HHS Public Access

Author manuscript

Chem Rev. Author manuscript; available in PMC 2019 July 03.

Published in final edited form as:

Chem Rev. 2018 February 14; 118(3): 1216–1252. doi:10.1021/acs.chemrev.7b00181.

Lysine Acetylation Goes Global: From Epigenetics to Metabolism and Therapeutics

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Abstract

Post-translational acetylation of lysine residues has emerged as a key regulatory mechanism in all eukaryotic organisms. Originally discovered in 1963 as a unique modification of histones, acetylation marks are now found on thousands of nonhistone proteins located in virtually every cellular compartment. Here we summarize key findings in the field of protein acetylation over the past 20 years with a focus on recent discoveries in nuclear, cytoplasmic, and mitochondrial compartments. Collectively, these findings have elevated protein acetylation as a major post-translational modification, underscoring its physiological relevance in gene regulation, cell signaling, metabolism, and disease.

Graphical Abstract

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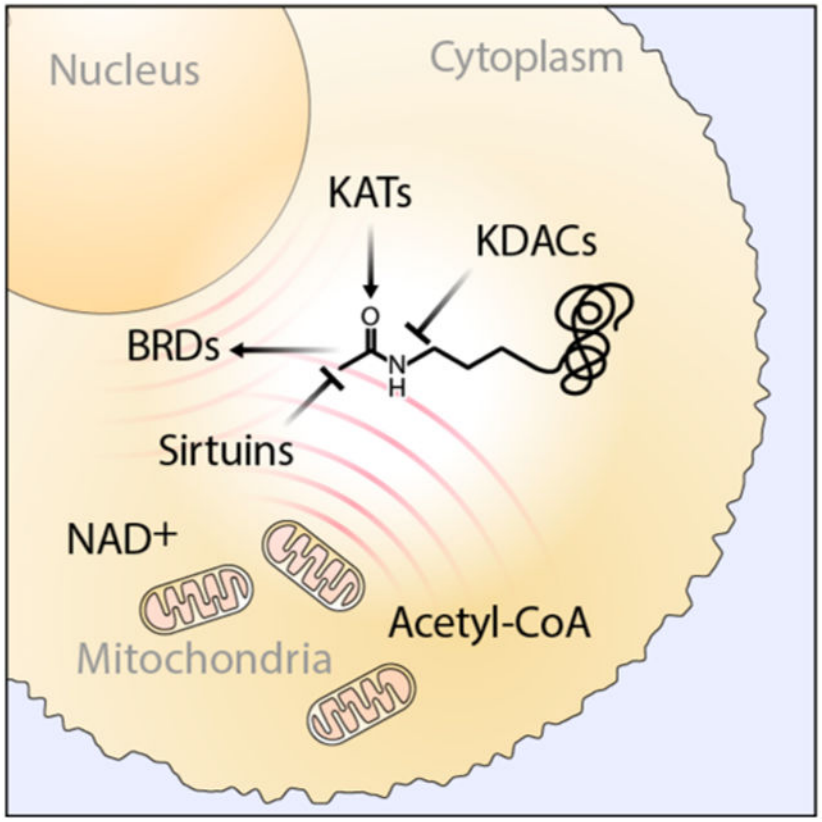
The authors declare no competing financial interest.



1. INTRODUCTION

During the lifetime of a protein there are many points at which an acetyl group may be added to influence function. As early as during its translation, a protein may be N-terminally acetylated to preserve its stability, interactions, or subcellular localization.[1] N-Terminal acetylation is a major covalent modification occurring on eukaryotic proteins, with >80% of human proteins bearing an acetyl group at the α-amino position of the first amino acid. Once a protein is properly localized, acetylation of key lysine residues can occur enzymatically or spontaneously to influence its intermolecular interactions, enzymatic functions, localization, and eventual degradation. Post-translational acetylation of lysine residues will be the primary focus of the current review.

Lysine acetylation describes the transfer of an acetyl group from acetyl-coenzyme A (acetyl-CoA) to the primary amine in the ε-position of the lysine side chain within a protein, a process that leads to neutralization of the position's positive electrostatic charge. Acetylation can occur nonenzymatically; however, in most known cases, the level of acetylation results from the balance of opposing enzymatic activities. Marks are "written" by lysine acetyltransferases (KATs) and "erased" by lysine deacetylases (KDACs). Acetylated lysine residues, amidst their many functions, can be functionally interpreted by a third group of proteins, the so-called "readers", which harbor specific acetyl–lysine binding domains, most prominently bromodomains. The dynamic interplay between the writers, erasers, and readers

of acetylation regulates critical epigenomic and metabolic processes, in addition to other major cellular functions.

Historically, investigators have focused on acetylation in the nucleus, where this mark regulates histone biology and transcription.[2-5] Advances in mass spectrometric technologies have since revealed relevant targets of acetylation in nearly all intracellular compartments.[6,7] Compartmentalization of cellular proteins and nutrients is essential for cell specialization and function. As such, cellular acetylation is driven by the localization of enzymes, metabolites, and cofactors required to balance acetylation and deacetylation levels. Importantly, mitochondria have emerged as organelles in which acetylation is more prominent than phosphorylation[8] and plays a key role in integrating metabolic cues with the bioenergetic equilibrium of the cell.

In this review, we give an overview of the chemistry and biology underlying protein lysine acetylation in mammals, review recent developments in the understanding of lysine acetylation, and provide examples of its function and regulation in distinct cellular compartments.

2. CHEMISTRY OF REVERSIBLE LYSINE ACETYLATION

The transfer of the acetyl group from acetyl-CoA to the ε-primary amine of a lysine residue can occur spontaneously or enzymatically. In mitochondria, acetylation is regulated in part by chemical, nonenzymatic mechanisms due to the high pH and high local acetyl-CoA concentrations within this compartment.[9] The mechanism of nonenzymatic acetylation proceeds first via deprotonation of the lysine primary amine by naturally occurring hydroxide ions, followed by attack of the acetyl-CoA terminal carbonyl by the nucleophilic amine. A putative tetrahedral intermediate is transiently formed and decomposes into the reaction products acetyl-lysine, coenzyme A, and hydroxide (Figure 1).[10]

2.1. Lysine Acetyltransferases

The human proteome contains 21 putative KATs that catalyze lysine acetylation (Table 1). The best characterized have been catalogued into three major families based on homology to yeast proteins but also on structural and biochemical features of catalysis: (1) GCN5-related *N*-acetyltransferases (GNAT), (2) the p300/CREB-binding protein (p300/CBP), (3) and the MOZ, Ybf2, Sas2, and Tip60 (MYST) family. A number of other proteins have acetyltransferase activity, such as TBP-associated factor 250kd (TAFII250 (KAT4)), αTubulin acetyltransferase (αTAT1), circadian locomoter output cycles protein kaput CLOCK (KAT13D), and nuclear receptor coactivator-1 (NCoA-1), but do not belong to any of the major acetyltransferase families.

The first cloned mammalian acetyltransferase was the GCN5 homologue PCAF (KAT2B). In this study, Nakatani and colleagues reported conserved sequence homology between *PCAF* and the *GCN5* genes in yeast and human. The authors performed *in vitro* acetylation assays using recombinant proteins to demonstrate that PCAF (KAT2B) can acetylate whole nucleosomes while the function of human GCN5 (KAT2A) was limited to free histones.[11]

Using similar assays, the enzymatic activity was demonstrated for CBP/p300 (KAT3A/B),[12] TAFII250 (KAT4),[13] TIP60 (KAT5),[14] and NCoA-1 (KAT13A).[15,16]

Despite considerable divergence in primary sequence, KATs from distinct families exhibit structurally homologous acetyl-CoA binding regions, which generally adopt a globular α/β fold (Figure 2). Regions flanking the central acetyl-CoA-binding cleft are not generally conserved, and they may serve to guide substrate specific activities.[84] Among the KAT subfamilies, three prevailing mechanisms have been identified. GNAT family members use an active site glutamate to deprotonate the lysine ε-amine, enabling nucleophilic attack of the acetyl-CoA carbonyl, followed by formation of a transient tetrahedral intermediate and its subsequent collapse into acetyl-lysine and coenzyme A (Figure 3).[85] The same mechanism has been proposed for KATs of the MYST family.[86] A two-step mechanism involving an active site acetyl-cysteine intermediate was originally proposed for MYST enzymes.[87] However, mutagenizing this cysteine residue does not affect enzymatic activity within the context of a preassembled ternary complex.[86] Mutagenesis of an active site glutamate, however, ablates activity without reducing levels of autoacetylation.[62,88] Collectively, these data suggest that the active site glutamate plays a particularly significant role for MYST family catalysis. However, acetyl-cysteine intermediates may still be relevant depending on cellular context for MYST family members with still undefined mechanisms.

The mechanism utilized by p300/CBP family members is categorized as a “hit and run” (Theorell–Chance) mechanism. It is ordered and rapid, and the ternary complex formed is kinetically irrelevant for catalysis.[89] Instead of an active site basic residue, aromatic residues lining a shallow catalytic pocket steer the lysine substrate and allow for nucleophilic attack of acetyl-CoA by lowering its pK_a.[90] A tyrosine residue then acts as an acid to protonate the sulfhydryl of CoA, leaving as reaction products acetyl-lysine and CoA (Figure 4). This may partially explain the relative substrate promiscuity observed for p300.[91] The mechanisms used by several KATs [i.e., KAT13D (CLOCK), KAT13A (SRC1), KAT13B (SRC3), KAT4 (TAF1), KAT9 (ELP3), and KAT12 (GTF3C4), among others] have not been formally investigated.

The enzymatic activity of HAT proteins may vary depending on the cellular microenvironment. For example, the substrate specificity and therefore the catalytic activity of KAT2A/B (GCN5/PCAF) may be influenced by accessory proteins within this complex that help target the acetyltransferase to its substrates, thus enhancing activity. For example, using immunoprecipitation followed by gel filtration chromatography, KAT2A/B (GCN5/PCAF) can be separated from a large macromolecular structure consisting of the TBP-free-TAF complex (TFTC) and the SPT3-TAF9-GCN5-acetyltransferase (STAGA) module.[92-94] These complexes are large, up to 2 megadaltons, and likely vary in composition across the genome to transduce highly specific stimuli.[95]

Recent studies have identified two putative mitochondrial KAT enzymes, suggesting that acetylation in the mitochondria can be enzymatically triggered which raises interesting questions about the catalytic mechanisms of these proteins. GCN5-like protein 1 (GCN5L1) was proposed to act as a mitochondrial KAT and a counter-regulator to SIRT3, a mitochondrial lysine deacetylase. Notably, robust *in vitro* acetylation required the presence

of additional mitochondrial factors, suggesting that GCN5L1 activity may not be direct.[70] In addition, KAT8 (MOF) localizes specifically to mitochondria in HeLa cells and its catalytic activity is required for appropriate mitochondrial gene expression.[65] However, it remains unclear whether KAT8 (MOF) enzymatic activity regulates mitochondrial protein acetylation. It is important to note that environmental conditions in mitochondria are unique. Investigators must consider the especially oxidative conditions when assessing the potential catalytic mechanisms for mitochondrial KATs.

