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## SIRT1 as a potential therapeutic target for treatment of nonalcoholic fatty liver disease

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### Summary

Sirtuins are members of the silent information regulator 2 (Sir2) family, a group of Class III histone/protein deacetylases. There are 7 different sirtuins in mammals (SIRT1-7), of which SIRT1 is the best known and most studied. SIRT1 is responsible for the regulation of protein activation by means of deacetylating a variety of proteins that play important roles in the pathophysiology of metabolic diseases. Recently, it has been shown that SIRT1 plays key roles in the regulation of lipid and glucose homeostasis, control of insulin secretion and sensitivity, antiinflammatory effects, control of oxidative stress and the improvements in endothelial function that result due to increased mitochondrial biogenesis and  $\beta$ -oxidation capacity.

Nonalcoholic fatty liver disease (NAFLD) is currently the most common liver disease, and it has been accepted as the hepatic component of metabolic syndrome. Recent studies have shown that SIRT expression in the liver is significantly decreased in an NAFLD model of rats fed a high-fat diet, and moderate SIRT1 overexpression protects mice from developing NAFLD. In addition to resveratrol, a natural SIRT1 activator, small-molecule pharmacologic SIRT1 activators have positive effects on metabolic diseases. These effects are particularly promising in the case of diabetes mellitus, for which phase studies are currently being performed. With this information, we hypothesized that the pharmacologic activation of SIRT1, which has been implicated in the pathogenesis of NAFLD, will be a potential therapeutic target for treating NAFLD. In this paper, we review the metabolic effects of SIRT1 and its association with the pathophysiology of NAFLD.

### Key words:

nonalcoholic fatty liver disease • sirtuin1 (SIRT1) • treatment

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## BACKGROUND

Nonalcoholic fatty liver disease (NAFLD) is among the most common causes of chronic liver disease worldwide [1]. The prevalence of NAFLD in the general population of Western countries is 20–30% [2]. Within the spectrum of NAFLD, only nonalcoholic steatohepatitis (NASH) has been convincingly shown to have a progressive course. Approximately 2–3% of the general population is estimated to have NASH [2]. NASH may lead to cirrhosis, hepatocellular carcinoma or liver failure. Most patients with NAFLD have risk factors such as insulin resistance, obesity or other indications of metabolic syndrome. Therefore, NAFLD is now recognized as the hepatic manifestation of metabolic syndrome.

Insulin resistance, oxidative stress, and inflammatory cascades are believed to play integral roles in the pathogenesis and progression of NAFLD [3]. As such, a “multi-hit” (formerly “double-hit”) hypothesis has been used to describe the pathogenesis of NAFLD [4,5]. As a result of the first “hit,” insulin resistance arises and increased fatty acid levels in the blood enter the liver (and/or are not removed from the liver), thus leading to hepatosteatosis. The second “hit” occurs as a result of the inflammation caused by the hepatosteatosis. The criterion standard method for the diagnosis of NAFLD, which most frequently presents with an asymptomatic increase of transaminase enzymes, is a liver biopsy [6].

Despite evidence that weight loss, dietary modifications, bariatric surgical operations, exercise and several drugs result in the biochemical and histological resolution of NAFLD, there is no current treatment regimen supported by valid, long-term studies that were properly randomized and controlled [7–10]. Currently, the basis for treatment includes managing risk factors such as hyperlipidemia through steps such as lifestyle modification and weight loss.

SIRT1 is an NAD<sup>+</sup>-dependent deacetylase and acts as a modulator of various metabolic pathways. In this article, we focus on the sirtuin 1 (SIRT1) protein, which has important effects on glucose homeostasis, lipid mobilization,  $\beta$ -oxidation, oxidative stress, insulin secretion and sensitivity, inflammation, cellular aging and apoptosis. We discuss the expression of SIRT1 in cases of NAFLD, the results of SIRT1 activation and the potential therapeutic role for SIRT1 in treating NAFLD.

