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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.

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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

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

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
α TAT1	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 Binding Domain	O15516	78–82
KAT14	CSR2B	N/A	Nuclear, Cytoplasmic	N/A	Q9H8E8	83

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 bromodo-

main. The dynamic interplay between the writers, erasers, and readers of acetylation regulates critical epigenomic and metabolic processes, in addition to other major cellular functions.

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

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 phosphorylation⁸ 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)), α Tubulin acetyltransferase (α TAT1), circadian locomotor 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}

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: 4ISI families). KDAC zinc and Sirtuin NAD are shown in yellow. Images rendered in Chimera (UCSF).

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

Table 2. Zn²⁺ 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

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

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

Figure 7. Proposed reaction mechanism for class III KDACs/sirtuins. Reprinted with permission from ref 201. Copyright 2010 The Royal Society of Chemistry.

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 Zn²⁺-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 (Zn²⁺) 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 Zn²⁺ 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 sub-

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	O95696	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
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 (SDKC)	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

^aProteins 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.

strates.^{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 *brhma* (*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 1992²⁰² 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-

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).

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 remodeling²⁰⁹ 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 (α Z, α A, α B, and α C) 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

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

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 approach³¹⁹ 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

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

	2571 PROTEINS	10,712 SITES	TISSUE TYPE *	BIOLOGICAL PROCESS
Nucleus	996	2911	Intestine, pancreas, thymus, spleen	DNA damage and repair, cell-cycle, chromatin architecture, RNA splicing, transcription
Mitochondria	483	2680	Brown fat, heart muscle, liver	TCA and urea cycle, fatty acid metabolism, ketogenesis, amino-acid catabolism
Cytoplasm	1092	5121	Liver, perirenal fat, testes fat	Autophagy, translation, viral infection, protein assembly, microtubule- and actin-based movement

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 fibroblasts³²⁸ 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}

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	MEFs	DNA repair, signaling, transcription factor assembly, transcription elongation, spliceosome assembly, fatty acid metabolism, TCA cycle, small molecule metabolism
	114 807	Mouse liver	
SIRT3	179 306	Mouse liver Mitochondria	Fatty acid metabolism, TCA cycle, amino acid catabolism, ketone body metabolism, electron transport chain

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).

Box 3. Histone lysine acetylation sites and their domain location³⁴¹

HISTONE	LYSINE MODIFICATION
	Tail Domain
H2A	K5, K9, K13, K15
H2B	K5, K11, K12, K15, K16, K23, K24
H3	K4, K9, K14, K18, K23, K27
H4	K5, K8, K12, K16, K20, K31
	Globular Domain
	K36, K118
	K46, K57, K120
	K36, K37, K56, K64, K79, K112, K115, K112
	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

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 phosphodiester 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 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- κ B, 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- κ B 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- κ B generally sequestered in the cytoplasm through its interaction with its negative regulator I κ B α . Upon cell stimulation, RelA is

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
ER α	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	Q96R11	397, 398
GABPB1	K69, K340, K369	KAT3B	SIRT7	Q06547	399
GATA1	K158, K246, K252, K312	KAT3A, KAT3B	KDAC5	P15976	400–403
HIF1 α	K10, K11, K12, K19, K21, K709	KAT2B, KAT3B	KDAC1, KDAC4, SIRT1, SIRT2	Q16665	404–408
HIF2 α	K385, K685, K741	KAT3A	SIRT1	Q99814	409, 410
HMG17	K2	KAT2B	Unknown	P05204	411
IFN α R2	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
RelA	K122, K123, K218, K221, K310, K314, K315	KAT2B, KAT3A, KAT3B	KDAC3, SIRT1, SIRT2	Q04206	426–430
Rb	K873, K874	PCAF	SIRT1	P06400	431
RORy	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
SREBP1c	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

acetylated by KAT3A/B (CBP/p300) at several residues. Acetylation at K221 disrupts the RelA-I κ B α 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} Acety-

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

lation 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 α TAT1, 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. α TAT1 overexpression destabilizes microtubules; however, this is mainly attributed to enhanced α TAT1-tubulin interactions and not considered a consequence of increased acetyltransferase activity.⁴⁹⁵ Tubulin is deacetylated by KDAC6¹¹² 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: HSP90 α , which is stress-inducible and tightly regulated, and HSP90 β , which is constitutively expressed.⁴⁹⁸ HSP90 acetylation is detected on up to 22 distinct residues on HSP90 α , and 5 distinct residues HSP90 β .^{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 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

Figure 11. Selected chemical structures of KDAC inhibitors.

(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 O₂ 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.⁵⁵⁵ β -Oxidation intermediates (e.g., long chain fatty acids) accumulate in mice that lack SIRT3.⁵⁵⁵ 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 amino-transferase 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 transcarbamoylase (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 (HIF1 α), 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 KDACs⁵⁶⁶ 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 hyperacetylation 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.

Figure 12. Selected chemical structures of sirtuin activators.

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 $IC_{50} \sim 60 \mu M$ 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 pyrazolone-furan (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 KAT3A/B(CBP/p300) BHC (bromodomain HAT-C/H3) domains. A-485 was also found to suppress proliferation in 61 cancer cell lines with an $EC_{50} < 2 \mu M$, 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

Figure 13. Selected chemical structures of sirtuin inhibitors.

Figure 14. Selected chemical structures of KAT inhibitors.

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 deacetylation 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

Figure 15. Selected chemical structures of BET inhibitors.

preclinical application in cancer and immunology disease models, their potential utility in modulating male fertility,²³³ neurocognitive function,⁶²³ cardiovascular disease,⁶²⁴ and viral infections⁶²⁵ 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 ERG⁶²⁸) 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 crotonylation, 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.

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REFERENCES

- (1) Aksnes, H.; Drazic, A.; Marie, M.; Arnesen, T. First Things First: Vital Protein Marks by N-Terminal Acetyltransferases. *Trends Biochem. Sci.* **2016**, *41*, 746–60.
- (2) Struhl, K. Histone Acetylation and Transcriptional Regulatory Mechanisms. *Genes Dev.* **1998**, *12*, 599–606.
- (3) Grunstein, M. Histone Acetylation in Chromatin Structure and Transcription. *Nature* **1997**, *389*, 349–52.
- (4) Strahl, B. D.; Allis, C. D. The Language of Covalent Histone Modifications. *Nature* **2000**, *403*, 41–5.
- (5) Turner, B. M. Histone Acetylation and an Epigenetic Code. *BioEssays* **2000**, *22*, 836–45.
- (6) Choudhary, C.; Weinert, B. T.; Nishida, Y.; Verdin, E.; Mann, M. The Growing Landscape of Lysine Acetylation Links Metabolism and Cell Signalling. *Nat. Rev. Mol. Cell Biol.* **2014**, *15*, 536–50.
- (7) Duan, G.; Walther, D. The Roles of Post-Translational Modifications in the Context of Protein Interaction Networks. *PLoS Comput. Biol.* **2015**, *11*, e1004049.
- (8) Gnad, F.; Forner, F.; Zielinska, D. F.; Birney, E.; Gunawardena, J.; Mann, M. Evolutionary Constraints of Phosphorylation in Eukaryotes, Prokaryotes, and Mitochondria. *Mol. Cell. Proteomics* **2010**, *9*, 2642–53.
- (9) Santo-Domingo, J.; Demareux, N. Perspectives On: Sgp Symposium on Mitochondrial Physiology and Medicine: The Renaissance of Mitochondrial Ph. *J. Gen. Physiol.* **2012**, *139*, 415–23.
- (10) Wagner, G. R.; Payne, R. M. Widespread and Enzyme-Independent Nepsilon-Acetylation and Nepsilon-Succinylation of Proteins in the Chemical Conditions of the Mitochondrial Matrix. *J. Biol. Chem.* **2013**, *288*, 29036–45.
- (11) Yang, X. J.; Ogryzko, V. V.; Nishikawa, J.; Howard, B. H.; Nakatani, Y. A P300/Cbp-Associated Factor That Competes with the Adenoviral Oncoprotein E1a. *Nature* **1996**, *382*, 319–24.
- (12) Ogryzko, V. V.; Schiltz, R. L.; Russanova, V.; Howard, B. H.; Nakatani, Y. The Transcriptional Coactivators P300 and Cbp Are Histone Acetyltransferases. *Cell* **1996**, *87*, 953–9.
- (13) Mizzen, C. A.; Yang, X. J.; Kokubo, T.; Brownell, J. E.; Bannister, A. J.; Owen-Hughes, T.; Workman, J.; Wang, L.; Berger, S. L.; Kouzarides, T.; Nakatani, Y.; Allis, C. D. The Taf(Ii)250 Subunit of Tfiid Has Histone Acetyltransferase Activity. *Cell* **1996**, *87*, 1261–70.
- (14) Yamamoto, T.; Horikoshi, M. Novel Substrate Specificity of the Histone Acetyltransferase Activity of Hiv-1-Tat Interactive Protein Tip60. *J. Biol. Chem.* **1997**, *272*, 30595–8.
- (15) Chen, H.; Lin, R. J.; Schiltz, R. L.; Chakravarti, D.; Nash, A.; Nagy, L.; Privalsky, M. L.; Nakatani, Y.; Evans, R. M. Nuclear Receptor Coactivator Actr Is a Novel Histone Acetyltransferase and Forms a Multimeric Activation Complex with P/Caf and Cbp/P300. *Cell* **1997**, *90*, 569–80.
- (16) Spencer, T. E.; Jenster, G.; Burcin, M. M.; Allis, C. D.; Zhou, J.; Mizzen, C. A.; McKenna, N. J.; Onate, S. A.; Tsai, S. Y.; Tsai, M. J.; O'Malley, B. W. Steroid Receptor Coactivator-1 Is a Histone Acetyltransferase. *Nature* **1997**, *389*, 194–8.
- (17) Taschner, M.; Vetter, M.; Lorentzen, E. Atomic Resolution Structure of Human Alpha-Tubulin Acetyltransferase Bound to Acetyl-CoA. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 19649–54.
- (18) Friedmann, D. R.; Aguilar, A.; Fan, J.; Nachury, M. V.; Marmorstein, R. Structure of the Alpha-Tubulin Acetyltransferase, Alphaatl1, and Implications for Tubulin-Specific Acetylation. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 19655–60.
- (19) Davenport, A. M.; Collins, L. N.; Chiu, H.; Minor, P. J.; Sternberg, P. W.; Hoelz, A. Structural and Functional Characterization of the Alpha-Tubulin Acetyltransferase Mec-17. *J. Mol. Biol.* **2014**, *426*, 2605–16.
- (20) Szyk, A.; Deaconescu, A. M.; Spector, J.; Goodman, B.; Valenstein, M. L.; Ziolkowska, N. E.; Kormendi, V.; Grigorieff, N.; Roll-Mecak, A. Molecular Basis for Age-Dependent Microtubule Acetylation by Tubulin Acetyltransferase. *Cell* **2014**, *157*, 1405–15.
- (21) Wu, H.; Moshkina, N.; Min, J.; Zeng, H.; Joshua, J.; Zhou, M. M.; Plotnikov, A. N. Structural Basis for Substrate Specificity and

Catalysis of Human Histone Acetyltransferase 1. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 8925–30.

