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Commentary

SIRT1-mediated deacetylation in MAFLD: Mechanisms and therapeutic implications

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Abstract

Metabolic dysfunction-associated fatty liver disease (MAFLD) has emerged as a leading cause of chronic liver disease worldwide, with its pathological mechanisms involving multiple factors such as hepatic steatosis, insulin resistance (IR), oxidative stress, and inflammatory responses. In recent years, Sirtuin 1 (SIRT1) has been recognized as a crucial molecular target for improving MAFLD due to its central role in metabolic regulation and cellular homeostasis. This article reviews the mechanisms by which SIRT1 intervenes in the progression of MAFLD: 1) promoting autophagy and enhancing mitochondrial function; 2) regulating lipid metabolism and oxidative stress-related proteins through deacetylation, thereby improving lipid metabolism disorders and reducing ROS accumulation; 3) suppressing inflammatory responses and alleviating liver inflammation damage; 4) ameliorating IR. Preclinical studies have shown that SIRT1 agonists or gene overexpression can significantly improve the histopathological features of MAFLD in animal models. However, the regulation of SIRT1 is tissue-specific and dose-dependent, and its long-term safety and targeted delivery strategies require further exploration. This article systematically summarizes the molecular mechanisms and therapeutic potential of SIRT1 in MAFLD, providing a theoretical basis for developing novel intervention strategies based on SIRT1 regulation.

Keywords: MAFLD, SIRT1, Deacetylation, SIRT1 agonists

Abbreviations: ACC1: Acetyl-CoA Carboxylase 1; AP-1: Activating Protein-1; ATG5: Autophagy-Related Protein 5; ChREBP: Carbohydrate Response Element-Binding Protein; COX2: Cyclooxygenase 2; CPT1A: Carnitine Palmitoyltransferase 1A; Drp1: Dynamin-Related Protein 1; FAO: Fatty Acid Oxidation; FAS: Fatty Acid Synthase; FGF21: Fibroblast Growth Factor 21; FOXO3: Forkhead Box Class O3; FXR: Farnesoid X Receptor; HDACs: Histone Deacetylases; IR: Insulin Resistance; LC3-I: Microtubule-Associated Protein 1 Light Chain 3; LXRs: Liver X Receptors; MAFLD: Metabolic Dysfunction-Associated Fatty Liver Disease; NAFL: Non-Alcoholic Fatty Liver; NAFLD: Non-Alcoholic Fatty Liver Disease; NASH: Non-Alcoholic Steatohepatitis; NF-κB: Nuclear Factor-κB; Nrf2: Nuclear Factor-erythroid 2-related factor 2; PGC-1α: Peroxisome Proliferator-Activated Receptor-γ Coactivator 1-α; PPARα: Peroxisome Proliferator-Activated Receptor-α; ROS: Reactive Oxygen Species; SIRT1: Sirtuin 1; SREBP-1c: Sterol Regulatory Element-Binding Protein-1c; T2DM: Type 2 Diabetes

Introduction

Apart from alcohol and other definitive factors, metabolic dysfunction-associated fatty liver disease (MAFLD), formerly known as non-alcoholic fatty liver disease (NAFLD), is a clinical-pathological syndrome characterized by hepatic steatosis and lipid accumulation. This condition encompasses non-alcoholic fatty liver (NAFL), the initial stage of MAFLD, and non-alcoholic steatohepatitis (NASH), an inflammatory progression triggered by lipotoxicity, potentially leading

