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Therapeutic Targeting of the SIRT1-SREBP Pathway in Metabolic Disorders

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The enzymes known as sirtuins, or silent information regulator 2, are histone deacetylases that depend on nicotinamide adenine dinucleotide (NAD+). In addition to its well-established role in prolonging longevity, further study is necessary to examine the beneficial effects of Sirtuin 1 (SIRT1), a member of the sirtuin group, on lipid metabolism. SIRT1 has been extensively associated with the control of gene expression. The SIRT1 substrate sterol regulatory element-binding protein (SREBP) has garnered a lot of attention because of its involvement in a number of biological processes, such as metabolic activities, DNA damage repair, and cell cycle control. Therefore, the aim of this investigation was to examine and clarify the relationship between SIRT1 and SREBPs and evaluate the role of SIRT1/SREBPs in reducing dysfunction in lipid metabolism. Investigating whether SIRT1 and SREBPs may be used as feasible targets for therapeutic intervention in the management of diabetic complications was the aim of this study.

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1. Introduction

Numerous obstacles to survival have emerged since the first animal life appeared on Earth, some 600 million years ago. The need for the whole cellular system to work in unison during the metabolization of ingested nutrients is a significant challenge faced by growing organisms [1]. SIRT1 is a histone deacetylase that is reliant on nicotinamide adenine dinucleotide (NAD+) and is involved in the control of metabolism. It has been shown that calorie restriction (CR) may activate SIRT1, which is responsible for deacetylating several proteins and transcription factors to activate them [2]. Initially generated as dormant precursors, sterol regulatory element-binding proteins (SREBPs) stay affixed to endoplasmic

Adeno-associated virus (AAV); acetyl-CoA (ACC); alcoholic liver disease (ALD); Asialoglycoprotein receptor 1 (ASGR1); BMI, body mass index; BS, bariatric surgery; BSCB, blood-spinal cord barrier; DiHEP-DPA, 7 S, 15R-Dihydroxy-16S, and 17S-epoxy-docosapentaenoic acid; CR, calorie restriction; Diabetic kidney disease, or DKD; ER stands for edoplasmic reticulum; DM for diabetes mellitus; DNL for de novo lipogenesis; ER stress for edoplasmic reticulum stress; HbA1c, hemoglobin A1c; HCC, hepatocellular cancer; HEK, human embryonic kidney; FOXO1, Frkhead box transcription factor o1; GPER, G protein-coupled estrogen receptor; FA, FAS, and FGF21, fibroblast growth factor 21; GH, gowth hormone; KO stands for knockout; LADC for lung adenocarcinoma; LSCC for lung squamous cell carcinoma; LXR for liver X receptor; MEFs for embryonic fibroblasts; MS for

metabolic syndrome; MVP for mevalonate pathway; HDACs for histone deacetylases; HFD for high-fat diet; IL-1β for interleukin-1β; INSIGs for insulin-induced genes; NRCMs (neonatal rat cardiomyocytes); OA (oleic acid); NAFLD (nonalcoholic fatty liver disease); NASH (nonalcoholic steatohepatitis); and NAD+ (nicotinamide adenine dinucleotide) Oxidized low-density lipoprotein, or ox-LDL; oral hypoglycemic medications, or OHA; PGC-1α, or proliferator-activated receptor coactivator 1 alpha; PA, or palmitic acid; Photothrombotic stroke, or PTS; S1P is for sphingosine 1-phosphate; SCI stands for spinal cord damage; PTPRO. stands for protein tyrosine phosphatase receptor type O. SREBPs, or sterol regulatory element-binding proteins; SD, or Sprague Dawley SQLE, squalene epoxidase; SRPK2, serine-arginine-rich protein kinase 2; Triglycerides (TG), Sirtuin 1 (SIRT1), T helper 17 (Th17), TH-DPA, 7 S, 15 R, 16 S, and 17S-tetra-hydroxy-docosapentaenoic acid Tetrahydroxy-docosapentaenoic acid (7 S, 15 R, 16 S, 17S); unsaturated fatty acids (UFAs); very low-density lipoprotein (VLDL); wild-type (WT).

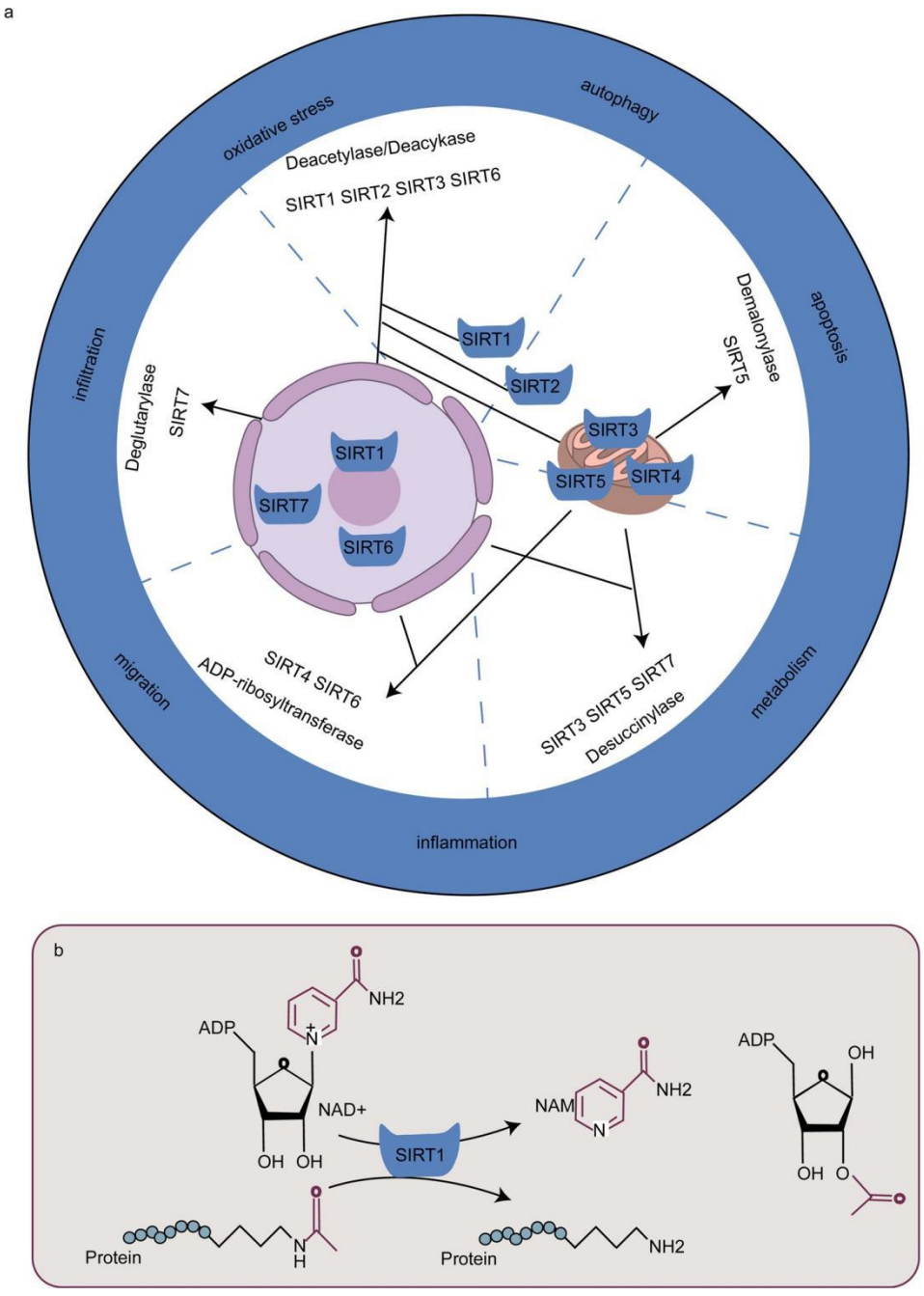


Fig. 1. primary roles of the seven members of the SIRT protein family. Each SIRT protein family member's cellular location, primary functional activity, and impact on physiological processes (a). Specifics of SIRT1 that lowers target protein acetylation levels via being regulated by the NAD +/NADH ratio (b). The nucleus is where SIRT1, SIRT6, and SIRT7 are mostly found. The mitochondria are home to SIRT3, SIRT4, and SIRT5. The cytoplasm is the primary location of SIRT2. Although Sirt1 is mostly nuclear, it may potentially affect cytoplasmic cellular function. SIRT4 preserves ADP-ribosyl transferase activity, while SIRT1–3 has deacetylase function. SIRT5 is involved in regulating post-translational modifications of proteins, including glutarylation, lysine succinylation, malonylation, and others. ADP-ribosyl transferase and long-chain fatty acyldeacetylase are present in SIRT6. With the exception of its desuccinylase and deglutarylase functions within the cell, the SIRT7 deacetylase enzyme is reliant on β-NAD +. Widely expressed, the SIRTs family plays a crucial role in triggering metabolic alterations, oxidative stress, autophagy, apoptosis, inflammation, cell migration, and infiltration (a). SIRT1 lowers the acetylation level of target proteins by cleaving acetyl groups off them using NAD + as a co-substrate. Consequently, SIRT1 activation is impacted by variations in NAD + levels (b).

reticulum membranes (ER). The SREBP family of transcription factors is responsible for coordinating the synthesis of unsaturated fatty acids (UFAs) and cholesterol, two crucial components of animal cell membranes [1]. The three SREBP proteins are encoded by two different genes. The SREBP-1 gene uses various promoters to create SREBP-1a and SREBP-1c, which are transcripts that splice different first exons to a common second exon. SREBP-2 comes from a different gene [3–6]. Experimental results demonstrated that SREBPs and SIRT1 could regulate many aspects of animal metabolism shortly after it was proposed that they may play a significant role in lowering the complications associated with diabetes. We outline our current knowledge of lipid metabolism, a crucial component of metabolism, in this synopsis. Lipid metabolism is centered on the liver, which is achieved via controlling the

Table 1
Summary of SIRT1 mediated cell function by deacetylase activity.

