Research progress on lysine acetylation (Review)

MINGHUI ZHANG[1,2], YUQI ZHANG[1,2], HAOXIN YIN[1,2], JUNYUAN YAN[1,2], YINGLING DONG[1,2], XIN ZHAO[1,2], TIANYI CUI[1,2], BIN LV[1,2] and XIUMEI GAO[1,2]

[1]Key Laboratory of Pharmacology of Traditional Chinese Medical Formulae, Ministry of Education, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, P.R. China; [2]State Key Laboratory of Chinese Medicine Modernization, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, P.R. China

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Abstract. Lysine acetylation is recognized as a critical and reversible post-translational modification that is essential for numerous cellular functions and biological processes. The dynamic interplay between lysine acetylation and deacetylation to regulates a wide spectrum of processes, including histone modification, gene expression, cell cycle progression, DNA repair and signal transduction. Emerging evidence has demonstrated that the dysregulation of lysine acetylation is strongly associated with multiple diseases, including cancer, cardiovascular diseases, chronic inflammatory diseases and neurological diseases. These alterations can modify gene expression and disrupt cellular homeostasis. The present review aimed to highlight the biological functions of lysine acetyltransferases and lysine deacetylases, their contributions to disease pathogenesis, and the interplay the crosstalk of lysine acetylation with other post-translational modifications. Drawing on the latest research findings, the therapeutic potential of targeting acetylation pathways is discussed, with the aim of providing new insight into the development of innovative treatment strategies and clinical applications.

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Correspondence to: Professor Xiumei Gao or Professor Bin Lv, Key Laboratory of Pharmacology of Traditional Chinese Medical Formulae, Ministry of Education, Tianjin University of Traditional Chinese Medicine, 10 Poyanghu Road, West Area, Tuanbo New Town, Jinghai, Tianjin 301617, P.R. China
E-mail: gaoxiumei@tjutcm.edu.cn
E-mail: lyubin@tjutcm.edu.cn

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1. Introduction

Post-translational modifications (PTMs) encompass a diverse range of chemical alterations that occur at the side chains or terminal ends of proteins following translation. According to data from the SWISS-PROT database, the five most prevalent PTMs are phosphorylation, acetylation, glycosylation, amidation and hydroxylation (1). These modifications play critical roles in the regulation of protein function, stability and interactions with other biomolecules. In eukaryotic cells, chromosomes consist of highly compacted DNA and proteins, and PTMs are indispensable for altering chromatin structure and function.

In 1964, Vincent Allfrey first identified protein acetylation in the calf thymus nucleus *in vitro* and established the foundation for subsequent research on this modification (2). Lysine acetylation is a reversible PTM that profoundly influences diverse cellular processes, including chromatin remodeling, transcriptional regulation, DNA damage repair, cellular metabolism, cytoskeletal organization and apoptosis (3).

Lysine acetylation is primarily controlled by two key enzyme families: Lysine acetyltransferases (KATs) and lysine deacetylases (KDACs) (4). KATs facilitate the addition of acetyl groups from acetyl-CoA to lysine residues, while KDACs catalyze the removal of these groups, thereby sustaining the dynamic equilibrium between acetylation and deacetylation.

Histones are the most frequently acetylated proteins. They serve as fundamental units for DNA organization, functioning as the structural core of chromatin. Canonical histones are modified by various KATs and KDACs (5). The acetylation of histone lysine residues neutralizes their positive charges, which weakens electrostatic attractions among nucleosomes, loosens chromatin structure, and consequently facilitates gene transcription (6). Proteomics analyses have demonstrated that numerous non-histone proteins can also be acetylated. These acetylated non-histone proteins participate in a wide range of metabolic regulation, RNA maturation, translational control, protein folding, chromatin remodeling, proteolysis and the maintenance of cytoskeletal architecture (7).

Lysine acetylation modulates protein function through altering protein stability, catalytic activity and intracellular distribution, as well as interacting with other PTMs. Moreover, this modification regulates both protein-protein and DNA protein interactions. As a flexible regulatory mechanism, lysine acetylation provides cells with a refined control over physiological processes and offers novel insights into disease pathogenesis. Recently, enzymes involved in acetylation have emerged as promising targets for drug development.

2. Discovery and classification of protein acetylation

Protein acetylation was first identified in nuclear histones in the 1960s and was initially regarded as a regulatory mechanism predominantly involved in chromatin organization and gene transcription. Accordingly, early studies referred to this modification as 'histone acetylation' (8). With the advent of proteomics and mass spectrometry in the early 21st century, it has become clear that acetylation is not restricted to histones, but is also widespread among numerous non-histone proteins in the cytoplasm and mitochondria. Consequently, the concept has been broadened and is now more accurately described as 'lysine acetylation', which is increasingly recognized as a pivotal regulator of diverse biological processes (9). Mass spectrometry remains the primary tool for the site-specific identification and quantitative analysis of protein acetylation. More recently, the Iseq-Kac (internal standard-assisted quantification) strategy has been introduced, allowing the efficient profiling of the acetylome under low-abundance conditions without enrichment procedures (10) (Fig. 1).

Based on their subcellular localization, KATs can be broadly classified into two major categories: Type A and Type B. Type A KATs are mainly localized in the nucleus and regulate chromatin accessibility, transcriptional activation and chromatin remodeling by catalyzing histone acetylation. Representative members include CBP and p300. By contrast, Type B KATs are predominantly cytoplasmic and are involved in the acetylation of newly synthesized histones and non-histone proteins, thereby playing essential roles in protein maturation, nuclear transport, and post-transcriptional regulation. In addition to their distinct subcellular localization, KATs exhibit specific substrate preferences. For example, GCN5 preferentially catalyzes histone H3K14 acetylation, while exhibiting relatively limited activity toward global nucleosome acetylation (11).

Furthermore, based on sequence homology and the characteristics of catalytic domains, eukaryotic KATs are mainly classified into several families, including the GCN5-related N-acetyltransferase (GNAT), CBP/p300, MYST, basal transcription factor, NCoA and other families. The GNAT family mainly consists of GCN5, PCAF and their associated transcriptional coactivator complexes such as SAGA, ATAC and TFTC, and has been implicated in cancer, cardiovascular disorders, inflammatory diseases and genetic disorders (12-19). The CBP/p300 family primarily functions as transcriptional coactivators with intrinsic acetyltransferase activity and plays critical roles in gene regulation, cellular differentiation and disease development, including cancer and developmental disorders (20-23). The MYST family comprises TIP60, MOZ, MORF and HBO1, as well as multiple associated protein complexes, including NuA4, MSL, NSL and SWR1-like complexes. Members of this family participate in the immune responses, and their dysregulation has been shown to be associated with various pathological conditions, particularly inflammation and malignancies (24-30). In addition, KATs associated with basal transcription factors and nuclear receptor coactivators, such as TFIID, TFIIIC and NCoA complexes, contribute to transcriptional regulation and have been linked to human diseases (31-33). Other KAT-associated complexes, such as the HAT1-containing HAT-B complex and HAT4, have also been implicated in specific pathological conditions, although their biological functions and disease associations remain less extensively characterized (34-36). The classification of KAT families, associated complexes and their disease relevance are summarized in Table I.

KDACs function together with KATs to maintain acetylation homeostasis. Based on their catalytic mechanisms, KDACs can be classified into Zn^{2+}-dependent histone deacetylases (HDACs) and NAD^{+}-dependent sirtuins (37).

According to structural features and sequence similarity, Zn^{2+}-dependent HDACs are further classified into classes I, II and IV, whereas NAD^{+}-dependent sirtuins constitute class III HDACs. Class I HDACs (HDAC1, HDAC2, HDAC3 and HDAC8) are predominantly localized in the nucleus and participate in histone deacetylation, thereby regulating various biological processes, including cell cycle progression, proliferation and differentiation (38-41). Class I HDACs dysregulation has been associated with cancer, cardiovascular disorders and metabolic diseases (42-52).

Class II HDACs consist of two subclasses: Class IIa (HDAC4, HDAC5, HDAC7, and HDAC9) and Class IIb (HDAC6 and HDAC10). These enzymes exhibit dynamic shuttling between the nucleus and cytoplasm (53-55). Among them, HDAC6 mainly targets non-histone substrates, such as tubulin, and plays important roles in regulating cell migration and stress responses (56-58). Abnormalities in Class II HDAC function have been implicated in inflammatory disorders, metabolic dysfunction, neurological injury and cancer (59-69).

