Protein acetylation and deacetylation: An important regulatory modification in gene transcription (Review)

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Abstract. Cells primarily rely on proteins to perform the majority of their physiological functions, and the function of proteins is regulated by post-translational modifications (PTMs). The acetylation of proteins is a dynamic and highly specific PTM, which has an important influence on the functions of proteins, such as gene transcription and signal transduction. The acetylation of proteins is primarily dependent on lysine acetyltransferases and lysine deacetylases. In recent years, due to the widespread use of mass spectrometry and the emergence of new technologies, such as protein chips, studies on protein acetylation have been further developed. Compared with histone acetylation, acetylation of non-histone proteins has gradually become the focus of research due to its important regulatory mechanisms and wide range of applications. The discovery of specific protein acetylation sites using bioinformatic tools can greatly aid the understanding of the underlying mechanisms of protein acetylation involved in related physiological and pathological processes.

Contents

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1. Introduction

The functions of biological systems are complicated and diverse, and are largely dependent on the regulation of protein function. After translation is complete, the proteins need to undergo different degrees of chemical modifications, known as post-translational modifications (PTMs), which can change structures by altering the physicochemical properties of the primary sequences and adjusting protein compactness by changing their charge (1). In addition, PTMs can interfere with the shift of protein state (2). The main types of PTM include methylation, acetylation, glycosylation, ubiquitination and phosphorylation (3). Enzymatic acetylation modifies ~50% of yeast proteins and up to 90% of higher eukaryotic proteins (4). Fewer acetylated proteins have been identified in prokaryotes (5). The main mechanism of protein acetylation, which is one of the most advanced topics in PTM studies, is that acetyl donors (such as acetyl-CoA) transfer acetyl groups to the proteins under the catalysis of acetyltransferase (6). Acetylation occurs mainly on lysine and can be divided into histone acetylation and non-histone protein acetylation (7). There are currently three well-known forms of acetylation: Nα-acetylation, Nε-acetylation and O-acetylation (8). Nα-acetylation refers to the addition of an acetyl group to the α-amino group of the N-terminal amino acid, which is an irreversible process; ~85% of human protein is modified by Nα-acetylation (9). Nε-acetylation refers to the addition of an acetyl group to the ε-amino group of the lysine residue, which is a reversible process (10). O-acetylation refers to the addition of an acetyl group to the tyrosine/serine/threonine hydroxyl group (11).

The research history of protein acetylation has spanned >50 years. Lysine acetylation in histones was first discovered and proposed by Vincent Allfrey in 1964 (12), which was considered to be related to the regulation of gene transcription (13). Histones contain a large number of two basic amino acids, lysine and arginine, and therefore have a positive charge. If lysine is acetylated, it will no longer be positively charged, so the binding of DNA to the histone is relaxed, which facilitates gene transcription (12). In 2009, >1,000 types of acetylated non-histone proteins were historically discovered by studying metabolic pathways of different species (14). In accordance with the large amount of non-histone protein acetylation,

histone acetyltransferases (HATs) and histone deacetylases (HDACs) were renamed to lysine acetyltransferases (KATs) and lysine deacetylases (KDACs), respectively (15,16). It was discovered that acetylation could affect the enzyme activity of nucleases, thereby regulating the level of substrate RNA (17). This discovery indicates that organisms can achieve self-regulation of cells through nucleases.

It has been reported that there is a wide range of protein acetylation, which could mean that they have crucial physiological functions in various biological activities. Protein acetylation is one of the major regulators of gene transcription (18). Most HATs are localized in the nucleus and function as transcriptional co-activators (19). Acetylation involves the regulation of >100 non-histone proteins, including transcription factors (TFs), transcriptional coactivators and nuclear receptors (20). Protein acetylation is also associated with protein degradation. Early studies demonstrated that proteins with free α-amino groups can be degraded by ATP-dependent ubiquitin degradation, and that ubiquitin-mediated protein degradation can be prevented when the N-terminal α-amino group is acetylated (21). Besides, protein acetylation can regulate a variety of signaling pathways and affect the cell cycle. In this review, the latest advances in protein acetylation of both histone and non-histone proteins will be presented, and the interaction between diseases and protein acetylation will be discussed.

2. Discovery and concepts of protein acetylation and deacetylation

Classification of acetyltransferase and deacetylase. Acetylation is catalyzed by KATs, which are distributed in both the nucleus and the cytoplasm. Previous studies have identified >20 types of KATs, they can be primarily divided into five groups on the basis of their similarity in several homology regions and acetylation-related motifs: i) General control of amino acid synthesis protein 5 (GCN5) family, including GCN5 (KAT2A), p300/CBP-associated factor (PCAF; KAT2B), histone acetyltransferase 1 (HAT1), elongator acetyltransferase complex subunit 3, histone acetyltransferase HPA2 (HPA2) and HPA3, which is currently the most typical family of KATs (22-25). ii) MYST family, primarily including 60 kDa tat-protein (KAT5), monocytic leukemia zinc finger protein (KAT6A), MOZ-related factor (KAT6B), histone acetyltransferase binding to ORC1 (KAT7), ortholog of Drosophila males-absent on the first protein (MOF; KAT8), histone acetyltransferase SAS2 (SAS2), SAS3 and ESA1. The classification of this family is due to the presence of the highly conserved MYST domain that consists of an acetyl-CoA binding motif and a zinc finger. According to additional structural features, members of this family can be classified (26-29). iii) p300/cAMP response element-binding protein (CBP or CREB) family (KAT3A/KAT3B), which is closely related to cell differentiation and apoptosis, and has >75 non-histone substrates. Members of this family have four separate trans-activation domains, including the cysteine-histidine-rich region 1, the CREB-interacting kinase-inducible domain interacting domain, another cysteine-histidine-rich region and the nuclear receptor co-activator binding domain. p300/CBP is also a coactivator of various TFs, and it can link chromatin remodeling and transcriptional processes to coordinate physiological activities, such as signal transduction, *in vivo* (30). iv) Transcription initiation factor TFIID 230/250 kDa subunit (TAFII230/250) family. This family in humans is TAFII250, and it is a component of the TF complex TAFIID (31). v) Others, including α-tubulin N-acetyltransferase 1, establishment of sister chromatid cohesion N-acetyltransferase (ESCO)1, ESCO2 and HAT1, among which ESCO1 and ESCO2 are two N-acetyltransferases. Different types of KATs play different roles in cells, and stable expression of various KATs is vital for maintaining the physiological activities of cells (Table I) (23-25,27-29,32-47).

Previous research has demonstrated that KDACs can be primarily divided into four categories (48). Class I includes HDAC1, HDAC2, HDAC3 and HDAC8, which can be found in the nucleus (49). Class II can be found in both the nucleus and the cytoplasm. According to the different catalytic sites, it can be further divided into class IIA and class IIB. Class IIA, including HDAC4, HDAC5, HDAC7 and HDAC9, have a catalytic site and they can perform nuclear transport under cell signal stimulation. Class IIB, including HDAC6 and HDAC10, have two catalytic sites and they are mainly located in the cytoplasm (49). Both class I and class II are zinc-dependent enzymes. Class III, including sirtuin 1-7 (SIRT1-7), are NAD^+-dependent enzymes. This class of enzymes have a wide range of subcellular localization (49). Class IV includes only one member, HDAC11, which is a zinc-dependent enzyme. HDAC11 mediates deacetylation of lysine on the N-terminal tail of the core histones (50). In addition to these four categories, T cell transcription factor 1 and lymphoid enhancer-binding factor 1 are also two KDACs located in the nucleus (Table II) (51-70). Typically, acetyltransferases and deacetylases work together to regulate lysine acetylation and other various physiological processes in the organism. If the balance of acetylation and deacetylation becomes dysregulated, it is likely to cause tumor growth and a number of non-neoplastic diseases such as inflammatory diseases and neurological disorders (71).

Histone acetylation and deacetylation. The study of protein acetylation began with histones. Chen *et al* (72) reported that the degree of acetylation at H4K16 was notably decreased in prematurely aging mice compared with normal mice. Moreover, the expression of MOF, which is the related KAT, was greatly reduced. The symptoms of premature aging can be improved by increasing the degree of acetylation of H4K16 or increasing the expression of MOF in a variety of ways. Michishita *et al* (73) revealed that SIRT6, which is primarily localized in the nucleus, is also involved in senescence. SIRT6 specifically binds to the chromatin telomere region and is capable of acetylating H3K9 and H3K56 in the way of Nε-acetylation. Blocking SIRT6 can lead to telomere dysfunction and chromatin terminal fusion. These ultimately result in cell senescence, and produce a symptom similar to Werner syndrome. Taken together, these studies suggest that histone acetylation or deacetylation is closely related to aging.