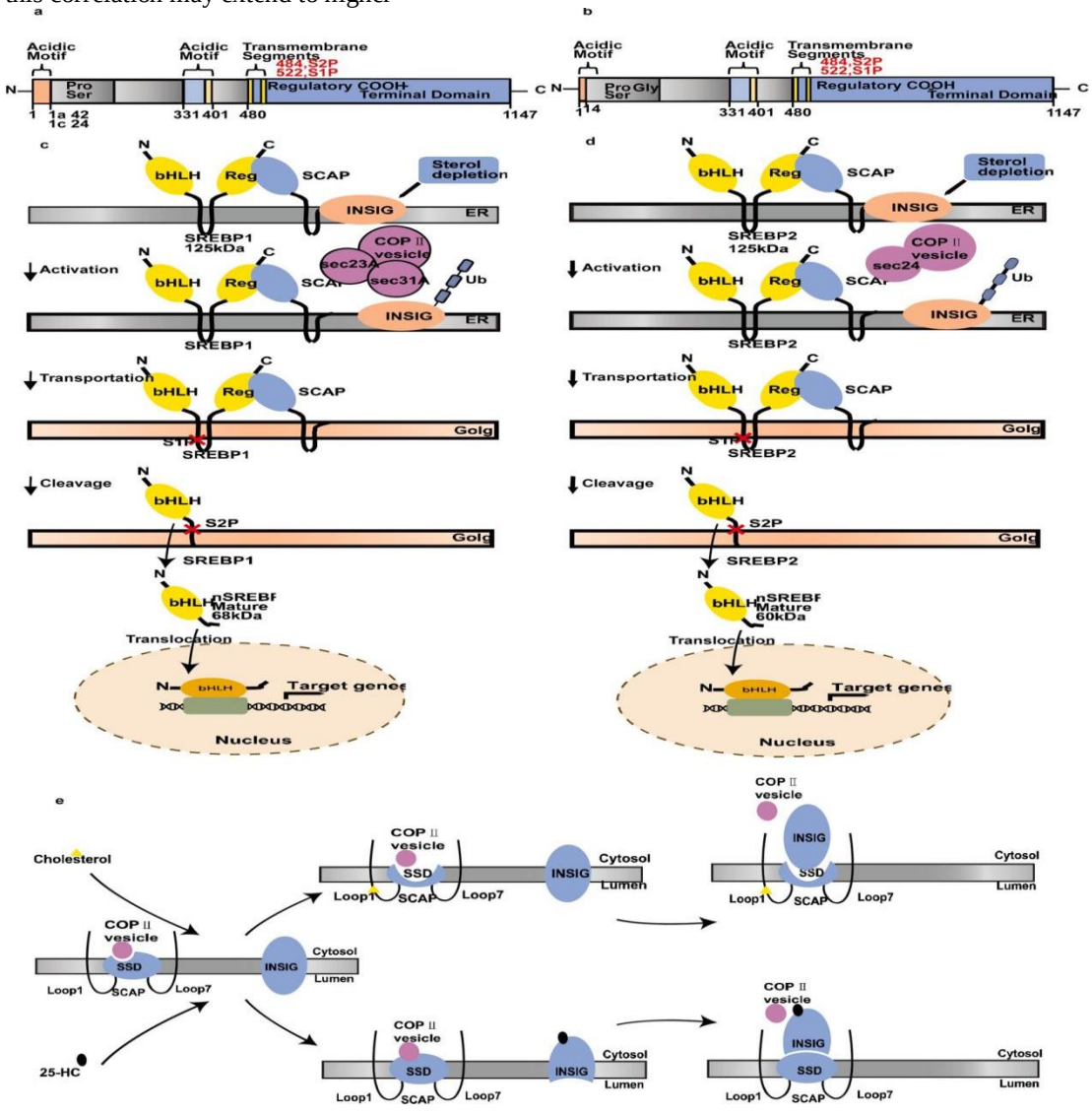
Sr. no	Function	Year	Human/animals/cells used in the study	In vivo/ in vitro	Axis	Effect	Reference
1.	Apoptosis	2018	Human (ER+) breast cancer Cell lines (MCF-7 and T-47D), human (ER-) breast cancer cells (MDA-MB 453, MDA-MB 231 and MDA-MB 468), a human normal breast cell line (MCF 10A), archival human breast cancer carcinoma samples.	Both	SIRT1/H3k4	The expression and activity of SIRT1 ↑ The acetylation of H3k4 and H3k9a ↓	[65]
2.		2021	Rat H9c2 cardiomyocytes, NRCMs, male C57BL/ 6 J mice.	Both	SIRT1/PIK3R 1	In Ang II treated mice- SIRT1 expression ↓ P53 ↑	[57]
3.		2023	Rat H9c2 cardiomyocytes, monkey kidney COS7 cells, male C57BL/6 J mice.	Both	SIRT1/ H2AX	The expression and activity of SIRT1 ↑ The phosphorylation of H2AX ↑	[66]
4.	Oxidative stress	2023	Mouse brain microvascular endothelial cells (bEnd.3 cells), HEK293T cells WT C57BL/6 J mice (8–10 weeks old), Tie2-Cre SIRT1 knockout (CKO) mice on C57BL/6 J background mice.	Both	SIRT1/ p66Shc	The axpression and activity of SIRT1 ↑ The acetylation of p66Shc ↓	[50]
5.		2023	HEK-293 T cells, HNCI-H1299 cells, Immortalized mouse podocyte MPC-5 cells, MEFs were derived from E14.5 embryos from Nr4a1 + /— C57BL/6 J mice, WT and Nr4a1- targeted mutant (No: 006187; Nr4a1 —/—) mice on a C57BL/6 J background mice.	Both	Nur77/SIRT1 /P53	The expression and activity of SIRT1 ↑ The acetylation and phosphorylation of p53 ↓	[51]
6.	Autophagic	2019	18 CDDP-sensitive group and 18 CDDP-resistant group, CDDP-resistant cell line H1299 (H1299/ CDDP) and the corresponding parental cells	Both	MiR-124/ SIRT1 MiR-142/ SIRT1	MiR-124 and miR-142 enhance the cytotoxic effect of CDDP through repressing autophagy via targeting SIRT1	[52]

			H1299.			in CDDP-resistant NSCLC	
7.		2021	Conditionally immortalized mouse podocytes · homozygous eNOS KO male mice on C57BL/6 J background mice, 30 non-DN DM patients and 30 DN DM patients.	Both	SIRT1/p53/AMPK	cells. Anti-miR-150–5p exerts reno-protective effects by targeting SIRT1 and restoring autophagy.	[54]
8.	Metabolism	2020	Male C57BL/6 J mice	In vivo	SIRT1/PGC1α/ FNDC5/irisin	SIRT1 expression ↓ PGC1α ↑ FNDC5 ↑ irisin ↑	[67]
9.		2022	Mouse 3T3-L1 preadipocytes	In vitro	AMPK/SIRT1	The expression and activity of AMPK and SIRT1 ↑ PPARγ ↑ CEBPα ↑ SREBP1c ↑ FABP4 ↑ ACC1 ↑ FAS ↑	[68]
10.		2022	A human proximal tubular cell line(HK-2 cells) and a human hepatocellular carcinoma cell line (HepG2 cells).	Both	ApoM/S1P/SIRT1	The activity of SIRT1 ↓ the activity of ApoM/S1P-S1P1 ↓ Sirt1 ↓ in turn	[69]
11.		2023	Male C57BL/6 J mice.	In vivo	SIRT1/ PPARα	The expression and activity of SIRT1 ↑ The level of serum TC, TG, and LDL-C ↓	[46]
12.	Inflammation	2023	Mouse RAW 264.7 macrophages.	In vitro	SIRT1/HDAC4	The expression and activity of SIRT1 ↑ HDAC4 ↓	[59]
13.		2022	Male C57BL/6 J mice.	In vivo	SIRT1/AMPK	The expression and activity of SIRT1 ↑ AMPK ↑	[70]
14.	Migration and invasion	2019	30 osteosarcoma patients, human osteosarcoma cell lines (MG-63, SAOS-2, and U2OS).	Both	SIRT1/ZEB1	The expression and activity of SIRT1 ↑ ZEB1 ↑	[62]
15.		2019	HEK-293 T, MDA-MB-231, MDA-MB-453, and Hs-578 T breast cancer cells, U87 glial cells, and HK-2 cells.	In vitro	SIRT1/the vacuolar-type H+ ATPase (V-ATPase)	SIRT1 expression ↓ V-ATPase ↓	[63]
16.		2020	80 radical or partial nephrectomy patients, epithelial human kidney cell lines (HKC-8, 786-O, Caki-1, Caki-2, and ACHN)	Both	Renal cell carcinomas (RCCs) /SIRT1	lactate contributes to increased RCC aggressiveness, likely through SIRT1 activity reduction.	[61]

dispersion of lipoprotein particles in living things, including a number of physiological activities such catabolism, synthesis, absorption, and storage. Hepatocytes transport cholesterol, triglycerides, and phospholipids to peripheral cells, synthesize low-density lipoprotein and high-density lipoprotein, absorb and store lipids, particularly cholesterol, in the liver, and then excrete them as bile acids (catabolism). We clarify the basic mechanism of lipid metabolism control using a number of well-established instances, highlighting the role of SIRT1/SREBPs in both normal physiology and pathological circumstances. Because we understand that the regulation of lipid metabolism by SIRT1/SREBPs may be a critical component of overall metabolism, lipid metabolism is our primary focus. Given the liver's critical role in lipid metabolism, this review focuses primarily on the regulation of SIRT1/SREBPs in the liver. We conclude by reviewing previous studies on SIRT1/SREBPs, examining both their basic functions and growing importance as disease markers.

2. Sirt1

The discovery of SIR2 [7], first seen in developing Saccharomyces cerevisiae [8], by Mortimer and Johnston in 1959 [9,10] is when the name "Sirtuin" first appeared. The conserved proteins that are members of the class III histone deacetylases family [12] and that resemble SIR2 in all species are known as sirtuins (SIRTs) [11]. Enzymes known as histone deacetylases (HDACs) help remove acetyl chemical groups from the lysine residues of histone and nonhistone proteins [13]. By deacetylating a variety of nuclear and cytoplasmic proteins of structural and functional importance, HDACs control important cellular functions [14]. They are divided into four classes (I, II, III, and IV) according to their duties and positions [15]. Importantly, SIR2 shows NAD+-dependent HDAC enzymatic activity, suggesting that NAD-dependent histone deacetylation might be connected to aging and genomic suppression. Additionally, this correlation may extend to higher



(caption on next page)

Fig. 2SREBPs (a and b) and the sterol regulatory element-binding protein pathway (c, d, and e) are shown schematically. when oxycholesterols (25-hydroxycholesterol and 27-hydroxycholesterol) and cholesterol are present. When sterols are not present, INSIGs are ubiquitylated (Ub) and rapidly break down. When delivered to the Golgi apparatus, SREBPs interacts with two proteases, a zinc metal-loprotease called a Site-2 protease (S2P) and a serine protease called a Site-1 protease (S1P), which releases the N-terminal region of SREBPs. S1P breaks down SREBPs in the luminal loop of the Golgi apparatus, causing the protein to divide into two membrane-bound parts. The N-terminal half of SREBP is broken down into three residues within the membrane as a substrate for S2P after Site-1 cleavage. In conclusion, a two-step cleavage mechanism known as RIP (regulated intramembrane proteolysis) has been discovered. The transcriptionally active portion of SREBP is released into the cytoplasm before traveling to the nucleus (c and d). Sterol-sensing domain (SSD) binding and COPII are inhibited by cholesterol and oxysterol 25-hydroxy-cholesterol (25-HC), which prevents SCAP from being transported to the Golgi apparatus (e). SIR2 enzymology, thereby offering a new viewpoint on the subject of eukaryotic metabolism [16]. SIRT1 through SIRT7 are the seven members of the SIRT protein family found in mammals [12]. SIRTs often have a conserved catalytic core with molecular structures that are comparable in both chemical and structural aspects. They could, however, differ somewhat in their targets, enzymatic activity, tissue selectivity, and subcellular localization [11,17]. These seven mammalian sirtuins have been divided into four classes by evolutionary analysis: SIRT1 is a member of class I [18]. It seems that SIRT1–7 may vary somewhat in the architecture of their active sites based on the analysis of their molecular structures [19]. However, the sirtuin clan is highly physically and functionally conserved, and its deacetylase activity depends on the co-factor β-NAD or NAD [20]. While SIRT4 preserves ADP-ribose transferase action [28–34], SIRT1-3 demonstrate strong deacetylase function [21–27]. SIRT5 is linked to the regulation of post-translational modifications of proteins [35, 36]. Meanwhile, SIRT6 has long-chain fatty acyl deacetylases and ADP-ribosyl transferase [36–38]. In contrast to its desuccinylase [41] and deglutarylase [42] activity inside the cell, more recent research has shown that SIRT7 [39,40], the most recent member of the SIRT family of proteins, works as a β-NAD+ -dependent deacetylase enzyme [40]. The seven sirtuin isoforms' catalytic core is made up of a large NADþ-binding (Rossmann Fold subunit) and a zinc-binding domain. By removing the acetyl group from N-ε-lysine residues, this highly conserved core carries out enzymatic activity, generating O-acetyl-ADP-ribose and nicotinamide [9,43]. N-ε-lysine protein residues undergo deacetylation and deacylases (Fig. 1). Since SIRT1 is mostly nuclear, its concentration has been adjusted to the total protein content in tissues or whole cell lysates in several in vivo and ex vivo lipid metabolic investigations. For instance, acute ethanol-induced increases in blood triglyceride (TG) levels may be considerably reduced, as can the deposition of fat droplets in mice's livers, by activating the hypothalamic SIRT1 gene expression [44]. SIRT1 activator medication has been shown to enhance the serum lipid profile by lowering the concentrations of triglycerides, low-density lipoprotein cholesterol, and total serum cholesterol in a randomized double-blind experiment of healthy cigarette smokers [45]. Furthermore, in a mouse model of diabetes, hepatocytes, muscle cells, and adipocytes with higher SIRT1 protein expression enhanced the effects of HDL and prevented diabetic nephropathy [46], while podocyte damage and kidney lipid accumulation were lessened when SIRT1 expression was inhibited. One of the main factors influencing diabetic kidney disease (DKD) is podocyte lipid buildup. Therefore, in order to provide a comprehensive perspective on renal lipid metabolism, it is important to talk about DKD [47]. It is important to note that these studies do not identify the precise site of SIRT1 activity, and because of the downstream modifications at the messenger RNA level, effects may be automatically ascribed to nuclear SIRT1. Although it may be found in different parts of cells, SIRT1 is mostly found in the nucleus. The function of SIRT1, which is found in the cytoplasm, in lipid metabolism has also been the subject of recent research. For example, SIRT1 is typically concentrated in the nucleus; however, due to photothrombotic stroke (PTS) or Pb-induced neurotoxic lesions, the nucleus's SIRT1 level falls after the cytoplasm's SIRT1 level rises. This suggests that SIRT1 has undergone a nucleocytoplasmic translocation, which the SIRT1 activator resveratrol may inhibit [48, 49]. Compared with existing studies on SIRT1 located in the nucleus and cytoplasm, studies on the SIRT1 predominantly in the cytoplasm have focused on the response of brain cells to ischemia and oxidative stress. Detailed analysis of the effect of cytoplasmic SIRT1 on lipid metabolism are of great significance for further investigating therapeutic targets and drug resistance. These in turn could inform more targeted use of the agonists and inhibitors of SIRT1, as well as better ameliorate their un- intended side effects. Furthermore, newer studies have additionally indicated that atypical SIRTs expression can impact cellular physiology through the induction of oxidative stress [50,51], autophagy [52–55], apoptosis [56,57], alterations in metabolism [58], inflammation [59, 60], cell migration, and infiltration [61–64] (Table 1). Lipid metabolism is a complex cellular process that, through these physiological processes and pharmacologic modulation plays a wide range of roles.