Class III HDACs, also known as the sirtuin family (SIRT1-SIRT7), play essential regulatory roles in multiple diseases, regulate metabolism, stress responses, mitochondrial function and aging processes, and are involved in diverse diseases, including cancer, cardiovascular disorders and metabolic diseases (70-88). Class IV HDACs mainly consist of HDAC11, which has been reported to participate in immune regulation and pathological processes (89,90). The classification of the different KDAC families and their associated diseases are summarized in Table II.

Lysine acetyltransferases and deacetylases play essential roles in cellular physiology. Their interplay modulates the acetylation status of lysine residues, thereby regulating chromatin dynamics and influencing gene expression, cellular metabolism, and other biological processes.

3. Biological functions

Regulation of gene transcription. Lysine acetylation plays a crucial role in regulating gene transcription by modulating chromatin structure, transcription factor activity and the assembly of transcriptional regulatory complexes.

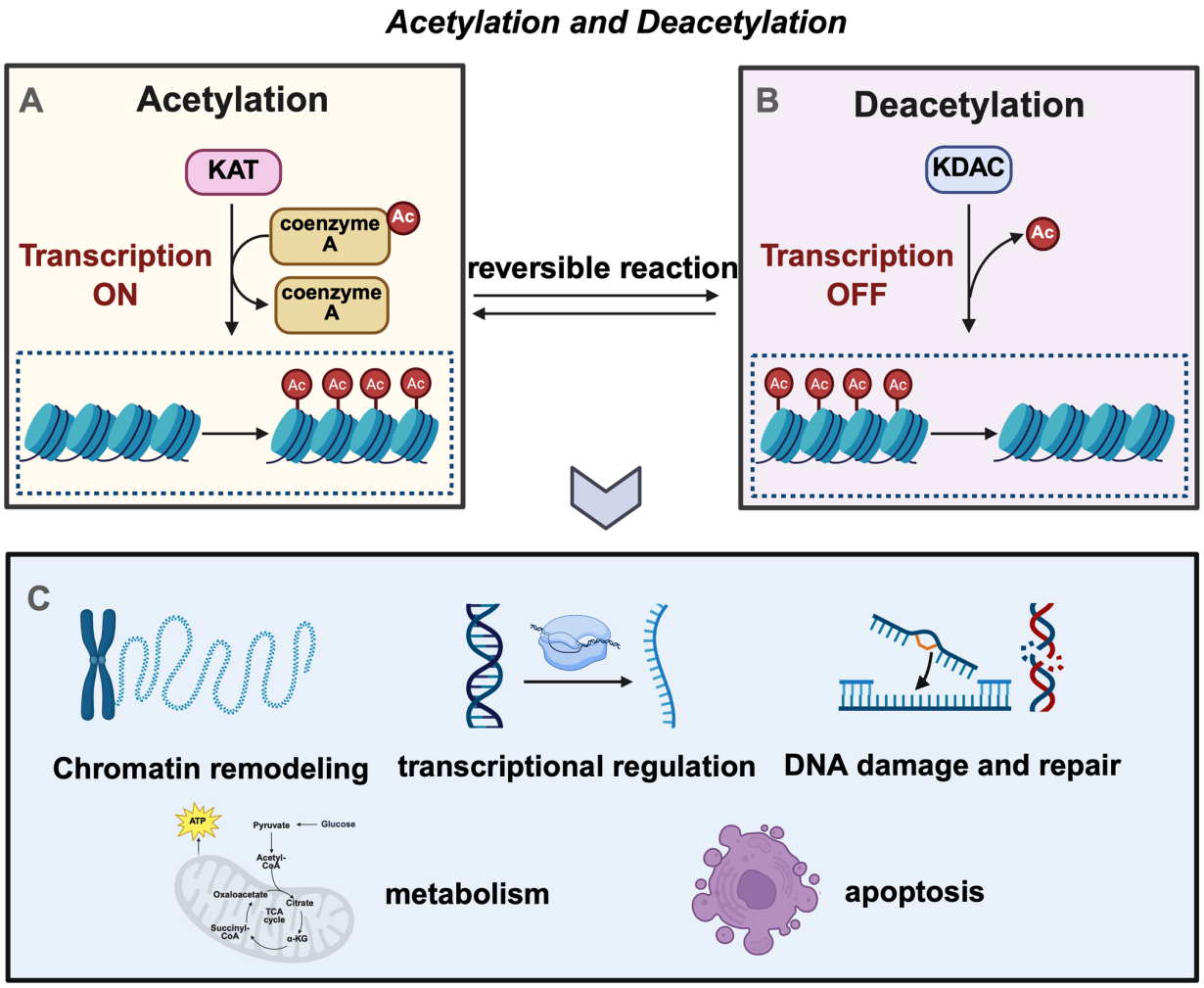


Figure 1. Acetylation and deacetylation. Acetylation and deacetylation are reversible post-translational modification processes. (A) Histone acetylation. KATs catalyze the transfer of acetyl groups to lysine residues on histones, resulting in chromatin relaxation and the activation of gene transcription. (B) Histone deacetylation. KDACs catalyze the removal of acetyl groups from lysine residues on histones, leading to chromatin condensation and the repression of gene transcription. (C) Coordinated regulation of cellular processes by acetylation and deacetylation. The dynamic balance between acetylation and deacetylation regulates chromatin conformation, gene transcription, DNA damage and repair, cellular metabolism, cell cycle progression, apoptosis, and other essential physiological processes. KAT, lysine acetyltransferase; KDAC, lysine deacetylase; AC, acetyl group. This figure was created using BioRender.

Ada3 is acetylated at lysine residues, together with its interaction with GCN5 and SPT7, promotes the formation of SAGA homodimers. This complex exhibits a high nucleosome acetylation efficiency, thereby enhancing its transcriptional activity. The findings underscore the essential contribution of acetylation to transcriptional regulation and the central role of the SAGA complex in gene expression (91). The expression of CCND1 results from the HDAC8-mediated deacetylation of PKM2, which subsequently affects its interaction with β-catenin (92). Additionally, the KAT5-mediated N-terminal acetylation of cGAS promotes the transcription of antiviral genes as part of the innate immune response (93). HDAC3 activity has been shown to initiate the transcription of the Ucp1 gene and enhance the expression of genes involved in mitochondrial oxidative phosphorylation, which are essential for thermogenesis in brown adipose tissue (94). PCAF-mediated acetylation of METTL3 at K177 disrupts its interaction with translation initiation factor subunit EIF3H, thereby reducing ribosomal translation efficiency (95). The acetylation of histone3 at K56 functions as a genome-wide transcriptional activator by enhancing promoter-proximal nucleosome destabilization and reassembly during the S-phase (96). Additionally, transcription assays using RNAP-II have revealed that nucleosomes bearing N-terminally acetylated H3 significantly reduced RNAP-II pause, resulting in increased transcript abundance (97).

Regulation of DNA damage and repair. In response to DNA damage, lysine acetylation regulates genome stability by modulating chromatin remodeling, facilitating the recruitment of DNA repair factors, and coordinating DNA repair pathway activation.

The acetylation of TDP-43 at K136 affects RNA binding and splicing, inducing phase separation and the accumulation of insoluble aggregates composed of TDP-43 that is pathologically phosphorylated and ubiquitinated (98). The acetylation and autophosphorylation of TIP60 initiate DNA damage responses by activating ataxia-telangiectasia mutated (ATM), while SIRT7 facilitates DNA repair by binding to and removing acetyl groups from ATM (99). The acetylation of nuclear lamin B1 (LMNB1) at K134 modulates nuclear peripheral stability, cell cycle progression, and DNA repair, in

Table I. Classification of acetyltransferases.