to severe outcomes like fibrosis. MAFLD is now the most prevalent chronic liver disease globally, affecting nearly one-quarter of the global population [1,2]. Growing clinical evidence highlights MAFLD as a major risk factor for liver cirrhosis, fibrosis, and hepatocellular carcinoma [3]. The disease pathogenesis involves complex, cascading mechanisms. The "two-hit theory" proposed that the initial metabolic disruptions, such as insulin resistance (IR), hyperglycemia, and triglyceride formation in hepatocytes, constitute the first hit, resulting in hepatic steatosis. The second hit involves oxidative stress and lipid peroxidation, causing pathological changes like cirrhosis, inflammation, fibrosis, and steatohepatitis [4]. However, this theory inadequately explains the intricate metabolic and pathological processes of MAFLD, leading to the emergence of the "multiple-hit theory." This model attributes MAFLD progression to numerous parallel factors, including dysregulated adipokines, cytokines, mitochondrial dysfunction, endoplasmic reticulum stress, gut microbiota alterations, lipid metabolism, lipotoxicity, oxidative stress, genetic susceptibility, and epigenetic changes [5]. Therapeutic strategies for MAFLD focus on regulating lipid and cholesterol metabolism, reducing hepatic steatosis and oxidative stress, combating inflammation, and improving fatty acid oxidation (FAO) and IR. Compared to the term NAFLD, the introduction of MAFLD represents a significant shift in the understanding of the condition. NAFLD is defined by exclusion, emphasizing that the disease is not caused by alcohol consumption, but this definition is overly broad and fails to accurately reflect the metabolic drivers of the disease. In contrast, MAFLD places metabolic dysfunction at the core of the condition, highlighting the critical role of metabolic risk factors such as obesity, insulin resistance, type 2 diabetes (T2DM), and dyslipidemia in its development and progression. This shift not only more accurately captures the essence of the disease but also provides a clearer direction for its diagnosis and treatment [1]. The transition from NAFLD to MAFLD reflects a patient-centered approach, shifting the focus from merely "non-alcoholic" to the overall metabolic health of individuals. This change facilitates more personalized and targeted interventions. Moreover, the diagnostic criteria for MAFLD are based on specific metabolic characteristics of patients rather than simply excluding alcohol consumption. This ensures a more homogeneous study population in clinical trials, thereby enhancing the accuracy and relevance of research findings. Such improvements enable researchers to delve deeper into the underlying mechanisms of the disease, potentially uncovering new therapeutic targets. The emphasis on metabolic risk factors in MAFLD also carries significant clinical implications. It aids in the early identification of high-risk individuals, allowing for timely interventions to prevent disease progression. Additionally, the adoption of this terminology may spur the development of therapies targeting metabolic pathways, offering patients more effective treatment options. Furthermore, MAFLD encourages clinicians to adopt a more comprehensive management approach, addressing not only liver health but also the overall metabolic status of patients [6]. In summary, MAFLD offers substantial advantages over NAFLD in clinical practice, research, and patient management. With its clear diagnostic criteria, it enables clinicians to more accurately identify high-risk individuals and develop targeted treatment plans. The adoption of this terminology not only advances disease research but also opens new avenues for improving patient outcomes. Despite advancements in understanding MAFLD pathogenesis, therapeutic targets, and drug development, no FDA-approved treatment for MAFLD currently exists [7].

The Regulatory Mechanisms of SIRT1 in MAFLD

Members of the sirtuin family (SIRTs) have been demonstrated to play crucial roles in the dynamic pathophysiology of MAFLD. SIRTs are a group of highly conserved NAD^+-dependent histone and protein deacetylases, classified as class III histone deacetylases (HDACs). In mammals, seven homologs (SIRT1-SIRT7) have been identified, each with distinct subcellular localizations and biological functions. Among these, SIRT1, predominantly distributed in the nucleus and cytoplasm, is considered a key metabolic regulator in various tissues. It functions as a post-translational modulator, participating in gene transcription, apoptosis, cell cycle regulation, metabolism, and development. Studies have revealed that SIRT1 exerts profound effects on lipid metabolism, systemic inflammation, lifespan regulation, and anticancer activity. These effects are primarily attributed to its therapeutic potential in enhancing insulin sensitivity, promoting lipid homeostasis, combating hyperlipidemia, reducing inflammation, and exerting anti-aging and autophagy-modulating properties [8-10]. SIRT1 is expressed in various tissues, including the liver, pancreas, adipose tissue, muscle, and heart, and plays a key role in regulating metabolic functions through its ability to deacetylate proteins. As the most extensively studied member of the sirtuin family in the context of MAFLD pathophysiology, SIRT1's deacetylation of cellular proteins serves to link the metabolic state of cells with their functional outcomes, thereby influencing the development and progression of metabolic disorders like MAFLD. Clinical studies have demonstrated a significant downregulation of hepatic SIRT1 transcription in patients with MAFLD [11]. Moreover, hepatic mRNA levels of SIRT1 negatively correlate with the severity of hepatic steatosis and portal fibrosis [12]. Experimental studies using animal models further underscore the role of SIRT1 in the treatment of hepatic steatosis. Hepatic SIRT1 knockdown or systemic SIRT1 inactivation exacerbates HFD-induced hepatic steatosis, while SIRT1 overexpression attenuates liver damage and improves metabolic profiles [13,14]. Notably, pharmacological activation of SIRT1 has shown promising effects in ameliorating MAFLD. For instance, SIRT1 activators like SRT1720 and E1231 have been reported to improve hepatic steatosis and reduce inflammation in MAFLD models [15,16].