3. SREBPs

As discovered in humans in 1993, SREBPs are a group of transcrip- tion factors found in the cell membrane [4,71]. The SREBPs consist of a bHLH-Zip transcription factor as their N-terminal domain and a regu- latory domain as their C-terminal domain. The regulatory domain fa- cilitates the interaction with SCAP, a membrane protein responsible for activating SREBP and is crucial for its activation [72–74]. It consists of three members that are encoded by two

different genes. SREBP-1a and SREBP-1c originate from SREBP-1, which is obtained through the utili- zation of different promoters and splicing distinct first exons to a shared second exon. SREBP2 is derived from a distinct gene [3–6].

The human SREBP1 gene, which consists of 26 kilobases, 22 exons, and 20 introns, is located on chromosome 17p11.2. This gene is formed through alternative splicing at both the 5′ and 3′ terminals [75,76]. SREBP1a and SREBP1c, which are two variations of SREBP1, are
generated by employing different transcription start sites and having distinct first exons (exon 1a and exon 1c) [77]. The levels of extreme N-terminal acidic amino acids vary between them, but they have a comparable composition consisting of an NH2-terminal transcription factor domain (480 amino acids), a middle hydrophobic region (80 amino acids), and a COOH-terminal regulatory domain (590 amino acids) (Fig. 2a) [78]. In the current body of work, SREBP-1 is commonly associated with SREBP-1c, as initially noted by Goldstein and Brown's research group, who observed a significantly greater expression of SREBP-1c mRNA compared to SREBP-1a [79]. The study demonstrated a potential direct connection between SREBP-1a phosphorylation and the regulation of lipid metabolism by growth hormone (GH). This finding aids in understanding the molecular mechanisms underlying GH's impact on lipid metabolism and the possible significance of the SREBP-1a isoform [80]. GH can mediate the phosphorylation of SREBP1a by enhancing the expression of nuclear receptors like FXR, LXRa, or PPARa, and the activity of LXR is positively correlated with the expression of SREBP1c [81]. From a physiological standpoint, SREBP1a exerts a potent stimulation on overall lipid production in swiftly proliferating cells, whereas SREBP1c plays a part in governing the levels of fatty acids and triglycerides in lipogenic organs like the liver [82]. Regarding embryogenesis, the maintenance of mouse embryonic fibro- blasts (MEFs) membrane and the expression of the fatty acid desaturase SCD are sustained by AdipoR1/2-derived sphingosine 1-phosphate (S1P) signals. These signals act in parallel through S1PR3-SREBP1 and PPARγathways[83].

It is reported that SREBP1 plays an important role in lipid regulation in various organs including the brain, liver and heart. The brain is the organ with the highest concentration of cholesterol, and cholesterol is primarily synthesized through de novo pathways. In human pluripotent stem cells, SREBP1 is linked to the movement of lipid rafts and serves as a subject of the RAC1/CDC42/actin network [84]. Defective expression of regulators of oligodendrocyte development is caused by the activation of the SREBP1 pathway, which regulates the de novo production of unsaturated fatty acids [85]. Unsaturated fatty acids have the ability to restore the abnormal connections in the brains of mice with p97 muta- tions, which lead to neurodegeneration, as indicated by a recent inves- tigation demonstrating the negative effect on the SREBP1-SCD1 pathway [86]. The SREBP pathway in the liver, which is a significant location for cholesterol and UFA production, undergoes transcriptional regulation through various mechanisms. Activation of SREBP1 can occur through SCAP when there is a shortage of sterols, while SREBP1/2 can be activated by caspase-2 when there is hypernutrition and ER stress. The two pathways control the transition from hepatosteatosis to steatohepatitis with regulatory crosstalk in between [87]. In mice and patients with alcoholic liver disease (ALD), SREBP-1 facilitates the production of fats due to its activation by serine-arginine-rich protein kinase 2 (SRPK2), a crucial enzyme that regulates alternative splicing in liver cells in response to alcohol, as well as chronic-plus-binge alcohol feeding [88]. Nevertheless, the consequences of increased SREBP1 expression are not entirely detrimental. Over-expression of SREBP1 augments hepatic NADPH levels, obstructs ferroptosis, and provides protection to the liver from Ischemia/Reperfusion injury [89]. In in- dividuals with good health, the heart has very little lipid storage. However, this study indicates that the presence of defective Asialogly- coprotein receptor 1 (ASGR1) forms is linked to decreased cholesterol levels and a lower likelihood of cardiovascular disease. This is achieved by blocking SREBP1 and lipogenesis, which in turn encourages the elimination of cholesterol and reduction of lipid levels in the liver [90]. SREBP1 helps mitigate tumor proliferation by regulating lipid metabolism during the occurrence and development of the tumor. Mitochondrial division in hepatocellular carcinoma (HCC) leads to an elevation in the acetylation level of SREBP1 and peroxisome proliferator-activated receptor coactivator 1 alpha (PGC-1α) through the inhibition of NAD+ /SIRT1 [91]. Furthermore, the metabolic rewiring facilitated by SREBP1-ACLY plays a crucial role in promoting cancer stemness upon activation of Ephrin-A3/EphA2 forward-signaling [92]. Ammonia and DAXX can facilitate the activation of SREBP-1 in breast cancer, CRC, and various other types of cancer, revealing a unique metabolic function of ammonia as a crucial stimulant for lipogenesis and the proliferation of tumors [93–95]. Conversely, SREBP1 has the ability to inhibit cancer growth by altering lipid metabolism through the involvement of protein tyrosine phosphatase receptor type O (PTPRO), which belongs to the PTP group. This occurs by regulating the AKT/mTOR/SREBP1/ACC1 pathways [96].

The human gene SREBP2 is located at 22p13 on the chromosome, and it consists of 72 kb with 19 exons and 18

introns. This positioning is a result of utilizing alternative promoters and transcription start sites. The structure of SREBP-2, resembling SREBP-1, consists of 1141 amino acids and comprises a transcription factor domain at the NH2-terminal (480 amino acids), a hydrophobic region in the middle (80 amino acids), and a regulatory domain at the COOH-terminal (590 amino acids) (Fig. 2b). SREBP-2 originates from an independent gene. The cleavage process of SREBP2, which involves five extra proteins, trans- forms the membrane-bound precursor forms (pSREBP2) into their active, nuclear forms (nSREBP2) through a two-step mechanism, resembling that of SREBP1[97]. Modification with ubiquitin, SUMO, or phosphorus regulates the fate and function of nSREBP2s. The phos- phorylation of SREBP-2 induced by growth factors hinders SUMOyla- tion, thus promoting the transcriptional activity of SREBP [98]. It has been reported that SREBP2 plays an important role in various

physiological and pathological lipid regulation, including circulatory system, consumptive system and motor system, with the core function of controlling cholesterol metabolism. In circulatory system, inhibiting the transcriptional activation of SREBP2 leads to a decrease in PCSK9, consequently enhancing the LDLR expression and LDLc clearance [99]. Controlling the balance of cholesterol also regulates the process of erythroid differentiation. By binding to GATA1, SREBP2 inhibits the production of cholesterol and establishes a feedback mechanism to control globin expression by regulating NFE2 transcription [100]. The SREBP2-related cholesterol biosynthesis signals are efficiently enhanced with Lp-PLA independently of insulin-induced genes (INSIGs) in dietary cholesterol-induced atherosclerosis rabbits [101]. The epithelium of Hmgcr intestinal knockout mice exhibited strong activation of SREBP2 target genes, including the LDLR [102]. Deficiency lowers cholesterol levels and can protect against atherosclerosis. The reduced levels of SREBP1 and SREBP2, along with the increased levels of Activin A in the liver, led to a decrease in the accumulation of white fat tissue and a reduction in the size of adipocytes [103]. Osteoclastogenesis can be promoted by the dual-activation of cholesterol synthesis. Activating SREBP2 increases cholesterol biosynthesis with Hsp90β, and promots osteoclastogenic gene expression and bone loss in osteoporosis [104].

In contrast to SREBP1, SREBP2 plays a significant role in autoim-
mune diseases and specific forms of cancer because of its abnormal role in the differentiation of T helper 17 (Th17) cells in tumor cholesterol metabolism and the impaired function of natural killer T cells in the liver of obese individuals [105,106]. The Zika virus infection in human dendritic cells is increased by the transcription of lipid genes that are dependent on SREBP2 [107]. In terms of physiology, a range of exper- iments conducted on transgenic and knockout mice have shown that SREBP2 controls the transcription of genes associated with cholesterol metabolism and plays a role in regulating sterol levels in all tissues, distinguishing it from SREBP1 [79,108]. In hepatocellular carcinoma (HCC), an imbalance in the intestinal microbiota triggers the start of the disease by altering the metabolism of tryptophan and increasing the expression of SREBP2 [109]. However, the ERK signaling pathway de- creases the phosphorylation of SREBP2, which results in decreased cholesterol biosynthesis and eventually impedes HCC cell growth [110]. Additionally, the binding of STAT3 to the promoter of SREBP2 in triple-negative breast cancer enhances the transcription of SREBP2, which plays a crucial role in regulating cholesterol biosynthesis [111]. SREBP2 activation in PTEN/p53 deficient tumors with castration-resistant prostate cancer leads to increased reliance on cholesterol metabolism, resulting in therapeutic vulnerabilities through the transcriptional up-regulation of squalene epoxidase (SQLE) [112]. In glioblastoma stem cells, SREBP2 additionally enhanced the production of cholesterol, particularly during periods of starvation, while also facilitating cell proliferation, self-renewal, and tumor development [113]. Moreover, mature SREBP2 binds to USP28, leading to deubi- quitination and stabilization, as well as regulation of the mevalonate pathway (MVP), which drives the synthesis of cholesterol, thus driving tumor growth in squamous cancer [114].

Thus, deregulation of SREBPs activity due to certain conditions can
lead to lipid metabolic disorders due to the destructive effects of SREBPs. The most typical example is the increase of serum LDL level and the decrease of serum HDL level, which is more common in metabolic fatty liver, diabetes, and various tumors. In addition to the complications caused by the syndrome, the local imbalance of lipid metabolism caused by uncontrolled SREBPs may also involve the brain, liver, and bone.

4. Influence of SIRT1 on SREBPs

As mentioned above, the process of SREBPs' function is as follows: SIRT1 is transcribed into mRNA in the nucleus, transferred to the endoplasmic reticulum, transferred to Golgi apparatus, cut and trans- ferred to the nucleus,

and regulated by downstream genes in the nucleus. The existing studies on SIRT1 regulation of SREBPs mainly involve the

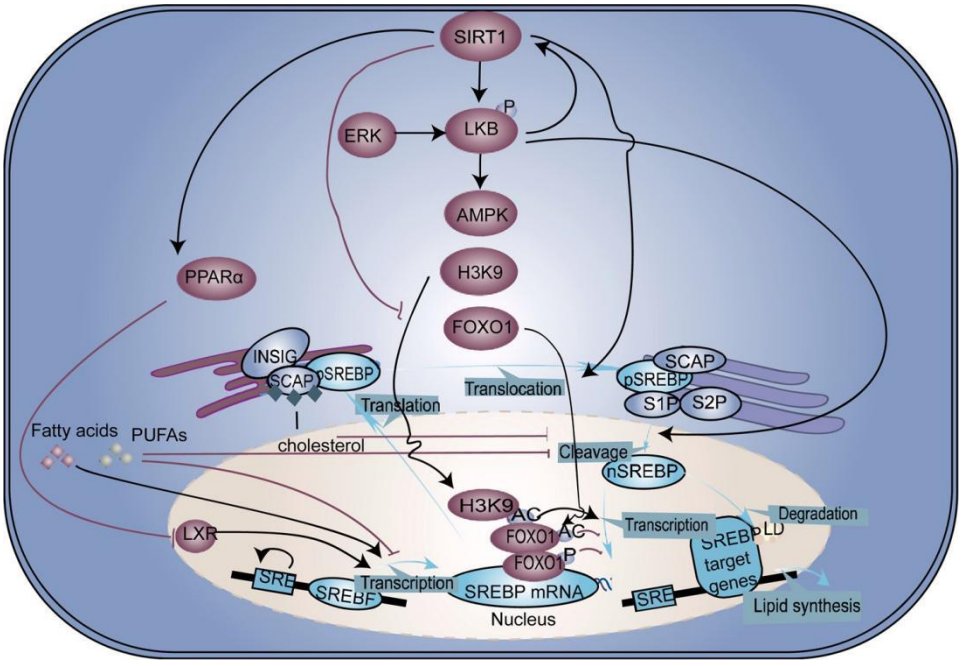
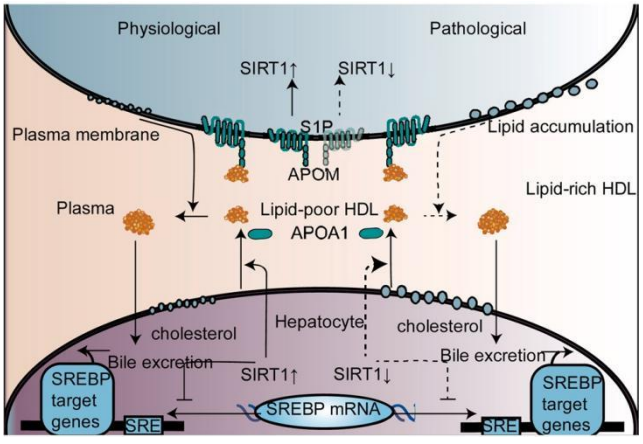


Fig. 3. Influence of SIRT1 on SREBPs. SIRT1-PPAR-LXR, Fatty, and PUFAs are involved in activation and regulation of transcription of SREBP gene (SREBF) and stability of SREBP mRNA (1). SIRT1-LKB-AMPK and ERK-AMPK-SIRT1 are the main pathways that regulate the shearing of SREBP into the nucleus in Golgi apparatus
(2). SIRT1-H3K9 and SIRT1-FOXO1 are the main pathways that regulate the transcription of nSREBPs in the nucleus and affect the downstream target genes (3). Activation and inhibition effects are displayed in "arrows" and "inhibitors", respectively.



