


REVIEW

Protein posttranslational modifications in metabolic diseases: basic concepts and targeted therapies

Yunuo Yang^{1,2} | Jiaxuan Wu^{1,2} | Wenjun Zhou^{1,2} | Guang Ji^{1,2,*} | Yanqi Dang^{1,2,*} 

¹Institute of Digestive Diseases, China-Canada Center of Research for Digestive Diseases (ccCRDD), Shanghai University of Traditional Chinese Medicine, Shanghai, China

²State Key Laboratory of Integration and Innovation of Classic Formula and Modern Chinese Medicine (Shanghai University of Traditional Chinese Medicine), Shanghai, China

*Correspondence

Guang Ji, No. 725 Wanping South Road, Xuhui District, Shanghai, China.

Email: jiliver@vip.sina.com; jg@shutcm.edu.cn

Yanqi Dang, No. 725 Wanping South Road, Xuhui District, Shanghai, China.

Email: dangyanqi9022@126.com; yq_dang@shutcm.edu.cn

Funding information

The Shanghai Rising-Star Program, Grant/Award Number: 21QA1409000; Shanghai Frontier Research Base of Disease and Syndrome Biology of Inflammatory Cancer Transformation, Grant/Award Number: 2021KJ03-12; Natural Science Foundation of Shanghai, Grant/Award Number: 21Y11902300

Abstract

Metabolism-related diseases, including diabetes mellitus, obesity, hyperlipidemia, and nonalcoholic fatty liver disease, are becoming increasingly prevalent, thereby posing significant threats to human health and longevity. Proteins, as the primary mediators of biological activities, undergo various posttranslational modifications (PTMs), including phosphorylation, ubiquitination, acetylation, methylation, and SUMOylation, among others, which substantially diversify their functions. These modifications are crucial in the physiological and pathological processes associated with metabolic disorders. Despite advancements in the field, there remains a deficiency in contemporary summaries addressing how these modifications influence processes of metabolic disease. This review aims to systematically elucidate the mechanisms through which PTM of proteins impact the progression of metabolic diseases, including diabetes, obesity, hyperlipidemia, and nonalcoholic fatty liver disease. Additionally, the limitations of the current body of research are critically assessed. Leveraging PTMs of proteins provides novel insights and therapeutic targets for the prevention and treatment of metabolic disorders. Numerous drugs designed to target these modifications are currently in preclinical or clinical trials. This review also provides a comprehensive summary. By elucidating the intricate interplay between PTMs and metabolic pathways, this study advances understanding of the molecular mechanisms underlying metabolic dysfunction, thereby facilitating the development of more precise and effective disease management strategies.

KEYWORDS

diabetes mellitus, hyperlipidemia, nonalcoholic fatty liver disease, obesity, protein posttranslational modification

1 | INTRODUCTION

With socio-economic development, human habits are changing. Concurrently, an aging population exacerbates the incidence of metabolic diseases marked by dysregulated metabolism, notably including diabetes mellitus

(DM), obesity, hyperlipidemia, and nonalcoholic fatty liver disease (NAFLD), posing significant threats to human health and longevity.^{1,2}

DM is a metabolic disorder distinguished by elevated blood glucose levels. Globally, its prevalence among adults is estimated at 9%, with type 2 diabetes mellitus (T2DM)

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2024 The Author(s). *MedComm* published by Sichuan International Medical Exchange & Promotion Association (SCIMEA) and John Wiley & Sons Australia, Ltd.

comprising 90% of cases.^{3,4} In 2017, approximately 425 million individuals were affected by DM, a figure projected to rise to 642 million by 2040.⁵ Obesity, characterized by an abnormal accumulation of fat detrimental to health, is typically diagnosed when an individual's body mass index reaches or exceeds 30, as defined by the World Health Organization. As of 2016, over 1.9 billion adults worldwide, along with more than 340 million children and adolescents aged from 5 to 19 years, were classified as overweight or obese,^{6–9} with the number of obese individuals having tripled since 1975. Hyperlipidemia is characterized by elevated levels of lipids, including cholesterol, lipoproteins. In the United States, over 50% of adults exhibit elevated low-density lipoprotein (LDL) levels.¹⁰ NAFLD, a clinicopathological syndrome, is typified by excessive accumulation of intracellular fat within hepatocytes, often accompanied by obesity, insulin resistance or T2DM, and dyslipidemia. Globally, the prevalence of NAFLD is approximately 25%,^{11,12} with rates exceeding 30% in South America.^{13,14} As one of the foremost chronic liver diseases worldwide, NAFLD imposes a substantial burden on healthcare systems.¹⁵ These metabolic diseases are independent of each other, but also interrelated and interact with each other. The combination of two or more metabolism-related diseases often occurs in clinical practice. NAFLD is closely related to insulin resistance and often coexists with T2DM, and studies have shown that NAFLD can increase the risk of T2DM.¹⁶ A meta-analysis of 80 studies suggests T2DM promotes disease progression in NAFLD.¹⁷ Quek et al.¹⁸ analyzed that the prevalence of NAFLD was 75.7% in the obese population. T2DM is a major risk factor for the development of cardiovascular disease, and obesity (especially the accumulation of visceral fat) also increases the risk of T2DM and cardiovascular disease by affecting cardiac metabolism.¹⁹ The increasing prevalence of metabolic diseases poses significant risks and challenges to human health and societal healthcare systems. Immediate and effective measures are essential for the prevention and treatment of metabolic disorders.

Epigenetics encompasses heritable changes in gene function, with the epigenome comprising DNA methylation, histone modifications, and noncoding RNAs.²⁰ Among them, proteins serve as vital components in the functioning of living organisms, acting as primary agents for life processes. The human genome encodes approximately 20,000 genes, which undergo transcription and translation to produce proteins. Human metabolism is regulated by a variety of proteins, and protein function is affected by a variety of factors. Recent evidence suggests that posttranslational modifications (PTMs) of proteins affect glycolipid metabolism and are an important part of the development of metabolism-related diseases.²¹ PTMs represents a crucial mechanism wherein proteins undergo covalent alterations, involving the addition of functional

groups to amino acid residues or enzymatic cleavage. PTMs significantly enhance the functional diversity of proteins, leading to an exponential increase in protein variants, thereby contributing to the intricacies of biological activities. Current advancements in science and technology have identified over 600 types of PTMs. Numerous studies have demonstrated that PTMs are crucial in the onset and progression of various diseases. Among the diverse array of PTMs, phosphorylation, ubiquitination, acetylation, methylation, palmitoylation, succinylation, crotonylation, lactylation, malonylation, SUMOylation, S-sulfhydration, glycosylation, and others are intimately associated with metabolic homeostasis. Consequently, this discussion will concentrate on the roles of these specific modifications in metabolic diseases.^{22,23} Understanding the pathogenesis of metabolic diseases from the perspective of PTMs may provide new perspectives on the prevention and treatment of the diseases.

This review systematically elucidates the relationship between PTMs of proteins and metabolic disease processes, including DM, obesity, hyperlipidemia, and NAFLD, as well as therapeutic agents targeting PTMs. Additionally, we critically assess the limitations of current studies, providing new insights into the development of novel diagnostic biomarkers and therapeutic interventions for metabolic diseases.

2 | PROTEIN PTMs

Precursor proteins undergo covalent processing, specifically PTMs, to transform into mature proteins with appropriate physiological functions. These PTMs have significantly expanded the diversity of proteins and added complexity to biological processes. Research has identified over 600 distinct types of protein PTMs. Among these, the most extensively studied modifications, particularly those closely associated with metabolism-related diseases, include the following.

2.1 | Phosphorylation

Phosphorylation represents one of the most prevalent types of covalent modifications in proteins. This biochemical process involves the transfer of a phosphoryl group from the γ -position of adenosine triphosphate (ATP) or guanosine triphosphate to specific amino acid residues on the substrate protein.²⁴ Phosphorylation of proteins leads to the incorporation of a net negative charge onto the amino acid residues of the phosphate group receptor. The regulation of histone modifications involves three principal classes of proteins: Writers, Erasers, and Readers. In the context of phosphorylation modifications, protein kinases

(Writers) are responsible for the addition of phosphoryl groups, phosphorylation-binding proteins (Readers) recognize and interact with the phosphorylated groups, and protein phosphatases (Erasers) facilitate the removal of the phosphoryl groups.²⁵ Phosphorylation typically occurs on serine, threonine, or tyrosine residues within the protein structure.

2.2 | Ubiquitination

Ubiquitination is a process wherein ubiquitin binds covalently to a target protein catalyzed by a series of enzymes. The C-terminal glycine residue of ubiquitin forms a covalent bond with the amino group of the lysine side chain of other protein molecules. This process involves three enzymes (Writers) working together in a cascade: E1 ubiquitin-activating enzyme, E2 ubiquitin-conjugating enzyme, and E3 ubiquitin-conjugating enzyme. Ubiquitination is a tightly regulated and reversible process. Deubiquitinating enzymes (Erasers) can reverse ubiquitination modifications by hydrolyzing peptide or isopeptide bonds between ubiquitin molecules or between ubiquitin and substrate proteins.²⁶ In addition, proteins (Readers) that recognize ubiquitinated proteins by their ubiquitin-binding domains are involved in the coordinated activity of ubiquitination.²⁷

2.3 | Acetylation

Acetylation modifications of proteins encompass both histone acetylation and nonhistone acetylation. Histone acetylation, pioneered by Vincent Allfrey in 1964, involves the transfer of the acetyl group from acetyl coenzyme A to specific lysine residues at the amino-terminus of histones, facilitated by histone acetyltransferases (HATs). This process neutralizes the positive charge of lysine, leading to relaxation of the nucleosome structure and activation of transcription (lysine +1 to 0). Histone acetylation is mediated by HATs (Writers), with brominated chains acting as readers for read recognition. Conversely, deacetylation, catalyzed by histone deacetylases (HDACs, Erasers), is associated with transcriptional repression. Additionally, acetylation modifications extend beyond histones to include nonhistone proteins, playing diverse roles in various biological processes.²⁸

2.4 | Methylation

Methylation stands as a pivotal form of epigenetic regulation, involving the transfer of reactive methyl groups to tar-

get molecules catalyzed by methyltransferases (Writers). Histone methyltransferases are divided into two groups based on their structure and modification sites: histone lysine methyltransferases and protein arginine methyltransferases. Protein methylation predominantly occurs on arginine and lysine residues of histones and nonhistone proteins. Histone methylation primarily targets H3 and H4, where arginine residues can undergo monomethylation and demethylation, while lysine residues can be monomethylated, dimethylated, and trimethylated.²⁹ Non-histone methylation, on the other hand, typically modulates signal transduction and serves as a crucial regulator of cellular signaling.³⁰

The counterpart to methylation is demethylation, facilitated by members of the Jumonji C-terminal structural domain family and lysine-specific demethylase 1 primarily responsible (Erasers) for lysine demethylation. Additionally, certain members of the Jumonji C-terminal structural domain family are known to catalyze arginine demethylation.²⁹

2.5 | SUMOylation

SUMO, the small ubiquitin-like modifier, is a highly conserved molecule.³¹ It conjugates to lysine residues in proteins via isopeptide linkage, a process catalyzed by SUMO-specific activating enzyme (E1), conjugating enzyme (E2), and ligase (E3) (Writers).³² Mammalian cells contain five SUMO isoforms: SUMO1, SUMO2, SUMO3, SUMO4, and SUMO5.³³ SUMOylation regulates cellular transcription, nuclear integrity, proliferation, and senescence.³³ DeSUMOylation is mainly mediated by SUMO-specific peptidases (SENPs, Erasers).

2.6 | Glycosylation

Protein glycosylation entails the covalent bonding of monosaccharides or glycans to particular residues of targeted proteins. Within eukaryotic cells, this process predominantly unfolds across the secretory pathway, initiating in the endoplasmic reticulum (ER) and culminating in the Golgi apparatus.³⁴ Protein glycosylation encompasses both N-terminal and O-terminal glycosylation.

2.7 | The lysine modifications

2.7.1 | Succinylation

Succinylation entails the covalent attachment of succinyl groups to lysine residues facilitated by succinyl

donors mediated by succinyl-coenzyme A.³⁵ Succinylation accompanied by changes in amino acid charge (lysine +1 to -1). This modification can significantly impact enzymatic processes and metabolic pathways, particularly within mitochondrial metabolic pathways, thereby exerting diverse effects on cellular metabolism. Such effects extend to crucial pathways including the tricarboxylic acid cycle, electron transport chain, glycolysis, ketone body formation, fatty acid oxidation, and the urea cycle.³⁶

2.7.2 | Crotonylation

Crotonylation, a lesser-known protein modification, has gained attention in metabolic diseases. First identified in 2011,³⁷ lysine crotonylation occurs not only in core histones but also in a variety of nonhistone proteins across a wide range of organisms. Like other PTMs, protein crotonylation is reversible and has been implicated in processes such as DNA damage and repair,³⁸ tissue damage,³⁹ inflammation,⁴⁰ as well as self-renewal and differentiation of stem cells.⁴¹ Among the various types of protein crotonylation, lysine crotonylation predominates, with HATs, like P300/CBP, PCAF, and MOF being the main enzymes responsible for catalyzing crotonylation reactions, while HDACs (HDAC1/2/3) and sirtuins (SIRT1/2/3) function to reverse these modifications.⁴²

2.7.3 | Lactylation

Lactylation, the modification of lysine residues on histones by lactic acid during cellular metabolism, represents an important mechanism through which lactic acid exerts its functions. This modification plays a pivotal role in various cellular activities, including glycolysis-related functions, macrophage polarization, vascular regulation, mitochondrial function, and nervous system regulation. The involvement of lactylation in these crucial processes suggests promising avenues for research in fields such as oncology and immunology.

2.7.4 | Malonylation

Protein malonylation, identified in 2011, predominantly occurs on lysine residues.⁴³ The enzymatic machinery responsible for catalyzing protein malonylation includes malonyl coenzyme A, malonyl coenzyme A decarboxylase, and SIRT5.

2.8 | The cysteine modifications

2.8.1 | Palmitoylation

Palmitic acid undergoes conversion to palmitoyl coenzyme A facilitated by palmitoyl acyl transferase, which is covalently bound to the sulfhydryl group of the C-terminal cysteine residue of proteins through an unstable thioester bond, a process known as S-palmitoylation. Notably, palmitoylation represents a reversible protein modification, with the reverse process catalyzed by a family of serine hydrolases B.⁴⁴

2.8.2 | S-sulfhydration

S-sulfhydration, alternatively known as persulfation, represents a novel PTM mechanism involving the modification of cysteine residues through the utilization of hydrogen sulfide (H₂S) or persulfide.⁴⁵

3 | PROTEIN PTMs IN DM

The prevalence of DM is increasing year by year and is accompanied by numerous complications that are increasingly threatening human public health. Current evidence suggests that PTMs of proteins play an important role in diabetes and its complications (Figure 1).⁴⁶

3.1 | Phosphorylation in DM

Phosphorylation plays a crucial role in the pathogenesis of DM. Phosphorylation mediates this disease by affecting the insulin signaling pathway, AMP-activated protein kinase (AMPK) signaling pathway, and others. The dynamic interplay of phosphorylation and dephosphorylation processes involving the insulin receptor and its downstream proteins significantly impacts energy metabolism. Glucose present in the bloodstream stimulates insulin secretion from pancreatic β -cells, which then travels through the bloodstream to tissues, activating the insulin receptor. This activation initiates a cascade of phosphorylation-dephosphorylation processes.^{47,48} The insulin receptor consists of α and β subunits, with the β subunit containing a structural domain expressing insulin-stimulated kinase activity. Mutations at phosphorylation sites (sites 1158, 1163, and 1162) of the β subunit impair kinase activity, thereby reducing the metabolic effects of insulin. In muscle and liver, insulin receptor substrate-1 (IRS-1) and IRS-2 act as major docking

Diabetes

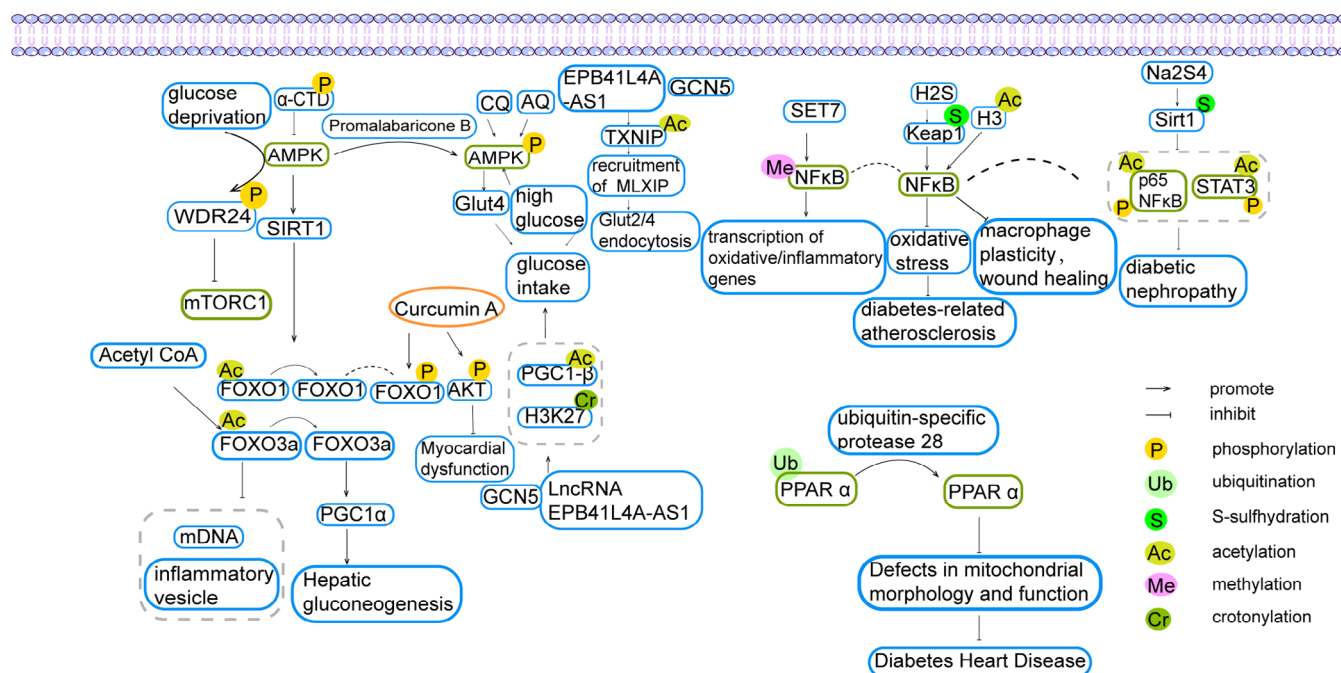


FIGURE 1 PTMs in DM. Posttranslational modifications (PTMs) of proteins are closely related to the development of diabetes. (A) Deubiquitination of peroxisome proliferator-activated receptor (PPAR) inhibits diabetic heart disease. (B) Methylation of nuclear factor kappa-B (NF-κB) promotes transcription of inflammation-related genes. Acetylation and phosphorylation of NF-κB are associated with diabetic neuropathy. Acetylated H3 and sulfated Keap1 modulate the activity of NF-κB, thereby affecting oxidative stress. (C) AMP-activated protein kinase (AMPK) promotes hepatic gluconeogenesis by promoting the phosphorylation of WD repeat domain 24 (WDR24), inhibits mammalian target of rapamycin complex 1 (mTORC1). AMPK promotes hepatic gluconeogenesis by promoting deacetylation of Forkhead box O (FOXO). The phosphorylation of AMPK itself is regulated by rosemary extract, chloroquine (CQ), amodiaquine (AQ), hyperglycemia, and affects glucose uptake.

proteins, respectively, undergoing tyrosine phosphorylation in response to insulin receptor tyrosine kinase.⁴⁹ Phosphorylation of IRS-1 is inhibited by saturated fatty acid-mediated ER stress, further impacting insulin signaling and sensitivity.^{50,51} Additionally, diacylglycerol activates protein kinase C θ in muscle and protein kinase C ϵ in the liver, promoting phosphorylation of IRS-1 at Ser1101 and insulin receptor at Thr1160, consequently inhibiting insulin signaling.⁵⁰ Inhibition of vascular endothelial protein tyrosine phosphatase dephosphorylates endothelial nitric oxide synthase at Tyr81, thereby enhancing diabetes-induced endothelial function and lowering blood pressure.⁵² Moreover, glycogen synthase kinase 3 beta (GSK3 β) regulates the phosphorylation of mitsugumin 53 at S255, a process induced by aberrant insulin signaling in diabetic mice. Consequently, inhibition of the insulin receptor-IRS1-GSK3 β -mitsugumin 53 pathway protects diabetic hearts in mice.⁵³