SIRT1-mediated deacetylation in the autophagy and mitochondrial function of MAFLD

Autophagy, a lysosome-mediated intracellular degradation and recycling process, is critical for maintaining cellular homeostasis. It facilitates the degradation of abnormal protein aggregates, organelles, and lipid droplets [17]. SIRT1 has been shown to regulate autophagy through deacetylation of autophagy-related proteins. Specifically, SIRT1 deacetylates forkhead box class O3 (FOXO3), promoting its binding to the BNIP3 promoter and initiating autophagy [18]. Additionally, SIRT1 deacetylates autophagy-related protein 5 (ATG5) and ATG12, increasing the ATG16-ATG5-ATG12 complex, thereby promoting autophagosome formation [19]. SIRT1 also deacetylates microtubule-associated protein 1 light chain 3 (LC3-I), inducing the conversion of LC3-I to LC3-II and facilitating autophagosome maturation [20]. These autophagy-regulating functions of SIRT1 play a protective role against MAFLD. For example, ginsenoside Rb2 alleviates hepatic steatosis by upregulating SIRT1 and promoting autophagy, while inhibition of SIRT1 abrogates these protective effects [21]. Similarly, nicotinamide induces autophagy through SIRT1 activation, protecting hepatocytes from palmitic

acid-induced cytotoxicity [22]. Not only does autophagy play a critical role in cellular homeostasis, but mitochondrial function is also essential for maintaining cellular energy balance. Mitochondrial dysfunction, including mitochondrial swelling, impaired oxidative phosphorylation, and increased reactive oxygen species (ROS) production, is closely associated with the pathogenesis of MAFLD. Mitochondrial damage occurs in the liver tissue of obese (ob/ob) mice, characterized by increased mitochondrial ROS and decreased ATP levels. This disrupts intracellular oxidative stress and lipid metabolism, thereby promoting the progression of MAFLD [23]. SIRT1 alleviates MAFLD by enhancing mitochondrial function. Activation of the SIRT1-Peroxisome Proliferator-Activated Receptor-γ Coactivator 1-α (PGC-1α) pathway promotes mitochondrial biogenesis and reduces hepatic lipid accumulation [24]. Aerobic exercise enhances SIRT1 expression, inhibits dynamin-related protein 1 (Drp1) acetylation and activity, and improves mitochondrial dysfunction and hepatic steatosis [25]. These findings reveal the critical role of SIRT1-mediated activation of autophagy and regulation of mitochondrial homeostasis in ameliorating MAFLD **(Figure 1)**.

SIRT1-mediated deacetylation in the lipid metabolism and oxidative stress of MAFLD

Lipid metabolism dysregulation is a central feature of MAFLD. Hepatic lipid accumulation arises from an imbalance between lipid uptake/synthesis and lipid oxidation/export. SIRT1 regulates lipid metabolism by deacetylating key proteins involved in these processes. For instance, SIRT1 deacetylates carnitine palmitoyltransferase 1A (CPT1A), preventing its ubiquitination and degradation, thereby enhancing FAO and alleviating hepatic steatosis [11]. Additionally, Sterol Regulatory Element-Binding Protein-1c (SREBP-1c) and Carbohydrate Response Element-Binding Protein (ChREBP) work synergistically to induce the synthesis of hepatic triglycerides and fatty acids through phosphorylation and acetylation. They are also positive regulators of fatty acid synthase (FAS) and acetyl-CoA carboxylase 1 (ACC1) [26,27]. Overexpression of SIRT1 enhances AMPK expression through the interaction between SREBP-1c and ChREBP. SIRT1 deacetylates SREBP-1c and ChREBP, suppressing the expression of their downstream lipogenic genes, ultimately inhibiting lipogenesis and mitigating MAFLD [28,29].