It has been reported that combinations of monomethylation of histone H3 at lysine 4 (H3K4me1) and histone 3 lysine 27 acetylation (H3K27ac) or H3K27me3 are often used as a basis to differentiate active enhancers from inactive enhancers and

Table I. Published data of KATs.

Author, year	KAT family	Members	Localization	Substrate	(Refs.)
Fournier *et al*, 2016	GNAT	GCN5 (KAT2A)	Nucleus	PLK4 and TBX5	(34)
Ghosh *et al*, 2018		PCAF (KAT2B)			(36)
Ruiz-Garcia *et al*, 1998		HAT1	Cytoplasm/ nucleus	Histone	(23)
Miskiewicz *et al*, 2011		ELP3	Cytoplasm/ nucleus	Brunchpilot	(24)
Sampath *et al*, 2013		HPA2	Cytoplasm	Histone/Polyamines/ Small basic proteins	(25)
		HPA3	Cytoplasm	Histone/Polyamines/ D-amino acids	
Bao *et al*, 2018	MYST				(35)
Cheng *et al*, 2019		Tip60 (KAT5)	Nucleus	Ran and Pacer	(37)
Rokudai *et al*, 2013		MOZ (KAT6A)	Nucleus	p53	(33)
Pelletier *et al*, 2002		MORF (KAT6B)	Nucleus	Runx2	(32)
Miotto *et al*, 2002		HBO1 (KAT7)	Nucleus	CDT1	(38)
Yuan *et al*, 2012		MOF (KAT8)	Nucleus	Histone	(39)
Reiter *et al*, 2015		SAS2	Nucleus	Histone	(27)
Church *et al*, 2017		SAS3	Nucleus	Histone	(28)
Yan *et al*, 2000		ESA1	Nucleus	Histone	(29)
Chang *et al*, 2017	p300/CBP	p300 (KAT3B)	Nucleus	Snail/Smad4/PCNA/	(40)
Yang *et al*, 2015				FoxO1	(41)
Cazzalini *et al*, 2014					(42)
Senf *et al*, 2011		CBP (KAT3A)	Nucleus	Snail/FoxO1/PCNA	(43)
Lee *et al*, 2018	TAFII230/250	TAFII250	Nucleus	Histone	(44)
Nakakura *et al*, 2016	Others	ATAT1	Cytoplasm	α-tubulin	(45)
Zhang *et al*, 2008		ESCO1	Nucleus	SMC3	(46)
		ESCO2	Nucleus		
Wu *et al*, 2012		HAT1 (KAT1)	Nucleus	Histone	(47)

GNAT, GCN5-related N-acetyltransferases family; GCN5, general control of amino acid synthesis protein 5; PCAF, p300/CBP-associated factor; Tip60, 60 kDa tat-interactive protein; MOZ, monocytic leukemia zinc finger protein; MORF, MOZ-related factor; HBO1, histone acetyltransferase binding to ORC1; MOF, ortholog of Drosophila males-absent on the first; CBP, CREB-binding protein; TAFII250, transcription initiation factor TFIID 250 kDa subunit; ATAT1, α-tubulin N-acetyltransferase 1; PLK4, polo-like kinase 4; TBX5, T-box protein 5; Runx2, runt-related transcription factor 2; CDT1, chromatin licensing and DNA replication factor 1; PCNA, proliferating cell nuclear antigen; ESCO, establishment of sister chromatid cohesion N-acetyltransferase; HAT1, histone acetyltransferase 1; Ran, ras-related nuclear protein; Snail, zinc finger protein SNAI1; FoxO1, forkhead box protein O1; SMC3, structural maintenance of chromosomes 3; ELP3, elongator complex protein 3; HPA2, histone acetyltransferase HPA2; SAS2, histone acetyltransferase SAS2; ESA1, Histone acetyltransferase ESA1.

poised enhancers (74,75). However, this method of identification does not completely distinguish between other types of enhancers, such as super-enhancer (76). It has been found that H3K122ac is also enriched with H3K27ac on the active enhancer. H3K122ac can be used as a marker to identify some novel enhancers, but some of these novel enhancers will also be enriched in H3K27ac. This characteristic provides new ideas for comprehensive identification enhancers (77). Histone acetylation also plays a role in the repair of DNA replication forks. Nucleosome acetyltransferase of H4 (NuA4) is involved in acetylation of H4 on four lysine residues at position 5, 8, 12 and 16, which is Nε-acetylation. This modification changes the structure of chromatin, facilitating the repair of broken DNA replication forks (78). SWI1 promotes histone H4 acetylation by stabilizing the expression of NuA4. Loss of SWI1 leads to the instability of chromatin modification-related protein vid21, a regulatory subunit of NuA4, leading to a reduction in histone H4 acetylation (79). It is reported that the level of H3K56ac increases from low to high cell density and H3K56ac was observed to increase when lactic acid levels rose. This phenomenon may be attributed to changes in the levels of SIRT6. Furthermore, the level of H3K56ac was increased in cells with

Table II. Published data of KDACs.

Author, year	Classes	Members	Localization	Functions	(Refs.)
Muller *et al*, 2013	Class I	HDAC1	Nucleus	Mediates deacetylation of lysine	(51,52)
Miller *et al*, 2010		HDAC2	Nucleus	residues on the N-terminal part of	
		HDAC3	Nucleus	the core histones and plays an	
Saito *et al*, 2019		HDAC8	Nucleus	important role in transcriptional regulation, cell cycle progression and developmental events.	(53)
Winbanks *et al*, 2011	Class II	HDAC4	Nucleus		(54)
Cho *et al*, 2013	Class IIA	HDAC5	Nucleus		(55)
Bradley *et al*, 2015		HDAC7	Nucleus		(56)
Hu *et al*, 2019		HDAC9	Nucleus		(57)
Bitler *et al*, 2017	Class IIB	HDAC6	Cytoplasm		(58)
Radhakrishnan *et al*, 2015		HDAC10	Cytoplasm	Involved in MSH2 deacetylation	(59)
Zerr *et al*, 2016	Class III	SIRT1	Nucleus	Deacetylates TGF-β	(60)
Yuan *et al*, 2015		SIRT2	Cytoplasm	Deacetylates α-tubulin	(61)
Ahn *et al*, 2008		SIRT3	Mitochondria	Regulates tissue-specific ATP levels	(62)
Jeong *et al*, 2013		SIRT4	Mitochondria	Regulates the cellular metabolic response to DNA damage	(63)
Rardin *et al*, 2013		SIRT5	Mitochondria	Regulates the mitochondrial lysine succinylome and metabolic networks	(64)
Kaluski *et al*, 2017		SIRT6	Nucleus	Involved in energy metabolism	(65)
Barber *et al*, 2012		SIRT7	Nucleolus	Mediates deacetylation of H3K18ac	(66)
Yuan *et al*, 2018	Class IV	HDAC11	Nucleus	Mediates deacetylation of lysine residues on the N-terminal part of the core histones. Plays an important role in transcriptional regulation, cell cycle progression and developmental events.	(67)
Chatterjee *et al*, 2015	Others	TCF1	Nucleus	Mediates differentiation of embryonic stem cells	(69)
Abu-Elmagd *et al*, 2010		LEF1	Nucleus	Participates in the Wnt signaling pathway.	(70)

TCF1, T cell transcription factor 1; LEF1, lymphoid enhancer-binding factor 1; MSH2, human mutS homolog 2; TGF-β, transforming growth factor-β; HDAC, histone deacetylase; SIRT, sirtuin; ac, acetylation.

low acetylation immediately after DNA damage, and the level was decreased in cells with high acetylation immediately after DNA damage, which indicates the association between acetylation and repair after DNA damage (80). Moreover, histone acetyltransferase Gcn5p is a catalytic subunit of a nuclear HAT. Gcn5p catalyzes the acetylation of histone H3 and H4 at specific lysines, which is N-ε acetylation at specific lysines in the amino-terminal domains, promoting cell growth. These results suggest that the acetylation of specific lysines at H3 and H4 is essential for normal cell cycle progression (81). Oridonin is a tetracycline diterpenoid compound that is an important traditional Chinese herb. It has been reported that oridonin inhibits tumor cell proliferation and induces apoptosis, possibly by inducing the hyperacetylation of histone H3 (82).