(22) Yang, X.; Li, L.; Liang, J.; Shi, L.; Yang, J.; Yi, X.; Zhang, D.; Han, X.; Yu, N.; Shang, Y. Histone Acetyltransferase 1 Promotes Homologous Recombination in DNA Repair by Facilitating Histone Turnover. *J. Biol. Chem.* **2013**, *288*, 18271–82.

(23) Verreault, A.; Kaufman, P. D.; Kobayashi, R.; Stillman, B. Nucleosomal DNA Regulates the Core-Histone-Binding Subunit of the Human Hat1 Acetyltransferase. *Curr. Biol.* **1998**, *8*, 96–108.

(24) Chang, L.; Loranger, S. S.; Mizzen, C.; Ernst, S. G.; Allis, C. D.; Annunziato, A. T. Histones in Transit: Cytosolic Histone Complexes and Diacetylation of H4 During Nucleosome Assembly in Human Cells. *Biochemistry* **1997**, *36*, 469–80.

(25) Schuetz, A.; Bernstein, G.; Dong, A.; Antoshenko, T.; Wu, H.; Loppnau, P.; Bochkarev, A.; Plotnikov, A. N. Crystal Structure of a Binary Complex between Human Gcn5 Histone Acetyltransferase Domain and Acetyl Coenzyme A. *Proteins: Struct., Funct., Genet.* **2007**, *68*, 403–7.

(26) Ringel, A. E.; Wolberger, C. Structural Basis for Acyl-Group Discrimination by Human Gcn5L2. *Acta Crystallogr. D Struct. Biol.* **2016**, *72*, 841–8.

(27) Filippakopoulos, P.; Picaud, S.; Mangos, M.; Keates, T.; Lambert, J. P.; Barsyte-Lovejoy, D.; Felletar, I.; Volkmer, R.; Muller, S.; Pawson, T.; Gingras, A. C.; Arrowsmith, C. H.; Knapp, S. Histone Recognition and Large-Scale Structural Analysis of the Human Bromodomain Family. *Cell* **2012**, *149*, 214–31.

(28) Martinez, E.; Palhan, V. B.; Tjernberg, A.; Lymar, E. S.; Gamper, A. M.; Kundu, T. K.; Chait, B. T.; Roeder, R. G. Human Staga Complex Is a Chromatin-Acetylating Transcription Coactivator That Interacts with Pre-mRNA Splicing and DNA Damage-Binding Factors in Vivo. *Mol. Cell. Biol.* **2001**, *21*, 6782–95.

(29) Hudson, B. P.; Martinez-Yamout, M. A.; Dyson, H. J.; Wright, P. E. Solution Structure and Acetyl-Lysine Binding Activity of the Gcn5 Bromodomain. *J. Mol. Biol.* **2000**, *304*, 355–70.

(30) Clements, A.; Rojas, J. R.; Trievel, R. C.; Wang, L.; Berger, S. L.; Marmorstein, R. Crystal Structure of the Histone Acetyltransferase Domain of the Human Pcaf Transcriptional Regulator Bound to Coenzyme A. *EMBO J.* **1999**, *18*, 3521–32.

(31) Shi, S.; Lin, J.; Cai, Y.; Yu, J.; Hong, H.; Ji, K.; Downey, J. S.; Lu, X.; Chen, R.; Han, J.; Han, A. Dimeric Structure of P300/Cbp Associated Factor. *BMC Struct. Biol.* **2014**, *14*, 2.

(32) Zeng, L.; Zhang, Q.; Geron-Navarro, G.; Moshkina, N.; Zhou, M. M. Structural Basis of Site-Specific Histone Recognition by the Bromodomains of Human Coactivators Pcaf and Cbp/P300. *Structure* **2008**, *16*, 643–52.

(33) Dhalluin, C.; Carlson, J. E.; Zeng, L.; He, C.; Aggarwal, A. K.; Zhou, M. M. Structure and Ligand of a Histone Acetyltransferase Bromodomain. *Nature* **1999**, *399*, 491–6.

(34) Panne, D.; Maniatis, T.; Harrison, S. C. Crystal Structure of Atf-2/C-Jun and Irf-3 Bound to the Interferon-Beta Enhancer. *EMBO J.* **2004**, *23*, 4384–93.

(35) Laughlin, J. D.; Nwachukwu, J. C.; Figueroa-Losada, M.; Cherry, L.; Nettles, K. W.; LoGrasso, P. V. Structural Mechanisms of Allostery and Autoinhibition in Jnk Family Kinases. *Structure* **2012**, *20*, 2174–84.

(36) Lau, E.; Kluger, H.; Varsano, T.; Lee, K.; Scheffler, I.; Rimm, D. L.; Ideker, T.; Ronai, Z. A. Pkcepsilon Promotes Oncogenic Functions of Atf2 in the Nucleus While Blocking Its Apoptotic Function at Mitochondria. *Cell* **2012**, *148*, 543–55.

(37) Wang, L.; Payton, R.; Dai, W.; Lu, L. Hyperosmotic Stress-Induced Atf-2 Activation through Polo-Like Kinase 3 in Human Corneal Epithelial Cells. *J. Biol. Chem.* **2011**, *286*, 1951–8.

(38) Iioka, T.; Furukawa, K.; Yamaguchi, A.; Shindo, H.; Yamashita, S.; Tsukazaki, T. P300/Cbp Acts as a Coactivator to Cartilage Homeoprotein-1 (Cart1), Paired-Like Homeoprotein, through Acetylation of the Conserved Lysine Residue Adjacent to the Homeodomain. *J. Bone Miner. Res.* **2003**, *18*, 1419–29.

(39) Popp, T. A.; Tallant, C.; Rogers, C.; Fedorov, O.; Brennan, P. E.; Muller, S.; Knapp, S.; Bracher, F. Development of Selective Cbp/

P300 Benzoxazepine Bromodomain Inhibitors. *J. Med. Chem.* **2016**, *59*, 8889–8912.

(40) Crawford, T. D.; Romero, F. A.; Lai, K. W.; Tsui, V.; Taylor, A. M.; de Leon Boenig, G.; Noland, C. L.; Murray, J.; Ly, J.; Choo, E. F.; Hunsaker, T. L.; Chan, E. W.; Merchant, M.; Kharbanda, S.; Gascoigne, K. E.; Kaufman, S.; Beresini, M. H.; Liao, J.; Liu, W.; Chen, K. X.; Chen, Z.; Conery, A. R.; Cote, A.; Jayaram, H.; Jiang, Y.; Kiefer, J. R.; Kleinheinz, T.; Li, Y.; Maher, J.; Pardo, E.; Poy, F.; Spillane, K. L.; Wang, F.; Wang, J.; Wei, X.; Xu, Z.; Xu, Z.; Yen, I.; Zawadzke, L.; Zhu, X.; Bellon, S.; Cummings, R.; Cochran, A. G.; Albrecht, B. K.; Magnuson, S. Discovery of a Potent and Selective in Vivo Probe (Gne-272) for the Bromodomains of Cbp/Ep300. *J. Med. Chem.* **2016**, *59*, 10549–10563.

(41) Pradhan, A.; Liu, Y. The Calcium-Responsive Transactivator Recruits Creb Binding Protein to Nuclear Bodies. *Neurosci. Lett.* **2004**, *370*, 191–5.

(42) Delvecchio, M.; Gaucher, J.; Aguilar-Gurreri, C.; Ortega, E.; Panne, D. Structure of the P300 Catalytic Core and Implications for Chromatin Targeting and Hat Regulation. *Nat. Struct. Mol. Biol.* **2013**, *20*, 1040–6.

(43) Kaczmarek, Z.; Ortega, E.; Goudarzi, A.; Huang, H.; Kim, S.; Marquez, J. A.; Zhao, Y.; Khochbin, S.; Panne, D. Structure of P300 in Complex with Acyl-CoA Variants. *Nat. Chem. Biol.* **2017**, *13*, 21–29.

(44) Curtis, A. M.; Seo, S. B.; Westgate, E. J.; Rudic, R. D.; Smyth, E. M.; Chakravarti, D.; FitzGerald, G. A.; McNamara, P. Histone Acetyltransferase-Dependent Chromatin Remodeling and the Vascular Clock. *J. Biol. Chem.* **2004**, *279*, 7091–7.

(45) Lill, N. L.; Grossman, S. R.; Ginsberg, D.; DeCaprio, J.; Livingston, D. M. Binding and Modulation of P53 by P300/Cbp Coactivators. *Nature* **1997**, *387*, 823–7.

(46) Crawford, T. D.; Tsui, V.; Flynn, E. M.; Wang, S.; Taylor, A. M.; Cote, A.; Audia, J. E.; Beresini, M. H.; Burdick, D. J.; Cummings, R.; Dakin, L. A.; Duplessis, M.; Good, A. C.; Hewitt, M. C.; Huang, H. R.; Jayaram, H.; Kiefer, J. R.; Jiang, Y.; Murray, J.; Nasveschuk, C. G.; Pardo, E.; Poy, F.; Romero, F. A.; Tang, Y.; Wang, J.; Xu, Z.; Zawadzke, L. E.; Zhu, X.; Albrecht, B. K.; Magnuson, S. R.; Bellon, S.; Cochran, A. G. Diving into the Water: Inducible Binding Conformations for Brd4, Taf1(2), Brd9, and Ccr2 Bromodomains. *J. Med. Chem.* **2016**, *59*, 5391–402.

(47) Wang, H.; Curran, E. C.; Hinds, T. R.; Wang, E. H.; Zheng, N. Crystal Structure of a Taf1-Taf7 Complex in Human Transcription Factor Iid Reveals a Promoter Binding Module. *Cell Res.* **2014**, *24*, 1433–44.

(48) Louder, R. K.; He, Y.; Lopez-Blanco, J. R.; Fang, J.; Chacon, P.; Nogales, E. Corrigendum: Structure of Promoter-Bound Tfid and Model of Human Pre-Initiation Complex Assembly. *Nature* **2016**, *536*, 112.

(49) Flynn, E. M.; Huang, O. W.; Poy, F.; Oppikofer, M.; Bellon, S. F.; Tang, Y.; Cochran, A. G. A Subset of Human Bromodomains Recognizes Butyryllysine and Crotonyllysine Histone Peptide Modifications. *Structure* **2015**, *23*, 1801–14.

(50) Li, B.; Samanta, A.; Song, X.; Iacono, K. T.; Bembas, K.; Tao, R.; Basu, S.; Riley, J. L.; Hancock, W. W.; Shen, Y.; Saouaf, S. J.; Greene, M. I. Foxp3 Interactions with Histone Acetyltransferase and Class II Histone Deacetylases Are Required for Repression. *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 4571–6.

(51) Yi, J.; Huang, X.; Yang, Y.; Zhu, W. G.; Gu, W.; Luo, J. Regulation of Histone Acetyltransferase Tip60 Function by Histone Deacetylase 3. *J. Biol. Chem.* **2014**, *289*, 33878–86.

