Online Journal of Biological Sciences

Review

SIRT1 Controls Lipid Metabolism Under Physiological and Pathological Conditions: Implications in Atherosclerosis

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Article history
Received: 17-10-2023
Revised: 29-01-2024
Accepted: 23-02-2024

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Abstract: This comprehensive review examines the multifaceted role of Sirtuin 1 (SIRT1) in cellular metabolism and energy regulation, with a particular focus on its involvement in lipid metabolism and glucose regulation. Additionally, SIRT1's impact on several pathologies, including osteoarthritis, diabetes, and cardiovascular disease, is explored. Notably, this review sheds light on the unique contribution of SIRT1 in the development and progression of atherosclerosis, a key precursor to cardiovascular disease. By analyzing SIRT1's function in both physiological and pathological contexts, including its associations with diabetes and cardiovascular diseases, this study aims to provide valuable insights into the complex interplay between SIRT1 and atherosclerosis. Ethical considerations, where relevant, are carefully considered throughout this review. Overall, this review summarizes SIRT1's novel aspects and highlights its significance in relevant pathological conditions, thereby contributing to the field's knowledge and providing a foundation for future research.

Keywords: SIRT1, Sirtuins, CVD, Atherosclerosis

Introduction

The primary objective of this review article is to provide a comprehensive summary of the role of SIRT1 in lipid metabolism, focusing on its implications in atherosclerosis, a cardiovascular disease featured by the buildup of lipid plaques in vessel walls. The paper aims to consolidate existing knowledge on how SIRT1 influences lipid metabolism, including lipid synthesis, breakdown, and transport, and to explore how dysregulation of SIRT1 activity may contribute to the development and progression of atherosclerosis.

This review contributes to the field by synthesizing findings from various studies and discussing the mechanisms through which SIRT1 modulates lipid metabolism, such as its impact on gene expression, cellular signaling pathways, and epigenetic modifications. Moreover, it highlights the potential therapeutic implications of targeting SIRT1 activity for managing lipid-related disorders, including atherosclerosis. By unraveling the intricate relationship between SIRT1 and lipid metabolism in the context of atherosclerosis, this review provides valuable insights for further research and the development of potential therapeutic strategies.

To obtain relevant sources, we conducted a comprehensive search using the PubMed database, employing various combinations of the keywords "SIRT1," "lipid metabolism" and "atherosclerosis."

Sirtuins form a group of proteins widely expressed throughout the mammalian body, with seven known variants named SIRT1 to SIRT7. While sharing a Catalytic Core Domain (CCD), these proteins exhibit variations in enzymatic activities, subcellular localization, and target proteins (Satoh *et al*., 2011). Among the sirtuin proteins, SIRT1 has been particularly extensively studied. In mammals, SIRT1 is the orthologue of the yeast gene Silent Information Regulator 2 (SIR2), initially identified as a gene encoding transcriptional regulators that suppress gene expression (Michan and Sinclair, 2007). Subsequent research revealed that SIR2 and later SIRT1 possess the ability to extend life expectancy, classifying them as longevity proteins (De Oliveira *et al*., 2012).

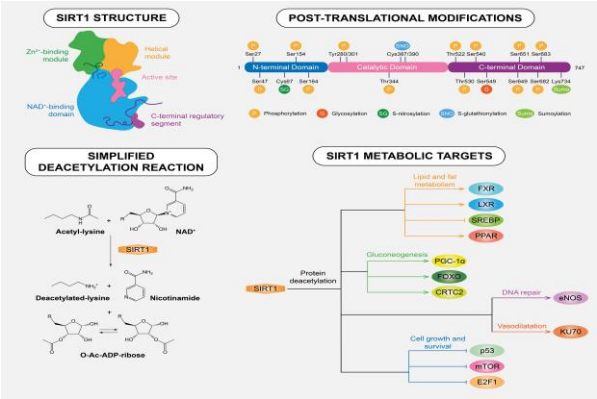

Fig. 1: SIRT1 structure, post-translational modifications and metabolism

SIRT1 is an NAD+ dependent enzyme that catalyzes histone deacetylation. Figure 1 provides a schematic representation of the SIRT1 structure. Recent studies have demonstrated its involvement in the deacetylation of various non-histone regulatory proteins, including nuclear transcription receptors that play crucial roles in stress response, aging, metabolism, and other biological mechanisms (Peng *et al*., 2012). Examples of SIRT1-mediated deacetylation-controlled transcription regulators involved in cellular metabolism and stress response include P53, Liver X Receptors (LXRs), Farnesoid X Receptor (FXR), Forkhead box proteins (FOXOs), Sterol Regulatory Element-Binding Proteins (SREBPs), CREB-Regulated Transcription Coactivator 2 (CRTC2), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and PPAR-gamma coactivator-1α (PGC-1α) (Elibol and Kilic, 2018).