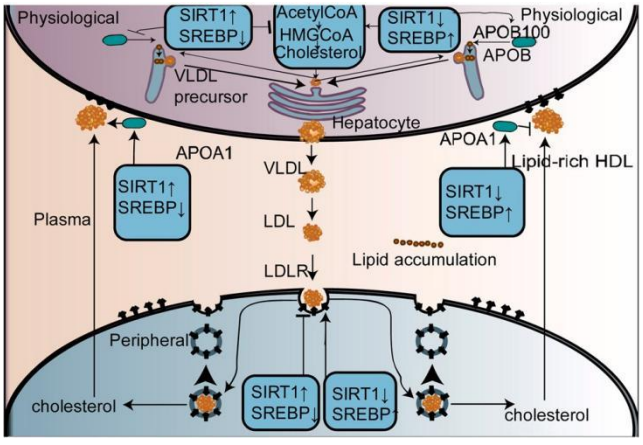


Fig. 4. HDL biogenesis and control by SIRT1-SREBPs in hepatocytes. High density lipoprotein (HDL) is produced by binding apolipoproteins APOA1 and APOA2 to lipids. Hepatocytes gather extracellular lipid-deficient high-density lipoprotein particles, which are then enriched with lipids (mainly cholesterol) from peripheral cells, thus producing fat-rich high-density lipoprotein (1). The apolipoprotein APOM promotes the binding of S1P on the peripheral cell membrane to HDL in serum, and the overexpression of APOM increases the S1P and SIRT1 level in peripheral cells (2). Increased SIRT1 in serum or peripheral cells and decreased SREBPs promote lipid uptake by lipid-deficient HDL par- ticles into fat-rich HDL particles (3). In hepatocytes, SIRT1 increases, which promotes the transportation of fat-rich high-density lipoprotein cholesterol back to the liver through bile for excretion, and inhibits the translation of SREBPs, thus inhibiting its downstream target genes (4). Pathologically, SIRT1 decreases, SREBPs increase, lipid-deficient high density lipoprotein particles increase in serum, fat-rich high-density lipoprotein decrease, and lipid accu- mulated in peripheral cells and liver decrease. Arrow symbols indicate activa- tion pathways or signaling pathways (5).

Fig. 5. Control of lipid metabolism and LDL biogenesis/turnover by SIRT1- SREBPs. SIRT1/SREBPs inhibit the synthesis and insertion of apolipoprotein B-100 (APOB100) into the endoplasmic reticulum of hepatocytes and initiate the assembly of very low-density lipoprotein (VLDL) complex in endoplasmic reticulum. Similarly, an increase in SIRT1 levels and a decrease in SREBPs also inhibit sterol biosynthesis by converting the metabolite acetyl-coenzyme A into cholesterol (1). Very low-density lipoprotein is transported to the Golgi appa- ratus, where it matures through fat metabolism and is then secreted from liver cells into the circulatory system. Very low-density lipoprotein is oxidized into low density lipoprotein, which reaches the surrounding cells. There, LDL binds to a low-density lipoprotein receptor (LDLR) and is endocytosed by surrounding cells (2). Sterols and other lipids are transferred from the endocytosis of pe- ripheral cells, where they are used. The endobody is recovered by the plasma membrane, LDLR is redeposited on the surface, and cholesterol is transported to the liver with the assistance of APOA1 in serum (3) Under pathological con- ditions, SIRT1 level decreases, SREBPs level increases, LDL synthesis in liver increases, HDL uptake decreases, and lipid accumulation in serum and cholesterol uptake in peripheral cells increases (4).

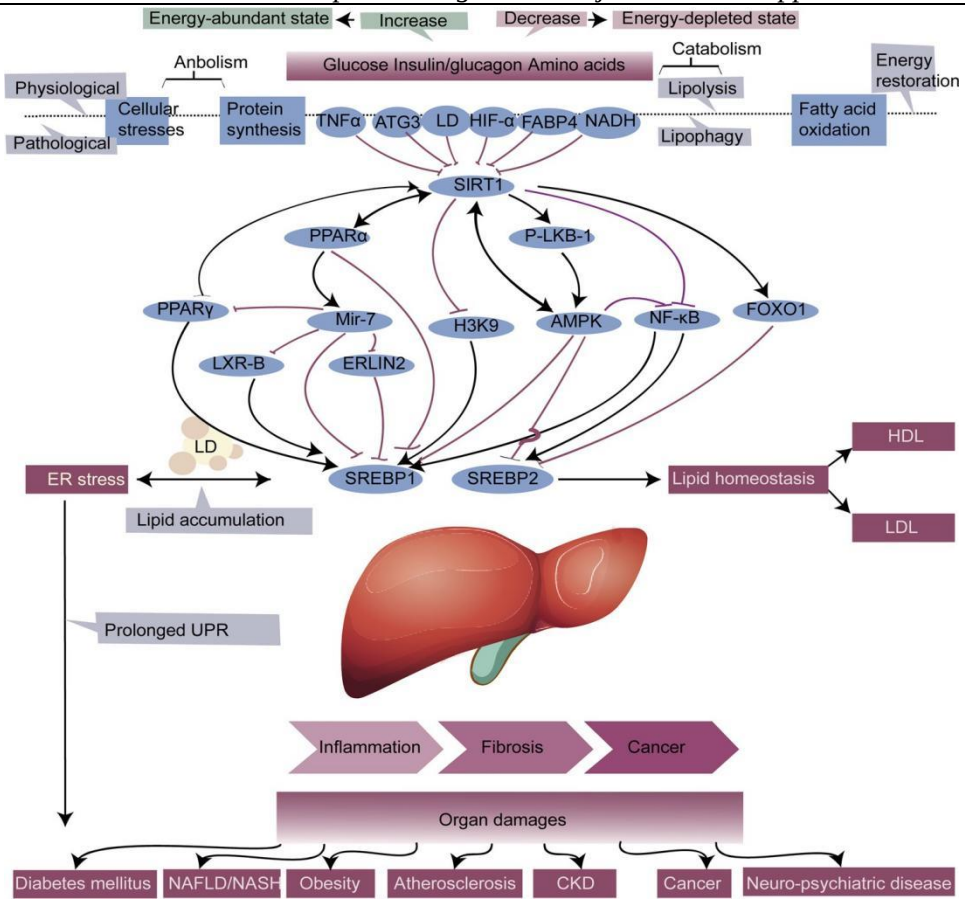


Fig. 6SIRT1-SREBPs mediate lipotoxicity. Under pathological situations, the equilibrium between energy expenditure and intake is upset, and SIRT1 expression and activity are suppressed, which stops SREBPs from being regulated under normal physiological conditions (1). The transcription of SREBPs is increased by endoplasmic reticulum stress and liver lipid buildup, which exacerbates the lipid problem under pathological situations and ultimately results in liver inflammation that progresses to fibrosis and may potentially turn into malignancies (2). In addition to directly causing lipid buildup in the circulatory system, disruptions in the liver lipid metabolism system may also cause lipid regulation to collapse in other organs, including diabetes, non-alcoholic fatty liver disease, obesity, osteoarthritis, kidney damage, various cancers, diseases of the nervous system, and other syndromes (3).

SREBP gene transcription in the nucleus, SREBP mRNA stability, cleavage to the nucleus, and control of downstream genes in the nucleus.

The primary regulator of SREBP gene transcription and SREBP mRNA stability is PPAR γ-LXR. SIRT6 crosstalk to SIRT1 also contributes to the up-regulation of PPAR γ by suppressing LXR expression, which in turn adversely influences SREBP gene transcription and SREBP mRNA stability. Furthermore, in contrast to the beneficial impact of fatty acid levels on SREBP gene transcription, PUFs might adversely influence SREBP gene transcription by up-regulating SIRT1 expression level [115,116]. Additionally, PUFs take involved in the shearing process that converts pSREBP into nSREBP as it moves from the Golgi apparatus to the nucleus. LKB, AMPK, ERK, and cholesterol are the primary molecules involved in this process. However, it should be mentioned that cholesterol is involved in both the Golgi apparatus entering the nucleus and the nucleus exiting the endoplasmic reticulum.

One thing to think about is that the SIRT1/AMPK pathway inhibits SREBP1 expression, which regulates the synthesis of fatty acids. Moreover, it inhibits the expression of SREBP2, regulates cholesterol synthesis, and improves lipid storage in cells [117,118]. The SIRT1-LKB1-AMPK-SREBP1 axis mediates lipid accumulation [119], and p-LKB is also necessary for the SIRT1/AMPK signaling pathway to operate [120]. It is possible for the ERK-SREBP2 pathway to decrease the synthesis of cholesterol, preventing cancer cells from proliferating and spreading [110]. According to reference [121], the ERK1/2/AMPK/SIRT1 pathway may inhibit lipogenesis, which lowers SREBP1-driven PNPLA3. SIRT1 primarily performs a deacetylation function in the translation process of downstream genes, which is mediated by H3K9 and FOXO1. SREBP functions in the nucleus. Through its influence on SREBP-1-driven transcription, SIRT1 can control the expression of the PNPLA3 gene by altering the acetylation of H3K9. Both at rest and when stimulated by SREBP-1c, elevated SIRT1 levels

suppress PNPLA3 gene expression. It also prevents SREBP-1c and PNPLA3 from interacting naturally [122]. By boosting the deacetylation of forkhead box transcription factor o1 (FOXO1) and promoting its nuclear translocation, SIRT1 overexpression suppresses SREBP2 expression [123]. Furthermore, this mechanism also involves the phosphorylation of FOXO1. In cultured chondrocytes, inhibiting FOXO1 but not SIRT1 increases the buildup of cholesterol and reduces FOXO1 phosphorylation [124]. The timing of SIRT1 inhibitory effects on SREBPs, however, is unclear from several other research. By activating the PI3K/AKT signaling pathway, which is regulated by the SREBP2 protein, deletion of the SIRT1 gene may exacerbate inflammation and cellular degeneration [125]. Furthermore, it has been shown that the activation of SREBP-2 may control SIRT1 activity in an inflammatory environment treated with interleukin-1β (IL-1β). The communication between SIRT6

Table 2
SIRT1/SREBPs associated with lipid accumulation regulation liver diseases.