Non-histone protein acetylation and deacetylation. As studies of histone acetylation have gradually deepened, researchers proposed the idea that non-histone proteins, such as p53, could also be acetylated. Although non-histone protein acetylation has been studied for a shorter period of time compared with histone acetylation, non-histone protein acetylation has been highlighted recently due to its extensive regulatory functions.

There are numerous types of non-histone proteins that can be acetylated, among which TFs are the main members (83). These non-histone proteins are widely involved in a variety of physiological processes in different ways, including gene transcription and protein folding (71).

As a tumor suppressor, p53 actively participates in the regulation of tumor formation and can be acetylated by the p300/CBP family in the way of Nε-acetylation. The p300/CBP family can acetylate the C-terminal lysine of p53 and further activate specific DNA binding sites on p53 (84). When DNA is damaged, p300/CBP family members binds to the promoter of p53 to increase the transcriptional activity of its gene in order to enhance p53 stability (85). p300/CBP not only regulates p53 activity in cells by acetylating p53, but also causes the inactivation of E3 ubiquitin-protein ligase murine double minute 2 (MDM2) to regulate p53. MDM2 also inhibits p300/CBP-mediated p53 acetylation, and p53 can be effectively degraded by MDM2 after being deacetylated (86). p53 acetylation is also associated with the regulation of apoptosis. p300 is a key TF that promotes cell transformation from G_1 to S phase and regulates p53 transcriptional activity via acetylation (87,88). It has been demonstrated that DEAD-box RNA helicase 24 (DDX24) interacts with p300 to inhibit p300-mediated p53 acetylation. When DDX24 was knocked out in human lung cancer cells, it was found that the level of p53 acetylation was significantly increased, and G_1/S arrest was observed in these cells. Following which, cells showed apoptosis (88). Inhibitor of DNA binding 4 is a differentiation inhibitory protein that promotes p53-dependent apoptosis by increasing the level of p53 acetylation (89). Moreover, it has been reported that the acetylation of p53 is associated with aging (90). Transcriptional coactivator with a PDZ-binding motif (TAZ) inhibits p300-mediated p53 acetylation by suppressing the binding of p53 and p300 (91). Furthermore, experiments have revealed that TAZ-knockout causes p53-dependent cellular senescence in normal human fibroblasts, which may contribute to tumorigenesis by suppressing p53-mediated cellular senescence (91). The association of p53 acetylation with apoptosis and senescence suggests that p53 is related to cancer (92). Overexpression of HDAC2 is found in a variety of cancer cells, such as breast cancer and gastric cancer cells (93,94). HDAC2 causes the deacetylation of the C-terminal lysine on p53, and functions as a corepressor involved in the regulation of target genes. If KDAC inhibitors (KDACIs) are used to keep some key lysine residues highly acetylated on p53, the stability of p53 can be enhanced (95). KDACIs also inhibit HDAC6 and promote the degradation of mutant p53 via MDM2 and CHIP ligase, which is hypothesized to be a mechanism for eliminating mutant p53 (96). Iron overload and fluoride may also be associated with p53 acetylation. Some studies have demonstrated that iron overload in macrophages may promote the production of reactive oxygen species, increase p53 acetyltransferase activity, and ultimately lead to macrophage M1 polarization by inducing the expression and acetylation of p53 (97,98). Fluoride can induce the acetylation of K379 on p53, which can be recovered by SIRT1 (85,99). Further study has indicated that SIRT1 deacetylates fluoride-induced p53 acetylation to attenuate fluorescence-induced cell growth inhibition, mitochondrial damage, DNA damage and apoptosis (85). As one of the typical representatives of non-histone protein acetylation, p53 acetylation broadens the scope of acetylation modification, providing an important basis for further studies on protein acetylation.

Signal transducer and activator of transcription 3 (STAT3) serves a dual role in transmitting signals and initiating gene transcription (100). The nuclear receptor Nur77 can recruit p300 and reduce HDAC1 expression, which promotes STAT3 acetylation in the way of Nε-acetylation and enhance the transcriptional activity of STAT3 (101). Decreased transcriptional capacity of STAT3-dependent genes can be reversed using KDACI trichostatin A or ITF2357 to inhibit acetylation of STAT1 or STAT3. This may be useful in the treatment of chronic mucocutaneous candidiasis (102). In the nucleus, lysyl oxidase like 3 associates with STAT3 to deacetylate and deacetyliminate STAT3 on multiple acetyl-lysine sites. As the result of this, STAT3 dimerization is disrupted and STAT3 transcription activity is inhibited (103). The acetylation of K685 on STAT3 can be regulated by p300/CBP, which enhances sequence-specific DNA binding ability and transcriptional activity of STAT3. Microglia are the innate immune cells of the central nervous system, which can inhibit the toxic toxic accumulation of β-amyloid. However, activated microglia can engulf synapses and activate inflammatory cytokines, causing the loss of synapses and the damage of neurons (104). It is reported that the activation of microglia is related to the deposition of amyloid protein (105). The synthetic form of Aβ peptides was used to treat primary and immortalized microglial cells, and then the relative abundance of acetylated and phosphorylated STAT3 was measured at different stages. In the early stage, the level of STAT3 acetylation on K685 was increased. Then, in the delayed one, its isoform will be phosphorylated on Y705 residue (106). Although the association between acetylation and phosphorylation is still unknown in this event, the acetylation of STAT3 is associated with the nervous system (106). Studies have also found that acetylation and deacetylation of STAT3 can regulate the tricarboxylic acid cycle (107,108). Serum starvation and reintroduction or insulin stimulation can induce STAT3 CBP acetylation in serum starved cells and result in the transfer of STAT3 into mitochondria (107). If STAT3 is deacetylated by SIRT5, STAT3 will reduce the association with the pyruvate dehydrogenase complex E1 and slow the conversion of pyruvate to acetyl-CoA (107).

Transcription factor EB (TFEB), a primary TF for autophagy and lysosome-related gene expression, can be acetylated by GCN5 at K274 and K279 in the way of Nε-acetylation, which inhibits the binding of TFEB to promoters of its target genes chloride voltage-gated channel 7, galactosidase α and cathepsin D by interfering with TFEB dimerization (109). Interfered TFEB dimerization results in a decreased binding affinity to DNA, which inhibits its transcriptional activity and ultimately suppresses the biogenesis of lysosomes and aggregation of autophagosomes (Fig. 1) (109). NAD^+-dependent deacetylase SIRT1 deacetylates TFEB at K116, enhancing lysosomal function by upregulating transcriptional levels of TFEB downstream targets (110). HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) upregulates TFEB acetylation by recruiting increased levels of acetyl-Coenzyme A acetyltransferase 1 to TFEB; the acetylation sites on TFEB induced