## OVERVIEW OF SIRT1 AND SIRT1 ACTIVATORS

Silent information regulator 2 (Sir2) proteins, or sirtuins, are a class of proteins that possess either histone deacetylase or mono-ADP-ribosyl transferase activity. They are found in organisms ranging from bacteria to humans. SIRT1, an NAD<sup>+</sup>-dependent protein deacetylase, is an important regulator of energy homeostasis in response to nutrient availability. Currently, the best-studied sirtuin homolog, SIRT1, is expressed in metabolic tissues such as liver, skeletal muscle, adipose tissue, pancreas and brain; its actions in these tissues include regulation of  $\beta$ -cell and neuron survival, hepatic gluconeogenesis, insulin secretion and adiposity [11].

Resveratrol (*trans*-3,5,4'-trihydroxystilbene) is a polyphenol found in red wines and a wide variety of plants including grapes, berries and peanuts [12]. Resveratrol has been

shown to be a potent agonist of SIRT1 [13–15]. In mammalian cells, resveratrol promotes cellular expression of the SIRT1 protein and dramatically stimulates SIRT1 activity [16]. Furthermore, small-molecule SIRT1 activators with structures unrelated to resveratrol but with 1000 times the potency have been identified [17]. The effects of SIRT1 activation, especially in metabolic tissues, lead to the inhibition of various pathways important for NAFLD pathogenesis. These pathways represent potential therapeutic targets for NAFLD treatment.

## 1. EFFECTS OF SIRT1 IN THE LIVER

The liver is the central metabolic organ and regulates several key aspects of lipid metabolism (fatty acid  $\beta$ -oxidation, lipogenesis and lipoprotein uptake and secretion) in response to nutritional and hormonal signals [18].

Nutritional intake in excess of the  $\beta$ -oxidation capacity of the cell, lipoprotein synthesis and defects in excretion form the foundation of hepatosteatosis. Over time, the transcriptional network of the liver contributes to an inflammatory process that progressively leads to NASH associated with fibrosis, liver cirrhosis, hepatocellular carcinoma and death due to liver disease [19].

In several recent studies, SIRT1 has been shown to play an important role in the dynamics of NAFLD pathophysiology. Using an experimental NAFLD model consisting of rats fed a high-calorie diet, SIRT1 expression was found to decrease significantly. Another study in rats with NAFLD showed a significant increase in hepatic SIRT1 expression and histological improvement with calorie limitation [20,21].

In a study by Purushotham et al. [22], hepatocyte-specific loss of SIRT1 (through hepatocyte-specific deletion of SIRT1) was shown to cause peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ) signal failure and a decrease in fatty acid  $\beta$ -oxidation. However, SIRT1 overexpression increased levels of PPAR $\alpha$  and its coactivator PPAR $\gamma$  coactivator 1 $\alpha$  (PGC-1 $\alpha$ ). PGC-1 $\alpha$  impairs PPAR $\alpha$  signaling and decreases fatty acid  $\beta$ -oxidation, whereas overexpression of SIRT1 induces the expression of PPAR $\alpha$ 's targets. SIRT1 interacts with PPAR $\alpha$  and is required to activate the PPAR $\gamma$  coactivator PGC-1 $\alpha$ . In a recently reported study in rats, SIRT1 was shown to confer protection against age-associated metabolic damage, lead to healthier aging, decrease the frequency of liver cancer related to metabolic syndrome and protect the liver from carcinogenic damage [23].

Studies performed at the molecular level have demonstrated that SIRT1 plays an important role in the regulation of the transcriptional networks controlling various critical metabolic processes in the liver [24–26]. Along those lines, SIRT1 has been shown to deacetylate many nonhistone proteins, including p53, nuclear factor kappa B (NF- $\kappa$ B), forkhead box class O 3 (FOXO3) transcription factors, PGC-1 $\alpha$ , liver X-receptor (LXR), CLOCK, PER2 and TORC2 [27–36].