(52) Sun, Y.; Jiang, X.; Chen, S.; Fernandes, N.; Price, B. D. A Role for the Tip60 Histone Acetyltransferase in the Acetylation and Activation of Atm. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 13182–7.

(53) Holbert, M. A.; Sikorski, T.; Carten, J.; Snowflake, D.; Hodawadekar, S.; Marmorstein, R. The Human Monocytic Leukemia Zinc Finger Histone Acetyltransferase Domain Contains DNA-Binding Activity Implicated in Chromatin Targeting. *J. Biol. Chem.* **2007**, *282*, 36603–13.

(54) Xiong, X.; Panchenko, T.; Yang, S.; Zhao, S.; Yan, P.; Zhang, W.; Xie, W.; Li, Y.; Zhao, Y.; Allis, C. D.; Li, H. Selective Recognition

of Histone Crotonylation by Double Phd Fingers of Moz and Dpf2. *Nat. Chem. Biol.* **2016**, *12*, 1111–1118.

(55) Dreveny, I.; Deeves, S. E.; Fulton, J.; Yue, B.; Messmer, M.; Bhattacharya, A.; Collins, H. M.; Heery, D. M. The Double Phd Finger Domain of Moz/Myst3 Induces Alpha-Helical Structure of the Histone H3 Tail to Facilitate Acetylation and Methylation Sampling and Modification. *Nucleic Acids Res.* **2014**, *42*, 822–35.

(56) Ullah, M.; Pelletier, N.; Xiao, L.; Zhao, S. P.; Wang, K.; Degerny, C.; Tahmasebi, S.; Cayrou, C.; Doyon, Y.; Goh, S. L.; Champagne, N.; Cote, J.; Yang, X. J. Molecular Architecture of Quartet Moz/Morf Histone Acetyltransferase Complexes. *Mol. Cell. Biol.* **2008**, *28*, 6828–43.

(57) Ali, M.; Yan, K.; Lalonde, M. E.; Degerny, C.; Rothbart, S. B.; Strahl, B. D.; Cote, J.; Yang, X. J.; Kutateladze, T. G. Tandem Phd Fingers of Mof/Moz Acetyltransferases Display Selectivity for Acetylated Histone H3 and Are Required for the Association with Chromatin. *J. Mol. Biol.* **2012**, *424*, 328–38.

(58) Burke, T. W.; Cook, J. G.; Asano, M.; Nevins, J. R. Replication Factors Mcm2 and Orc1 Interact with the Histone Acetyltransferase Hbo1. *J. Biol. Chem.* **2001**, *276*, 15397–408.

(59) Doyon, Y.; Cayrou, C.; Ullah, M.; Landry, A. J.; Cote, V.; Selleck, W.; Lane, W. S.; Tan, S.; Yang, X. J.; Cote, J. Ing Tumor Suppressor Proteins Are Critical Regulators of Chromatin Acetylation Required for Genome Expression and Perpetuation. *Mol. Cell* **2006**, *21*, 51–64.

(60) Havasi, A.; Haegele, J. A.; Gall, J. M.; Blackmon, S.; Ichimura, T.; Bonegio, R. G.; Panchenko, M. V. Histone Acetyl Transferase (Hat) Hbo1 and Jade1 in Epithelial Cell Regeneration. *Am. J. Pathol.* **2013**, *182*, 152–62.

(61) Siriwardana, N. S.; Meyer, R.; Havasi, A.; Dominguez, I.; Panchenko, M. V. Cell Cycle-Dependent Chromatin Shuttling of Hbo1-Jade1 Histone Acetyl Transferase (Hat) Complex. *Cell Cycle* **2014**, *13*, 1885–901.

(62) Yuan, H.; Rossetto, D.; Mellert, H.; Dang, W.; Srinivasan, M.; Johnson, J.; Hodawadekar, S.; Ding, E. C.; Speicher, K.; Abshiru, N.; Perry, R.; Wu, J.; Yang, C.; Zheng, Y. G.; Speicher, D. W.; Thibault, P.; Verreault, A.; Johnson, F. B.; Berger, S. L.; Sternglanz, R.; McMahon, S. B.; Cote, J.; Marmorstein, R. Myst Protein Acetyltransferase Activity Requires Active Site Lysine Autoacetylation. *EMBO J.* **2012**, *31*, 58–70.

(63) McCullough, C. E.; Song, S.; Shin, M. H.; Johnson, F. B.; Marmorstein, R. Structural and Functional Role of Acetyltransferase Hmof K274 Autoacetylation. *J. Biol. Chem.* **2016**, *291*, 18190–8.

(64) Sun, B.; Guo, S.; Tang, Q.; Li, C.; Zeng, R.; Xiong, Z.; Zhong, C.; Ding, J. Regulation of the Histone Acetyltransferase Activity of Hmof Via Autoacetylation of Lys274. *Cell Res.* **2011**, *21*, 1262–6.

(65) Chatterjee, A.; Seyffert, J.; Lucci, J.; Gilsbach, R.; Preissl, S.; Bottinger, L.; Martensson, C. U.; Panhale, A.; Stehle, T.; Kretz, O.; Sahyoun, A. H.; Avilov, S.; Eimer, S.; Hein, L.; Pfanner, N.; Becker, T.; Akhtar, A. Mof Acetyl Transferase Regulates Transcription and Respiration in Mitochondria. *Cell* **2016**, *167*, 722–738 (e23)..

(66) Cai, Y.; Jin, J.; Swanson, S. K.; Cole, M. D.; Choi, S. H.; Florens, L.; Washburn, M. P.; Conaway, J. W.; Conaway, R. C. Subunit Composition and Substrate Specificity of a Mof-Containing Histone Acetyltransferase Distinct from the Male-Specific Lethal (Msl) Complex. *J. Biol. Chem.* **2010**, *285*, 4268–72.

(67) Creppe, C.; Malinouskaya, L.; Volvert, M. L.; Gillard, M.; Close, P.; Malaise, O.; Laguesse, S.; Cornez, I.; Rahmouni, S.; Ormenese, S.; Belachew, S.; Malgrange, B.; Chapelle, J. P.; Siebenlist, U.; Moonen, G.; Chariot, A.; Nguyen, L. Elongator Controls the Migration and Differentiation of Cortical Neurons through Acetylation of Alpha-Tubulin. *Cell* **2009**, *136*, 551–64.

(68) Pokholok, D. K.; Hannett, N. M.; Young, R. A. Exchange of Rna Polymerase Ii Initiation and Elongation Factors During Gene Expression in Vivo. *Mol. Cell* **2002**, *9*, 799–809.

(69) Pu, J.; Schindler, C.; Jia, R.; Jamik, M.; Backlund, P.; Bonifacino, J. S. Borc, a Multisubunit Complex That Regulates Lysosome Positioning. *Dev. Cell* **2015**, *33*, 176–88.

(70) Scott, I.; Webster, B. R.; Li, J. H.; Sack, M. N. Identification of a Molecular Component of the Mitochondrial Acetyltransferase Programme: A Novel Role for Gcn5l1. *Biochem. J.* **2012**, *443*, 655–61.

(71) Hsieh, Y. J.; Kundu, T. K.; Wang, Z.; Kovelman, R.; Roeder, R. G. The Tfiic90 Subunit of Tfiic Interacts with Multiple Components of the Rna Polymerase Iii Machinery and Contains a Histone-Specific Acetyltransferase Activity. *Mol. Cell. Biol.* **1999**, *19*, 7697–704.

(72) Laganier, J.; Deblais, G.; Giguere, V. Functional Genomics Identifies a Mechanism for Estrogen Activation of the Retinoic Acid Receptor Alpha1 Gene in Breast Cancer Cells. *Mol. Endocrinol.* **2005**, *19*, 1584–92.

(73) Flajollet, S.; Lefebvre, B.; Cudejko, C.; Staels, B.; Lefebvre, P. The Core Component of the Mammalian Swi/Snf Complex Smarcd3/Baf60c Is a Coactivator for the Nuclear Retinoic Acid Receptor. *Mol. Cell. Endocrinol.* **2007**, *270*, 23–32.

(74) Kang, D.; Oh, S.; Ahn, S. M.; Lee, B. H.; Moon, M. H. Proteomic Analysis of Exosomes from Human Neural Stem Cells by Flow Field-Flow Fractionation and Nanoflow Liquid Chromatography-Tandem Mass Spectrometry. *J. Proteome Res.* **2008**, *7*, 3475–80.

(75) Oda, Y.; Ishikawa, M. H.; Hawker, N. P.; Yun, Q. C.; Bikle, D. D. Differential Role of Two Vdr Coactivators, Drip205 and Src-3, in Keratinocyte Proliferation and Differentiation. *J. Steroid Biochem. Mol. Biol.* **2007**, *103*, 776–80.

(76) Atkins, G. B.; Hu, X.; Guenther, M. G.; Rachez, C.; Freedman, L. P.; Lazar, M. A. Coactivators for the Orphan Nuclear Receptor Roralpha. *Mol. Endocrinol.* **1999**, *13*, 1550–7.

(77) Kruse, S. W.; Suino-Powell, K.; Zhou, X. E.; Kretschman, J. E.; Reynolds, R.; Vonnrhein, C.; Xu, Y.; Wang, L.; Tsai, S. Y.; Tsai, M. J.; Xu, H. E. Identification of Coup-Tfii Orphan Nuclear Receptor as a Retinoic Acid-Activated Receptor. *PLoS Biol.* **2008**, *6*, e227.

(78) Wang, Z.; Wu, Y.; Li, L.; Su, X. D. Intermolecular Recognition Revealed by the Complex Structure of Human Clock-Bmal1 Basic Helix-Loop-Helix Domains with E-Box DNA. *Cell Res.* **2013**, *23*, 213–24.

(79) Lee, C.; Etchegaray, J. P.; Cagampang, F. R.; Loudon, A. S.; Reppert, S. M. Posttranslational Mechanisms Regulate the Mammalian Circadian Clock. *Cell* **2001**, *107*, 855–67.

(80) Kwon, I.; Lee, J.; Chang, S. H.; Jung, N. C.; Lee, B. J.; Son, G. H.; Kim, K.; Lee, K. H. Bmal1 Shuttling Controls Transactivation and Degradation of the Clock/Bmal1 Heterodimer. *Mol. Cell. Biol.* **2006**, *26*, 7318–30.

(81) Zhao, W. N.; Malinin, N.; Yang, F. C.; Staknis, D.; Gekakis, N.; Maier, B.; Reischl, S.; Kramer, A.; Weitz, C. J. Cipc Is a Mammalian Circadian Clock Protein without Invertebrate Homologues. *Nat. Cell Biol.* **2007**, *9*, 268–75.

(82) Kondratov, R. V.; Chernov, M. V.; Kondratova, A. A.; Gorbacheva, V. Y.; Gudkov, A. V.; Antoch, M. P. Bmal1-Dependent Circadian Oscillation of Nuclear Clock: Posttranslational Events Induced by Dimerization of Transcriptional Activators of the Mammalian Clock System. *Genes Dev.* **2003**, *17*, 1921–32.