Autoacetylation is an important mechanism of HAT enzymatic regulation. In 2004, Cole and colleagues identified a cluster of key lysine residues within an activation loop motif of KAT3B (p300) that must be acetylated in order for the enzyme to have robust catalytic activity.[96,97] In this model, the activation loop regulates KAT3B (p300) activity by competing with substrates for the active site. Upon hyperacetylation, the activation loop is displaced, allowing for substrates to interact with the active site.[98,99] Active site autoacetylation appears to be a conserved process as RTT109, a yeast acetyltransferase, autoacetylates its active site at K290 to increase its affinity for acetyl-CoA.[100] Similar to KAT3B (p300), KAT8 (MOF) also requires autoacetylation for its activity, shifting the structure of the protein to allow for better substrate binding and catalytic activity *in vitro* and *in vivo*.[62] In contrast, KAT13D (CLOCK) acetylates its dimerization partner BMAL1, a modification that facilitates the assembly of a CRY1-CLOCK-BMAL1 complex and suppresses its activity in a negative feedback loop essential for circadian rhythmicity.[101]

2.2. Lysine Deacetylases and Sirtuins

The reversible nature of lysine acetylation is essential to its function in the regulation of critical cellular processes. The possible existence of enzymatic deacetylation was first suggested in 1978 when it was observed that *n*-butyrate treatment induced the differentiation of Friend erythroleukemic cells into hemoglobin-synthesizing normoblast-like cells, a phenotype that correlated with strong histone hyperacetylation.[102] This early work characterizing *n*-butyrate and Trapoxin[103,104] as KDAC inhibitors paved the way for Schreiber and colleagues to purify the first KDAC from bovine calf thymus lysates using a Trapoxin based affinity matrix.[105] Following this, and in rapid succession, KDACs 2–11 were discovered through sequence homology analyses to yeast deacetylases.[106-112]

At the same time, the silent information regulator (Sir) protein family, known to suppress gene expression at telomeres and rDNA,[113,114] gained attention as potential deacetylase enzymes. Mutation of Sir proteins in yeast induced hyperacetylation of histones.[115] In 1999, Frye and colleagues identified five human cDNAs with sequence homology to the yeast Sir2 gene, and shortly after, Sir2 was identified as an NAD^+ dependent histone deacetylase.[116,117] The family known as Sirtuins was completed using a phylogenetic classification scheme identifying the last two members, SIRT6 and SIRT7.[118]

KDACs and sirtuin proteins are mechanistically and structurally distinct (Figure 5). They are formally categorized into four distinct enzyme classes based on structural homology with yeast transcriptional repressors and unique catalytic mechanisms.[119,120] (Table 2) Class I, II, and IV enzymes are Zn^{2+}-dependent and are comprised by KDACs 1–11. Class I enzymes (KDAC1, 2, 3, 8) localize mainly to the nucleus, while class II (KDAC4–7, 9, 10) and Class

IV (KDAC11) enzymes generally shuttle between the nucleus and cytoplasm. The Sirtuin proteins 1–7 encompass the class III enzymes and are described in the text below (Table 3). Similar to KATs, KDACs are also often found in large, macromolecular complexes that function primarily in gene repression. For example CoREST, NuRD, and Sin3 complexes harbor a catalytic core composed of a KDAC1:KDAC2 dimer, and the NCoR complex contains KDAC3.[121,122]

Mechanistic insight into KDAC catalysis derives from studies of HDLP, a deacetylase homologue from the bacterium *Aquifex aeolicus*.[156] Like HDLP, KDACs utilize an active site histidine to deprotonate a critical water molecule, enabling nucleophilic attack of the acetyl group carbonyl (Figure 6). Decomposition of the oxyanionic tetrahedral intermediate releases acetate and the deacetylated lysine as reaction products. The divalent cation (Zn^{2+}) is important for positioning and polarizing a catalytic water molecule, and it is positioned itself by aspartic acid and histidine residues of a classical catalytic triad (charge-relay network). This Zn^{2+} is a critical target of inhibitors of the class I, II, and IV KDACs, which mainly function via chelation.

Class III KDACs function independently of an active site metal and, instead, rely on nicotinamide adenine dinucleotide (NAD^+) as a cofactor for catalytic activity.[158] Of the seven sirtuins in mammals, only SIRT1, 2, and 3 have robust lysine deacetylase activity. More limited deacetylase activity has been reported for SIRT5, SIRT6, and SIRT7, while SIRT4 has no reported deacetylase activity (Table 3).[159-163] SIRT6 and SIRT7 localize primarily to the nucleus, SIRT1 and SIRT2 shuttle between the nucleus and cytoplasm, and SIRT3 is a bona fide mitochondrial matrix protein.[164] Unlike class I, II, and IV KDACs, sirtuins are not found in large repressive macromolecular complexes. However, certain binding partners regulate their enzymatic activity. For example, the active regulator of sirtuin (AROS) has been shown to stimulate SIRT1-mediated deacetylation of p53,[165] while deleted in breast cancer 1 (DBC1) negatively impacts SIRT1 activity.[166,167]

The sirtuin reaction mechanism proceeds by nucleophilic addition of acetyl oxygen to the anomeric (C1′) carbon of the nicotinamide ribose via S_N1, concerted S_N2, or dissociative S_N2-like mechanisms, resulting in the formation of a C1′-O-alkylamidate intermediate (Figure 7). Next, a histidine residue extracts an electron from the 2′-hydroxyl group of the NAD+ ribose, which then attacks the C1′-O-alkylamidate carbon, generating a bicyclic intermediate. A base deprotonates a water molecule, enabling its attack of the bicyclic intermediate. Collapse of the bicyclic intermediate generates the deacetylated lysine and O-acetyl-ADP-ribose.[198] Sirtuins likely also have weak ADP ribosyltransferase activity via incomplete catalysis through this described mechanism. ADP ribosyltransferase activity has been formally reported for SIRT4 and SIRT6.[199] The mitochondrial SIRT5 enzyme exhibits broad deacylase activity, accepting malonyl- and succinyl-lysine substrates.[188,191,200] The biological function of this distinct activity is not yet clear.

2.3. Acetyl–Lysine Binding Modules

An important function of lysine acetylation is the generation of novel recognition surfaces for the binding of proteins harboring “reader” domains specific for the post-translationally modified residue. The best-characterized reader module of acetyl-lysines is a structurally

conserved protein domain called the bromodomain. The first reference to the bromodomain is traced to the characterization of the *Drosophila* gene brahma (*brm*), a regulator of homeotic genes now known to be a core catalytic component of SWI/SNF chromatin remodelers.[202] The conserved structural motif discovered in the *brm* gene was termed a bromodomain, yet it is etymologically distinct from elemental bromine. Apart from the observation of its frequent occurrence in transcriptional regulators, the bromodomain was relatively uncharacterized from the time of its discovery in 1992 [202] to the determination of its structure by Zhou and colleagues in 1999.[33] NMR studies of the KAT2B (PCAF) bromodomain revealed that this domain binds acetyl-lysine residues on histones and described the structural details of this interaction.

The bromodomain is approximately 110 amino acids in length, and there are 61 distinct bromodomains encoded by 46 proteins (Table 4). The bromodomain is conserved from yeast to humans and are encoded in an increasing number of factors during eukaryotic evolution. [203] In mammals, bromodomains can be divided into several distinct subfamilies based mostly on structural homology.[204,205] While most bromodomain-containing proteins encode one bromodomain, up to six bromodomains have been documented in a single protein (Polybromo-1). The so-called bromo- and extraterminal (ET) domain-containing (BET) proteins encode a characteristic double bromodomain motif and are implicated in recruiting the positive transcription elongation factor b (P-TEFb) and other factors to signal inducible genes, including those regulated by the transcription factor *c-myc* in several cancers.[206-208] Nearly all bromodomain-containing proteins are nuclear factors that bind chromatin to regulate its structure and function. They function mostly as transcriptional coactivators (i.e., KAT3B (p300), BRD4), but repressive functions of certain bromodomain-containing proteins are also known (i.e., BAZ2A, ZYMND11). Remarkably, many nuclear KATs harbor bromodomains. The KAT2A (GCN5) bromodomain is important for chromatin remodeling[209] and regulation of sequential histone acetylation events.[210] A recent structural analysis of the core catalytic domain of KAT3B (p300) showed an assembled configuration of the bromodomain and of PHD, RING, and KAT domains with the RING domain positioned over the KAT domain substrate-binding pocket, providing insight into how chromatin–substrate targeting and KAT regulation might be linked.[42]

The bromodomain structure is well characterized, with >400 high-resolution X-ray crystal structures available and near complete structural coverage across the protein family. The domain is composed of four left-handed α-helices (αZ, αA, αB, and αC) connected by two loops (ZA and BC loops, Figure 8).[33] This structure forms a hydrophobic cavity that serves as the acetyl-lysine recognition site. A hydrogen bond mediated by a conserved bromodomain asparagine residue and the acetyl-lysine carbonyl serves as the ligand recognition mechanism. Tyrosine residues lining the bromodomain cleft also play a significant role in ligand positioning via π–π stacking and hydrogen bond formation with critical water molecules. Helical regions of bromodomains are moderately conserved, but the length and sequence of the loop regions vary considerably. Some bromodomains cooperatively bind multiply acetylated peptides, such as the testis-specific BET protein BRDT.[235] Others are controlled by post-translational modifications on nearby proteins. *In vitro*, the bromodomain:acetyl-lysine interaction is relatively weak (K_d = low micromolar).

In vivo, the combined affinities of adjacent or proximal protein domains (i.e., helicase, SAND, distinct bromodomain) may modulate specificities and/or strength of binding.

Several other protein domains have been reported to accept acetyl-lysine residues as ligands. The plant homeodomain (PHD) finger domain is generally recognized as a methyl-lysine reader domain, but when present in tandem in the protein DPF3b, it binds acetylated lysine residues on histone H3 and H4 molecules (Figure 8).[294] The tandem PHD:acetyl-lysine binding mode is mechanistically distinct from that of the bromodomain, utilizing aspartic acid within the first PHD domain to form a hydrogen bond with the acetyl amide of the ligand. Interestingly, this aspartic acid also serves to recognize N-terminally acetylated peptides in addition to acetyl-lysine residues. Notably, proteins other than DPF3b encode tandem PHD domains, such as the CHD4 chromatin remodeler and KAT6A (MOZ), both of which have been shown to bind acetylated histones.[295,296]

The YEATS domain also recognizes acetyl-lysine residues.[297] YEATS domains are present in five human proteins (YEATS2, ENL, AF9, TFIIF, and GAS41). AF9 and ENL are both components of the so-called superelongation complex (SEC), a multimeric complex containing P-TEFb, AFF1/AFF4 scaffolds, and the ELL1/ELL4 elongation factors.[298] Structurally, the YEATS domain adopts an Immunoglobulin fold (Figure 8), and its interaction with acetyl-lysine is mediated by several hydrogen bonds in addition to aromatic residues important for ligand positioning.[298] Acetylated H3K9 is a ligand for the AF9 YEATS domain, and the ENL YEATS domain exhibits a preference for acetylated H3K27, although ENL correlates genome-wide with both acetylated H3K9 and H3K27 in acute myeloid leukemia (AML) cells.[299] The two other YEATS domain-containing proteins, GAS41 and YEATS2, belong to chromatin-remodeling complexes. The AF9 YEATS domain has an expanded binding repertoire of acyl-lysine marks, and it can also accommodate modifications, such as crotonylation.[300] Importantly, translocations between genes encoding ENL/AF9 and MLL methyltransferase occur frequently, and the resultant fusion proteins are oncogenic drivers.[301] Specifically, the ENL YEATS domain is required for tethering the SEC to enforce oncogenic gene expression programs in AML.[299]

While the bromodomain and YEATS and tandem PHD domains specifically recognize acetyl-lysine residues, readers have recently been found that specifically bind unmodified lysine residues. The SET protein functions through its acidic-domain to bind the C-terminus of the transcription factor p53 only when p53 is not acetylated. The function appears to be conserved, as proteins with similar domains, such as VPRBP, DAXX, and PELP1, also bound preferentially to nonacetylated p53. In addition, the SET acidic-domain recognizes non-acetylated lysine-rich domains of histone H3, KU70, and FOXO1, suggesting broad implications for this mechanism of recognition.[302]

3. WIDENING SCOPE OF PROTEIN ACETYLATION

In 1997, over three decades after the discovery of acetylation on histones and tubulin, the transcription factor p53 was identified as a nonhistone KAT substrate.[303] By 2000, 10 more nuclear proteins and transcription factors were found to be substrates of acetylation, leading to speculation that acetylation may rival phosphorylation as a post-translational

modification.[304] Six years later, the first acetylome screen identified 388 acetylation sites in 195 proteins, more acetylation sites than were identified in the previous 40 years.[305] Since then, more than 155 systems-wide acetylome studies have revealed the existence of thousands of acetylation sites on many cellular proteins, connecting lysine acetylation to virtually every cellular function and most biological outcomes (Figure 9). Mass spectrometry analyses of acetylation have been conducted in a wide variety of species ranging from Gram-positive[306,307] and -negative bacteria,[308] to budding yeast,[309] to plants, [310-312] to eukaryotic human pathogens,[313,314] rodents, and humans. These have provided valuable insight into the stoichiometry and dynamics of lysine acetylation, as well as interactions with other PTMs.

Proteomic-based studies generally rely on an enrichment step in which pan-acetyl lysine antibodies are used to purify acetylated proteins from trypsin-digested lysates.[305,315] Notably, the use of an antibody raised against a single antigen can conceivably bias which proteins are purified from lysates, suggesting that most current studies only capture a subset of cellular acetylation sites.[316,317] Stable isotope labeling of amino acids in culture (SILAC)[318] and a label-free approach[319] have been used to assess the dynamics of acetylated protein stoichiometry. These studies have revealed that in mammalian cells individual acetylation sites appear conserved across species but not across tissue types.[4,5] A high degree of overlap is observed in human, rat, and mouse liver tissues, yet little overlap exists between rat liver and rat heart.[320,321] Acetylation occurs in regions with defined secondary structure, such as α-helices and β-sheets, unlike phosphorylation.[305,315]

Nuclear protein acetylation levels are high in tissues with actively dividing cells and in tumors. Many acetylation sites are found on proteins related to DNA damage, cell-cycle control, and transcription (Box 1).[305,322,315] Mitochondrial acetylation is primarily found on proteins related to cellular metabolic processes and is enriched in highly metabolically active tissues such as brown fat, heart, and liver, and it likely plays a role in other tissue types depending on their metabolic activity and capacity to respond to insulin.[319-321] Cytoplasmic acetylation has been relatively understudied despite the fact that tubulin was the second protein discovered to be acetylated.[323-325] Notably, it is difficult to exclusively study cytoplasmic acetylation because cellular fractionation methods are imperfect, and many proteins tend to shuttle between the cytoplasm and other subcellular compartments. With these caveats in mind, cytoplasmic acetylation is observed predominantly in liver, peri-renal, and testis fat, tissues with high cellular concentrations of acetyl-CoA.[73]

Several groups have taken genetic approaches to probe KAT-or sirtuin-specific acetylation sites. Examples include KAT2A/KAT2B knockdown studied in HeLa cells,[326] KAT13D-(CLOCK) knockout studied in mouse liver tissues,[327] SIRT1 knockout studied in mouse embryonic fibroblasts[328] or liver tissues,[329] and SIRT3 knockout studies in mouse liver tissues[319,330] (Box 2).