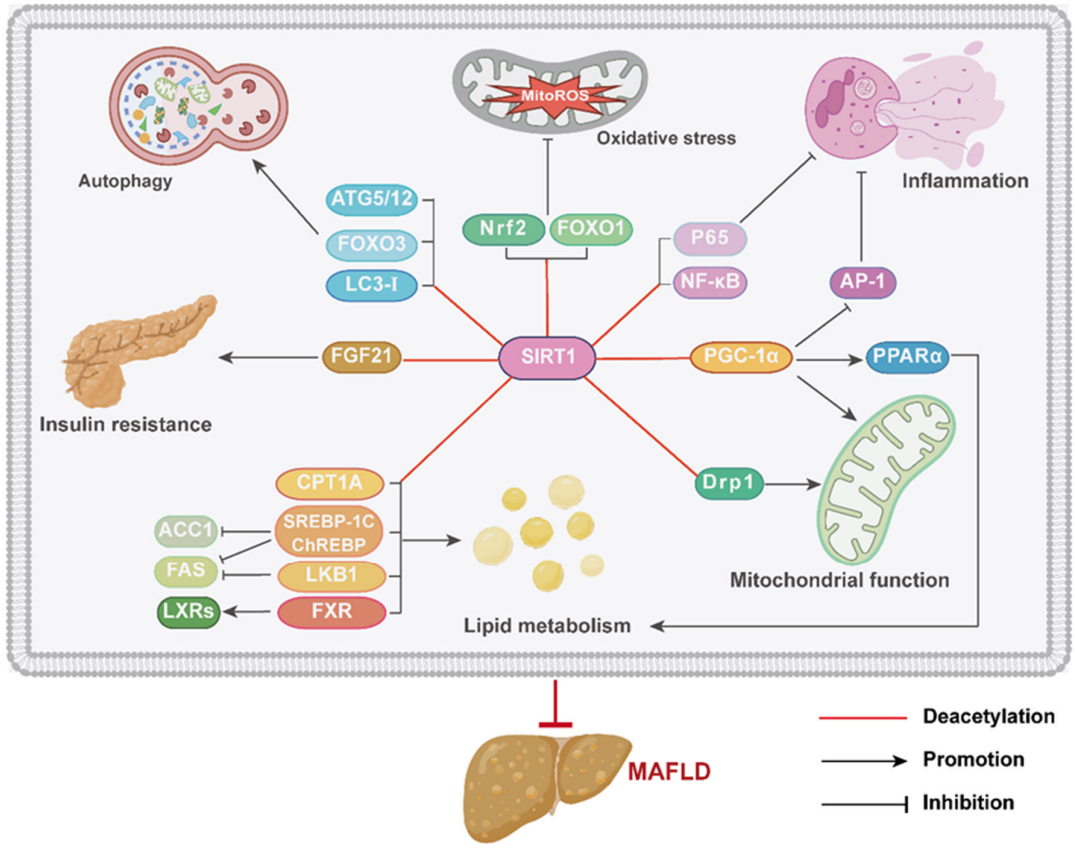

Figure 1. Mechanisms of SIRT1 Deacetylation in the Treatment of MAFLD. Abbreviations: SIRT1: Sirtuin1; FOXO3: Forkhead Box Class O3; ATG5/12: Autophagy-Related Protein 5/12; LC3 : Microtubule-Associated Protein 1 Light Chain 3; FOXO1: Forkhead Box Class O1; Nrf2: Nuclear Factor-Erythroid 2-Related Factor 2; P65: relA; NF-κB: Nuclear Factor-κB; PGC-1α: Peroxisome Proliferator-Activated Receptor-Γ Coactivator 1-α; AP-1: Macrophage-Activating Protein-1; PPARα: Peroxisome Proliferator-Activated Receptor-α; Drp1: Dynamin-Related Protein 1; CPT1A: Carnitine Palmitoyltransferase 1A; SREBP-1c: Sterol Regulatory Element-Binding Protein-1c; ChREBP: Carbohydrate Response Element-Binding Protein; ACC1: Acetyl-CoA Carboxylase 1; LKB1: Liver Kinase B1; FAS: Fatty Acid Synthase; FXR: Farnesoid X Receptor; LXRs Liver X Receptors; FGF21: Fibroblast Growth Factor 21.

Liver X Receptors (LXRs) and Farnesoid X Receptor (FXR) are two nuclear receptors that act as intracellular sensors for sterols and bile acids, respectively. Their interaction maintains systemic lipid and cholesterol homeostasis [30]. SIRT1 directly interacts with FXR, deacetylating it and increasing the expression of LXRs and their downstream target genes, thereby promoting reverse cholesterol transport in the liver and alleviating hepatic steatosis [28]. Moreover, SIRT1 inhibits FAS expression and lipid accumulation by deacetylating Liver Kinase B1 (LKB1), regulating hepatic lipid metabolism [31]. FAO is the primary pathway for fatty acid consumption in the liver. Research indicates that the FAO pathway in hepatocytes is closely linked to the occurrence and progression of MAFLD. Impaired FAO leads to lipid accumulation and excessive ROS production, resulting in oxidative stress and further promoting the development of MAFLD. Oxidative stress refers to an imbalance between pro-oxidant and antioxidant mechanisms in the body, favoring oxidation. ROS are the primary mediators of oxidative stress [32]. At normal levels, ROS maintain cellular physiological functions, but at high concentrations, they induce oxidative damage to cells. In MAFLD, hepatic lipid accumulation induces excessive ROS production, which in turn promotes lipid peroxidation, accelerates lipid accumulation, and induces cellular damage. Oxidative stress can cause or exacerbate hepatocyte injury, leading