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REVIEW

Role of Protein Lysine Acetylation in the Pathogenesis and Treatment of Obesity and Metabolic Syndrome

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Abstract

Purpose of Review This review aimed to highlight the known role of histone deacetylases (HDACs) and lysine acetyltransferases (KATs) in individuals with obesity, better understand the role of HDACs and KATs enzymes in obesity and related metabolic disorders.

Recent Findings Numerous cellular activities, including DNA replication, DNA repair, cell cycle regulation, RNA splicing, signal transmission, metabolic function, protein stability, transportation, and transcriptional regulation, are influenced by lysine acetylation. Protein lysine acetylation serves several purposes, which not only contribute to the development of metabolic disorders linked to obesity but also hold promise for therapeutic approaches. The current study demonstrates that HDACs and KATs control lysine acetylation.

Summary This review details the advancements made in the study of obesity, related metabolic diseases, and protein lysine acetylation. It contributes to our understanding of the function and mechanism of protein lysine acetylation in obesity and MS and offers a fresh method for treating these diseases.

Keywords Epigenetic modification · Lysine acetylation · Histone deacetylases · Lysine acetyltransferase · Obesity · Metabolic syndrome

Abbreviations

MS	Metabolic Syndrome
KATs	Acetyltransferase
HDACs	Histone Deacetylases
HDL	High-Density Lipoprotein
CBP	CREB-Binding Protein
HAT	Histone Acetyltransferase
LDs	Lipid Droplets
Foxo1	Forkhead box O1
TSA	Trichostatin A
p-AMPK	phosphorylated AMP-activated protein kinase
CTCL	Cutaneous T Cell Lymphoma
TGs	Triacylglycerols
WAT	White Adipose Tissue
BAT	Brown Adipose Tissue
IWAT	White Adipose Tissue
CIDEC	Cell Death-Inducing DFFA-like effector C
T2DM	Type 2 Diabetes Mellitus
HFD	High-Fat Diet

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Introduction

Obesity is defined as a medical condition caused by an imbalance between energy intake and energy consumption in the body [1]. In 2016, the World Health Organization reported that over 1.9 billion adults were overweight, with more than 650 million classified as obese. Additionally, over 340 million children and adolescents were either overweight or obese [2]. The prevalence of obesity has tripled since 1975, highlighting it as a critical health issue that is garnering increasing attention. Obesity is closely linked to various health conditions, including cardiovascular diseases, insulin resistance, diabetes, hypertension, cancer, DOX-induced cardiotoxicity, and COVID-19 [3–8]. Metabolic syndrome (MS) is marked by increased abdominal obesity, insulin resistance, decreased high-density lipoprotein (HDL), and elevated low-density lipoprotein (LDL) [9]. Obesity is considered a pivotal factor in the development of MS [10].

Numerous studies have demonstrated that various signaling pathways regulate the mechanisms underlying obesity and MS. Researchers have proposed that excessive energy intake can lead to hyperglycemia, hyperinsulinemia, and increased fat mass, contributing to the development of obesity [11]. Disruptions in circadian rhythms can impact metabolic health and regulate obesity through effects on lipid metabolism [12]. Obesity can also trigger systemic inflammation due to chronic low-grade inflammation in adipose tissue, promoting insulin resistance, type 2 diabetes mellitus (T2DM), and hormonal imbalances [13]. Additionally, obesity is associated with cancer progression due to systemic and local changes [11]. Various mechanisms, including protein lysine acetylation—an post-translational modification—can regulate obesity and MS. Studies have explored the relationship between protein lysine acetylation and conditions such as cardiovascular disease, inflammatory disease, and cancer [3, 14–18].

Current research underscores the relationship between epigenetic modifications, obesity, and MS. These modifications can regulate the development and progression of obesity and MS through complex mechanisms primarily affecting DNA, histones, and chromatin-associated proteins, inheritable during cell division without altering the DNA sequence [19]. Lysine acetylation, a key aspect of post-translational modification, has become a focal point of research in relation to obesity and MS. This reversible post-translational modification is involved in various cellular processes, including signaling, chromatin remodeling, the cell cycle, RNA splicing, and protein stability [20, 21]. Studies have frequently reported a close association between lysine acetylation and diseases such as obesity and MS [22]. Recent research indicates that lysine acetyltransferases (KATs) and histone deacetylases (HDACs) are involved in lysine acetylation [22]. KATs facilitate the acetylation of lysine residues by transferring an acetyl group from acetyl CoA, while acetyl-CoA or acetyl-phosphate can also non-enzymatically regulate lysine residues. HDACs, conversely, promote the deacetylation process [23]. Researchers have emphasized that HDACs can regulate immune signaling pathways, immune responses, interferon and TLR signaling pathways related to chronic inflammation, antigen presentation, and pathogen infection, as well as immune metabolic homeostasis. This suggests that KATs and HDACs play significant roles in metabolic diseases, including cardiovascular disease, inflammatory disease, obesity, and MS, by regulating the insulin signaling cascade and lipid, glucose, and carbon metabolism [22, 24–31]. Lysine acetylation is crucial for maintaining energy balance and regulating metabolism [32]. Many studies have focused on the relationship between HDACs, obesity, and MS.

In this review, we aim to elucidate the established roles of HDACs and KATs in individuals with obesity, enhance our understanding of these enzymes in obesity and related metabolic disorders, and inform the application of HDAC and KAT regulators in these contexts. Additionally, this study seeks to identify novel approaches for the treatment and prevention of obesity and associated metabolic disorders.

Methods

In light of numerous publications underscoring the regulatory significance of HDACs and KATs in obesity and MS, we conducted a comprehensive literature review. Utilizing the PubMed database via Google Browser, we amassed 116 pertinent articles, culminating in a detailed summary of the regulatory mechanisms, enzymes, and clinical applications of HDACs and KATs in the context of obesity and MS.

Enzymes

HDAC

In humans and rodents, HDACs are usually divided into four categories: Class I (HDAC 1, 2, 3, and 8), Class II (HDAC 4, 5, 6, 7, 9, and 10), Class III (sirtuin1,2, 3, 4, 5, 6, and 7), and Class IV (HDAC 11). Class II HDACs are subdivided into Class IIa (HDAC 4, 5, 6, 7, and 9) and Class IIb (HDAC 6 and 10) [33]. Classes I, II, and IV belong to the same family, and their activity depends on Zn^{2+}, whereas Class III exhibits an NAD^{+}-dependent mechanism [33]. Classes I, II, and IV are found in the nucleus [24], whereas Class II proteins were also found in the cytoplasm. Regarding Class III, SIRT1 and SIRT6 are located in the nucleus,

SIRT7 in the nucleolus, and SIRT2 in the cytoplasm, while SIRT3, SIRT4, and SIRT5 are located in the mitochondria [34] (Fig. 1). The effects of HDACs on obesity and metabolic disorders are summarized in Table 1.