(83) Guelman, S.; Kozuka, K.; Mao, Y.; Pham, V.; Solloway, M. J.; Wang, J.; Wu, J.; Lill, J. R.; Zha, J. The Double-Histone-Acetyltransferase Complex Atac Is Essential for Mammalian Development. *Mol. Cell. Biol.* **2009**, *29*, 1176–88.

(84) Berndsen, C. E.; Denu, J. M. Catalysis and Substrate Selection by Histone/Protein Lysine Acetyltransferases. *Curr. Opin. Struct. Biol.* **2008**, *18*, 682–9.

(85) Jiang, J.; Lu, J.; Lu, D.; Liang, Z.; Li, L.; Ouyang, S.; Kong, X.; Jiang, H.; Shen, B.; Luo, C. Investigation of the Acetylation Mechanism by Gcn5 Histone Acetyltransferase. *PLoS One* **2012**, *7*, e36660.

(86) Berndsen, C. E.; Albaugh, B. N.; Tan, S.; Denu, J. M. Catalytic Mechanism of a Myst Family Histone Acetyltransferase. *Biochemistry* **2007**, *46*, 623–9.

(87) Yan, Y.; Harper, S.; Speicher, D. W.; Marmorstein, R. The Catalytic Mechanism of the Esa1 Histone Acetyltransferase Involves a Self-Acetylated Intermediate. *Nat. Struct. Biol.* **2002**, *9*, 862–9.

(88) Yan, Y.; Barlev, N. A.; Haley, R. H.; Berger, S. L.; Marmorstein, R. Crystal Structure of Yeast Esa1 Suggests a Unified Mechanism for

Catalysis and Substrate Binding by Histone Acetyltransferases. *Mol. Cell* **2000**, *6*, 1195–205.

(89) Liu, X.; Wang, L.; Zhao, K.; Thompson, P. R.; Hwang, Y.; Marmorstein, R.; Cole, P. A. The Structural Basis of Protein Acetylation by the P300/Cbp Transcriptional Coactivator. *Nature* **2008**, *451*, 846–50.

(90) Zhang, X.; Ouyang, S.; Kong, X.; Liang, Z.; Lu, J.; Zhu, K.; Zhao, D.; Zheng, M.; Jiang, H.; Liu, X.; Marmorstein, R.; Luo, C. Catalytic Mechanism of Histone Acetyltransferase P300: From the Proton Transfer to Acetylation Reaction. *J. Phys. Chem. B* **2014**, *118*, 2009–19.

(91) Dancy, B. M.; Cole, P. A. Protein Lysine Acetylation by P300/Cbp. *Chem. Rev.* **2015**, *115*, 2419–52.

(92) Ogryzko, V. V.; Kotani, T.; Zhang, X.; Schiltz, R. L.; Howard, T.; Yang, X. J.; Howard, B. H.; Qin, J.; Nakatani, Y. Histone-Like Tafs within the Pcaf Histone Acetylase Complex. *Cell* **1998**, *94*, 35–44.

(93) Martinez, E.; Kundu, T. K.; Fu, J.; Roeder, R. G. A Human Spt3-Tafii31-Gcn5-L Acetylase Complex Distinct from Transcription Factor Iid. *J. Biol. Chem.* **1998**, *273*, 23781–5.

(94) Demeny, M. A.; Soutoglou, E.; Nagy, Z.; Scheer, E.; Janoshazi, A.; Richardot, M.; Argentini, M.; Kessler, P.; Tora, L. Identification of a Small Taf Complex and Its Role in the Assembly of Taf-Containing Complexes. *PLoS One* **2007**, *2*, e316.

(95) Nagy, Z.; Tora, L. Distinct Gcn5/Pcaf-Containing Complexes Function as Co-Activators and Are Involved in Transcription Factor and Global Histone Acetylation. *Oncogene* **2007**, *26*, 5341–57.

(96) Karanam, B.; Jiang, L.; Wang, L.; Kelleher, N. L.; Cole, P. A. Kinetic and Mass Spectrometric Analysis of P300 Histone Acetyltransferase Domain Autoacetylation. *J. Biol. Chem.* **2006**, *281*, 40292–301.

(97) Thompson, P. R.; Wang, D.; Wang, L.; Fulco, M.; Pediconi, N.; Zhang, D.; An, W.; Ge, Q.; Roeder, R. G.; Wong, J.; Leverro, M.; Sartorelli, V.; Cotter, R. J.; Cole, P. A. Regulation of the P300 Hat Domain Via a Novel Activation Loop. *Nat. Struct. Mol. Biol.* **2004**, *11*, 308–15.

(98) Karukurichi, K. R.; Wang, L.; Uzasci, L.; Manlandro, C. M.; Wang, Q.; Cole, P. A. Analysis of P300/Cbp Histone Acetyltransferase Regulation Using Circular Permutation and Semisynthesis. *J. Am. Chem. Soc.* **2010**, *132*, 1222–3.

(99) Karanam, B.; Wang, L.; Wang, D.; Liu, X.; Marmorstein, R.; Cotter, R.; Cole, P. A. Multiple Roles for Acetylation in the Interaction of P300 Hat with Atf-2. *Biochemistry* **2007**, *46*, 8207–16.

(100) Albaugh, B. N.; Arnold, K. M.; Lee, S.; Denu, J. M. Autoacetylation of the Histone Acetyltransferase Rtt109. *J. Biol. Chem.* **2011**, *286*, 24694–701.

(101) Hirayama, J.; Sahar, S.; Grimaldi, B.; Tamaru, T.; Takamatsu, K.; Nakahata, Y.; Sassone-Corsi, P. Clock-Mediated Acetylation of Bmal1 Controls Circadian Function. *Nature* **2007**, *450*, 1086–90.

(102) Riggs, M. G.; Whittaker, R. G.; Neumann, J. R.; Ingram, V. M. N-Butyrate Causes Histone Modification in Hela and Friend Erythroleukaemia Cells. *Nature* **1977**, *268*, 462–4.

(103) Kijima, M.; Yoshida, M.; Sugita, K.; Horinouchi, S.; Beppu, T. Trapoxin, an Antitumor Cyclic Tetrapeptide, Is an Irreversible Inhibitor of Mammalian Histone Deacetylase. *J. Biol. Chem.* **1993**, *268*, 22429–35.

(104) Yoshida, M.; Horinouchi, S.; Beppu, T. Trichostatin A and Trapoxin: Novel Chemical Probes for the Role of Histone Acetylation in Chromatin Structure and Function. *BioEssays* **1995**, *17*, 423–30.

(105) Taunton, J.; Hassig, C. A.; Schreiber, S. L. A Mammalian Histone Deacetylase Related to the Yeast Transcriptional Regulator Rpd3p. *Science* **1996**, *272*, 408–11.

(106) Yang, W. M.; Yao, Y. L.; Sun, J. M.; Davie, J. R.; Seto, E. Isolation and Characterization of Cdnas Corresponding to an Additional Member of the Human Histone Deacetylase Gene Family. *J. Biol. Chem.* **1997**, *272*, 28001–7.

(107) Zeng, Y.; Tang, C. M.; Yao, Y. L.; Yang, W. M.; Seto, E. Cloning and Characterization of the Mouse Histone Deacetylase-2 Gene. *J. Biol. Chem.* **1998**, *273*, 28921–30.

(108) Emiliani, S.; Fischle, W.; Van Lint, C.; Al-Abed, Y.; Verdin, E. Characterization of a Human Rpd3 Ortholog, Hdac3. *Proc. Natl. Acad. Sci. U. S. A.* **1998**, *95*, 2795–800.

(109) Fischle, W.; Emiliani, S.; Hendzel, M. J.; Nagase, T.; Nomura, N.; Voelter, W.; Verdin, E. A New Family of Human Histone Deacetylases Related to *Saccharomyces Cerevisiae* Hda1p. *J. Biol. Chem.* **1999**, *274*, 11713–20.

(110) Gao, L.; Cueto, M. A.; Asselbergs, F.; Atadja, P. Cloning and Functional Characterization of Hdac11, a Novel Member of the Human Histone Deacetylase Family. *J. Biol. Chem.* **2002**, *277*, 25748–55.

(111) Guardiola, A. R.; Yao, T. P. Molecular Cloning and Characterization of a Novel Histone Deacetylase Hdac10. *J. Biol. Chem.* **2002**, *277*, 3350–6.

(112) Hubbert, C.; Guardiola, A.; Shao, R.; Kawaguchi, Y.; Ito, A.; Nixon, A.; Yoshida, M.; Wang, X. F.; Yao, T. P. Hdac6 Is a Microtubule-Associated Deacetylase. *Nature* **2002**, *417*, 455–8.

(113) Fritze, C. E.; Verschuere, K.; Strich, R.; Easton Esposito, R. Direct Evidence for Sir2 Modulation of Chromatin Structure in Yeast Rdn. *EMBO J.* **1997**, *16*, 6495–509.

(114) Gotta, M.; Strahl-Bolsinger, S.; Renauld, H.; Laroche, T.; Kennedy, B. K.; Grunstein, M.; Gasser, S. M. Localization of Sir2p: The Nucleolus as a Compartment for Silent Information Regulators. *EMBO J.* **1997**, *16*, 3243–55.

(115) Braunstein, M.; Rose, A. B.; Holmes, S. G.; Allis, C. D.; Broach, J. R. Transcriptional Silencing in Yeast Is Associated with Reduced Nucleosome Acetylation. *Genes Dev.* **1993**, *7*, 592–604.

(116) Frye, R. A. Characterization of Five Human Cdnas with Homology to the Yeast Sir2 Gene: Sir2-Like Proteins (Sirtuins) Metabolize Nad and May Have Protein Adp-Ribosyltransferase Activity. *Biochem. Biophys. Res. Commun.* **1999**, *260*, 273–9.

(117) Imai, S.; Armstrong, C. M.; Kaeberlein, M.; Guarente, L. Transcriptional Silencing and Longevity Protein Sir2 Is an Nad-Dependent Histone Deacetylase. *Nature* **2000**, *403*, 795–800.

(118) Frye, R. A. Phylogenetic Classification of Prokaryotic and Eukaryotic Sir2-Like Proteins. *Biochem. Biophys. Res. Commun.* **2000**, *273*, 793–8.

(119) Seto, E.; Yoshida, M. Erasers of Histone Acetylation: The Histone Deacetylase Enzymes. *Cold Spring Harbor Perspect. Biol.* **2014**, *6*, a018713.

(120) Delcuve, G. P.; Khan, D. H.; Davie, J. R. Roles of Histone Deacetylases in Epigenetic Regulation: Emerging Paradigms from Studies with Inhibitors. *Clin. Epigenet.* **2012**, *4*, 5.

(121) Kelly, R. D.; Cowley, S. M. The Physiological Roles of Histone Deacetylase (Hdac) 1 and 2: Complex Co-Stars with Multiple Leading Parts. *Biochem. Soc. Trans.* **2013**, *41*, 741–9.