Subclass	Name	Aliases	Cellular localization	Complexes	Disease	(Refs.)
Type A KATs						
GNAT family	KAT2A	GCN5; GCN5L2; PCAF-b	Nucleus	TFTC; STAGA; ATAC	DCM; ALI; XP-B; CS	(12-14)
	KAT2B	PCAF	Nucleus	PCAF	CIA; CCA; MI	(15-17)
	KAT9	ELP3	Nucleus; cytoplasm	Elongator	HCC	(18)
	α-TAT1		Cytoplasm	ATAC	AB	(19)
	KAT14	CSRP2BP				
	ATF-2	CREB2				
p300/CBP family	CBP	KAT3A; CREBBP	Nucleus; cytoplasm		BC; RSTS; RA	(21,22)
	p300	KAT3B; EP300	Nucleus; cytoplasm		RA; IDD	(22,23)
MYST family	TIP60	KAT5; HTATIP	Nucleus; cytoplasm	NuA4; TIP60; SWR1-like	ALI; RA	(24)
	MOZ	MYST3; KAT6A	Nucleus		AML	(24,25)
	MORF	MYST4; KAT6B	Nucleus		AML	(25)
	HBO1	MYST2; KAT7	Nucleus	HBO1-containing complexes	OS; AML	(27,28)
	MOF	MYST1; KAT8	Nucleus	MSL; NSL	CRC; AML; NSCLC	(28-30)
Basal family	TAF1	KAT4; BA2R; CCG1; CCGS; TAF2A	Nucleus	TFIID	AML; XDP	(31,32)
	GTF3C4	KAT12	Nucleus	TFIIIC		
NCoA family	NCoA1	KAT13A; BHLHE74; SRC1	Nucleus			
	NCoA2	KAT13C; BHLHE75; SRC2; TIF2	Nucleus			
	NCoA3	KAT13B; AIB1; BHLHE42; RAC3; TRAM1	Nucleus; cytoplasm		HCC	(33)
Type B KATs						
	HAT1	KAT1	Nucleus; cytoplasm	HAT-B	HBV; PTS	(34,35)
	HAT4	NAA60	Golgi		PFBC	(36)

DCM, dilated cardiomyopathy; ALI, acute lung injury; XP-B, xeroderma pigmentosa; CS, Cushing's syndrome; CIA, collagen-induced arthritis; CCA, cholangiocarcinoma; MI, myocardial infarction; HCC, hepatocellular carcinoma; AB, ameloblastoma; BC, breast cancer; RSTS, Rubinstein-Taybi syndrome; RA, rheumatoid arthritis; IDD, immunodeficiency disease; AML, acute myeloid leukemia; OS, osteosarcoma; CRC, carcinoma of colon and rectum; NSCLC, non-small cell lung cancer; XDP, X-linked dystonia parkinsonism; HBV, viral hepatitis type B; PTS, post-phlebitic syndrome; PFBC, primary familial brain calcification; GNAT, GCN5-related N-acetyltransferase; KAT2A, lysine acetyltransferase 2A (also known as GCN5, PCAF-b; formerly GCN5L2); TFTC, TATA-binding protein-free TAF-containing complex; STAGA, SPT3-TAFII31-GCN5 acetyltransferase complex; ATAC, Ada two A-containing acetyltransferase complex; KAT2B, lysine acetyltransferase 2B; PCAF, p300/CBP-associated factor; KAT9, elongator acetyltransferase complex subunit 3 (also known as ELP3); α-TAT1, α tubulin acetyltransferase 1; KAT14, CSRP2 binding protein (also known as CSRP2BP); ATF2, activating transcription factor 2 (also known as CREB2); CBP, CREB-binding protein (also known as CREBBP, KAT3A); p300, E1A-binding protein p300 (also known as EP300, KAT3B); TIP60, HIV-1 Tat interactive protein 60 kDa (also known as KAT5, HTATIP); MOZ, monocytic leukemia zinc finger protein (also known as MYST3, KAT6A); MORF, MOZ-related factor (also known as KAT6B, MYST4); HBO1, histone acetyltransferase binding to ORC1 (also known as KAT7, MYST2); MOF, males absent on the first (also known as KAT8, MYST1); NuA4, nucleosome acetyltransferase of H4 complex; TIP60 complex, Tat-interactive protein 60 kDa complex; SWR1-like complex, SWR1-like chromatin-remodeling complex; MSL, male-specific lethal complex; NSL, non-specific lethal complex; basal family, basal transcription factor-associated KATs; TAF1, TATA-box binding protein-associated factor 1 (also known as KAT4, BA2R, CCG1, CCGS and TAF2A); GTF3C4, general transcription factor IIIC subunit 4 (also known as KAT12); NCoA, nuclear receptor coactivator; NCOA1, nuclear receptor coactivator 1 (also known as KAT13A, BHLHE74, SRC1); NCOA2, nuclear receptor coactivator 2 (also known as KAT13C, BHLHE75, SRC2, TIF2); NCOA3, nuclear receptor coactivator 3 (also known as KAT13B; AIB1; BHLHE42; RAC3; TRAM1); HAT1, histone acetyltransferase 1 (also known as KAT1); NAA60, N(alpha)-acetyltransferase 60 (also known as HAT4); HAT-B, type B histone acetyltransferase.

Table II. Classification of deacetylases.

Subclass	Name	Aliases	Cellular localization	Cofactor	Disease	(Refs.)
Class I	HDAC1	RPD3L1	Nucleus	Zn^{2+}	AP; DIO; MAFLD	(42-44)
	HDAC2		Nucleus, cytoplasm	Zn^{2+}	CRC; CCA; HCC	(45-47)
	HDAC3		Nucleus, cytoplasm	Zn^{2+}	PDAC; MM; HF	(48-50)
	HDAC8	HDACL1; CDA07	Nucleus, cytoplasm	Zn^{2+}	HCC; AML	(51,52)
Class IIA	HDAC4	KIAA0228	Nucleus, cytoplasm	Zn^{2+}	Asthma; NPC; MAFLD	(59-61)
	HDAC5	KIAA0600	Nucleus, cytoplasm	Zn^{2+}	UC; DKD	(62,63)
	HDAC7	HDAC7A	Nucleus, cytoplasm	Zn^{2+}	LC; HIBD	(64,65)
	HDAC9	HDRP; MITR	Nucleus, cytoplasm	Zn^{2+}	IVDD	(66)
Class IIB	HDAC6	KIAA0901	Nucleus, cytoplasm	Zn^{2+}	TNBC; AD	(67,68)
	HDAC10		Nucleus, cytoplasm	Zn^{2+}	ALI	(69)
Class III (SIRTs)	SIRT1	SIR2L1	Nucleus, cytoplasm	NAD^+	SAKI; HF; ALI; AD	(70-73)
	SIRT2	SIR2L; SIR2L2	Cytoplasm	NAD^+	LC; AD	(73,74)
	SIRT3	SIR2L3	Mitochondria	NAD^+	I/R; ALI	(75,76)
	SIRT4	SIR2L4	Mitochondria	NAD^+	COPD; HCC	(77,78)
	SIRT5	SIR2L5	Mitochondria	NAD^+	PDAC; IBD	(79-81)
	SIRT6	SIR2L6	Nucleus	NAD^+	NSCLC; MAFLD	(82,83)
	SIRT7	SIR2L7	Nucleus	NAD^+	HCC	(84.85)
Class IV	HDAC11		Nucleus	Zn^{2+}	PJI; AS	(89,90)

AP, acute pancreatitis; DIO, diet-induced obesity; MAFLD, metabolic dysfunction-associated fatty liver disease; PDAC, pancreatic ductal adenocarcinoma; MM, multiple myeloma; HF, heart failure; NPC, Niemann-Pick disease type C; UC, ulcerative colitis; DKD, diabetic kidney disease; LC, liver cirrhosis; HIBD, hypoxic-ischemic brain damage; IVDD, intervertebral disc disease; TNBC, triple-negative breast cancer; AD, Alzheimer's disease; SAKI, sepsis-associated acute kidney injury; I/R, ischemia-reperfusion injury; COPD, chronic obstructive pulmonary disease; IBD, inflammatory bowel disease; PJI, periprosthetic joint infection; AS, atherosclerosis; HDAC1, histone deacetylase 1 (also known as RPD3L1); HDAC2, histone deacetylase 2; HDAC3, deacetylase 3; HDAC8, histone deacetylase 8 (also known as HDACL1); HDAC4, histone deacetylase 4 (also known as KIAA0228); HDAC5, histone deacetylase 5 (also known as KIAA0600); HDAC7, histone deacetylase 7 (also known as HDAC7A); HDAC9, histone deacetylase 9 (also known as HDRP and MITR); HDAC6, histone deacetylase 6 (also known as KIAA0901); HDAC10, histone deacetylase 10; SIRT1, sirtuin 1 (also known as SIR2L1); SIRT2, sirtuin 2 (also known as SIR2L2); SIRT3, sirtuin 3 (also known as SIR2L3); SIRT4, sirtuin 4 (also known as SIR2L4); SIRT5, sirtuin 5 (also known as SIR2L5); SIRT6, sirtuin 6 (also known as SIR2L6); SIRT7, sirtuin 7 (also known as SIR2L7); HDAC11, histone deacetylase 11.

part by impairing 53BP1 recruitment to DNA lesions, thereby inhibiting non-homologous end joining and delaying the G1/S transition (100). In response to poly-ADP-ribosylation, pyruvate dehydrogenase E1α is rapidly localized to chromatin, where it produces acetyl-CoA at sites of DNA double-strand breaks, promoting chromatin relaxation and facilitating repair factor recruitment and genome stability (101). Upon DNA damage, acetylation of E2F1 generates a specific recognition motif for the bromodomains of KAT3A and KAT3B, facilitating their recruitment to sites of double-strand breaks. This localization promotes further acetylation processes and the assembly of chromatin-remodeling and DNA repair complexes, including Tip60, BRG1 and NBS1 (102).