KAT

Current research divides the KATs family into five groups of proteins: the GNAT family (Gcn5, PACF, Hat1, and Elp3), the MYST family (MOZ, Tip60, mof, morf, and Hbo1), and the p300/ CREB-binding protein (CBP) family. The fourth group is the nuclear receptor coactivator family, which includes NCOA1 and NCOA3 proteins. The fifth group comprises basal transcription factors, such as TAF1 and TAF1L [22, 35–38]. KATs have three domains: catalytic, bromodomains, and other modification recognition domains [22, 39]. We summarize the KATs related to obesity and MS in Table 1.

Enzymes and Adipose Tissue

Adipose tissue in the human body functions as an energy reservoir, storing energy in adipocytes that undergo hypertrophy and proliferation to accommodate increased energy demands. Hypertrophy involves the accumulation of triglycerides, while proliferation denotes an increase in adipose precursor cells, both processes collectively facilitating enhanced energy storage. These precursor cells proliferate and differentiate through a process termed adipogenesis [40]. The quantity and functionality of adipocytes vary between individuals with obesity and those who are healthy. Recent studies have identified that HDACs play significant roles in adipocyte proliferation and differentiation.

It is widely acknowledged that the Class I HDAC family has a strong association with adipose tissue. One hypothesis postulates that the absence of HDAC1/2 leads to reduced lipid accumulation, suggesting that HDAC1/2 positively regulates adipogenesis [41]. Another study demonstrated that during the differentiation of brown adipocytes, sympathetic activation of brown adipose tissue (BAT) results in the downregulation of HDAC1. This reduction in HDAC1 expression promotes BAT-specific gene expression in

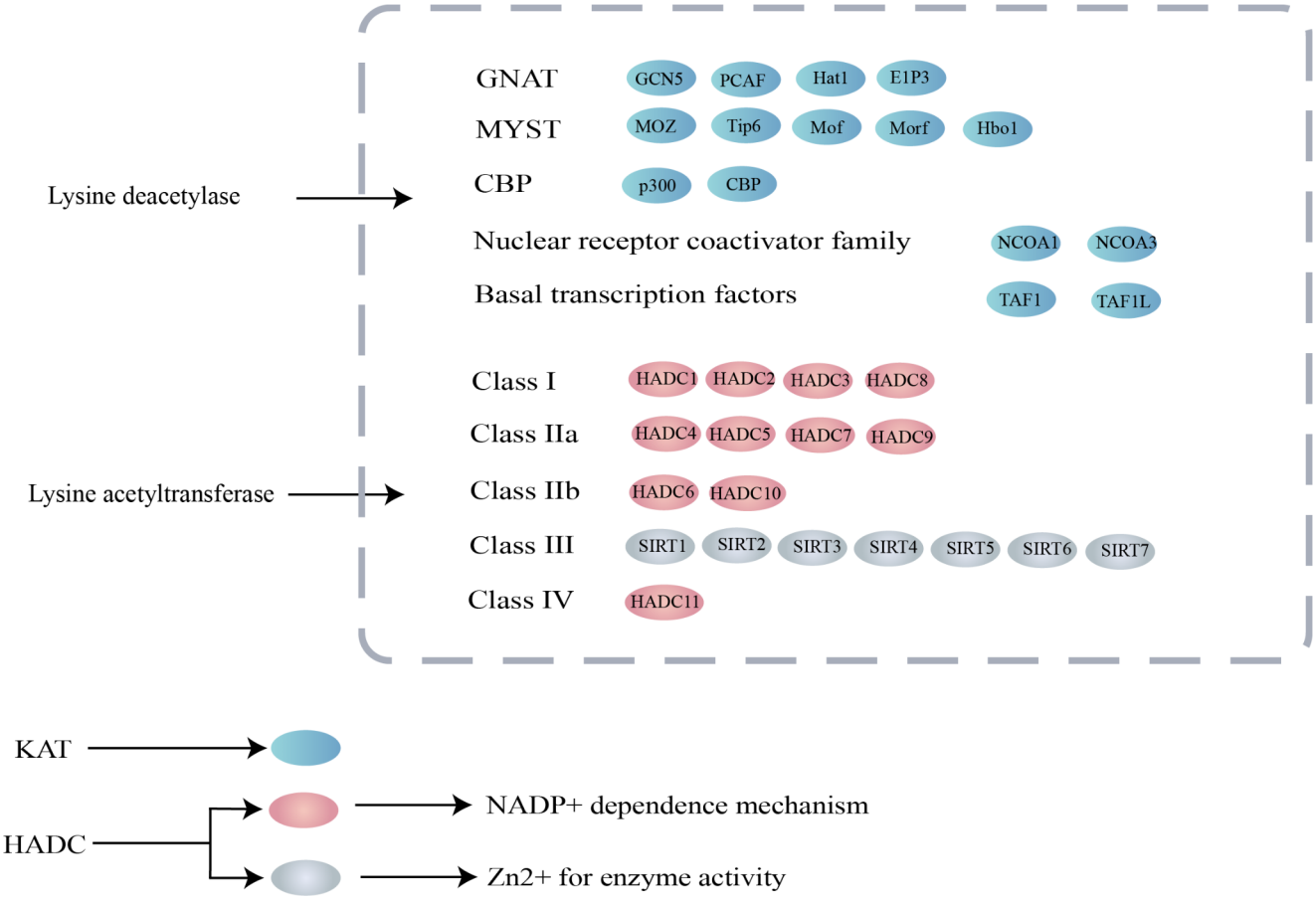

Fig. 1 Classification of lysine acetyltransferase and lysine deacetylase

Table 1 List of lysine acetylation enzymes discussed in this review

Action target	HDAC specificity	Finding	Reference
Adipose tissue	Class I	Promote the adipogenesis, inhibite the browning of adipocyte, decrease the oxidative metabolism and energy consumption	[40, 41, 43, 44, 46, 47, 48, 85, 87, 89, 90, 106]
	Class II	Reduce adipogenesis.	
	Class III	Regulate the proliferation and differentiation of adipose tissue, promote the oxidative metabolism and energy consumption.	
	Class IV	Promote the differentiation and development of the adipocyte, increase the lipid accumulation, decrease oxygen consumption, and inhibit lipid metabolism	
	KAT family	Regulate the brown adipocyte differentiation and adipogenesis	
The intestinal mucosal epithelium	HDAC3	Promote the lipid uptake, and regulated the circadian rhythm of serum triglyceride concentration, decrease lipid oxidationgene expression.	[61–65]
	HDAC6	Changes in intestinal flora regardless.	
The glucose tolerance and Insulin resistance	Class I	Have a negative effect in glucose tolerance and Insulin sensitivity.	[66, 68, 70–75]
	Class II	Regulate glucose tolerance and Insulin resistance.	
	Class III	Improve the glucose tolerance and regulate Insulin resistance.	
	Class IV	Have a positive effect insulin resistance	
	KAT family	Regulate the gluconeogenesis and reduce the accumulation of intracellular insulin	
Inflammation	Class I	Stimulate effects in inflammation.	[65, 70, 79–83]
	Class II	Have inhibitory effects in inflammation.	
	Class IV	Have a negative effect in inflammation.	
	KAT family	Promote the development of the inflammation	