AMPK serves as a critical cellular energy sensor, playing a pivotal role in regulating glucose metabolism and uptake in DM. Comprising three subunits, α , β , and γ , phosphorylation of serine 485/491 on the C-terminal

structural domain of the α subunit can modulate AMPK activity.⁵⁴ Phosphorylation of AMPK enhances glucose uptake in muscle cells and reduces blood glucose levels by upregulating glucose transporter protein 4 (GLUT4) expression.^{55,56} Chloroquine and amodiaquine have been shown to alleviate diabetic tubulopathy by promoting AMPK phosphorylation in renal tubular cells of diabetic nephropathic mice.⁵⁷ High glucose levels induce reactive oxygen species production, leading to AMPK α phosphorylation at S485/491 and the recruitment of E3 ligase mitsugumin 53.⁵⁸ Fisetinone inhibits mitochondrial superoxide production and reduces AMPK phosphorylation in the kidneys of diabetic mice.⁵⁹ Moreover, glucose deprivation inhibits mechanistic target of rapamycin complex 1 (mTORC1) activation by promoting AMPK-mediated phosphorylation of WD repeat domain 24 at S155.⁶⁰

3.2 | Ubiquitination in DM

Ubiquitination plays a role in the development and progression of DM mainly by affecting the IRS signaling

pathway and the ubiquitin–proteasome system. First, ubiquitin deficiency leads to the downregulation of IRS signaling, which is associated with the production of suppressor of cytokine signaling 1 and suppressor of cytokine signaling 3 induced by inflammatory cytokines. Second, it results in the downregulation of insulin receptor. Additionally, ubiquitination is associated with impaired insulin biological responses.⁶¹

The ubiquitin–proteasome system serves as the principal pathway for cellular protein degradation, with the multicatalytic complex 26S proteasome recognizing and degrading ubiquitin-tagged proteins. Studies have revealed elevated levels of ubiquitination in proteins within β -cells of patients diagnosed with T2DM.⁶² Additionally, reductions in ubiquitin–proteasome system components have been observed in retinal cells of diabetic rats, with a concomitant decrease in ubiquitin-activating enzyme E1 during induced ER stress.⁶³ S-phase kinase-associated protein 2 ubiquitin ligase, a receptor component of the SCF ubiquitin ligase complex, facilitates ubiquitination and degradation of p27, a protein closely linked to β -cell production and insulin resistance.⁶⁴ Defects in protein degradation within β -cells of T2DM patients have been associated with misfolding of pancreatic amyloid-derived polypeptide h-IAPP, leading to diminished levels of the deubiquitinating enzyme UCH-L1 and consequent impairment of β -cell function.⁶⁵ Furthermore, the ubiquitin-specific protease has been shown to mitigate diabetic heart disease in mice by deubiquitinating and stabilizing peroxisome proliferator-activated receptor α (PPAR α), thereby inhibiting mitochondrial morphofunctional defects.⁶⁶ In a randomized controlled trial, it was found that the PPAR γ activator rosiglitazone suppressed ubiquitin–proteasome activity in atherosclerotic lesions in diabetic patients, potentially through the downregulation of NF- κ B-mediated inflammatory pathways.⁶⁷

3.3 | Acetylation in DM

In the context of DM, HDACs and HATs influence maturity-onset diabetes of the young (MODY) by modulating the acetylation levels of relevant factors. Deacetylation of Forkhead box O3a (FOXO3a), liver X receptor alpha (LXR α), and signal transducer and activator of transcription 3 (STAT3) mediated by the deacetylase Sirtuin family is implicated in DM. Furthermore, protein acetylation regulates glucose uptake.

The activity of HDACs or HATs plays a pivotal role in the transcriptional regulation of genes, thereby influencing cellular function and metabolic homeostasis.⁶⁸ MODY is a monogenic chromosomal form of T2DM. Acetylation of hepatocyte nuclear factor 4 α (HNF4 α) associated

with MODY1 is regulated by CBP.⁶⁹ The expression of glucokinase (GCK) associated with MODY2 is regulated by HNF4 α and involves transcriptional complexes containing HAT activity. HNF1 α associated with MODY3 affects the hyperacetylation of nucleosomes on the promoters of the GLUT2 and pyruvate kinase L/R genes in pancreatic islets.⁷⁰ MODY4 development is linked to mutations in pancreatic and duodenal homology cassette-1/insulin promoter factor-1, which indirectly regulates insulin production and is regulated by the acetylation of histones H3 and H4.⁷¹ MODY5 development is associated with mutations in the HNF 1/transcription factor 2 gene, the activity of which may be influenced by HDAC1.⁷² MODY6 is associated with neuronal differentiation 1, and HAT regulates insulin transcription through direct acetylation of neuronal differentiation 1.⁷³

Palmitate induces acetylation of FOXO3a, leading to downregulation of ATP-induced mitochondrial DNA release and inflammatory vesicle activation in diabetic macrophages.⁷⁴ SIRT6 inhibits notch receptor 3 and notch receptor 9 transcription by deacetylating histone, thereby preventing podocyte injury and diabetic nephropathy.⁷⁵ Animal experiments have demonstrated that SIRT3 reduces diabetic neuropathic pain by deacetylating and stabilizing FOXO3a, inhibiting oxidative stress.⁷⁶ Diabetic Goto-Kakizaki rats exhibit significant cardiac hypertrophy and dysfunction, associated with the activation of FOXO3a–SIRT1.⁷⁷ SIRT1 plays a crucial role in glucose metabolism. Fasting promotes SIRT1-mediated deacetylation of LXR α to alleviate diabetic retinopathy.⁷⁸ Fasting induces gluconeogenic genes and hepatic glucose output by promoting hepatic SIRT1-mediated deacetylation of peroxisome proliferative-activated receptor, gamma, coactivator 1 alpha (PGC-1 α).⁷⁹ SIRT1 mediates the deacetylation of STAT3, and baicalein can maintain the acetylation level of STAT3 by downregulating SIRT1 activity and inhibiting downstream PGC-1 α , thus inhibiting hepatic gluconeogenesis.⁸⁰ AMPK controls energy metabolism in mouse skeletal muscle by activating SIRT1, leading to deacetylation of FOXO1 and FOXO3a.⁸¹

Glucose uptake is intricately regulated by protein acetylation mechanisms. For instance, the binding of lncRNA EPB41L4A-AS1 to HAT GCN5 enhances acetylation at histone marks histone H3 lysine 27 (H3K27) and H3K14 within the promoter region of thioredoxin interacting protein, facilitating transcriptional activation. This process is mediated by the recruitment of the transcriptional activator MLX interacting protein, which enhances the endocytosis of GLUT2/4 transporters, ultimately leading to the inhibition of glucose uptake. Conversely, EPB41L4A-AS4 modulates the nonhistone acetylation of PGC1 β in the GLUT3 promoter region through its interaction with GCN1. This interaction results in the suppression of

GLUT4 transcription and subsequent glucose uptake by muscle cells.⁸² Moreover, diabetic patients with increased protein glycation exhibit reduced aspirin-mediated protein acetylation.⁸³

The cyclin-dependent kinase 4 (CDK4) nucleotide substitution confers protection to CDK4 from inhibition by the INK family of cell cycle inhibitors, thereby ameliorating glucose intolerance in IRS2-deficient mice. Conversely, CDK4 inhibits the expression of pancreatic and duodenal homeobox 1 via the insulin signaling mediator FOXO1. This inhibition is associated with deacetylation and reduced abundance of FOXO1.⁸⁴ Additionally, lysine acetyltransferase KAT8, also known as MOF, mediates the acetylation of histone H4 at lysine 16 (H4K16ac). Dysfunction of MOF in mice leads to an imbalance in glucolipid metabolism and an increased risk of developing T2DM.⁸⁵

3.4 | Methylation in DM

Protein methylation levels play a crucial role in the development of diabetes and its associated complications. Diabetic vascular complications (DVC) encompass both macrovascular and microvascular diseases, including cardiovascular disease, diabetic nephropathy, retinopathy, and neuropathy.⁸⁶ DVC significantly diminishes quality of life, imposes substantial economic burdens on individuals and society, and stands as the leading cause of death in individuals with diabetes.⁸⁷ Gene regulation mediated by histone methylation on arginine and lysine residues is implicated in the pathogenesis of DVC. Mice exhibiting diabetic nephropathy demonstrated a consistent decrease in histone H3 lysine 27 trimethylation (H3K27m3), a silencing mark, and a concurrent increase in the level of H3 lysine 4 dimethylation, an activation mark. Moreover, there was an elevation in the abundance of H3K27m3 and the demethylase KDM6A in the kidney.⁸⁸

Histone methyltransferase SET7 is upregulated in peripheral blood mononuclear cells from patients with T2DM, where it mediates the monomethylation of H3K4 at the nuclear factor kappa-B (NF- κ B) p65 promoter. This epigenetic alteration is associated with the upregulation of NF- κ B, transcription of oxidative/inflammatory genes, and elevated plasma levels of intercellular adhesion molecule-1 and monocyte chemoattractant protein-1.⁸⁹ In diabetic patients, SET domain bifurcated histone lysine methyltransferase 2 is impaired, resulting in decreased trimethylation levels of histone 3 and increased NF- κ B-mediated inflammation. SET domain bifurcated histone lysine methyltransferase 2 deficiency also impacts macrophage plasticity and wound healing.⁹⁰ Additionally, hepatic levels of H3K4 monomethylation and H3K9 dimethylation were found to be elevated in dia-

betic mice, which were mitigated by treatment with exonuclease-4.⁹¹

3.5 | SUMOylation in DM

Protein SUMOylation influences glucose tolerance and is associated with diabetic heart disease and diabetic neuropathy. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) maintains metabolic homeostasis through glycolysis and undergoes increased activity through SUMOylation. The key metabolic enzyme is SUMOylated, and activated activity of GAPDH at lysine 332.⁹² The activity of GAPDH is reduced by treatment with SUMO specific peptidase 1, a SUMO-specific isopeptidase. Mice lacking SUMOylation exhibit exacerbated neuropathology and sensory loss in diabetic neuropathy.⁹²

X-box binding protein 1 (XBP1) is a crucial transcription factor for maintaining ER homeostasis, activated in response to disruptions in ER protein folding. Diabetic mice develop significant myocardial structural abnormalities, cardiac hypertrophy, and impaired cardiac function. Impaired nuclear translocation of XBP1 is observed in the hearts of diabetic mice. However, phosphorylation of XBP1 at S348 and SUMOylation of XBP1 at K276 promote its nuclear translocation, ameliorating the progression of diabetic cardiomyopathy.⁹³ UBC9, as a SUMOylated E2-coupled enzyme, knockout downregulates SUMOylation levels in pancreatic β -cells, impairing glucose tolerance and leading to progressive destruction of β -cells, ultimately resulting in fasting hyperglycemia and diabetes. Conversely, UBC9 overexpression upregulates sumoylation levels, preventing β -cell loss while inhibiting β -cell function, leading to glucose intolerance.⁹⁴

3.6 | Glycosylation in DM

Protein glycosylation plays a critical role in regulating insulin secretion and is intricately linked to diabetes and its various complications.

Abnormal N-glycosylation of proteins, such as GLUT2 in pancreatic β -cells, contributes to impaired insulin secretion and the development of T2DM. Furthermore, defects in N-glycosylation of T-cells are strongly correlated with the onset of T1DM.⁹⁵

The involvement of protein glycosylation extends to various diabetic complications. Proteins undergo nonenzymatic modification by glucose, resulting in the formation of advanced glycosylation end products (AGEs), which are implicated in tissue damage. AGE proteins bind to their high-affinity receptors, triggering degradation and clearance processes, along with the synthesis and secretion

of potent cytokines. Accumulation of tissue AGEs contributes significantly to diabetic vasculopathy, highlighting the potential of AGE inhibitors like aminoguanidine hydrochloride as a therapeutic target for DM.⁹⁶ Plasma protein N-glycosylation patterns are associated with complications of T2DM. Recent meta-analyses have revealed that elevated levels of certain glycans, such as bifurcation on dibasic glycans and increased 2,6-glycosylation on ternary glycans, are strongly linked to the prevalence of CVD and diabetic nephropathy, respectively.⁹⁷ Moreover, protein glycosylation is intricately involved in the pharmacodynamic mechanisms underlying the treatment of diabetes. Medications such as metformin and statins have been shown to modulate protein glycosylation, leading to decreased fucosylation and increased galactosylation and sialylation.⁹⁸

3.7 | The lysine modifications in DM

3.7.1 | Succinylation in DM

Succinylation plays a pivotal role in the pathogenesis of DM. In T2DM, pancreatic β -cells, retinal cells, and kidneys are subjected to glucotoxicity, leading to elevated levels of succinylation. This elevation exacerbates oxidative stress, resulting in the inactivation of key enzymes and chaperones within cells, thereby promoting apoptosis and contributing to diabetic tissue damage.⁹⁹

3.7.2 | Crotonylation in DM

Glucose uptake and insulin function are tightly regulated by protein crotonylation. EPB41L4A-AS1 modulates histone H27K4 crotonylation in the GLUT3 promoter region, thereby epigenetically controlling the transcription of GLUT14 and thioredoxin interacting protein. Overexpression of EPB41L4A-AS1 leads to a reduction in glucose uptake, while its knockdown enhances glucose uptake levels.⁸² Additionally, GFP-W, a novel heteropolysaccharide derived from *Ashwagandha*, has shown potential as a hypoglycemic agent, with its antidiabetic activity associated with alterations in protein lysine crotonylation levels. GFP-W enhances insulin sensitivity through regulation of protein lysine crotonylation.¹⁰⁰ Diabetic kidney disease, a significant complication of diabetes, is a major contributor to chronic kidney disease.¹⁰¹ Histone crotonylation contributes to increased renal SIRT3 and PGC-1 α expression, while decreasing C-C motif chemokine ligand 2 expression to safeguard the kidney from acute injury.³⁹

3.7.3 | Malonylation in DM

In the context of DM, dysregulated levels of protein malonylation have been observed. Liver-specific lysine malonylation emerges as the predominant acylation pattern in animal models of T2DM, such as db/db and ob/ob mice. Proteomic analysis reveals an enrichment of malonylated proteins in metabolic pathways, particularly those governing glucose and fatty acid metabolism.¹⁰² Protein malonylation appears to modulate enzyme activity in glucose metabolism, thus implicating its involvement in the pathogenesis of T2DM.¹⁰³ Investigation into histone PTM sites in a pre-diabetic mouse model unveils seven loci of malonylated proteins. However, the regulatory mechanisms governing gene expression at these sites remain elusive and warrant further investigation.¹⁰⁴

3.8 | The cysteine modifications in DM

3.8.1 | Palmitoylation in DM

In the context of DM, palmitoylation levels of key proteins such as GLUT4 and mucin 2 are significantly implicated. Impaired palmitoylation of GLUT4 adversely affects insulin-stimulated glucose uptake in muscle and adipose tissue, representing a critical feature of insulin resistance.¹⁰⁵ Among the palmitoyltransferases, DHHC7 emerges as a pivotal mediator of GLUT4 palmitoylation. DHHC7 deficiency hampers insulin-dependent GLUT4 membrane translocation by modulating the palmitoylation status of GLUT4.¹⁰⁶ Moreover, fatty acid synthase (FAS), an insulin-responsive enzyme crucial for *de novo* lipogenesis, undergoes induction by insulin. However, in diabetic states, FAS levels are diminished while intestinal permeability is heightened. Functionally, FAS aids in maintaining the intestinal mucus barrier integrity by facilitating S-palmitoylation of mucin 2 at its N-terminus.¹⁰⁷

3.8.2 | S-sulphydration in DM

S-sulphydration of SIRT1 and Kelch-like ECH-associated protein 1 (KEAP1) plays a significant role in diabetic complications, particularly in the context of diabetic nephropathy, a critical complication of DM. SIRT1, when sulphydrated by Na₂S₄, exerts a protective effect against diabetic nephropathy by impeding the phosphorylation and acetylation of p65 and STAT3.¹⁰⁸ Similarly, H₂S sulphydrates KEAP1 at Cys151, leading to the activation of nuclear factor erythroid 2-related factor 2 (NRF2) signaling. This

activation helps to alleviate oxidative stress and mitigate diabetes-related atherosclerosis.¹⁰⁹

3.9 | Drugs targeting PTM in DM

3.9.1 | SGLT-2 inhibitor

Phosphorylation of Kelch like family member 3 at serine 433 was detected in the kidneys of db/db mice. Treatment with a sodium-glucose cotransporter-2 (SGLT-2) inhibitor reduced protein kinase C activity and decreased the phosphorylation level of Kelch like family member 3 at serine 433, thereby improving T2DM.^{110,111} Additionally, the SGLT-2 inhibitor empagliflozin was found to enhance inflammation resolution and alleviate diabetic microvascular injury by modulating AMPK-mediated phosphorylation of dynamin related protein 1.^{112,113}

3.9.2 | GLP-1 agonist

The glucagon-like peptide-1 receptor (GLP1R) agonist exenatide effectively regulates blood glucose levels in patients with T2DM by enhancing glucose-dependent insulin secretion.¹¹⁴ Animal experiments have demonstrated that exendin-4 promotes the phosphorylation of hepatic AMPK and acetyl-CoA carboxylase in diet-induced obesity mice.¹¹⁵ Clinical studies have corroborated the efficacy of GLP1R agonist treatment in reducing appetite and body weight in patients with T2DM.^{115,116} Furthermore, a randomized placebo-controlled crossover study revealed that liraglutide administration increased AMPK phosphorylation and mitigated peripheral insulin resistance.¹¹⁷ A meta-analysis showed that GLP1R agonist treatment significantly reduced renal composite outcomes by reducing urinary albumin excretion.¹¹⁸

3.9.3 | GCK agonist

GCK plays a pivotal role in β -cell glycolysis, facilitating the phosphorylation of glucose to glucose 6-phosphate. It serves as a critical rate-limiting enzyme, regulating insulin secretion. GCK agonists exert their effects by promoting insulin secretion and enhancing hepatic glucose uptake.

Dorzagliatin, a dual-acting GCK activator, represents a significant milestone as the first NDA filing for the treatment of DM. A phase 2 clinical study of Dorzagliatin as a monotherapy for Chinese patients with T2DM showcased beneficial outcomes in terms of glycemic control, safety, and tolerability.¹¹⁹ Subsequent phase 3 clinical trials fur-

ther underscored the favorable efficacy and safety profile of Dorzagliatin,¹²⁰ either as an initial treatment for T2DM or as an add-on therapy to metformin.¹²¹

3.9.4 | SIRT1 activator

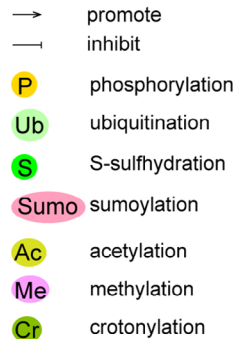
The SIRT1 activator SRT3025 has demonstrated efficacy in attenuating cell proliferation, reducing plasma glucagon concentration, and improving glycemic control in diabetic mice.¹²² Additionally, SRT3025 has been shown to enhance glycemic control, beta-cell mass, and plasma insulin concentration in obese type 2 diabetic mice.¹²³ In a double-blind randomized controlled trial involving 71 patients with T2DM, resveratrol was found to significantly increase the levels of p53 and p21 while decreasing the serum cluster of differentiation 163 to TNF-like weak apoptosis inducer ratio.¹²⁴ Moreover, resveratrol has been shown to promote the phosphorylation level of AMPK, thereby enhancing its activity.¹²⁵ Furthermore, SRT1720 has been demonstrated to improve renal function and mitigate renal pathologies including glomerular hypertrophy, thylakoid dilatation, glomerulosclerosis, and interstitial fibrosis in diabetic mice through modulation of the SIRT1/HIF1 α /GLUT1 pathway.¹²⁶ Additionally, SRT1720 ameliorates diet-induced insulin resistance, possibly through direct deacetylation of PGC-1 α , FOXO1, and p53.¹²⁷

3.9.5 | HDAC inhibitor

The HDAC inhibitor NaB has been shown to promote pluripotent human embryonic stem cells to generate insulin-producing islet-like cell clusters.¹²⁸ Furthermore, NaB exhibits the ability to attenuate the hyperglycemia-induced inflammatory response by downregulating the acetylation level of NF- κ B p65 in human monocytes.¹²⁹ Valproic acid has been identified to enhance pancreatic endoderm formation and induce the differentiation of adipose-derived stem cells into insulin-secreting cells. HC toxin, another HDAC inhibitor, has demonstrated efficacy in enhancing β -cell function in primary mouse and human pancreatic islets. This effect is mediated by regulating the accumulation of IRS-1 and promoting AKT serine/threonine kinase (AKT) phosphorylation.¹³⁰

3.9.6 | Others

O-GlcNAc modification on AKT affects AKT phosphorylation, leading to impaired activation and thus glucose metabolism.¹³¹ Animal experiments showed that



the transferase inhibitor ST0458490-GlcNAc reduced gluconeogenesis.¹³²

SREBP1 orchestrates the expression of lipogenic genes, contributing to the development of obesity. CREB-regulated transcriptional coactivator 2 interacts with the COPII complex, competitively disrupting COPII-dependent SREBP1 transport, thereby modulating lipid

metabolism.¹³³ Mammalian target of rapamycin (mTOR), a serine/threonine protein kinase of the PIKK family, regulates the phosphorylation of CREB-regulated transcriptional coactivator 2, subsequently downregulating the expression of lipogenic genes.¹³⁴ Phosphorylation of mTOR further contributes to lipid metabolism disorders by modulating SREBP1.¹³⁵ Activated AKT in hepatocellular carcinoma cells promotes the phosphorylation of cytosolic phosphoenolpyruvate carboxykinase 1, which translocates to ER and phosphorylates insulin induced gene 1 and insulin induced gene 2. This cascade of phosphorylation events activates SREBP1 or SREBP2, leading to the transcription of downstream adipogenesis-related genes.