Maintenance of cellular homeostasis. The process of autophagy is fundamental to the maintenance of intracellular equilibrium, particularly during nutrient deprivation, by degrading stored energy sources. Acetyl-CoA, a primary intracellular acetyl donor, promotes mTORC1 activation by enhancing ep300-mediated acetylation of raptor at K1097, thereby inhibiting autophagy (103,104).

GCN5-mediated acetylation inhibits TFEB transcriptional activity by preventing its dimerization, owing to a non-conserved K116 site within the MiT/TFE family, thereby impairing autophagosome formation (105). SIRT1-deficient embryos and neonatal mice accumulate mitochondria, and exhibit elevated p62 levels, AMPK activation and lethality. NAD^+, essential for cellular processes and a cofactor for some histone deacetylases, is critical for autophagy regulation, particularly under starvation conditions where SIRT1 activity is NAD^+-dependent (106). NAMPT expression is regulated by the acetylation of upstream enhancers and modulates intracellular NAD^+ levels (107). The acetylation also affects metabolism-related gene expression, and metabolic states reciprocally influence acetyltransferase and deacetylase activities. KAT8 is crucial for metabolic regulation, and MOF depletion during neuronal development is associated with the accumulation of stearic acid and long-chain fatty acids (108). NatB-mediated N-terminal acetylation of Act1 promotes actin filament assembly, aiding Atg9 vesicle trafficking and autophagosome formation. Acetylation of the N-terminus of Vps1 enhances its interaction with SNARE proteins, facilitating autophagosome-vacuole fusion (109). RB1CC1/FIP200, a key autophagy regulator, is acetylated at K276 by CREB, which reduces its ubiquitination and degradation, thereby enhancing autophagic activity in diseases, such as breast cancer (110).

Regulation of pluripotency and differentiation. Lysine acetylation is also a key factor involved in the dynamic changes in chromatin organization and transcriptional regulation. Thus, lysine acetylation plays an essential role in maintaining pluripotency and directing cellular differentiation by modulating gene expression programs.

KAT5 is essential for embryonic stem cell development, and its deficiency impairs embryogenesis (111). The proper regulation of KAT enzymatic function is crucial for sustaining equilibrium between hematopoietic stem cell self-renewal and lineage commitment. MOF deficiency impairs erythroid development, likely due to reduced H4K16ac levels and altered chromatin accessibility (112). Acetyl-CoA influences endodermal differentiation by promoting the acetylation of Smad3 at lysine 19, a key transcription factor in endodermal lineage commitment (113). KAT7 regulates adult HSCs, and its deletion causes HSC quiescence, hematopoietic failure, and pancytopenia in mice (114). Histone deacetylase SIRT6 interacts with Pol II to inhibit NELF release and, maintain Pol II pausing. SIRT6 deficiency or chromatin defects enrich H3K9ac and H3K56ac under glucose starvation, activating CDK9 phosphorylation of NELF and Pol II and recruiting MYC, BRD4, PAF1, AFF4 and ELL2, which enhances transcriptional regulation of genes that participate in metabolism, protein synthesis and development (115).

Regulation of the cell cycle. Cell cycle progression requires dynamic regulation of chromatin structure and gene expression. Lysine acetylation contributes to this process by controlling histone modification patterns and regulating the activity of cell cycle-associated proteins. KATs and KDACs function differently during interphase and mitosis. KAT5 acetylates multiple lysine residues on H2A, H3 and H4 during interphase. During mitosis, KAT5 acetylates Aurora-B at residue K215, preventing its dephosphorylation by PP2A and ensuring an accurate metaphase-to-anaphase transition (116). KAT5 deficiency disrupts metaphase alignment and inhibits cell growth during mitosis (117). The inhibition of the CBP bromodomain by CCS1477 results in cell cycle arrest and enhances differentiation in a range of tumor (118). Tip60 reverses HDAC8-mediated deacetylation at K202, limiting HDAC8 activity, enhancing SMC3 acetylation, impairing cohesion and cell cycle progression, and inducing G2/M arrest (119). Aberrant CHK2 activation induces cell cycle inhibition and subsequent cell death, while SIRT1 directly engages CHK2 to mediate its deacetylation at the K520 site, thereby reducing CHK2 phosphorylation, dimerization, and activation, and maintaining genome integrity and homeostasis (120). Taken together, these findings highlight lysine acetylation as a dynamic epigenetic regulatory layer that integrates transcriptional regulation, genome maintenance, metabolism, cell fate determination and cell cycle progression (Fig. 2).

Crosstalk between acetylation and other protein modifications. Lysine acetylation does not function independently, but interacts extensively with other PTMs, including ubiquitination, phosphorylation, methylation and lactylation. These interactions regulate protein stability, activity and cellular signaling. Acetylation protects proteins from ubiquitination by masking lysine residues, thereby preventing their degradation. For example, HDAC inhibitors, such as TSA, enhance ENaC acetylation and abundance, while reducing its ubiquitination. By contrast, HDAC7 promotes ENaC ubiquitination (121). Conversely, acetylation enhances protein ubiquitination and degradation. PEPCK1 acetylation recruits the E3 ligase UBR5, which leads to its degradation (122). AMPK phosphorylates ASPP2 in response to irradiation (IR), promoting apoptosis. BRD4 inhibition by JQ-1 disrupts histone acetylation and sensitizes AMPK-deficient cells to IR (123). PGAM5 mediates ME1 dephosphorylation at S336 and promotes ACAT1 at residue K337 acetylation (124). COP1, an E3 ligase and tumor suppressor, enhances JNK phosphorylation and c-Jun nuclear translocation and inhibits HDAC3 expression (125). The acetylation of LHPP inhibits GSK3B phosphorylation, and modulates HIF1A-driven glycolysis and metastasis in gastric cancer (126). N-terminal acetyltransferase modulates H3K4 methylation by blocking Set1-COMPASS acetylation via Shg1 proline mutation (127). The MOF-mediated acetylation of UHRF1 at K670 reduced its recruitment of DNMT1 during replication, thereby lowering DNA methylation (128). KAT8 acetylates ALKBH5 at residue K235, enhancing its m6A demethylation activity (129). The acetylation of the H3 tail facilitates access to other H3K4 methyl readers (130). SIRT3 downregulation increased PDHA1 acetylation in renal tubular epithelial cells, leading to lactate overproduction and Fis1 K20 lactylation, thereby promoting mitochondrial fission, ATP depletion, mtROS generation and apoptosis (131). RBM25 interacts with Acly, mediating exon 14 skipping to generate the acly isoform, which promotes K918/995 lactylation and glycolysis-driven acetyl-CoA production by pro-inflammatory macrophages (132) (Fig. 3).

4. Roles of lysine acetylation in the pathogenesis of diseases

Lysine acetylation plays a pivotal role in the pathogenesis of diseases. In cancer, acetylation or deacetylation tightly regulate gene transcription and host immune response. Acetylation can exert an inhibitory effect on tumor progression and promote differentiation by modulating the expression of cancer-related genes (133). It also enhances the infiltration and cytotoxicity of innate immune cells, such as T-cells, while reducing the immunosuppressive function of Tregs, ultimately leading to cancer cell clearance. In cardiovascular diseases, the dysregulation of lysine acetylation has been linked to the onset and progression of hypertension, atherosclerosis, myocardial infarction and cardiac hypertrophy (134-137). The modulation of lysine acetylation also reduces ameliorates pulmonary damage in inflammation-induced lung injury (138) (Fig. 4).