KAT, Lysine Acetyltransferase; HDAC, Histone Deacetylases

Table 2 List of HDAC regulators

HDAC inhibitor	HDAC specificity	diseases	reference
Chidamide	Class I, IIb	Breast cancer	[107]
Panobinostat	Class I, II, IV	Myltiplemyeloma	[108]
Valproic acid	Class I, IIa	Epilepsia	[109]
Sodium butyrate	Class I, II	Amyotrophic lateral sclerosis	[23]
Cambinol	SIRT1, SIRT2	Cancer, neurology	[110]
Nicotinamide	Class III	Cancer	[23]
RG2833	HDAC3	Cancer	[111]
Rocilinostat	HDAC6	Friedreich's ataxia	[23]
Apicidin	Class I	Cancer	[112]
Mocetinostat	Class I, IV	Cancer	[113]
Givinostat	Class I, II, IV	Cancer	[114]
Entinostat	Class I	Cancer	[23]
Romidepsin	Class I	Cancer	[115]
Tubastatin A	HDAC6	Inflammation, neurology	[116]
Trichostatin A	Class I, II, IV	Broad	[117]
Resminostat	Class I, II, IV	Cancer	[93]
Quisinostat	Class I, II, IV	Cancer	[93]
Depsipeptid	Class I	Cancer	[93]

HDAC, histone deacetylase; SIRT, sirtuin

response to β-adrenergic agonist stimulation. Additionally, HDAC1 is known to interact with polycomb repressive complex 1 and 2, an interaction that β-adrenergic signaling activation can disrupt. HDAC1 recruits UTX to these promoters, which can reduce H3K27me3 levels while increasing H3K27 acetylation, indicating that HDAC1 negatively regulates the thermogenic program of brown adipocytes through H3K27 deacetylation. Another recent study found that HDAC3 silencing at the onset of differentiation enhances adipocyte functionality by boosting the expression of genes involved in differentiation, oxidative metabolism, browning, and mitochondrial activity [42]. Collectively, Class I HDACs are implicated in the regulation of adipocyte differentiation, often exerting a negative influence on the gene expression of brown adipocytes.

Within the Class II HDAC family, HDAC4 has been found to promote the presence of beige adipocytes, which may play a supportive role in energy metabolism. These non-target effects of HDAC4 could indirectly enhance the proliferation and metabolic function of beige adipocytes in inguinal white adipose tissue (IWAT) [43]. The deletion of HDAC6 in white adipose tissue increases the acetylation of DNA fragmentation factor subunit α-like effector proteins induced by cell death, leading to greater lipid droplet storage. HDAC6 deacetylation of CIDEC results in its instability and reduced lipid droplet fusion, indicating that HDAC-deficient adipocytes and adipose tissue exhibit higher levels of CIDEC and acetylation, alongside increased lipid storage [44]. Additionally, in HDAC6 knockout mice,

researchers observed a decrease in body temperature under normal housing conditions, with lower surface temperatures around the interscapular BAT depot and reduced rectal temperatures. The cAMP and UCP1 protein expression levels in brown adipocytes derived from BAT of these mice were also diminished, accompanied by increased lipid accumulation in BAT. This study suggests that HDAC6 activates the cAMP-PKA signaling pathway to elevate UCP1 expression, thereby contributing to thermogenesis in BAT [45]. Furthermore, HDAC9 inhibits the expression of C/EBPα genes in preadipocytes, likely by suppressing USF1 transcriptional activity. The accumulation of HDAC9-USF1 in the E-box region of the C/EBPα gene promoter inhibits adipogenic gene expression in preadipocytes. Upon induction of adipocyte differentiation, HDAC9 is downregulated and replaced by p300 at the E-box site, initiating the expression of adipogenic genes [46]. Overall, the Class II HDAC family exerts a negative regulatory effect on adipogenesis and adipogenic differentiation.

The Class III HDAC family primarily includes the sirtuins. Studies have shown that the mRNA expression levels of SIRT1, SIRT3, and SIRT6 are higher in subcutaneous adipose tissue compared to the liver. Weight loss leads to an increase in the expression of SIRT1, SIRT3, and SIRT6 in subcutaneous adipose tissue, and significantly enhances the mRNA expression of SIRT3 and SIRT6 in the liver [47]. Consequently, SIRT1, SIRT3, and SIRT6 are believed to play a role in adipose tissue proliferation and differentiation. Animal experiments indicate that SIRT3 enhances oxidative phosphorylation and energy expenditure. Some researchers propose that the SENP1-SIRT3 signaling pathway modulates SIRT3 activation and mitochondrial metabolism during metabolic stress [48]. Low expression of SIRT1 in adipose tissue may result in the interaction of exons with PPARγ, promoting lipid accumulation and eventually leading to obesity [49]. Inhibition of SIRT3 upregulates MCUE expression via an AMPK-dependent epigenetic pathway, increasing MCU-mediated mitochondrial calcium uptake, leading to elevated ROS production and promotion of BAT whitening. Thus, capsaicin can inhibit mitochondrial calcium overload and enhance SIRT3 expression in brown adipocytes by activating AMPK, thereby preventing BAT whitening [50]. SIRT3 also promotes the browning of white adipose tissue (WAT), with its RNA expression being higher in BAT than in WAT. Research has demonstrated that SIRT3 promotes the expression of PGC-1α and UCP1, enhancing mitochondrial electron transport activity and uncoupling capacity, which in turn stimulates mitochondrial respiration. Additionally, diminished SIRT3 function may reduce thermogenesis and energy expenditure. Studies have found that the expression of SIRT3, UCP1, and mitochondria-related genes is decreased in obesity, suggesting that SIRT3 regulates adaptive thermogenesis by promoting mitochondrial respiration [51]. Overall, the sirtuin family is involved in adipose tissue proliferation and differentiation, as well as promoting oxidative metabolism and energy expenditure.

The Class IV HDAC family is represented by HDAC11, which has been found to suppress thermogenic gene expression, thereby decreasing energy expenditure and thermogenesis [52]. There are two primary strategies for treating obesity: increasing UCP-1 expression, and activating BAT while inhibiting WAT expansion. Excess energy is stored in WAT as fat, whereas BAT converts fat into calories [53]. Silencing the HDAC11 gene with small interference RNA reduces the expression of key adipose transcription factors such as PPARγ2, Adipoq, and Perilipin, leading to a decrease in intracellular lipid droplets and inhibiting adipocyte differentiation [54]. HDAC11 regulates the expression of transcription factors and adipose tissue factors, promoting adipocyte differentiation and development while inhibiting lipid accumulation and energy expenditure.