The NAD+ dependent activity of SIRT1 enables it to sense nutrient availability and link cellular energy and metabolic status to transcriptional outcomes, making it crucial for the regulation of metabolic and energy homeostasis (Chang and Guarente, 2014). Recent studies have shown that cellular NAD+ levels can be increased by factors such as starvation, caloric restriction, strenuous exercise, and other stressors. Elevated NAD+ levels, in turn, activate SIRT1 deacetylase activity. Furthermore, investigations suggest that cellular NAD+ levels may fluctuate in response to circadian rhythms and SIRT1's regulatory influence on clock genes (Ji and Yeo, 2022). The activation of AMP-activated Protein Kinase (AMPK), a vital energy sensor governing metabolic and energy homeostasis, has been found to promote SIRT1 activity and increase cellular NAD+ levels when stimulated by agonists like 5-Aminoimidazole-4-Carboxamide Ribonucleotide (AICAR). Cellular NAD+ concentrations serve as indicators of energy levels and these studies collectively demonstrate SIRT1's ability to sense changes in these concentrations (Ruderman *et al*., 2010). Additionally, SIRT1 regulates energy outputs by deacetylating proteins that control the concentration and activity of transcriptional regulators involved in metabolism. It is important to note that SIRT1 can induce changes in transcriptional programs governing cellular metabolic mechanisms in specific cases (Houtkooper *et al*., 2012).

Functions of SIRT1 in Mammalian Physiology

The SIRT1 signaling pathways in various cell types are summarized in Fig. 2. Initial studies reported that SIRT1 deacetylates essential transcription factors such as FOXO, p53, and KU proteins, promoting stress resistance by suppressing apoptosis and inducing cell repair mechanisms (Gu *et al*., 2016). SIRT1 not only plays a role in lipid homeostasis but also in glucose regulation. In White Adipose Tissue (WAT), SIRT1 reduces fat accumulation in differentiated cells and suppresses adipogenesis (Braud *et al*., 2021). One mechanism underlying this effect is the suppression of PPAR-γ through SIRT1's interaction with cofactors NCoR and SMRT at the promoters of target genes. However, other processes may also contribute, as this function alone cannot explain the lipolysis induced by caloric restriction in adipocytes (Mottis *et al*., 2024).

SIRT1 plays a significant role in glucose homeostasis in three different tissues. In pancreatic beta-cells, SIRT1 positively regulates insulin secretion (Kitada and Koya, 2013). Decreased SIRT1 levels through RNA suppression result in impaired insulin secretion in insulinoma cells. Conversely, transgenic murine models with overexpression of SIRT1 in beta-cells exhibit improved glucose tolerance. Decreased SIRT1 levels lead to increased Ucp-2 gene transcription in insulinoma cells, while SIRT1 transgenic murine models exhibit lower concentrations of Ucp-2 (Pinho *et al*., 2015). The Ucp-2 gene encodes a mitochondrial uncoupling protein, which can uncouple adenosine triphosphate synthesis from respiration. By inhibiting Ucp-2 through SIRT1, the efficiency of ATP synthesis in the presence of glucose is improved, thereby positively regulating insulin secretion (Demine *et al*., 2019).

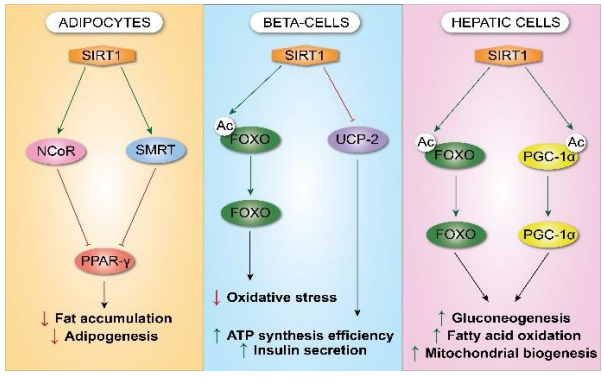

Fig. 2: SIRT1 signaling in mammalian physiology

SIRT1 also protects beta-cells against Oxidative Stress (OS) through deacetylation of FOXO proteins. This protective mechanism helps prevent beta-cell loss during the aging process and slows down the severe decrease in insulin secretion observed in the early stages of Diabetes Mellitus (DM) (Iside *et al*., 2020).

In hepatic cells, SIRT1 appears to regulate Gluconeogenesis (GNG) by binding to PGC-1α, deacetylating, and activating it. SIRT1 concentrations in the liver significantly increase after overnight fasting, stimulating glucose production. In cases of severe energy deficiency, SIRT1 may influence glucose production in different ways, as both PGC-1α and FOXO control genes involved in GNG (Cao *et al*., 2016). In neurons, SIRT1 seems to suppress the action of PGC-1α rather than stimulate it, indicating the complex regulation of PGC-1α by SIRT1 (Panes *et al*., 2020).

Furthermore, SIRT1 affects glucose homeostasis by maintaining the response of target cells to insulin, which triggers intracellular kinase pathways. These intracellular kinases control forkhead transcription factors that are regulated by SIRT1 (Zhou *et al*., 2018a). Additionally, PGC-1α induces the activation of genes involved in fatty acid oxidation, respiration, and mitochondrial biogenesis. By regulating PGC-1α, SIRT1 can impact the ability of muscle and hepatic cells to metabolize carbohydrates and fats, influencing the homeostasis of both lipids and glucose (Supruniuk *et al*., 2017).