to mitochondrial dysfunction, lipid peroxidation, and apoptosis. Therefore, reducing oxidative stress is a crucial strategy for treating MAFLD. As mitochondria are the primary source of ROS, improving mitochondrial function is a key mechanism by which SIRT1 mitigates oxidative stress to alleviate MAFLD. Additionally, studies show that Yinchen Linggui Zhugan decoction activates SIRT1 to deacetylate nuclear factor-erythroid 2-related factor 2 (Nrf2), reducing hepatic oxidative stress and inhibiting HFD-induced MAFLD [33]. Exogenous hydrogen sulfide activates SIRT1 to deacetylate forkhead box class O1 (FOXO1), enhancing its binding to the PCSK9 promoter and suppressing hepatic ER stress and steatosis [34]. Moreover, MAFLD exacerbates ROS production, impairs FAO, and disrupts mitochondrial dynamics [35]. The PGC-1α/Peroxisome proliferator-activated receptor-α (PPARα) signaling pathway influences MAFLD by regulating FAO. SIRT1 deacetylates PGC-1α, enhancing the transcription of PPARα. This process ultimately promotes FAO and increases hepatic lipid consumption [36]. Therefore, SIRT1 ameliorates MAFLD by deacetylating key proteins in lipid metabolism and oxidative stress pathways.

SIRT1-mediated deacetylation in the inflammation of MAFLD

Inflammation is a key driver of MAFLD progression. Persistent inflammation contributes to the transition from hepatic steatosis to NASH and fibrosis. SIRT1 deacetylates P65 in the liver, reducing the production of inflammatory factors and thereby inhibiting NASH [37]. The Nuclear Factor-κB (NF-κB) signaling pathway is a central mechanism in the inflammatory process. During inflammation, NF-κB translocates to the nucleus, initiating its transcriptional activity and upregulating the expression of inflammation-related genes. SIRT1 deacetylates NF-κB, suppressing its transcriptional activity, which ultimately reduces macrophage infiltration and the release of pro-inflammatory cytokines [38]. Additionally, macrophage-activating protein-1 (AP-1) is a transcription factor involved in the expression of inflammation-related genes. SIRT1 suppresses AP-1 transcriptional activity and its downstream inflammatory mediator, cyclooxygenase 2 (COX2), by deacetylating PGC-1α, thereby exerting anti-inflammatory effects [39]. In summary, these findings highlight the anti-inflammatory potential of SIRT1 in mitigating MAFLD-related liver damage.