The first integrative studies provided evidence for coordinated regulation of PTMs.[7] For example, one study noted coordination between acetylation and phosphorylation in the nucleus upon DNA damage, but most changes in phosphorylation occurred in the cytoplasm. [322] Surveys of acetylation and succinylation sites found substantial overlap between both

acylation sites in mitochondria, suggesting potential competition between these modifications.[331,332] Environmental cues, such as caloric restriction, microbiome components, and viral infection, and drugs, such as KDAC inhibitors and aspirin, also affect global acetylation levels [318,333-336]

4. NUCLEAR ACETYLATION REGULATES GENE EXPRESSION

4.1. Histone Acetylation

When nucleosomal histones are assembled with DNA, each subunit displays an N-terminal tail that can be post-translationally modified. Core nucleosomes are composed of pairs of histones H2A, H2B, H3, and H4; variants of these histones are important in chromatin regulation and gene expression. Histone H1 and its accompanying variants are regarded as “linker” histones as they connect core nucleosomes into denser 30 nm fibers.[337] Acetylation sites have been observed on all histone subunits, including linker histones, and the occur in both the tail and globular domains (Summarized in Box 3). Acetylation occurs abundantly in the tail domains while acetylation in the globular domain appears less abundant.[338] Tail acetylation sites are evenly spaced among the nucleosomal histone subunits and possess some functional redundancy.[339] Acetylation sites are well conserved, in contrast to methylation, where species-specific differences exist.[340] Together, the specific array of histone modifications, known as the “histone code”, may serve as a highly dynamic regulatory system for gene expression control in mammalian cells.

Acetylation of key lysine residues is generally thought to disrupt the electrostatic interactions between the phospho-diester backbones of DNA and lysine-rich nucleosomes to expose DNA to transcription machinery.[342] Key advances in the analysis of histone acetylation come from the use of electron transfer dissociation and electron capture dissociation mass spectrometry.[343,344] These methods allow for the analysis of long histone peptides (>20 a.a.) and therefore the identification of multiple modifications on individual histone proteins. Using this and other methodologies, several comprehensive studies have observed the combinatorial patterns of histone modifications on each subunit.[338,345-348] These analyses are essential to determine whether specific modifications are compatible on the same histone at the same time, potentially identifying important rules by the histone code.

The best-studied acetylation sites are found on histone H3 and H4, but acetylation of H2A and H2B tails has also been correlated with increased transcriptional activity.[349,350] Histone 3 lysine acetylation has been observed on 14 residues, six of which are located on the tail region and eight in the globular domain.[341] H4 is acetylated at nine lysines, six in the tail region and three in the globular domain.[341] In addition, lysine acetylation has been observed on H2A tails at four sites,[338,351,352] and the globular domain at two sites Box 3.[353] Turnover of histone acetylation is unequal at different sites.[351] While acetylation of histone tails generally has a fast turnover (<30 min), with the exception of H3K4, H2AK13, and H2AK15, nearly all globular domain modifications were more stable with a half-life greater than 2 h.[351]

Histone H1 is highly modified and was first identified to be acetylated *in vivo* in 2004.[354,355] Multiple proteomic approaches have identified H1 acetylation sites at 11 lysine residues (K16, K33, K45, K63, K74, K89, K96, K105, K167, K168, K190), albeit at low frequency.[191,338,348,356-358] Given its role in DNA condensation, histone H1 was originally thought to act primarily as a suppressor of gene expression, but its function is now understood to be more nuanced.[359] For example, H1.4K34ac is detected in distal and proximal promoter regions of highly transcribed genes in induced pluripotent stem cells and cancer cancer cell lines, induced pluripotent stem cells (iPSCs), and testicular germ cell tumors.[358] In addition, an inverse relationship between the presence of H1 on chromatin and acetylation marks on H3 and H4 has been described.[360,361]

4.2. Transcription Factor Acetylation

Notably, nuclear lysine acetylation is not restricted to histones but is also found on numerous transcription factors including p53, NF-κB, and STAT3. Mechanistically, acetylation modulates transcription factor activity at multiple steps. These include inducing nuclear translocation or protein stabilization, sterically preventing ubiquitination, modifying molecular complex composition, and facilitating chromatin binding specificities. Proteomics studies have identified many known acetylation sites on transcription factors, of which we only list those with additional functional studies (Table 5). We illustrate these phenomena using well-characterized case studies below (Figure 10).

Several excellent reviews have documented the functions of transcription factor acetylation.[6,454-456] Here we exemplify a few key principles (Figure 10). In the case of transcription factors such as NF-κB and STAT3 that are cytoplasmic when inactive, signaling begins with an extracellular stimulus that leads to a cascade of PTMs resulting in changes in dimer structures and translocation from the cytoplasm to the nucleus.[457,458] STAT3 activation is marked by specific phosphorylation and acetylation events that allow for dimerization and subsequent nuclear localization.[459] While phosphorylation is thought to be dominant for dimerization and DNA binding, several studies suggest a phosphorylation-independent mechanism of dimerization.[460,461] Chin and colleagues demonstrate that acetylation at K685 by KAT3A/B (CBP/p300) induces homodimerization and nuclear translocation of STAT proteins.[462] RelA is a subunit of NF-κB generally sequestered in the cytoplasm through its interaction with its negative regulator IκBα. Upon cell stimulation, RelA is acetylated by KAT3A/B (CBP/p300) at several residues. Acetylation at K221 disrupts the RelA-IκBα interaction, allowing for nuclear translocation and increased DNA binding (Figure 10(A).[427,463]

Changes in acetylation can also induce changes in protein stability, as is the case for the p53 transcription factor. Acetylation can directly compete with ubiquitination at distinct lysine residues.[464] It can also mediate structural changes to prevent ubiquitination by sterically hindering interaction with ubiquitin ligases.[464,465] At homeostasis, p53 is maintained at low levels in the nucleus primarily through ubiquitin-mediated proteolysis.[466] Upon DNA damage, p53 becomes highly acetylated at its carboxy-terminal domain (CTD), preventing MDM2-mediated ubiquitination and degradation.[467,468] Acetylation of the p53 CTD is catalyzed primarily by KAT3B (p300), but KAT6A (MOZ) also acetylates p53 at K120 and

K382.[418,467] Crosstalk exists between factor acetylation and other PTMs, notably lysine methylation. For example, lysine methyltransferase 7 (KMT7, SET7/9)-mediated monomethylation at K372 promotes acetylation and stabilization of p53 by disrupting its interaction with the deacetylase SIRT1 (Figure 10B).[469-472] A similar phenomenon has been reported for RelA acetylation at K310 which prevents KMT7-mediated monomethylation at K314 and K315, thus stabilizing the protein.[473] Furthermore, acetylation of p53 is recognized by KAT3A/B (CPB/p300) and KAT4 bromodomains to facilitate acetylation of histone H3 and histone H4 at p53 response genes, which induces cell-cycle arrest or apoptosis.[474-476]

Acetylation can further influence the DNA binding affinity and promoter specificity of transcription factors such as the T cell lineage master regulators RAR-related orphan receptor gamma (RORγ) and Forkhead box O proteins (FoxO). RORγ is acetylated by KAT3B(p300) and deacetylated by KDAC1 and SIRT1 at K69, K81, K99, and K112, with the latter activating DNA binding of this lineage-determining transcription factor.[432,433] Deacetylation of RORγ increases transcription of the interleukin-17 (IL-17) gene but decreases activation of IL-2 (Figure 10C).[433] Similarly, acetylation of FoxO proteins by KAT3B (p300) facilitates dissociation from promoters of genes such as *p27* and *MnSOD*, a process that is reversible upon SIRT1, SIRT2, or SIRT3 overexpression.[477] Interestingly, acetylation of the Forkhead box P3 protein (FOXP3) enhances the stability and function of the transcription factor, a master regulator of regulatory T cell identity.[478] FOXP3 acetylation is regulated by a balance between KAT3B (p300) and KAT5 (TIP60) acetylation and KDAC7, KDAC9, and SIRT1 deacetylation at K31, K263, and K274.[50,394,395,479] Of note, acetylation of KAT5 (TIP60) by KAT3B (p300) increases its ability to acetylate FOXP3, highlighting the multiple layers of KAT cooperation required for appropriate signaling and regulatory T cell function. [395,396,480]

4.3. Acetylation of the Basal Transcription Machinery

In addition to transcription factors, a growing number of factors associated with the RNA polymerase II complex are acetylated. Basal transcription factor acetylation has been studied in less detail, and these data are summarized here. Choudhary et al. list eight TBP-associated proteins (TAFs) that are acetylated in the nucleus.[315] These proteins compose the basal transcription factor TFIID and contribute to transcription initiation of the RNA polymerase II complex.[481] The function of TAF acetylation in the TFIID complex remains largely unknown, but acetylation of TAF(I)68, the second largest subunit of the TATA box-binding protein-containing factor TIF-IB/SL1, enhances binding to rDNA and was linked to enhanced RNA polymerase I transcription.[482] A more recent study highlighted the importance of CBP in RNA Pol II regulation at promoters in Drosophila. In this system, CBP was present at the promoters of nearly all expressed genes and was found to play a role in promoter-proximal pausing, especially at genes with CBP and GAF co-occupancy.[483]

Acetylation of the positive transcription factor b (P-TEFb) is studied in detail.[369,371,378] P-TEFb is composed of a cyclin T subunit, and the cyclin-dependent kinase CDK9. When assembled in an active elongation complex, is critical to phosphorylate negative elongation factors and the C-terminal domain (CTD) of the largest RNA polymerase II subunit at serine

2, activating transcription elongation by the polymerase complex.[484,485] P-TEFb is stored predominantly in the nucleoplasm in a ribonucleoprotein complex (7SK RNP) but is released and activated upon increased transcriptional demand.[486,487] This release is caused in part by acetylation of four sites in cyclin T1 (K380, K386, K390, K404), which dissociates acetylated cyclin T1/CDK9 from the 7SK RNP and activates CDK9 activity on negative elongation factors and the polymerase CTD.[378] CDK9 also is subject to acetylation at two lysine residues (K44, K48).[369,371] K48 acetylation disrupts ATP binding and inhibits CDK9 kinase activity directly,[371,488] while K44 acetylation activates P-TEFb activity. Additional cellular elongation factors found to be acetylated by mass spectrometry include FACT members SUP16H and SSRP1, but also the RTF1 subunit of the PAF1 complex as well as SUB1 and the CTD phosphatase FCP1,[315] but these marks have not yet been studied functionally.