SIRT1, a NAD-dependent deacetylase, undergoes phosphorylation at Ser-164 catalyzed by casein kinase 2, inhibiting its nuclear localization in obese mice.¹³⁶ Decreased SIRT1 activity impairs fatty acid oxidation and exacerbates hepatic steatosis.¹³⁶ Conversely, phosphorylation of SIRT1 at Ser-46 by c-Jun N-terminal kinase 1 activates SIRT1 function, ameliorating hepatic steatosis in obesity.¹³⁷ Glucose deficiency promotes AMPK-induced phosphorylation of GAPDH, activating SIRT1 and initiating autophagy.¹³⁸ SIRT1 overexpression in the striatum and hippocampus promotes fat accumulation and upregulates lipogenic gene expression in white adipose tissue (WAT).¹³⁹ Additionally, nuclear factor 1 A improves glucose homeostasis, enhances energy expenditure for adaptive thermogenesis, and mitigates obesity by promoting mitochondrial oxidative phosphorylation and inhibiting inflammation.¹⁴⁰

Treatment with canagliflozin for 8 weeks has been shown to promote AMPK phosphorylation and induce mitochondrial remodeling in WAT in mice.¹⁴¹ Specifically, phosphorylation of AMPK β 1 at Ser108 has been linked to the promotion of fatty acid oxidation and mitochondrial biogenesis.¹⁴² Furthermore, tschimganidine has been found to increase AMPK phosphorylation, thereby reducing adipogenesis.¹⁴³

4.2 | Ubiquitination in obesity

The functions of ubiquitination and ubiquitination-related enzymes within the AKT signaling pathway exert significant influence on lipid metabolism. Ubiquitination of K63 stands out as a pivotal aspect of AKT activation in insulin signaling. G protein pathway suppressor 2 plays a crucial role in preventing AKT ubiquitination by inhibiting the activity of the ubiquitin-conjugating enzyme Ubc13. Consequently, deficiency of G protein pathway suppressor 2 in adipose tissue in mice leads to constitutive ubiquitination and subsequent AKT activation, resulting in disrupted lipid metabolism, increased obesity, and elevated levels of

lipocalin.¹⁴⁴ Upon induction by insulin, AKT undergoes ubiquitination and activation in the presence of adaptor protein phosphotyrosine interacting with PH domain and leucine zipper 1. Knockdown of ubiquitination factor E4A inhibits this ubiquitination process in mice.¹⁴⁵ Enhanced expression of the ubiquitin editing enzyme A20 has been shown to suppress adipogenesis and the expression of key markers associated with adipogenesis, concomitant with attenuated activation of p38 and AKT signaling.¹⁴⁶ AKT3 facilitates lysine-free protein kinase-1 specific phosphorylation and its subsequent degradation via the ubiquitin-proteasome pathway, thereby alleviating high-fat diet (HFD)-induced obesity in mice.¹⁴⁷

Deletion of the ubiquitin E3 ligase CUL2-APPBP2 enhances protein stability of PR/SET domain 2, counteracting diet-induced obesity and ameliorating insulin resistance and dyslipidemia.¹⁴⁸ Furthermore, the deubiquitinase ubiquitin-specific protease 1 promotes lipid accumulation by deubiquitinating and upregulating the level of CCAAT/enhancer-binding protein β , thus inducing adipogenesis.¹⁴⁹

4.3 | Acetylation in obesity

Lysine deacetylases, such as HDACs, play pivotal roles in fat differentiation and production. The acetylation levels of PPAR also exert profound effects on lipid metabolism and homeostasis. Various isoforms of HDACs exhibit distinct effects on lipid metabolism. HDAC1 or HDAC2 positively regulate lipid production, as evidenced by reduced lipid levels in mice deficient in these HDAC isoforms. Conversely, SIRT1, SIRT2, and HDAC9 negatively regulate lipid content. SIRT1 promotes lipid mobilization, with its overexpression leading to reduced adipogenesis. In contrast, alterations in SIRT2 expression either inhibit or promote adipogenesis. Knockdown of HDAC9 is a crucial factor in adipocyte differentiation and adipogenesis, accelerating the process in mice.¹⁵⁰

SIRT1 enhances thermogenesis and energy expenditure by promoting WAT expression akin to brown adipose tissue (BAT) through deacetylation of PPAR γ .¹⁵¹ Elevated levels of histone acetylation have been observed in obese children, potentially linked to the downregulation of SIRT1 levels in vivo.¹⁵² Mice with SIRT1 adipocyte-specific knock-out display increased adipogenesis.¹⁵³ Additionally, SIRT1 mediates the deacetylation of SIRT3 to mitigate obesity.¹⁵⁴

Obesity is strongly correlated with disrupted circadian rhythms. Obese mice exhibit altered circadian rhythms of PPAR γ acetylation, thereby impacting metabolic rhythms.¹⁵⁵ Mechanistically, impaired PPAR γ downregulates solute carrier family 1 member 5 level, leading to reduced glutamine and methionine uptake by adipocytes,

as well as decreased levels of H3K27ac and H3K4me3 on the promoter of basic helix-loop-helix ARNT like 1.¹⁵⁶ Mice harboring a PPAR γ acetylation mutation display a white phenotype in BAT.¹⁵⁷ Acetylation of PR structural domain-containing protein 16 by acetyl-CoA derived from branched keto acids inhibits WAT browning. Disrupting the interaction between PR structural domain-containing protein 16 and PPAR γ helps maintain WAT properties.¹⁵⁸

4.4 | Methylation in obesity

Protein methylation levels play a crucial role in the development of obesity. Findings from a Mendelian randomization study involving 1021 participants suggest a causal association between the methylation of Janus kinase 2 (JAK2) and obesity.¹⁵⁹ Histone-lysine N-methyltransferase 2D is indispensable for adipogenesis, acting as the primary H3K4 single and double methyltransferase on enhancers related to lipogenesis and myogenesis. Histone-lysine N-methyltransferase 2D facilitates the activation of cell-type-specific enhancers during both lipogenesis and myogenesis processes.¹⁶⁰ Nicotinamide N-methyltransferase plays a significant role in histone methylation, polyamine fluxes, and the regulation of SIRT1 through the modulation of NAD and S-adenosylmethionine levels in adipose tissue. Knockdown of nicotinamide N-methyltransferase effectively prevents diet-induced obesity.¹⁶¹ Additionally, nutrient restriction triggers AMPK-dependent phosphorylation of FOXO3a, resulting in increased dimethylation of histone H3 Arg17 due to transcriptional inhibition of S-phase kinase-associated protein 2, which upregulates the level of arginine methyltransferase 1.¹⁶²

4.5 | SUMOylation in obesity

Protein SUMOylation plays a crucial role in regulating lipid production and storage. UBC9, a key enzyme in the SUMOylation pathway, exhibits significant upregulation in visceral adipocytes of both obese patients and mice. Mice with UBC9 knockout display a remarkable reduction in weight gain, and adipocyte-specific UBC9 deficiency protects against high-fat diet-induced obesity, insulin resistance, hepatic steatosis, and inflammation. Mechanistically, UBC9 mediates the SUMOylation of ER protein 44 at K76, thereby enhancing its stability and protecting it from ubiquitin-mediated degradation. This process exacerbates adipocyte ER stress and insulin resistance.¹⁶³

Adipocyte-specific knockout of SENP2 confers resistance to diet-induced obesity. Inhibition of homeobox C10 is crucial for adipocyte differentiation in the inguinal WAT of SENP2-knockout mice. CCAAT/enhancer-binding

protein β regulates homeobox C10 expression in a SUMOylation-dependent manner.¹⁶⁴ Furthermore, SENP2 regulates adipose lipid storage by de-SUMOylating SET domain bifurcated histone lysine methyltransferase 1.¹⁶⁵

4.6 | Glycosylation in obesity

AGE-specific receptor (AGER) activity plays a pivotal role in the development of obesity. Autophagy is intricately linked with normal intracellular lipid metabolism, where HMGB1 enhances autophagy by binding to the AGER, thus mitigating cell death.¹⁶⁶ In HFD-induced obese mice, adipocytes display elevated expression of AGER. Conversely, adipose tissue in AGER-deficient mice demonstrates a mitigated phenotype, characterized by reduced adipocyte hypertrophy, diminished macrophage infiltration, and improved insulin sensitivity.¹⁶⁷ Notably, oligofructose, utilized in the management of diet-induced obesity, elicits an increase in the expression of genes associated with mucus production, glycosylation, and secretion.¹⁶⁸

4.7 | The lysine modifications in obesity

4.7.1 | Succinylation in obesity

Succinylation levels of proteins in BAT influence lipid metabolism. BAT is crucial for regulating energy expenditure, thermogenesis, and glucose homeostasis, with its abundance negatively correlated with body mass index, suggesting a potential role in metabolism.¹⁶⁹ SIRT5 modulates succinylation and malonylation of mitochondrial proteins in BAT, and its knockout in BAT leads to metabolic inflexibility and disrupts mitochondrial homeostasis.¹⁷⁰ Recent studies have revealed that allicin activates BAT and enhances energy expenditure. Allicin significantly increases the succinylation level of uncoupling protein 1 (UCP1) in BAT by inhibiting SIRT5.¹⁷¹

4.7.2 | Crotonylation in obesity

Crotonylation also plays a pivotal role in obesity, particularly in the browning of WAT and its impact on fat thermogenesis. WAT, responsible for energy storage, can be induced to undergo browning, a process that enhances energy expenditure and heat production while reducing fat accumulation. Elevated levels of crotonylation have been found to inhibit the expression of glycerol-3-phosphate dehydrogenase 1 and fatty acid binding protein 4, thereby suppressing lipolysis and browning of white adipocytes.

Conversely, increased crotonylation promotes the expression of adenylate kinase 2, triosephosphate isomerase 1, and NADH:ubiquinone oxidoreductase subunit A8, which enhances lipolysis and browning of white adipocytes. Modulating the function of target proteins through control of their crotonylation levels presents a promising strategy for obesity treatment.¹⁷² Furthermore, HDAC1 has been shown to inhibit adipocyte-mediated thermogenesis by upregulating the crotonylation level of PGC1 α /UCP1 in inguinal WAT.¹⁷³

4.7.3 | Malonylation in obesity

In the context of obesity, malonylation is linked to the AMPK–acetyl-CoA carboxylase (ACC) signaling pathway and SIRT5. AMPK phosphorylates ACC1 at Ser79 and ACC2 at Ser212, thereby inhibiting the conversion of acetyl coenzyme A to malonyl coenzyme A.¹⁷⁴ Malonyl coenzyme A serves as a precursor for fatty acid synthesis and as a malonyl donor in lysine malonylation.¹⁰⁴ Reduced malonyl coenzyme A levels may impede protein malonylation and attenuate fatty acid synthesis, thereby influencing obesity development. Recent studies have shown that SIRT5 deficiency leads to elevated levels of protein malonylation, reduced glycolysis, and diminished basal mitochondrial respiration in primary chondrocytes.¹⁷⁵

4.8 | The cysteine modifications

4.8.1 | Palmitoylation in obesity

CD36 molecule (CD36) facilitates fatty acid uptake via a mechanism involving dynamic palmitoylation-regulated endocytosis. Upon binding of fatty acids to CD36, its downstream kinase LYN is activated. Adenine phosphoribosyltransferase APT1 depalmitoylates CD36, subsequently recruiting another tyrosine kinase, SYK, which promotes the phosphorylation of c-Jun N-terminal kinase, thus initiating fatty acid endocytosis. Inhibition of CD36 endocytosis by targeting either LYN or SYK effectively hinders CD36-dependent lipid droplet growth in adipocytes and attenuates HFD-induced weight gain in mice.¹⁷⁶

4.8.2 | S-sulfhydration in obesity

S-sulfhydration related to H₂S is intricately linked with lipid accumulation and catabolism. Acting as a novel adipokine, H₂S plays a pivotal role in modulating various metabolic processes including glucose uptake, lipid storage, and mobilization, thereby contributing to the

development of obesity. Notably, H₂S induces sulfhydration of perilipin 1, a protein intimately involved in lipid droplet dynamics. This sulfhydration event results in reduced phosphorylation of perilipin 1, consequently impeding isoprenaline-stimulated lipolysis.¹⁷⁷

4.9 | Drugs targeting PTM in obesity

4.9.1 | β 3 Agonist

Mirabegron, a beta3 agonist, has gained approval for treating overactive bladder syndrome. In a recent clinical study, mirabegron was found to induce the expression of beige adipose markers, along with phosphorylation of hormone-sensitive lipase at serine 660. This effect was observed in obese, insulin-resistant subjects, leading to the production of beige adipose tissue in the subcutaneous WAT of humans.¹⁷⁸

4.9.2 | GLP-1

Semaglutide, a GLP-1 agonist, presents a promising option for weight loss therapy in obese patients. In a randomized, double-blind trial involving 1961 overweight or obese adults with a body mass index ≥ 30 and without diabetes, significant weight reduction was observed in the Semaglutide group compared with the placebo group, with mean weight changes of -15.3 kg (-14.9%) and -2.6 kg (-2.4%), respectively. Notably, nausea and diarrhea were the predominant adverse effects reported.¹⁷⁹ Furthermore, Semaglutide has been shown to reverse the reduction in serine phosphorylation of calcium voltage-gated channel subunit α 1A, calcium voltage-gated channel subunit α 1B, and calcium voltage-gated channel subunit α 1D proteins induced by HFD in obese mice.¹⁸⁰ In a 68-week phase 3b clinical trial, weekly subcutaneous injections of semaglutide demonstrated significantly greater weight loss compared with once-daily subcutaneous injections of liraglutide, when combined with dietary and physical activity guidance.¹⁸¹

4.9.3 | SIRT1 agonist

SRT3025 administration has been found to elevate hepatic p65 and skeletal muscle Foxo1 deacetylation levels, consequently leading to reductions in plasma LDL cholesterol and total cholesterol (TC) levels, ultimately preventing atherosclerosis in high cholesterol diet-fed ApoE(–/–) mice.¹⁸² In a randomized, double-blind crossover study involving 11 healthy obese men, resveratrol was shown

to ameliorate metabolic parameters in obese individuals. Resveratrol's mechanisms involve the activation of citrate synthase through upregulation of SIRT1 and PGC-1 α protein levels in muscle, along with modulation of intracellular lipid levels and inflammatory markers.¹⁸³ Moreover, resveratrol demonstrates efficacy in alleviating diet-induced obesity in mice by inhibiting PGC-1 α acetylation and subsequently enhancing its activity.¹⁸⁴

4.9.4 | HAT inhibitor

Salt inducible kinase 2 functions by directly phosphorylating p300 at Ser89, leading to inhibition of its HAT activity. Consequently, downregulation of salt inducible kinase 2 expression promotes enhanced lipogenesis and contributes to the development of hepatic steatosis.¹⁸⁵

4.9.5 | Others

I κ B kinase promotes phosphorylation of CYLD lysine 63 deubiquitinase to promote ubiquitination of NRF2 and exacerbates oxidative stress injury in obesity-associated nephropathy, and in vitro experiments have demonstrated that inhibitors of I κ B kinase reduce lipid deposition and reactive oxygen species production, among others.¹⁸⁶

5 | PROTEIN PTMS IN HYPERLIPIDEMIA

With economic development and changes in dietary habits, hyperlipidemia, characterized by high blood lipid levels, is increasingly affecting human health and can lead to a series of more serious diseases such as atherosclerosis and coronary heart disease.¹⁸⁷ It has been shown that PTMs mediate the onset of hyperlipidemia and related disorders in a variety of ways (Figure 3).

5.1 | Phosphorylation in hyperlipidemia

Phosphorylation of LXR α and the AMPK pathway are key players in hyperlipidemia. LXR α , a central transcriptional regulator of inflammatory and metabolic genes, exhibits differential effects based on the phosphorylation status of serine 196 (S196). Phosphorylation at S196 promotes an inflammatory response, whereas unphosphorylated LXR α inhibits inflammation. Mice with phosphorylation-deficient LXR α show reduced levels of LDL cholesterol (LDL-C) and increased levels of high-density lipoprotein cholesterol, resulting in a decreased

risk of atherosclerosis.¹⁸⁸ Additionally, phosphorylation of LXR α at S196 has been implicated in promoting atherosclerosis by regulating the macrophage transcriptome.¹⁸⁹ The physical activity of LXR α induces the biosynthesis of prosolubilized lipid mediators and enhances mitochondrial metabolism through AMPK phosphorylation, thereby offering protection against cardiovascular disease.¹⁹⁰ AMPK plays a crucial role in phosphorylating SREBP-1c at Ser372, inhibiting its activity and consequently attenuating atherosclerosis.¹⁹¹ Polo-like kinase 1 stimulates AMPK phosphorylation, thus alleviating atherosclerosis.¹⁹² Furthermore, peptide H3 has been shown to reduce cholesterol levels in hepatocyte cells by upregulating the phosphorylation of 3-hydroxy-3-methylglutaryl-coenzyme A reductase and inhibiting its activity through the AMPK pathway.¹⁹³

5.2 | Ubiquitination in hyperlipidemia

IDOL, also referred to as myosin-regulated light chain-interacting protein, possesses the RING structural domain and plays a crucial role in regulating lipid metabolism, thus impacting the development of hyperlipidemia. Acting as an E3-ubiquitin ligase, IDOL facilitates the direct transfer of ubiquitin from E2 to target proteins. Particularly, IDOL targets the LDL receptor (LDLR) for ubiquitination and subsequent degradation. Mice with IDOL knockout exhibit reduced serum cholesterol levels, decreased body weight, diminished adipose tissue mass, and mitigated liver lipid accumulation.¹⁹⁴ The regulation of cholesterol uptake via the LDLR pathway is orchestrated by LXR, which transcriptionally induces IDOL expression to prompt ubiquitination of the cytoplasmic structural domain of LDLR.¹⁹⁵ Mice expressing IDOL variants with inhibited degradation mechanisms, such as IDOL-antidegraded or dominantly active forms, demonstrate elevated plasma LDL-C levels and heightened atherosclerotic lesion formation.¹⁹⁶ Notably, the G51S variant of IDOL disrupts IDOL self-ubiquitination and enzymatic degradation, leading to stabilized IDOL protein, enhanced LDLR degradation, and increased levels of LDL-C.¹⁹⁷

5.3 | Acetylation in hyperlipidemia

Lipid metabolism is intricately linked to the acetylation of dynamin-related protein and cyclic AMP-responsive element-binding protein 3-like 3, hepatocyte specific (CREBH). Moreover, the Sirtuin family of deacetylases plays a crucial role in regulating lipid levels.