Role of SIRT1 in Fat Metabolism in the Liver

Disorders related to fat metabolism pose substantial risks in the progression of Fatty Liver Diseases (FLD). The underlying mechanism of FLD involves the abnormal accumulation of lipids within the liver. During hepatic steatosis, imbalanced lipid levels are primarily attributed to dysregulated lipogenesis and fatty acid beta-oxidation (Pei *et al*., 2020). Recent research highlights the vital role of SIRT1 in regulating lipid metabolism in the liver, offering protection against alcohol-induced or High-Fat Diet (HFD) induced steatosis by modulating lipid synthesis and utilization (Ding *et al*., 2017).

Lipogenesis

One of the main sources of lipid accumulation in the liver, leading to triglyceride buildup, is hepatic De Novo Lipogenesis (DNL). The synthesis of triglycerides is primarily regulated by two transcription factors: Carbohydrate Response Element Binding Protein (ChREBP) and SREBP-1c. Both factors have been shown to positively regulate acetyl-CoA Carboxylase (ACC1), FAS, and several other genes involved in lipogenesis. SREBPs are transcription factors capable of binding to DNA (Song *et al*., 2018) with isoforms SREBP-1a, SREBP-1c, and SREBP-2. They bind to the promoter regions of target genes, exerting a significant impact on lipogenesis. SREBP-1c is involved in the regulation of triglyceride synthesis and is predominantly expressed in the liver. Once activated, SREBP-1c binds to downstream target genes (such as acetyl-CoA carboxylase 1, fatty acid synthase, stearoyl-CoA desaturase-1, etc.,) and triggers their activation, thereby promoting hepatic lipid synthesis (Sanders and Griffin, 2016).

Recent trials have demonstrated that SIRT1 deacetylates Lys-289 and Lys-309 in the deoxyribonucleic acid binding site of SREBP-1c, thereby inhibiting its transcriptional activity (Ponugoti *et al*., 2010). Conversely, SREBP-1c transactivation is enhanced when acetylated at the same domain by p300/CBP acetylase. SIRT1-mediated deacetylation reduces the stability and occupancy of SREBP-1c at lipogenic genes, leading to proteasomal degradation and ubiquitination (Park *et al*., 2015). In a murine model, overexpression of SIRT1 using Adenovirus (AV) reduces the concentration of acetylated SREBP-1c, downregulates lipogenic genes and SREBP-1c, while inhibition of SIRT1 expression by adenoviral small interfering RNA, sirtinol, or nicotinamide results in elevated SREBP-1c levels and expression of lipogenic genes (Hu *et al*., 2017). Interestingly, in a murine model of obesity induced by a High-Fat Diet (HFD), there is a notable increase in SREBP-1c acetylation levels in the liver. However, excessive SIRT1 expression mediated by AV is capable of reducing steatosis and the associated lipogenesis signaling mediated by SREBP-1c (Liou *et al*., 2019). Similarly, therapy with SIRT1 activators such as resveratrol, SRT1720, or the NAD+ precursor NR can reduce SREBP-1c, as well as the expression levels of lipogenic genes and proteins in the liver. This could help protect the liver against fatty liver disease in cases of a high-fat or high-fat and sucrose diet (Colak *et al*., 2011). SIRT1 demonstrates a similar positive effect on alcohol-related fatty liver disease and non-alcoholic fatty liver disease. Its activation triggered by resveratrol inhibits the excessive acetylation of SREBP-1c caused by ethanol, suppressing its elevated transcriptional activity and downregulating lipogenesis mediated by SREBP-1c, ultimately leading to a reduction in alcoholic liver steatosis (You *et al*., 2015). In a murine model, SIRT1 deficiency in the liver exacerbates the acetylated active nuclear expression of SREBP-1 caused by alcohol and the mRNA expression of lipogenic enzymes such as acetyl-CoA carboxylase 1, fatty acid synthase, and stearoyl-CoA desaturase-1 (Walker *et al*., 2010).

ChREBP is another important transcription factor that contributes to lipid synthesis. When combined with SREBP-1c, ChREBP promotes triglyceride synthesis. In a murine model, SIRT1 deficiency can increase free fatty acids and glucose concentrations in the blood, promoting the activation of ChREBP through various posttranscriptional modifying processes, e.g., acetylation

and phosphorylation (Iizuka *et al*., 2020). It has been discovered that increased acetylation of ChREBP is associated with enhanced transcriptional activity and the expression of its target genes, as well as fatty liver disease caused by either a high-fat diet or alcohol consumption. This aligns with the inhibition of expression and deacetylation of SIRT1 observed in non-alcoholic fatty liver disease and alcoholic fatty liver disease (Santos-Laso *et al*., 2022). Furthermore, several studies using a liver-specific murine model of SIRT1 knockout have revealed an upregulation of ChREBP expression, along with increased H3K9 and H4K16 acetylation upstream of the carbohydrate-response element-binding protein promoter region and elevated expression of ChREBP-targeted genes (acetyl-CoA carboxylase 1, fatty acid synthase and ELOVL6), resulting in fatty liver disease under normal nutrition conditions (Wang *et al*., 2010). These findings demonstrate the important role of SIRT1 in hepatic lipid homeostasis, as SIRT1 controls lipogenesis associated with ChREBP, likely through deacetylation of histones upstream of the ChREBP promoter region (Hu *et al*., 2022).