The CTD of RNA polymerase II is acetylated. The CTD is a long and flexible domain structure composed of heptapeptide repeats with the consensus sequence YSPTSPS, which is conserved across eukaryotes. Interestingly, the CTD has expanded in metazoans to include a C-terminal region of heptad repeats that are less strictly aligned with the consensus sequence. In mammals, this region contains eight heptad repeats where the serine in position 7 is replaced with a lysine.[435] Acetylation of these lysine residues is mediated by KAT3B(p300) and is enriched downstream of transcription start sites in actively transcribed genes, linking this modification to polymerase pausing.[434] Accordingly, activation of signal-induced genes is inhibited when lysines are mutated to arginines in the CTD. However, the acetylated RNA polymerase II is not only found on signal-induced genes but also on many actively transcribed genes, implicating additional functions for CTD acetylation in transcription.[434] Notably, both RNA polymerase I and III subunits are also acetylated.[315] PAF53, a regulatory subunit of RNA polymerase I, is acetylated by KAT3A(CBP) at K373.[423] PAF53 acetylation is maintained at low levels by SIRT7, which facilitates robust rRNA transcription. Induction of stress by glucose deprivation suppresses SIRT7 activity, leading to hyperacetylation of PAF53 and repression of rRNA transcription.[423]

5. PROTEIN STABILITY AND AGGREGATION IN THE CYTOPLASM

5.1. Tubulin and HSP90 Are Regulated by KDAC6

Lysine acetylation in the cytoplasm is historically a very “old” concept, as tubulin was the first nonhistone acetylation substrate identified.[323-325,489] Tubulin forms microtubules, a major structural element in the cytoplasm, composed of α/β tubulin dimers.[490-492] Acetylation of α-tubulin occurs on the luminal side of microtubules at K40 and is catalyzed predominantly by α-tubulin acetyltransferase αTAT1, a non-canonical KAT homologous to zebrafish or *C. elegans* MEC17.[493-495] It is unclear whether acetylation is a cause or a consequence of tubulin stability, although this modification is generally considered a marker of protein stability. αTAT1 overexpression destabilizes microtubules; however, this is mainly attributed to enhanced αTAT1-tubulin interactions and not considered a consequence of increased acetyltransferase activity.[495] Tubulin is deacetylated by KDAC6 [112] and SIRT2.[161] KDAC6 is the major tubulin deacetylase, and KDAC6 overexpression increases the chemotactic motility of murine fibroblasts, possibly due to tubulin destabilization.[112] SIRT2

plays an important role in tubulin deacetylation in response to macrophage and NLRP3 inflammasome activation[161,496] and also regulates tubulin acetylation on mitotic spindles.[497]

HSP90 gained considerable attention due to its potential as a therapeutic target in hematologic malignancies.[498] HSP90 exists in two major isoforms: HSP90α, which is stress-inducible and tightly regulated, and HSP90β, which is constitutively expressed.[498] HSP90 acetylation is detected on up to 22 distinct residues on HSP90α, and 5 distinct residues HSP90β.[315,498,499] KDAC6 deacetylates HSP90, influencing glucocorticoid receptor (GR) or mineralocorticoid receptor (MR) signaling.[500,501] KDAC1 may also influence HSP90 acetylation,[502] though the KATs responsible remain elusive. Acetylation predominantly occurs on the middle domain of HSP90, where it regulates intermolecular interactions and chaperone activity.[501]

5.2. Tau and Alzheimer's Disease

Acetylation also regulates microtubule-associated proteins (MAPs) with Tau as a prominent example.[503,504] Tau is highly expressed in neurons, and mutations in Tau serve as important markers for dementia and Alzheimer's disease.[505] These mutations are linked to microtubule-binding repeats causing neurological defects associated with the disruption of Tau–microtubule interactions. Tau aggregation produces paired helical filaments seen in neurofibrillary tangles present in the brains of individuals afflicted with neurodegeneration.[506]

Acetylation was identified on more than a dozen lysine residues in Tau using *in vitro*, cell-based, and mass spectrometric assays.[507-509] Acetylation is a common feature across MAP family members as the microtubule-binding domains of MAP2 and MAP4 are also acetylated.[510] Tau, like MAP2 and 4 proteins, possesses intrinsic acetyltransferase activity.[510-512] In addition, several KATs have been identified to modify Tau, including KAT3A/B(CBP/p300) and KAT2B-(PCAF).[507,508] Deacetylases that target Tau include SIRT1, SIRT2, and KDAC6 with robust activities by SIRT1 and KDAC6.[508,513,514]

Several acetylation sites on Tau are well characterized.[515] These include K274, K280, and K281. Acetylation of these sites reduces Tau interaction with microtubules by interfering with functions of the microtubule-interacting domain.[507,516] Acetylation of K274 and K281 leads to mislocalization of Tau, while K280 acetylation promotes Tau aggregation.[507,517] Acetylation of a distinct site, K174, slows cellular turnover of Tau and contributes to cognitive defects in mouse models of Alzheimer's disease. Notably, acetylation of specific RXGS motifs in Tau inhibit phosphorylation and aggregation of the protein, indicating opposing effects of different acetylation sites in Tau on neurogenerative pathogenesis.[518] These sites are also targeted by distinct KDACs: RXGS motifs are preferentially deacetylated by KDAC6, while SIRT1 targets K174, K274, K280, and K281.[508,518] As Tau is decorated with many post-translational modifications, including lysine methylation and ubiquitination, these modifications can competitively inhibit Tau acetylation *in vitro* and *in vivo*.[509,519,520]

6. MITOCHONDRIA

6.1. Mitochondrial Acetylation Regulates Cell Metabolism

Acetylation is widespread in mitochondrial proteins: 1/3 of mitochondrial proteins are acetylated,[521] and many proteins carry multiple acetylated lysines.[305,315] Mitochondrial acetylation is strongly conserved from *Drosophila* to humans.[522] Not surprisingly, acetylated proteins are involved in major functions of mitochondria (e.g., TCA cycle, oxidative phosphorylation, β-oxidation of lipids, amino acid metabolism, carbohydrate metabolism, nucleotide metabolism, and the urea cycle).[523,524] Mitochondrial metabolism results from high concentrations of acetyl-CoA from aerobic catabolism of pyruvate, β-oxidation of long-chain fatty acids, and decarboxylation of malonyl-CoA.[525]

Three of the seven class III deacetylases (SIRT3, 4, and 5) are mitochondrial.[526] SIRT3 has robust NAD^+-dependent protein deacetylase activity, and mice lacking SIRT3 show significant hyperacetylation of mitochondrial proteins,[527] while mice lacking SIRT4 or SIRT5 do not. Proteins that become hyperacetylated in the absence of SIRT3 control the shift to a fasting metabolism when the source of energy switches from glucose to lipids and amino acids. Thus, SIRT3 is linked to the energy status of the cell,[528-532] and it is expressed at the highest levels in metabolically active tissues (e.g., liver, kidney, and heart).[533,534] SIRT3 expression is also increased in glucose-poor, fasting states, including calorie restriction in liver and kidney.[535-539]

An important unresolved question regarding mitochondrial protein acetylation is the mechanism of acetylation itself. Is a mitochondrial KAT required? Mitochondria contain high concentrations of acetyl-CoA in millimolar amounts,[540] and therefore, a nonenzymatic mechanism could account for the high level of mitochondrial protein acetylation.[541] Indeed, increased mitochondrial protein acetylation is associated with physiological conditions that result in higher levels of acetyl-CoA (e.g., fasting, calorie restriction, high-fat diet, and ethanol $_{\text{intoxication}}$).[535,542-545]

Three mitochondrial KATs have been reported. One is GCN5L1, which is homologous to a prokaryotic acetyltransferase.[70] Mitochondrial protein acetylation is lower when the enzyme is lacking and increased when it is overexpressed.[546] The second is the nuclear MYST family acetyltransferase KAT8 (MOF). It controls nuclear and mitochondrial respiratory genes by regulating oxidative phosphorylation.[65] KAT8 (MOF) is important in tissues that are energetically demanding. For example, conditional knockouts of this gene result in hypertrophic cardiomyopathy and cardiac failure in mouse. However, the function of KAT8 (MOF) mediated mitochondrial acetylation in these cell types is not yet clear. Third, is acetyl-CoA acetyltransferase 1 (ACAT1), a regulator of the pyruvate dehydrogenase complex in mitochondria. ACAT1 was reported to influence acetylation of two mitochondrial proteins: PDHA1 and PDP1.[547] ACAT1 knockdown led to a decrease in acetylation of PDHA1 and PDP1, inhibiting their function and leading to changes in glucose homeostasis that could contribute to the Warburg effect. It is critical to note that none of the studies of mitochondrial KATs use *in vitro* methodologies to show that acetylation of mitochondrial substrates is direct. This leaves a possibility that GCN5L1, KAT8 (MOF), or

ACAT1 may modulate mitochondrial Acetyl-CoA levels or pH, influencing the efficiency of spontaneous acetylation in this cellular compartment.

SIRT3 is also important to the respiratory chain. Mice without SIRT3 use 10% less O_2 and make 50% less ATP than wild-type mice.[534,548] SIRT3 deacetylates and activates mitochondrial respiratory chain complexes (e.g., NDUFA9 (complex I)[534] and SDHA (complex II))[549,550] and regulates ATP synthase.[551]

6.2. Metabolic Targets of SIRT3

SIRT3 is a key enzyme in metabolism, necessary for efficient fatty acids utilization in the liver and for utilization of lipid-derived acetate and ketone bodies in peripheral tissues during fasting. The first identified target of SIRT3 is acetyl-CoA synthetase 2, which generates acetyl-CoA from acetate in extrahepatic tissues during fasting.[552,553] During fasting, acetate is made by the liver from acetyl-CoA and can be used as energy by other tissues.[554] SIRT3 regulates fatty acid oxidation by deacetylation and activation of long chain acyl-CoA dehydrogenase during fasting.[535] β-Oxidation intermediates (e.g., long chain fatty acids) accumulate in mice that lack SIRT3.[535] SIRT3 also regulates ketone body production by deacetylating and activation of 3-hydroxy-3-methylglutaryl-CoA synthase 2, a key step in the synthesis of ketone bodies.

In amino acid metabolism, SIRT3 regulates the aminotransferase that forms glutamine by transferring an α-amino to α-ketoglutarate. Another enzyme, glutamate dehydrogenase (GLUD1), regenerates α-ketoglutarate from glutamate and releases nitrogen as ammonia in the urea cycle.[525] SIRT3 accelerates the urea cycle by activating ornithine trans-carbamoylase (OTC). Humans with urea cycle disorders and mice without SIRT3 have similar metabolic profiles, including increased levels of serum ornithine and reduced levels of citrulline.[537]

Other pathological conditions exhibit lower levels of SIRT3. Tumors often have reduced levels of SIRT3. As a result, glucose use is enhanced because of increased levels of reactive oxygen species (ROS) that activate hypoxia-inducible factor 1 alpha (HIF1α), which, in turn, activates glycolytic genes.[549,555,556] SIRT3 also deacetylates and activates isocitrate dehydrogenase 2 and increases ROS levels as a byproduct of oxidative phosphorylation.[557] SIRT3 deacetylates and activates the ROS-scavenging enzyme manganese superoxide dismutase to reduce oxidative damage in the liver.[558-560] Mice without SIRT3 show greater oxidative stress,[558] particularly on a high-fat diet,[543] and have higher ROS levels than normal under calorie restriction.[557]

7. THERAPEUTIC TARGETING OF LYSINE ACETYLATION

7.1. KDAC Inhibitors

The manipulation of lysine acetylation using small molecules now known to be KDAC inhibitors was instrumental in the discovery of this modification. *N*-Butyrate was known to control gene expression and to induce differentiation of acute erythroid leukemia cells.[102,561,562] Trichostatin A and tetrapeptide trapoxin are potent KDAC inhibitors.[103,563,564] Suberoylanilide hydroxamic acid (SAHA) induces terminal differentiation and apoptosis in

transformed cells and inhibits KDAC1 and KDAC3.[565] SAHA (also known as Vorinostat) was approved by the Food and Drug Administration (FDA) to treat cutaneous T cell lymphoma. The antiepileptic drug valproic acid also inhibits KDACs[566] and is in clinical trials for various indications. Other KDAC inhibitors are approved by the FDA (some of which are displayed in Figure 11), while others remain in clinical development.[567,568]

Several hypotheses may explain the mechanisms of action of KDAC inhibitors. These small molecules might induce DNA damage and cell cycle interruption, cause ROS to accumulate, or activate apoptotic pathways.[569] Most likely, in some way, these small molecules encourage apoptosis or hinder proliferation.[570] Hyper-acetylation from small-molecule KDAC inhibitors has been observed at the tumor suppressor gene *CDKN1A*[571] and in reactivation of latent HIV.[572] Thus, acetylation-mediated transcriptional disruptions might explain the effects of KDAC inhibition on cellular proliferation and other phenotypes.

KDAC inhibitors targeting class I/II/IV enzymes generally chelate the divalent metal ion required for catalysis, although not all inhibitors exploit this mechanism.[149] Available small molecules mostly target class I and II KDACs with limited selectivity for individual KDACs.[573] However, emergent small molecules are active against a more restricted range of KDACs. Preclinical examples include specific inhibition of the cytoplasmic KDAC6 by Tubastatin A and of KDAC8 by PCI-34051.[574,575] Importantly, the subset of differentially acetylated proteins differs depending on the KDAC inhibitor used.[335]

7.2. Sirtuin Modulators

SIRT1 is an attractive target for modulation given early connections between Sir2 and replicative lifespan in yeast.[528,576] Indeed, as discussed, sirtuin activity closely ties key metabolic and epigenomic processes. However, specific targeting of sirtuins, while exciting, has proven difficult. Adding to this challenge, initial clinical studies with sirtuin activators have been inconsistent. While it is clear that sirtuin genetic deletion results in large changes in acetylation substrates and gross chromosomal abnormalities that lead to DNA damage,[351,569] more extensive work is required to understand this family of genes and their therapeutic potential.

Polyphenolic compounds, namely the phytochemical resveratrol, were originally shown to activate sirtuin activity by enhancing cofactor and substrate binding via engagement of the SIRT1 N-terminus.[577,578] These polyphenols lack potency in sirtuin binding, have low retention times in humans, and likely have considerable off-target effects.[579,580] More recent high-throughput screening methodologies uncovered other SIRT1 activators, such as SRT1720, with interesting biological effects that lead to extended lifespan and improved health in mice and some efficacy against xenografted tumor growth models.[581-583]

Controversy has erupted about the action of resveratrol and SRT1720 (Figure 12). Two studies demonstrated *in vitro* that resveratrol-mediated SIRT1 activation required the presence of a fluorophore conjugated to substrate peptides,[584,585] an observation that was supported by structural data.[174] *In vivo*, resveratrol induces hypoacetylation for a subset of non-fluorophore labeled peptides, but also induces hypteracetylation of other substrates while leaving a large proportion of genes unchanged.[586,587] These contradictory effects in

global protein acetylation could be due to off target effects, such as inhibition of SIRT3 or activation of SIRT5.[187] Importantly, they also may be explained by significant sequence specificities of resveratrol-mediated SIRT1 activation due to allosteric mechanisms.