Recent studies on KAT family members have revealed that TIP60 is involved in adipogenesis. Researchers have shown that knocking out TIP60 inhibits fat-cell differentiation [55]. Another study found that disrupting TIP60 activity blocks fatty acid-induced triacylglycerol synthesis [56]. GCN5 has been shown to promote PPARγ transcription and facilitate the recruitment of RNA polymerase II to PRDM16, regulating brown adipocyte differentiation [57]. Inhibition of KAT activity in 3T3-L1 cells has been found to impair adipogenesis, with CBP and p300 playing essential roles in adipocyte formation. The histone acetyltransferase activities of CBP and p300 are crucial for regulating adipocyte differentiation and maintaining mature adipocyte functions [58]. Additionally, increased acetylation of SREBP-1c at K289 and K309 by histone acetyltransferase (HAT) CBP/p300 during hepatic lipogenesis leads to the upregulation of lipogenic genes [59].

A study also showed that p300/CBP regulates gluconeogenesis in the fasting state [60]. Moreover, diminishing the HAT activity of p300/CBP can lead to a reduction in Forkhead box O1 (Foxo1) expression in the liver, thereby lowering fasting blood glucose levels. It is proposed that the cAMP-PKA pathway may stimulate p300 activity to activate the Foxo1 gene. Consequently, this regulates the expression of the Foxo1 gene, which in turn triggers the gluconeogenic program during fasting to sustain euglycemia [60].

The HDAC and KAT families modulate the proliferation and differentiation of adipose tissue through distinct mechanisms. Investigating the roles of HDAC and KAT families can provide valuable insights into the differentiation and proliferation processes of adipose tissue in patients with obesity, and offer novel approaches for the treatment and management of obesity (Fig. 2).

Enzymes in the Intestinal Mucosal Epithelium

Several studies have indicated that the proliferation, differentiation, and function of intestinal mucosal epithelial cells often undergo changes during obesity [61]. Given the strong connection between epigenetics and obesity, some researchers have sought to elucidate the alterations in the intestinal mucosal epithelium in patients with obesity through the lens of epigenetic modifications, particularly focusing on the Class I HDAC family.

One hypothesis suggests that reduced expression of HDAC3 in intestinal epithelial cells in mice can enhance energy expenditure and glucose tolerance, thereby mitigating obesity in the context of a high-fat diet. The research supporting this theory demonstrated that low HDAC3 expression promoted triglyceride accumulation in IECs, which increased energy expenditure and decreased serum triglyceride levels, body fat, and body weight. Inhibiting HDAC3 activity or inducing its degradation in the intestinal mucosal epithelium may improve metabolic status and reduce body weight in obese mice [62]. This study highlights the role of HDAC3 in affecting intestinal mucosal epithelial cells in obese mice. Additionally, some researchers discovered that intestinal microbes could regulate HDAC3 to participate in the circadian metabolic rhythm of the mouse small intestine. HDAC3 was found to enhance the expression of the lipid transporter CD36 and increase lipid uptake by IECs, while also regulating the circadian rhythm of serum triglyceride concentrations. Furthermore, the intestinal microbiota was shown to induce the expression of intestinal epithelial HDAC3 and promote its interaction with chromatin, resulting in synchronized diurnal changes in histone acetylation, metabolic gene expression, and nutrient uptake.

Thus, the differential expression of HDAC3 in the intestines of obese and normal mice suggests that intestinal HDAC3 may play a role in regulating obesity [63]. Another theory posits that HDAC3 can inhibit the transcription of the nuclear receptor PPAR family, leading to