Sr. no	Year	Human/animals/cells used in the study	Drug/method used	Effect	Reference
1.	2023	human hepatoma cell lines (Hep3B, HepG2), NAFLD patients	The Hep3B cells are wild-type for the PNPLA3 gene, while the HepG2 cells carry the rs738409 C > G (I148M) PNPLA3 polymorphism in homozygosity. Hepatic expression of genes related to NAD metabolism was evaluated by RNAseq in bariatric NAFLD patients (n = 183; Transcriptomic cohort).	Niacin inhibited de novo lipogenesis through the ERK1/2/AMPK/SIRT1 pathway, with the consequent SREBP1-driven PNPLA3 reduction only in Hep3B and HepG2(I148M+) cells.	[121]
2.	2022	60 adult male Sprague Dawley rats	Using high-fat diet hyperlipidemia diabetes was induced in Sprague-Dawley rat with selenium and VitB(6) cosupplementation. Rats received 0.83 μg Se/kg body weight per day (low dosage supplement group) or 8.33 μg Se/kg body weight per day (high dosage supplement group) by intragastric adminis- tration. On days 0, 20, 40, and 60 of the Se combined VitB 6 intervention, whole blood was collected from the eye canthus in each animal. At the end of the experiment, rats were fasted for 12 h and blood samples were taken. The livers and perirenal white adipose tissue surrounding the kidney were removed and weighed stored in liquid nitrogen.	SIRT1 expression ↑ SREBP1c ↓ liver lipid deposition ↓ steatosis ↓ adipocyte size of white adipose tissue ↓ the activities of hepatic lipase ↑ total lipase ↑	[131]
3.	2022	HepG2 cells, 7–8-week-old C57BL/6 mice	A cellular model to simulate fasting/refeeding in mice were established by culturing HepG2 cells in DMEM containing 5.5 mM glucose and 10% FBS for 24 h firstly, and then	SIRT1 expression ↑ Acetylation of H3K9 at PNPLA3 promoter ↓ (SREBP1c driven)	[122]

			switched to glucose- and serum- free medium for 12 h, and followed by additional 12 h incubation with re-addition of 25 mM glucose. Mice were randomly divided into 3 groups- Control group (Ctrl, n = 9), Fasted group (Fasted, n = 9) and Refed group (Refed, n = 6).	Endogenous binding of SREBP-1c to PNPLA3 ↓	
4.	2022	C57BL/6 mice, HepG2 cells	HFD induced NAFLD in C57BL/6 J mice with Pt and OHPt treatment	The expression and activity of SIRT1 ↑ SREBP1 ↓ FA β-oxidation ↑ FA synthesis ↓ healthy populations or abundances of considered vital microbiota ↑	[120]
5.	2022	Hepatocellular carcinoma cells (HepG2)	HepG2 cells were incubated with 100 μM of OA for 24 h. The extracts (5 or 10 μg/mL) were pretreated to the OA group.	The expression and activity of SIRT1 ↑ p-LKB ↑ SREBP1 ↓ SREBP2 ↓FA β-oxidation ↑ FA synthesis ↓	[154]
6.	2022	HepG2 cells	HepG2 cells were incubated with HG (30 mM) for 24 h and treated with Puerarin	The expression and activity of SIRT1 ↑ SREBP1↓	[145]
7.	2022	Male C57BL/6 J mice, AML12 cells	Male C57BL/6 J mice fed with a high-fat diet (HFD) were used to establish the NAFLD model. Furthermore, AML12 cells with lipid accumulation induced by fatty acids were treated with LZG and EX527 (SIRT1 inhibitor) or Compound C (AMPK inhibitor).	The expression and activity of SIRT1 ↑ SREBP1↓	[118]
8.	2021	HepG2 cells	HepG2 cells were incubated with OA (300 μM) and treated with Neochlorogenic Acid	The expression and activity of SIRT1 ↑ SREBP1↓	[117]
9.	2021	HepG2 cells	A steatosis cell model was induced in HepG2 cell line fed with FFA (0.5 mmol/L, oleic acid:palmitic acid = 2:1), and then treated with three concentrations of BBR	The expression and activity of SIRT1 ↑ SREBP2 ↓	[123]

and SIRT1 is associated with AMPK acetylation. However, it is still unclear exactly how p-AMPK/AMPK contributes to this function [126] (Fig. 3). Consequently, it is shown that SIRT1 suppresses cholesterol synthesis and lipid metabolism via regulating SREBP expression, while SIRT6 also exhibits crosstalk in this process. It is important to note that, based on the findings mentioned above, SIRT1 functions in the nucleus or in cell localization, although the latter has not been thoroughly investigated. Which of these processes is more crucial in any particular situation is still unclear. The benefits of any method presumably vary depending on the situation and the cells.

5. The regulation of HDL levels by SIRT1/SREBPs

SIRT1/SREBPs have been identified as important regulators of HDL production in Fig. 4. Hepatic HDLs are produced via controlling the synthesis of HDL's apolipoproteins and modifying the efflux of cholesterol from hepatocyte membranes onto lipid-poor APOA1. Inhibition of SIRT1 synergist and SREBPs has been shown to lower circulating HDL levels in mice tested for motor function.

The binding of S1P on the renal cell membrane to HDL in blood is made easier in peripheral cells, such as kidney cells, by the ApoM is an apolipoprotein. Increases in the S1P content of the cell membrane caused by overexpression of ApoM raise SIRT1

protein levels and boost mitochondrial activity. In the end, this lowers the levels of urine albumin and plasma creatinine and protects against the signs and symptoms of diabetic nephropathies, such as thickening of the basement membrane, renal fibrosis, and enlargement [46].

Higher serum SIRT1 levels are associated with lower serum SREBP levels, and SIRT1/SREBPs reduce hyperlipidemia by raising serum high density lipoprotein levels. In the early phases of coronary artery disease, calorie restriction is associated with changes in serum SIRT1 levels and HDL function [127]. In mice given a high-fat diet, octacosanol supplementation reduces cholesterol levels via changing signal pathways linked to lipid metabolism, including SIRT1, SREBP1c, and HDL-c [70]. Furthermore, medications that target lipid mediators and the AMPK/mTOR signaling pathway, such as 7 S, 15R-Dihydroxy-16S, 17S-epoxy-docosapentaenoic acid (diHEP-DPA) and 7 S, 15 R, 16 S, 17S-tetrahydroxy-docosapentaenoic acid (TH-DPA), can restore normal levels of serum HDL-C in mice while reducing abnormalities in the aforementioned markers [128]. For instance, a decrease in SIRT1 levels in nonalcoholic fatty liver disease (NAFLD) is accompanied by an increase in SREBP1 levels in liver cells [129]. medications such as dulaglutide, resveratrol,

Table 3

Circulating SIRT1/SREBPs from adipose tissue are associated with lipid accumulation. Selenium, vitamin B(6), and other nutrients aid to reduce NAFLD and pathological obesity by increasing blood HDL-c levels and restoring down-regulated SIRT1 gene expression in the liver of metabolic syndrome (MS) patients.

Preadipocytes **in vitro**	
In vitro HIF1α/ SIRT1/ SREBP1-C HIF1α ↓	[163]
SIRT1 expression ↑SREBP1-c ↓SREBP1 ↓	

Thus, it can be said that SIRT1/SREBPs have a net impact of increasing the efflux of cholesterol into HDLs, encouraging the reflow of HDL into hepatocytes, and facilitating the entry and breakdown of cholesterol into the biliary circulation.

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6. The regulation of LDL levels by SIRT1/SREBPs

By influencing the metabolism of hepatic lipids and the incorporation of lipids into LDL, SIRT1/SREBPs regulate the production of LDL in the liver. Additionally, they control the development of extremely low-density lipo-

2022 6 weeks male C57BL/6 J mice
2022 Mouse 3T3-L1 preadipocytes

3. 2022 Male C57BL/ 6 J mice

4. 2022 3 weeks male C57BL/6 J

Table 4

In vivo
In vitro
In vivo
In vivo
GABA/ SIRT1/ SREBP1 AMPK/ SIRT1 SIRT1/ SREBP1- c SIRT1/ NF-κB/ FGF21/ SREBP- 1c SIRT1 expression ↑ SREBP1 ↓ The expression and activity of AMPK and SIRT1 ↑ PPARγ ↑ CEBPα ↑ SREBP1c ↑ FABP4 ↑ ACC1 ↑ FAS
↑
SIRT1
expression ↑ SREBP1-c ↓ SIRT1
expression↑ NF-κB ↓ FGF21 ↑ SREBP-1c ↓

The precursor of LDL is a protein called VLDL (Fig. 5). Raising Srit1 expression and lowering SREBP-1 raises ApoA1 levels and lowers the serum ApoB/ApoA1 ratio. Furthermore, in order for the liver to create VLDL and LDL, freshly manufactured ApoB must be lipidated. LDL concentrations in the blood are decreased when the production and release of these lipoproteins containing ApoB are inhibited [131,133]. The LDLR, which is likewise controlled by SIRT1/SREBPs, allows cells to take up lipids from circulating LDL. Lower levels of low-density lipoprotein in plasma are correlated with higher levels of SIRT1 protein in white adipose tissue [134]. Following a high-fat meal, mice's blood TC, TG, and LDL-C levels significantly drop due to the increase of PPARα and the lowering of SREBP1, alleviating hyperlipidemia and its accompanying symptoms [69,132,135]. The development of MAFLD is significantly influenced by the SIRT1/AMPK/SREBP-1c and mTOR/SREBPs pathways, which are involved in the synthesis and degradation of liver lipids and are connected to blood levels of LDL-c [118,128,136]. They help restore autophagy flux and inhibit the absorption of oxidized low-density lipoprotein (ox-LDL) and the development of foam cells by upregulating the expression of SRIT1 and FOXO1 and improving their direct connection. This demonstrates how these pathways may be used to treat atherosclerosis. SIRT1/SREBPs from skeletal muscle that circulate and are linked to lipid buildup.
[137]. Ox-LDL buildup triggers the induction of interactions between endoplasmic reticulum stress (ER stress) and mitochondria [138]. By

Sr. no
ear Human/ animals/ cells used in the study
In vivo/ in vitro
Axis Effect Reference

Drugs may improve MAFLD and pathological obesity by restoring the elevated SREBPs and the downregulated SIRT1 gene expression in the liver of MS patients. As a result, HDL production is upregulated and serum LDL-c levels are decreased.

7. SIRT1/SREBPs and hepatic metabolism of lipids

Furthermore, the liver is essential for the body's lipid metabolism and is in charge of producing lipoproteins [87,139]. Current research has shown that the liver is the most significant organ for lipid metabolism in the whole body, even though other organs can also metabolize lipids. Large amounts of SIRT1 and SREBPs are seen in the liver. Previous research indicates that SIRT1/SREBPS regulates many pathways associated with hepatic cholesterol [125,140]. Nevertheless, this regulation is accomplished by focusing on certain metabolic pathways rather than 2016 4 weeks old male C57Bl/ 6j mice

In vivo SIRT1/ SREBP1-c SIRT1expression ↑ SREBP1-c Moreover, the liver produces lipoproteins and is crucial for the body's lipid metabolism [87,139]. Although other organs may also metabolize lipids, recent studies have shown that the liver is the most important organ for lipid metabolism overall. The liver has high levels of SIRT1 and SREBPs. Numerous pathways linked to hepatic cholesterol are regulated by SIRT1/SREBPS, according to prior study [125,140]. However, this control is achieved by concentrating on certain metabolic pathways instead of

Table 5

Summary of research involving SIRT1-SREBPs signaling pathway in deregulated lipoprotein metabolism and organ damage.

Sr. no	Related disease condition	Year	Human/animals/cells used in the study	Drug/method used	Effect	Reference
1.	Atherosclerosis	2023	Rabbit aorta endothelial cells, New Zealand white rabbits.	Rabbit aorta endothelial cells were collected from the aortas of homozygous knockout and WT rabbits. Lp-PLA2 knockout rabbits were created by CRISPR/ Cas9-mediated gene editing.	SREBP2 expression ↓ Plasma lipids ↓	[101]
2.	Diabetic kidney disease (DKD)	2020	A murine podocyte cell line (MPC), C57BL/6 J mice, Jaml KO male mice on C57BL/6 J background mice, DKD patients.	Cells treated with high glucose, PA, cholesterol, oxLDL, ADR. Male mice (10 weeks of age) were administered ADR (12 mg/kg) intravenously by tail vein injection. All the samples of renal biopsies diagnosed as DKD were classified in accordance with a new pathologic classification provided by the Renal Pathology Society. The samples of renal biopsies were obtained from DKD patients.	The activity of SIRT1 ↓ SREBP1 ↑ lipid accumulation ↑ podocyte injury ↑ proteinuria ↑	[47]
3.	Diabetic nephropathy	2023	A human proximal tubular cell line (HK-2 cells) and a human hepatocellular carcinoma cell line (HepG2 cells).	104 T2DM patients were recruited and determined according to the 2014 classification of diabetic nephropathy published by the Research Group of Diabetic Nephropathy in Japan. HepG2 cells treated with ApoM-overexpressing HepG2 cells (CM-ApoM) or HepG2 cells infected with a blank adenoviral vector (CM-Null). HK-2 cells treated with siRNA against SIRT1 or control siRNA, or siRNA against S1P1, S1P2, or	The activity of SIRT1 ↓ The activity of ApoM/ S1P-S1P1 ↓ Sirt1 ↓ in turn	[46]

