitochondrial biogenesis, and inflammation. Functionally linked with caloric restriction and metabolic adaptation. SIRT1 also exists in circulation, as a potential biomarker for metabolic health. (4) The dichotomous nature of SIRT1 in T2DM is being a drug target or a novel diagnostic marker is highlighted in this review.

2. BIOLOGY OF SIRTUIN-1

The most well-studied class III histone deacetylase is SIRT1, which regulates transcription initiation, metabolism, and stress responses (5). It senses the energy state in metabolic tissues such as liver, muscle, and fat and activates the regulators like PGC-1 α , stimulating mitochondrial biogenesis and oxidative metabolism. It suppresses lipogenesis and stimulates fatty-acid oxidation and enhances insulin sensitivity. SIRT1 is also a mediator of cellular stress response by deacetylating FOXO and Nrf2, promoting antioxidant defense, DNA repair, and autophagy. Pharmacological activation of SIRT1 by resveratrol or NAD^+ precursors increase glucose and lipid metabolism and anti-inflammatory effects in preclinical models (6).

2.1 Structure and Localization

SIRT1 is a 747-amino acid nuclear enzyme capable of shuttling between nucleus and cytoplasm (7). It possesses an NAD^+ -binding and deacetylase domains-containing conserved catalytic core. Substrate recognition is controlled by the N-terminal domain, whereas enzymatic activity and subcellular localization are managed by the C-terminal domain. Its dynamic localization allows for integration of environmental and metabolic signals to enable energy homeostasis and genomic stability (7).

2.2 Enzymatic Function

SIRT1 deacetylates histones and non-histone proteins (7) and regulates transcription factors such as PGC-1 α , FOXO, NF- κ B, and p53. Through these, SIRT1 enhances mitochondrial biogenesis, oxidative metabolism, and insulin signaling and suppresses inflammation and apoptosis (8).

2.3 Regulation of SIRT1 Expression

SIRT1 function is tightly controlled by the availability of nutrients, AMPK signaling, and post-transcriptional factors. Fasting elevates NAD^+ levels, triggering SIRT1 activation (9). AMPK activation indirectly activates SIRT1 through NAD^+ biosynthesis. MicroRNAs such as miR-34a and miR-2 repress SIRT1 translation, but FOXO1 and PPARs activate its

transcription. These multilayered processes position SIRT1 as a cellular energy and stress sensor.

2.4 Physiological Role

SIRT1 co-ordinates glucose and lipid metabolism, mitochondrial function, and inflammation regulation. It enhances hepatic insulin sensitivity, suppresses gluconeogenesis, enhances fatty-acid oxidation, and suppresses lipogenesis (9). It also suppresses NF- κ B-mediated inflammation and facilitates antioxidant defense. SIRT1 thus maintains systemic metabolic homeostasis, and its dysregulation is pathogenic in obesity, cardiovascular disease, and T2DM.

3. SIRT1 RELEVANCE TO T2DM

Deficient SIRT1 activity in T2DM causes insulin resistance, enhanced gluconeogenesis, mitochondrial damage, and oxidative stress. Its restoration through drug or lifestyle therapy might rectify these metabolic abnormalities (9).

4. SIRT1 DYSREGULATION IN TYPE 2 DIABETES MELLITUS

T2DM pathophysiology involves genetic, epigenetic, and environmental pathways that disrupt metabolic signaling (3). Reduced expression of SIRT1 in adipose tissue, liver, skeletal muscle, and pancreatic β -cells is responsible for insulin resistance, steatosis, and impaired insulin secretion. Reduced NAD⁺ levels and oxidative stress also decrease SIRT1, perpetuating a vicious circle (10).

4.1 Mechanisms of Downregulation

Chronic hyperglycemia inhibits SIRT1 by epigenetic modifications like, oxidative stress depletes NAD⁺, pro-inflammatory cytokines such as TNF- α and IL-6 inhibit its expression, and elevated levels of miR-34a and miR-132 inhibit SIRT1 post-transcriptionally (11).

4.2 Effects of Reduced SIRT1

Loss of SIRT1 activity abolishes IRS and PGC-1 α signaling, adding to insulin resistance and hepatic glucose output. It enhances lipogenesis through SREBP-1c and evokes β -cell apoptosis. Moreover, decreased deacetylation of NF- κ B increases inflammation, and impaired mitochondrial function aggravates oxidative stress (11).

5. THERAPEUTIC TARGETING OF SIRT1 IN T2DM

5.1 Synthetic Activators

Small-molecule activators like SRT1720 and SRT2104 enhance insulin sensitivity, lipid metabolism, and mitochondrial function. NAD⁺ precursors, i.e., nicotinamide riboside and nicotinamide mononucleotide, indirectly stimulate SIRT1 by elevating intracellular NAD⁺ (12)

5.2 Mechanism of Action

SIRT1 activators enhance insulin signaling via IRS and AMPK pathways, suppress hepatic gluconeogenesis by FOXO1 and PGC-1 α deacetylation, promote fat oxidation, induce mitochondrial biogenesis, inhibit inflammatory cascades, and prevent β -cells from apoptosis (12).

6. SIRT1 AS A CIRCULATING BIOMARKER

Aside from its intracellular roles in metabolism, Sirtuin-1 (SIRT1) has been identified as a putative circulating biomarker of metabolic disease, especially Type 2 Diabetes Mellitus (T2DM). Plasma or serum measurement of SIRT1 offers an easy, dynamic disease diagnostic, disease progression and therapeutic monitoring tool. Its dual interest—both as a regulator of metabolic homeostasis and as an assayable peripheral marker—provides encouraging lines of translational research.