Excessive lipid accumulation has been associated with increased acetylation of dynamin-related protein, leading

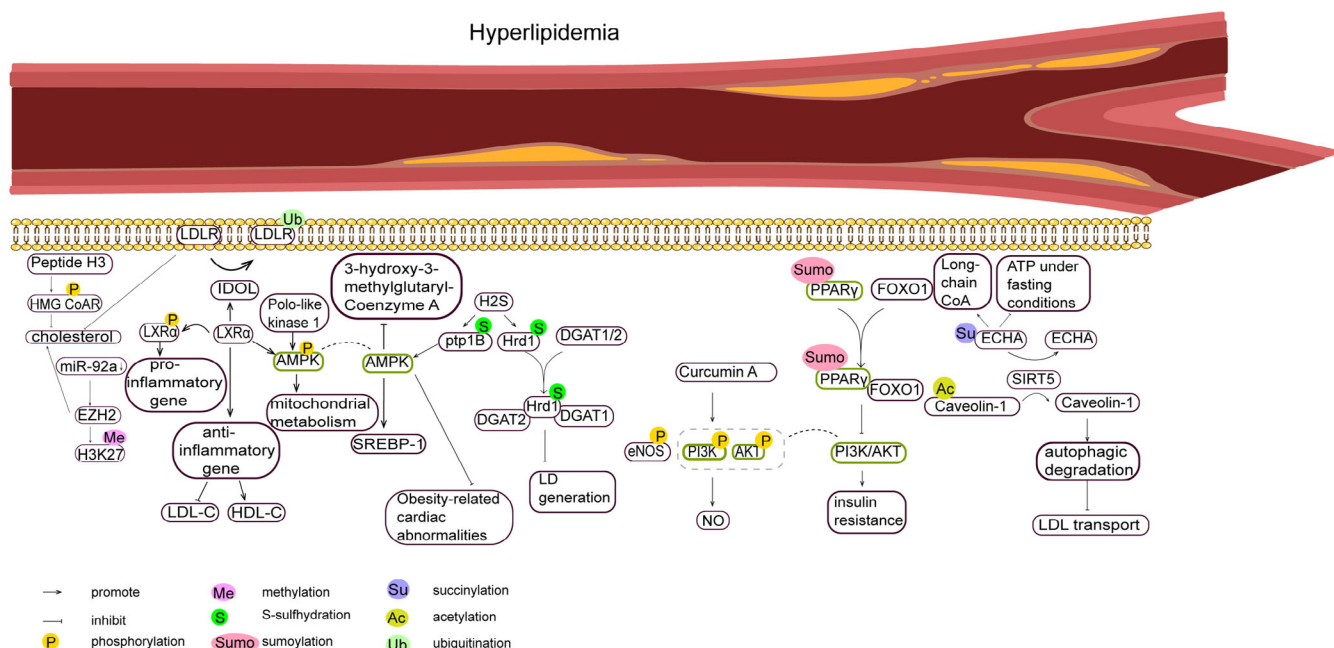


FIGURE 3 PTMs in hyperlipidemia. Stimulated by internal and external factors, multiple protein posttranslational modifications influence the course of hyperlipidemia. (A) The level of phosphorylation of AMP-activated protein kinase (AMPK) is regulated by recombinant liver X receptor alpha (LXR α), poly-like kinase1, and so on, which affects mitochondrial metabolism, and obesity-related cardiovascular abnormalities. (B) SUMOylation modification of peroxisome proliferator-activated receptor γ (PPAR γ) affects the activity of the phosphatidylinositol 3-kinase (PI3K)/AKT serine/threonine kinase (AKT) pathway, which in turn leads to insulin resistance, and the level of phosphorylation of PI3K/AKT itself affects the production of NO. (C) Sirtuin 5 (SIRT5) mediates deacetylation of Caveolin-1 and desuccinylation of hydroxyacyl-CoA dehydrogenase trifunctional multienzyme complex subunit alpha (ECHA), thereby affecting lipid transport and fatty acid oxidation.

to its activation and subsequent mitochondrial translocation, thereby exacerbating cardiomyocyte dysfunction.¹⁹⁸ Acetylation of CREBH at lysine 294 enhances its transcriptional activity and is vital for maintaining hepatic lipid homeostasis during fasting. Mutation of lysine 294 in CREBH results in hepatic steatosis and hyperlipidemia in animals subjected to prolonged fasting.¹⁹⁹

SIRT5 facilitates the deacetylation of Caveolin-1, a membrane-intrinsic protein, promoting its autophagic degradation. This process inhibits LDL transport in the presence of Caveolin-1, thus delaying the progression of atherosclerosis.²⁰⁰ Additionally, SIRT6-mediated deacetylation of histone H3 by FOXO3 promotes a repressive chromatin state, contributing to the regulation of hypercholesterolemia in mice.²⁰¹

5.4 | Methylation in hyperlipidemia

Histone methylation levels play a pivotal role in the pathogenesis of atherosclerosis. Primarily involving H3K9 and H3K27, alterations in histone methylation are significant in atherosclerotic lesions. Studies have indicated reduced levels of H3K9me2 and H3K27me2 in these lesions, with no observable changes in H3K4me2. However, there is

an upregulation in the expression of the histone methyltransferases MLL2 and G9a. Additionally, decreased levels of H3K9me2 in smooth muscle cells and inflammatory cells, as well as reduced dimethylated H3K27 in inflammatory cells, have been observed.²⁰² These findings suggest a potential association between histone methylation and the development of atherosclerosis.

Hyperhomocysteinemia (HHcy) stands as an independent risk factor for cardiovascular diseases, including atherosclerosis. MiR-92a has been identified as a regulator of EZH2 expression in HHcy-induced atherosclerosis. Overexpression of EZH2 promotes the level of H3K27me3 and leads to the accumulation of triglycerides (TG) and TC. Therefore, targeting miR-92a may hold promise as a novel therapeutic approach for managing HHcy-associated atherosclerosis.²⁰³

5.5 | Glycosylation in hyperlipidemia

The status of glycosylation is intricately associated with lipid metabolism. Congenital dysglycosylation perturbs both protein and lipid glycosylation processes, along with abnormalities in glycogenes. Transmembrane protein 199 regulates serum levels of LDL-C, TC, and non-high-density

lipoprotein cholesterol, thereby influencing the development of hypercholesterolemia. Altered glycosylation status may impact lipoprotein metabolism by enhancing protein degradation and affinity for proatherogenic lipoproteins, reducing secretion, modifying lipid profiles, and influencing correct localization.²⁰⁴ Furthermore, the glycosylation profiles of immunoglobulin G were cross-sectionally correlated with the risk of cardiovascular disease and subclinical atherosclerosis, with immunoglobulin G glycoprotein GP18 exhibiting a highly negative correlation with very LDL.²⁰⁵

5.6 | The lysine modifications in hyperlipidemia

5.6.1 | Succinylation in hyperlipidemia

Succinylation also participates in hyperlipidemia. It regulates cardiac function through SIRT5 and impedes fatty acid oxidation by downregulating the activity of hydroxyacyl-CoA dehydrogenase trifunctional multi-enzyme complex subunit alpha (ECHA), a key protein involved in this process. Hearts from mice lacking SIRT5 exhibit reduced ECHA activity, elevated levels of long-chain acyl-CoA, and decreased ATP levels under fasting conditions. Therefore, targeting SIRT5 holds promise for mitigating cellular damage induced by ischemia and reperfusion injury.²⁰⁶

5.6.2 | Crotonylation in hyperlipidemia

Adenosine extract of *Ganoderma lucidum* (AEGL) exhibits lipid-lowering and antiatherogenic properties. In HFD-induced hyperlipidemic mice, AEGL intervention significantly alters the acetylation and crotonylation of proteins involved in fatty acid metabolism. Specifically, the levels of crotonylation of acyl-CoA oxidase 1 and acyl-CoA synthetase long-chain family member 5 are upregulated, while the levels of crotonylation of fatty acid binding protein 2, acyl-CoA synthetase long-chain family member 1, and acyl-CoA synthetase medium-chain family member 3 are downregulated following AEGL treatment. These proteins play crucial regulatory roles in peroxisomal oxidation and fatty acid β -oxidation pathways.²⁰⁷

5.6.3 | Lactylation in hyperlipidemia

In the context of hyperlipidemia, lactylation plays a significant role. Upon M1 activation, the substantial production of lactate resulting from aerobic glycolysis initiates the endogenous “lactate clock.” Lactylation is linked to

genomic alterations in macrophages, driving metabolic reprogramming and promoting the transition of M1-type macrophages to M2-type macrophages. This transition induces the expression of genes involved in tissue repair.²⁰⁸ Additionally, exercise training has been found to enhance lactylation of methyl-CpG binding protein 2, thereby inhibiting atherosclerosis. Further investigations have revealed that lactylation of methyl-CpG binding protein 2 suppresses the expression of extra-epitope regulatory proteins by binding to chromatin.²⁰⁹

5.6.4 | Malonylation in hyperlipidemia

Malonylation is implicated in hyperlipidemia, where short-chain fatty acids such as propionate, malonate, butyrate, 2-hydroxyisobutyrate, β -hydroxybutyrate, crotonate, succinate, and glutarate, along with their corresponding acylations (propionylation, malonylation, butyration, 2-hydroxyisobutyrylation, β -hydroxybutyrylation, crotonylation, succinylation, and glutarylation), play pivotal roles in CVD.²¹⁰

Studies have revealed that knockdown of FAS and elevated levels of malonyl coenzyme A induce malonylation of mTOR at lysine 1218 (K1218). This malonylation of mTOR K1218 detrimentally affects mTORC1 activity.²¹¹ Presently, research on the relationship between malonylation and hyperlipidemia predominantly focuses on malonylation-associated enzymes, with limited exploration into the specific regulatory mechanisms underlying malonylation. Further in-depth investigation in this area holds promise for the development of targeted therapies for hyperlipidemia.

5.7 | The cysteine modifications in hyperlipidemia

5.7.1 | Palmitoylation in hyperlipidemia

CD36 levels are elevated in atherosclerosis.²¹² DHHC4 and DHHC5 play distinct roles in different subcellular compartments, regulating the palmitoylation, plasma membrane localization, and fatty acid uptake activity of the scavenger receptor CD36. Mice lacking DHHC4 or DHHC5 exhibit reduced fatty acid uptake activity in adipose tissue.²¹³

5.7.2 | S-sulfhydration in hyperlipidemia

S-sulfhydration emerges as a critical player in the context of hyperlipidemia. Within endothelial cells, the catabolism of cysteine and cystathionine leads to the generation of

H₂S and its associated sulfur compounds (H₂Sn) through a process termed the trans-sulfuration pathway. This pathway assumes particular significance in the vascular system, where cystathionine gamma cleavage enzyme plays a pivotal role in the production of vascular H₂S/H₂Sn. Notably, GYY4137, a novel slow-release H₂S compound, exerts inhibitory effects on ox-LDL-induced lipid accumulation. Furthermore, it mitigates vascular inflammation and oxidative stress, enhances endothelial function, and attenuates the formation of atherosclerotic plaques.²¹⁴ The downregulation of protein tyrosine phosphatase protein tyrosine phosphatase nonreceptor type 1 prevents obesity-related cardiac abnormalities by activating AMPK.²¹⁵ Conversely, the inhibition of H₂S activity, achieved through the induction of protein tyrosine phosphatase nonreceptor type 1 sulfation at Cys 215, serves as a protective mechanism for the cardiovascular system.²¹⁶ Additionally, the S-sulfation of HMG-CoA reductase degradation protein 1 (HRD1) mediated by NaHS enhances the interaction of HRD1 with diacylglycerol O-acyltransferase 1/2, thereby impeding the formation of lipid droplets.²¹⁷

5.8 | Drugs targeting PTM in hyperlipidemia

5.8.1 | Statin

Rosuvastatin, a selective inhibitor of HMG-CoA reductase, has shown promising outcomes in clinical trials. In a study involving 543 Chinese patients with subclinical atherosclerosis, rosuvastatin significantly attenuated the progression of carotid intima-media thickness over a span of 2 years, with favorable tolerability.²¹⁸ Moreover, a multicenter, clinically randomized trial conducted in South Korea, which included 1,894 patients, demonstrated that a combination therapy comprising moderate-intensity rosuvastatin and ezetimibe led to a higher proportion of patients achieving LDL concentrations below 70 mg/dL.²¹⁹ Additionally, rosuvastatin was found to enhance SIRT1 expression and modulate protein acetylation levels, with 12 proteins showing upregulation and 6 proteins exhibiting downregulation out of 100 proteins with detectable acetylation signals.²²⁰

6 | PROTEIN PTMs IN NAFLD

NAFLD, as one of the most common liver diseases in the world, affects about one-third of the global population, and its prevalence is increasing year by year, which is seriously threatening the world's public health security. Epigenetic modification of histone proteins has

been confirmed in many studies as an important mechanism affecting the development of NAFLD, among others (Figure 4).²²¹

6.1 | Phosphorylation in NAFLD

Protein phosphorylation plays a pivotal role in regulating NAFLD. Elevated levels of serine/threonine kinase 17b lead to reduced phosphorylation of serine/arginine-rich splicing factor 6 thereby influencing the alternative splicing of genes related to mitochondrial function and exacerbating lipid accumulation. Pharmacological intervention targeting serine/threonine kinase 17b has shown promising results in ameliorating hepatic steatosis and nonalcoholic steatohepatitis (NASH).²²² Nicotine exposure has been implicated in the progression of NAFLD to NASH by promoting the phosphorylation of sphingomyelin phosphodiesterase 3 via AMPK α in the ileum, thereby increasing intestinal ceramide formation.²²³ Leptin deficiency in pigs enhances fatty acid β -oxidation by downregulating JAK2-STAT3 and AMPK phosphorylation, which triggers mitochondrial autophagy and oxidative stress in hepatocytes, contributing to the development of NASH.²²⁴ AMPK-mediated phosphorylation of caspase-6 has been associated with liver damage in NASH, with phosphorylation inhibiting caspase-6 activity.²²⁵ Additionally, β -aminoisobutyric acid has been shown to exert anti-inflammatory and anti-insulin resistance effects by inducing AMPK phosphorylation.²²⁶

Inhibition of ACC hinders the metabolic shifts essential for inducing glycolysis and oxidative phosphorylation during hepatic stellate cell activation.²²⁷ Mutations in the phosphorylation sites of ACC1 and ACC2 promote hepatic de novo lipogenesis and liver lesions in mice.²²⁸ The bioactive peptide leucine-glutamine-proline attenuates the severity of NASH in mice by upregulating AMPK and ACC.²²⁹

Zinc supplementation and strength exercise have been shown to increase the phosphorylation level of AKT at Ser473, thereby improving insulin signaling and mitigating NAFLD in rats with T2DM.²³⁰ Hepatocyte-derived exosome miR-192-5p induces the activation of macrophage M1-type polarization by inhibiting mammalian rapamycin target protein Rictor, downregulating the phosphorylation levels of AKT and FOXO1 and activating FOXO1.²³¹ The long noncoding RNA LncARSR promotes lipid accumulation by activating the IRS-2/AKT pathway through inhibiting the phosphorylation level of Yes1 associated transcriptional regulator, whereas silencing LncARSR alleviates NAFLD in mice.²³² Oxyberberine, a gut microbiota-mediated oxidative metabolite of berberine, inhibits the

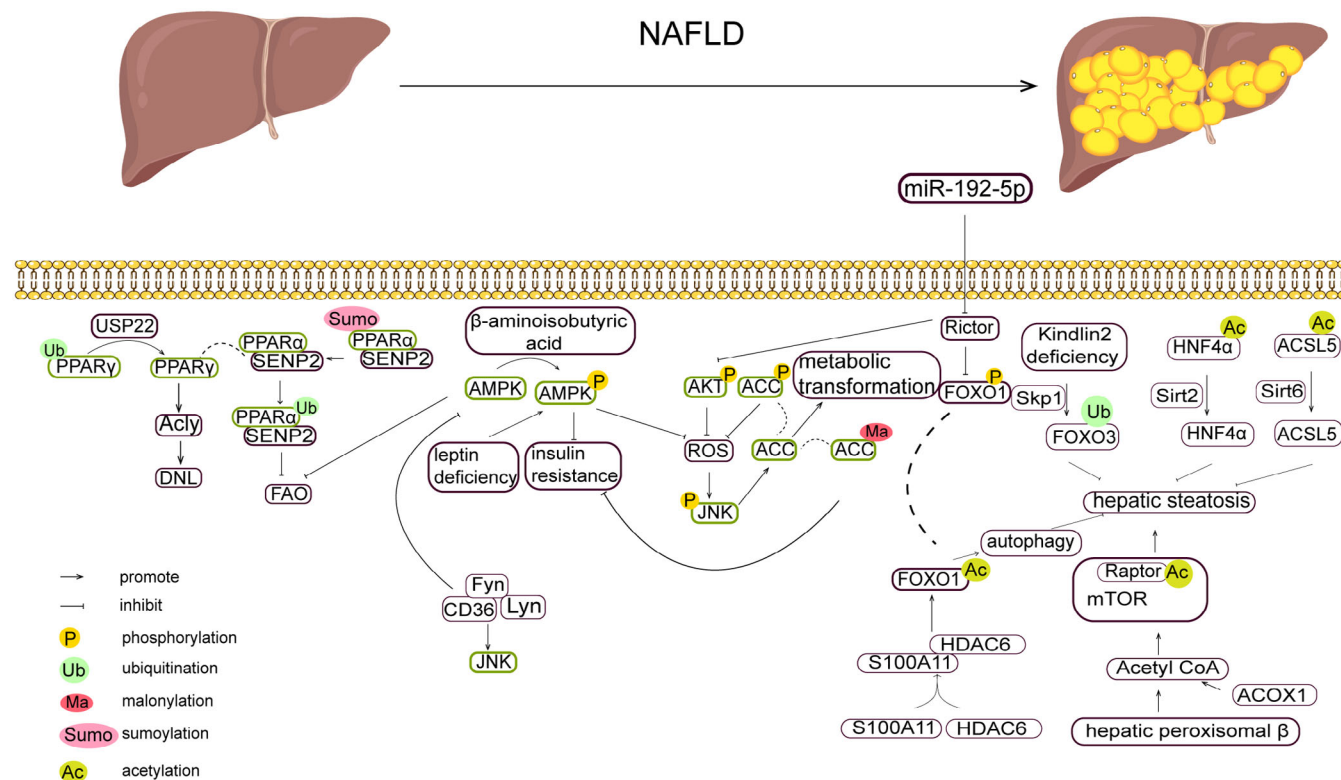


FIGURE 4 PTMs in NAFLD. Nonalcoholic fatty liver disease (NAFLD) is characterized by excessive hepatic lipid deposition, including simple fatty liver, nonalcoholic steatohepatitis (NASH) and its associated cirrhosis, and a variety of protein modifications are involved in the NAFLD disease process. (A) Peroxisome proliferator-activated receptor (PPAR) is involved in the process of NAFLD, and ubiquitin specific peptidase 22 (USP22)-mediated deubiquitination of PPAR γ promotes de novo lipogenesis (DNL), and de SUMOylation inhibited fatty acid oxidation. (B) The phosphorylation level of AMP-activated protein kinase (AMPK) was regulated by leptin, β -aminoisobutyric acid, and so on, which affected insulin resistance and reactive oxygen species (ROS) production. (C) Liver steatosis levels are regulated by ubiquitination of Forkhead box O3 (FOXO3), acetylation of Forkhead box O1 (FOXO1), hepatocyte nuclear factor 4 α (HNF4 α), acyl-CoA synthetase long-chain family member 5 (ACSL5), and Raptor.

aberrant phosphorylation of IRS-1 and promotes phosphorylation levels of its downstream, thereby improving insulin signaling to alleviate NAFLD.²³³

6.2 | Ubiquitination in NAFLD

Hepatic steatosis is intricately associated with the ubiquitination of ATP citrate lyase (ACLY), lipid droplet-encapsulated protein, and Kindlin-2-related proteins.