Fatty Acid Beta-Oxidation

Fatty acid beta-oxidation is a vital mechanism for utilizing triglycerides in the liver. The key regulatory pathway involved in this process is the PPARα/PGC-1α (peroxisome proliferator-activated receptor-alpha/PPAR-gamma coactivator-1alpha) signaling pathway. PPARα, a transcription factor, is activated by ligands, with fatty acids being its main endogenous ligands (Fougerat *et al*., 2020). By binding to fatty acids, PPARα enhances the gene expression involved in fatty acid catabolism in the mitochondrial matrix. On the other hand, PGC-1α, a transcriptional coactivator, stimulates the transcription of PPARα, thereby increasing the expression of genes involved in fatty acid catabolism (Mello *et al*., 2016).

The deacetylation of PGC-1α by SIRT1 primarily induces the transcriptional activity of PPARα, leading to the stimulation of fatty acid beta-oxidation in the liver. Studies have demonstrated that liver-specific SIRT1 knockout or acute suppression of SIRT1 mediated by Adenovirus (AV) in murine models results in impaired PPARα signaling (Purushotham *et al*., 2009). This leads to enhanced acetylation of PGC-1-alpha, a decrease in fatty acid beta-oxidation, and higher susceptibility to fatty liver disease triggered by a high-fat diet. Conversely, excessive expression of SIRT1 mediated by AV reduces PGC-1-alpha acetylation, enhances the expression of PPARα/PGC-1-alpha target genes, and promotes ligand-dependent transcriptional signaling of PPARα. As a result, fatty acid beta-oxidation is enhanced and steatosis is decreased (Zeng and Chen, 2022).

Similar results have been observed in studies conducted on mice with fatty liver caused by a high-fat diet or a high-fat and sucrose diet and treated with SIRT1 agonists such as resveratrol, SRT1720, or NR. SIRT1 activation counteracts the inhibition of fatty acid beta-oxidation in the liver caused by alcohol consumption. This inhibition occurs through the suppression of PGC-1α and SIRT1 activity, as well as the decreased expression of their target genes and proteins (Ajmo *et al*., 2008). In a liver-specific knockout murine model on a high-ethanol diet, SIRT1 deficiency inhibits the mRNA expression of enzymes involved in PPARα/PGC-1α signaling for fatty acid beta-oxidation. Conversely, resveratrol-induced SIRT1 activation reverses this outcome by activating PGC-1α, thus reducing hepatic steatosis (De Gregorio *et al*., 2020).

Existing evidence suggests that SIRT1 plays a crucial regulatory role in liver lipid metabolism by controlling SREBP-1c/ChREBP-dependent formation of lipids and PPARα/PGC-1-alpha-dependent fatty acid beta-oxidation. As a result, SIRT1 suppresses lipogenesis and enhances fatty acid beta-oxidation, thereby alleviating steatosis caused by alcohol consumption or a high-fat diet (Ramatchandirin *et al*., 2023).

SIRT1 has also been found to upregulate SIRT6 expression by acting together with Forkhead box O3 (FOXO3a) and NRF1 in the promoter region of SIRT6. Subsequently, SIRT6 activates deacetylation of methylation of histone H3 at lysine 9 (H3K9) on the promoter of multiple genes involved in lipid synthesis, glycolysis, and fatty acid beta-oxidation (Liu *et al*., 2021). In a liver-specific SIRT6 knockout murine model, hepatic steatosis progresses rapidly from five to six months of age (with a frequency of 3/7 or 43%), reaching a frequency of 90% by the age of 7.5-13 months. Hence, it can be concluded that SIRT1 is crucial for maintaining lipid metabolism through SIRT6 (Dong, 2023).

Pathologies

Lipid Metabolism Regulation in Osteoarthritic Chondrocytes

Imbalanced metabolism and aging are significant risk factors for Osteoarthritis (OA) (Wang *et al*., 2016). Initially, SIRT1 was identified as a crucial nutrient-sensitive regulator and longevity factor in osteoarthritis, implicated in the control of chondrocyte homeostasis. Interestingly, both individuals with osteoarthritis and experimental models of bone diseases commonly exhibit deficiency in the NAD+ co-factor and SIRT1 (Sun *et al*., 2022).