Cancer. Acetylation and deacetylation exert profound effects on cancer initiation and progression. Programmed death-ligand 1 (PD-L1) is commonly found to be highly expressed across some solid malignancies, such as melanoma, non-small cell lung cancer and breast carcinoma. Increasing evidence suggests that the inhibition or downregulation of PD-L1 expression represents a valuable and promising therapeutic approach for the treatment of these types of cancer (139). Programmed cell death protein 1 (PD-1) signaling enhances PD-L1 expression and reduces the apoptotic susceptibility of tumor cells. Furthermore, multiple clinical studies have

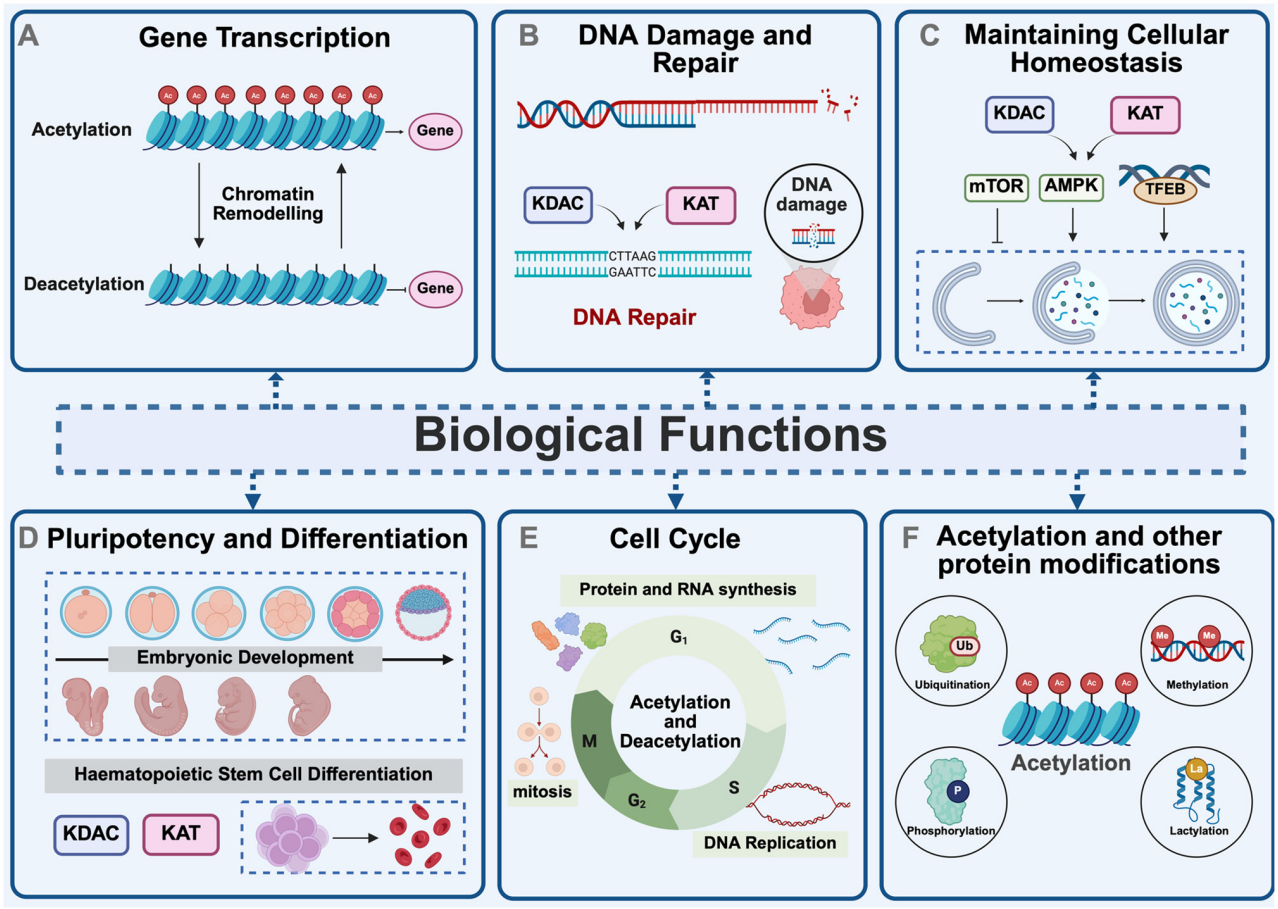


Figure 2. Biological functions of lysine acetylation. Acetylation and deacetylation are important reversible post-translational modifications that regulate protein function and gene expression. By dynamically maintaining the acetylation status of lysine residues, these modifications are extensively involved in diverse cellular biological processes. (A) Regulation of gene transcription. Histone acetylation promotes chromatin accessibility and activates gene transcription, whereas deacetylation facilitates chromatin condensation and represses gene expression. (B) DNA damage repair. KATs and KDACs regulate the acetylation status of DNA damage repair-related proteins, thereby participating in DNA damage recognition, damage signaling transduction, and DNA repair processes to maintain genome stability. (C) Maintenance of cellular homeostasis. Acetylation and deacetylation regulate key signaling pathways, including mTOR, AMPK, and TFEB, thereby modulating autophagy, lysosomal function, and metabolic homeostasis to maintain normal cellular physiological functions. (D) Stem cell pluripotency and cell differentiation. Acetylation modifications participate in embryonic development, maintenance of stem cell pluripotency, and differentiation of various cellular lineages, including hematopoietic stem cells, by regulating the expression of developmental genes and determining cell fate. (E) Regulation of the cell cycle. Acetylation and deacetylation regulate DNA replication, RNA and protein synthesis, thereby influencing cell proliferation and mitosis. (F) Acetylation can interact with and coordinate with various PTMs, including ubiquitination, phosphorylation, lactylation and methylation. KAT, lysine acetyltransferase; KDAC, lysine deacetylase; mTOR, mammalian target of rapamycin; AMPK, AMP-activated protein kinase; TFEB, transcription factor EB. This figure was created using BioRender.

demonstrated that HDAC2 is significantly overexpressed in tumor tissues from patients with various malignancies, including colorectal, gastric and breast cancer. Elevated HDAC2 expression levels are closely associated with a reduced overall survival (OS), a poor prognosis and advanced tumor stages, indicating its potential clinical value as a diagnostic and prognostic biomarker (140). Mechanistically, the deacetylase HDAC2 in mice has been shown to interacts with PD-L1 and reduces its acetylation level (141). In addition, HAT1 expression is increased in clinical pancreatic cancer samples, and its high expression is closely associated with a poor prognosis of patients with pancreatic cancer, suggesting the clinical relevance of HAT1 in pancreatic tumor tissues (142). Further research has revealed that HAT1 acetylates PD-L1 at H4 at K5 and K12, promoting BRD4 recruitment and increasing PD-L1 transcription in pancreatic cancer. HAT1 knockdown enhances the infiltration of $CD45^+$ $CD4^+$ and $CD45^+$ and $CD8^+$ T-cells, suppresses $CD11b^+$ $Gr1^+$ myeloid infiltration, and reduces tumor growth and metastasis by downregulating PD-L1 (142). These findings indicate that acetylation regulation directly controls tumor cell intrinsic signaling and shapes the tumor immune microenvironment by modulating of immune checkpoint expression.