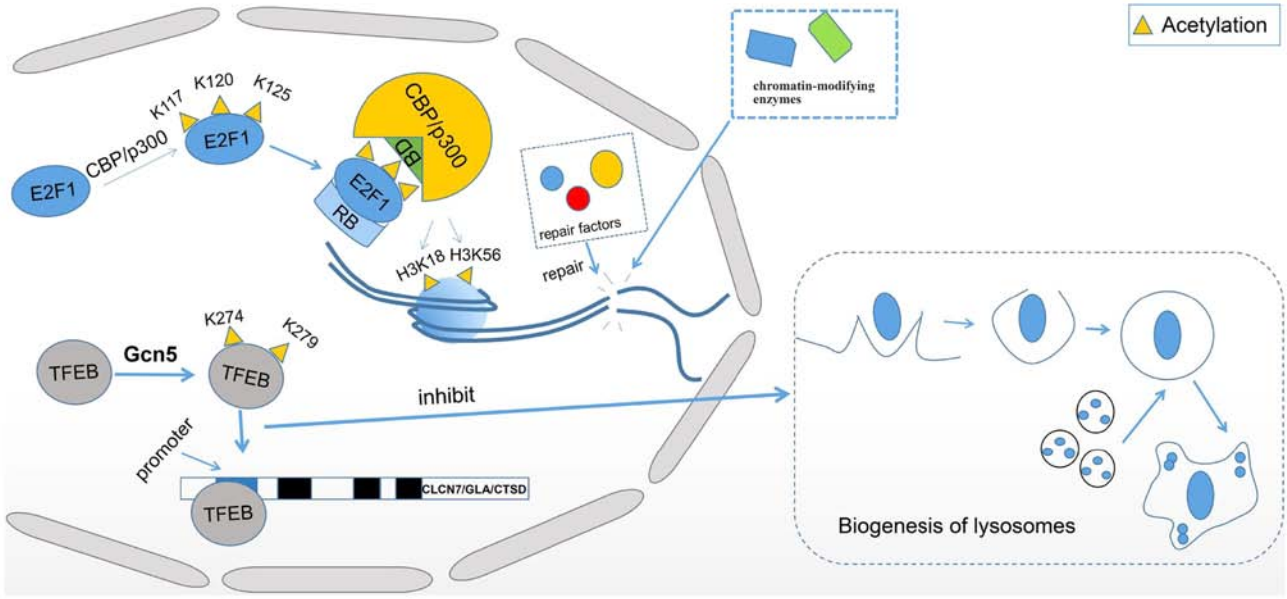

Figure 1. Biological processes regulated by acetyltransferase GCN5 and p300/CBP. GCN5 acetylates TFEB at K274 and K279, hindering the binding of TFEB to its target gene promoters CLCN7, GLA and CTSD. This process inhibits the biogenesis of lysosomes and aggregation of autophagosomes. In addition, the acetylation of E2F1 at K117, K120 and K125 by acetyltransferase p300/CBP creates a binding motif at the BD of the p300/CBP protein to attract more p300/CBP with the help of RB tumor-suppressor protein. Subsequently, the recruitment of p300/CBP induces the acetylation of H3K18 and H3K56, and then facilitates the binding of chromatin-modifying enzymes and repair factors for DNA double-strand breaks. GCN5, general control of amino acid synthesis protein 5; CBP, CREB-binding protein; TFEB, transcription factor EB; CLCN7, chloride voltage-gated channel 7; GLA, galactosidase α; CTSD, cathepsin D; E2F1, E2F transcription factor 1; BD, bromodomains; RB, retinoblastoma.

by SAHA are K91, K103, K116 and K430 (111). It has been reported that SIRT1 deacetylates TFEB at lysine residue 116 and the deacetylation of TFEB in microglia induces the regulatory ability of microglia to degrade fibrillar Aβ, the deacetylation process further reduces the number of deposited amyloid plaques by facilitating lysosomal biogenesis, which could be helpful in the treatment of Alzheimer's disease (110). In human diabetic kidney disease, deacetylation of TFEB by HDAC6 has been observed, which promotes its activation (112). Tubastatin A, an inhibitor of HDAC6, increases the acetylation level of TFEB accordingly (113). In addition, experiments have demonstrated that the use of tubastatin A can attenuate renal injury, which indicates that TFEB may be a promising target for renal diseases treatment (112). Recently, it has been demonstrated that acetylation of E2F transcription factor 1 (E2F1) is associated with the repair of DNA double-strand breaks (DSBs). The acetylation of E2F1 at K117, K120 and K125 by acetyltransferase p300/CBP creates a binding motif for the bromodomains of p300/CBP, which results in the recruitment of p300/CBP to DSBs with the help of retinoblastoma tumor-suppressor protein, an important regulator of E2F1. Subsequently, p300/CBP acetylates H3K18 and H3K56, and then facilitates the recruitment of chromatin-modifying enzymes and repair factors for DSBs (Fig. 1) (114). GCN5 catalyzes the histone acetylation at the promoter regions of E2F1, enhancing the transcription of target genes *cyclin D1 and cyclin E1*. The expression of GCN5 promotes cell growth and the G1/S phase transition in lung cancer cells, which is aided by E2F1 to control the transcription of cyclin E1 and cyclin D1. These data suggest that the interaction between GCN5 and E2F1 may be a potential target for lung cancer treatment (115).

Zinc finger protein SNAI1 (Snail) is involved in the induction of epithelial-mesenchymal transition (EMT) and plays a crucial role in the metastasis of malignant tumors (116). The Snail protein is usually comprised of a C-terminal zinc finger domain and an N-terminal SNAG domain. The C-terminal zinc finger domain recognizes the E-box sequence in the promoter region of E-cadherin. The SNAG domain associates with HDAC1/2 and corepressor mSin3A, and then recruits the repressor complex to E-cadherin promoter, here HDAC1/2 deacetylates histone H3 and H4, inhibiting the expression of E-cadherin (Fig. 2) (117). In previous years, numerous studies have reported that there are lysine acetylation sites on Snail and Snail acetylation activates the expression of Snail gene (40,118). It has been demonstrated that the interaction of CBP and Snail can cause the acetylation of K146 and K187 on Snail in the way of Nε-acetylation. Snail can be used as a transcriptional activator to induce the expression of cytokines in the tumor microenvironment during tumor metastasis, or as a transcriptional repressor to inhibit the expression of E-cadherin during tumor metastasis (118). Cancer cells containing acetylated Snail have increased metastatic ability compared with primary cancer cells (116,118). In addition, it has been found that Snail binds to the E-box motif on the E-cadherin promoter and recruits HDACs to suppress the expression of E-cadherin. In lung cancer cells, if recombinant Snail and p300 are incubated with acetyl-CoA, acetylation of Snail will be observed (40). In addition to CBP and p300, KDACIs can also promote the expression of Snail and induce EMT in hepatoma cells. One of the possible reasons is that KDACIs regulate the stability of Snail by upregulating the expression of COP9 signalosome 2 (CSN2). CSN2 binds to Snail and exposes its acetylation site, which then promotes the acetylation of Snail. Therefore,

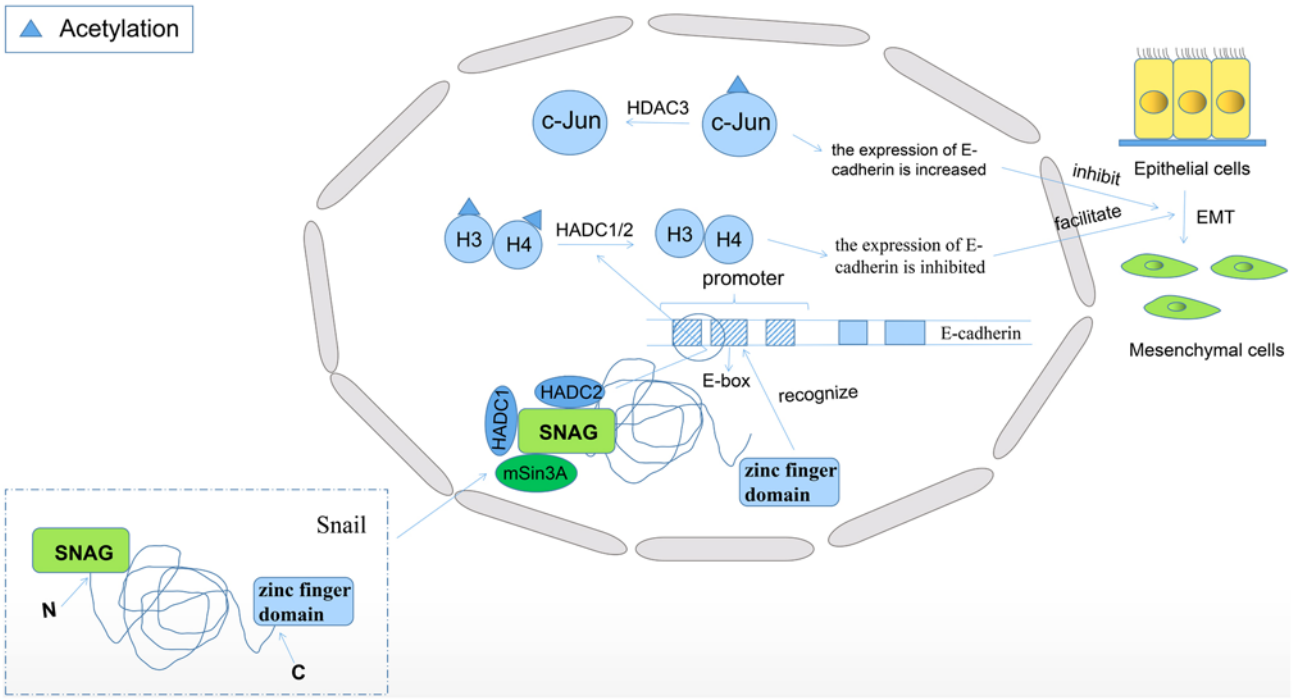

Figure 2. Acetylation and deacetylation associated with EMT. Snail, a zinc finger protein, comprises a C-terminal zinc finger domain and an N-terminal SNAG domain. The C-terminal zinc finger domain recognizes the E-box sequence in the promoter region of E-cadherin. The SNAG domain associates with HDAC1/2 and corepressor mSin3A, and then recruits the repressor complex to the E-cadherin promoter, where HDAC1/2 deacetylate histone H3 and H4, inhibiting the expression of E-cadherin and promoting the process of EMT. Human c-Jun is a transcriptional regulator of JUN proto-oncogene. It is reported that the downregulation of HDAC3 expression can increase the acetylation of c-Jun and may lead to the degradation of c-Jun, which ultimately increases the expression of E-cadherin and decreases the expression of snail, thus inhibiting the process of EMT. EMT, epithelial-mesenchymal transition; Snail, zinc finger protein SNAI1; HDAC, histone deacetylase.

its phosphorylation and ubiquitination are inhibited and its degradation is inhibited (119). Human c-Jun is a transcriptional regulator of JUN proto-oncogene, and c-Jun N-terminal kinase gene is associated with the expression of E-cadherin and snail. It has been reported that the downregulation of HDAC3 expression can increase the acetylation of c-Jun and may lead to the degradation of c-Jun, which ultimately increases the expression of E-cadherin and decreases the expression of snail, thus inhibiting the process of EMT (Fig. 2) (120). Due to the promotion of tumor metastasis by acetylated Snail, Snail could become an effective target for cancer therapy.