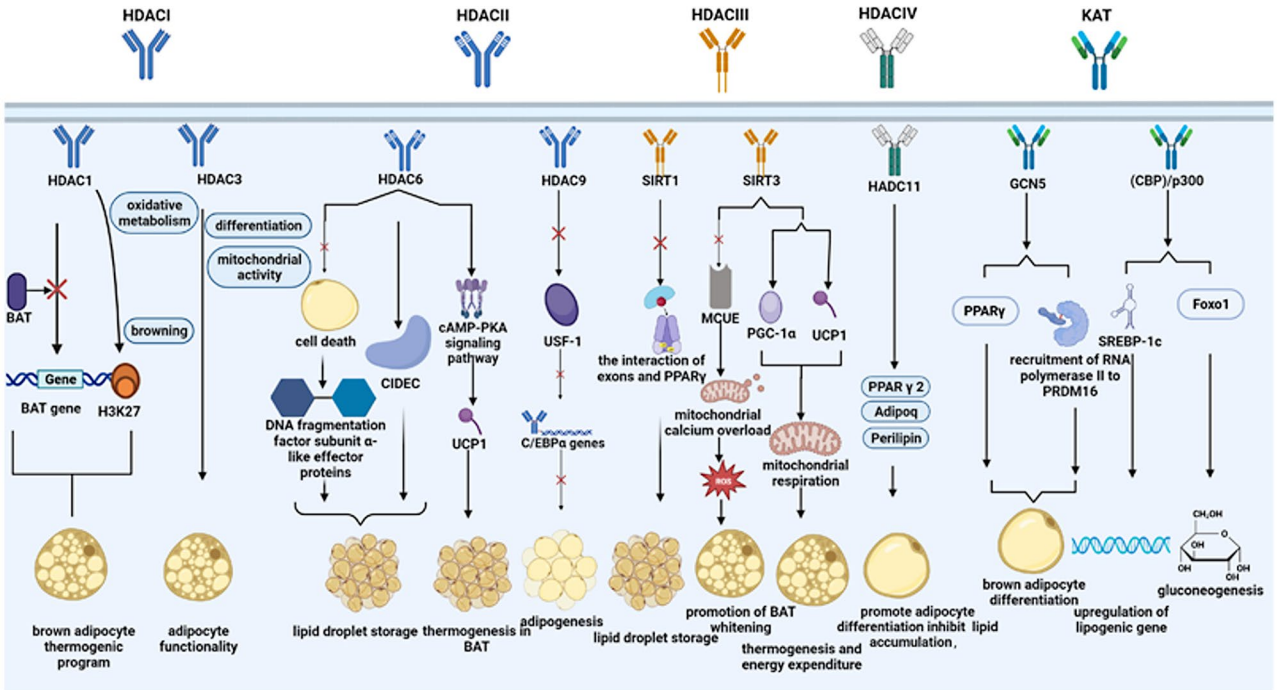

Fig. 2 HDACs and KATs that are involved in adipose tissue regulation. While negatively regulating the thermogenic program in brown adipocytes via H3K27 deacetylation, HDAC1 can also regulate the BAT-specific gene expression in brown adipocytes by the BAT. By controlling differentiation, oxidative metabolism, browning, and mitochondrial activity, HDAC3 can control the functionality of adipocytes. Acetylation of DNA fragmentation factor subunit -like effector proteins can be reduced by HDAC6 regulation of CIDEC. As a result, the storage of lipid droplets is reduced, and the cAMP-PKA signaling pathway is activated, increasing the production of UCP1 and promoting thermogenesis in BAT. HDAC9 can inhibit the expression of adipogenic genes in preadipocytes by downregulating the expression of C/EBP genes, which in turn downregulates the expression of adipogenic genes in preadipocytes. Exon-PPAR interaction can be controlled by SIRT1, which also reduces lipid synthesis. SIRT3 can control the expression of MCUE, increasing ROS generation, enhancing BAT whitening, encouraging the expression of PGC-1 and UCP1, which can trigger mitochondrial respiration and controll adaptive thermogenesis. HDAC11 can control the expression of PPAR-2, AdipoQ, and Perilipin, which decreases lipid droplets and prevents the development of adipocytes. To control the development of brown adipocytes, GCN5 can increase PPAR transcription and enable the recruitment of RNA polymerase II to PRDM16. The (CBP)/p300 can activate the Foxo1 gene to control gluconeogenesis and enhance SREBP-1c acetylation, which in turn can boost the expression of the lipogenic gene

a decrease in the expression of genes involved in fatty acid oxidation in intestinal cells. This study demonstrated that a deficiency in intestinal HDAC3 regulates fatty acid oxidation and reduces obesity in mice, even in the context of a high-fat diet. Researchers observed that the loss of HDAC3 enhances PPAR activity, inducing the expression of lipid oxidation genes and promoting weight loss. In summary, intestinal HDAC3 deficiency can potentiate the effects of PPAR agonists, inducing lipid oxidation, gene expression, and weight reduction [64]. Furthermore, studies have shown that HDAC3 can decrease the expression of lipid oxidation genes in intestinal cells, contributing to weight gain. Additionally, research on HDAC6-deficient mice has revealed that these mice are more susceptible to weight gain when exposed to a high-fat diet, developing hyperlipidemia and hepatic steatosis. It was indicated that HDAC6 deficiency alters the composition of obesogenic microbes in the gut, thus suggesting that the loss of HDAC6 can lead to changes in intestinal flora and induce obesity [65].

In conclusion, this exploration of the relationship between lysine acetylation and the intestinal mucosal epithelium highlights several areas that require further investigation. These studies offer new avenues for regulating the intestinal mucosal epithelium and gut microbiota, which may aid in the prevention and treatment of obesity and related metabolic disorders.

The Enzymes' Relationship With Insulin Resistance and Glucose Tolerance

Patients with obesity generally exhibit significant insulin resistance and poor glucose tolerance. Increasing research into epigenetic modifications has led many scientists to explore the mechanisms underlying impaired insulin resistance and glucose tolerance in obesity from this perspective. Reduced HDAC3 expression enhances lipid synthesis and storage in lipid droplets (LDs) in metabolic precursors, reduces hepatic glucose production, and increases insulin sensitivity without altering insulin signaling or body weight [66]. HDAC3 expression is inversely correlated with insulin resistance. Thus, the Class I HDAC family is negatively associated with glucose tolerance and insulin sensitivity.

Conversely, the Class II HDAC family shows an association with glucose tolerance and insulin resistance. Some studies have found a significant reduction in HDAC4 levels in patients with obesity, which inversely correlates with metabolic indices and normalizes after weight loss. Researchers propose that decreased HDAC4 levels reduce obesity, insulin resistance, and type 2 diabetes [67]. It is established that GLUT4, a glucose transporter protein, mediates glucose uptake facilitated by insulin, and low GLUT4 expression can induce insulin resistance. Interestingly, HDAC4 and HDAC5 regulate the GLUT4 promoter during adipocyte differentiation. Specifically, HDAC5 first associates with the GLUT4 promoter in preadipocytes, while HDAC4 only binds when HDAC5 is knocked out [68]. This suggests that HDAC4 and HDAC5 modulate insulin resistance through GLUT4 regulation. Further research indicates that diminished HDAC5 and HDAC6 expression may cause reacetylation of various cytoplasmic and/or nuclear proteins, potentially leading to ICER deregulation, impaired adipocyte secretion, dysfunction, and systemic insulin resistance in obesity [69]. Overall, the Class II HDAC family more effectively regulates glucose tolerance and insulin resistance.

Within the Class III HDAC family (SIRT family), one theory posits that SIRT1 regulates food intake and energy expenditure via SF1 neurons and enhances skeletal muscle insulin sensitivity. High SIRT1 expression improves skeletal muscle insulin sensitivity, suggesting protection against diet-induced obesity and promoting glucose/insulin balance [70]. Another theory proposes that SIRT1 activates fibroblast growth factors, which regulate glycolipid homeostasis in obesity-induced diabetes. Key regulators of gluconeogenesis, such as hepatocyte nuclear factor 4α, PGC1, and glucose-6-phosphatase, are modulated by SIRT1. Additionally, SIRT1 activates the PI3K signaling pathway to increase skeletal muscle insulin sensitivity and affects GLUT4 translocation, enhancing insulin resistance in adipose tissue [71]. Furthermore, studies show that SIRT1 in adipose tissue can bind to exosomes and be partly activated by the TLR4/NF-κB signaling pathway, impairing insulin sensitivity [72]. In summary, SIRT1 can promote insulin resistance.

A significant research focus is on SIRT6. Studies have demonstrated that SIRT6 deficiency in cells enhances glucose uptake, glycolysis, and Hif1 activity while diminishing mitochondrial respiration. Researchers propose that SIRT6 plays a regulatory role in glucose metabolism [73]. Deficiency in the IRS1/PI3K pathway can inhibit Akt-dependent glucose uptake and lead to insulin resistance. Phosphorylation at the KSer307 site of IRS1 inhibits PI3 recruitment. Elevated serine phosphorylation of IRS1 causes insulin resistance, which can be mitigated by high SIRT6 expression. This implies that SIRT6 can prevent IRS1 phosphorylation, thereby averting insulin resistance in cardiomyocytes. Additionally, high SIRT6 expression inhibits lipid accumulation and ROS production, promoting mitochondrial health. Researchers have posited that SIRT6 mitigates insulin resistance through multiple mechanisms. Activation of Foxo1 in cardiomyocytes has been shown to exacerbate insulin resistance, while SIRT6 depletion increases Foxo1 expression in these cells. These findings indicate that elevated whole-body SIRT6 expression can protect against

obesity and insulin resistance and inhibit the progression of diabetes [74]. In summary, sirtuin family members enhance glucose tolerance and modulate insulin resistance.

For the Class IV HDAC family, HDAC11 deficiency has been found to elevate plasma adiponectin levels and adiponectin expression. Adiponectin, primarily produced by adipose tissue, reduces fat density through its plasma concentration and gene expression [75]. Adiponectin regulates lysophospholipid levels, which influence insulin resistance and glucose tolerance [76]. These findings suggest that adiponectin enhances fatty acid oxidation, improves insulin sensitivity, and regulates glucose tolerance [75]. In summary, HDAC11 promotes insulin resistance and impairs glucose tolerance.