A prospective clinical study found that patients with CBP mutations had a significantly reduced OS, progression-free survival and event-free survival, suggesting that CBP mutations are an independent predictor of a poor prognosis in cancer (143). Further investigations demonstrated that the CBP-mediated acetylation of MOB1 at K11 activates LATS1, which in turn stimulates the Hippo signaling cascade, restricts YAP/TAZ nuclear localization, and suppresses tumorigenesis (144). Similarly, the acetylation of RRM2 by KAT7 at K95 disrupts its dimerization, functioning as a molecular switch to inhibit dNTP synthesis, stall DNA replication forks, and suppress tumor cell proliferation (145). Finally, WEE1 is a potential target for cancer therapy; SIRT1 interacts with and

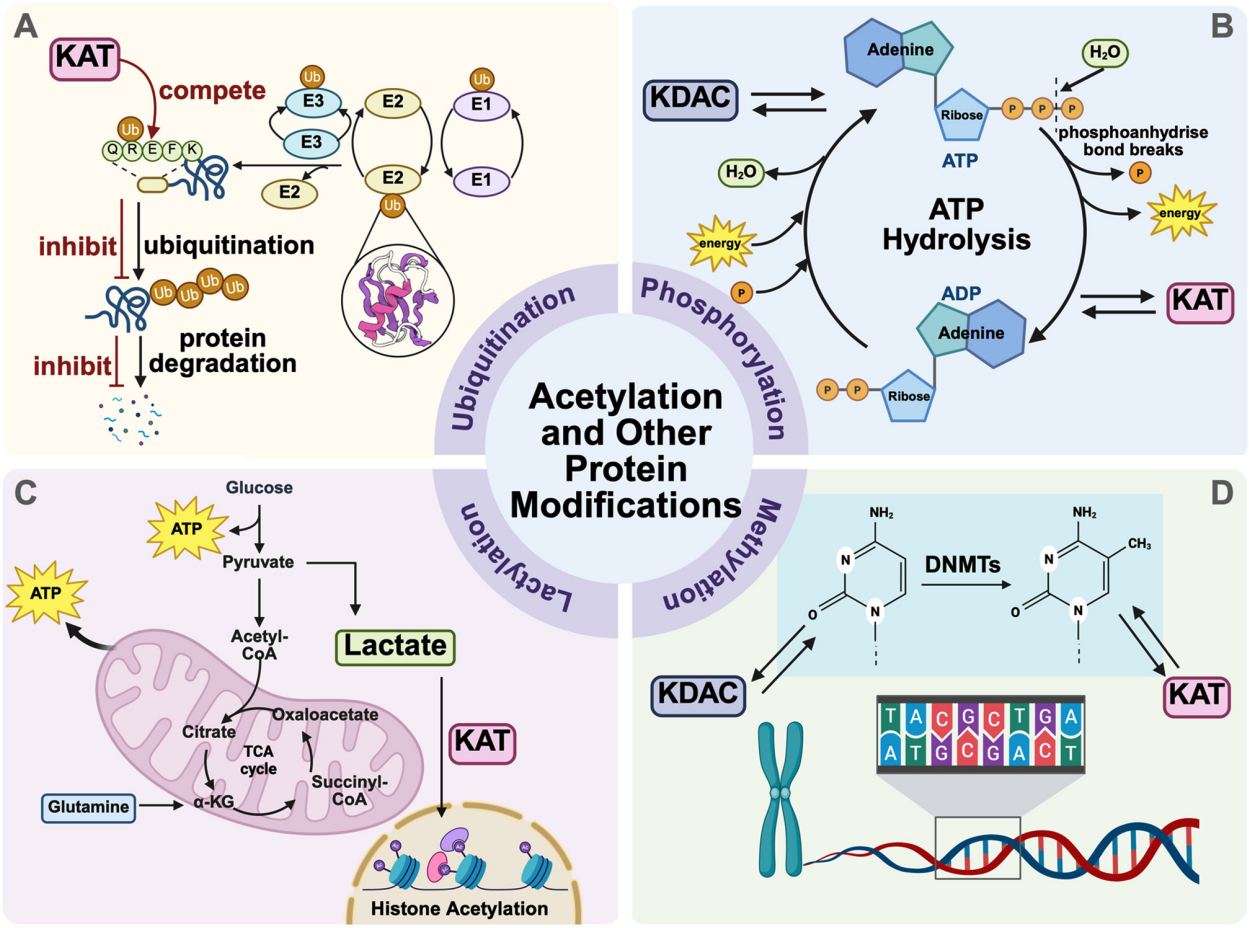


Figure 3. Crosstalk between acetylation and other protein modifications. (A) Acetylation and ubiquitination. Acetylation and ubiquitination can competitively modify lysine residues on proteins. Acetylation inhibits ubiquitin chain formation and proteasome-mediated protein degradation, thereby regulating protein stability and function. (B) Acetylation and phosphorylation. Acetylation and phosphorylation influence each other by regulating ATP hydrolysis and phosphate group transfer processes. These modifications participate in cellular signal transduction, energy metabolism, and protein activity regulation, and can synergistically or antagonistically modulate diverse biological processes. (C) Acetylation and lactylation. Both acetylation and lactylation are regulated by cellular metabolic states and jointly participate in histone modification, gene expression regulation and immunometabolic responses. (D) Acetylation and methylation. Acetylation and DNA methylation cooperatively contribute to epigenetic regulation. KATs and KDACs regulate DNA methylation levels by modulating the activity of DNMTs and chromatin accessibility, whereas DNA methylation can also influence the recruitment of acetylation-related enzymes and transcriptional activity. KAT, lysine acetyltransferase; KDAC, lysine deacetylase; E1, ubiquitin-activating enzyme; E2, ubiquitin-conjugating enzyme; E3, ubiquitin ligase; DNMTs, DNA methyltransferases. This figure was created using BioRender.

deacetylates WEE1 to maintain its inactive state (146). This pathway opens new avenues for anticancer strategies by elucidating the complex acetylation/deacetylation regulation in the tumor microenvironment.

Cardiovascular diseases. In hypertension research, the inhibition of HDACs has proven to be effective in preventing hypertension. In spontaneously hypertensive models, the HDAC inhibitor, valproic acid, reduces inflammatory responses, myocardial hypertrophy and oxidative stress indicators (147). Clinical studies have demonstrated that the acetylation level of the mitochondrial protein cyclophilin D is markedly increased (by ~280%) in small arterial tissues from patients with hypertension. This alteration is accompanied by the decreased expression of SIRT3 and increased GCN5L1 levels, suggesting that dysregulated mitochondrial protein acetylation may contribute to hypertension-associated endothelial dysfunction (148). Mechanistic analyses have revealed that SIRT3 protects against angiotensin II-induced hypertension by promoting mitophagy and clearing damaged mitochondria, thereby reducing production of reactive oxygen species (149). This mechanism alleviates vascular injury and myocardial fibrosis, and improves hypertensive cardiovascular pathology.

In the context of heart failure and pathological cardiac hypertrophy, the acetyltransferase p300 plays a key regulatory role. Clinical sample analyses have demonstrated that, compared with normal cardiac tissues, p300 expression is significantly increased in left ventricular tissues from patients with ischemic cardiomyopathy, dilated cardiomyopathy and end-stage heart failure, suggesting that p300 may contribute to pathological cardiac remodeling (150). p300 functions as a coactivator of cardiac hypertrophic transcription factors (151). p300 directly acetylates GATA4, boosting hypertrophic gene expression during cardiac remodeling (152). p300 also enhances MEF2 transcriptional activity via acetylation, further promoting hypertrophy. SIRT1 deacetylates p300, attenuates acetyltransferase activity, and delays cardiac hypertrophy. SIRT1 knockout mice exhibit increased MEF2 acetylation and dilated cardiomyopathy, underscoring the protective role of SIRT1 (153). In heart failure, the reduced expression