On the other hand, lectin-like Oxidized LDL receptor-1 (LOX-1), initially identified as the primary receptor for oxidized Low-Density Lipoprotein (LDL) in endothelial cells linked to the development of AS, has been found to play a role in osteoarthritis. AS and osteoarthritis share similar pathophysiology, as both disorders are associated with aging and have significant metabolic components. Increased expression of lectin-like oxidized LDL

receptor-1 leads to an abnormal influx of oxidized LDL in osteoarthritic articular chondrocytes, which in turn stimulates the modulation of extracellular matrix hydroxyapatite-calcium and cartilage calcification, thereby affecting cell viability (Reiss *et al*., 2009).

In osteoarthritis, the concentrations of lectin-like oxidized LDL receptor-1 are significantly elevated, while the concentrations of SIRT1 are noticeably decreased. The suppressed expression of SIRT1 and enhanced expression of lectin-like oxidized LDL receptor-1 has been observed in osteoarthritic tissues (Batshon *et al*., 2020). Furthermore, the expression of SIRT1 decreases with age, with a similar decrease found in aged and osteoarthritic chondrocytes. Additionally, a negative correlation between lectin-like oxidized LDL receptor-1 and SIRT1 has been observed in osteoarthritic chondrocytes (Papageorgiou *et al*., 2021). Notably, the expression of lectin-like oxidized LDL receptor-1 shows a negative correlation with the loss of SIRT1 expression in osteoarthritic chondrocytes from areas of cartilage with severe lesions. Conversely, the expression of the LOX-1 protein is decreased in osteoarthritic chondrocytes derived from cartilage with minimal lesions, where the expression of SIRT1 is enhanced. The precise nature of this inverse correlation between LOX-1 and SIRT1 concentrations remains to be explored (Hashimoto *et al*., 2017).

The interaction between autophagy and metabolic homeostasis in the context of osteoarthritis is complex, emphasizing the intricacy of autophagy. Intracellular fat is stored in Lipid Droplets (LDs) and during starvation, lipophagy (lysosomal degradation of lipid droplets) becomes crucial as lipids are stored in cells when autophagy is inactive (Shin, 2020). Furthermore, it has been observed that during fasting, lysosomes and autophagosomes target the surface of lipid droplets to organize lipophagy. Conversely, lipid activity can impact autophagy. Increased lipid uptake in beta-cells may stimulate autophagy, while prolonged lipid storage can suppress it. SIRT1, which promotes lipophagy and autophagy, has been identified as a key factor (Filali-Mouncef *et al*., 2022). Specifically, the activation of adipose triglyceride lipase is necessary and sufficient to induce lipophagy and autophagy in the liver. Similarly, lipophagy can promote the oxidation of hydrolyzed fatty acids and the catabolism of lipid droplets, mediated by adipose triglyceride lipase (Schulze *et al*., 2017). Additionally, SIRT1 is required to induce PPAR-alpha/PGC-1-alpha target genes, serving as an important component of cellular respiration in response to enhanced lipolysis mediated by adipose triglyceride lipase. Several studies have demonstrated that SIRT1 can stimulate lipophagy and autophagy through adipose triglyceride lipase signaling, acting as a compensatory mechanism to regulate lipid droplet catabolism in the liver and the oxidation of fatty acids (Chen *et al*., 2022).

Sirt1 in Cardiovascular Disease

SIRT1, the most extensively studied isoform among all sirtuins, predominantly resides in the cytoplasm and nucleus. Its association with Endothelial Cells (ECs) was initially identified based on its activation of endothelial Nitric Oxide Synthase (eNOS) (Wei *et al*., 2022). Subsequent investigations using genetically modified mice uncovered SIRT1's ability to protect against atherosclerosis by activating endothelial nitric oxide or by reducing Nuclear Factor kappa-light-chain-enhancer of activated B cells (NFκB) activity in macrophages and ECs. Moreover, pharmacological activation of SIRT1 has shown potential in countering EC aging due to impaired blood flow. In VSM cells, SIRT1 exerts atheroprotective influence, medial degeneration, and DNA damage. Collectively, the evidence underscores the pivotal roles of ECs, VSMCs, and macrophages in the atheroprotective actions of SIRT1 (Khayatan *et al*., 2022).

Crucially, SIRT1 profoundly impacts metabolic homeostasis by regulating mitochondrial integrity. Its activation yields improvements in lipid homeostasis, glucose tolerance, and diminished inflammation, thereby mitigating atherosclerosis (Lu *et al*., 2023).

Notably, pharmacological reduction in SIRT1 suppresses Tissue Factor (TF) activation via NFκB, leading to heightened thrombotic tendencies. Conversely, SIRT1-dependent inhibition of TF is seen through the activation of PPAR-delta and Cyclooxygenase-2 (COX-2)-derived PGI2, thereby reducing thrombosis. This highlights SIRT1's protective role in counteracting thrombus formation (Yang *et al*., 2012). Activation of SIRT1 inhibits PCSK9 secretion, resulting in decreased Low-Density Lipoprotein (LDL) cholesterol levels in the plasma. Consequently, more low-density lipoprotein receptors become available in the liver, facilitating LDL cholesterol clearance. Notably, the atherosclerosis-protective effects of SIRT1 are absent in the absence of an LDL receptor. This clarifies the seemingly contradictory finding that elevated genetic expression of SIRT1 exacerbates atherosclerosis in a low-density Lp receptor KO mouse model. Additionally, SIRT1 has been found to stimulate angiogenesis by suppressing Notch signaling in ECs (Akil *et al*., 2021).