In terms of KAT, research has indicated that the NuA4/Tip60 HAT complex can impact insulin resistance. Studies have shown that deletion of complex proteins results in the accumulation of intracellular insulin and reduced baseline insulin secretion [77]. p300 can acetylate IRS1/2, inhibiting the interaction between insulin receptors and IRS1/2, ultimately disrupting insulin signaling. It has been demonstrated that p300 can lead to hepatic insulin resistance [78].

In conclusion, protein lysine acetylation is intimately linked with glucose tolerance and insulin resistance. Further research into regulating the expression of HDAC and KAT families could provide therapeutic avenues for treating and preventing complications such as obesity-induced insulin resistance. (Fig. 3).

Enzymes and Inflammation

Obesity is frequently linked to chronic systemic or tissue inflammation [79]. Consequently, several researchers have investigated the association between chronic inflammation and HDAC family members in obese individuals. The initial hypothesis suggests a positive correlation between HDAC2 and IL-1b gene expression in obese mice. The inhibition of Class I HDAC in the aorta of mice can reduce the expression of pro-inflammatory cytokines such as TNF-a, IL-1b, and MCP-1 [80]. This indicates that Class I HDACs may facilitate chronic inflammation in obesity.

In contrast, T_{reg} cells are upregulated in the spleen and mesenteric lymphocytes in HDAC6-deficient individuals, while T_{reg} cells can reduce inflammation in adipose tissue [65]. The second theory proposed that HDAC2, 4, 5, 6 can regulate the expression of pro-inflammatory markers, which may indicate that Class I HDAC and Class II HDAC may have stimulating and inhibitory effects on inflammation. A negative correlation has been found between HDAC5 and inflammatory marker levels, possibly related to the low expression of HDAC5 in inflammatory tissues [69]. HDAC11 can regulate IL-10 secretion to modulate metabolic inflammation [81]. Low HDAC11 expression can increase the expression of IL-10 in macrophages. In contrast, high HDAC11 expression has the opposite effect. This is because HDAC11 binds to the distal region of the IL-10 promoter [82, 83]. Interestingly, some researchers have also observed an increase in the expression of pro-inflammatory markers upon silencing the expression of the HDAC3 [42]. This also indicates that Class I HDACs are involved in the development of inflammation.

Another study noted that SIK2 suppresses p300 HAT activity by direct phosphorylation of Ser89 and decreases lipogenesis in hepatocytes and mice overexpressing SIK2. Both liver-specific SIK2 knockdown and p300 overexpression can induce the development of hepatic steatosis, insulin resistance, and inflammation and can be inhibited by SIK2/p300 co-overexpression [84]. These results indicate that p300 regulates the development and occurrence of inflammation in obesity.

In summary, the expression of chronic inflammation in patients with obesity is closely related to HDAC and KAT families. The study of HDACs and KATs expression in patients with obesity can provide insights into the treatment of complications caused by chronic inflammation in these patients.

The Regulators' Relationship With Obesity and MS

Numerous studies have underscored the role of HDAC regulators, indicating that protein lysine acetylation is implicated in the onset and progression of obesity and MS.

One particular study demonstrated that HDAC3 modulates adipocytes. PRDM16, a transcriptional cofactor, governs brown and beige adipose tissue. Researchers observed that HDAC3 protein levels are lower in brown adipose tissue (BAT) compared to inguinal white adipose tissue (iWAT). Upon cold exposure, HDAC3 protein levels in adipocytes, especially in BAT, were reduced, suggesting that HDAC3 inhibition can trigger thermogenesis. Additionally, in genetic loss-of-function models of PRDM16, the HDAC3 inhibitor significantly decreased Ucp1 expression. Therefore, HDAC3 inhibits PRDM16-mediated thermogenesis in brown and beige adipocytes [85].

A study identified Trichostatin A (TSA) as a novel histone deacetylase inhibitor (HDACI). TSA was proposed to activate the AMPK pathway, thereby inhibiting adipogenesis in 3T3-L1 preadipocytes. The study found that the expression of leptin, FABP4, SREBP1C, PPARγ, and C/EBPα was suppressed while phosphorylated AMP-activated protein kinase (p-AMPK) was significantly upregulated [86].