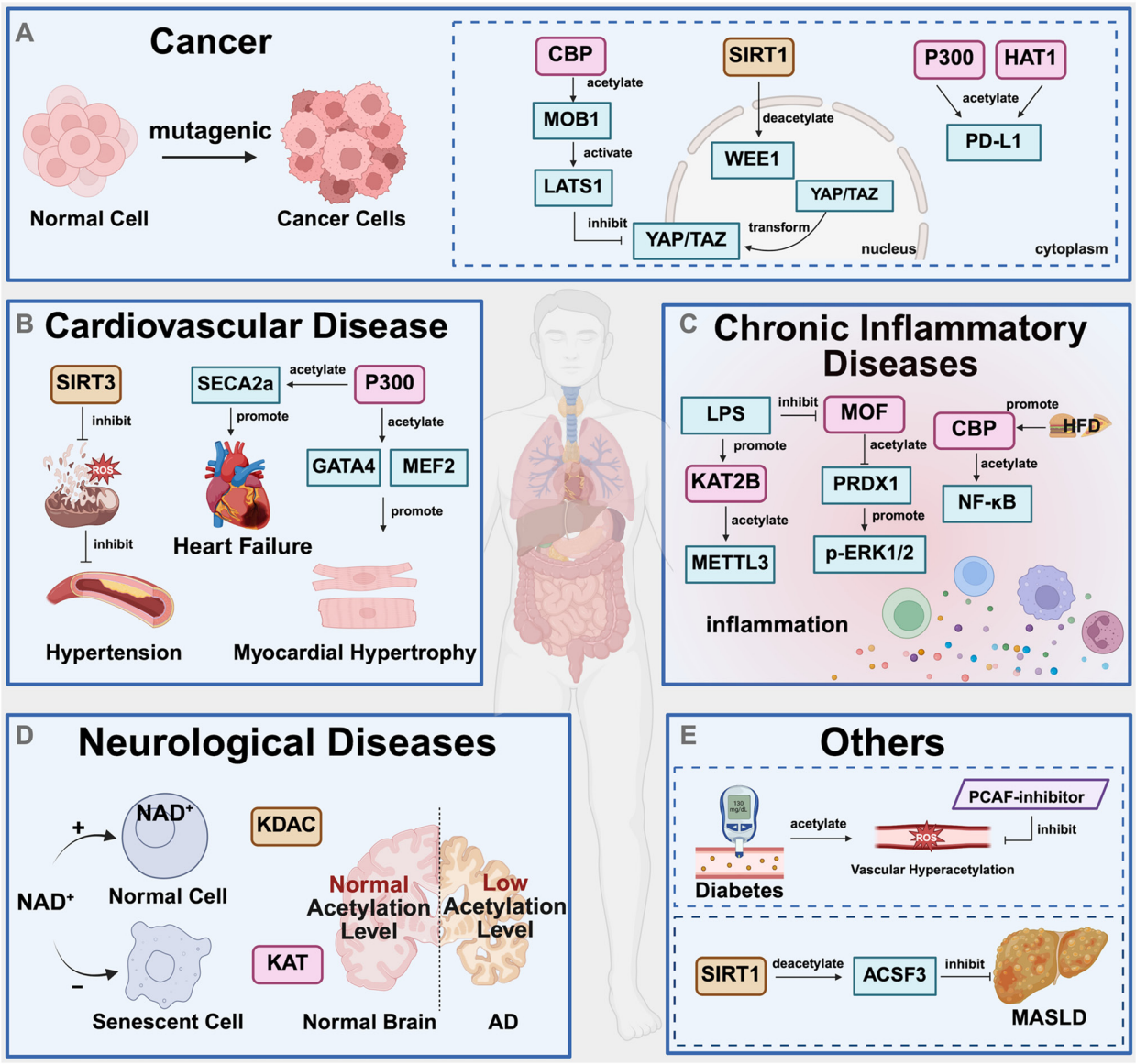


Figure 4. Roles of lysine acetylation in disease. Lysine acetylation is a critical reversible post-translational modification that regulates the acetylation status of histone and non-histone substrates, thereby contributing to the initiation and progression of various diseases, including cancer, cardiovascular diseases, chronic inflammatory disorders, and neurodegenerative diseases. (A) Cancer: Acetylation modifications contribute to tumorigenesis by regulating multiple biological processes, including cell proliferation, cell cycle progression, migration, invasion and immune evasion. The CBP-mediated acetylation of MOB1 promotes Hippo signaling pathway activation, enhances LATS1 activity and suppresses YAP/TAZ signaling. SIRT1 regulates WEE1 activity through deacetylation, thereby affecting tumor cell proliferation. p300 and HAT1 mediated PD-L1 acetylation enhances PD-L1 stability and promotes immune evasion. (B) Cardiovascular diseases: Acetylation participates in the pathogenesis of cardiovascular diseases, including hypertension, cardiac hypertrophy and heart failure. SIRT3 alleviates hypertension-associated pathological alterations by reducing mitochondrial oxidative stress. p300-mediated acetylation of GATA4 and MEF2 promotes the expression of cardiac hypertrophy-related genes. The abnormal acetylation of SERCA2a is closely associated with heart failure. (C) Chronic inflammatory diseases: Acetylation regulates inflammatory responses by modulating inflammatory signaling pathways and immune cell functions. Stimulation with LPS induces KAT2B expression and promotes METTL3 acetylation, thereby enhancing METTL3 protein stability. MOF attenuates inflammatory responses by regulating PRDX1, whereas CBP-mediated NF-κB acetylation enhances the transcription of inflammation-related genes. (D) Neurodegenerative diseases: NAD^+ imbalance is closely associated with cellular senescence and neurodegenerative diseases. The dysregulation of KAT and KDAC activities alters the acetylation landscape in brain tissues, thereby affecting neuronal function, synaptic plasticity, and the development and progression of neurodegenerative disorders such as AD. (E) Other diseases: Acetylation also contributes to metabolic disorders, including diabetes mellitus and MASLD. PCAF inhibitors reduce vascular hyperacetylation and ameliorate diabetes-associated vascular injury. SIRT1 improves MASLD and related metabolic abnormalities through deacetylation-mediated regulation of metabolic proteins, such as ACSF3. MOB1, Mps one binder kinase activator-like 1; LATS1, large tumor suppressor kinase 1; YAP, yes-associated protein; TAZ, transcriptional coactivator with PDZ-binding motif; WEE1, Wee1-like protein kinase; PD-L1, programmed cell death ligand 1; SECA2a, sarcoplasmic/endoplasmic reticulum calcium ATPase 2a; GATA4, GATA binding protein 4; MEF2, myocyte enhancer factor 2; LPS, lipopolysaccharide; METTL3, methyltransferase-like protein 3; PRDX1, peroxiredoxin 1; p-ERK1/2, phosphorylated extracellular signal-regulated kinase 1/2; NF-κB, nuclear factor κB; AD, Alzheimer's disease; ACSF3, acyl-CoA synthetase family member 3; MASLD, metabolic dysfunction-associated steatotic liver disease; HFD, high-fat diet; ROS, reactive oxygen species. This figure was created using BioRender.

and activity of SERCA2a are hallmarks. The p300-mediated acetylation of SERCA2a at K492 impairs its function, whereas SIRT1 restores SERCA2a levels and cardiac function (154). Taken together, these findings reveal that dysregulated acetylation homeostasis contributes to the progression of cardiovascular disease by affecting mitochondrial function,

inflammatory responses and cardiac remodeling, suggesting acetylation regulators as potential therapeutic targets.

Chronic inflammatory diseases. Recent evidence has demonstrated that acetylation-regulating enzymes not only influence the transcription of inflammation-related genes, but also contribute to disease progression by modulating immune cell functions, oxidative stress responses and tissue fibrotic processes.

In chronic obstructive pulmonary disease (COPD), HDAC3 has been suggested to function as a key regulator of glucocorticoid [inhaled corticosteroid (ICS)] treatment responsiveness. Recent clinical research has revealed that HDAC3 expression is elevated in airway smooth muscle cells from patients with COPD who are unresponsive to ICS therapy, whereas patients who respond to ICS treatment exhibit relatively lower HDAC3 levels. These findings suggest that the dysregulated expression of HDAC3 may influence glucocorticoid-mediated anti-inflammatory effects (155). STAT1 regulates NF-κB pathway activity. Valproic acid promotes the nuclear translocation of HDAC3, while inhibiting its activity, which enhances STAT1 expression and increased NF-κB p65 acetylation following spinal cord injury, thereby mitigating inflammation (156). Simultaneously, lipopolysaccharide (LPS) stimulation upregulates KAT2B, which acetylates METTL3 at K14, enhancing METTL3 stability and increasing Spi2a m6A methylation in macrophages. The methylation of Spi2a enables its association with IKKβ, which blocks IKK complex assembly and attenuates NF-κB activation (157).

In diabetic kidney disease, the acetylation modifications participate in the regulation of inflammatory responses and renal fibrosis. Clinical data analyses have revealed that p300 is highly expressed in renal tissues from patients with diabetic kidney disease and promotes the activation of HIF-related signaling pathways, thereby exacerbating fibrosis in renal tubular epithelial cells (158). p300/CBP-mediated increase in H3K27ac activates inflammation-related genes, exacerbating the renal inflammatory microenvironment (159).

Beyond the direct regulation of inflammation-related gene transcription, cellular metabolic reprogramming has emerged as another critical mechanism by which acetylation modulates inflammatory responses. A high-fat diet activates ACLY and promotes nuclear acetyl-CoA production, thereby activating CBP, which increases p65 acetylation and heightens inflammation (160). MOF-mediated acetylation of PRDX1 at K197 maintains redox regulation, while LPS-induced PRDX1 K197ac reduction leads to hydrogen peroxide accumulation, ERK1/2 phosphorylation, glycolysis stimulation, H3S28 phosphorylation and increased pro-inflammatory cytokine production (161). Collectively, these observations highlight the significance of lysine acetylation in the chronic inflammatory diseases through coordinated control of inflammatory transcription, immune cell function and metabolic reprogramming.