SIRT1-mediated deacetylation in the IR of MAFLD

T2DM is a key risk factor for the progression of hepatic steatosis to steatohepatitis, and the relationship between MAFLD and T2DM is well-established. IR plays a central role in this process by suppressing fatty acid metabolism, leading to hepatic steatosis, inflammation, and fibrosis. Meanwhile, chronic hepatitis is an important pathophysiological mechanism contributing to systemic IR [40]. Fibroblast Growth Factor 21 (FGF21), a hepatocyte-derived hormone, regulates glucose and lipid homeostasis as well as insulin sensitivity in obesity-induced diabetes. FGF21 lowers blood glucose, insulin, and lipid levels, thereby inhibiting hepatic steatosis and exerting therapeutic effects on MAFLD and T2DM. SIRT1 enhances insulin sensitivity and regulates energy homeostasis and hepatic lipid metabolism by activating FGF21 [41]. Additionally, a recent study demonstrated that in T2DM-associated fatty liver disease, activating SIRT1 deacetylates PGC-1α, improving mitochondrial function, promoting FAO, and reducing hepatic lipotoxicity [42]. In summary, SIRT1 reduces the negative interaction between T2DM and MAFLD by enhancing insulin sensitivity and mitigating IR.

Pharmacological Targeting of SIRT1 in MAFLD

Currently, there are no approved specific drugs for MAFLD, and lipid-lowering medications such as statins and fibrates have limited efficacy and are associated with significant side effects in clinical practice. In contrast, SIRT1 activators have shown great potential in the treatment of MAFLD due to their high efficacy, safety, and low cost. A substantial number of preclinical studies have been conducted on SIRT1-targeting compounds for MAFLD treatment. These include natural compounds such as resveratrol, quercetin, and pterostilbene; natural products like curcumin and phloretin [43]; as well as synthetic SIRT1 activators such as SRT1720 and E1231 [15,16]. Although SIRT1-targeted drugs for MAFLD are still in the early stages, these studies provide novel insights and directions for the prevention and treatment of MAFLD. It is worth noting that previous studies extensively explored the effects of resveratrol on MAFLD through clinical trials, but the results have been inconsistent [44,45]. The discrepancies may be attributed to small sample sizes, racial differences, variations in dosage and treatment duration, as well as the poor bioavailability and metabolic stability of resveratrol. Therefore, large-scale, multicenter clinical trials are necessary to evaluate the effects of resveratrol on MAFLD. To address the issues of low bioavailability, complex mechanisms of action, and inconsistent clinical efficacy of resveratrol in modulating metabolic diseases, researchers have developed SRT2104, a more targeted and stable SIRT1 agonist. Through structural optimization, SRT2104 significantly improves bioavailability, exerts pharmacological activity at lower doses, and demonstrates high specificity in activating SIRT1, avoiding the multi-target confounding effects of resveratrol. Clinical studies have shown that SRT2104 has clear efficacy in improving lipid metabolism and enhancing mitochondrial function, with good tolerability. However, although the bioavailability of SRT2104 (14%) is significantly higher than that of resveratrol, further improvement is needed to support broader clinical applications. Additionally, due to the pleiotropic effects of SIRT1 in various organs, systemic administration of SRT2104 may lead to off-target tissue side effects, necessitating the development of targeted delivery

systems to enhance tissue specificity. At the same time, long-term safety data for SRT2104 remain insufficient, and the impact of other potential side effects requires further evaluation [46-48].