ACLY undergoes ubiquitination and subsequent degradation mediated by HRD1, thereby inhibiting its lipogenic effects. Overexpression of ACLY in db/db mice led to a reduction in the severity of NAFLD and diminished steatosis in isolated liver progenitor cells.²³⁴ Ubiquitin-specific protease 22 stabilizes PPAR γ by deubiquitination in hepatocellular carcinoma, consequently upregulating ACLY expression and promoting de novo lipogenesis.²³⁵

The essential dietary amino acids leucine and isoamino acid bind strongly to the ubiquitin protein ligase E3 com-

ponent recognin 1, facilitating the ubiquitination of lipid droplet-encapsulated protein perilipin 2 and counteracting hepatic steatosis. These findings were corroborated in studies involving *Drosophila melanogaster* cells and hepatocyte-like cells.²³⁶ Additionally, during adipocyte differentiation, perilipin 2 is degraded via the ubiquitin-proteasome pathway.²³⁷

Kindlin-2 indirectly impacts NAFLD by modulating the ubiquitination of associated proteins. Kindlin-2 deficiency inhibits hepatic steatosis by promoting Skp1-dependent ubiquitination and proteasomal degradation of the transcription factor FOXO2. Mice with hepatocyte-specific Kindlin-2 deficiency exhibited enhanced weight gain, reduced abnormal accumulation of hepatic lipid droplets, lower serum levels of TG, TC, and LDL, and markedly improved hepatic function.²³⁸ Furthermore, Kindlin-2 deficiency facilitates the ubiquitination and degradation of the antioxidant glutathione S-transferase P1 in hepatocytes, leading to oxidative stress and inflammatory factors in hepatocytes.²³⁹

6.3 | Acetylation in NAFLD

Protein acetylation plays a significant role in the pathogenesis of NAFLD by influencing hepatic fatty acid oxidation, lipogenesis, and lactate accumulation.

NAFLD is characterized by the excessive accumulation of lipids in the liver, a process regulated by various genes. Cytoplasmic SIRT6 exerts its effect by deacetylating acyl-CoA synthetase long-chain family member 5, thereby promoting fatty acid oxidation and reducing lipid accumulation.²⁴⁰ SIRT2 also plays a role in NAFLD by deacetylating HNF4 α , delaying the onset of hepatic steatosis.²⁴¹ Additionally, a high-fat diet has been shown to upregulate the expression of S100 calcium-binding protein A11, which, in turn, promotes adipogenesis and lipid accumulation by enhancing the acetylation of the transcription factor FOXO1 and activating autophagy and adipogenic processes.²⁴² The pathological damage resulting from excessive lipid uptake, known as lipotoxicity, is a crucial step in the progression from simple steatosis to NASH.²⁴³ Studies in rodents, pigs, and rhesus monkeys have demonstrated that arachidonate 12-lipoxygenase inhibits the lysosomal degradation of ACC1, a pivotal enzyme involved in the conversion of acetyl coenzyme A to malonyl coenzyme A. Reduced arachidonate 12-lipoxygenase activity leads to decreased ACC1 expression and lower levels of malonyl coenzyme A, resulting in the accumulation of acetyl coenzyme A.²⁴⁴

Lactate accumulation stands out as a notable feature in the progression of NAFLD. The clearance of lactate, a crucial process, is mediated by lactate dehydrogenase B (LDHB) and plays a significant role in influencing NAFLD advancement. Studies have revealed that the lysine residue at position 82 of LDHB is acetylated by P300/CBP-associated factor, resulting in LDHB inactivation. This acetylation event significantly impairs hepatic lactate clearance, leading to lactate accumulation and exacerbating the progression of NAFLD.²⁴⁵

Moreover, hyperuricemia has been implicated in promoting hepatic fat accumulation and the upregulation of lipogenic genes, thereby contributing to NAFLD development. It has been demonstrated that hyperuricemia activates c-Jun N-terminal kinase, consequently increasing the expression of lipogenic enzymes such as FAS and acetyl-CoA carboxylase 1, both in vivo and in vitro.²⁴⁶ Additionally, a study suggests that acetyl-CoA generated from the oxidation of hepatic peroxisomal β inhibits autophagy and promotes hepatic steatosis through the activation of mTORC1. The enzyme acyl-CoA oxidase 1, which is involved in hepatic lipid metabolism, regulates the cellular membrane acetyl-CoA content. This, in turn, mediates the acetylation of Raptor, a component of mTORC1, and its lysosomal localization, ultimately leading to the activation

of mTORC1, a key regulator of autophagy.²⁴⁷ Furthermore, the E3 ligase SH3 structural domain-containing ring finger 2 has been identified as an inhibitor of cell membrane acetyl-CoA production. It promotes ubiquitin-dependent degradation, resulting in reduced synthesis and deposition of de novo lipids and cholesterol.²⁴⁸

6.4 | Methylation in NAFLD

Protein methylation levels intricately regulate liver tissue regeneration and hepatic metabolism. Histone methylation plays a pivotal role in promoting the regeneration of damaged liver tissue. Research by Wang et al.²⁴⁹ suggests that a decrease in DNA methylation triggers the redistribution of repressive histone methylation, such as H3K27me3, thereby enhancing the regeneration process in liver tissues. The knockout of brain-specific oxidation resistance 1a stimulates the accumulation of H3K2me2, which in turn modulates the production of growth hormone in the pituitary gland. Growth hormone is known to exert significant effects on hepatic metabolism and the development of fatty liver. Male mice lacking oxidation resistance 1a display a propensity for developing fatty liver, a condition further corroborated by the concurrent reduction in intrahepatic growth hormone levels.²⁵⁰ Moreover, HFD is associated with increased expression of retinoic acid-inducible gene-I, which promotes cholesterol synthesis and steatosis, thereby inducing NASH. The demethylase Jumonji domain containing 4 counters this process by demethylating retinoic acid-inducible gene-I, leading to its reduced expression and consequently inhibiting the progression of NASH.²⁵¹

6.5 | SUMOylation in NAFLD

SUMOylation levels within the farnesoid X receptor (FXR), and PPAR α pathways exhibit distinct effects on the progression of NAFLD. SUMO specific peptidase 1 catalyzes the de-SUMOylation of receptor-interacting protein kinase 1. This action inhibits receptor-interacting protein kinase 1-driven cell death and inflammatory activation, thereby delaying the development of NAFLD.²⁵² Additionally, mice lacking SENP2 demonstrate resistance to hepatic steatosis and obesity induced by a high-fat diet. SENP2 interacts with PPAR α , promoting its de-SUMOylation, ubiquitination, and subsequent degradation. Consequently, this inhibits fibroblast growth factor 21 expression and fatty acid oxidation.²⁵³

Furthermore, FXR agonists have exhibited therapeutic potential in the treatment of NASH and liver fibrosis. However, recent research has revealed that activation of hepatic

stellate cells can upregulate FXR SUMOylation, thereby inhibiting FXR signaling. This attenuation diminishes the efficacy of FXR agonists. Consequently, the combination of SUMOylation inhibitors with FXR agonists has emerged as a promising strategy against hepatic fibrosis.²⁵⁴

6.6 | Glycosylation in NAFLD

The glycosylation levels of proteins undergo significant alterations in NAFLD. Specifically, in NAFLD, binding bead protein and transferrin glycosylation sites become hyperglycosylated, whereas these glycosylation sites are differentially occupied under physiological conditions. Serum protein hyperglycosylation is anticipated to serve as a biomarker for the early stages of NAFLD.²⁵⁵ Furthermore, loss of glycosylation of key uptake and efflux transporter proteins upon progression to NASH affects the function of transporter proteins.²⁵⁶ NASH is associated with increased expression of mannose, complex/fucoidan glycosylated, and heterogeneous N-glycan structures, and the spatial distribution of free N-glycan abundance correlates with NASH severity.²⁵⁷

CREBH undergoes covalent modification by N-acetylglucosamine, and deglycosylation of CREBH inhibits its hydrolysis. The addition of unglycosylated CREBH promotes lipogenesis, induces expression of lipotoxicity and inflammation, and exacerbates liver injury in mice with NAFLD. Moreover, overexpression of alpha-1,6-mannosylglycoprotein 6-beta-N-acetylglucosaminyltransferase promotes N-glycosylation of CREBH, which ameliorates liver lesions by enhancing its transcriptional activity and affecting the activities of PPAR α and stearoyl-CoA desaturase-1.²⁵⁸

6.7 | The lysine modifications in NAFLD

6.7.1 | Succinylation in NAFLD

Alterations in metabolism-related protein succinylation levels have been observed in NAFLD. A comprehensive quantitative analysis of the succinylome in rat livers with NAFLD revealed 243 succinylation sites on 178 proteins exhibiting altered succinylation levels. These succinylated proteins were primarily localized in the cytoplasm and mitochondria, and they were implicated in a diverse array of metabolic pathways and cellular processes. These pathways include carbon metabolism, amino acid metabolism, fatty acid metabolism, as well as functions related to binding, catalysis, antioxidant defense, and xenobiotic metabolism.²⁵⁹

6.7.2 | Crotonylation in NAFLD

Crotonylation also plays a significant role in NAFLD, particularly in liver fibrosis. Liver fibrosis, a critical step in the progression of NAFLD to cirrhosis, involves the replacement of healthy liver tissue with fibrotic tissue and regenerative nodules due to chronic inflammation.²⁶⁰ Spearman's correlation analysis reveals a negative correlation between the degree of lysine crotonylation and serum fibrosis indicators. Sorafenib, a multikinase inhibitor known for its antihepatic fibrosis effects, is shown to reverse the crotonylation of H2BK12 and H3K18, suggesting that lysine crotonylation mediates the antifibrotic effects of sorafenib.²⁶¹

6.7.3 | Lactylation in NAFLD

In the context of NAFLD, protein lactylation influences hepatic lipid deposition. Elevated levels of mitochondrial pyruvate carrier 1 (MPC1) positively correlate with hepatic lipid accumulation in NAFLD. However, hepatic lipid accumulation is attenuated in MPC1-knockout mice. Mechanistically, MPC1 knockout modulates lactate levels in hepatocytes, leading to the downregulation of lactylation at K673 of FAS, thereby inhibiting FAS activity and reducing hepatic lipid accumulation.²⁶²

6.7.4 | Malonylation in NAFLD

Malonylated ACC1 plays a pivotal role in regulating NAFLD progression. Treatment with ML355 effectively reduces ACC1 abundance, malonyl coenzyme A production, and protein malonylation in the livers of mice. Additionally, the metabolite IMA-1, derived from ML355, exhibits high levels and stability in plasma, serving as the active metabolite of ML355. IMA-1 treatment inhibits lipid accumulation, enhances fatty acid β -oxidation, reduces ACC1 levels, blocks protein malonylation, and suppresses hepatocyte cell death.²⁶³ Furthermore, an intermittent ketogenic diet alleviates steatosis and insulin resistance in NAFLD by downregulating hepatic lysine malonylation of ACC1.²⁶⁴

6.8 | The cysteine modifications in NAFLD

6.8.1 | Palmitoylation in NAFLD

Palmitoylation of CD36 contributes to the progression of NASH. CD36 expression increases during the transition

from normal liver to simple steatosis and further to NASH. Notably, the distribution of CD36 on the plasma membrane of hepatocytes significantly increases in NASH patients, mirroring findings from mouse experiments. Palmitoylation of CD36 facilitates its translocation to the plasma membrane of hepatocytes in NASH, enhancing the binding and uptake of long-chain fatty acids and promoting the formation of CD36/Lyn complexes. An imbalance between fatty acid uptake and oxidation, along with activation of inflammatory responses, contributes to the development of NASH.²⁶⁵ Exploring inhibitors of CD36 palmitoylation may represent a promising avenue for NASH treatment.

6.8.2 | S-sulphydration in NAFLD

S-sulphydration of unc-51 like kinase 1, FXR, and KEAP1 emerges as pivotal regulators of hepatic lipid deposition and inflammation. The transcription factor SREBP-1c plays a central role in inducing hepatic lipid accumulation by upregulating lipid synthesis and concurrently down-regulating autophagy, thus impairing lipid degradation.²⁶⁶ Notably, SREBP-1c exerts inhibitory effects on unc-51 like kinase 1 persulfation, consequently disrupting autophagic lipolytic metabolism, and promoting the development of fatty liver. This dysregulation is facilitated by alterations in H₂S levels orchestrated by SREBP-1c, which in turn down-regulates cystathionine γ -lyase expression through miR-216a, further exacerbating hepatic lipid accumulation.²⁶⁷ Furthermore, endogenous hepatic cystathionine gamma cleavage enzyme/H₂S promotes the thiolation of FXR at the Cys138/141 locus, consequently regulating lipid and glucose metabolism and exerting protective effects against inflammation, fibrosis, and NASH.²⁶⁸ Additionally, H₂S mediates the S-sulphydration of KEAP1, activating NRF2 signaling and thereby attenuating HFD-induced hepatic lipid deposition and liver injury.²⁶⁹

6.9 | Drugs targeting PTM in NAFLD

6.9.1 | FXR agonist

The FXR serves as a pivotal player in various pathogenic pathways associated with NASH, including bile acid synthesis, enterohepatic circulation, lipid and glucose metabolism, inflammation, fibrosis, intestinal barrier integrity, and intestinal microbiota regulation. Its activation by bile acids has positioned FXR as one of the most promising targets for current NASH treatments.²⁷⁰ FXR is susceptible to PTMs, including phosphorylation, SUMOylation, and acetylation, which can modulate its activity.²⁷¹ Animal experiments have shown that enhanced

SUMOylation of FXR strongly impairs FXR signaling and that SUMOylation inhibitors can enhance the efficacy of FXR agonists to delay the progression of liver fibrosis.²⁵⁴

Cilofexor (GS-9674), a small molecule nonsteroidal agonist that acetylates FXR, has emerged as a potential therapeutic agent. In a double-blind, placebo-controlled, phase 2 trial involving 140 noncirrhotic NASH patients, cilofexor demonstrated efficacy in reducing hepatic steatosis, improving liver biochemistry, and enhancing serum bile acids levels.²⁷²

6.9.2 | ACC inhibitor

Firsocostat (GS-0976), a liver-targeted ACC inhibitor, promotes ACC phosphorylation and subsequent activation. In a phase 2 clinical trial comprising 126 NASH and fibrosis patients, Firsocostat demonstrated efficacy in inhibiting de novo lipogenesis and reducing hepatic steatosis.²⁷³ Curcumin, alternatively, has been found to inhibit the O-GlcNAc signaling pathway, thereby reducing hepatic lipid accumulation and inflammation. In NAFLD mice, curcumin also enhances antioxidant responses, thus mitigating the condition.²⁷⁴ A randomized, double-blind, placebo-controlled trial involving 77 subjects corroborated these findings, showing that curcumin significantly decreased liver fat content and improved serum lipid and transaminase levels in NAFLD patients.²⁷⁵

6.9.3 | SGLT-2 inhibitor

Empagliflozin, an SGLT-2 inhibitor, triggers autophagy activation by enhancing AMPK phosphorylation. This action results in decreased mTOR levels and increased microtubule associated protein 1 light-chain 3 beta expression, effectively slowing down the progression of NAFLD.²⁷⁶

6.9.4 | AMPK agonist

Ginsenoside Rb2 demonstrates significant improvement in glucose tolerance in male db/db mice while concurrently restoring hepatic autophagy function. This restoration leads to a reduction in hepatic lipid accumulation, thereby ameliorating NAFLD by reversing the inhibition of the autophagic pathway induced by elevated levels of fatty acids and glucose.²⁷⁷ Additionally, Rb2 phosphorylates AKT, thereby enhancing insulin sensitivity in mice with diet-induced obesity.²⁷⁸ Furthermore, triptolide induces hepatic ACC1 phosphorylation by activating AMPK,

TABLE 1 PTMs and their targets in metabolic diseases.

PTM	DM-related targets of PTM	Obesity-related targets of PTM	Hyperlipidemia-related targets of PTM	NAFLD-related targets of PTM	References
Phosphorylation	AMPK, GLUT1, IRS1, AKT, IRS, endothelial nitric oxide synthase, mitsugumin 53	SIRT1, AMPK	LXR α , AMPK, HMGCoAR, AKT, eNOS	SRSF6, JAK2-STAT3, AMPK, ACC, AKT	52,222,224
Acetylation	HNF-4 α , neuronal differentiation 1, FOXO3a, thioredoxin interacting protein, PGC1 β , LXR α , FOXO1	PRDM16	DRP1, CREBH, Caveolin-1	Acyl-CoA synthetase long-chain family member 5, HNF4 α , FOXO1, LDHB, RAPTOR (a component of mTORC1)	73,82,200,247
Methylation	NF- κ B,	JAK2	–	Retinoic acid-inducible gene-I	159,251
Ubiquitination	p27	AKT	LDLR	ACLY, PLIN2	64,234,236
Palmitoylation	GLUT4, Mucin 2	CD36	CD36	FOXO2	107,176
Succinylation	–	UCP1	–	–	
Crotonylation	GLUT3	–	ACOX1, ACSL5, FABP2, ACSL1, ACSM3	–	82,207
Lactation	–	–	MECP2	FAS	209
Malonylation	–	–	mTOR	ACC1	211
Sumoylation	GAPDH, XBPIs, Tomosyn1	ERp44, C/EBP β , SETDB1	PPAR γ 1	RIPK1, FXR	163,165,252
S-sulfhydration	SIRT1, KEAP1	pLIN1	PTP1B	ULK1, FXR, KEAP1	215,266
Glycosylation	AGEs	RAGE	PMM2, ALG6, B4GALT1, CCDC115, TMEM199	Binding bead protein, transferrin, Mac-2-binding protein, CREBH, AGEs	204,258

consequently ameliorating hepatic lipogenesis, fatty acid oxidation, and fibrosis in NAFLD.^{[279](#)}

6.9.5 | HDAC inhibitor

Givinostat demonstrated efficacy in mitigating hepatic fibrosis induced by methionine–choline-deficient diet in NASH mice, accompanied by a notable suppression of inflammation-related gene expression. Additionally, Givinostat exhibited a significant reduction in lipid accumulation induced by palmitic acid, thus showcasing its potential as a promising therapeutic agent for human NASH treatment.^{[280](#)} Moreover, Givinostat exerts its antifibrotic effects and inhibits hepatic stellate cell proliferation by upregulating the acetylation level of superoxide dismutase 2.^{[281](#)}

6.9.6 | Others

Animal experiments demonstrated that the de-O-GlcNAcylase OGA inhibitor Thiamet-G alleviated APAP-induced liver injury by inhibiting GSH supplementation.^{[282](#)}

7 | DISCUSSION

Metabolism-related diseases such as diabetes, obesity, hyperlipidemia, and NAFLD present escalating challenges to human well-being. The main metabolism-related PTMs include phosphorylation, ubiquitination, acetylation, methylation, palmitoylation, succinylation, crotonylation, lactylation, malonylation, sumoylation, S-sulfhydration, glycosylation, and others, offer novel avenues and

TABLE 2 Drugs targeting PTM in metabolic diseases.

Metabolic diseases	Targets	Drugs	References
Diabetes	SGLT-2 inhibitor	Ipragliflozin	117
	GLP1R agonist	Exendin 4, liraglutide	119
	GCK agonist	Dorzagliatin	124
	SIRT1 activator	Resveratrol	128
	HDAC inhibitor	NaB, HC toxin	220
Hyperlipidemia	HHMG-CoA reductase inhibitor	Rosuvastatin	178
Obesity	β 3-adrenergic receptor agonist	Mirabegron	179
	GLP-1	Semaglutide	182
	SIRT1 agonist	SRT3025, resveratrol	185
	HAT inhibitor	SIK2	272
NAFLD	FXR agonist	Cilofexor	273
	ACC inhibitor	Firsocostat, curcumin	276
	SGLT-2 inhibitor	Empagliflozin	277
	AMPK agonist	Ginsenoside Rb2, triptolide	280
	HDAC inhibitor	Givinostat	

strategies for addressing the prevention and treatment of these conditions. AMPK, PPAR and their upstream and downstream proteins are inhibited or activated through PTM, which in turn affects lipid metabolism and mediates the development of hyperlipidemia. PTM can mediate NAFLD development by affecting oxidative stress, lactate accumulation, autophagy, insulin resistance, and inflammation, and the major signaling pathways affected include PPAR, AMPK, AKT, and JAK2–STAT3. In obesity, PTM affects cellular autophagy, leukolipid browning, lipogenesis and metabolism mediated by signaling pathways such as AMPK, PPAR, and AKT (Table 1).

PTM plays a pivotal role in the pathogenesis of metabolism-related diseases and offers innovative avenues for clinical intervention. Developing agonists or inhibitors targeting PTM has emerged as a prominent focus in drug development for these conditions (Table 2).

Despite substantial advancements in understanding the relationship between PTMs of proteins and metabolic diseases, several deficiencies and limitations persist. The diversity and complexity of PTMs, as well as the mechanisms by which they influence metabolic diseases, remain incompletely elucidated. Furthermore, the translation of preclinical findings to clinical applications is inefficient, the development of targeted interventional drugs is lagging, and research into novel PTMs is still in its infancy and requires urgent, in-depth exploration.