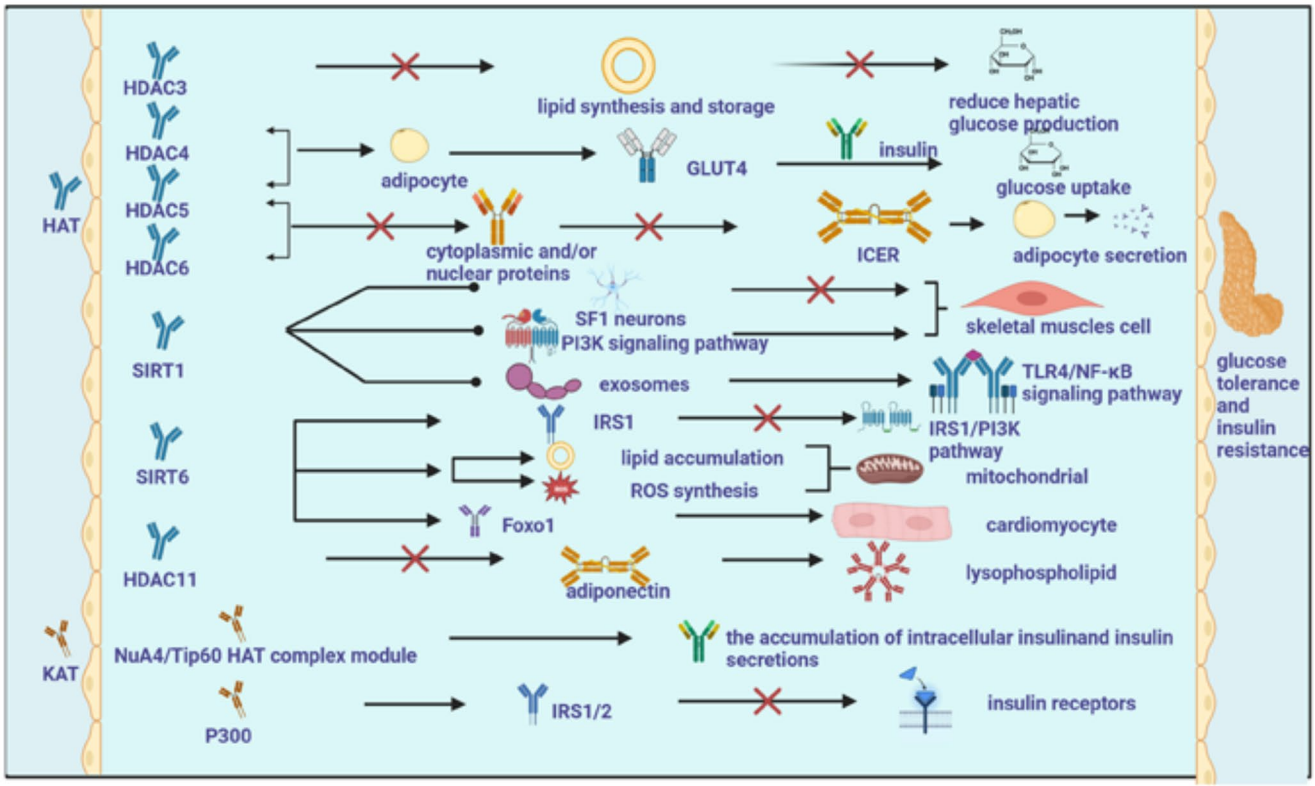

Fig. 3 KATs and HDACs play a role in glucose tolerance and insulin resistance. HDAC3 can contribute to increased insulin sensitivity, decreased hepatic glucose production, and promotion of lipid synthesis and storage within lipid droplets (LDs). By controlling GLUT4 to control glucose uptake, HDAC4 and HDAC5 can have an impact on insulin resistance. A number of cytoplasmic and/or nuclear proteins are reacetylated by HDAC5 and HDAC6, which results in the dysregulation of ICER, poor adipocyte secretion, adipocyte malfunction, and systemic insulin resistance. SIRT1 can control skeletal muscle insulin sensitivity by way of SF1 neurons. SIRT1 can activate the PI3K signaling pathway to improve skeletal muscle insulin sensitivity. By attaching to exosomes and activating the TLR4/NF-B signaling pathway, SIRT1 can reduce insulin sensitivity. Sirt6 has the ability to inhibit IRS1 phosphorylation, which stops cardiomyocytes from developing insulin resistance. SIRT6 promotes mitochondrial health by preventing the generation of ROS and lipid buildup. In cardiomyocytes, SIRT6 can control Foxo1 expression, which in turn controls insulin resistance. HDAC11 deficiency can impact lysophospholipid levels, plasma adiponectin levels, and adiponectin expression, all of which can impair glucose tolerance and insulin resistance. NuA4/Tip60 complex protein loss can result in intracellular insulin buildup and decreased basal insulin production. P300 has the ability to acetylate IRS1/2, block the interaction of insulin receptors with IRS1/2, and sabotage insulin signaling

MS-275 is widely acknowledged as a Class I HDAC inhibitor. In MS-275-treated mice, researchers observed an increased expression of UCP-1, Adrb3, Cidea, Dio2, and Ppara genes. There was a notable increase in brown adipose tissue (BAT) in subcutaneous and visceral organs, which led to enhanced oxidative metabolism and energy expenditure in adipose tissue. Furthermore, lipase expression was elevated, promoting triglyceride breakdown in adipocytes [87]. MS-275 has been extensively studied for its effects on glucose tolerance. One hypothesis suggests that MS-275 increases PPARG expression, enhancing typical adipose tissue functions. Except for Glut4, most genes were upregulated in visceral fat, while Glut4 and Plin were specifically upregulated in subcutaneous adipose tissue, potentially improving glucose tolerance [87]. Another hypothesis posits that MS-275 enhances the expression of the GLP-1 receptor, Gα's subunit of heterotrimer G protein, βarrestin-1, and Adcy-8, thereby promoting GLP-1R-mediated cAMP production and boosting insulin secretion, thus improving blood glucose levels in patients with obesity [88]. Fatty acids are crucial pathological factors affecting pancreatic β-cell vitality.

Saturated fatty acid palmitate promotes fatty acid oxidation, leading to reactive oxidant production and lipotoxicity. Researchers investigated whether a Class I HDAC inhibitor could influence pancreatic β-cell vitality under fatty acid stress. They found that MS-275 treatment increased the expression of cytoplasmic oxidoreductases Prdx4, Prdx1, Prdx6, Gpx2, Txnrd1, and Txnrd3, indicating enhanced neutralization of reactive oxidants compared with controls. Palmitate-treated cells showed reduced ROS generation when pre-treated with MS-275, correlating with decreased pancreatic beta cell death, increased insulin secretion, and improved blood glucose levels [88]. Therefore, researchers

believe that MS-275 enhances glucose tolerance and insulin sensitivity.

The third theory proposes that inhibiting Class I HDAC expression during the early phase of adipose differentiation can promote a highly oxidative metabolic phenotype in adipocytes. Class I HDAC inhibition can activate lipolysis and fatty acid β-oxidation, inducing genes such as Plin, which can reduce lipid droplet size. The effects of Class I HDAC inhibitor on adipose differentiation are primarily due to its regulation of PPARγ, which plays a crucial role in the browning of adipocytes and promoting adipogenesis. Therefore, Class I HDAC inhibitors can enhance the thermogenesis and browning of visceral and subcutaneous white fat, promoting the function of visceral adipocytes. Low expression of Class I HDAC can also promote oxidative metabolism and para expression [89]. The third theory also suggests that Class I HDAC inhibitors can prevent adipogenesis by reducing C/EBPβ binding affinity and transcriptional activation potential. A study showed that adipogenesis and the dynamic balance of adipocytes are controlled by HDAC1 and HDAC2, with Class I HDAC inhibitors effectively inhibiting adipogenesis [41]. Class I HDAC inhibitors can enhance the expression of key regulatory factors in mitochondria, increasing mitochondrial biogenesis and oxygen consumption in muscle cells and primary brown adipocytes. They enhance BAT function by increasing the expression of oxidative and uncoupled metabolic markers. These changes underlie increased heat production and may help improve circulating lipid levels. Researchers have also discovered that selective Class I HDAC inhibitors can promote the expression of oxidation genes and browning of WAT in skeletal muscle and BAT by reducing the binding of HDAC3 to the PGC-1α promoter and inducing PGC-1α transcription [90]. The Class I HDAC family can facilitate lipid accumulation, inhibit adipocyte browning, and diminish oxidative metabolism and energy expenditure in adipose tissue.

Additionally, some studies have demonstrated that HDAC11 inhibitors enhance adiponectin signaling, oxygen consumption, and lipid metabolism. Compared to the control group, there was a reduction in WAT weight in HDAC11-knockout mice and those fed a high-fat diet (HFD), likely due to smaller adipocytes and decreased lipid accumulation. Moreover, HDAC inhibitors have the potential to stimulate BAT formation and induce the browning of WAT [75].

In summary, regulators of protein lysine acetylation have been implicated in the development and prevention of obesity and metabolic syndrome, offering a novel approach for treating these conditions.