				S1P3 or control siRNA.		
4.	BSCB	2023	Mouse brain microvascular endothelial cells (bEnd.3 cells), HEK293T cells wild-type (WT) C57BL/6 J mice (8–10 weeks old), Tie2-Cre SIRT1 knockout (CKO) mice on C57BL/6 J background mice.	SCI was induced by a spinal cord impactor. SCI mice were divided into two groups: control group and SIRT1 CKO mice group.	The expression and activity of SIRT1 ↑ The acetylation of p66Shc ↓	[50]
5.	LSCC and LADC	2023	LSCC cell lines (NCI-H520, LUDLU1, CALU-1), human epidermal cancer cells (A431), human osteosarcoma cells (U2OS), human embryonic kidney cells (HEK293T), human non-small cell, lung cancer adenocarcinoma cell lines (NCI-H522, NCI-H1299, A549cells), adult 7–8 weeks B6(C)-Gt (ROSA)26Sor$^{em1.1(CAG-cas9*,-EGFP)Rsky/J}$ mice, lung cancer patients.	Lung tumours are induced by intratracheal delivery of AAV particles into Rosa26:Cas9 transgenic mice.	In LSCC compared to LADC SREBP2↑ · MVP enzymes↑	[114]
6.	Obesity	2022	Human preadipocyte cells	Pure ONON (5, 10 and 25 μM), MACK (5, 10, 25 and 50 μM) or 0.02% DMSO as vehicle was treated.	The expression and activity of SIRT1 ↑ SREBP1 ↓ anti-lipogenic ↑	[173]
7.	Obesity	2022	HepG2 cells	Taurine	The expression and activity of SIRT1 ↑ SREBP1 ↓ lipid production ↓	[174]
8.	Osteoarthritis	2023	Hondrocytes collected from 4-week-old mice, 60 4 weeks old mice, 3 male and 3 female Osteoarthritis or femoral neck fractures patients.	IL-1β-induced chondrocytes cholesterol accumulation with Resveratrol (RES)treated · three male and three female patients with Osteoarthritis or femoral neck fractures. Mice were randomly divided into three groups. Sham group (n = 15), DMM group (n = 15), and RES+DMM group (n = 15). Mice were killed at the end of week eight and bilateral knee cartilage tissue separated	Cartilage cells treated with RES SREBP2 ↓ SIRT1 ↑	[126]

				out.		
9.	Osteoarthritis	2022	Second passage chondrocytes collected from 6 newborn Wistar rats, 3 osteoarthritis patients.	Metformin (0, 5, 10, 15 mM) was treated.	SREBPs expression ↓ SIRT1 ↑	[126]
10.	ALD	2020	10 weeks old male C57BL/6 mice.	40-Hz light flicker group (40 Hz): a control group, ethanol group (ETOH), 40 Hz light flicker group (40 Hz) and an ETOH plus 40 Hz light flicker group (ETOH + 40 Hz). The mice were euthanized at 4 h after the last ethanol dosing.	The expression and activity of SIRT1 ↑ SREBP1 ↓ alcoholic liver steatosis↓	[44]

Through its influence on SREBP1-driven transcription, SIRT1 may control the expression of the PNPLA3 gene by altering the acetylation of H3K9 [129,142–144].
The body's metabolic capacity is exceeded when energy intake and expenditure diverge, resulting in excessive liver lipid metabolism, which is often linked to abnormalities in the SIRT1/SREBPs pathway. Studies in both living things and lab settings have shown that the SIRT1/SREBP-1c-axis plays an essential role in managing inflammation, fatty liver disease, hepatic insulin resistance, and the associated ER stress [129,142–144]. SIRT1/AMPK, which is linked to the synthesis and degradation of hepatic lipids, may also have a major effect on its biological activity [118,145]. SIRT1/NF-κB may act as a central regulator and is implicated in the regulation of inflammation [146].
Through SIRT1/SREBPs, transcription factor genes and miRNAs are additional regulatory hubs that prevent the manufacture of cholesterol. Verification

SIRT1/SREBPs as potential biomarkers and therapeutics in metabolic diseases**.**

[146] lipogenesis. In summary, current research indicates that SIRT1 expression upregulation is inversely associated with DNL; nevertheless, RT1 controls DNL via SREBPs, which requires more favorable AMPK/SREBP1 1 2020 SiRT1/LKB1 2 2020 SiRT1/SREBP1

ALD	As a potential therapeutic target
DKD	As a biomarker and a potential therapeutic target

To sum up, the participation of SIRT1/SREBPs in physiology state can be observed in numerous stages of overall lipid metabolism, ulti- mately leading to a decrease in cholesterol levels in the liver. Accord- ingly, the disruption of the SIRT1/SREBPs pathway under pathological conditions is also an important cause of liver lipid accumulation leading to inflammation, fibrosis and even tumor (Fig. 6).

MAFLD is characterized by the presence of triglycerides and free

3 2023 SIRT1/ SREBP1c FLD Biomarker

cholesterol in plasma, while Cholesteryl ester does not show a corresponding increase. In this process, SREBP2 maturity increases. MiR-34a

4 2023 USP28/ SREBP2/ MVP LSCC As a biomarker and a potential therapeutic target

is a microRNA that is increased in MAFLD, which inhibits SIRT1 and up- regulates SREBP2 through AMP kinase [152]. In both in vitro and in vivo

5 2023 BS/SRGN/ SREBP1/ SIRT1

NAFLD Biomarker [177]

MAFLD models, niacin inhibits de novo adipogenesis by involving SIRT1, which leads to a decrease in PNPLA3 caused by SREBP1. These two factors, SIRT1 and SREBP1, work together to regulate triglyceride

6	2022	SIRT1/ SREBP1c
7	2021	IQGAP2/ CREB/ SIRT1/ SREBPs
8	2021	SIRT1/ AMPK/ SREBPs
9	2023	ERK1/2/ AMPK/ SIRT1/ SREBP1/ PNPLA3
10	2021	SIRT1/ Foxo1/ SREBP2
11	2021	SIRT1/ SREBPs
12	2022	SIRT1/ SREBP

NAFLD to provide ideas for the research and development of targeted drugs
NAFLD As a potential therapeutic target

NAFLD As a potential therapeutic target
NAFLD As a potential therapeutic target
NAFLD As a potential therapeutic target

Synthesis In their investigation, Xu revealed that SIRT1 can modulate H3k9 acetylation to control hepatic PNPLA3 transcription that is controlled by SREBP-1c [122]. In this mechanism, the p-LKB-1/AMPK and FXR/p53 axis are essential [118,119,123], and those pathways could also regulate SREBP2 [117,153,154]. Furthermore, SIRT1 and calcium signaling pathways linked to G protein-coupled estrogen receptor (GPER) signaling may aid in AMPK activation [145]. It is noteworthy that nonalcoholic fatty liver develops in many people with type 2 diabetes, and that more and more study is being done on this condition each year.
Excessive lipid metabolism in the liver brought on by various stimuli, including viruses and alcohol, is also mediated via the SIRT1/SREBPs pathway. In the development of ALD, the SIRT1/SREBP pathway has been well studied. It is also used for targeted therapies in ALD therapy [44,155]. In hepatitis C, the accumulation of these compounds might hinder the activation of the SIRT1/SREBPs pathway [156,157], which can result in the accumulation of β fatty acids [158], the presence of liver macrophages, and ultimately liver destruction [159]. In accordance with the most current AOP, SIRT1 inhibition sets off toxicological processes that activate SREBP-1c, the

In order to mitigate FFA-induced steatosis in HepG2 cells, SIRT1 and FOXO1 inhibitors have been activated via the SIRT1-FOXO1-SREBP2 signaling pathway [123]. A transcriptional factor called FOXO1 regulates the metabolism of fatty acids. The transcription factor PPARα, which regulates the metabolism of fatty acids, triggers the activation of miR-7, which in turn activates the expression of SREBP1 and SREBP2, hence upregulating sterol production [147].
Fatty acid de novo lipogenesis (DNL) is a crucial stage in the liver's control of the equilibrium of lipid metabolism. Acetyl-CoA (ACC), a crucial byproduct of glycolysis and the tricarboxylic acid cycle, provides the starting point for the synthesis of DNL. According to earlier research, once fructose-fed rats' inflammation from a lipid metabolic issue improved, SIRT1 expression in rat hepatocytes was markedly up-regulated, whereas the known DNL genes, such as SREBP1-c, did not substantially alter [148]. Conversely, recent research indicates that liver DNL may be considerably inhibited and hepatic steatosis protected by activating the SIRT1/SREBPs pathway [149,150]. Furthermore, an AMPK inhibitor experiment demonstrated that AMPK mediates the inhibitory effects on adipogenesis [67,151]. Considering the absorption of HDL-loaded material by hepatocytes, the liver seems to be a likely receiver of SIRT1 signals sent from the circulation. Circulating fibroblast growth factor 21 (FGF21) levels and the NAD(+)/NADH ratio increased as a result of SIRT1/NF-κB pathway activation. Hepatic SREBP-1c expression may decline as a consequence of the reduction in inflammation, which is accompanied by the down-regulation of NF-κB. This, in turn, may lead to reduced the accumulation of fatty acids and triglycerides, as well as the synthesis of new fatty acids, which ultimately leads to hepatic steatosis [160].
Therefore, targeting SIRT1/SREBPs may be beneficial in treating liver illnesses linked to fat storage (Table 2).

8. Circulating SIRT1/SREBPs from adipose tissue and skeletal muscle

With the discovery of proteins in circulation, interest in investigating the origins, locations, and functions of these proteins has increased. Skeletal muscle, adipose tissue, and liver tissue are important metabolic sources because they contribute significantly to the release of SIRT1 and SREBPs into the circulation. As was previously mentioned, the liver regulates SIRT1/SREBPs in lipid metabolism. SREBP-1c is a crucial transcription factor that controls cellular lipogenesis in the liver, skeletal muscle, and adipose tissue, among other recognized regulators of lipogenesis. It is evident that skeletal muscle (Table 4) and adipose tissue (Table 3) also produce circulating SIRT1/SREBPs, and in recent years, their function in lipid metabolism has drawn more attention. The adipose tissue-derived SIRT1 and SREBP1-c have a major impact on metabolism control. Circulating SREBP1c levels are significantly lower in obese mice with retroperitoneal white adipocytes (105.5%, $p < 0.01$) than in the HFD group due to an increase in SIRT1 levels [161,162]. The SIRT1/AMPK signaling pathway reduced SREBP-1c expression by phosphorylating AMPKα. HIF-1 α dramatically elevated in fat in obese mice without leptin.

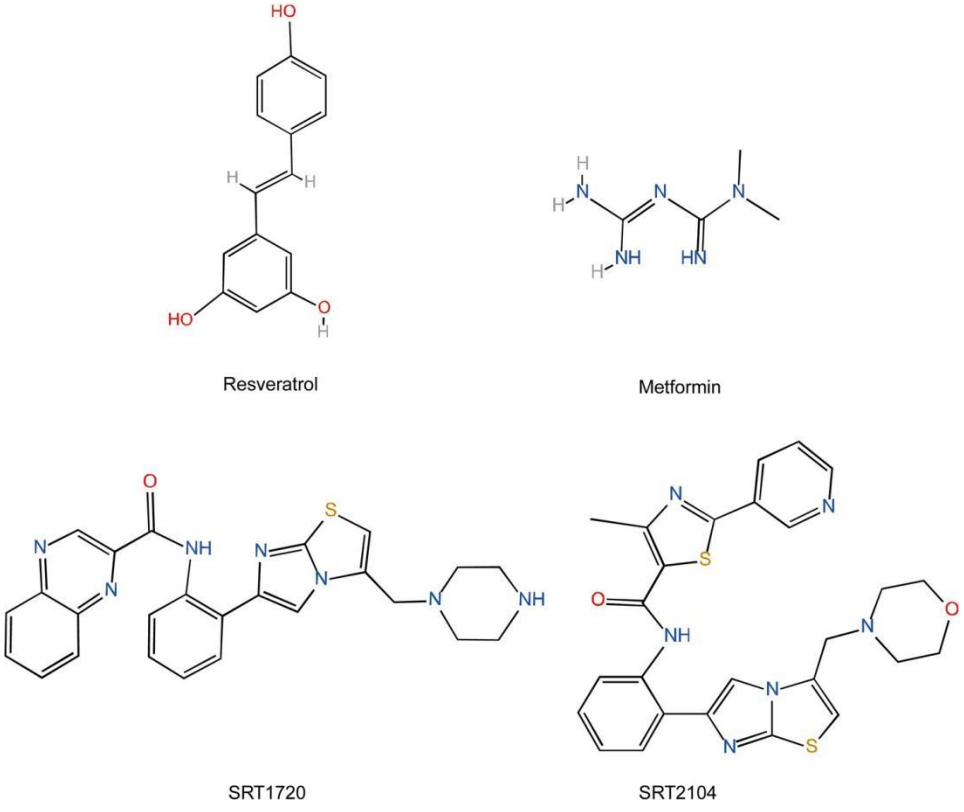

Fig. 7. Chemical structure formula of SIRT1 activator.

This caused the liver and serum to activate the SIRT1/SREBP1 pathway [163]. Notably, recent studies have shown that, in a citrate metabolite-dependent way, deletion of the Mrs2 channel rewires systemic DNL, which is mediated via HIF-1α transcriptional regulation in the liver and adipose tissues [164]. Furthermore, HIF1 α was identified as a SIRT3 target as early as 2014 [23]. These investigations show that the SIRT1/SREBPs pathway, which is connected to DNL and interacts with SIRT3, controls lipid metabolism in fat.