A number of specific inhibitors of sirtuin activity have been identified (Figure 13). Examples include indols, such as EX-527 targeting SIRT1, along with compounds such as sirtinol and tenovin derivatives.[175,588-590] A growing number of SIRT2-specific inhibitors have been tested, including AGK2,[591-593] SirReal inhibitors,[594] and most recently 33i.[595] Due to the high degree of conservation among sirtuin active sites, not surprisingly, several inhibitors bind to two or more sirtuins: cambinol with an IC_{50} ~ 60 μM for SIRT1 and SIRT2,[596] salermide targeting SIRT1 and SIRT2,[597,598] and suramin that inhibits SIRT5 but also strongly inhibits SIRT2 and SIRT1.[190,599] Inhibitors that target SIRT3 are also being tested.[600,601] Not much is known about the mechanism behind sirtuin inhibitors; however, in some cases, they likely function by interfering with NAD^+ engagement.[175]

7.3. KAT Inhibitors

KAT3A/B(CBP/p300) has emerged as a potential therapeutic target for respiratory diseases, HIV infection, metabolic diseases, and cancer.[602] However, the relatively shallow substrate-binding site in p300 is a challenging drug target, and most compounds to date target the acetyl-CoA binding site in the enzyme.[603] Early KAT inhibitors include several phytochemicals, such as curcumin,[604] garcinol,[605] and anacardic acid.[606] Chemical inhibitors were originally developed as bisubstrate acetyl-CoA mimics,[607] pioneered by the Cole laboratory, and later replaced by smaller, more selective synthetic compounds, such as C646.[608] C646 is a pyrazolonefuran (Figure 14) that was discovered via virtual ligand screening. It efficiently reduces histone acetylation levels within cells and displays cytotoxic properties toward certain cancer cells.[608] Notably, a recent study characterized A-485, the most potent and specific p300 inhibitor identified to date.[609] A-485 was found to be 1000-fold more potent than other cell permeable HAT inhibitors, including C646, and highly specific to the KA3A/B(CBP/p300) BHC (bromodomain HAT-C/H3) domains. A-485 was also found to suppress proliferation in 61 cancer cell lines with an EC50 < 2 μM, indicating the compound may have some therapeutic potential, especially against hematological malignancies and prostate cancer.[609] Importantly, further characterization of the potential off target effect and studies in preclinical animal models are likely necessary prior to moving forward in any clinical setting.

Another study used naturally occurring acyl-CoA derivatives conjugated to biotin to affinity-purify KATs. Palmitoyl-CoA was recovered and found to inhibit GCN5 (KAT2A). This metabolite, among other acyl-CoA derivatives, was also able to bind PCAF (KAT2B) and MOF (KAT8) and modestly reduce levels of histone acetylation, underscoring that Acyl-CoA cofactors may act as endogenous regulators of lysine acetyltransferase activities.[610] Interestingly, some long chain fatty acid metabolites such as myristic acid (required to produce myristoyl-CoA) have also been reported to activate deacylation activity in sirtuins, especially SIRT6.[611]

Salicylate inhibits KAT3A/B(CBP/p300) acetyltransferase activity by directly competing with acetyl-CoA and down-regulates the specific acetylation of histones and nonhistone

proteins in cells.[612] Furthermore, diflunisal, an FDA-approved drug containing a salicylic acid substructure, inhibited KAT3A/B(CBP/p300) more potently than salicylate. Both drugs are orally bioavailable and inhibited p300-dependent myelogenous leukemic cell growth *in vitro* and *in vivo*, pointing to a potential new clinical application. In addition, p300-induced Tau acetylation was inhibited by salicylate or its derivative salsalate, which enhanced Tau turnover and reduced Tau level.[613] In a mouse model of Alzheimer's disease, administration of salsalate after disease onset rescued Tau-induced memory deficits and prevented hippocampal atrophy, underscoring the clinical potential of KAT inhibitors in Alzheimer's disease.

7.4. Bromodomain Inhibitors

Small-molecule inhibition of bromodomains is the most recent advancement in efforts to pharmacologically target the protein acetylation network. Rather than disrupting enzymatic catalysis, these compounds target protein:protein interactions by inhibiting bromodomain recognition of its acetyl-lysine residue-containing ligand. The first bromodomain drug discovery attempts were described in the HIV field targeting the interaction of the acetylated form of the viral transactivator Tat (acK50) with the bromodomain of KAT2B/PCAF, a critical step in transcription from the integrated HIV provirus.[614-616] The structure-based approach led to the discovery of a class of N1-aryl-propane-1,3-diamine compounds that selectively inhibited the acTat:PCAF interaction, albeit with relatively low potency. Also, the intracellular introduction of acetylated histone H4 peptides induced dissociation of BRD4 from chromatin and reduced cell growth.[617] A year later, a patent from Mitsubishi Pharmaceuticals indicated that thienodiazepines bind BRD4 bromodomains.[618] This patent report spurred the discovery of a lead compound, JQ1, with therapeutic activity against a rare squamous epithelial cancer called the NUT midline carcinoma.[619] The NUT midline carcinoma is cytogenetically defined by a translocation of the BRD4 gene that results in an in-frame fusion with the nuclear protein in testis (NUT), a tissue-specific acetyltransferase.[620]

At the same time as the initial report of JQ1, the laboratory of Alexander Tarakhovsky in collaboration with GlaxoSmithKline reported the discovery of I-BET, a synthetic compound mimicking acetylated histones and disrupting chromatin complexes responsible for expression of inflammatory genes in activated macrophages, thus conferring protection against lipopolysaccharide-induced endotoxic shock and bacteria-induced sepsis.[621] Interestingly, BET inhibitors also support immunotherapeutic applications by suppressing expression of Programmed Cell Death Protein Ligand 1 (PDL1),[622] which increases cytotoxic T-cell activity and limits tumor progression in mice. Since the characterization of BET inhibitors and their preclinical application in cancer and immunology disease models, their potential utility in modulating male fertility,[233] neurocognitive function,[623] cardiovascular disease,[624] and viral infections[625] has been described.

JQ1, I-BET, and related compounds are powerful inhibitors of both bromodomains of the BET protein BRD4, with similar activity also against bromodomains of BRD2, BRD3 and the testis-specific BET protein BRDT.[619] They function primarily by competing with acetyl-lysine binding by forming a hydrogen bond with a critical asparagine residue that otherwise

engages the acetyl-lysine. The pharmacophore is a methyltriazole that is common to most available BET inhibitors (Figure 15). Recently, second generation BET inhibitors have been described, including bivalent compounds that target both BET bromodomains and achieve potency orders of magnitude above that of JQ1.[236] Phthalimide-conjugated BET inhibitors that function as heterobifunctional small molecules have also been reported, which direct BET proteins to E3 ligase activity of cereblon, allowing for rapid and exquisitely specific destruction of BET proteins within the cell.[626]

More than 20 early clinical trials are in process with BET inhibitors.[619,627] Their focus is primarily on the treatment of various hematological malignancies, as BET proteins are coactivators of several critical oncogenes, including *MYC*,[206] in addition to important regulators of cell proliferation and fate, such as *MYB*,[628] *BCL2*, and *FOSL1*.[629] Transcriptional disruption of these genes is linked to antineoplastic phenotypes observed under BET inhibition, likely operating via local removal of BRD4 and associated transcription factors (i.e., P-TEFb) from acetylated chromatin or acetylated transcription factors (i.e., TWIST,[630] GATA-1,[622,631] and ERG[628]) in addition to indirect effects on transcription and the cell cycle. Several BET inhibitor trials have completed Phase I or reported tolerability and partial clinical outcomes.[632,633] Thus far, BET inhibitors appear well-tolerated with dose-limiting side effects such as diarrhea, fatigue, and reversible thrombocytopenia.[634]

As BET inhibitors are rapidly advancing into clinical trials, inhibitors of non-BET bromodomains are also being developed.[269,635] Current non-BET bromodomain inhibitors have been described mainly for bromodomains of acetyl-transferases (i.e., p300/CBP) and chromatin remodeling components (i.e., BRD7, BRG1). Most non-BET targeting small molecules are at the stage of being chemical probes,[636] and it has emerged that druggability varies among individual bromodomains.

8. CONCLUSIONS AND PERSPECTIVES

Lysine acetylation has moved from being a specialized mark on histones to a critical modification controlling cell fate, proliferation, and metabolism. The modification causes a change in the electrostatic charge of its cognate lysine residue, recruits reader proteins, and is tightly linked to fluctuations in key cellular metabolites, such as NAD^+ and acetyl-CoA. In respective cellular compartments, lysine acetylation regulates diverse molecular outcomes, such as gene-specific chromatin processes, enzymatic regulation, protein multimerization, localization, and stability. Reader protein domains, including the bromodomain, tandem PHD, YEATS, and acidic domains, have evolved to specifically bind to acetylated or nonacetylated lysine residues, thus coordinating the acetylation response. Our understanding of other acylation marks is rapidly evolving; examples include lysine crotonylaton, succinylation, and malonylation, with shared enzymes that place and remove the marks, such as KAT3A/B and sirtuins, respectively.[637,638] Pharmacological targeting of lysine acetylation is an established and briskly advancing field, starting from KDAC inhibitors, moving to sirtuin activators, and now including KAT and bromodomain inhibitors. The effects and mechanisms underlying these compounds are still being

uncovered, and future studies must consider the role of newer acylation marks in drug action.

Other open questions concern the issue how partitioning of critical metabolites contributes to the function of lysine acetylation in distinct cellular milieus. A considerable degree of diversity of nonhistone acetylation has emerged in metazoans, especially in mammals. This could be due to a more discrete compartmentalization of acetyl-CoA in lower eukaryotes. In yeast, acetyl-CoA is 20–30-fold enriched in mitochondria as compared to other cellular compartments.[639] In this context, acetyl-CoA does not permeate past the mitochondrial membrane and allows for distinction between acetyl-CoA as a metabolic intermediate and a cofactor for lysine acetylation. In mammals, this distinction is not as clear, and the question how other acyl group donors such as succinyl-CoA or malonyl-CoA compartmentalize remains yet unexplored. The opening of the lysine acetylation field to nutrition, exercise, and aging as well as its growing influence on disease pathogenesis and treatment of cancer, neurodegeneration, and HIV is exciting and signals far-reaching significance. Lysine acetylation may be key to the understanding of how such processes are molecularly defined. In the future, lysine acetylation and its directed intervention hold promise and are aimed at significantly improving health- and lifespan in humans.

ACKNOWLEDGMENTS

We thank John Carroll for assistance with graphics, Gary Howard for editorial support, and Veronica Fonseca for administrative support. We are thankful to members of the Ott lab for helpful discussions and to Ryan K. Quinn for important feedback on figures. We are grateful for funding from the UCSF Discovery Fellows Program and the American Society for Microbiology Robert D. Watkins Fellowship (to I.A.) and funding from the AmfAR Institute for HIV Cure Research and the NIH (to M.O., R01AI083139-06, R01DA043142, and 1DP1DA038043; to E.V., 5R24 DK085610-06 and R21AG051111). The authors declare no competing financial interest.

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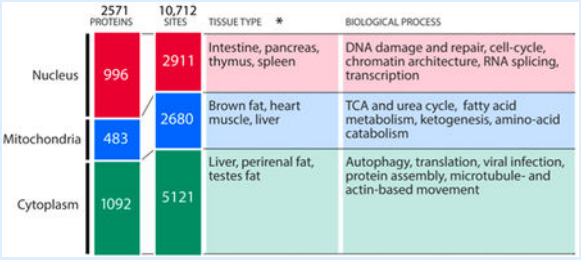
Box 1.

Acetylated proteins identified in proteomic studies: compartmentalization, tissue enrichment (*in rodent), and related biological processes as described in refs 315, 319, and 320



Box 2.

Genetic approaches to identify acetylation sites, tissue type, and biological process as described in refs 319, 326, 327, 328, 329, and 330

ENZYME	Δ ACETYLATED PROTEINS|SITES	TISSUE OR CELL TYPE	BIOLOGICAL PROCESS
KAT2A KAT2B	398|1569	HeLa cells	Chromatin organization, Pol II transcription elongation, histone lysine methylation, cell cycle, actin-mediated cell contraction
KAT13D	179|306	Mouse liver	Glycolysis, TCA cycle, amino acid metabolism, fatty acid metabolism
SIRT1	1800|4623 114 | 807	MEFs Mouse liver	DNA repair, signaling, transcription factor assembly, transcription elongation, spliceosome assembly, fatty acid metabolism, TCA cycle, small molecule metabolism
SIRT3	1791 | 306	Mouse liver Mitochondria	Fatty acid metabolism, TCA cycle, amino acid catabolism, ketone body metabolism, electron transport chain

Box 3.