Clinical Application

We found from published preclinical and clinical trials that many diseases, including inflammation, cardiovascular diseases, and cancer, are related to protein lysine acetylation [91–95]. Several drugs, such as romidepsin, vorinostat, panobinostat, and belinostat, have been approved by the Food and FDA for the treatment of cutaneous T-cell lymphoma (CTCL), peripheral T cell lymphoma, and multiple myeloma. Lysine acetylation regulators can be used to treat acute kidney Injury, Alzheimer's disease, and cancer [96–98]. The regulators are listed in Table 2. Given the close connection between lysine acetylation, obesity, and MS, it is expected that many drugs or therapeutic regimens will be designed to treat these conditions in the future.

Discussion

Over the years, the prevalence of obesity has been rising annually, drawing increasing attention to obesity and metabolic syndrome (MS). Obesity is a complex disease resulting from the interaction of lifestyle, environmental, genetic, and epigenetic factors [99]. This review focuses on acetylation modification, which is closely linked to obesity and MS. Adipose tissue, primarily composed of adipocytes, serves as the main storage site for triacylglycerols (TGs), which store excess energy [100]. WAT and BAT are the main types of adipose tissue in mammals. The accumulation of white fat causes obesity, while the main function of BAT is energy expenditure and the suppression of obesity [101]. Researchers have also identified a third type of fat, known as beige fat [102]. Based on the functional characteristics of WAT, BAT and beige adipose tissue, rational regulation of these tissues may represent a novel mechanism for the treatment of obesity [103]. Glucose is the energy source for most cellular functions. An increase in postprandial circulating glucose levels stimulates insulin release from pancreatic β-cells. Insulin plays a vital role in glucose homeostasis [104]. Insulin resistance and glucose tolerance are often observed in obesity. Lysine acetylation is also closely associated with obesity and MS.

Lysine acetylation has emerged as a promising therapeutic intervention for obesity and MS due to its significant role in regulating gene expression and metabolism. It can influence the development and progression of obesity and MS by modulating multiple signaling pathways and gene expression or by directly targeting receptors. Researchers have concentrated on the regulation of lysine acetylation in the pathogenesis of obesity and MS, uncovering various regulatory mechanisms. Researchers have found that MS-275, as a regulator of the Class I HDAC family, improves the

obese phenotype and insulin sensitivity [90] in diet-induced obese mice [87]. Researchers have also found that the expression of genes crucial for adipocyte metabolism and browning differentiation into adipocytes was amplified by MS-275 [89]. SIRT6 has been identified as a histone H3K9 deacetylase that controls the expression of multiple glycolytic genes. SIRT6-deficient cells exhibit increased Hif1α activity, upregulated glycolysis, and reduced mitochondrial respiration, resulting in increased glucose uptake. Studies have also indicated that SIRT6 plays a role in nutrient stress responses [73]. It was reported that SIRT 1 gene expression was reduced in PBMCs from children with obesity and adolescents and was associated with BMI [71]. Furthermore, SIRT1 gene expression is reduced in peripheral blood mononuclear cells (PBMCs) from obese children and adolescents and is associated with BMI. SIRT1 has been shown to activate fibroblast growth factor 21, which regulates glucose and lipid homeostasis in obesity-induced diabetes. Additionally, SIRT1 regulates the levels of PGC1α, hepatocyte nuclear factor 4α, and glucose-6-phosphatase, all of which are key factors in gluconeogenesis.

Additionally, SIRT1 enhances insulin sensitivity in skeletal muscle via the PI3K signaling pathway and reduces inflammation in adipose tissue, thereby inhibiting insulin resistance [105]. Researchers p300have demonstrated that glucagon may increase *Foxo1* expression in the fasted state through CREB coactivators. Insulin signaling terminates nuclear *Foxo1* activity by phosphorylating the protein, promoting its nuclear exclusion and degradation. specifically activates *Foxo1* gene expression at the transcriptional level. Thus, enhancing gluconeogenesis. Therefore, *Foxo1*, via p300 is considered to fully activate the gluconeogenic program during fasting to maintain euglycemia [60]. Considering the crucial role of protein lysine acetylation in obesity and MS, regulating HADCs and KATs may prove beneficial for the early prevention of obesity-associated complications. However, the role of lysine acetylation remains controversial and may vary in different diseases or depending on the disease course.

Recent research has shown that HDACs and KATs are active during adipocyte differentiation, play a crucial role in determining phenotypic fate, and serve as key regulators of glucose homeostasis. These findings could pave the way for new therapeutic strategies to combat metabolic diseases such as diabetes and obesity. Our review also highlighted the altered gene expression of HDACs and KATs in obesity. However, further investigation is required to elucidate the detailed molecular mechanisms underlying these effects.

In conclusion, numerous studies have demonstrated that various signaling pathways are involved in the regulation of obesity and metabolic syndrome (MS). Unlike previous studies, our work provides a comprehensive summary of current signaling pathways associated with HDACs and KATs. Ongoing research underscores the link between epigenetic modifications, obesity, and MS. By regulating the insulin signaling cascade and lipid, glucose, and carbon metabolism, KATs and HDACs play a significant role in metabolic diseases, including cardiovascular disease, inflammatory disease, obesity, and MS. Our study offers an integrative overview of these mechanisms and reviews the current clinical applications of HDACs and KATs as well as commonly used regulators.

Protein lysine acetylation is a critical mechanism involved in various processes that contribute to obesity and metabolic syndrome (MS), such as cell metabolism, gene transcription, and enzymatic activity. Despite its significance, studying protein lysine acetylation poses considerable challenges. Consequently, further research is warranted with a particular emphasis on the role of acetylation modifications in obesity. Targeting the enzymes responsible for protein lysine acetylation presents a promising avenue for research. Investigating protein lysine acetylation will offer a novel approach for treating obesity and MS effectively and will support the development of new therapeutic drugs for obesity. Protein lysine acetylation influences the development of obesity and metabolic syndrome (MS) through intricate mechanisms. The pathogenesis of obesity is intricate and difficult to comprehend, and the roles of lysine acetyltransferases (KATs) and histone deacetylases (HDACs) differ significantly, making it challenging to analyze their actions in various tissues of obese patients. Our study provides a summary of the relatively well-acknowledged regulatory mechanisms but does not offer a precise and detailed description of each mechanism. Consequently, future research will focus on the detailed study of each regulatory mechanism.

Conclusions

In summary, we highlight the known role of HDACs and KATs in individuals with obesity, understand the role of HDACs and KATs enzymes in obesity and related metabolic disorders, and guide the application of HDACs and KATs regulators in these conditions. Our review outlines the relationship between protein lysine acetylation in both obesity and MS. The role of various regulators is also highlighted in this article. However, its numerous underlying regulatory mechanisms remain unclear. This indicates the need for further, more detailed study in this area.

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Author Contributions Yu Li, Zhuoli Zhang and Tao Yu conceived the review. Zhaopeng Li conducted the literature search and drafted the manuscript. Zhao Li, Shuguang Liu, Yi Song collected the related article. Yancheng Song, Zhuoli Zhang, Tao Yu and Yu Li revised the manuscript. All authors have read and approved the article.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

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