(122) Watson, P. J.; Fairall, L.; Schwabe, J. W. Nuclear Hormone Receptor Co-Repressors: Structure and Function. *Mol. Cell. Endocrinol.* **2012**, *348*, 440–9.

(123) Millard, C. J.; Watson, P. J.; Celardo, I.; Gordiyenko, Y.; Cowley, S. M.; Robinson, C. V.; Fairall, L.; Schwabe, J. W. Class I Hdacs Share a Common Mechanism of Regulation by Inositol Phosphates. *Mol. Cell* **2013**, *51*, 57–67.

(124) Watson, P. J.; Millard, C. J.; Riley, A. M.; Robertson, N. S.; Wright, L. C.; Godage, H. Y.; Cowley, S. M.; Jamieson, A. G.; Potter, B. V.; Schwabe, J. W. Insights into the Activation Mechanism of Class I Hdac Complexes by Inositol Phosphates. *Nat. Commun.* **2016**, *7*, 11262.

(125) Cai, R. L.; Yan-Neale, Y.; Cueto, M. A.; Xu, H.; Cohen, D. Hdac1, a Histone Deacetylase, Forms a Complex with Hus1 and Rad9, Two G2/M Checkpoint Rad Proteins. *J. Biol. Chem.* **2000**, *275*, 27909–16.

(126) Liu, J.; Xu, D.; Wang, H.; Zhang, Y.; Chang, Y.; Zhang, J.; Wang, J.; Li, C.; Liu, H.; Zhao, M.; Lin, C.; Zhan, Q.; Huang, C.; Qian, H. The Subcellular Distribution and Function of Mta1 in Cancer Differentiation. *Oncotarget* **2014**, *5*, 5153–64.

(127) Bressi, J. C.; Jennings, A. J.; Skene, R.; Wu, Y.; Melkus, R.; De Jong, R.; O'Connell, S.; Grimshaw, C. E.; Navre, M.; Gangloff, A. R. Exploration of the Hdac2 Foot Pocket: Synthesis and Sar of

Substituted N-(2-Aminophenyl)Benzamides. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3142–5.

(128) Lauffer, B. E.; Mintzer, R.; Fong, R.; Mukund, S.; Tam, C.; Zilberleyb, I.; Flicke, B.; Ritscher, A.; Fedorowicz, G.; Vallerio, R.; Ortwine, D. F.; Gunzner, J.; Modrusan, Z.; Neumann, L.; Koth, C. M.; Lupardus, P. J.; Kaminker, J. S.; Heise, C. E.; Steiner, P. Histone Deacetylase (Hdac) Inhibitor Kinetic Rate Constants Correlate with Cellular Histone Acetylation but Not Transcription and Cell Viability. *J. Biol. Chem.* **2013**, *288*, 26926–43.

(129) Chini, C. C.; Escande, C.; Nin, V.; Chini, E. N. Hdac3 Is Negatively Regulated by the Nuclear Protein Dbc1. *J. Biol. Chem.* **2010**, *285*, 40830–7.

(130) Watson, P. J.; Fairall, L.; Santos, G. M.; Schwabe, J. W. Structure of Hdac3 Bound to Co-Repressor and Inositol Tetraphosphate. *Nature* **2012**, *481*, 335–40.

(131) Decroos, C.; Christianson, D. W. Design, Synthesis, and Evaluation of Polyamine Deacetylase Inhibitors, and High-Resolution Crystal Structures of Their Complexes with Acetylpolyamine Amidohydrolase. *Biochemistry* **2015**, *54*, 4692–703.

(132) Decroos, C.; Clausen, D. J.; Haines, B. E.; Wiest, O.; Williams, R. M.; Christianson, D. W. Variable Active Site Loop Conformations Accommodate the Binding of Macrocyclic Largazole Analogues to Hdac8. *Biochemistry* **2015**, *54*, 2126–35.

(133) Somoza, J. R.; Skene, R. J.; Katz, B. A.; Mol, C.; Ho, J. D.; Jennings, A. J.; Luong, C.; Arvai, A.; Buggy, J. J.; Chi, E.; Tang, J.; Sang, B. C.; Verner, E.; Wynands, R.; Leahy, E. M.; Dougan, D. R.; Snell, G.; Navre, M.; Knuth, M. W.; Swanson, R. V.; McRee, D. E.; Tari, L. W. Structural Snapshots of Human Hdac8 Provide Insights into the Class I Histone Deacetylases. *Structure* **2004**, *12*, 1325–34.

(134) Vannini, A.; Volpari, C.; Gallinari, P.; Jones, P.; Mattu, M.; Carfi, A.; De Francesco, R.; Steinkuhler, C.; Di Marco, S. Substrate Binding to Histone Deacetylases as Shown by the Crystal Structure of the Hdac8-Substrate Complex. *EMBO Rep.* **2007**, *8*, 879–84.

(135) Whitehead, L.; Dobler, M. R.; Radetich, B.; Zhu, Y.; Atadja, P. W.; Claiborne, T.; Grob, J. E.; McRiner, A.; Pancost, M. R.; Patnaik, A.; Shao, W.; Shultz, M.; Tichkule, R.; Tommasi, R. A.; Vash, B.; Wang, P.; Stams, T. Human Hdac Isoform Selectivity Achieved Via Exploitation of the Acetate Release Channel with Structurally Unique Small Molecule Inhibitors. *Bioorg. Med. Chem.* **2011**, *19*, 4626–34.

(136) Dowling, D. P.; Gantt, S. L.; Gattis, S. G.; Fierke, C. A.; Christianson, D. W. Structural Studies of Human Histone Deacetylase 8 and Its Site-Specific Variants Complexed with Substrate and Inhibitors. *Biochemistry* **2008**, *47*, 13554–63.

(137) Burli, R. W.; Luckhurst, C. A.; Aziz, O.; Matthews, K. L.; Yates, D.; Lyons, K. A.; Beconi, M.; McAllister, G.; Breccia, P.; Stott, A. J.; Penrose, S. D.; Wall, M.; Lamers, M.; Leonard, P.; Muller, I.; Richardson, C. M.; Jarvis, R.; Stones, L.; Hughes, S.; Wishart, G.; Haughan, A. F.; O'Connell, C.; Mead, T.; McNeil, H.; Vann, J.; Mangette, J.; Maillard, M.; Beaumont, V.; Munoz-Sanjuan, I.; Dominguez, C. Design, Synthesis, and Biological Evaluation of Potent and Selective Class Iia Histone Deacetylase (Hdac) Inhibitors as a Potential Therapy for Huntington's Disease. *J. Med. Chem.* **2013**, *56*, 9934–54.

(138) Bottomley, M. J.; Lo Surdo, P.; Di Giovine, P.; Cirillo, A.; Scarpelli, R.; Ferrigno, F.; Jones, P.; Neddermann, P.; De Francesco, R.; Steinkuhler, C.; Gallinari, P.; Carfi, A. Structural and Functional Analysis of the Human Hdac4 Catalytic Domain Reveals a Regulatory Structural Zinc-Binding Domain. *J. Biol. Chem.* **2008**, *283*, 26694–704.

(139) Liu, Y.; Randall, W. R.; Schneider, M. F. Activity-Dependent and -Independent Nuclear Fluxes of Hdac4 Mediated by Different Kinases in Adult Skeletal Muscle. *J. Cell Biol.* **2005**, *168*, 887–97.

(140) Wang, A. H.; Kruhlak, M. J.; Wu, J.; Bertos, N. R.; Vezmar, M.; Posner, B. I.; Bazett-Jones, D. P.; Yang, X. J. Regulation of Histone Deacetylase 4 by Binding of 14–3-3 Proteins. *Mol. Cell. Biol.* **2000**, *20*, 6904–12.

(141) Cohen, T. J.; Choi, M. C.; Kapur, M.; Lira, V. A.; Yan, Z.; Yao, T. P. Hdac4 Regulates Muscle Fiber Type-Specific Gene Expression Programs. *Mol. Cells* **2015**, *38*, 343–8.

(142) Grozinger, C. M.; Schreiber, S. L. Regulation of Histone Deacetylase 4 and 5 and Transcriptional Activity by 14–3-3-Dependent Cellular Localization. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 7835–40.

(143) McGee, S. L.; van Denderen, B. J.; Howlett, K. F.; Mollica, J.; Schertzer, J. D.; Kemp, B. E.; Hargreaves, M. Amp-Activated Protein Kinase Regulates Glut4 Transcription by Phosphorylating Histone Deacetylase 5. *Diabetes* **2008**, *57*, 860–7.

(144) McKinsey, T. A.; Zhang, C. L.; Lu, J.; Olson, E. N. Signal-Dependent Nuclear Export of a Histone Deacetylase Regulates Muscle Differentiation. *Nature* **2000**, *408*, 106–11.

(145) Dequiedt, F.; Kasler, H.; Fischle, W.; Kiermer, V.; Weinstein, M.; Herndier, B. G.; Verdin, E. Hdac7, a Thymus-Specific Class Ii Histone Deacetylase, Regulates Nur77 Transcription and Tcr-Mediated Apoptosis. *Immunity* **2003**, *18*, 687–98.

(146) Parra, M.; Kasler, H.; McKinsey, T. A.; Olson, E. N.; Verdin, E. Protein Kinase D1 Phosphorylates Hdac7 and Induces Its Nuclear Export after T-Cell Receptor Activation. *J. Biol. Chem.* **2005**, *280*, 13762–70.

(147) Navarro, M. N.; Goebel, J.; Feijoo-Carnero, C.; Morrice, N.; Cantrell, D. A. Phosphoproteomic Analysis Reveals an Intrinsic Pathway for the Regulation of Histone Deacetylase 7 That Controls the Function of Cytotoxic T Lymphocytes. *Nat. Immunol.* **2011**, *12*, 352–61.

(148) Bakin, R. E.; Jung, M. O. Cytoplasmic Sequestration of Hdac7 from Mitochondrial and Nuclear Compartments Upon Initiation of Apoptosis. *J. Biol. Chem.* **2004**, *279*, 51218–25.

(149) Lobera, M.; Madauss, K. P.; Pohlhaus, D. T.; Wright, Q. G.; Trocha, M.; Schmidt, D. R.; Baloglu, E.; Trump, R. P.; Head, M. S.; Hofmann, G. A.; Murray-Thompson, M.; Schwartz, B.; Chakravorty, S.; Wu, Z.; Mander, P. K.; Kruidenier, L.; Reid, R. A.; Burkhart, W.; Turunen, B. J.; Rong, J. X.; Wagner, C.; Moyer, M. B.; Wells, C.; Hong, X.; Moore, J. T.; Williams, J. D.; Soler, D.; Ghosh, S.; Nolan, M. A. Selective Class Iia Histone Deacetylase Inhibition Via a Non-chelating Zinc-Binding Group. *Nat. Chem. Biol.* **2013**, *9*, 319–25.

(150) Schuetz, A.; Min, J.; Allali-Hassani, A.; Schapira, M.; Shuen, M.; Loppnau, P.; Mazitschek, R.; Kwiatkowski, N. P.; Lewis, T. A.; Maglathin, R. L.; McLean, T. H.; Bochkarev, A.; Plotnikov, A. N.; Vedadi, M.; Arrowsmith, C. H. Human Hdac7 Harbors a Class Iia Histone Deacetylase-Specific Zinc Binding Motif and Cryptic Deacetylase Activity. *J. Biol. Chem.* **2008**, *283*, 11355–63.