Histone lysine acetylation sites and their domain location[341]

HISTONE	LYSINE MODIFICATION	
	Tail Domain	Globular Domain
H2A	K5,K9, K13, K15	K36, K118
H2B	K5, K11, K12, K15, K16, K23, K24	K46, K57, K120
H3	K4, K9, K14, K18, K23, K27	K36, K37, K56, K64, K79, K112, K115, K112
H4	K5, K8, K12, K16, K20, K31	K77, K79, K91
H1	*K16, K33	K45, K63, K74, K89, K96, K105, K167

Each histone has additional isoforms not listed in this table.

*Histone H1 N-terminal domain is structurally distinct from tail domains found in histone H2-4

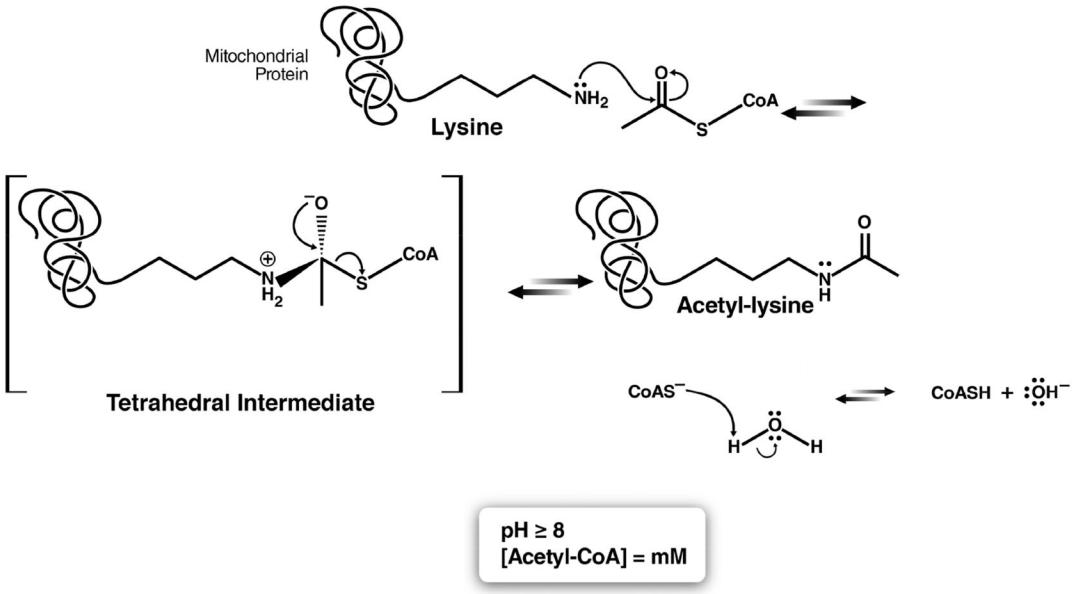


Figure 1.
Proposed reaction mechanism of spontaneous acetylation in the mitochondria.[10]

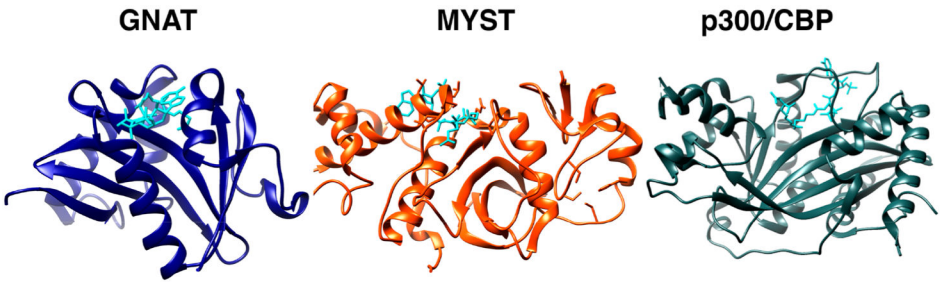


Figure 2.

Structures of catalytic KAT domains from GNAT (human GCN5, blue, PDB: 1Z4R), MYST (human MOZ, orange, PDB: 2RC4), and KAT3A/B(CBP/p300) (human KAT3B(p300), gray, PDB: 3BIY) families. Acetyl-CoA is shown in cyan. Images rendered in Chimera (UCSF).

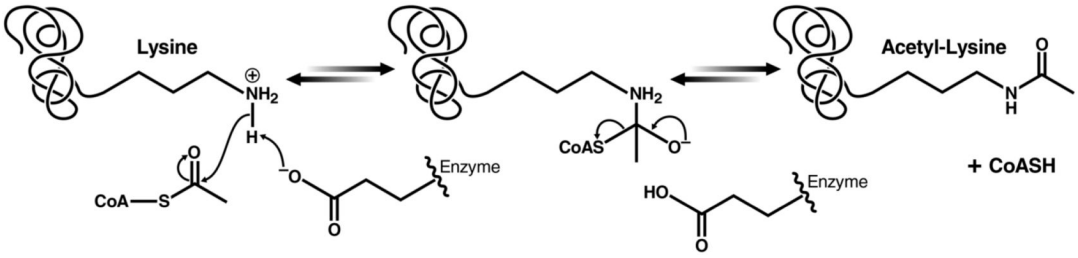


Figure 3.
Proposed reaction mechanism for GNAT family KATs.[85]

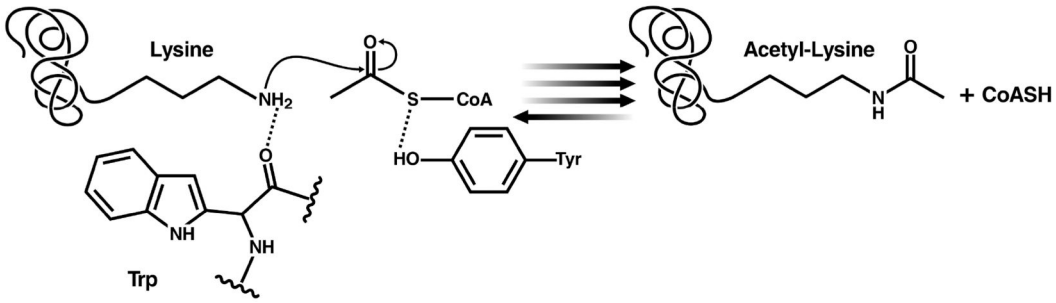


Figure 4.
Proposed reaction mechanism for p300 family KATs.[89]

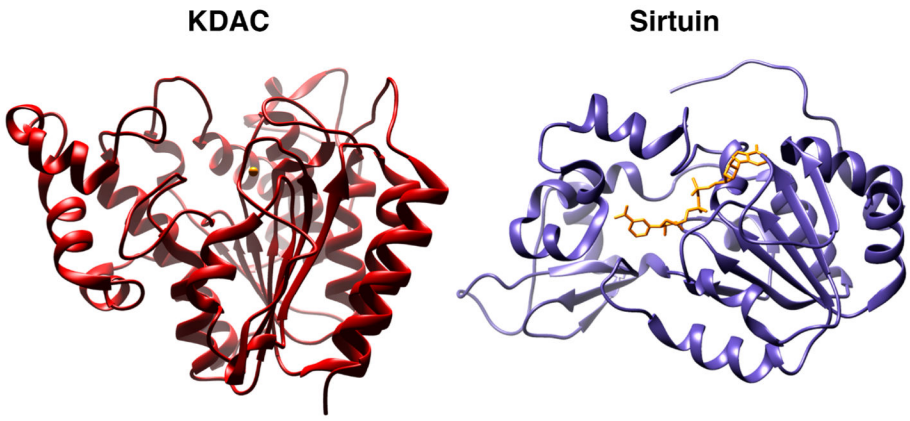


Figure 5.

Structures of catalytic KDAC domains from KDAC (human KDAC2, red, PDB: 4LXZ) and Sirtuin (human SIRT1, purple, PDB: 4I5I families). KDAC zinc and Sirtuin NAD are shown in yellow. Images rendered in Chimera (UCSF).

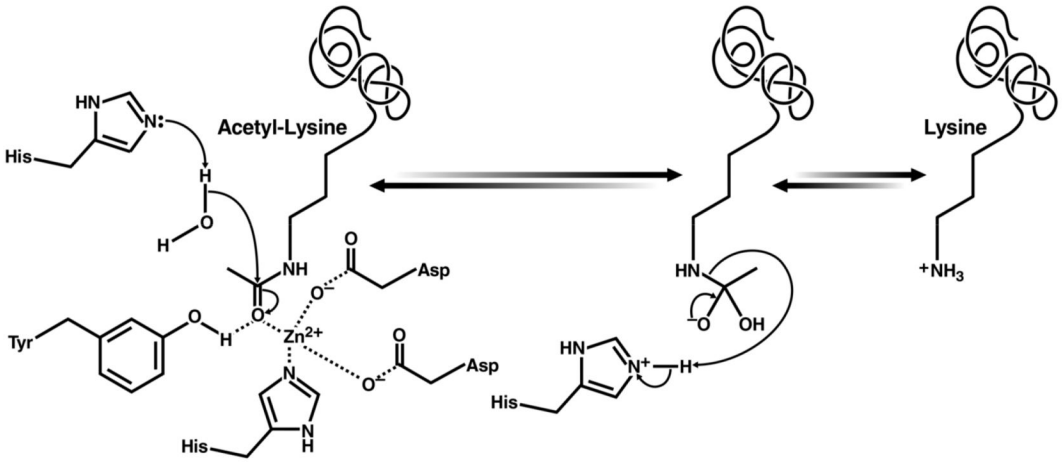


Figure 6.
Proposed reaction mechanism for class I, II, and IV KDACs.[157]

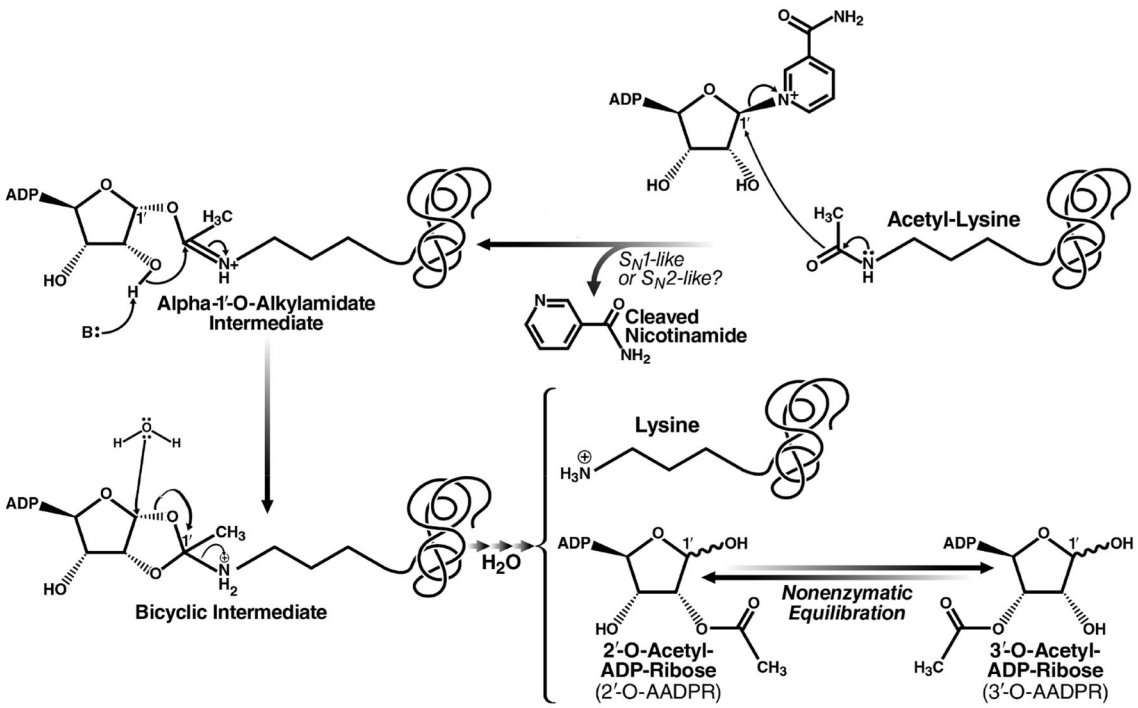


Figure 7.

Proposed reaction mechanism for class III KDACs/sirtuins. Reprinted with permission from ref 201. Copyright 2010 The Royal Society of Chemistry.