The LXR pathway is primarily involved in skeletal muscle lipid metabolism. In vitro and in vivo knockout studies suggested as early as 2012 that SIRT1 in skeletal muscle controls SREBP1-c and its downstream lipid metabolism via deacetylating LXR [165]. The functional assessment of different medications and therapies by the measurement of SIRT1/SREBPs and cholesterol levels in skeletal muscle and circulating blood has been the focus of recent in vivo animal investigations [44,166,167]. In conclusion, SIRT1 activation may enhance skeletal muscle and fat lipid metabolism by inhibiting SREBPs. More in vitro studies are required to investigate the mechanism, even though part of the SIRT1/SREBPs in circulation originate from skeletal muscle (Table 4) and fat (Table 3). Because it is easy to detect, circulating SIRT1/SREBPs level monitoring has a lot of promise as a medication effectiveness monitoring indicator. Its accuracy and stability as a medication impact monitoring metric, however, need further experimental validation since its identified sources include skeletal muscle, fat, and liver, particularly fat and skeletal muscle, which are extensively dispersed and confounded by diverse situations.

Roles of SIRT1/SREBPs in deregulated lipoprotein metabolism associated with organ damageNumerous tissue and organ problems have been studied to determine how the SIRT1/SREBP2 pathway affects lipid metabolism and target organ damage. Conversely, SIRT1 action sustains the generation

of the brain's cholesterol [169]. Studies on mice have shown that using medications to suppress SIRT1 lowers SREBP2 mRNA levels and reduces the brain's synthesis of cholesterol. However, by decreasing the activity of SREBP1 and FAS-associated enzymes, adiponectin prevents the synthesis of fatty acids (FAS). It was also confirmed that SIRT1 was important in mice that received breast tumor xenografts [170]. Similarly, the ablation of ApoM led to decreased SIRT1 expression, which exacerbated the symptoms of diabetic nephropathy in a mouse model of streptozotocin-induced diabetes. Urinary albumin and plasma creatinine levels rose as a result, and the kidneys became larger. Renal fibrosis also progressed, and the basement membrane thickened [46]. Apart from brain tissue, a number of diseases, such as endothelial cell oxidative stress [171], optic nerve cell injury [172], osteoarthritis [126,169], kidney injury, and breast cancer, generally show SIRT1 activation or expression along with a decrease in SREBPs, which reverses the damage that dysmetabolism causes to the target organ. In order to address these problems, SIRT1/S-REBPs may be suitable targets for therapeutic intervention for the reasons outlined above (Table 5, Fig. 6).

9. SIRT1/SREBPs as biomarkers for metabolic status and disease state

Given the alterations shown in animal models for metabolic disorders, one possible area of investigation is the analysis of liver SIRT1/SREBPs proliferation as a way to assess the state of human illness (Table 6). Atherosclerosis, obesity, and other lipid metabolism-related conditions may be predicted by a patient's liver's SIRT1/SREBP levels. It has been acknowledged that these levels are excellent biomarker candidates. Changes in the levels of SIRT1 and SREBP-1c in liver tissue were strongly correlated with lipid metabolism, according to the findings of Western blot and real-time quantitative PCR. Consequently, these indicators may be used to show how medications reduce cholesterol in mice given a high-fat diet by

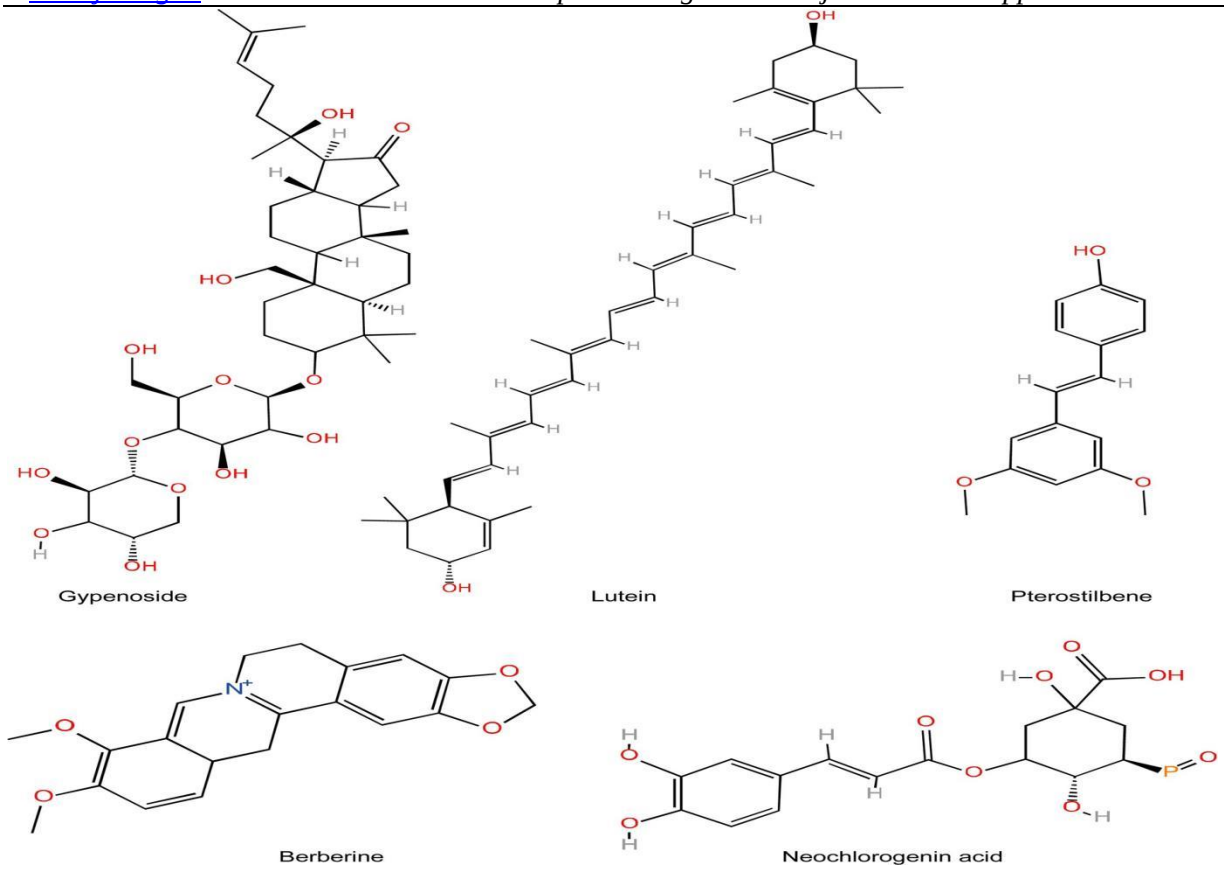

Fig. 8. Chemical structure formula of SIRT1 activator from natural plants.

controlling lipid metabolism-related signaling pathways [70, 128,175]. Furthermore, compared to mice that were freely fed a standard diet, mice that were given a time-limited high-fat diet showed discernible differences in the daily patterns of liver SIRT1 and SREBPs expression [141]. Numerous clinical and experimental investigations conducted throughout the last five years (2015–2020) have shown the effectiveness of SIRT1 activators in the treatment of MAFLD. In order to enhance MAFLD, these research have used SIRT1, SREBP-1c, and SREBP2 as important molecular targets [148,176]. In accordance with the latest AOP, SIRT1 inhibition sets off toxicological processes that activate SREBP-1c, produce new fatty acids, and cause fatty acid buildup.

triglycerides, ultimately leading to liver steatosis [160]. This instance suggests the possibility of the extensive utilization of circulatory SIRT1/SREBP-1c as premature indicators for metabolic dysfunction.

10. Clinical significance of SIRT1 activators and SREBPs in lipid metabolism

The therapeutic significance of SIRT1 activators and SREBPs in lipid metabolism has been shown by several animal studies. According to these investigations, synthetic small molecules (SRT1720 and SRT2104) and natural activators like resveratrol and metformin can be effectively

An overview of the chemical substances found in herbal remedies that serve as SIRT1 activators

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Sr. no	chemical compounds	Related disease condition	Year	Human/animals/cells used in the study	Effect	Reference
1.	Green cardamom (PubChem SID: 482038499)	T2DM	2019	83 patients with T2DM	SIRT1 expression ↑ TG ↓	[1]
2.	Gypenoside (PubChem CID: 92043183)	Atherosclerosis	2021	THP1 cells	SIRT1 expression ↑ FOXO1 ↑	[2]
3.	Chrysanthemum morifolium flower (PubChem SID: 482037233)	Obesity	2020	3T3-L1 preadipocytes	The expression and activity of AMPK and SIRT1 ↑ PPARγ ↑ CEBPα ↑ SREBP1c ↑ FABP4 ↑ ACC1 ↑ FAS ↑	[3]
4.	Lutein (PubChem CID: 5281243)	Obesity	2021	3T3-L1 cells and male SD rats	SIRT1 expression ↑ FOXO1 ↑ SREBP1 ↓	[4]
5.	Pterostilbene (PubChem CID: 5281727)	NAFLD	2020	BRL-3A cells and HepG2 cells	SIRT1 expression ↑ SREBP1 ↓	[5]
6.	Berberine (PubChem CID: 2353)	NAFLD	2021	HepG2 cells	The expression and activity of SIRT1 ↑ SREBP2 ↓	[6]
7.	Neochlorogenic acid (PubChem CID: 5280633)	NAFLD	2021	HepG2 cells	MiR-34a↓ SIRT1 expression ↑ SREBP1 ↓ SREBP2 ↓ hepatic lipid acumination ↓	[7]

used to cure a variety of illnesses and ailments. Four typical molecular structures are compiled in this research (Fig. 7). The potential health benefits of these drugs have also been examined in clinical data that is now accessible.
The most significant SIRT1 activator, resveratrol, has been extensively researched in both in vitro and in vivo settings in relation to a variety of lipid metabolism-related disorders, such as nonalcoholic fatty liver disease and obesity. By preventing miR-34a-induced SIRT1 activation in rats given a high-fat diet, RSV reduces the effects of HFD on insulin resistance and hepatic steatosis [153]. Furthermore, by activating SIRT1, it may counteract the negative effects of obesity resistance brought on by CD38 deficiency [181]. Resveratrol analogs were created and produced as anti-lipid accumulation medications in 3T3-L1 preadipocytes. By encouraging SIRT1 activation, inhibiting SREBP1-c, and downregulating the lipogenesis and lipogenesis pathway, these pharmaceuticals decreased lipid accumulation in 3T3-L1 cell lines [182]. Resveratrol has been extensively studied in pre-clinical and clinical settings as a possible SIRT1 activator in diabetes. A research found that the buildup of cholesterol and the reduction of the expression of SREBP2, a factor connected to cholesterol production, are related to the decline in the SIRT1/FOXO1 pathway. The research also shown that the rise in SREBP2 expression is due to increased SIRT1 expression [124]. Further results from clinical tissue tests indicate that resveratrol mainly targets the miR-34a/SIRT1 pathway to lessen the effects of MAFLD in rats that is brought on by a high-fat diet [153]. To sum up, resveratrol is a plant-derived SIRT1 activator that is often employed in research on fat synthesis and nonalcoholic fatty liver disease. In addition to helping people with type 2 diabetes, metformin may also help people with lipid metabolism-related conditions such osteoarthritis and perimenopausal fatty liver by activating SIRT1 in the chondrocytes that produce cholesterol. Metformin has been extensively studied in preclinical and clinical settings as a possible SIRT1 activator in diabetes. Other compounds that activate SIRT1, such as diHEP-DPA and TH-DPA, which are produced via recombinant lipoxygenase and are derivatives of docosahexaenoic acid, may enhance lipid metabolism and hepatic inflammation in HFD-fed mice [129]. Forty female Sprague Dawley (SD) rats between the ages of four and six weeks were used in the experiment, which used a combination of metformin (75 mg/kg/day) and peptide-8 (0.5 mg/kg/day). By regulating the SIRT1/SREBP-1c pathway, PSTi8 in conjunction with metformin was shown to alleviate ER stress linked to perimenopause-induced steatohepatitis. It also increased fatty liver disease, associated ER stress, and hepatic insulin resistance [143]. Likewise, the