Furthermore, SIRT1 demonstrates a cardioprotective role. SIRT1 deficiency in murine models leads to increased susceptibility to Ischemia-Reperfusion Injury (IRI), while SIRT1 transgenic models exhibit reduced IRI. Moreover, SIRT1 plays a protective function against catecholamine-induced cardiomyopathy in murine models (Nadtochiy *et al*., 2011).

SIRT1 in Diabetes

Sirtuin-1 plays a pivotal role in the regulation of mitochondrial function, Insulin Resistance (IR), and glucose and lipid metabolism. Under conditions of nutrient deficiency, skeletal muscle relies on elevated mitochondrial Fatty Acid (FA) oxidation to maintain energy and nutrient homeostasis (Tang, 2016). Notably, elderly individuals, as well as patients with Type 2 Diabetes Mellitus (T2DM) and IR, exhibit decreased mitochondrial Oxidative Phosphorylation (OXPHOS) activity and increased storage of Intramyocellular Lipids (IMCL) in skeletal muscle, highlighting impaired mitochondrial function as a critical contributor to diabetes pathogenesis (Genders *et al*., 2020). A key player in mitochondrial respiration regulation is PGC-1-alpha, which promotes beta-oxidation of FAs and is closely associated with mitochondrial OXPHOS. While type 2 diabetes is characterized by lower concentrations of oxidative phosphorylation proteins and active mitochondria, PGC-1-alpha helps maintain their levels. SIRT1 exerts control over PGC-1-alpha, thereby regulating metabolic homeostasis, mitochondrial function, mitochondrial biogenesis, and gene expression related to oxidative phosphorylation. Furthermore, SIRT1 activation increases oxygen uptake in muscle fibers (Li *et al*., 2011a). Intriguingly, SIRT1 knockout prevents PGC-1-alpha from up-regulating genes involved in mitochondrial FA utilization, underscoring the importance of SIRT1 for FA oxidation. Additionally, SIRT1 controls the activation of PPAR-alpha by deacetylating PGC-1-alpha, leading to enhanced FA oxidation. Consequently, activated SIRT1 can improve insulin resistance by increasing the rate of FA oxidation and promoting mitochondrial biogenesis in skeletal muscle (Zhou *et al*., 2018b). Apart from its role in enhancing lipid utilization through PGC-1-alpha-mediated mitochondrial biogenesis, PGC-1-alpha also significantly enhances glucose transport activity and the expression of GLUT4 in mouse C2C12 myotubes, thus influencing insulin sensitivity under the regulation of SIRT1 (Brown *et al*., 2018).

Hepatic glucose and lipid metabolism are also subject to SIRT1 regulation. During nutrient deficiency, hepatic fatty acid oxidation and glucose production increase to maintain energy balance. Several transcriptional regulators modulate hepatic glucose production. In the early stages of starvation, glucagon stimulates CREB and CRTC2, which promote the expression of genes associated with gluconeogenesis to provide glucose to the organism (Rui, 2014). As starvation progresses, activated SIRT1 deacetylates CRTC2, reducing the impact of glucagon. At that point, SIRT1 can activate Forkhead box protein O1 (FOXO1) and PGC-1-alpha through deacetylation, inducing the expression of genes related to gluconeogenesis. Thus, SIRT1 serves as a partial controller of the metabolic switch from initial to advanced gluconeogenesis during nutrient deficiency, thereby maintaining glucose homeostasis (Liu *et al*., 2008). However, despite these findings, numerous studies in animal models have demonstrated the protective role of SIRT1 against diabetes. Transgenic mice with moderately elevated SIRT1 expression exhibited improved glucose tolerance owing to reduced hepatic glucose production. Wang *et al*. (2022) also demonstrated SIRT1's ability to inhibit gluconeogenesis. In a liver-specific mouse model with SIRT1 deficiency, suppressed expression of Rictor (a core component of mTOR complex 2) led to FOXO1-S253 hypophosphorylation, impaired AKT-S473 phosphorylation and elevated expression of Glucose 6-Phosphatase (G6Pase) and Phosphoenolpyruvate Carboxykinase (PEPCK), resulting in chronic hyperglycemia (Wang *et al*., 2022). However, other SIRT1 knockout mice with and without nutrient deficiencies exhibited normal glucose concentrations. Moreover, acute SIRT1 knockdown in the liver using adenovirus and SIRT1 knockdown in type 2 diabetic rats using Antisense Oligonucleotides (ASOs) increased insulin sensitivity to glucose and reduced basal glucose output in the liver. SIRT1 was also found to control gluconeogenesis by deacetylating STAT3 protein, which represses the transcriptional activity of genes associated with gluconeogenesis, effectively inhibiting gluconeogenesis (Wang *et al*., 2011; Li *et al*., 2011b). The deacetylation of STAT3 by SIRT1 diminishes its activity and suppresses gluconeogenesis. Therefore, SIRT1 promotes hepatic glucose output in response to nutrient deficiency through STAT3 deacetylation, leading to its downregulation. These findings highlight the significant role of SIRT1 as a key regulator of glucose metabolism in the liver under various conditions, modulating the expression of gluconeogenesis-related genes as well as the activity of PGC-1-alpha, FOXO1, STAT3, and CRTC2 (Zhang *et al*., 2019).