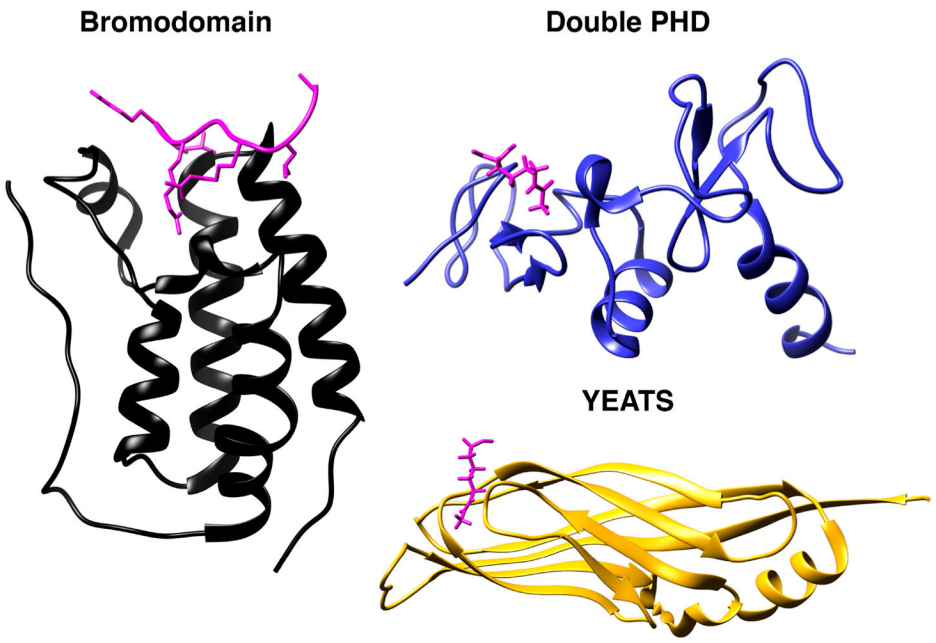


Figure 8.

Structures of acetylation reader domains: Bromodomain (human BRD4, black, PDB: 3UVW), double PHD (human DPF3, blue, PDB: 2KWJ), and YEATS (human AF9, yellow, PDB: 4TMP). Acetyl-lysine ligands shown in pink. Images rendered in Chimera (UCSF).

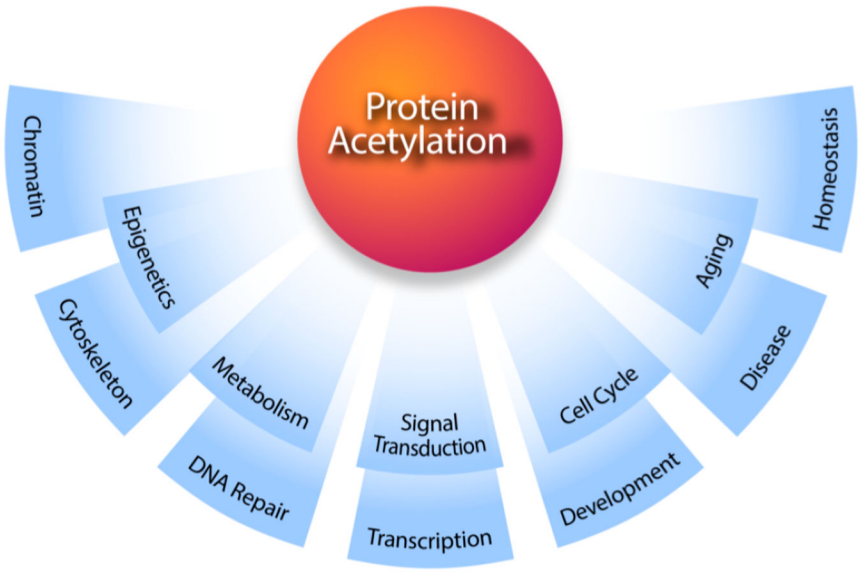


Figure 9.
Acetylome studies reveal the scope of biological functions regulated by acetylation in mammalian cells.

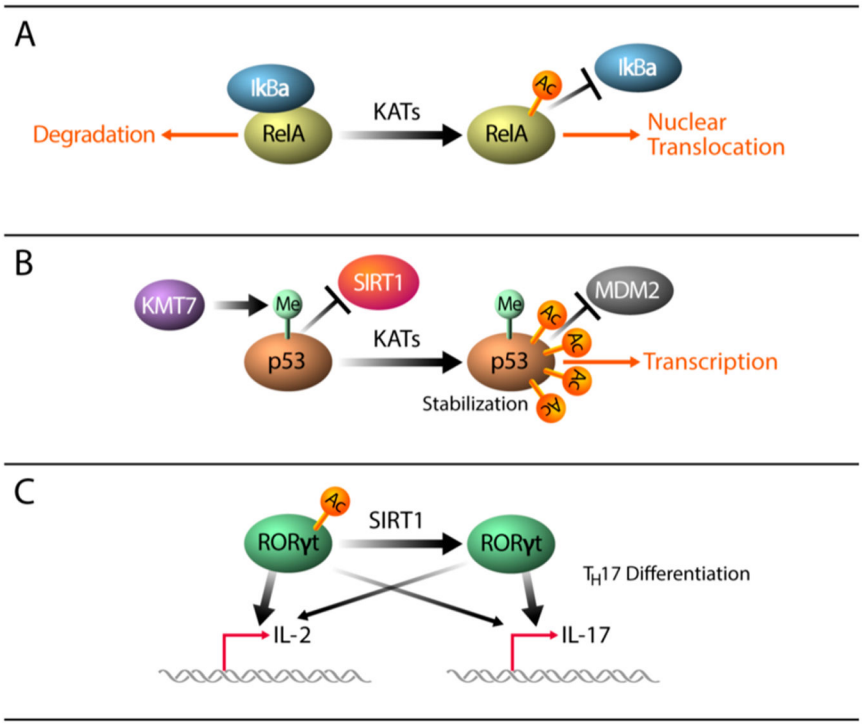


Figure 10.
Mechanisms driving acetylation dependent regulation of transcription factors.

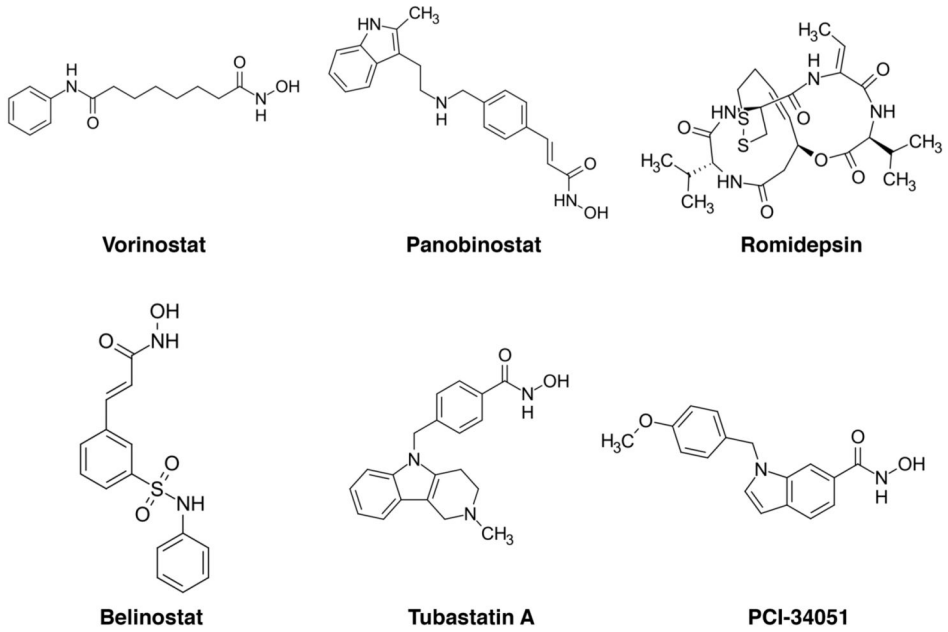
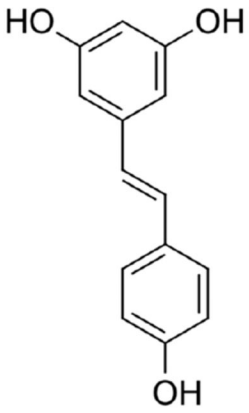
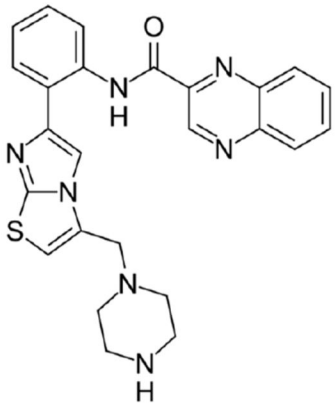


Figure 11.
Selected chemical structures of KDAC inhibitors.



Resveratrol



SRT1720

Figure 12.
Selected chemical structures of sirtuin activators.

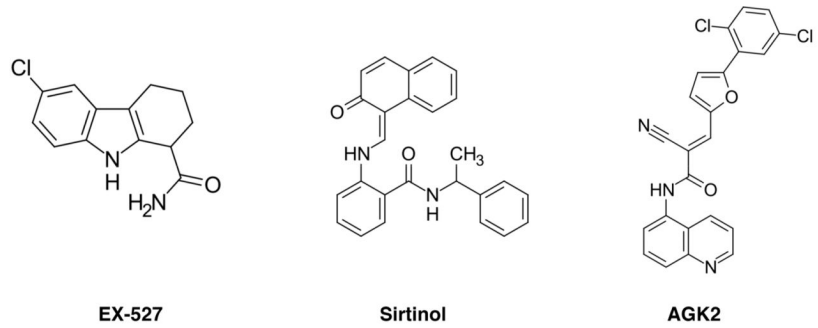


Figure 13.
Selected chemical structures of sirtuin inhibitors.

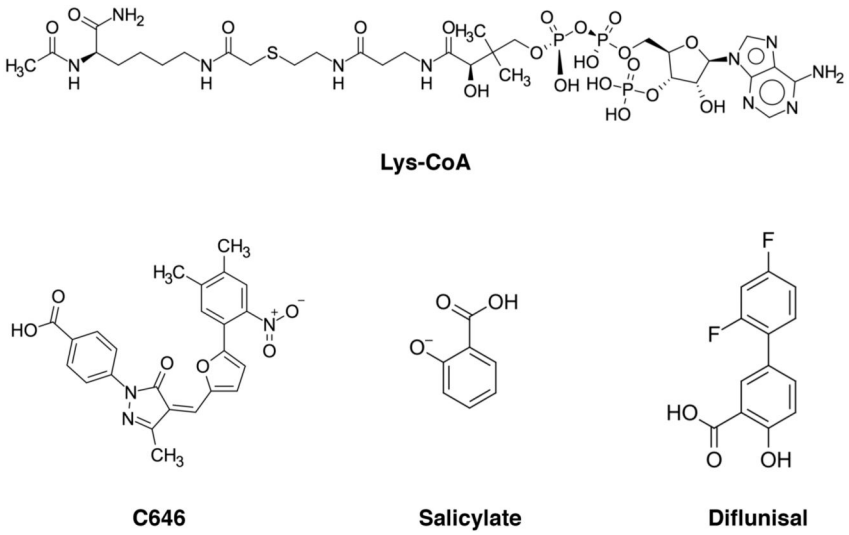


Figure 14.
Selected chemical structures of KAT inhibitors.

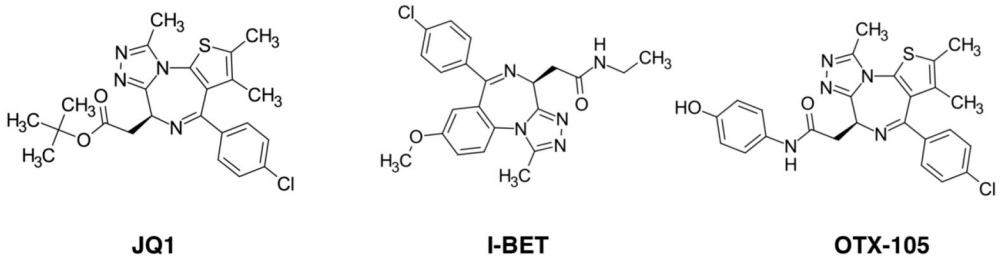


Figure 15.
Selected chemical structures of BET inhibitors.

Table 1.