To advance PTM-based treatments for metabolism-related diseases, several avenues warrant exploration: First, establishing a comprehensive data management platform to integrate existing research findings on PTM

and metabolism-related diseases is imperative. This unified platform will facilitate comprehensive analysis and interpretation of available data. Second, further research is essential to elucidate the mechanistic relationship between PTM and metabolism-related diseases. Leveraging animal studies and clinical trials, we can delve deeper into understanding the underlying mechanisms. This approach will enable the identification of potential PTM targets for the prevention and treatment of metabolic diseases.

AUTHOR CONTRIBUTIONS

Design, and supervision; revising of original draft: Yanqi Dang. *Design, and supervision; manuscript editing and revision:* Guang Ji. *Writing of original draft:* Yunuo Yang. *Manuscript editing and revision:* Jiaxuan Wu and Wenjun Zhou. The final manuscript has been reviewed and approved by all the authors.

ACKNOWLEDGMENTS

This work is funded by The Shanghai Rising-Star Program (21QA1409000), the Shanghai Frontier Research Base of Disease and Syndrome Biology of Inflammatory Cancer Transformation (2021KJ03-12), and Natural Science Foundation of Shanghai (21Y11902300).

CONFLICT OF INTEREST STATEMENT

All the authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Not applicable.

ETHICS STATEMENT

Not applicable.

ORCID

Yanqi Dang  <https://orcid.org/0000-0002-0316-7880>

REFERENCES

1. Cani PD. Microbiota and metabolites in metabolic diseases. *Nat Rev Endocrinol.* 2019;15(2):69-70.
2. Garus-Pakowska A. Metabolic diseases—a challenge for public health in the 21st century. *Int J Environ Res Public Health.* 2023;20(18):6789.
3. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. *Diabetes Res Clin Pract.* 2019;157:107843.
4. Einarsson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. *Cardiovasc Diabetol.* 2018;17(1):83.
5. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol.* 2018;14(2):88-98.
6. Ghaus S, Ahsan T, Sohail E, Erum U, Aijaz W. Burden of elevated body mass index and its association with non-communicable diseases in patients presenting to an endocrinology clinic. *Cureus.* 2021;13(2):e13471.
7. Ahmed B, Konje JC. The epidemiology of obesity in reproduction. *Best Pract Res Clin Obstet Gynaecol.* 2023;89:102342.
8. Armoon B, Karimy M. Epidemiology of childhood overweight, obesity and their related factors in a sample of preschool children from Central Iran. *BMC Pediatr.* 2019;19(1):159.
9. Jebeile H, Kelly AS, O'Malley G, Baur LA. Obesity in children and adolescents: epidemiology, causes, assessment, and management. *Lancet Diabetes Endocrinol.* 2022;10(5):351-365.
10. Vital signs: prevalence, treatment, and control of high levels of low-density lipoprotein cholesterol—United States, 1999–2002 and 2005–200. *MMWR Morb Mortal Wkly Rep.* 2011;60(4):109-114.
11. Godoy-Matos AF, Silva Junior WS, Valerio CM. NAFLD as a continuum: from obesity to metabolic syndrome and diabetes. *Diabetol Metab Syndr.* 2020;12:60.
12. Wong VW, Ekstedt M, Wong GL, Hagstrom H. Changing epidemiology, global trends and implications for outcomes of NAFLD. *J Hepatol.* 2023;79(3):842-852.
13. Younossi ZM. Non-alcoholic fatty liver disease - A global public health perspective. *J Hepatol.* 2019;70(3):531-544.
14. Rojas YAO, Cuellar CLV, Barron KMA, Arab JP, Miranda AL. Non-alcoholic fatty liver disease prevalence in Latin America: A systematic review and meta-analysis. *Ann Hepatol.* 2022;27(6):100706.
15. Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol.* 2018;15(1):11-20.
16. Targher G, Corey KE, Byrne CD, Roden M. The complex link between NAFLD and type 2 diabetes mellitus—mechanisms and treatments. *Nat Rev Gastroenterol Hepatol.* 2021;18(9):599-612.
17. Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. *J Hepatol.* 2019;71(4):793-801.
18. Quek J, Chan KE, Wong ZY, et al. Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol.* 2023;8(1):20-30.
19. Piché ME, Tchernof A, Després JP. Obesity phenotypes, diabetes, and cardiovascular diseases. *Circ Res.* 2020;126(11):1477-1500.
20. Ling C, Rönn T. Epigenetics in human obesity and type 2 diabetes. *Cell Metab.* 2019;29(5):1028-1044.
21. Yang YH, Wen R, Yang N, Zhang TN, Liu CF. Roles of protein post-translational modifications in glucose and lipid metabolism: mechanisms and perspectives. *Mol Med.* 2023;29(1):93.
22. Millan-Zambrano G, Burton A, Bannister AJ, Schneider R. Histone post-translational modifications—cause and consequence of genome function. *Nat Rev Genet.* 2022;23(9):563-580.
23. Fan J, Krautkramer KA, Feldman JL, Denu JM. Metabolic regulation of histone post-translational modifications. *ACS Chem Biol.* 2015;10(1):95-108.
24. Chader GJ, Fletcher RT, O'Brien PJ, Krishna G. Differential phosphorylation by GTP and ATP in isolated rod outer segments of the retina. *Biochemistry.* 1976;15(8):1615-1620.
25. Jin J, Pawson T. Modular evolution of phosphorylation-based signalling systems. *Philos Trans R Soc Lond B Biol Sci.* 2012;367(1602):2540-2555.
26. Komander D, Rape M. The ubiquitin code. *Annu Rev Biochem.* 2012;81:203-229.
27. Kliza K, Husnjak K. Resolving the complexity of ubiquitin networks. *Front Mol Biosci.* 2020;7:21.
28. Narita T, Weinert BT, Choudhary C. Functions and mechanisms of non-histone protein acetylation. *Nat Rev Mol Cell Biol.* 2019;20(3):156-174.
29. Dai X, Ren T, Zhang Y, Nan N. Methylation multiplicity and its clinical values in cancer. *Expert Rev Mol Med.* 2021;23:e2.
30. Biggar KK, Li SS-C. Non-histone protein methylation as a regulator of cellular signalling and function. *Nat Rev Mol Cell Biol.* 2015;16(1):5-17.
31. Sheng Z, Zhu J, Deng YN, Gao S, Liang S. SUMOylation modification-mediated cell death. *Open Biol.* 2021;11(7):210050.
32. Chang HM, Yeh ETH. SUMO: from bench to bedside. *Physiol Rev.* 2020;100(4):1599-1619.
33. Sahin U, de Thé H, Lallemand-Breitenbach V. Sumoylation in Physiology, Pathology and Therapy. *Cells.* 2022;11(5):814.
34. Eichler J. Protein glycosylation. *Curr Biol.* 2019;29(7):R229-R231.
35. Zhang Z, Tan M, Xie Z, Dai L, Chen Y, Zhao Y. Identification of lysine succinylation as a new post-translational modification. *Nat Chem Biol.* 2011;7(1):58-63.
36. Yang Y, Gibson GE. Succinylation links metabolism to protein functions. *Neurochem Res.* 2019;44(10):2346-2359.
37. Tan M, Luo H, Lee S, et al. Identification of 67 histone marks and histone lysine crotonylation as a new type of histone modification. *Cell.* 2011;146(6):1016-1028.
38. Yu H, Bu C, Liu Y, et al. Global crotonylome reveals CDYL-regulated RPA1 crotonylation in homologous recombination-mediated DNA repair. *Sci Adv.* 2020;6(11):eaay4697.

39. Ruiz-Andres O, Sanchez-Niño MD, Cannata-Ortiz P, et al. Histone lysine crotonylation during acute kidney injury in mice. *Dis Model Mech*. 2016;9(6):633-645.
40. Sabari BR, Tang Z, Huang H, et al. Intracellular crotonyl-CoA stimulates transcription through p300-catalyzed histone crotonylation. *Mol Cell*. 2015;58(2):203-215.
41. Fang Y, Xu X, Ding J, et al. Histone crotonylation promotes mesoendodermal commitment of human embryonic stem cells. *Cell Stem Cell*. 2021;28(4):748-763. e7.
42. Jiang G, Li C, Lu M, Lu KA-O, Li HA-O. Protein lysine crotonylation: past, present, perspective. *Cell Death Dis*. 2021;12(7):703.
43. Peng C, Lu Z, Xie Z, et al. The first identification of lysine malonylation substrates and its regulatory enzyme. *Mol Cell Proteomics*. 2011;10(12):M111.012658.
44. Qu M, Zhou X, Wang X, Li H. Lipid-induced S-palmitoylation as a vital regulator of cell signaling and disease development. *Int J Biol Sci*. 2021;17(15):4223-4237.
45. Paul BD, Snyder SH. H2S: a novel gasotransmitter that signals by sulfhydration. *Trends Biochem Sci*. 2015;40(11):687-700.
46. Sharma C, Hamza A, Boyle E, Donu D, Cen Y. Post-translational modifications and diabetes. *Biomolecules*. 2024;14(3):310.
47. Fu Z, Gilbert ER, Liu D. Regulation of insulin synthesis and secretion and pancreatic beta-cell dysfunction in diabetes. *Curr Diabetes Rev*. 2013;9(1):25-53.
48. Rorsman P, Ashcroft FM. Pancreatic beta-cell electrical activity and insulin secretion: of mice and men. *Physiol Rev*. 2018;98(1):117-214.
49. DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. *Med Clin North Am*. 2004;88(4):787-835. ix.
50. Yang Q, Vijayakumar A, Kahn BB. Metabolites as regulators of insulin sensitivity and metabolism. *Nat Rev Mol Cell Biol*. 2018;19(10):654-672.
51. Copps KD, White MF. Regulation of insulin sensitivity by serine/threonine phosphorylation of insulin receptor substrate proteins IRS1 and IRS2. *Diabetologia*. 2012;55(10):2565-2582.
52. Siragusa M, Oliveira Justo AF, Malacarne PF, et al. VE-PTP inhibition elicits eNOS phosphorylation to blunt endothelial dysfunction and hypertension in diabetes. *Cardiovasc Res*. 2021;117(6):1546-1556.
53. Lv F, Wang Y, Shan D, et al. Blocking MG53(S255) phosphorylation protects diabetic heart from ischemic injury. *Circ Res*. 2022;131(12):962-976.
54. Entezari M, Hashemi D, Taheriazam A, et al. AMPK signaling in diabetes mellitus, insulin resistance and diabetic complications: A pre-clinical and clinical investigation. *Biomed Pharmacother*. 2022;146:112563.
55. Vlacheski F, Baron D, Vlachogiannis IA, MacPherson REK, Tsiani E. Carnosol increases skeletal muscle cell glucose uptake via AMPK-dependent GLUT4 glucose transporter translocation. *Int J Mol Sci*. 2018;19(5):1321.
56. Li S, Huang Q, Zhang L, et al. Effect of CAPE-pNO(2) against type 2 diabetes mellitus via the AMPK/GLUT4/GSK3beta/PPARalpha pathway in HFD/STZ-induced diabetic mice. *Eur J Pharmacol*. 2019;853:1-10.
57. Jeong HY, Kang JM, Jun HH, et al. Chloroquine and amodiaquine enhance AMPK phosphorylation and improve mitochondrial fragmentation in diabetic tubulopathy. *Sci Rep*. 2018;8(1):8774.
58. Jiang P, Ren L, Zhi L, et al. Negative regulation of AMPK signaling by high glucose via E3 ubiquitin ligase MG53. *Mol Cell*. 2021;81(3):629-637. e5.
59. Dugan LL, You YH, Ali SS, et al. AMPK dysregulation promotes diabetes-related reduction of superoxide and mitochondrial function. *J Clin Invest*. 2013;123(11):4888-4899.
60. Dai X, Jiang C, Jiang Q, et al. AMPK-dependent phosphorylation of the GATOR2 component WDR24 suppresses glucose-mediated mTORC1 activation. *Nat Metab*. 2023;5(2):265-276.
61. Popovic D, Vucic D, Dikic I. Ubiquitination in disease pathogenesis and treatment. *Nat Med*. 2014;20(11):1242-1253.
62. Liu Z, Wang P, Zhao Y, Po Lai K, Li R. Biomedical importance of the ubiquitin-proteasome system in diabetes and metabolic transdifferentiation of pancreatic duct epithelial cells into β -cells. *Gene*. 2023;858:147191.
63. Shruthi K, Reddy SS, Reddy GB. Ubiquitin-proteasome system and ER stress in the retina of diabetic rats. *Arch Biochem Biophys*. 2017;627:10-20.
64. Uruno A, Yagishita Y, Yamamoto M. The Keap1-Nrf2 system and diabetes mellitus. *Arch Biochem Biophys*. 2015;566:76-84.
65. Costes S, Huang CJ, Gurlo T, et al. β -cell dysfunctional ERAD/ubiquitin/proteasome system in type 2 diabetes mediated by islet amyloid polypeptide-induced UCH-L1 deficiency. *Diabetes*. 2011;60(1):227-238.
66. Xie SY, Liu SQ, Zhang T, et al. USP28 serves as a key suppressor of mitochondrial morphofunctional defects and cardiac dysfunction in the diabetic heart. *Circulation*. 2023;149(9):684-706.
67. Marfella R, D'Amico M, Esposito K, et al. The ubiquitin-proteasome system and inflammatory activity in diabetic atherosclerotic plaques: effects of rosiglitazone treatment. *Diabetes*. 2006;55(3):622-632.
68. Gray SG, De Meyts P. Role of histone and transcription factor acetylation in diabetes pathogenesis. *Diabetes Metab Res Rev*. 2005;21(5):416-433.
69. Soutoglou E, Ktrakili N, Talianidis I. Acetylation regulates transcription factor activity at multiple levels. *Mol Cell*. 2000;5(4):745-751.
70. Párrizas M, Maestro MA, Boj SF, et al. Hepatic nuclear factor 1- α directs nucleosomal hyperacetylation to its tissue-specific transcriptional targets. *Mol Cell Biol*. 2001;21(9):3234-3243.
71. Gerrish K, Van Velkinburgh Jc Fau - Stein R, Stein R. Conserved transcriptional regulatory domains of the pdx-1 gene. *Mol Endocrinol*. 2004;18(3):533-548.
72. Barbacci E, Chalkiadaki A, Masdeu C, et al. HNF1beta/TCF2 mutations impair transactivation potential through altered co-regulator recruitment. *Hum Mol Genet*. 2004;13(24):3139-3149.
73. Qiu Y, Guo M Fau-Huang S, Huang S Fau-Stein R, Stein R. Acetylation of the BETA2 transcription factor by p300-associated factor is important in insulin gene expression. *J Biol Chem*. 2004;279(11):9796-9802.
74. Gupta P, Sharma G, Lahiri A, Barthwal MK. FOXO3a acetylation regulates PINK1, mitophagy, inflammasome activation in murine palmitate-conditioned and diabetic macrophages. *J Leukoc Biol*. 2022;111(3):611-627.
75. Liu M, Liang K, Zhen J, et al. Sirt6 deficiency exacerbates podocyte injury and proteinuria through targeting Notch signaling. *Nat Commun*. 2017;8(1):413.
76. Zhou C, Zhang Y, Jiao X, Wang G, Wang R, Wu Y. SIRT3 alleviates neuropathic pain by deacetylating FoxO3a in the

- spinal dorsal horn of diabetic model rats. *Reg Anesth Pain Med*. 2021;46(1):49-56.
77. Vahtola E, Louhelainen M, Merasto S, et al. Forkhead class O transcription factor 3a activation and Sirtuin1 overexpression in the hypertrophied myocardium of the diabetic Goto-Kakizaki rat. *J Hypertens*. 2008;26(2):334-344.
 78. Hammer SS, Vieira CP, McFarland D, et al. Fasting and fasting-mimicking treatment activate SIRT1/LXR α and alleviate diabetes-induced systemic and microvascular dysfunction. *Diabetologia*. 2021;64(7):1674-1689.
 79. Rodgers JT, Lerin C, Haas W, Gygi SP, Spiegelman BM, Puigserver P. Nutrient control of glucose homeostasis through a complex of PGC-1 α and SIRT1. *Nature*. 2005;434(7029):113-118.
 80. Xu J, Li Y, Lou M, et al. Baicalin regulates SirT1/STAT3 pathway and restrains excessive hepatic glucose production. *Pharmacol Res*. 2018;136:62-73.
 81. Cantó C, Gerhart-Hines Z, Feige JN, et al. AMPK regulates energy expenditure by modulating NAD⁺ metabolism and SIRT1 activity. *Nature*. 2009;458(7241):1056-1060.
 82. Liao W, Xu N, Zhang H, et al. Persistent high glucose induced EPB41L4A-AS1 inhibits glucose uptake via GCN5 mediating crotonylation and acetylation of histones and non-histones. *Clin Transl Med*. 2022;12(2):e699.
 83. Watala C, Pluta J, Golanski J, et al. Increased protein glycation in diabetes mellitus is associated with decreased aspirin-mediated protein acetylation and reduced sensitivity of blood platelets to aspirin. *J Mol Med (Berl)*. 2005;83(2):148-158.
 84. Stamateris RE, Landa-Galvan HV, Sharma RB, et al. Non-canonical CDK4 signaling rescues diabetes in a mouse model by promoting β cell differentiation. *J Clin Invest*. 2023;133(18):e166490.
 85. Pessoa Rodrigues C, Chatterjee A, Wiese M, et al. Histone H4 lysine 16 acetylation controls central carbon metabolism and diet-induced obesity in mice. *Nat Commun*. 2021;12(1):6212.
 86. Cole JB, Florez JC. Genetics of diabetes mellitus and diabetes complications. *Nat Rev Nephrol*. 2020;16(7):377-390.
 87. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the WHO multinational study of vascular disease in diabetes. *Diabetologia*. 2001;44(Suppl 2):S14-S21.
 88. Komers R, Mar D, Denisenko O, Xu B, Oyama TT, Bomszyk K. Epigenetic changes in renal genes dysregulated in mouse and rat models of type 1 diabetes. *Lab Invest*. 2013;93(5):543-552.
 89. Paneni F, Costantino S, Battista R, et al. Adverse epigenetic signatures by histone methyltransferase Set7 contribute to vascular dysfunction in patients with type 2 diabetes mellitus. *Circ Cardiovasc Genet*. 2015;8(1):150-158.
 90. Kimball AS, Davis FM, denDekker A, et al. The histone methyltransferase Setdb2 modulates macrophage phenotype and uric acid production in diabetic wound repair. *Immunity*. 2019;51(2):258-271. e5.
 91. Tu P, Li X, Ma B, et al. Liver histone H3 methylation and acetylation may associate with type 2 diabetes development. *J Physiol Biochem*. 2015;71(1):89-98.
 92. Agarwal N, Taberner FJ, Rangel Rojas D, et al. SUMOylation of enzymes and ion channels in sensory neurons protects against metabolic dysfunction, neuropathy, and sensory loss in diabetes. *Neuron*. 2020;107(6):1141-1159. e7.
 93. Wang T, Wu J, Dong W, et al. The MEK inhibitor U0126 ameliorates diabetic cardiomyopathy by restricting XBPI's phosphorylation dependent SUMOylation. *Int J Biol Sci*. 2021;17(12):2984-2999.
 94. MacDonald PE. A post-translational balancing act: the good and the bad of SUMOylation in pancreatic islets. *Diabetologia*. 2018;61(4):775-779.
 95. Rudman N, Gornik O, Lauc G. Altered N-glycosylation profiles as potential biomarkers and drug targets in diabetes. *FEBS Lett*. 2019;593(13):1598-1615.
 96. Vlassara H. Chronic diabetic complications and tissue glycosylation. Relevant concern for diabetes-prone black population. *Diabetes Care*. 1990;13(11):1180-1185.
 97. Memarian E, Hart LM, Sliker RC, et al. Plasma protein N-glycosylation is associated with cardiovascular disease, nephropathy, and retinopathy in type 2 diabetes. *BMJ Open Diabetes Res Care*. 2021;9(1):e002345.
 98. Singh SS, Naber A, Dotz V, et al. Metformin and statin use associate with plasma protein N-glycosylation in people with type 2 diabetes. *BMJ Open Diabetes Res Care*. 2020;8(1):e001230.
 99. Frizzell N, Lima M, Baynes JW. Succination of proteins in diabetes. *Free Radic Res*. 2011;45(1):101-109.
 100. Chen Y, Liu Y, Sarker MMR, et al. Structural characterization and antidiabetic potential of a novel heteropolysaccharide from *Grifola frondosa* via IRS1/PI3K-JNK signaling pathways. *Carbohydr Polym*. 2018;198:452-461.
 101. The L. GBD 2017: a fragile world. *Lancet*. 2018;392(10159):1683.
 102. Du Y, Cai T, Li T, et al. Lysine malonylation is elevated in type 2 diabetic mouse models and enriched in metabolic associated proteins. *Mol Cell Proteomics*. 2015;14(1):227-236.
 103. Zou L, Yang Y, Wang Z, et al. Lysine malonylation and its links to metabolism and diseases. *Aging Dis*. 2023;14(1):84-98.
 104. Nie L, Shuai L, Zhu M, et al. The landscape of histone modifications in a high-fat diet-induced obese (DIO) mouse model. *Mol Cell Proteomics*. 2017;16(7):1324-1334.
 105. Graham TE, Kahn BB. Tissue-specific alterations of glucose transport and molecular mechanisms of intertissue communication in obesity and type 2 diabetes. *Horm Metab Res*. 2007;39(10):717-721.
 106. Du K, Murakami S, Sun Y, Kilpatrick CL, Luscher B. DHHC7 palmitoylates glucose transporter 4 (Glut4) and regulates Glut4 membrane translocation. *J Biol Chem*. 2017;292(7):2979-2991.
 107. Wei X, Yang Z, Rey FE, et al. Fatty acid synthase modulates intestinal barrier function through palmitoylation of mucin 2. *Cell Host Microbe*. 2012;11(2):140-152.
 108. Sun HJ, Xiong SP, Cao X, et al. Polysulfide-mediated sulfhydrylation of SIRT1 prevents diabetic nephropathy by suppressing phosphorylation and acetylation of p65 NF- κ B and STAT3. *Redox Biol*. 2021;38:101813.
 109. Xie L, Gu Y, Wen M, et al. Hydrogen sulfide induces Keap1 S-sulfhydration and suppresses diabetes-accelerated atherosclerosis via Nrf2 activation. *Diabetes*. 2016;65(10):3171-3184.
 110. Ishizawa K, Wang Q, Li J, et al. Inhibition of sodium glucose cotransporter 2 attenuates the dysregulation of Kelch-Like 3 and NaCl cotransporter in obese diabetic mice. *J Am Soc Nephrol*. 2019;30(5):782-794.
 111. Schaub JA, AlAkwa FM, McCown PJ, et al. SGLT2 inhibitors mitigate kidney tubular metabolic and mTORC1