Myc is involved in the development of tumors and the induction of apoptosis (121). As reported, KAT2A interacts closely with Myc. KAT2A can acetylate K323 on Myc to maintain its stability in the way of Nε-acetylation, and Myc can recruit KAT2A into the RNA polymerase III template to facilitate the transcription of the Myc target gene (122). Besides acetylation, SIRT1 deacetylates c-Myc and promotes its binding to Max, which is a partner essential for its activation. This process increases the activity of c-Myc and promotes the proliferation of K562 cells (123). Previous studies that used KDACIs reported an association between Myc acetylation and disease (124,125). For example, the gene expression profiles of normal acute myelocytic leukemia (AML) cell lines were compared with KDACI-treated AML primary blasts, it was found that MYC gene was significantly upregulated. Treatment with KDACI led to a significant decrease in the expression of c-Myc. The process would also activate TNF-related apoptosis-inducing ligand, a member of the tumor necrosis factor family, and cause apoptosis (125).

When an organism is exposed to high temperatures, heat shock protein 90 (Hsp90) is synthesized by thermal excitation to protect the organism, and it has molecular chaperone activity (126). The deacetylation of Hsp90 is effectively regulated by HDAC6. The inactivation of HDAC6 leads to a higher degree of acetylation of Hsp90, which causes Hsp90 to separate from P23 and lose its chaperone activity (127). If K294 on Hsp90 is not normally acetylated, the life cycle of Hsp90 will be shorter and the function will be weakened (128). In breast cancer cells, carbamazepine can inhibit the effect of HDAC6 on Hsp90 and further promote the degradation of HER2 protein (129). This finding is expected to contribute to the development of breast cancer treatment strategies.

Additionally, it has been demonstrated that acetylation at lys1053 of the activation loop of the kinase domain may positively regulate kinase activity of VEGFR-2 (130). Also, KAT7, a member of MYST family, colocalizes with vascular endothelial growth factor receptor 2 (VEGFR-2), directly regulating the chromatin structure of the VEGFR-2 locus and affecting VEGFR-2 transcriptional activity. KAT7 depletion was demonstrated to reduce the expression of VEGFR-2 (131). Also, using KAT7 morpholino inhibitor in zebrafish embryos lead to abnormal vessel formation (131). All these results indicate that KAT7 plays a critical role in endothelial function.

ESCO1 and ESCO2 are two KATs that are involved in the aggregation of sister chromatids in the S phase of the cell cycle. K105 and K106 on human structural maintenance

Table III. Summary of acetylated proteins.

Author, year	Protein names	Acetylation site	Functions	(Refs.)
Gallinari *et al*, 2007	Histone	H3K9	Affects heart development	(134)
Schlesinger *et al*, 2011		H3K14	Affects heart development	(135)
Pradeepa *et al*, 2017		H3K27	Identification enhancer	(77)
Michishita *et al*, 2008		H3K56	Related to cellular aging	(73)
Pradeepa *et al*, 2017		H3K122	Identification enhancer	(77)
Chen *et al*, 2016		H4K16	Improves premature aging	(72)
Leszczynska *et al*, 2015	p53	K120 K164	Regulation of apoptosis	(136)
Suzuki *et al*, 2018				(85)
Shi *et al*, 2016		K305	Regulate the transcriptional activity of p53	(88)
Marrogi *et al*, 2001		K379	Related to fluorosis	(97)
Shi *et al*, 2016		K382	Regulate the activity of p53 apoptotic	(88)
Eufemi *et al*, 2015	STAT3	K685	Enhance sequence-specific DNA binding ability, transcriptional activity and transactivation activity	(106)
Kenneth *et al*, 2007	Myc	K323	Activate TRAIL and cause apoptosis	(122)
Meng *et al*, 2011	Hsp90	K294	Related to the activity and cycle of Hsp90	(129)
Hsu *et al*, 2014	Snail	K146 K187	Prevents the repressor complex formation	(118)
Rowland *et al*, 2009	Smc3	K105 K106	Condensation of sister chromatids	(133)
Vadvalkar *et al*, 2017	MPC2	K19 K26 K27 K122	Related to pyruvate transport activity	(137)
Hu *et al*, 2017	PGK1	K323	Related to cancer cell proliferation	(138)

STAT3, signal transducer and activator of transcription 3; Hsp90, heat shock protein 90; Snail, zinc finger protein SNAI1; Smc3, structural maintenance of chromosomes 3; MPC2, mitochondrial pyruvate carrier 2; TRAIL, TNF-related apoptosis-inducing ligand; PGK1, phosphoglycerate kinase 1.

of chromosomes 3 (SMC3) are two conserved amino acid residues that can be acetylated by ESCO1 and ESCO2 (46). If these sites are mutated to non-acetylated, the sister chromatid will lose cohesion and the human genome will be unstable (46,132). Further study revealed that the acetylation of SMC3 altered the function of the N-terminal ATPase of SMC3 and transformed the chromosome-bound cohesin complex into a cohesive complex (133). These results indicate that acetylation of SMC3 regulates the aggregation of sister chromatids and keeps the cell cycle functioning normally. In addition, some of the proteins and acetylation sites involved in this review are listed in Table III (72,73,77,85,97,106,118,122, 129,133-138).

Although protein acetylation has been well studied in eukaryotes, new insights into protein acetylation in prokaryotes has gained more attention in recent years. *Shewanella baltica* is one of the specific spoilage organism of aquatic products and numerous lysine acetylation sites have been detected in its protein, such as key enzymes involved in fat metabolism and putrescine biosynthesis that are related to the spoilage ability of *Shewanella baltica* (139). Previously, putrescine was demonstrated to have effects on proliferation, migration and apoptosis of human skin fibroblasts (140). Cyanobacteria are the only prokaryotes capable of performing oxygenic photosynthesis. Experimental data have demonstrated that lysine acetylation in cyanobacteria plays an important role in the regulation of photosynthesis (141). Also, acetylation is abundant in *Escherichia coli* (142).

As mitochondria carry out a number of essential functions in metabolism, the study of Mechanisms and Dynamics of Protein Acetylation in Mitochondria becomes necessary. PCAF functions as a lysine acetyltransferase inside mitochondria (143). PCAF affects intermediary metabolism by acetylating isocitrate dehydrogenase 2 (IDH2) at K180 in the mitochondrial matrix, which interferes with the catalytic mechanisms of isocitrate binding and oxidation (143). A number of central enzymes in mitochondria are deacetylated by SIRT3, which reverses the suppressive effect of acetylation,

leading to enhanced oxidative metabolism (144). It was proposed that most protein lysine acetylation in mitochondria is due to non-enzymatic modification of protein lysine residues. The environment of the mitochondrial matrix has an alkaline pH and abundant acetyl-CoA, which increases the number of amino groups acting as nucleophiles towards the inherently reactive acetyl-CoA, resulting in an acetylated lysine (145). Pyruvate is a principal source of acetyl-CoA. The data suggest excessive lysine acetylation in the mitochondrial matrix can be prevented by decreasing the matrix acetyl-CoA formation (146). In the mitochondria, when acetyl-CoA levels exceed physiological requirements, a signal is generated to slow flux through oxidative energy production (144). A substrate-level braking system is established via the induction of acetyl-CoA-dependent protein acetylation. When energy demands require increased oxidative metabolism, SIRT3 expression is induced, which removes the brake and allows the cell to increase energy production (144). Acetylation in mitochondria is primarily the result of nonenzymatic modification of lysine residues, some enzyme-mediated acetylation also exists in mitochondria. PCAF acetylates isocitrate dehydrogenase 2 (IDH2) at lysine 180, which may reduce IDH2 affinity for isocitrate. In this way, PACF influences myoblast differentiation (143). CCAAT/enhancer-binding protein a (C/EBPα), which can be acetylated by p300, regulates the transcription of metabolic genes and further enhances its transactivation activity (147). In addition, C/EBPα can be deacetylated by SIRT1 and low acetylation levels of C/EBPα enhances mitochondrial function. When energy is required, SIRT1 is activated by high levels of nicotinamide adenine dinucleotide; mitochondrial biogenesis and functions are regulated in this way (147).