In a study by Yamazaki et al. [37], treatment of mice modeling NAFLD with a SIRT1 activator (SRT1720) resulted in decreases in expression of lipogenic genes (such as those encoding sterol regulatory element-binding protein-1c [SREBP-1c], acyl-CoA carboxylase [ACC] and fatty acid

synthase [FAS]), serum lipid profile, fat accumulation in the liver, expression of genes related to oxidative stress and the production of inflammatory cytokines.

In a study of bariatric surgical cases performed by Costa et al. [38], morbidly obese patients with severe hepatosteatosis were determined to have reduced expression of SIRT1 in adipose tissue when compared to patients with mild hepatosteatosis.

## 2. EFFECTS OF SIRT1 ON INSULIN SECRETION

Insulin resistance forms the primary mechanism underlying the pathogenesis of NAFLD. Recent studies have shown that SIRT1 plays important roles in both insulin resistance and insulin regulation in diabetics (such as increasing insulin secretion from pancreatic  $\beta$ -cells, stimulating lipolysis in adipose tissue and increasing glucose utilization in muscle tissue) [31,32,36].

In pancreatic  $\beta$ -cells, SIRT1 has been shown to increase insulin secretion through the repression of uncoupling protein 2 (UCP2) [39]. It was also demonstrated that SIRT1 activation increases ATP production in  $\beta$ -cells and improves glucose-dependent insulin secretion, which typically decreases with age [39,40]. A recent study demonstrated that inhibiting SIRT1 overexpression and NF- $\kappa$ B signaling decreases cytokine-induced pancreatic  $\beta$ -cell damage [41].

As a result, SIRT1 activation prevents the development of insulin resistance and limits the pancreatic  $\beta$ -cell dysfunction that develops in response to insulin resistance.

## 3. EFFECTS OF SIRT1 ON LIPID METABOLISM

The liver also plays an important role in lipid homeostasis. It has been shown that SIRT1 activation increases lipolysis by repressing PPAR $\gamma$  in adipose tissue, thereby inhibiting adipogenesis [42]. SIRT1 also regulates the production and/or secretion of insulin-sensitizing factors such as adiponectin and FGF21 through the regulation of FOXO1 and PPAR $\gamma$  [43–45].

LXRs regulate the transfer of cholesterol from peripheral tissues to the liver (reverse cholesterol transport) [46,47]. SIRT1 activates LXRs and accelerates reverse cholesterol transport, thereby regulating cholesterol homeostasis [33].

## 4. EFFECTS OF SIRT1 IN SKELETAL MUSCLE

SIRT1 is an important regulator of energy metabolism in skeletal muscle. PGC-1 $\alpha$  deacetylation by SIRT1 in skeletal muscle is necessary for the activation of mitochondrial fatty acid oxidation genes [48]. As further evidence of the importance of SIRT1 in muscle, patients with type 2 diabetes show reduced expression of PGC-1 $\alpha$  and mitochondrial *oxidative phosphorylation* (*OXPHOS*) genes in skeletal muscle [49,50]. Based on these data, the SIRT1-dependent activation of PGC-1 $\alpha$  is thought to contribute to an improvement in insulin sensitivity in skeletal muscle. Sun et al. [51] showed that SIRT1 improves insulin sensitivity in skeletal myotubes through transcriptional repression of the protein tyrosine phosphatase 1B (PTP1B) gene. PTP1B is a key insulin receptor phosphatase, and PTP1B-deficient mice have been

shown to be more insulin-sensitive and more resistant to diet-induced obesity compared to controls [52].

## 5. OTHER EFFECTS OF SIRT1

Recent studies have begun to address the relationship between sirtuins and age-related metabolic and cardiovascular diseases, antiinflammatory properties, anticarcinogenic effects, effects on oxidative stress and the cell cycle and anti-aging effects.