- perturbations in youth-onset type 2 diabetes. *J Clin Invest.* 2023;133(5):e164486.
112. Zhou H, Wang S, Zhu P, Hu S, Chen Y, Ren J. Empagliflozin rescues diabetic myocardial microvascular injury via AMPK-mediated inhibition of mitochondrial fission. *Redox Biol.* 2018;15:335-346.
 113. Koyani CN, Plastira I, Sourij H, et al. Empagliflozin protects heart from inflammation and energy depletion via AMPK activation. *Pharmacol Res.* 2020;158:104870.
 114. Aung MM, Slade K, Freeman LAR, et al. Locally delivered GLP-1 analogues liraglutide and exenatide enhance microvascular perfusion in individuals with and without type 2 diabetes. *Diabetologia.* 2019;62(9):1701-1711.
 115. Samson SL, Sathyanarayana P, Jogi M, et al. Exenatide decreases hepatic fibroblast growth factor 21 resistance in non-alcoholic fatty liver disease in a mouse model of obesity and in a randomised controlled trial. *Diabetologia.* 2011;54(12):3093-100.
 116. Su K, Yi B, Yao BQ, et al. Liraglutide attenuates renal tubular ectopic lipid deposition in rats with diabetic nephropathy by inhibiting lipid synthesis and promoting lipolysis. *Pharmacol Res.* 2020;156:104778.
 117. Koska J, Lopez L, D'Souza K, et al. Effect of liraglutide on dietary lipid-induced insulin resistance in humans. *Diabetes Obes Metab.* 2018;20(1):69-76.
 118. Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol.* 2019;7(10):776-785.
 119. Zhu D, Gan S, Liu Y, et al. Dorzagliatin monotherapy in Chinese patients with type 2 diabetes: a dose-ranging, randomised, double-blind, placebo-controlled, phase 2 study. *Lancet Diabetes Endocrinol.* 2018;6(8):627-636.
 120. Zhu D, Li X, Ma J, et al. Dorzagliatin in drug-naïve patients with type 2 diabetes: a randomized, double-blind, placebo-controlled phase 3 trial. *Nat Med.* 2022;28(5):965-973.
 121. Yang W, Zhu D, Gan S, et al. Dorzagliatin add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled phase 3 trial. *Nat Med.* 2022;28(5):974-981.
 122. Zhang Y, Thai K, Jin T, Woo M, Gilbert RE. SIRT1 activation attenuates α cell hyperplasia, hyperglucagonaemia and hyperglycaemia in STZ-diabetic mice. *Sci Rep.* 2018;8(1):13972.
 123. Gilbert RE, Thai K, Advani SL, et al. SIRT1 activation ameliorates hyperglycaemia by inducing a torpor-like state in an obese mouse model of type 2 diabetes. *Diabetologia.* 2015;58(4):819-827.
 124. Toupchian O, Abdollahi S, Salehi-Abargouei A, et al. The effects of resveratrol supplementation on PPAR α , p16, p53, p21 gene expressions, and sCD163/sTWEAK ratio in patients with type 2 diabetes mellitus: a double-blind controlled randomized trial. *Phytother Res.* 2021;35(6):3205-3213.
 125. Baur JA, Pearson KJ, Price NL, et al. Resveratrol improves health and survival of mice on a high-calorie diet. *Nature.* 2006;444(7117):337-342.
 126. Han W, Wang C, Yang Z, et al. SRT1720 retards renal fibrosis via inhibition of HIF1 α /GLUT1 in diabetic nephropathy. *J Endocrinol.* 2019.
 127. Feige JN, Lagouge M, Canto C, et al. Specific SIRT1 activation mimics low energy levels and protects against diet-induced metabolic disorders by enhancing fat oxidation. *Cell Metab.* 2008;8(5):347-358.
 128. Jiang J, Au M, Lu K, et al. Generation of insulin-producing islet-like clusters from human embryonic stem cells. *Stem Cells.* 2007;25(8):1940-1953.
 129. Moon HR, Yun JM. Sodium butyrate inhibits high glucose-induced inflammation by controlling the acetylation of NF- κ B p65 in human monocytes. *Nutr Res Pract.* 2023;17(1):164-173.
 130. Helker CSM, Mullapudi ST, Mueller LM, et al. A whole organism small molecule screen identifies novel regulators of pancreatic endocrine development. *Development.* 2019;146(14):dev172569.
 131. Chen Y, Zhao X, Wu H. Metabolic stress and cardiovascular disease in diabetes mellitus: the role of protein O-GlcNAc modification. *Arterioscler Thromb Vasc Biol.* 2019;39(10):1911-1924.
 132. Jeon JH, Suh HN, Kim MO, Ryu JM, Han HJ. Glucosamine-induced OGT activation mediates glucose production through cleaved Notch1 and FoxO1, which coordinately contributed to the regulation of maintenance of self-renewal in mouse embryonic stem cells. *Stem Cells Dev.* 2014;23(17):2067-2079.
 133. Han J, Li E, Chen L, et al. The CREB coactivator CRTC2 controls hepatic lipid metabolism by regulating SREBP1. *Nature.* 2015;524(7564):243-246.
 134. Lu B, Bridges D, Yang Y, et al. Metabolic crosstalk: molecular links between glycogen and lipid metabolism in obesity. *Diabetes.* 2014;63(9):2935-2948.
 135. Chu H, Du C, Yang Y, et al. MC-LR aggravates liver lipid metabolism disorders in obese mice fed a high-fat diet via PI3K/AKT/mTOR/SREBP1 signaling pathway. *Toxins (Basel).* 2022;14(12):833.
 136. Choi SE, Kwon S, Seok S, et al. Obesity-linked phosphorylation of SIRT1 by casein kinase 2 inhibits its nuclear localization and promotes fatty liver. *Mol Cell Biol.* 2017;37(15):e000006.
 137. Gao Z, Zhang J, Kheterpal I, Kennedy N, Davis RJ, Ye J. Sirtuin 1 (SIRT1) protein degradation in response to persistent c-Jun N-terminal kinase 1 (JNK1) activation contributes to hepatic steatosis in obesity. *J Biol Chem.* 2011;286(25):22227-22234.
 138. Chang C, Su H, Zhang D, et al. AMPK-dependent phosphorylation of GAPDH triggers Sirt1 activation and is necessary for autophagy upon glucose starvation. *Mol Cell.* 2015;60(6):930-940.
 139. Wu D, Qiu Y, Gao X, Yuan XB, Zhai Q. Overexpression of SIRT1 in mouse forebrain impairs lipid/glucose metabolism and motor function. *PLoS One.* 2011;6(6):e21759.
 140. Hiraike Y, Saito K, Oguchi M, et al. NFIA in adipocytes reciprocally regulates mitochondrial and inflammatory gene program to improve glucose homeostasis. *Proc Natl Acad Sci USA.* 2023;120(31):e2308750120.
 141. Yang X, Liu Q, Li Y, et al. The diabetes medication canagliflozin promotes mitochondrial remodelling of adipocyte via the AMPK-Sirt1-Pgc-1 α signalling pathway. *Adipocyte.* 2020;9(1):484-494.
 142. Desjardins EM, Smith BK, Day EA, et al. The phosphorylation of AMPK β 1 is critical for increasing autophagy and maintaining mitochondrial homeostasis in response to fatty acids. *Proc Natl Acad Sci USA.* 2022;119(48):e2119824119.

143. Hwang MS, Baek JH, Song JK, Lee IH, Chun KH. Tschimganine reduces lipid accumulation through AMPK activation and alleviates high-fat diet-induced metabolic diseases. *BMB Rep.* 2023;56(4):246-251.
144. Cederquist CT, Lentucci C, Martinez-Calejman C, et al. Systemic insulin sensitivity is regulated by GPS2 inhibition of AKT ubiquitination and activation in adipose tissue. *Mol Metab.* 2016;6(1):125-137.
145. Mukherjee S, Chakraborty M, Msengi EN, et al. Ube4A maintains metabolic homeostasis and facilitates insulin signaling in vivo. *Mol Metab.* 2023;75:101767.
146. Ai L, Wang X, Chen Z, et al. A20 reduces lipid storage and inflammation in hypertrophic adipocytes via p38 and Akt signaling. *Mol Cell Biochem.* 2016;420(1-2):73-83.
147. Ding L, Zhang L, Biswas S, et al. Akt3 inhibits adipogenesis and protects from diet-induced obesity via WNK1/SGK1 signaling. *JCI Insight.* 2017;2(22):e95687.
148. Wang Q, Li H, Tajima K, et al. Post-translational control of beige fat biogenesis by PRDM16 stabilization. *Nature.* 2022;609(7925):151-158.
149. Kim MS, Baek JH, Lee J, Sivaraman A, Lee K, Chun KH. Deubiquitinase USP1 enhances CCAAT/enhancer-binding protein beta (C/EBP β) stability and accelerates adipogenesis and lipid accumulation. *Cell Death Dis.* 2023;14(11):776.
150. Iyer A, Fairlie DP, Brown L. Lysine acetylation in obesity, diabetes and metabolic disease. *Immunol Cell Biol.* 2012;90(1):39-46.
151. Qiang L, Wang L, Kon N, et al. Brown remodeling of white adipose tissue by SirT1-dependent deacetylation of Ppar γ . *Cell.* 2012;150(3):620-632.
152. Taghizadeh N, Mohammadi S, Yousefi Z, et al. Assessment of global histone acetylation in pediatric and adolescent obesity: Correlations with SIRT1 expression and metabolic-inflammatory profiles. *PLoS One.* 2023;18(10):e0293217.
153. Mayoral R, Osborn O, McNelis J, et al. Adipocyte SIRT1 knockout promotes PPAR γ activity, adipogenesis and insulin sensitivity in chronic-HFD and obesity. *Mol Metab.* 2015;4(5):378-391.
154. Kwon S, Seok S, Yau P, Li X, Kemper B, Kemper JK. Obesity and aging diminish sirtuin 1 (SIRT1)-mediated deacetylation of SIRT3, leading to hyperacetylation and decreased activity and stability of SIRT3. *J Biol Chem.* 2017;292(42):17312-17323.
155. He Y, B'Nai Taub A, Yu L, et al. PPAR γ acetylation orchestrates adipose plasticity and metabolic rhythms. *Adv Sci (Weinh).* 2023;10(2):e2204190.
156. Wang S, Lin Y, Gao L, et al. PPAR- γ integrates obesity and adipocyte clock through epigenetic regulation of Bmal1. *Theranostics.* 2022;12(4):1589-1606.
157. He Y, Zhang R, Yu L, et al. PPAR γ acetylation in adipocytes exacerbates BAT whitening and worsens age-associated metabolic dysfunction. *Cells.* 2023;12(10):1424.
158. Ma QX, Zhu WY, Lu XC, et al. BCAA-BCKA axis regulates WAT browning through acetylation of PRDM16. *Nat Metab.* 2022;4(1):106-122.
159. Tu R, Liu X, Dong X, et al. Janus kinase 2 (JAK2) methylation and obesity: a Mendelian randomization study. *Nutr Metab Cardiovasc Dis.* 2021;31(12):3484-3491.
160. Lee JE, Wang C, Xu S, et al. H3K4 mono- and dimethyltransferase MLL4 is required for enhancer activation during cell differentiation. *Elife.* 2013;2:e01503.
161. Kraus D, Yang Q, Kong D, et al. Nicotinamide N-methyltransferase knockdown protects against diet-induced obesity. *Nature.* 2014;508(7495):258-262.
162. Shin HJ, Kim H, Oh S, et al. AMPK-SKP2-CARM1 signalling cascade in transcriptional regulation of autophagy. *Nature.* 2016;534(7608):553-557.
163. Xie H, Wang YH, Liu X, et al. SUMOylation of ERp44 enhances Ero1 α ER retention contributing to the pathogenesis of obesity and insulin resistance. *Metabolism.* 2023;139:155351.
164. Lee JS, Chae S, Nan J, et al. SENP2 suppresses browning of white adipose tissues by de-conjugating SUMO from C/EBP β . *Cell Rep.* 2022;38(8):110408.
165. Zheng Q, Cao Y, Chen Y, et al. Senp2 regulates adipose lipid storage by de-SUMOylation of Setdb1. *J Mol Cell Biol.* 2018;10(3):258-266.
166. Brenner C, Galluzzi L, Kepp O, Kroemer G. Decoding cell death signals in liver inflammation. *J Hepatol.* 2013;59(3):583-594.
167. Monden M, Koyama H, Otsuka Y, et al. Receptor for advanced glycation end products regulates adipocyte hypertrophy and insulin sensitivity in mice: involvement of Toll-like receptor 2. *Diabetes.* 2013;62(2):478-489.
168. Paone P, Suriano F, Jian C, et al. Prebiotic oligofructose protects against high-fat diet-induced obesity by changing the gut microbiota, intestinal mucus production, glycosylation and secretion. *Gut Microbes.* 2022;14(1):2152307.
169. Cypess AM, Lehman S, Williams G, et al. Identification and importance of brown adipose tissue in adult humans. *N Engl J Med.* 2009;360(15):1509-1517.
170. Wang G, Meyer JG, Cai W, et al. Regulation of UCPI and mitochondrial metabolism in brown adipose tissue by reversible succinylation. *Mol Cell.* 2019;74(4):844-857. e7.
171. Zhang C, He X, Sheng Y, et al. Allicin regulates energy homeostasis through brown adipose tissue. *iScience.* 2020;23(5):101113.
172. Yang L, Lin W, Nugent CA, et al. Lingguizhugan decoction protects against high-fat-diet-induced nonalcoholic fatty liver disease by alleviating oxidative stress and activating cholesterol secretion. *Int J Genomics.* 2017;2017:2790864.
173. Tian D, Zeng X, Gong Y, Zheng Y, Zhang J, Wu Z. HDAC1 inhibits beige adipocyte-mediated thermogenesis through histone crotonylation of Pgc1 α /Ucp1. *Cell Signal.* 2023;111:110875.
174. Fullerton MD, Galic S, Marcinko K, et al. Single phosphorylation sites in Acc1 and Acc2 regulate lipid homeostasis and the insulin-sensitizing effects of metformin. *Nat Med.* 2013;19(12):1649-1654.
175. Zhu S, Batushansky A, Jopkiewicz A, et al. Sirt5 deficiency causes posttranslational protein malonylation and dysregulated cellular metabolism in chondrocytes under obesity conditions. *Cartilage.* 2021;13(2_suppl):1185s-1199s.
176. Hao JW, Wang J, Guo H, et al. CD36 facilitates fatty acid uptake by dynamic palmitoylation-regulated endocytosis. *Nat Commun.* 2020;11(1):4765.
177. Ding Y, Wang H, Geng B, Xu G. Sulfhydration of perilipin 1 is involved in the inhibitory effects of cystathionine gamma lyase/hydrogen sulfide on adipocyte lipolysis. *Biochem Biophys Res Commun.* 2020;521(3):786-790.
178. Finlin BS, Memetimin H, Confides AL, et al. Human adipose beigeing in response to cold and mirabegron. *JCI Insight.* 2018;3(15):e121510.

179. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384(11):989-1002.
180. Chen X, Chen S, Li Z, et al. Effect of semaglutide and empagliflozin on cognitive function and hippocampal phosphoproteomic in obese mice. *Front Pharmacol*. 2023;14:975830.
181. Rubino DM, Greenway FL, Khalid U, et al. Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: the STEP 8 randomized clinical trial. *Jama*. 2022;327(2):138-150.
182. Miranda MX, van Tits LJ, Lohmann C, et al. The Sirt1 activator SRT3025 provides atheroprotection in Apoe^{-/-} mice by reducing hepatic Pcsk9 secretion and enhancing Ldlr expression. *Eur Heart J*. 2015;36(1):51-59.
183. Timmers S, Konings E, Bilet L, et al. Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. *Cell Metab*. 2011;14(5):612-622.
184. Lagouge M, Argmann C, Gerhart-Hines Z, et al. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1 α . *Cell*. 2006;127(6):1109-1122.
185. Bricambert J, Miranda J, Benhamed F, Girard J, Postic C, Dentin R. Salt-inducible kinase 2 links transcriptional coactivator p300 phosphorylation to the prevention of ChREBP-dependent hepatic steatosis in mice. *J Clin Invest*. 2010;120(12):4316-4331.
186. Chen YY, Hong H, Lei YT, Zou J, Yang YY, He LY. I κ B kinase promotes Nrf2 ubiquitination and degradation by phosphorylating cylindromatosis, aggravating oxidative stress injury in obesity-related nephropathy. *Mol Med*. 2021;27(1):137.
187. Jia X, Xu W, Zhang L, Li X, Wang R, Wu S. Impact of gut microbiota and microbiota-related metabolites on hyperlipidemia. *Front Cell Infect Microbiol*. 2021;11:634780.
188. Voisin M, Shrestha E, Rollet C, et al. Inhibiting LXRA α phosphorylation in hematopoietic cells reduces inflammation and attenuates atherosclerosis and obesity in mice. *Commun Biol*. 2021;4(1):420.
189. Gage MC, Becares N, Louie R, et al. Disrupting LXRA α phosphorylation promotes FoxM1 expression and modulates atherosclerosis by inducing macrophage proliferation. *Proc Natl Acad Sci USA*. 2018;115(28):E6556-E6565.
190. Calderin EP, Zheng JJ, Boyd NL, et al. Exercise-induced specialized proresolving mediators stimulate AMPK phosphorylation to promote mitochondrial respiration in macrophages. *Mol Metab*. 2022;66:101637.
191. Li Y, Xu S, Mihaylova MM, et al. AMPK phosphorylates and inhibits SREBP activity to attenuate hepatic steatosis and atherosclerosis in diet-induced insulin-resistant mice. *Cell Metab*. 2011;13(4):376-388.
192. Hu HJ, Wang XH, Zhang TQ, et al. PLK1 promotes cholesterol efflux and alleviates atherosclerosis by up-regulating ABCA1 and ABCG1 expression via the AMPK/PPAR γ /LXR α pathway. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2022;1867(12):159221.
193. Li J, Bollati C, Bartolomei M, et al. Hempseed (Cannabis sativa) peptide H3 (IGFLIIWV) exerts cholesterol-lowering effects in human hepatic cell line. *Nutrients*. 2022;14(9):1804.
194. van Loon NM, Ottenhoff R, Kooijman S, et al. Inactivation of the E3 ubiquitin ligase IDOL attenuates diet-induced obesity and metabolic dysfunction in mice. *Arterioscler Thromb Vasc Biol*. 2018;38(8):1785-1795.
195. Zelcer N, Hong C, Boyadjian R, Tontonoz P. LXR regulates cholesterol uptake through idol-dependent ubiquitination of the LDL receptor. *Science*. 2009;325(5936):100-104.
196. Calkin AC, Lee SD, Kim J, et al. Transgenic expression of dominant-active IDOL in liver causes diet-induced hypercholesterolemia and atherosclerosis in mice. *Circ Res*. 2014;115(4):442-449.
197. Adi D, Lu XY, Fu ZY, et al. IDOL G51S variant is associated with high blood cholesterol and increases low-density lipoprotein receptor degradation. *Arterioscler Thromb Vasc Biol*. 2019;39(12):2468-2479.
198. Hu Q, Zhang H, Gutiérrez Cortés N, et al. Increased Drp1 acetylation by lipid overload induces cardiomyocyte death and heart dysfunction. *Circ Res*. 2020;126(4):456-470.
199. Kim H, Mendez R, Chen X, Fang D, Zhang K. Lysine acetylation of CREBH regulates fasting-induced hepatic lipid metabolism. *Mol Cell Biol*. 2015;35(24):4121-4134.
200. Zhao Y, Jia X, Yang X, et al. Deacetylation of Caveolin-1 by Sirt6 induces autophagy and retards high glucose-stimulated LDL transcytosis and atherosclerosis formation. *Metabolism*. 2022;131:155162.
201. Tao R, Xiong X, DePinho RA, Deng CX, Dong XC. Hepatic SREBP-2 and cholesterol biosynthesis are regulated by FoxO3 and Sirt6. *J Lipid Res*. 2013;54(10):2745-2753.
202. Greißel A, Culmes M, Napieralski R, et al. Alternation of histone and DNA methylation in human atherosclerotic carotid plaques. *Thromb Haemost*. 2015;114(2):390-402.
203. Xiaoling Y, Li Z, ShuQiang L, et al. Hyperhomocysteinemia in ApoE^{-/-} mice leads to overexpression of enhancer of zeste homolog 2 via miR-92a regulation. *PLoS One*. 2016;11(12):e0167744.
204. Pirillo A, Svecla M, Catapano AL, Holleboom AG, Norata GD. Impact of protein glycosylation on lipoprotein metabolism and atherosclerosis. *Cardiovasc Res*. 2021;117(4):1033-1045.
205. Menni C, Gudelj I, Macdonald-Dunlop E, et al. Glycosylation profile of immunoglobulin G is cross-sectionally associated with cardiovascular disease risk score and subclinical atherosclerosis in two independent cohorts. *Circ Res*. 2018;122(11):1555-1564.
206. Liu YP, Wen R, Liu CF, Zhang TN, Yang N. Cellular and molecular biology of sirtuins in cardiovascular disease. *Biomed Pharmacother*. 2023;164:114931.
207. Li H, Du Y, Ji H, et al. Adenosine-rich extract of Ganoderma lucidum: a safe and effective lipid-lowering substance. *iScience*. 2022;25(11):105214.
208. Xu R, Yuan W, Wang Z. Advances in glycolysis metabolism of atherosclerosis. *J Cardiovasc Transl Res*. 2023;16(2):476-490.
209. Wang Y, Chen L, Zhang M, et al. Exercise-induced endothelial Mecp2 lactylation suppresses atherosclerosis via the Ereg/MAPK signalling pathway. *Atherosclerosis*. 2023;375:45-58.
210. Chen XF, Chen X, Tang X. Short-chain fatty acid, acylation and cardiovascular diseases. *Clin Sci (Lond)*. 2020;134(6):657-676.

211. Bruning U, Morales-Rodriguez F, Kalucka J, et al. Impairment of angiogenesis by fatty acid synthase inhibition involves mTOR malonylation. *Cell Metab.* 2018;28(6):866-880. e15.
212. Shu H, Peng Y, Hang W, Nie J, Zhou N, Wang DW. The role of CD36 in cardiovascular disease. *Cardiovasc Res.* 2022;118(1):115-129.
213. Wang J, Hao JW, Wang X, et al. DHHC4 and DHHC5 facilitate fatty acid uptake by palmitoylating and targeting CD36 to the plasma membrane. *Cell Rep.* 2019;26(1):209-221. e5.
214. Liu Z, Han Y, Li L, et al. The hydrogen sulfide donor, GYY4137, exhibits anti-atherosclerotic activity in high fat fed apolipoprotein E(-/-) mice. *Br J Pharmacol.* 2013;169(8):1795-1809.
215. Kandadi MR, Panzhinskiy E, Roe ND, Nair S, Hu D, Sun A. Deletion of protein tyrosine phosphatase 1B rescues against myocardial anomalies in high fat diet-induced obesity: Role of AMPK-dependent autophagy. *Biochim Biophys Acta.* 2015;1852(2):299-309.
216. Krishnan N, Fu C, Pappin DJ, Tonks NK. H2S-Induced sulfhydration of the phosphatase PTP1B and its role in the endoplasmic reticulum stress response. *Sci Signal.* 2011;4(203):ra86.
217. Yu M, Du H, Wang B, et al. Exogenous H(2)S induces Hrd1 S-sulfhydration and prevents CD36 translocation via VAMP3 ubiquitylation in diabetic hearts. *Aging Dis.* 2020;11(2):286-300.
218. Szarek M, Amarenco P, Callahan A, et al. Atorvastatin reduces first and subsequent vascular events across vascular territories: the SPARCL trial. *J Am Coll Cardiol.* 2020;75(17):2110-2118.
219. Kim BK, Hong SJ, Lee YJ, et al. Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomised, open-label, non-inferiority trial. *Lancet.* 2022;400(10349):380-390.
220. Lin MC, Hsing CH, Li FA, et al. Rosuvastatin modulates the post-translational acetylome in endothelial cells. *Acta Cardiol Sin.* 2014;30(1):67-73.
221. Lee J, Kim Y, Friso S, Choi SW. Epigenetics in non-alcoholic fatty liver disease. *Mol Aspects Med.* 2017;54:78-88.
222. Li Y, Xu J, Lu Y, et al. DRAK2 aggravates nonalcoholic fatty liver disease progression through SRSF6-associated RNA alternative splicing. *Cell Metab.* 2021;33(10):2004-2020.
223. Chen B, Sun L, Zeng G, et al. Gut bacteria alleviate smoking-related NASH by degrading gut nicotine. *Nature.* 2022;610(7932):562-568.
224. Tan T, Song Z, Li W, et al. Modelling porcine NAFLD by deletion of leptin and defining the role of AMPK in hepatic fibrosis. *Cell Biosci.* 2023;13(1):169.
225. Zhao P, Sun X, Chagga C, et al. An AMPK-caspase-6 axis controls liver damage in nonalcoholic steatohepatitis. *Science.* 2020;367(6478):652-660.
226. Jung TW, Park HS, Choi GH, Kim D, Lee T. β -aminoisobutyric acid attenuates LPS-induced inflammation and insulin resistance in adipocytes through AMPK-mediated pathway. *J Biomed Sci.* 2018;25(1):27.
227. Bates J, Vijayakumar A, Ghoshal S, et al. Acetyl-CoA carboxylase inhibition disrupts metabolic reprogramming during hepatic stellate cell activation. *J Hepatol.* 2020;73(4):896-905.
228. Lally JSV, Ghoshal S, DePeralta DK, et al. Inhibition of acetyl-CoA carboxylase by phosphorylation or the inhibitor ND-654 suppresses lipogenesis and hepatocellular carcinoma. *Cell Metab.* 2019;29(1):174-182. e5.
229. Kawaguchi T, Ueno T, Nogata Y, Hayakawa M, Koga H, Torimura T. Wheat-bran autolytic peptides containing a branched-chain amino acid attenuate non-alcoholic steatohepatitis via the suppression of oxidative stress and the upregulation of AMPK/ACC in high-fat diet-fed mice. *Int J Mol Med.* 2017;39(2):407-414.
230. Vivero A, Ruz M, Rivera M, et al. Zinc supplementation and strength exercise in rats with type 2 diabetes: Akt and PTP1B phosphorylation in nonalcoholic fatty liver. *Biol Trace Elem Res.* 2021;199(6):2215-2224.
231. Liu XL, Pan Q, Cao HX, et al. Lipotoxic hepatocyte-derived exosomal microRNA 192-5p activates macrophages through Rictor/Akt/Forkhead Box transcription factor O1 signaling in nonalcoholic fatty liver disease. *Hepatology.* 2020;72(2):454-469.
232. Chi Y, Gong Z, Xin H, Wang Z, Liu Z. Long noncoding RNA IncARSR promotes nonalcoholic fatty liver disease and hepatocellular carcinoma by promoting YAP1 and activating the IRS2/AKT pathway. *J Transl Med.* 2020;18(1):126.
233. Xu R, Luo X, Ye X, et al. SIRT1/PGC-1 α /PPAR- γ correlate with hypoxia-induced chemoresistance in non-small cell lung cancer. *Front Oncol.* 2021;11:682762.
234. Li K, Zhang K, Wang H, et al. Hrd1-mediated ACLY ubiquitination alleviate NAFLD in db/db mice. *Metabolism.* 2021;114:154349.
235. Ning Z, Guo X, Liu X, et al. USP22 regulates lipidome accumulation by stabilizing PPAR γ in hepatocellular carcinoma. *Nat Commun.* 2022;13(1):2187.
236. Zhang Y, Lin S, Peng J, et al. Amelioration of hepatic steatosis by dietary essential amino acid-induced ubiquitination. *Mol Cell.* 2022;82(8):1528-1542.
237. Takahashi Y, Shinoda A, Kamada H, Shimizu M, Inoue J, Sato R. Perilipin2 plays a positive role in adipocytes during lipolysis by escaping proteasomal degradation. *Sci Rep.* 2016;6:20975.
238. Gao H, Zhou L, Zhong Y, et al. Kindlin-2 haploinsufficiency protects against fatty liver by targeting Foxo1 in mice. *Nat Commun.* 2022;13(1):1025.
239. Zhong Y, Zhou L, Wang H, et al. Kindlin-2 maintains liver homeostasis by regulating GSTP1-OPN-mediated oxidative stress and inflammation in mice. *J Biol Chem.* 2023:105601.
240. Hou T, Tian Y, Cao Z, et al. Cytoplasmic SIRT6-mediated ACSL5 deacetylation impedes nonalcoholic fatty liver disease by facilitating hepatic fatty acid oxidation. *Mol Cell.* 2022;82(21):4099-4115.
241. Ren H, Hu F, Wang D, et al. Sirtuin 2 prevents liver steatosis and metabolic disorders by deacetylation of hepatocyte nuclear factor 4 α . *Hepatology.* 2021;74(2):723-740.
242. Zhang L, Zhang Z, Li C, et al. S100A11 promotes liver steatosis via FOXO1-mediated autophagy and lipogenesis. *Cell Mol Gastroenterol Hepatol.* 2021;11(3):697-724.
243. Marra F, Svegliati-Baroni G. Lipotoxicity and the gut-liver axis in NASH pathogenesis. *J Hepatol.* 2018;68(2):280-295.
244. Zhang X-J, She Z-G, Wang J, et al. Multiple omics study identifies an interspecies conserved driver for nonalcoholic steatohepatitis. *Sci Transl Med.* 2021;13(624):eabg8117.

245. Wang T, Chen K, Yao W, et al. Acetylation of lactate dehydrogenase B drives NAFLD progression by impairing lactate clearance. *J Hepatol*. 2021;74(5):1038-1052.
246. Xie D, Zhao H, Lu J, et al. High uric acid induces liver fat accumulation via ROS/JNK/AP-1 signaling. *Am J Physiol Endocrinol Metab*. 2021;320(6):E1032-E1043.
247. He A, Chen X, Tan M, et al. Acetyl-CoA derived from hepatic peroxisomal β -oxidation inhibits autophagy and promotes steatosis via mTORC1 activation. *Mol Cell*. 2020;79(1):30-42. e4.
248. Yang X, Sun D, Xiang H, et al. Hepatocyte SH3RF2 deficiency is a key aggravator for NAFLD. *Hepatology*. 2021;74(3):1319-1338.
249. Wang S, Zhang C, Hasson D, et al. Epigenetic compensation promotes liver regeneration. *Dev Cell*. 2019;50(1):43-56. e6.
250. Yang M, Lin X, Segers F, et al. OXR1A, a coactivator of PRMT5 regulating histone arginine methylation. *Cell Rep*. 2020;30(12):4165-4178. e7.
251. Li Z, Zhou Y, Jia K, et al. JMJD4-demethylated RIG-I prevents hepatic steatosis and carcinogenesis. *J Hematol Oncol*. 2022;15(1):161.
252. Yan L, Zhang T, Wang K, et al. SENP1 prevents steatohepatitis by suppressing RIPK1-driven apoptosis and inflammation. *Nat Commun*. 2022;13(1):7153.
253. Liu Y, Dou X, Zhou WY, et al. Hepatic small ubiquitin-related modifier (SUMO)-specific protease 2 controls systemic metabolism through SUMOylation-dependent regulation of liver-adipose tissue crosstalk. *Hepatology*. 2021;74(4):1864-1883.
254. Zhou J, Cui S, He Q, et al. SUMOylation inhibitors synergize with FXR agonists in combating liver fibrosis. *Nat Commun*. 2020;11(1):240.
255. Hülsmeyer AJ, Tobler M, Burda P, Hennet T. Glycosylation site occupancy in health, congenital disorder of glycosylation and fatty liver disease. *Sci Rep*. 2016;6:33927.
256. Clarke JD, Novak P, Lake AD, Hardwick RN, Cherrington NJ. Impaired N-linked glycosylation of uptake and efflux transporters in human non-alcoholic fatty liver disease. *Liver Int*. 2017;37(7):1074-1081.
257. Ochoa-Rios S, O'Connor IP, Kent LN, et al. Imaging mass spectrometry reveals alterations in N-linked glycosylation that are associated with histopathological changes in nonalcoholic steatohepatitis in mouse and human. *Mol Cell Proteomics*. 2022;21(5):100225.
258. Zhang N, Wang Y, Zhang J, et al. N-glycosylation of CREBH improves lipid metabolism and attenuates lipotoxicity in NAFLD by modulating PPAR α and SCD-1. *Faseb J*. 2020;34(11):15338-15363.
259. Cheng Y, Hou T, Ping J, Chen G, Chen J. Quantitative succinylome analysis in the liver of non-alcoholic fatty liver disease rat model. *Proteome Sci*. 2016;14:3.
260. Ginès P, Krag A, Abiralde JG, Solà E, Fabrellas N, Kamath PS. Liver cirrhosis. *Lancet*. 2021;398(10308):1359-1376.
261. Chen XF, Ji S. Sorafenib attenuates fibrotic hepatic injury through mediating lysine crotonylation. *Drug Des Devel Ther*. 2022;16:2133-2144.
262. Gao R, Li Y, Xu Z, et al. Mitochondrial pyruvate carrier 1 regulates fatty acid synthase lactylation and mediates treatment of nonalcoholic fatty liver disease. *Hepatology*. 2023;78(6):1800-1815.
263. Zhang X-J, Ji Y-Y, Cheng X, et al. A small molecule targeting ALOX12-ACC1 ameliorates nonalcoholic steatohepatitis in mice and macaques. *Sci Transl Med*. 2021;13(624):eabg8116.
264. Cao H, Cai Q, Guo W, et al. Malonylation of Acetyl-CoA carboxylase 1 promotes hepatic steatosis and is attenuated by ketogenic diet in NAFLD. *Cell Rep*. 2023;42(4):112319.
265. Zhao L, Zhang C, Luo X, et al. CD36 palmitoylation disrupts free fatty acid metabolism and promotes tissue inflammation in non-alcoholic steatohepatitis. *J Hepatol*. 2018;69(3):705-717.
266. Nguyen TTP, Kim DY, Im SS, Jeon TI. Impairment of ULK1 sulphydration-mediated lipophagy by SREBF1/SREBP-1c in hepatic steatosis. *Autophagy*. 2021;17(12):4489-4490.
267. Nguyen TTP, Kim DY, Lee YG, et al. SREBP-1c impairs ULK1 sulphydration-mediated autophagic flux to promote hepatic steatosis in high-fat-diet-fed mice. *Mol Cell*. 2021;81(18):3820-3832. e7.
268. Xu W, Cui C, Cui C, et al. Hepatocellular cystathionine γ lyase/hydrogen sulfide attenuates nonalcoholic fatty liver disease by activating farnesoid X receptor. *Hepatology*. 2022;76(6):1794-1810.
269. Zhao S, Song T, Gu Y, et al. Hydrogen sulfide alleviates liver injury through the S-sulhydrylated-Kelch-like ECH-associated protein 1/nuclear erythroid 2-related factor 2/low-density lipoprotein receptor-related protein 1 pathway. *Hepatology*. 2021;73(1):282-302.
270. Adorini L, Trauner M. FXR agonists in NASH treatment. *J Hepatol*. 2023;79(5):1317-1331.
271. Appelman MD, van der Veen SW, van Mil SWC. Post-translational modifications of FXR; implications for cholestasis and obesity-related disorders. *Front Endocrinol (Lausanne)*. 2021;12:729828.
272. Patel K, Harrison SA, Elkhatab M, et al. Cilofexor, a nonsteroidal FXR agonist, in patients with noncirrhotic NASH: a phase 2 randomized controlled trial. *Hepatology*. 2020;72(1):58-71.
273. Alkhoury N, Lawitz E, Noureddin M, DeFronzo R, Shulman GI. GS-0976 (Firsocostat): an investigational liver-directed acetyl-CoA carboxylase (ACC) inhibitor for the treatment of non-alcoholic steatohepatitis (NASH). *Expert Opin Investig Drugs*. 2020;29(2):135-141.
274. Lee DE, Lee SJ, Kim SJ, Lee HS, Kwon OS. Curcumin ameliorates nonalcoholic fatty liver disease through inhibition of O-GlcNAcylation. *Nutrients*. 2019;11(11):2702.
275. Rahmani S, Asgary S, Askari G, et al. Treatment of non-alcoholic fatty liver disease with curcumin: a randomized placebo-controlled trial. *Phytother Res*. 2016;30(9):1540-1548.
276. Nasiri-Ansari N, Nikolopoulou C, Papoutsis K, et al. Empagliflozin attenuates non-alcoholic fatty liver disease (NAFLD) in high fat diet fed ApoE(-/-) mice by activating autophagy and reducing ER stress and apoptosis. *Int J Mol Sci*. 2021;22(2):818.
277. Huang Q, Wang T, Yang L, Wang HY. Ginsenoside Rb2 alleviates hepatic lipid accumulation by restoring autophagy via induction of Sirt1 and activation of AMPK. *Int J Mol Sci*. 2017;18(5):1063.
278. Dai S, Hong Y, Xu J, Lin Y, Si Q, Gu X. Ginsenoside Rb2 promotes glucose metabolism and attenuates fat accumulation via AKT-dependent mechanisms. *Biomed Pharmacother*. 2018;100:93-100.

279. Huang R, Guo F, Li Y, et al. Activation of AMPK by triptolide alleviates nonalcoholic fatty liver disease by improving hepatic lipid metabolism, inflammation and fibrosis. *Phytomedicine*. 2021;92:153739.
280. Huang HM, Fan SJ, Zhou XR, et al. Histone deacetylase inhibitor givinostat attenuates nonalcoholic steatohepatitis and liver fibrosis. *Acta Pharmacol Sin*. 2022;43(4):941-953.
281. Wang YG, Xu L, Wang T, et al. Givinostat inhibition of hepatic stellate cell proliferation and protein acetylation. *World J Gastroenterol*. 2015;21(27):8326-8339.
282. McGreal SR, Bhushan B, Walesky C, et al. Modulation of O-GlcNAc levels in the liver impacts acetaminophen-induced

liver injury by affecting protein adduct formation and glutathione synthesis. *Toxicol Sci*. 2018;162(2):599-610.

How to cite this article: Yang Y, Wu J, Zhou W, Ji G, Dang Y. Protein posttranslational modifications in metabolic diseases: basic concepts and targeted therapies. *MedComm*. 2024;5:e752.
<https://doi.org/10.1002/mco2.752>