Putative Lysine Acetyltransferases (KATs) and Their Common Aliases Listed with the Subcellular Localization, Crystal Structures (if Available), and UniProt ID

PROTEIN NAME	ALIASES	SUBFAMILY	LOCALIZATION	STRUCTURES AVAILABLE	UNIPROT ID	REFERENCES
αTAT1	MEC17	N/A	Cytoplasmic	KAT Domain	Q5SQ10	17-20
KAT1	HAT1	GNAT	Nuclear, Cytoplasmic	KAT Domain	O14929	21-24
KAT2A	GCN5		Nuclear	KAT Domain, Bromodomain	Q92830	25-29
KAT2B	PCAF		Nuclear	KAT Domain, Bromodomain	Q92831	27, 30-33
ATF2	CREB2		Nuclear, Mitochondrial	DNA Binding Domain	P15336	34-37
KAT3A	CBP	P300/CBP	Nuclear, Cytoplasmic	Bromodomain	Q92793	27, 38-41
KAT3B	p300		Nuclear, Cytoplasmic	KAT Domain, Bromodomain	Q09472	27, 42-45
KAT4	TAF1, TAFII250	TAFII250	Nuclear	Complete Protein	P21675	27, 46-49
KAT5	TIP60	MYST	Nuclear, Cytoplasmic	KAT Domain (PDB: 2OU2)	Q92993	50-52
KAT6A	MYST3, MOZ		Nuclear	KAT Domain, PhD Finger	Q92794	53-55
KAT6B	MYST4, MORF		Nuclear	N/A	Q8WYB5	56, 57
KAT7	MYST2, HBO1		Nuclear	N/A	O95251	58-61
KAT8	MYST1, MOF		Nuclear, Mitochondrial	KAT Domain	Q9H7Z6	62-66
KAT9	ELP3	ELP3	Nuclear, Cytoplasmic	N/A	Q9H9T3	67, 68
GCN5L1	BLOS1	N/A	Cytoplasmic, Mitochondrial	N/A	P78537	69, 70
KAT12	GTF3C4	N/A	Nuclear	N/A	Q9UKN8	71
KAT13A	NCoA-1, SRC1	SRCs	Nuclear, Cytoplasmic	NR Binding Domain	Q15788	72, 73
KAT13B	NCoA-3, TRAM1		Nuclear,Cytoplasmic, Exosome	NR Binding Domain	Q9Y6Q9	74, 75
KAT13C	NCoA-2, TIF2, SRC3		Nuclear, Cytoplasmic	NR Binding Domain	Q15596	73, 76, 77
KAT13D	CLOCK		Nuclear, Cytoplasmic	DNA Bindinq Domain	O15516	78-82
KAT14	CSR2B	N/A	Nuclear, Cytoplasmic	N/A	Q9H8E8	83

Table 2.

Zn^{2+} Dependent Lysine Deacetylases (KDACs) Listed with Subcellular Localization, Relevant Crystal Structures (if Available), Common Inhibitors, and UniProt ID

PROTEIN NAME	SUBFAMILY	LOCALIZATION	STRUCTURES AVAILABLE	INHIBITORS	UNIPROT ID	REFERENCES
KDAC1	I	Nuclear, Cytoplasmic	Complete Protein	Panobinostat, Vorinostat, Romidepsin	Q13547	123-125
KDAC2		Nuclear, Cytoplasmic	Deacetylase Domain	Panobinostat, Vorinostat, Romidepsin	Q92769	126-128
KDAC3		Nuclear, Cytoplasmic	Deacetylase Domain	Panobinostat, Vorinostat	O15379	128-130
KDAC8		Nuclear, Cytoplasmic	Complete Protein	Panobinostat, Vorinostat, PCI-34051	Q9BY41	131-136
KDAC4	IIA	Nuclear, Cytoplasmic	Deacetylase Domain	Panobinostat, Romidepsin	P56524	137-141
KDAC5		Nuclear, Cytoplasmic	N/A	Panobinostat	Q9UQL6	142-144
KDAC7		Nuclear, Cytoplasmic, Mitochondrial	Deacetylase Domain	Panobinostat	Q8WUI4	145-150
KDAC9		Nuclear, Cytoplasmic	N/A	Panobinostat, Vorinostat	Q9UKV0	151, 152
KDAC6	IIB	Nuclear, Cytoplasmic	Deacetylase Domain	Panobinostat, Vorinostat, Romidepsin, Tubastatin A	Q9UBN7	112, 153
KDAC10		Nuclear, Cytoplasmic	N/A	Panobinostat	Q969S8	111, 154
KDAC11	IV	Nuclear, Cytoplasmic	N/A	N/A	Q96DB2	110, 155

Table 3.

NAD^+ Dependent Sirtuin Deacetylases Listed with Subcellular Localization, Relevant Crystal Structures (if Available), Common Inhibitors, and UniProt ID

PROTEIN NAME	LOCALIZATION	STRUCTURES AVAILABLE	INHIBITORS	UNIPROT ID	REFERENCES
SIRT1	Nuclear, Cytoplasmic	Deacetylase Domain	EX-527, Nicotinamide	Q96EB6	168-175
SIRT2	Nuclear, Cytoplasmic	Complete Protein	EX-527, Nicotinamide	Q8IXJ6	175-181
SIRT3	Mitochondrial	Deacetylase Domain	EX-527, Nicotinamide	Q9NTG7	175, 180, 182-186
SIRT5	Mitochondrial, Nuclear, Cytoplasmic	Deacetylase Domain	Nicotinamide, Suramin	Q9NXA8	186-191
SIRT6	Nuclear	Complete Protein	N/A	Q8N6T7	164, 192-195
SIRT7	Nuclear	N/A	N/A	Q9NRC8	196, 197

Table 4.

Bromodomain Containing Proteins[a]

PROTEIN NAME	BROMODOMAINS	LOCALIZATION	BROMODOMAIN STRUCTURE	UNIPROT ID	REFERENCES
BPTF	1	Nuclear, Cytoplasmic	Yes	Q12830	27, 211, 212
KAT3A (CBP)	1	Nuclear, Cytoplasmic	Yes	Q92793	27
KAT3B (p300)	1	Nuclear, Cytoplasmic	Yes	Q09472	27
BRWD1	2	Nuclear, Cytoplasmic	1 of 2	Q9NSI6	27
PHIP	2	Nuclear, Cytoplasmic	1 of 2	Q8WWQ0	27, 213, 214
BRPF1	1	Nuclear, Cytoplasmic	Yes	P55201	56, 215-219
TRIM24	1	Nuclear, Cytoplasmic	Yes	O15164	220, 221
SP100	1	Nuclear, Cytoplasmic	Yes (4PTB)	P23497	222, 223
KAP1	1	Nuclear, Cytoplasmic	Yes	Q13263	224-228
ZMYND11	1	Nuclear, Cytoplasmic	Yes	Q15326	229, 230
KAT2A (GCN5)	1	Nuclear	Yes	Q92830	27
KAT2B (PCAF)	1	Nuclear	Yes	Q92831	27
CECR2	1	Nuclear	Yes	Q9BXF3	27
BRDT	2	Nuclear	2 of 2	Q58F21	27, 231-235
BRD4	2	Nuclear	2 of 2	O60885	27, 46, 236-239
BRD3	2	Nuclear	2 of 2	Q15059	27, 240
BRD2	2	Nuclear	2 of 2	P25440	241-244
BAZ1A	1	Nuclear	No	Q9NRL2	245, 246
BRD8B	2	Nuclear	No	Q9H039	247
BAZ1B	1	Nuclear	No	Q9UIG0	248, 249
BRD9	1	Nuclear	Yes	Q9H8M2	27, 46, 250-252
BRD7	1	Nuclear	Yes	Q9NPI1	250, 253
BRPF3	1	Nuclear	No	Q9ULD4	59, 254, 255
BRD1	1	Nuclear	Yes	095696	27, 256
ATAD2B	1	Nuclear	Yes	Q9ULI0	27, 257, 258
TRIM33	1	Nuclear	Yes	Q9UPN9	259-262
SP110	1	Nuclear	No	Q9HB58	263, 264
SP140	1	Nuclear	No	Q13342	265, 266

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PROTEIN NAME	BROMODOMAINS	LOCALIZATION	BROMODOMAIN STRUCTURE	UNIPROT ID	REFERENCES
SP140L	1	Nuclear	No	Q9H930	267
BAZ2B	1	Nuclear	Yes	Q9UIF8	268, 269
BAZ2A	1	Nuclear	Yes	Q9UIF9	270, 271
KMT2A	1	Nuclear	Yes	Q03164	272-275
TAF1L	1	Nuclear	Yes	Q8IZX4	27, 237
TAF1	2	Nuclear	2 of 2	P21675	27, 46, 48, 49, 276, 277
ZMYND8	1	Nuclear	Yes	Q9ULU4	278-280
PBRM1	6	Nuclear	6 of 6	Q86U86	27, 281, 282
BRG1	1	Nuclear	Yes	P51532	27, 283-285
SMARCA2	1	Nuclear	Yes (5DKC)	P51531	286
BRWD3	2	Nuclear, Extracellular	No	Q6RI45	287
ATAD2	1	Nuclear, Exosome	Yes	Q6PL18	27, 288-291
ASH1L	1	Nuclear,Tight Junctions	Yes	Q9NR48	27, 292, 293

[a]Proteins are organized according to their observed subcellular localization. UniProt IDs refer to human proteins. References correspond to protein localization and relevant crystal structures drawn from mouse and human data.

Table 5.

Selection of Acetylated Transcription Factors and Their Writers and Erasers

PROTEIN NAME	ACETYL-LYSINE	WRITER	ERASER	UNIPROT ID	REFS
AR	K630, K632, K633	KAT2B, KAT3A, KAT3B, KAT5	KDAC1, KDAC7	P10275	362-365
ATM	K3016	KAT5	Unknown	Q13315	52, 366
BCL6	K379	KAT3B	Unknown	P41182	367
BMAL1	K537	KAT13D	SIRT1	000327	101, 368
CDK9	K44, K48	KAT2A, KAT2B, KAT3B	KDAC3, SIRT2	P50750	369-372
ChREBP	K672	KAT3B	SIRT1	Q9NP71	373, 374
CREB	K91, K94, K136	KAT3A, KAT3B	SIRT1, KDAC8	P16220	375, 376
CRTC2	K628	KAT3A, KAT3B	SIRT1	Q53ET0	377
CycT1	K380, K386, K390, K404	KAT3B	KDAC1, KDAC3	060563	315, 378, 379
E2F1	K117, K120, K125	KAT2A, KAT2B, KAT3B	HDAC1	Q01094	380-382
EKLF	K270, K284	KAT3A, KAT3B	Unknown	Q13351	383, 384
ERα	K226, K268, K299, K302, K303	KAT3A	SIRT1	P03372	385-387
Foxo1	K242, K245, K248, K262, K265, K274	KAT3B	SIRT1, SIRT2, SIRT3	Q12278	379-393
Foxp3	K31, K327, K263, K268	KAT3B, KAT5	KDAC7, KDAC9, SIRT1	Q9BPZS1	50, 394-396
FXR	K217	KAT3B	SIRT1	Q96RI1	397, 398
GABPB1	K69, K340, K369	KAT3B	SIRT7	Q06547	399
GATA1	K158, K246, K252,K312	KAT3A, KAT3B	KDAC5	P15976	400-403
HIF1α	K10, K11, K12, K19, K21, K709	KAT2B, KAT3B	KDAC1, KDAC4, SIRT1, SIRT2	Q16665	404-408
HIF2α	K385, K685, K741	KAT3A	SIRT1	Q99814	409, 410
HMG17	K2	KAT2B	Unknown	P05204	411
IFNαR2	K399	KAT3A	Unknown	P48551	412
Myc	K143, K148, K157, K275, K317, K323, K371	KAT2B, KAT3B, KAT5	SIRT1, SIRT2	P01106	315, 413-416
Notch 1	K1764, K1770, K1771, K1772, K1785, K1935, K2050, K2068, K2146, K2147, K2150, K2154, K2161, K2164	KAT2B, KAT3B	SIRT1	P46531	417
p53	K120, K321, K373, K381, K382	KAT6A, KAT3B	KDAC1, SIRT1, SIRT2	P04637	315,418-422
PAF53	K373	KAT2B	SIRT7	Q9GZS1	423
PRLR	K277, K339, K412, K456, K466, K472, K505, K514, K517, K526, K533, K536, K590, K601	KAT3A	KDAC6, SIRT2	P15471	424
Pygo2	K11, K43, K44, K47	KAT3A, KAT3B	Unknown	Q9BRQ0	425

PROTEIN NAME	ACETYL-LYSINE	WRITER	ERASER	UNIPROT ID	REFS
RelA	K122, K123, K218, K221, K310, K314, K315	KAT2B, KAT3A, KAT3B	KDAC3, SIRT1, SIRT2	Q04206	426-430
Rb	K873, K874	PCAF	SIRT1	P06400	431
RORγ	K69, K81, K99, K112	KAT3B	KDAC1, SIRT1	P51449	432, 433
RPB1	K1888, K1909, K1916, K1923, K1937, K1958, K1972, K1986	KAT3B	Unknown	P24928	434, 435
SMAD7	K64, K70	KAT3B	KDAC1, KDAC3, KDAC5, KDAC6	O15105	436, 437
Sp1	K703	KAT3B	Unknown	P08047	315, 438
Sp3	K551	KAT3B	Unknown	Q02447	439-441
SREBPIc	K289, K309	KAT3B	SIRT1	P36956	442
STAT2	K390	KAT3A	Unknown	P52630	412, 443
STAT3	K49, K87, K685	KAT3A, KAT3B	KDAC1, KDAC2, KDAC3	P40763	444-446
STAT5b	K359, K694, K696, K701	KAT3A	SIRT2, KDAC6	P51692	424, 447
HIV-1 Tat	K28, K50, K51	KAT2A, KAT2B, KAT3B	SIRT1	P04608, P04610	448-451
UBF1	K352	KAT3A	Unknown	P17480	452
YY1	K173, K174, K178, K179, K180, K181	KAT2B, KAT3B	KDAC1, KDAC2	P25490	453