Neurological diseases. Aging is accompanied by declining NAD^+ levels, which are closely associated with age-related diseases (162). The analysis of clinical brain magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopy (^{1}H-MRS) data has demonstrated that NAD^+ metabolism in brain tissues gradually declines with aging (163). Furthermore, SIRT1 expression is significantly reduced (by ~4-fold) in brain tissues from patients with Alzheimer's disease (AD) (164). These findings indicate that SIRT1 serves as a key regulator of NAD^+ metabolism, and the activation of SIRT1 has been shown to promote lifespan extension (165). In addition to SIRT1, the mitochondrial deacetylase SIRT3 is also reduced by ~40% in the inferior parietal cortex of patients with AD. Mechanistically, SIRT3 protects parvalbumin- and calretinin-expressing interneurons from Aβ-induced dysfunction and degeneration, thereby suppressing aberrant neuronal network hyperexcitability and maintaining neuronal functional stability (166).

The NAD^+-dependent deacetylase SIRT2 exhibits elevated levels in aged brains. Genetic deletion or pharmacological inhibition of SIRT2 improves cognitive deficits by enhancing acetylation of amyloid precursor protein (APP), increasing soluble sAPPα and reducing amyloidogenic APP processing. APP lysines K132 and K134 are deacetylation targets of SIRT2 (167).

In AD, reduced global acetylation impairs tau interaction with chaperones and E3 ligases, hindering ubiquitin-proteasome system mediated tau clearance and leading to aggregation. HDAC6 has been also closely associated with amyloid and tau pathology in AD. Clinical research has revealed that HDAC6 expression is significantly increased in the cerebral cortex of patients with AD. Mechanistically, HDAC6 may promote Aβ production by regulating the acetylation status and stability of β-site amyloid precursor protein cleaving enzyme 1 (BACE1) (168). The HDAC6 inhibitor, CKD-504, increases protein acetylation, promotes tau-chaperone/E3 binding, enhances tau degradation and significantly improves cognition in mouse models of AD (169). Research indicates that the expression level of HDAC6 is elevated in patients with AD, which in turn affects the acetylation balance of α-tubulin and contributes to neuronal dysfunction (170). In another protective mechanism, deacetylation of NF-κB RelA in response to ischemic stress promotes pro-apoptotic gene transcription. The HDAC inhibitor, MS-275, combined with the SIRT1 activator, resveratrol, restores RelA acetylation in tMCAO and OGD mouse models, providing neuroprotection (171).

Other conditions. Clinical studies have demonstrated that SIRT1 expression is reduced in adipose tissues from individuals with obesity and type 2 diabetes mellitus, and decreased SIRT1 levels are associated with impaired insulin sensitivity. Moreover, adipose tissue SIRT1 expression exhibits an inverse correlation with the homeostatic model assessment of insulin resistance index and other insulin resistance-related parameters, suggesting that SIRT1-mediated deacetylation regulation may play a critical role in maintaining glucose homeostasis (172,173). SR18292 selectively inhibits gluconeogenesis without affecting lipogenesis by increasing PCK1 acetylation and reversing the gluconeogenic pathway, thus showing anti-diabetic efficacy (174). Vascular smooth muscle cell (VSMC) dysfunction and hyperacetylation are exacerbated under type 2 diabetic conditions, thereby promoting vascular pathology. The inhibition of PCAF reduces the production of reactive oxygen species in VSMCs under high glucose conditions, and attenuates vascular injury (175). Clinical research has revealed that SIRT3 expression is decreased in liver tissues from patients with metabolic dysfunction-associated steatotic liver disease (MASLD), accompanied by impaired mitochondrial β-oxidation, increased reactive oxygen species

accumulation and enhanced hepatic lipid deposition (176). Further investigations demonstrated that MASLD impairs hepatic fatty acid metabolism. SIRT3 deacetylates ACSF3, and alleviates dysregulation of fatty acid metabolism (177).

5. Acetylation-based therapeutic agents

The US Food and Drug Administration (FDA) has approved four HDAC inhibitors for clinical use to date. Vorinostat (SAHA) approved in 2006, is the first HDAC inhibitor introduced into clinical practice. It is mainly indicated for the treatment of cutaneous T-cell lymphoma and exerts its pharmacological effects by inhibiting class I, II and IV histone deacetylases, thereby enhancing histone acetylation, modulating gene expression, and ultimately inducing tumor cell differentiation and apoptosis (178). Romidepsin (FK228/depsipeptide), which was approved in 2009, is indicated in patients experiencing recurrence or resistance in cutaneous and peripheral T-cell lymphomas. Upon entering the cell, romidepsin enhances acetylation by inhibiting class I HDACs, primarily through the release of an active moiety (179). Belinostat was approved in 2014 for the treatment of relapsed or refractory peripheral T-cell lymphoma and functions as a broad HDAC inhibitor (180). Panobinostat (LBH589), a pan HDAC inhibitor, was approved in 2015 for use in combination regimens to treat multiple myeloma and mantle cell lymphoma, where it activates apoptosis-related pathways (181).

Additionally, multiple HDAC inhibitors are under clinical investigation. Mocetinostat (MGCD0103) is a benzamide-derived histone deacetylase inhibitor, which specifically targets HDAC1, HDAC2, HDAC3 and HDAC11; it is currently undergoing phase I/II clinical evaluation for the treatment of a range of malignancies, including both Hodgkin's and non-Hodgkin's lymphomas. Clinical data have demonstrated encouraging efficacy for Hodgkin's lymphoma (182,183). Pracinostat (SB939) is a hydroxamate-derived small-molecule inhibitor that acts on class I, II and IV HDACs. In recognition of its therapeutic potential, FDA granted it orphan drug designation in 2014 for the treatment of elderly patients with acute myeloid leukemia and T-cell lymphoma (184). Resminostat (4SC-201), an orally available HDAC inhibitor, was evaluated in phase I/II trials for relapsed or refractory Hodgkin's lymphoma and colorectal cancer (185). Ricolinostat (ACY-1215), a selective HDAC6 inhibitor, is currently undergoing clinical evaluation in combination with bortezomib for myeloma (186).

Although HDAC inhibitors have demonstrated therapeutic benefits in the treatment of various types of cancer, including hematologic malignancies such as T-cell lymphomas and multiple myeloma, only four have been approved by the FDA, with indications largely restricted to a limited spectrum of cancers. Considering the widespread biological functions of acetylation in diverse pathological contexts, the pace of drug development remains relatively slow. Notably, the therapeutic exploration of acetylation-based interventions for non-malignant diseases continues to represent an unmet need.

6. Conclusion and future perspectives

The widespread occurrence of lysine acetylation underscores its critical biological functions. However, current knowledge of the specific processes and regulatory pathways associated with lysine acetylation, particularly different cell types and physiological conditions, remains incomplete. The detection and quantification methods for lysine acetylation currently in use are relatively limited, and the specificity and sensitivity of identifying acetylation sites require further improvement. Additionally, clinical studies exploring lysine acetylation as a tool for early disease diagnosis and targeted therapy are lacking. Future research efforts are warranted to prioritize investigating the underlying molecular mechanisms that govern the activity of lysine acetylation enzymes, such as acetyltransferases and deacetylases, and their regulation in both normal physiological states and disease-related conditions. Particular attention needs to be paid to the role and functional impact of lysine acetylation on specific biological processes, including development, cellular senescence and tumorigenesis. The development of more efficient and sensitive analytical techniques is essential for quantitative and functional studies of lysine acetylation sites. Additionally, the clinical potential of lysine acetylation in diagnostics, disease monitoring and therapeutic applications, particularly in the context of personalized medicine, warrants further exploration. Investigating the crosstalk of lysine acetylation with other PTMs can provide valuable information of the complex regulatory networks controlling cellular signaling. Strengthening the research in these areas will greatly improve the understanding of the biological significance of lysine acetylation and support its application in medical science.

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Availability of data and materials

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Authors' contributions

MZ and YZ conducted the literature review and wrote the manuscript. HY, JY and YD constructed the figures and were also involved in the conception of the study. XZ and TC constructed the tables and were involved in manuscript revision. BL and XG wrote the manuscript and provided supervision. All authors have read and approved the final manuscript. Data authentication is not applicable.

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.

Use of artificial intelligence tools

During the preparation of this manuscript, AI-assisted tools (ChatGPT) was used to enhance the clarity and readability of the text. The authors subsequently reviewed, revised, and edited the AI generated content as necessary and take full responsibility for the final version of the manuscript.

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