(151) Zhou, X.; Marks, P. A.; Rifkind, R. A.; Richon, V. M. Cloning and Characterization of a Histone Deacetylase, Hdac9. *Proc. Natl. Acad. Sci. U. S. A.* **2001**, *98*, 10572–7.

(152) Mahlknecht, U.; Schnittger, S.; Will, J.; Cicek, N.; Hoelzer, D. Chromosomal Organization and Localization of the Human Histone Deacetylase 9 Gene (Hdac9). *Biochem. Biophys. Res. Commun.* **2002**, *293*, 182–91.

(153) Hai, Y.; Christianson, D. W. Histone Deacetylase 6 Structure and Molecular Basis of Catalysis and Inhibition. *Nat. Chem. Biol.* **2016**, *12*, 741–7.

(154) Tong, J. J.; Liu, J.; Bertos, N. R.; Yang, X. J. Identification of Hdac10, a Novel Class Ii Human Histone Deacetylase Containing a Leucine-Rich Domain. *Nucleic Acids Res.* **2002**, *30*, 1114–23.

(155) Liu, H.; Hu, Q.; Kaufman, A.; D'Ercole, A. J.; Ye, P. Developmental Expression of Histone Deacetylase 11 in the Murine Brain. *J. Neurosci. Res.* **2008**, *86*, 537–43.

(156) Finnin, M. S.; Donigian, J. R.; Cohen, A.; Richon, V. M.; Rifkind, R. A.; Marks, P. A.; Breslow, R.; Pavletich, N. P. Structures of a Histone Deacetylase Homologue Bound to the Tsa and Saha Inhibitors. *Nature* **1999**, *401*, 188–93.

(157) Newkirk, T. L.; Bowers, A. A.; Williams, R. M. Discovery, Biological Activity, Synthesis and Potential Therapeutic Utility of Naturally Occurring Histone Deacetylase Inhibitors. *Nat. Prod. Rep.* **2009**, *26*, 1293–320.

(158) Katsyuba, E.; Auwerx, J. Modulating Nad(+) Metabolism, from Bench to Bedside. *EMBO J.* **2017**, *36*, 2670–2683.

(159) Laurent, G.; German, N. J.; Saha, A. K.; de Boer, V. C.; Davies, M.; Koves, T. R.; Dephoure, N.; Fischer, F.; Boanca, G.;

- Vaitheeswaran, B.; Lovitch, S. B.; Sharpe, A. H.; Kurland, I. J.; Steegborn, C.; Gygi, S. P.; Muoio, D. M.; Ruderman, N. B.; Haigis, M. C. Sirt4 Coordinates the Balance between Lipid Synthesis and Catabolism by Repressing Malonyl CoA Decarboxylase. *Mol. Cell* **2013**, *50*, 686–98.
- (160) Nakagawa, T.; Lomb, D. J.; Haigis, M. C.; Guarente, L. Sirt5 Deacetylates Carbamoyl Phosphate Synthetase 1 and Regulates the Urea Cycle. *Cell* **2009**, *137*, 560–70.
- (161) North, B. J.; Marshall, B. L.; Borra, M. T.; Denu, J. M.; Verdin, E. The Human Sir2 Ortholog, Sirt2, Is an Nad^{+} -Dependent Tubulin Deacetylase. *Mol. Cell* **2003**, *11*, 437–44.
- (162) Liszt, G.; Ford, E.; Kurtev, M.; Guarente, L. Mouse Sir2 Homolog Sirt6 Is a Nuclear Adp-Ribosyltransferase. *J. Biol. Chem.* **2005**, *280*, 21313–20.
- (163) Ford, E.; Voit, R.; Liszt, G.; Magin, C.; Grummt, I.; Guarente, L. Mammalian Sir2 Homolog Sirt7 Is an Activator of Rna Polymerase I Transcription. *Genes Dev.* **2006**, *20*, 1075–80.
- (164) Michishita, E.; Park, J. Y.; Burneskis, J. M.; Barrett, J. C.; Horikawa, I. Evolutionarily Conserved and Nonconserved Cellular Localizations and Functions of Human Sirt Proteins. *Mol. Biol. Cell* **2005**, *16*, 4623–35.
- (165) Kim, E. J.; Kho, J. H.; Kang, M. R.; Um, S. J. Active Regulator of Sirt1 Cooperates with Sirt1 and Facilitates Suppression of P53 Activity. *Mol. Cell* **2007**, *28*, 277–90.
- (166) Zhao, W.; Kruse, J. P.; Tang, Y.; Jung, S. Y.; Qin, J.; Gu, W. Negative Regulation of the Deacetylase Sirt1 by Dbc1. *Nature* **2008**, *451*, 587–90.
- (167) Kim, J. E.; Chen, J.; Lou, Z. Dbc1 Is a Negative Regulator of Sirt1. *Nature* **2008**, *451*, 583–6.
- (168) Langley, E.; Pearson, M.; Faretta, M.; Bauer, U. M.; Frye, R. A.; Minucci, S.; Pelicci, P. G.; Kouzarides, T. Human Sir2 Deacetylates P53 and Antagonizes Pml/P53-Induced Cellular Senescence. *EMBO J.* **2002**, *21*, 2383–96.
- (169) Vaziri, H.; Dessain, S. K.; Ng Eaton, E.; Imai, S. I.; Frye, R. A.; Pandita, T. K.; Guarente, L.; Weinberg, R. A. Hsir2(Sirt1) Functions as an Nad -Dependent P53 Deacetylase. *Cell* **2001**, *107*, 149–59.
- (170) Nasrin, N.; Kaushik, V. K.; Fortier, E.; Wall, D.; Pearson, K. J.; de Cabo, R.; Bordone, L. Jnk1 Phosphorylates Sirt1 and Promotes Its Enzymatic Activity. *PLoS One* **2009**, *4*, e8414.
- (171) Zhao, X.; Allison, D.; Condon, B.; Zhang, F.; Gheyi, T.; Zhang, A.; Ashok, S.; Russell, M.; MacEwan, I.; Qian, Y.; Jamison, J. A.; Luz, J. G. The 2.5 Å Crystal Structure of the Sirt1 Catalytic Domain Bound to Nicotinamide Adenine Dinucleotide (Nad^{+}) and an Indole (Ex527 Analogue) Reveals a Novel Mechanism of Histone Deacetylase Inhibition. *J. Med. Chem.* **2013**, *56*, 963–9.
- (172) Davenport, A. M.; Huber, F. M.; Hoelz, A. Structural and Functional Analysis of Human Sirt1. *J. Mol. Biol.* **2014**, *426*, 526–41.
- (173) Dai, H.; Case, A. W.; Riera, T. V.; Considine, T.; Lee, J. E.; Hamuro, Y.; Zhao, H.; Jiang, Y.; Sweitzer, S. M.; Pietrak, B.; Schwartz, B.; Blum, C. A.; Disch, J. S.; Caldwell, R.; Szczepankiewicz, B.; Oalmann, C.; Yee Ng, P.; White, B. H.; Casaubon, R.; Narayan, R.; Koppetsch, K.; Bourbonais, F.; Wu, B.; Wang, J.; Qian, D.; Jiang, F.; Mao, C.; Wang, M.; Hu, E.; Wu, J. C.; Perni, R. B.; Vlasuk, G. P.; Ellis, J. L. Crystallographic Structure of a Small Molecule Sirt1 Activator-Enzyme Complex. *Nat. Commun.* **2015**, *6*, 7645.
- (174) Cao, D.; Wang, M.; Qiu, X.; Liu, D.; Jiang, H.; Yang, N.; Xu, R. M. Structural Basis for Allosteric, Substrate-Dependent Stimulation of Sirt1 Activity by Resveratrol. *Genes Dev.* **2015**, *29*, 1316–25.
- (175) Gertz, M.; Fischer, F.; Nguyen, G. T.; Lakshminarasimhan, M.; Schutkowski, M.; Weyand, M.; Steegborn, C. Ex-527 Inhibits Sirtuins by Exploiting Their Unique Nad^{+} -Dependent Deacetylation Mechanism. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, E2772–81.
- (176) Rack, J. G.; VanLinden, M. R.; Lutter, T.; Aasland, R.; Ziegler, M. Constitutive Nuclear Localization of an Alternatively Spliced Sirtuin-2 Isoform. *J. Mol. Biol.* **2014**, *426*, 1677–91.
- (177) Finnin, M. S.; Donigian, J. R.; Pavletich, N. P. Structure of the Histone Deacetylase Sirt2. *Nat. Struct. Biol.* **2001**, *8*, 621–5.
- (178) Moniot, S.; Schutkowski, M.; Steegborn, C. Crystal Structure Analysis of Human Sirt2 and Its Adp-Ribose Complex. *J. Struct. Biol.* **2013**, *182*, 136–43.
- (179) Feldman, J. L.; Dittenhafer-Reed, K. E.; Kudo, N.; Thelen, J. N.; Ito, A.; Yoshida, M.; Denu, J. M. Kinetic and Structural Basis for Acyl-Group Selectivity and Nad^{+} Dependence in Sirtuin-Catalyzed Deacylation. *Biochemistry* **2015**, *54*, 3037–50.
- (180) Rumpf, T.; Gerhardt, S.; Einsle, O.; Jung, M. Seeding for Sirtuins: Microseed Matrix Seeding to Obtain Crystals of Human Sirt3 and Sirt2 Suitable for Soaking. *Acta Crystallogr., Sect. F: Struct. Biol. Commun.* **2015**, *71*, 1498–510.
- (181) Knyphausen, P.; de Boor, S.; Kuhlmann, N.; Scislawski, L.; Extra, A.; Baldus, L.; Schacherl, M.; Baumann, U.; Neundorff, I.; Lammers, M. Insights into Lysine Deacetylation of Natively Folded Substrate Proteins by Sirtuins. *J. Biol. Chem.* **2016**, *291*, 14677–94.
- (182) Schwer, B.; North, B. J.; Frye, R. A.; Ott, M.; Verdin, E. The Human Silent Information Regulator (Sir)2 Homologue Hsirt3 Is a Mitochondrial Nicotinamide Adenine Dinucleotide-Dependent Deacetylase. *J. Cell Biol.* **2002**, *158*, 647–57.
- (183) Jin, L.; Wei, W.; Jiang, Y.; Peng, H.; Cai, J.; Mao, C.; Dai, H.; Choy, W.; Bemis, J. E.; Jirousek, M. R.; Milne, J. C.; Westphal, C. H.; Perni, R. B. Crystal Structures of Human Sirt3 Displaying Substrate-Induced Conformational Changes. *J. Biol. Chem.* **2009**, *284*, 24394–405.
- (184) Gai, W.; Li, H.; Jiang, H.; Long, Y.; Liu, D. Crystal Structures of Sirt3 Reveal That the Alpha2-Alpha3 Loop and Alpha3-Helix Affect the Interaction with Long-Chain Acyl Lysine. *FEBS Lett.* **2016**, *590*, 3019–28.
- (185) Disch, J. S.; Evindar, G.; Chiu, C. H.; Blum, C. A.; Dai, H.; Jin, L.; Schuman, E.; Lind, K. E.; Belyanskaya, S. L.; Deng, J.; Coppo, F.; Aquilani, L.; Graybill, T. L.; Cuzzo, J. W.; Lavu, S.; Mao, C.; Vlasuk, G. P.; Perni, R. B. Discovery of Thieno[3,2-D]Pyrimidine-6-Carboxamides as Potent Inhibitors of Sirt1, Sirt2, and Sirt3. *J. Med. Chem.* **2013**, *56*, 3666–79.
- (186) Szczepankiewicz, B. G.; Dai, H.; Koppetsch, K. J.; Qian, D.; Jiang, F.; Mao, C.; Perni, R. B. Synthesis of Carba- Nad and the Structures of Its Ternary Complexes with Sirt3 and Sirt5. *J. Org. Chem.* **2012**, *77*, 7319–29.
- (187) Gertz, M.; Nguyen, G. T.; Fischer, F.; Suenkel, B.; Schlicker, C.; Franzel, B.; Tomaschewski, J.; Aladini, F.; Becker, C.; Wolters, D.; Steegborn, C. A Molecular Mechanism for Direct Sirtuin Activation by Resveratrol. *PLoS One* **2012**, *7*, e49761.
- (188) Du, J.; Zhou, Y.; Su, X.; Yu, J. J.; Khan, S.; Jiang, H.; Kim, J.; Woo, J.; Kim, J. H.; Choi, B. H.; He, B.; Chen, W.; Zhang, S.; Cerione, R. A.; Auwerx, J.; Hao, Q.; Lin, H. Sirt5 Is a Nad -Dependent Protein Lysine Demethylase and Desuccinylase. *Science* **2011**, *334*, 806–9.
- (189) Matsushita, N.; Yonashiro, R.; Ogata, Y.; Sugiura, A.; Nagashima, S.; Fukuda, T.; Inatome, R.; Yanagi, S. Distinct Regulation of Mitochondrial Localization and Stability of Two Human Sirt5 Isoforms. *Genes Cells* **2011**, *16*, 190–202.
- (190) Schuetz, A.; Min, J.; Antoshenko, T.; Wang, C. L.; Allali-Hassani, A.; Dong, A.; Loppnau, P.; Vedadi, M.; Bochkarev, A.; Sternglanz, R.; Plotnikov, A. N. Structural Basis of Inhibition of the Human Nad^{+} -Dependent Deacetylase Sirt5 by Suramin. *Structure* **2007**, *15*, 377–89.
- (191) Park, J.; Chen, Y.; Tishkoff, D. X.; Peng, C.; Tan, M.; Dai, L.; Xie, Z.; Zhang, Y.; Zwaans, B. M.; Skinner, M. E.; Lombard, D. B.; Zhao, Y. Sirt5-Mediated Lysine Desuccinylation Impacts Diverse Metabolic Pathways. *Mol. Cell* **2013**, *50*, 919–30.
- (192) Michishita, E.; McCord, R. A.; Berber, E.; Kioi, M.; Padilla-Nash, H.; Damian, M.; Cheung, P.; Kusumoto, R.; Kawahara, T. L.; Barrett, J. C.; Chang, H. Y.; Bohr, V. A.; Ried, T.; Gozani, O.; Chua, K. F. Sirt6 Is a Histone H3 Lysine 9 Deacetylase That Modulates Telomeric Chromatin. *Nature* **2008**, *452*, 492–6.
- (193) Kawahara, T. L.; Michishita, E.; Adler, A. S.; Damian, M.; Berber, E.; Lin, M.; McCord, R. A.; Ongaiqui, K. C.; Boxer, L. D.; Chang, H. Y.; Chua, K. F. Sirt6 Links Histone H3 Lysine 9 Deacetylation to Nf-Kappab -Dependent Gene Expression and Organismal Life Span. *Cell* **2009**, *136*, 62–74.