3. Diseases and protein acetylation and deacetylation

Acute kidney injury (AKI). AKI refers to a rapid decline in renal function in a short period of time and leads to the accumulation of metabolic waste (148). AKI primarily affects renal tubules. Tubular cells are rich in mitochondria, and changes in mitochondria of the tubules are an important indicator of the occurrence and development of renal diseases (149). AKI can be caused by various factors, such as bacterial infection, drugs and sepsis (150). At present, the clinical diagnosis of AKI primarily depends on the detection of elevated serum creatinine levels and decreased urine output (151). It has been demonstrated that the KDACI participates in the process of renal regeneration and repair, and plays different roles in AKI models (152). Differences in cell type and etiology will determine activation of KDACs, thus leading to cell survival or death (153). Using SIRT1, which is currently studied more, as an example, SIRT1 can participate in the regulation of a variety of signaling pathways, and plays a role in anti-oxidative stress and anti-apoptotic effects to protect kidney function (154). For example, in the mouse model of AKI induced by sepsis, SIRT1 activity is significantly decreased. However, if the SIRT1 activity was increased by resveratrol, the damage of mouse mitochondria will be reduced and the survival time will be significantly prolonged (155). Cisplatin is a commonly used anti-tumor drug, but it is also associated with an increased risk of causing serious side effects, such as AKI. Its pathogenesis is related to a number of factors, such as mitochondrial damage, oxidative stress and apoptosis (156). Inducing AKI in SIRT3-deficient mice and wild-type mice using cisplatin revealed that the SIRT3-deficient mice suffered more severe kidney damage and even death (157). Further study reported that the expression of SIRT3 was significantly decreased in kidney cells of cisplatin-induced AKI. Due to the loss of SIRT3 regulation, mitochondria are damaged and unable to carry out normal functions (158). If the activity of SIRT3 is restored by treating with the adenosine monophosphate-activated protein kinase activator AICAR or Acetyl-L-Carnitine, the symptoms of AKI are relieved to some extent (157). Ning *et al* (159) demonstrated that short-term caloric restriction could protect AKI induced by cisplatin in aged rats because it has anti-apoptotic effects and promotes the expression of SIRT1. Although the current treatment of AKI is still limited to intravenous rehydration, diuretic therapy and continuous renal replacement therapy, the study of the relationship between protein acetylation and AKI is useful (160). These results suggest that restoring the activity of SIRT1/3 may be a novel therapeutic target for AKI. Using resveratrol, the activity of SIRT1/3 can be restored efficiently (161). In addition, oxidative stress and mitochondrial function of renal tubular epithelial cells tend to be ameliorated (155). Also, dexmedetomidine plays a role in treating AKI because it induces the upregulation SIRT3 (162).

Heart diseases. Congenital heart disease (CHD) is the most common type of congenital malformation (163). The main cause of CHD is the failure of heart or blood vessel formation and dysplasia during embryonic development (164). Additionally, it is also the result of structural and functional abnormalities caused by the channel failing to close automatically after birth (164). Wu *et al* (165) induced the abnormal expression of crucial genes in cardiac development by exposing mice to sodium valproate to decrease the activity of KDACs. This experiment led to malformation of the heart, and indicated that acetylation modification may be related to CHD. There have also been experiments that use ethanol and metabolites of ethanol to increase the degree of acetylation of H3K9 (166). It has been found that cardiac precursor cells are abnormally differentiated (165). Study has also reported that valproic acid may cause teratogenic effects by directly inhibiting expression levels and activity of KDAC, thus leading to an imbalance in the ratio of acetylation/deacetylation. As a result of this, the expression levels of VANGL planar cell polarity protein 2, scribble planar cell polarity protein and Rac family small GTPase 1, the key genes of the H9C2 cardiomyocyte planar cell polarity pathway, are decreased (134), which can lead to CHD. Schlesinger *et al* (135) screened multiple acetylation sites and found that the acetylation levels of H3K9 and H3K14 had significant effects on the expression of NK2 homeobox 5, methyltransferase like 2A, GATA binding protein 4 and serum response factor, which are important factors involved in cardiac development. If the expression of KAT2A in H3K9 is downregulated, the development process of mesenchymal stem cells into myocardium will be blocked, resulting in abnormal myocardial development (167).

In addition to CHD, protein acetylation may also be associated with heart disease caused by oxidative damage (168). During oxidative stress, the content of SIRT3 in mitochondria and nucleus of cardiomyocytes increased significantly (169). It is speculated that SIRT3 is associated with heart disease (168). In a previous study, ku70 was used as a target protein of SIRT3, thereby promoting the interaction between ku70 and the proapoptotic protein Bax. When a stress response is present, SIRT3 protects cardiomyocytes effectively by blocking the translocation of Bax to the mitochondria and preventing cytotoxic stress-mediated cell death (169). Meanwhile, it has been demonstrated that the decrease in cardiac metabolic activity in patients with diabetes may be related to the decreased pyruvate transport activity induced by acetylation of mitochondrial pyruvate carriers 2 (137). As a crucial regulator for myocardial ischemia and reperfusion injury, HDAC4 overexpression increases autophagy microtubule-associated protein light chain 3 and active caspase 3, decreases superoxide dimutase 1 in the myocardium, and ultimately promotes myocardial ischemia/reperfusion injuries (170). Myocardial fibrosis is common in patients with CHD (171); it has reported that HDAC overactivation causes atrial fibrosis and HDAC inhibitors have been demonstrated to be useful in the treatment of heart diseases. Therefore, regulating the activity of HDACs may be a possible therapeutic target of CHD (172). Curcumin, the main ingredient of turmeric, which inhibits p300 activity, prevents the development of cardiomyocyte hypertrophy that leads to heart dysfunction. As a result of this, curcumin could be a positive therapeutic method to aid in the treatment of heart diseases (173).

Cancer. The acetylation of some proteins may have an impact on the occurrence of cancer. Colon cancer-associated transcription factor 1 (CCAT1) is significantly higher in esophageal squamous cell carcinoma (ESCC) cells compared with corresponding non-tumor tissue cells (174). As commonly known, high expression of CCAT1 promotes cell proliferation and invasion, while downregulation of CCAT1 can inhibit cell proliferation and invasion (175). It has been demonstrated that the acetylation of H3K27 can partially upregulate the expression of CCAT1, which has the potential to induce cancer (176). Apart from TFs, the proliferation of cancer cells requires glycolysis to provide a large amount of energy. Phosphoglycerate kinase 1 (PGK1) is an important reductase in the glycolysis process, and the functional changes as a result of its acetylation may also be closely related to the changes in cancer cell proliferation. Using liver cancer cells, acetylation of K323 at PGK1 upregulates its activity and enhances its proliferative capacity (138).

The deacetylation of certain proteins is also very important in the occurrence of cancer. Forkhead box protein O1 (FoxO1) is a tumor suppressor that mediates autophagy, specifically autophagy that is produced by oxidative stress and serum starvation in cancer cells (177). In the cytosol, SIRT2 binds to FoxO1 to deacetylate it and inhibit FoxO1-mediated autophagy. When a stress response occurs, SIRT2 is separated from FoxO1 and results in the acetylation of FoxO1. This process will promote autophagy and finally lead to cell death. This mechanism links the autophagy signal pathway to cancer and is regulated by the acetylation of FoxO1 (178). SIRT7 was demonstrated to be overexpressed in colorectal cancer cells compared with normal cells. Additionally, SIRT7 is an important facilitator of metastasis in human colorectal cancers, whose overexpression leads to lung and skin metastases (179). Abnormal SIRT7 overexpression accelerates cancer cell growth and enhances invasiveness, and leads to the upregulation of mesenchymal markers vimentin and fibronectin (179). It has reported that SIRT7 can cause carcinogenic transformation of human cancer cells by deacetylating H3K18 (66). In pancreatic cancer, upregulation or downregulation of HDAC6 expression has no significant effect on cancer cell proliferation and cell cycle progression, but overexpression of HDAC6 in combination with cytoplasmic linker protein-170 can enhance cancer cell migration activity significantly (180).