Dyslipidemia often coexists with type 2 diabetes. During periods of nutrient or energy deficiency, hepatic synthesis of cholesterol and lipids decreases, while lipid utilization becomes enhanced. Reduced fatty acid oxidation in the liver results in hepatic steatosis, which is closely associated with insulin resistance. SIRT1 promotes mitochondrial fatty acid oxidation in response to starvation by activating PPAR-alpha and PGC-1-alpha (Dabravolski *et al*., 2021). Additionally, SIRT1 exerts control over LXR and Sterol Regulatory Element-Binding Protein (SREBP), which regulate hepatic lipid synthesis. By deacetylating SREBP-1C, SIRT1 reduces its activity, subsequently downregulating lipid synthesis. Furthermore, SIRT1 deacetylates and upregulates LXR, facilitating Reverse Cholesterol Transport (RCT).

Activation of LXR by SIRT1 contributes to cholesterol catabolism in the liver (Kemper *et al*., 2013). In a liver-specific mouse model of SIRT1 knockout, the induction of PPAR-alpha/PGC-1-alpha-mediated fatty acid oxidation was diminished, resulting in increased concentrations of free fatty acids and fatty liver disease. Moreover, in a mouse model, fatty liver disease induced by a high-fat diet was alleviated through increased SIRT1 expression and therapy with resveratrol and other SIRT1 activators. Remarkably, recent studies have demonstrated that resveratrol therapy reduces liver fat content and improves insulin sensitivity in human patients with adiposity (Todisco *et al*., 2022).

SIRT1 in Atherosclerosis

To prevent cholesterol overload, Liver X Receptors (LXRs) act as cholesterol sensors. Activation of LXRs has a positive impact on cardiovascular diseases and lipid metabolism by promoting cholesterol efflux to HDL (reverse cholesterol transport) through ABC transporters, particularly ABCA1 and ABCG1, which convert cholesterol into bile acids (Lee and Tontonoz, 2015). Disruption of reverse cholesterol transport can lead to cholesterol overload and the formation of foam cells. SIRT1 interacts with LXRs, deacetylates them (K432 in LXR-alpha and K433 in LXR-beta), and activates them, thereby maintaining cholesterol efflux through the SIRT1-LXR-ABCA1/ABCG1 signaling pathway. However, this pathway is suppressed during the development and manifestation of Atherosclerosis (AS), resulting in the formation of foam cells from macrophages (Endo Umeda and Makishima, 2019). Moreover, in a high-triglyceride and high-cholesterol environment, SIRT1 inhibition during foam cell formation inhibits the liver X receptor signaling pathway (Zeng *et al*., 2013). Activated SIRT1 increases the expression of LXRs and related target genes such as ABCG1, ABCA1, and CCR7. These genes are upregulated in foam cells and promote their migration from AS lesions. Therefore, SIRT1 prevents the development of AS by stimulating the liver X receptor-ABCG1/ABCA1/CCR7 pathway to inhibit foam cell formation from macrophages (Jun *et al*., 2013).

One important stage in AS is the infiltration of monocyte-derived macrophages into the subendothelial space, followed by the release of inflammatory mediators by macrophages and their interaction with cytotoxic T lymphocytes and helper T cells (Yousaf *et al*., 2023). In vitro, incubation of macrophages or monocytes with unmodified Low-Density Lipoprotein (LDL) does not result in cholesterol deposition, whereas incubation with modified low-density Lp causes rapid cholesterol deposition. Scavenger receptors such as SR-A, CD36, LOX-1, and SR-PSOX/CXCL16 mediate the active uptake of modified LDL, particularly oxidized LDL. Uncontrolled deposition of modified LDL leads to foam cell and lipid droplet formation (Papotti *et al*., 2021).