- (194) Pan, P. W.; Feldman, J. L.; Devries, M. K.; Dong, A.; Edwards, A. M.; Denu, J. M. Structure and Biochemical Functions of Sirt6. *J. Biol. Chem.* **2011**, *286*, 14575–87.
- (195) You, W.; Rotili, D.; Li, T. M.; Kambach, C.; Meleshin, M.; Schutkowski, M.; Chua, K. F.; Mai, A.; Steegborn, C. Structural Basis of Sirtuin 6 Activation by Synthetic Small Molecules. *Angew. Chem., Int. Ed.* **2017**, *56*, 1007–1011.
- (196) Kiran, S.; Chatterjee, N.; Singh, S.; Kaul, S. C.; Wadhwa, R.; Ramakrishna, G. Intracellular Distribution of Human Sirt7 and Mapping of the Nuclear/Nucleolar Localization Signal. *FEBS J.* **2013**, *280*, 3451–66.
- (197) Singh, S.; Kumar, P. U.; Thakur, S.; Kiran, S.; Sen, B.; Sharma, S.; Rao, V. V.; Poongothai, A. R.; Ramakrishna, G. Expression/Localization Patterns of Sirtuins (Sirt1, Sirt2, and Sirt7) During Progression of Cervical Cancer and Effects of Sirtuin Inhibitors on Growth of Cervical Cancer Cells. *Tumor Biol.* **2015**, *36*, 6159–71.
- (198) Sauve, A. A.; Schramm, V. L. Sir2 Regulation by Nicotinamide Results from Switching between Base Exchange and Deacetylation Chemistry. *Biochemistry* **2003**, *42*, 9249–56.
- (199) Haigis, M. C.; Mostoslavsky, R.; Haigis, K. M.; Fahie, K.; Christodoulou, D. C.; Murphy, A. J.; Valenzuela, D. M.; Yancopoulos, G. D.; Karow, M.; Blander, G.; Wolberger, C.; Prolla, T. A.; Weindruch, R.; Alt, F. W.; Guarente, L. Sirt4 Inhibits Glutamate Dehydrogenase and Opposes the Effects of Calorie Restriction in Pancreatic Beta Cells. *Cell* **2006**, *126*, 941–54.
- (200) Rardin, M. J.; He, W.; Nishida, Y.; Newman, J. C.; Carrico, C.; Danielson, S. R.; Guo, A.; Gut, P.; Sahu, A. K.; Li, B.; Uppala, R.; Fitch, M.; Riiff, T.; Zhu, L.; Zhou, J.; Mulhern, D.; Stevens, R. D.; Ilkayeva, O. R.; Newgard, C. B.; Jacobson, M. P.; Hellerstein, M.; Goetzman, E. S.; Gibson, B. W.; Verdin, E. Sirt5 Regulates the Mitochondrial Lysine Succinylome and Metabolic Networks. *Cell Metab.* **2013**, *18*, 920–33.
- (201) Hirsch, B. M.; Zheng, W. Sirtuin Mechanism and Inhibition: Explored with N(Epsilon)-Acetyl-Lysine Analogs. *Mol. Biosyst.* **2011**, *7*, 16–28.
- (202) Tamkun, J. W.; Deuring, R.; Scott, M. P.; Kissinger, M.; Pattatucci, A. M.; Kaufman, T. C.; Kennison, J. A. Brahma: A Regulator of Drosophila Homeotic Genes Structurally Related to the Yeast Transcriptional Activator Snf2/Swi2. *Cell* **1992**, *68*, 561–72.
- (203) Haynes, S. R.; Dollard, C.; Winston, F.; Beck, S.; Trowsdale, J.; Dawid, I. B. The Bromodomain: A Conserved Sequence Found in Human, Drosophila and Yeast Proteins. *Nucleic Acids Res.* **1992**, *20*, 2603.
- (204) Fujisawa, T.; Filippakopoulos, P. Functions of Bromodomain-Containing Proteins and Their Roles in Homeostasis and Cancer. *Nat. Rev. Mol. Cell Biol.* **2017**, *18*, 246.
- (205) Sanchez, R.; Zhou, M. M. The Role of Human Bromodomains in Chromatin Biology and Gene Transcription. *Curr. Opin Drug Discov Devel* **2009**, *12*, 659–65.
- (206) Delmore, J. E.; Issa, G. C.; Lemieux, M. E.; Rahl, P. B.; Shi, J.; Jacobs, H. M.; Kastiris, E.; Gilpatrick, T.; Paranal, R. M.; Qi, J.; Chesi, M.; Schinzel, A. C.; McKeown, M. R.; Heffernan, T. P.; Vakoc, C. R.; Bergsagel, P. L.; Ghobrial, I. M.; Richardson, P. G.; Young, R. A.; Hahn, W. C.; Anderson, K. C.; Kung, A. L.; Bradner, J. E.; Mitsiades, C. S. Bet Bromodomain Inhibition as a Therapeutic Strategy to Target C-Myc. *Cell* **2011**, *146*, 904–17.
- (207) Ott, C. J.; Kopp, N.; Bird, L.; Paranal, R. M.; Qi, J.; Bowman, T.; Rodig, S. J.; Kung, A. L.; Bradner, J. E.; Weinstock, D. M. Bet Bromodomain Inhibition Targets Both C-Myc and Il7r in High-Risk Acute Lymphoblastic Leukemia. *Blood* **2012**, *120*, 2843–52.
- (208) Mertz, J. A.; Conery, A. R.; Bryant, B. M.; Sandy, P.; Balasubramanian, S.; Mele, D. A.; Bergeron, L.; Sims, R. J., 3rd Targeting Myc Dependence in Cancer by Inhibiting Bet Bromodomains. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 16669–74.
- (209) Syntichaki, P.; Topalidou, I.; Thireos, G. The Gcn5 Bromodomain Co-Ordinates Nucleosome Remodelling. *Nature* **2000**, *404*, 414–7.
- (210) Cieniewicz, A. M.; Moreland, L.; Ringel, A. E.; Mackintosh, S. G.; Raman, A.; Gilbert, T. M.; Wolberger, C.; Tackett, A. J.; Taverna, S. D. The Bromodomain of Gcn5 Regulates Site Specificity of Lysine Acetylation on Histone H3. *Mol. Cell. Proteomics* **2014**, *13*, 2896–910.
- (211) Li, H.; Fischle, W.; Wang, W.; Duncan, E. M.; Liang, L.; Murakami-Ishibe, S.; Allis, C. D.; Patel, D. J. Structural Basis for Lower Lysine Methylation State-Specific Readout by Mbt Repeats of L3mbtl1 and an Engineered Phd Finger. *Mol. Cell* **2007**, *28*, 677–91.
- (212) Ruthenburg, A. J.; Li, H.; Milne, T. A.; Dewell, S.; McGinty, R. K.; Yuen, M.; Ueberheide, B.; Dou, Y.; Muir, T. W.; Patel, D. J.; Allis, C. D. Recognition of a Mononucleosomal Histone Modification Pattern by Bptf Via Multivalent Interactions. *Cell* **2011**, *145*, 692–706.
- (213) De Semir, D.; Nosrati, M.; Bezrookove, V.; Dar, A. A.; Federman, S.; Bienvenu, G.; Venna, S.; Rangel, J.; Climent, J.; Meyer Tamguney, T. M.; Thummala, S.; Tong, S.; Leong, S. P.; Haqq, C.; Billings, P.; Miller, J. R., 3rd; Sagebiel, R. W.; Debs, R.; Kashani-Sabet, M. Pleckstrin Homology Domain-Interacting Protein (Phip) as a Marker and Mediator of Melanoma Metastasis. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 7067–72.
- (214) Cox, O. B.; Collins, P.; Monteiro, O.; Talon, R.; Bradley, A.; Fedorov, O.; Amin, J.; Marsden, B.; Spencer, J.; von Delft, F.; Brennan, P. A Poised Fragment Library Enables Rapid Synthetic Expansion Yielding the First Reported Inhibitors of Phip(2), an Atypical Bromodomain. *Chem. Sci.* **2016**, *7*, 2322.
- (215) Lubula, M. Y.; Eckenroth, B. E.; Carlson, S.; Poplawski, A.; Chruszcz, M.; Glass, K. C. Structural Insights into Recognition of Acetylated Histone Ligands by the Brpf1 Bromodomain. *FEBS Lett.* **2014**, *588*, 3844–54.
- (216) Bamborough, P.; Barnett, H. A.; Becher, I.; Bird, M. J.; Chung, C. W.; Craggs, P. D.; Demont, E. H.; Diallo, H.; Fallon, D. J.; Gordon, L. J.; Grandi, P.; Hobbs, C. I.; Hooper-Greenhill, E.; Jones, E. J.; Law, R. P.; Le Gall, A.; Lugo, D.; Michon, A. M.; Mitchell, D. J.; Prinjha, R. K.; Sheppard, R. J.; Watson, A. J.; Watson, R. J. Gsk6853, a Chemical Probe for Inhibition of the Brpf1 Bromodomain. *ACS Med. Chem. Lett.* **2016**, *7*, 552–7.
- (217) Zhu, J.; Caflisch, A. Twenty Crystal Structures of Bromodomain and Phd Finger Containing Protein 1 (Brpf1)/Ligand Complexes Reveal Conserved Binding Motifs and Rare Interactions. *J. Med. Chem.* **2016**, *59*, 5555–61.
- (218) Demont, E. H.; Bamborough, P.; Chung, C. W.; Craggs, P. D.; Fallon, D.; Gordon, L. J.; Grandi, P.; Hobbs, C. I.; Hussain, J.; Jones, E. J.; Le Gall, A.; Michon, A. M.; Mitchell, D. J.; Prinjha, R. K.; Roberts, A. D.; Sheppard, R. J.; Watson, R. J. 1,3-Dimethyl Benzimidazolones Are Potent, Selective Inhibitors of the Brpf1 Bromodomain. *ACS Med. Chem. Lett.* **2014**, *5*, 1190–5.
- (219) Unzue, A.; Zhao, H.; Lolli, G.; Dong, J.; Zhu, J.; Zechner, M.; Dolbois, A.; Caflisch, A.; Nevado, C. The “Gatekeeper” Residue Influences the Mode of Binding of Acetyl Indoles to Bromodomains. *J. Med. Chem.* **2016**, *59*, 3087–97.
- (220) Tsai, W. W.; Wang, Z.; Yiu, T. T.; Akdemir, K. C.; Xia, W.; Winter, S.; Tsai, C. Y.; Shi, X.; Schwarzer, D.; Plunkett, W.; Aronow, B.; Gozani, O.; Fischle, W.; Hung, M. C.; Patel, D. J.; Barton, M. C. Trim24 Links a Non-Canonical Histone Signature to Breast Cancer. *Nature* **2010**, *468*, 927–32.
- (221) Palmer, W. S.; Poncet-Montange, G.; Liu, G.; Petrocchi, A.; Reyna, N.; Subramanian, G.; Theroiff, J.; Yau, A.; Kost-Alimova, M.; Bardenhagen, J. P.; Leo, E.; Shepard, H. E.; Tieu, T. N.; Shi, X.; Zhan, Y.; Zhao, S.; Barton, M. C.; Draetta, G.; Toniatti, C.; Jones, P.; Geck Do, M.; Andersen, J. N. Structure-Guided Design of Iacs-9571, a Selective High-Affinity Dual Trim24-Brpf1 Bromodomain Inhibitor. *J. Med. Chem.* **2016**, *59*, 1440–54.
- (222) Seeler, J. S.; Marchio, A.; Losson, R.; Desterro, J. M.; Hay, R. T.; Chambon, P.; Dejean, A. Common Properties of Nuclear Body Protein Sp100 and Tif1alpha Chromatin Factor: Role of Sumo Modification. *Mol. Cell. Biol.* **2001**, *21*, 3314–24.
- (223) Milovic-Holm, K.; Kriehoff, E.; Jensen, K.; Will, H.; Hofmann, T. G. Flash Links the Cd95 Signaling Pathway to the Cell Nucleus and Nuclear Bodies. *EMBO J.* **2007**, *26*, 391–401.
- (224) Moosmann, P.; Georgiev, O.; Le Douarin, B.; Bourquin, J. P.; Schaffner, W. Transcriptional Repression by Ring Finger Protein Tif1