In recent years, KDACIs have been found to be effective in treating diseases such as diabetes, heart disease, chronic fibrosis and cancer (181-184). If the balance of acetylation/deacetylation becomes dysregulated, several physiological and pathological cellular processes will be disrupted and some genes will be abnormally expressed and become carcinogenic factors, eventually leading to diseases (184,185). KDACs can deacetylate histones, which positively charges them again. This will result in tight binding of histones to DNA and make this section of the gene difficult to transcribe. However, KDACIs can selectively inhibit the deacetylation of certain cancer suppressor genes, including p53, TGF β type II receptor gene, and restores their transcriptional activity (184). Therefore, indicating that KDACIs may show anticancer effects.

A number of studies have shown that a large proportion of histones have a low degree of acetylation, and this discovery has led to the use of KDACIs in the treatment of cancer (186-189). KDACIs can slow down the proliferation rate of cancer cells, which may inhibit the growth of cancer cells and eventually lead to apoptosis (190). Comparing the targets of two HDAC inhibitors, SAHA and MS-275, KDACIs have a high substrate specificity and provide an important basis for the treatment application of KDACIs (14). In addition, a number of studies have demonstrated that KDACIs can inhibit cancer cells and reduce the resistance of cancer cells to other drugs, which makes it possible to use KDACIs in combination with other drugs to treat cancer (191). There are studies showing that KDACIs can promote the differentiation of CSCs to treat cancer (192,193). It has reported that HDACIs can induce the differentiation of cancer cells to assist cancer therapy by affecting the developmental signaling pathway. These findings could suggest that the underlying mechanisms of KDACIs in cancer therapy may be diverse (193). Resveratrol is a type of natural polyphenolic KDACI that has been studied a large amount. The main target of resveratrol is SIRT1, which has achieved initial success in the treatment of tumor diseases, such as liver cancer and breast cancer (194). Li *et al* (195) cultured PC-3 and LNCaP prostate cancer cell lines, which were induced by lipopolysaccharides to produce EMT. After being treated with resveratrol, these cells showed significant changes. The results revealed that EMT no longer occurred, and the mesenchymal cells restored the epithelial cell phenotype. This study further promoted the treatment application of resveratrol in cancer (195). However, due to the lack of development of detection techniques, the use of KDACIs to treat cancer has only achieved some initial

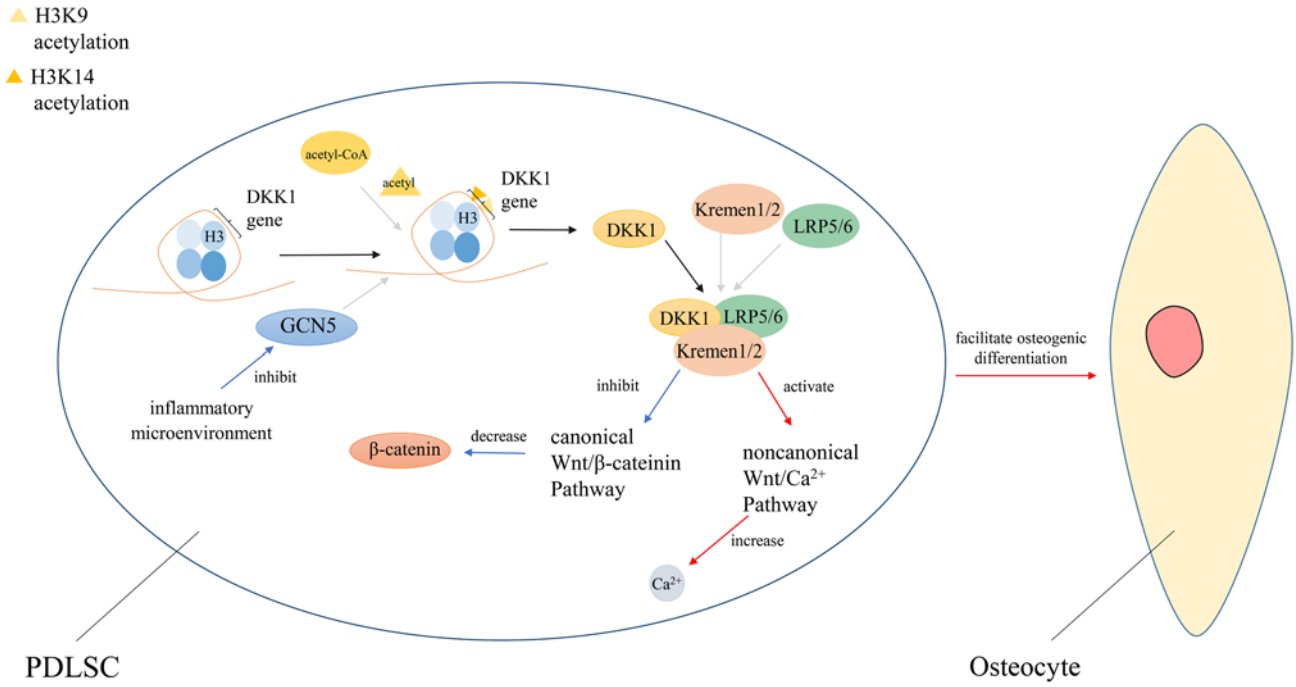

Figure 3. GCN5 enhances the osteogenic differentiation of PDLSCs. GCN5 is a type of KAT that catalyzes the acetylation of H3K9 and H3K14, and promotes the expression of DKK1. As a secreted protein, DKK1 can form trimers with LRP5/6 and Kremen1/2, inhibit the Wnt/β-catenin pathway, and activate the Wnt/Ca^{2+} pathway. The decrease of β-catenin and the increase of Ca^{2+} ultimately facilitates osteogenic differentiation of PDLSCs. GCN5, general control of amino acid synthesis protein 5; PDLSCs, periodontal ligament stem cells; KATs, lysine acetyltransferases; DKK1, dickkopf-related protein 1; LRP5/6, LDL-receptor-related protein 5/6.

results, and numerous mechanisms have not been studied in detail. Moreover, KDACIs have limitations in the inhibition of cancer. So, most of the drugs based on this have stayed in the clinical trial stage and have not been officially put into use.

4. Protein acetylation and deacetylation in stem cells

Stem cells are a type of pluripotent cell that can self-replicate and differentiate to produce other types of cells or divide to produce a large number of cells of the same type. They can be used for tissue and organ regeneration, and they have very broad clinical application prospects. It is currently known that acetylation of histones can regulate physiological activities, such as glycolysis, and thereby regulate the differentiation ability of stem cells (196).

Embryonic stem cells (ESCs) are isolated from early embryos or primitive gonads. Previous study has reported that the level of acetylation of H3K9 is related to the reprogramming ability of ESCs by analyzing multiple chromatin markers. The reprogramming ability of ESCs, of which the level of H3K9 acetylation is low, is also relatively weak. If KDACI is added to ESC colonies, its reprogramming ability is significantly improved (197). Actin-like protein 6a is a component of the ATP-dependent histone acetylation complexes. If it is knocked out, the pluripotency of ESCs will decrease (198). In neural stem cells cultured *in vitro*, the level of acetylation of H3K9 decreased first and then increased with the differentiation process. If KDACI is added to increase acetylation levels during the first 4 days of differentiation, cell pluripotency will be promoted and neural differentiation will be inhibited (199). The radiosensitivity of normal stem cells is higher compared with their isogenic differentiated progeny, and the DNA damage response of normal stem cells is stronger compared with their isogenic differentiated progeny. However, if H3K56 acetylation in stem cells is downregulated, their radiosensitivity is significantly decreased and survival rate is significantly increased (200).

Here is a particular example of acetylation regulating stem cell differentiation. In patients with periodontitis, periodontal ligament stem cells (PDLSCs), which are a novel population of mesenchymal stem cells, exhibit defects in osteogenic differentiation (201). Also, this may be due to the downregulation of GCN5 expression in a micro-inflammatory environment. GCN5 can induce H3K9 and H3K14 acetylation in the dickkopf-related protein 1 (DKK1) promoter region, thereby regulating the expression level of DKK1. DKK1 can inhibit the Wnt/β-catenin signaling pathway by binding to LDL-receptor-related protein 5/6 (LRP5/6) and Kremen1/2, and enhance the osteogenic differentiation of PDLSCs. If GCN5 is knocked out, the expression level of DKK1 decreases, resulting in decreased osteogenic differentiation of PDLSCs (Fig. 3) (202-204). Acetylation can also indirectly regulate the proliferation of stem cells. For example, SIRT6 is involved in maintaining the stability of the Wnt signaling pathway and SIRT6 deletion results in aberrant activation of the Wnt signaling pathway and promote the proliferation of hematopoietic stem cells (205).