6.1 Circulating SIRT1 Levels in T2DM

Both clinical and experimental research reliably show that SIRT1 is decreased in the serum of T2DM patients compared to normal controls. Gök et al. (23) reported that serum SIRT1 levels inversely relate to fasting glucose, HbA1c, and insulin resistance markers like HOMA-IR. Along the same lines, Biscetti et al. (14) associated low circulating SIRT1 with poor cardiovascular outcomes in diabetics, highlighting its prognostic value. Interestingly, in some subgroups, including T2DM patients with coronary artery disease, increased SIRT1 levels were found, perhaps indicative of compensatory or disease-related mechanisms. Together, these results indicate that reduced SIRT1 levels reflect metabolic stress, oxidative disequilibrium, and insulin resistance and are a useful marker of systemic metabolic derangement.

6.2 Diagnostic, Prognostic, and Therapeutic Utility

Reduced circulating SIRT1 levels can potentially function as a biomarker to differentiate between normoglycemic, prediabetic, and diabetic conditions. Initial data indicate that threshold values of serum SIRT1 may be helpful in disease stratification and risk stratification (4). In addition, reduced SIRT1 levels have been correlated with progression from prediabetes to classical diabetes and the emergence of complications like nephropathy and cardiovascular disease. Therapeutically, various interventions (metformin, caloric restriction, exercise, and SIRT1 activators) have been found to elevate circulating levels of SIRT1, together with enhanced insulin sensitivity and glycemic control. Such findings place SIRT1 at the forefront of dynamic biomarkers that are capable of both quantifying disease severity and measuring treatment response.

6.3 Combination Therapies

Synergistic metabolic benefits may result from combining SIRT1 activators with known antidiabetic medications—i.e., metformin, GLP-1 receptor agonists, and SGLT2 inhibitors—. Concurrent targeting of AMPK–SIRT1–PGC-1 α and insulin signaling cascades might additionally augment glycemic control, lipid regulation, and

cardiovascular benefits. Nutraceutical-pharmaceutical co-products, e.g., polyphenols with NAD⁺ precursors, might also maximize effect.

6.4 Investigating SIRT1 in Diabetic Complications

In addition to glucose control, SIRT1 modulation could reduce diabetes-related complications such as nephropathy, neuropathy, and retinopathy. SIRT1 pathway modulation can reduce oxidative stress and pro-inflammatory signaling pathways in target organs, with tissue-protective effects (14).

7. CHALLENGES AND LIMITATIONS

Although the clinical and mechanistic relevance of SIRT1 to T2DM is firmly established, certain scientific and translational challenges restrict its use as a biomarker and therapeutic target.

7.1 Limitations in Biomarker Reliability

The lack of standardized assays compromises the clinical validity of circulating SIRT1. Differences in ELISA kit specificity, sample handling, and storage create high inter-laboratory variability. In addition, physiological SIRT1 oscillations due to diet, circadian rhythms, and stress can complicate its disease-specific meaning. Cross-talk with other metabolic regulators—like AMPK, FOXO, and PGC-1 α —further complicates independent measurement.

8. FUTURE DIRECTIONS

New areas of research seek to optimize SIRT1-based diagnostics and therapeutics for better control of metabolic diseases.

9. DISCUSSION

Piling evidence highlights the pivotal role of SIRT1 in modulating metabolic homeostasis and inflammation in T2DM. Rodgers et al. (24) showed that activation of SIRT1 induces deacetylation of PGC-1 α to stimulate increased mitochondrial biogenesis, fatty acid oxidation, and insulin sensitivity. Likewise, Pfluger et al. (25) showed that SIRT1 overexpression improved glucose intolerance and steatosis in mouse liver. Clinical studies by Kitada et al. (15) also showed lower SIRT1 levels in diabetic patients, which were partially restored following resveratrol supplementation, although therapeutic efficacy was limited by low bioavailability.

SIRT1 is closely connected with current therapies. Zhang et al. (19) observed that metformin indirectly stimulates SIRT1 by AMPK signaling, enhancing mitochondrial function.

Clinically, circulating SIRT1 levels are inversely associated with glycemic and inflammatory markers. Cao et al. (18) showed that serum SIRT1 has a negative correlation with fasting glucose, HbA1c, and CRP, whereas Li et al. (20) showed low baseline SIRT1 to predict the onset of T2DM in five years. Genetic polymorphisms and

β -cell studies also corroborate SIRT1's role in maintaining insulin secretion and protecting against oxidative damage. Notwithstanding promising outcomes, drawbacks like limited bioavailability, assay heterogeneity, and toxicity issues remain. Prolonged overactivation has the potential to interfere with apoptosis or tumor suppression pathways, and thus careful dosing and long-term confirmation are warranted. Together, these results confirm SIRT1 as a pleiotropic target integrating therapeutic intervention and biomarker exploration.

10. CONCLUSION

Extensive preclinical and clinical evidence identifies SIRT1 as a key player in the regulation of glucose and lipid metabolism, mitochondrial fitness, and inflammation control, rendering SIRT1 a highly desirable therapeutic and diagnostic target in T2DM. Activation of SIRT1 enhances insulin sensitivity, stimulates mitochondrial biogenesis, and decreases hepatic steatosis. While natural activators-e.g., resveratrol-demonstrate relatively good effects as they exhibit low bioavailability. Synthetic compounds, such as SRT2104, are much stronger and more specific. Clinical studies report that serum SIRT1 levels correlate inversely with insulin resistance and inflammation. Various polymorphisms of the SIRT1 gene and protective effects against β -cell impairment also suggest possible benefits for personalized therapy. Standardization, outcome heterogeneity, and safety remain important problems. The targeting of SIRT1 through pharmacologic activation, nutraceutical modulation, and precision medicine may hold transformative potential against the global T2DM burden.

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