Epidemiological evidence gathered from NAFLD patients demonstrates that both cardiovascular disease risk and mortality are significantly increased when compared to a normal population [53–55]. Recent studies have shown the cardioprotective potential of SIRT1 activation. The cause of these effects may include vascular relaxation (both by increasing endothelial nitric oxide synthase activity and by potassium channel-mediated vasorelaxation), inhibition of thrombocyte aggregation or increasing cardiac myocontractility (by PGC-1 $\alpha$  regulation) [56–60]. In addition, individuals with a single nucleotide polymorphism in the *SIRT1* gene exhibit a lower incidence of cardiovascular mortality, myocardial infarction, myocardial ischemia, stroke, arterial surgery and intermittent claudication [61].

One of the important stages in the pathophysiology of NAFLD is the inflammatory process, which is considered the “second hit” after steatosis and results in the development of NASH. One important effect of SIRT1 activation, which was discovered recently, is its anti-inflammatory effect. An important aspect of this effect is performed through regulation of NF- $\kappa$ B (a master transcription factor involved in the regulation of proinflammatory cytokines and a key part of NAFLD pathogenesis) [29]. Recent studies have shown that SIRT1 also deacetylates and suppresses the transcriptional activity of activator protein-1 (AP-1), leading to a down-regulation of cyclooxygenase-2 (COX-2) gene expression [62]. In addition, the expression of multiple proinflammatory mediators, such as intracellular adhesion molecule 1 (ICAM1), MCP1, RANTES (also known as CCL5), macrophage colony stimulating factor (M-CSF), granulocyte-macrophage CSF (GM-CSF), G-CSF, and transforming growth factor- $\beta$  (TGF- $\beta$ ), is reduced by the SIRT1 activator resveratrol [63]. It has been demonstrated that SIRT1 activation protects cells from TNF $\alpha$ -induced insulin resistance. Thus, SIRT1 activity results in antiinflammatory effects through its regulation of multiple inflammatory pathways [64].

Another characteristic of SIRT1 activation, discovered in the last few years, is its effects on tumorigenesis. The antiproliferative, proapoptotic and tumor suppressing effects of SIRT1 activation have been elucidated by studies performed in rats [65,66]. Additionally, use of SIRT1 in cancer chemotherapy, based on its chemopreventive effects, has been considered [67]. Resveratrol has been shown to have anti-carcinogenic effects both *in vitro* and *in vivo* [68,69]. SIRT1 has been shown to indirectly reduce the cellular oxidative stress burden through deacetylation of FOXO3 (deacetylation of FOXO3 leads to upregulation of catalase and MnSOD) [70].

SIRT1 has also been shown to control the cell cycle, cell differentiation, cell proliferation and cell senescence by its regulation of the FOXO and p53 proteins [30].

## CONCLUSIONS

A sedentary lifestyle and variations in dietary habits has significantly increased the frequency of metabolic syndrome and its hepatic component, NAFLD, and the number of patients with this condition continues to rise. The most important etiologic factor of NAFLD is insulin resistance. Currently, there is no validated evidence-based treatment algorithm, and patients are currently treated with recommendations for caloric limitation and increased physical activity.

In recent years, the positive effects of SIRT1 activation have been shown in the metabolic activities related to NAFLD pathophysiology. These activities include glycemic regulation, lipid homeostasis, insulin secretion and sensitivity, inflammatory processes, oxidative stress, endothelial dysfunction, mitochondrial biogenesis and  $\beta$ -oxidation, cellular senescence, autophagy/apoptosis and skeletal and heart muscle function. From these results, we believe that SIRT1 activation has potential as a therapeutic target to prevent both the progression and development of NAFLD. Recent studies have demonstrated the positive effects of SIRT1 activation on these metabolic activities after induction by resveratrol, a natural polyphenol. In addition, SIRT1 activators that are 1000 times more efficient than resveratrol are currently being developed and studied. Current policy requires that therapeutic efficiency and security profile evaluations in randomized controlled studies be performed for new pharmaceutical agents.

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