Metformin's impact was also investigated in the rat model of OA, and it was shown to lower blood lipids and cholesterol via activating the AMPK/SIRT1 pathway [126]. Natural plant-based SIRT1 activators can control lipid metabolism in models of type 2 diabetes, cardiovascular disease, obesity, and non-alcoholic fatty liver disease. It is important to note that although the precise molecular structure (Fig. 8) of gypenoside, lutein, pterostilbene, berberine, and neochlorogenin acid has been determined, the molecular structure of many additional compounds is still unclear [67,117,123,137,155,162,183]. The characteristics, efficient dose forms, and hazardous and adverse consequences of SIRT1 activators made from natural plants need more investigation. However, Table 7 indicates that SIRT1 activators made from natural plants may be used to treat metabolic disorders linked to lipids as more thorough and in-depth study is conducted.
It has been shown that the synthetic small molecule SIRT1 activators SRT1720 and SRT2104 improve mice's health and lifespan [184, 185]. SRT1720 more effectively activates SIRT1 and is structurally independent of resveratrol [186]. Significant subtype differences are shown by the fact that SRT1720 is an efficient and partly selective SIRT3 inhibitor that competes with acetyllysine substrates but not with NAD + [187,188]. Following SCI, SRT1720 inhibits the breakdown of the blood-spinal barrier, deacetylates p66Shc by activating SIRT1, lowers ROS generation in the endothelium, and encourages the functional recovery of BSCB [50]. Cartilage formation and matrix protein synthesis are positively impacted when SIRT1 is activated by SRT1720 in embryonic stem cells [189]. SRT2104 has been the focus of fourteen clinical studies, making it the most researched small molecular actuator. With 14 clinical studies, SRT2104 is the most researched small molecular activator (www.clinicaltrials.gov) [190]. SRT2104 taken orally may reduce the concentration of triglycerides, low density lipoprotein cholesterol, and serum cholesterol while also improving vascular stiffness and the blood lipid spectrum [45,191]. SIRT1 activators often have a significant impact on the regulation of lipid metabolism in the liver, neuron, bone, and embryonic development. The specificity of synthetic small molecule activators is clearly higher than that of natural SIRT1 activators. This is consistent with the same notable drawbacks of current synthetic activators, such as SRT1720's off-target effects and its poor and inconsistent pharmacokinetics following oral administration. There have been no effective attempts to alter the release properties of SRT2104 preparations in order to decrease pharmacokinetic variability and maximize systemic exposure.
summarizes the clinical trials conducted with these phyto- chemicals and other substances that

Table 8
Summary of clinical trials of SIRT1 activators.

Sr. no	Year	Drug	Dose and duration of study	Main Inclusion Criteria	Effect	Reference
1.	2014	Resveratrol	A starting dose of 500 mg daily of either resveratrol or placebo. The dose was increased by 500 mg per day every 3 days to a maximum dose of 3 g per day in three divided doses if there was no hypoglycemia. 14 weeks	Patients were recruited between July 2009 and May 2010 from a single hospital in Singapore. Chinese males, aged between 40 and 69 years old, with T2DM with a HbA1c of 7.1–12.0% (54–108 mmol/mol IFCC) and who had been on a stable oral hypoglycemic regimen for the past 3 months. They must be willing to abstain from ingesting large quantities of resveratrolcontaining foods including alcohol during the study period. Subjects who were insulin-dependent, on 3 or more OHA, or had renal or liver impairment were excluded	GLUT4 ↑ AMPK ↑ p-AMPK ↑ ratio of p-AMPK to AMPK ↑ LDL ↑ basal energy expenditure ↑ physical activity ↓	[192]
2.	2011	Resveratrol	Resveratrol (150 mg/day (99%); resVida™) 30 days	11 healthy, obese, male volunteers without family history of diabetes or any other endocrine disorders participated in this study. None of the subjects were on medication or were engaged in sports activities for more than two hours per week.	Intramyocellular lipid level ↑ hepatic lipid level ↓ circulating glucose ↓ systolic blood pressure ↓	[193]
3.	2022	resveratrol	Capsules 500 mg resveratrol or placebo twice daily in the first treatment period and the opposite in the	With genetically verified CPTII or VLCAD deficiencies. Aged 18–80 years, ambulatory and with a clinical presentation.	No effect of resveratrol on fatty acid oxidation or exercise capacity in patients with fatty acid oxidation disorders.	[194]

		second treatment period. 20 weeks	Signs or symptoms suggestive of a metabolic myopathy.			
4.	2017	Resveratrol	Dose and duration of study a low-calorie diet (1000 cal/day) 250 mg of resveratrol twice daily 45 days	BMI ≥ 30 kg/m^2 Hypertension (use of anti-hypertensive medication or diastolic blood pressure ≥90 mm Hg) Dyslipidemia (use of lipid-lowering medication or serum triglyceride concentrations ≥1.7 mmol/L or total cholesterol ≥6.2 mmol/L) Fasting glucose ≥ 6.10 mmol/L or use of hypoglycemic medication hormone replacement therapy premenopausal women	Smokers	Caloric restriction and resveratrol significantly increased plasma concentrations of Sirt1. The longterm impact of these interventions on atherosclerosis should be assessed.	[195]
5.	2016	SRT2104	Participants were randomised to receive 2.0 g daily of oral SRT2104 or matched placebo (Sirtris, a GSK company, Massachusetts, USA) for a 28-day period, followed by cross-over to the alternate study arm for a further 28 days, giving a total dosing duration of 56 days.	Aged between 18 and 70 years. Healthy cigarette smokers were required to have smoked ≥ 10 cigarettes daily for at least 1 year (n = 24). Participants with type 2 diabetes were non-smokers and were selected on the basis of having a diagnosis of type 2 diabetes mellitus for at least 6 months prior to inclusion in the study, with no change in medications having been made for at least the preceding 3 months, a fasting blood glucose ≤ 13.9 mmol/L (250 mg/dL) and diabetes control and complications trial-aligned HbA1c< 9%		Arterial compliance ↑	[191]

				(75 mmol/mol) on screening. (n = 15)		
6.	2012	SRT2104	Oral doses of 0.5 or 2.0 g SRT2104 or matching placebo were administered once daily for 28 days.	Normal fasting glucose levels (4.4–6.0 mmol/L) at screening and a body mass index of at least 18 kg/m2 and no greater than 30 kg/m2.	Serum cholesterol and triglycerides ↓ HDL:LDL ratio ↑ LDL cholesterol ↓	[196]
7.	2019	Green cardamom	The intervention and the placebo group received 3 g of green cardamom or rusk powder, respectively for 10 weeks.	Eighty-three patients with T2DM, aged between 30 and 60 years old with a BMI between 25 and 34.9 kg m^2, HbA1c value greater than 7% that were treated with a stable dose of oral anti-diabetic drugs and with a diagnosis of T2DM for at least 2 years were recruited for this study.	TG ↓	[183]
8.	2007	Ephedrine, caffeine, and/or pioglitazone	1) placebo/ placebo (PP) 2) ephedrine HCl plus caffeine/ placebo (ECP) 3) placebo/pioglitazone (PPio)	Nondiabetic patients were enrolled in a clinical trial performed in Baton Rouge, Louisiana, at the Pennington Biomedical Research Center (14 men and 43 women	Body weight ↓ plasma triglycerides ↓ lipid metabolism in subcutaneous fat ↓	[197]

(*continued on next page*)

Table 8 (*continued*)

Sr. no	Year	Drug	Dose and duration of study	Main Inclusion Criteria	Effect	Reference
			4) ephedrine HCl plus caffeine/ pioglitazone (ECPio) The placebo, the pharmaceutical ephedrine HCl (25 mg) (Breathe Easy; Contract Pharmacal Corporation, Hauppauge, NY) and caffeine (200 mg) (Contract Pharmacal Corporation) were dosed as follows: one of each pill per day	between 18 and 50 years of age with BMI 30 –37 kg/m2). Subjects were healthy and not taking thiazolidinediones, β-blockers, orlistat, sibutramine, ephedrine, phenylpropanolamine (Dexatrim), corticosteroids, statins, fibrates, cholesterol-binding drugs, or herbal supplements containing ephedrine and/or caffeine; abusing alcohol; or using		

			for 7 days at breakfast, increased to one of each pill at breakfast and lunch for the next 7 days, and then increased to one of each pill at breakfast, lunch, and dinner for the remainder of the 16 weeks protocol.	other illicit drugs.		
9.	2018	A triple combination of leucine, metformin and sildenafil (NS-0200)	Capsules Low-dose (1.1 g leucine/0.5 g metformin/0.5 mg sildenafil) high-dose (1.1 g leucine/0.5 g metformin/ 1.0 mg sildenafil) 16 weeks	Age 18–75 years at study entry, MRI-PDFF ≥ 15%, ALT ≥ 30 U/L for men and ≥ 19 U/L for women, body mass index between 25 and 40 kg/m^2 and clinical and laboratory criteria consistent with NAFLD. Subjects with evidence of other chronic liver disease or with history of significant alcohol consumption, defined as > 7 drinks/wk for both males and females for the prior 6 months were excluded from the trial.	High-dose NS-0200 significantly reduced hepatic fat in NAFLD patients with elevated ALT, and correspondingly improved the NAFLD-associated metabolomic signature. NS-0200, either in high or low dose, did not improve hepatic fat in the ITT population, but the placebo-treated participants exhibited an unusually high response rate.	NS-0200[198]

articles published since 2007 that included the terms "SIRT1 activator," "SREBPs," and "lipid metabolism," but did not include the following: There were less than ten instances covered. Descriptive pharmacovigilance studies, single dose/concentration studies, studies measuring only one outcome, bioequivalence studies, or studies reporting only the pharmacokinetics profile of a compound are among the papers reporting the pharmacolog-ical activities of novel compounds if appropriate controls with known substances are not performed.

On the other hand, post-transcriptional modification of SREBPs is mostly regulated by cellular stress and growth factor signaling. There are several upstream elements that may modify the SREBP function. Targeting these components may either activate or deactivate SREBP activity, which can provide therapeutic advantages for a variety of medical disorders. Numerous compounds from different targets affect SREBP1-c's activity. For example, resveratrol has been shown to decrease the nuclear localization of SREBP-1c by activating SIRT1/AMPK [143]. Similarly, metformin affects SREBP2 in a similar way, but via the AMPK receptor. On the other hand, some drugs target FOXO1 to inhibit SREBP2 function [...]. Even if certain compounds and drugs already have research and clinical data, further investigations and comprehensive data are required to evaluate the positive effects of SIRT1 activators.

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11. Summary

Many people have chronic hyperlipidemia due to abnormal lipid metabolism, which disrupts many signaling pathways. SREBPs and SIRT1 have an impact in regulating aberrant lipid metabolism. Dual cleavage of two proteases, namely S1P and a zinc metal-loprotease called S2P, is necessary for SREBPs to function. The segment of SREBPs that is actively engaged in transcription is released into the cytosol before entering the nucleus, while SIRT1 is located in the nucleus. After membrane-bound precursor forms (pSREBPs) are transformed into their active nuclear forms (nSREBPs), nuclear SREBPs finally bind to SRE sequences in the

promoter region of many genes that generate the enzymes required for lipid synthesis and absorption. As a result, SIRT1 and SREBPS are regarded as crucial regulatory elements in lipid metabolism processes, where SIRT1 contributes to lipid reduction.

production, reducing blood cholesterol, and preventing organ damage brought on by lipid buildup by blocking SREBPs. SIRT1 activators have been shown to have positive effects in both human and animal models. Significant progress has been achieved in understanding the enzymatic reaction mechanism, developing isomer-specific small molecule modulators of sirtuins, and gaining insight into the pathophysiological consequences of sirtuins. It is highly recommended to carry out additional research and create novel SIRT1 activators that are either more selective or have superior pharmacokinetic properties that permit oral administration, since the preliminary clinical findings on SRT2104 in metabolic syndrome are encouraging. Furthermore, studies in animals have shown that regulating SREBPs also produces the beneficial effects mediated by SIRT1. As a result, concentrating on these signaling pathways and learning about the underlying processes might be beneficial. By evaluating the levels of SIRT1/SREBP in patients' livers, promising biomarker candidates for obesity, atherosclerosis, and other lipid metabolic diseases may be found. Changes in the expression levels of SIRT1 and SREBP-1c in liver tissue are strongly correlated with lipid metabolism, according to the findings of Western blot analysis and real-time quantitative PCR. By altering the signaling pathways linked to lipid metabolism, these alterations may potentially function as biomarkers to demonstrate the cholesterol-lowering benefits of medications on mice given a high-fat diet.

However, we also observed that there is still a lot of space for improvement in the therapeutic management of disorders linked to lipid metabolism. First, more stable and superior pharmacokinetics are required, even if synthetic small molecules have superior pharmacokinetic properties compared to organic activators. Additionally, it is advantageous to create more precise small molecule synthetic SIRT1 agonists with stable and high pharmacokinetics for the treatment of disorders related to lipid metabolism. Additionally, additional in vitro cytological studies are required to investigate the mode of action of current activators, particularly the SIRT1/SREBPs pathway. Lastly, it is critical to do more thorough clinical case studies for the SIRT1 activators now used in clinical settings.

In conclusion, these two proteins continue to astound us in spite of the extensive research done on SIRT1/SREBPs. Determining their exact metabolic processes should provide a wealth of potential directions for further investigation.

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