Notably, acetylation and cancer stem cells (CSCs) are also closely associated (206). In liver CSCs, there is high expression of HDAC3. If HDAC3 is knocked out by a specific inhibitor, stem cell markers, such as Nanog and Oct4, are expressed at low levels (207). HDAC1 has an inhibitory effect

on the expression of markers of cervical CSCs (208). HDAC1 can form a complex with lysine demethylase 1A, DNA methyltransferase 1 and lysine-specific demethylase 6A. This complex has the function of reducing the level of acetylation on the EMT-related TFs and inhibiting the proliferation of breast cancer CSCs (209). As a KDACI, abexinostat can induce the differentiation of CSCs from low-dose-sensitive breast cancer cell lines, but has no significant effect on high-dose-sensitive breast cancer cell lines. Therefore, it's necessary to choose an X-inactive specific transcript as a biomarker to select a population suitable for this treatment (210).

At present, methods to affect stem cell activity by acetylation have been applied to clinical treatments. Imatinib is a tyrosine kinase inhibitor for the treatment of chronic myeloid leukemia (CML), but has poor clearance for inactive leukemia stem cells (211). SIRT1 protein was labeled with an anti-SIRT1 antibody and SIRT1 expression was detected by western blotting. It was found that the expression of SIRT1 in CML $CD34^+$ cells in chronic and blast phase was much greater than that of normal cells. It is speculated that SIRT1 inhibitors can be used in combination with imatinib to treat CML to enhance efficacy (212). Different acetylation sites are regulated to varying degrees during differentiation, which plays an important role in regulating the differentiation direction of pluripotent stem cells and monitoring stem cell differentiation (213). In addition to the role mentioned above, acetylation may also play vital role in regulating stem cell self-renewal and cell cycle (214).

5. Tools to predict acetylation sites

In the process of studying protein acetylation, it was found that the acetylation site is first step to understand acetylation mechanism (215). Therefore, it is critical to predict acetylation sites with relatively simple methods. Bioinformatics is a new subject derived from the rapid development of biological sciences and computer science. It uses computer programs as a tool to retrieve and analyze biological data. The method obtains relevant information via the databases and processes the data to achieve the goal. As commonly known, bioinformatics methods have played an important role in the field of genomics and proteomics (216). There are some computational models that have been developed to predict acetylation sites.

One of these methods is called LAceP. The first step in this method, researchers need to collect data on protein and acetylation sites in the SysPTM2 and PhosphoSitePlus databases. By this way, researchers can obtain a certain number of acetylation sites in the protein after eliminating redundancy, and use this data as positive data. Then, a peptide containing lysine is selected from the acetylated protein, and negative data is obtained after knocking out the fragment containing the lysine acetylation site. After that, a sliding window strategy is used to determine the optimal length of the acetylated peptide. The homology of the peptides is carried out via the CD-hit software to avoid model over fitting. If the similarity of the two peptides exceeds 70%, they will be classified as one class. Only one of them will be retained while the other peptides will be discarded. The model uses three types of features, which are amino acid physicochemical property, transition probability matrix and position-specific symbol composition, to predict lysine acetylation sites. Because the calculations are performed by different algorithms, the probability of acetylation may be analyzed from three aspects. Then, the classification of the peptides in the training datasets, their class tags and features were used as input of the logistic regression model. After model training, the optimized parameters are generated as outputs. Researchers can analyze the probability of amino acid acetylation base on these data (215).

Another method is called ASEB. Firstly, it is necessary to collect acetylated human proteins from different families using PubMed. In this step, researchers need to query the detailed acetylation sites and KATs, and go to the UniProt database to obtain the UniProt IDs corresponding to the acetylated proteins. Then, using the idea of Gene Set Enrichment Analysis, the ASEB method was developed to form an acetylated polypeptide, which consists of the acetylation site, its first eight amino acids and its last eight amino acids. Different KAT families form different acetylated peptide groups. In order to determine whether a given peptide can be acetylated by a certain KAT family, it is only necessary to analyze how similar the given peptide is to the acetylated peptide in that family. For analysis, a set of predefined KAT specific polypeptides, including N-polypeptides, is inputted. Then, the similarity between the given polypeptide fragment and the peptide contained therein is searched in the set. The background peptide set can be calculated by BLOSUM 62 matrix. If the similarity with the polypeptide in a certain KAT family is extremely high, it will be possible that the polypeptide is a new substrate of the KAT family. Then, the enrichment score is calculated and estimated to obtain the relatively significant chance that the given peptides were acetylated by the KAT family (217).

GPS-PAIL, one of these methods, contains 702 known HAT-specific acetylation sites in 205 proteins for seven HATs, including CREBBP, p300, HAT1, KAT2A, KAT2B, KAT5 and KAT8, developed from the scientific literature and public data resources. The method predicts acetylation sites based on the principle that different HATs have distinct sequence specificities for the substrate modifications. GPS-PAIL develop a computational model for each HAT by training a previously established algorithm of Group-Based Prediction System. Online service and stand-alone packages of GPS-PAIL are also provided. The two tools mentioned above have their own distinct advantages on the inputting of the online service, which contained three parts: i) HAT types; ii) the protein sequences; and iii) four thresholds, including 'High', 'Medium', 'Low' and 'All' (218).

Moreover, other methods, such as N-Ace and PLMLA, are applied to predict acetylation sites. N-Ace predicts the protein acetylation sites based on the support of vector machine. The training of N-Ace depends on the amino acid sequence and other structural characteristics; it has higher predictive accuracy compared with models trained using only amino acid sequences (8). PLMLA combines protein sequences, secondary structures and amino acid properties to predict the methylation and acetylation of lysine residues in protein sequences (219).

In conclusion, LAceP, N-Ace and PLMLA are unable to predict HAT-specific acetylation sites. Compared with ASEB, LAceP can carry out acetylation peptide length assays and takes

more consideration to peptide redundancy and residue property, which may have an important impact on acetylation. In addition, LAceP has the potential for improved performance in the future when considering the Matthews correlation coefficient measurement. Conversely, ASEB have the ability to determine KATs are responsible for the acetylation of given proteins. The present version only predicts acetylation catalyzed by two KAT families, including CBP/p300 and GCN5/PCAF. Both GPS-PAIL and ASEB can predict HAT-specific acetylation sites. However, in general, GPS-PAIL generated an improved performance compared with ASEB. All of them have a high level of accuracy (8,215,217-219).

The use of bioinformatics to predict acetylation sites greatly facilitates the study of acetylation, and saves a lot of invaluable research time. The integration of the properties of different acetylated peptides is also conducive to the study of the functions and characteristics of protein acetylation.

6. Conclusions and prospects

Histone acetylation and non-histone protein acetylation are important for human biological functions, and are closely related to the mechanisms of various diseases. At present, the study process of PTM is still steadily advancing. The process of acetylation together with other modifications, such as methylation and glycosylation, regulates biological activities and its role in the whole metabolic network still needs further research. Moreover, the constant innovation of theory is destined to provide more space and possibility for clinical application. In-depth study of protein acetylation could lead to novel prospects in the clinical treatment of a number of diseases. The regulation of TFEB acetylation and deacetylation may be a useful biological process in the development of Alzheimer's disease and renal injury. The acetylation of E2F1 is associated with the treatment of lung cancer. Additionally, Snail has also been demonstrated as an effective target for cancer therapy. The effect of HDAC6 on Hsp90 is expected to promote the development strategies of breast cancer treatment. Activation of KDACs participates in the process of renal regeneration and repair, and plays different roles in AKI. By mediating the expression of KAT2A, HDAC and p300, the development process of CHD can be inhibited. Moreover, CCAT1 acetylation is associated with ESCC, and the PGK1 acetylation and deacetylation may be a promising target for cancer treatment. Also, FoxO1 acetylation and the expression of SIRT7 are associated with cancer. At present, KDACIs have been used in the treatment of diseases, such as diabetes, heart disease, chronic fibrosis and cancer. Protein acetylation is increasingly related to clinical treatment, which provides novel ideas and methods for the treatment of numerous intractable diseases.

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Availability of data and materials

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Authors' contributions

CX and YT conceived and drafted the manuscript. ML and TC contributed to the literature retrieval and manuscript modification. JQ supervised and designed the present study and contributed to the approval of the final version of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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