Overall, as a new-generation SIRT1 agonists, SRT2104 has significant advantages in specificity, pharmacokinetics, and clinical efficacy. However, its bioavailability, tissue specificity, and long-term safety still need further optimization. Future research could overcome these limitations through targeted delivery systems, precise dose adjustments, and long-term follow-up trials, thereby maximizing its therapeutic potential.

Conclusions

In summary, SIRT1-targeted therapy is advancing from basic research to clinical translation, with its core advantage lying in its multi-pathway regulatory capabilities, enabling simultaneous intervention in pathological processes such as inflammation, lipid metabolism, and oxidative stress. However, challenges such as low delivery efficiency, insufficient targeting, and long-term safety concerns remain significant hurdles. In the field of MAFLD, SIRT1 has been identified as a highly promising target, with various activators demonstrating potential in improving lipid metabolism, suppressing inflammation, and mitigating fibrosis in studies. Nonetheless, large-scale clinical trials are required for further validation. Given the widespread expression of SIRT1 throughout the body, the development of liver-specific targeted therapies is crucial to minimize side effects and enhance precision. Looking ahead, by optimizing delivery systems, exploring combination therapies (such as SIRT1 with GLP-1 agonists), incorporating SIRT1 gene polymorphisms for personalized treatment, and validating long-term safety, SIRT1 has the potential to evolve from a "promising target" to a "transformative therapy." SIRT1 deacetylates forkhead box class O3 (FOXO3), thereby initiating autophagy. Additionally, SIRT1 deacetylates autophagy-related protein 5 (ATG5) and ATG12, increasing the ATG16-ATG5-ATG12 complex, thereby promoting autophagy. SIRT1 also deacetylates microtubule-associated protein 1 light chain 3 (LC3-I), and promotes autophagy. Activation of the SIRT1-Peroxisome Proliferator-Activated Receptor-γ Coactivator 1-α (PGC-1α) pathway promotes mitochondrial biogenesis and reduces hepatic lipid accumulation. SIRT1 deacetylates dynamin-related protein 1 (Drp1), and improves mitochondrial dysfunction and hepatic steatosis. SIRT1 deacetylates CPT1A, preventing its ubiquitination and degradation, thereby enhancing fatty acid oxidation (FAO) and alleviating hepatic steatosis. SIRT1 deacetylates Sterol Regulatory Element-Binding Protein-1c (SREBP-1c) and Carbohydrate Response Element-Binding Protein (ChREBP), suppressing the expression of their downstream lipogenic genes fatty acid synthase (FAS) and acetyl-CoA carboxylase 1 (ACC1), ultimately inhibiting lipogenesis and mitigating MAFLD. Moreover, SIRT1 inhibits FAS expression and lipid accumulation by deacetylating Liver Kinase B1 (LKB1), regulating hepatic lipid metabolism. SIRT1 deacetylates Farnesoid X Receptor (FXR) and increases the expression of Liver X Receptors (LXRs), thereby promoting reverse cholesterol transport in the liver and alleviating hepatic steatosis. Moreover, SIRT1 deacetylates PGC-1α, enhancing the transcription of Peroxisome proliferator-activated receptor-α (PPARα), promoting FAO and increasing hepatic lipid consumption. SIRT1 deacetylates nuclear factor-erythroid 2-related factor 2 (Nrf2), reducing hepatic oxidative stress and inhibiting HFD-induced MAFLD. SIRT1 deacetylates forkhead box class O1 (FOXO1), suppressing hepatic ER stress and steatosis. SIRT1 deacetylates P65 in the liver, reducing the production of inflammatory factors and thereby inhibiting MAFLD. SIRT1 deacetylates Nuclear Factor-κB (NF-κB), suppressing its transcriptional activity, which ultimately reduces macrophage infiltration and the release of pro-inflammatory cytokines. Additionally, SIRT1 suppresses macrophage-activating protein-1 (AP-1) transcriptional activity, by deacetylating PGC-1α, thereby exerting anti-inflammatory effects. SIRT1 enhances insulin sensitivity and regulates energy homeostasis and hepatic lipid metabolism by activating Fibroblast Growth Factor 21 (FGF21).

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