SIRT1 regulates both inflammation and cholesterol metabolism in macrophages. It reduces the uptake of oxidized LDL, inhibits LOX-1 expression, and prevents foam cell formation. Studies involving bone marrow transplantation have demonstrated that SIRT1 derived from macrophages plays a critical role in preventing AS (Stein *et al*., 2010). SIRT1 also decreases inflammation induced by fatty acids, regulates insulin sensitivity, suppresses PGE secretion and COX-2 expression, and reduces the expression of proinflammatory molecules such as tumor necrosis factor-alpha, monocyte chemoattractant protein-1 and interleukins (Habtemariam, 2023). Furthermore, macrophages deprived of SIRT1 show hyperacetylation of nuclear factor-κB, which promotes the expression of various proinflammatory genes and increases the accumulation of activated macrophages in the liver and adipose tissue in a high-fat diet animal model. Multiple studies have suggested that macrophage-derived SIRT1 controls the expression of Matrix Metalloproteinases (MMPs) and Tissue Inhibitors of Metalloproteinase 3 (TIMP3) in pathological conditions. These findings support the notion that, in addition to regulating cholesterol uptake through scavenger receptors and exerting anti-inflammatory functions, SIRT1 reduces MMP expression and enhances the stability of AS plaques (Yoshizaki *et al*., 2010). Figure 3 provides a diagram illustrating the interactions between SIRT1 and macrophages as described.

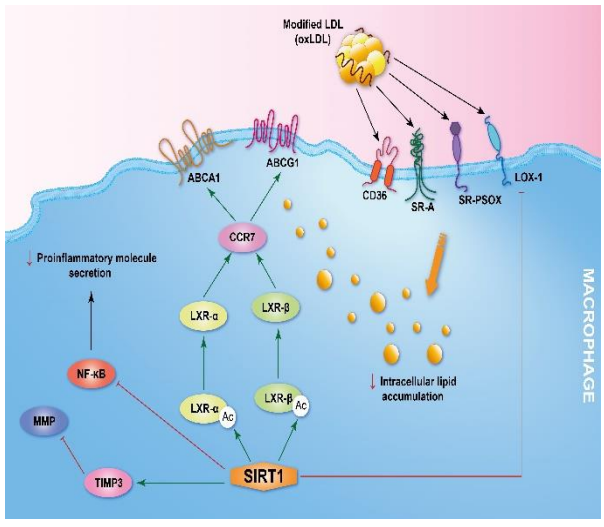

Fig. 3: The role of SIRT1 in macrophage function and atherosclerosis facilitation

Conclusion

In mice lacking SIRT1, impaired immune signaling, hepatic lipid metabolism, lipid maturation, and circadian gene expression suggest that pharmacological modulation of SIRT1 could be valuable in preventing adiposity-related disorders. Particularly, polyphenol resveratrol and other small-molecule activators of SIRTs have shown promise as potential therapeutic targets for metabolic disorders (Nogueiras *et al*., 2012). Nevertheless, there is ongoing debate regarding whether these drugs directly activate SIRT1 and confer protection against adiposity and Diabetes Mellitus (DM). Several studies have reported that mice fed a High-Fat Diet (HFD) and treated with resveratrol remained lean and maintained normal health, while untreated animals experienced excessive weight gain (Li *et al*., 2019). Furthermore, resveratrol significantly improved aerobic capacity, demonstrated by increased running time and oxygen consumption. These drugs are hypothesized to activate SIRT1 and function as Calorie Restriction Mimetics (CRMs) by enhancing lipid mobilization, and catabolism and modifying cholesterol homeostasis (Nishigaki *et al*., 2022).

Moreover, a correlation has been observed between three Single Nucleotide Polymorphisms (SNPs) in the SIRT1 gene and weight gain in older patients. Research findings demonstrated that common variants in SIRT1 are associated with a lower body mass index in two independent groups of Dutch patients (Zillikens *et al*., 2009). Individuals carrying these variants experience less weight gain and have a 13-18% reduced risk of adiposity. Another study conducted in Belgium revealed a correlation between a minor SIRT1 SNP and a lower risk of adiposity in patients with obesity (Schug and Li, 2011). Interestingly, the same variant allele was associated with higher visceral fat levels in obese male patients. In obese men, SIRT1 may improve insulin sensitivity by combining its protective function against obesity with elevated visceral adiposity, as elevated visceral adiposity has surprisingly been linked to higher insulin sensitivity. Lastly, if activated SIRT1 can facilitate fat loss without reducing calorie intake, it may introduce new possibilities in the treatment of obesity and related conditions (Hardy *et al*., 2012).

Acknowledgment

Thank you to the publisher for their support in the publication of this research article. We are grateful for the resources and platform provided by the publisher, which have enabled us to share our findings with a wider audience. We appreciate the efforts of the editorial team in reviewing and editing our work, and we are thankful for the opportunity to contribute to the field of research through this publication.

Funding Information

This study was financially supported by the Russian Science Foundation, grant #23-45-00031 (data interpretation, preparations of illustrations, draft preparation) and the Ministry of science and Higher Education of the Russian Federation, project # FGFU-2022-00008 (initial search, data collection).

Author's Contributions

Anastasia Vladimirovna Poznyak: Authored the initial draft of the manuscript.

Ludmila Viktorovna Nedosugova, Victoria Alexandrovna Khotina, Dmitry Felixovich Beloyartsev, Alexander Leonidovich Golovyuk, Vasily Nikolaevich Sukhorukov, Alexandra Alexandrovna Melnichenko and Alexander Nikolaevich Orekhov: Critically reviewed and provided substantial edits to the manuscript.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

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