Beta That Interacts with the Krab Repressor Domain of Kox1. *Nucleic Acids Res.* **1996**, *24*, 4859–67.

(225) Ryan, R. F.; Schultz, D. C.; Ayyanathan, K.; Singh, P. B.; Friedman, J. R.; Fredericks, W. J.; Rauscher, F. J., 3rd. Kap-1 Corepressor Protein Interacts and Colocalizes with Heterochromatic and Euchromatic Hp1 Proteins: A Potential Role for Kruppel-Associated Box-Zinc Finger Proteins in Heterochromatin-Mediated Gene Silencing. *Mol. Cell. Biol.* **1999**, *19*, 4366–78.

(226) Iyengar, S.; Ivanov, A. V.; Jin, V. X.; Rauscher, F. J., 3rd; Farnham, P. J. Functional Analysis of Kap1 Genomic Recruitment. *Mol. Cell. Biol.* **2011**, *31*, 1833–47.

(227) Wang, W.; Cai, J.; Wu, Y.; Hu, L.; Chen, Z.; Hu, J.; Chen, Z.; Li, W.; Guo, M.; Huang, Z. Novel Activity of Krab Domain That Functions to Reinforce Nuclear Localization of Krab-Containing Zinc Finger Proteins by Interacting with Kap1. *Cell. Mol. Life Sci.* **2013**, *70*, 3947–58.

(228) Zeng, L.; Yap, K. L.; Ivanov, A. V.; Wang, X.; Mujtaba, S.; Plotnikova, O.; Rauscher, F. J., 3rd; Zhou, M. M. Structural Insights into Human Kap1 Phd Finger-Bromodomain and Its Role in Gene Silencing. *Nat. Struct. Mol. Biol.* **2008**, *15*, 626–33.

(229) Harter, M. R.; Liu, C. D.; Shen, C. L.; Gonzalez-Hurtado, E.; Zhang, Z. M.; Xu, M.; Martinez, E.; Peng, C. W.; Song, J. B69/Zmynd11 C-Terminal Domains Bind and Inhibit Ebna2. *PLoS Pathog.* **2016**, *12*, e1005414.

(230) Wang, J.; Qin, S.; Li, F.; Li, S.; Zhang, W.; Peng, J.; Zhang, Z.; Gong, Q.; Wu, J.; Shi, Y. Crystal Structure of Human B69 Bromo-Znf-Pwpp Reveals Its Role in H3k36me3 Nucleosome Binding. *Cell Res.* **2014**, *24*, 890–3.

(231) Steilmann, C.; Cavalcanti, M. C.; Bartkuhn, M.; Pons-Kuhnemann, J.; Schuppe, H. C.; Weidner, W.; Steger, K.; Paradowska, A. The Interaction of Modified Histones with the Bromodomain Testis-Specific (Brdt) Gene and Its Mrna Level in Sperm of Fertile Donors and Subfertile Men. *Reproduction* **2010**, *140*, 435–43.

(232) Fukazawa, H.; Masumi, A. The Conserved 12-Amino Acid Stretch in the Inter-Bromodomain Region of Bet Family Proteins Functions as a Nuclear Localization Signal. *Biol. Pharm. Bull.* **2012**, *35*, 2064–8.

(233) Matzuk, M. M.; McKeown, M. R.; Filippakopoulos, P.; Li, Q.; Ma, L.; Agno, J. E.; Lemieux, M. E.; Picaud, S.; Yu, R. N.; Qi, J.; Knapp, S.; Bradner, J. E. Small-Molecule Inhibition of Brdt for Male Contraception. *Cell* **2012**, *150*, 673–84.

(234) Martin, M. P.; Olesen, S. H.; Georg, G. I.; Schonbrunn, E. Cyclin-Dependent Kinase Inhibitor Dinaciclib Interacts with the Acetyl-Lysine Recognition Site of Bromodomains. *ACS Chem. Biol.* **2013**, *8*, 2360–5.

(235) Moriniere, J.; Rousseaux, S.; Steuerwald, U.; Soler-Lopez, M.; Curtet, S.; Vitte, A. L.; Govin, J.; Gaucher, J.; Sadoul, K.; Hart, D. J.; Krijgsvel, J.; Khochbin, S.; Muller, C. W.; Petosa, C. Cooperative Binding of Two Acetylation Marks on a Histone Tail by a Single Bromodomain. *Nature* **2009**, *461*, 664–8.

(236) Tanaka, M.; Roberts, J. M.; Seo, H. S.; Souza, A.; Paulk, J.; Scott, T. G.; DeAngelo, S. L.; Dhe-Paganon, S.; Bradner, J. E. Design and Characterization of Bivalent Bet Inhibitors. *Nat. Chem. Biol.* **2016**, *12*, 1089–1096.

(237) Picaud, S.; Leonards, K.; Lambert, J. P.; Dovey, O.; Wells, C.; Fedorov, O.; Monteiro, O.; Fujisawa, T.; Wang, C. Y.; Lingard, H.; Tallant, C.; Nikbin, N.; Guetzoyan, L.; Ingham, R.; Ley, S. V.; Brennan, P.; Muller, S.; Samsonova, A.; Gingras, A. C.; Schwaller, J.; Vassiliou, G.; Knapp, S.; Filippakopoulos, P. Promiscuous Targeting of Bromodomains by Bromosporine Identifies Bet Proteins as Master Regulators of Primary Transcription Response in Leukemia. *Sci. Adv.* **2016**, *2*, e1600760.

(238) Albrecht, B. K.; Gehling, V. S.; Hewitt, M. C.; Vaswani, R. G.; Cote, A.; Leblanc, Y.; Nasveschuk, C. G.; Bellon, S.; Bergeron, L.; Campbell, R.; Cantone, N.; Cooper, M. R.; Cummings, R. T.; Jayaram, H.; Joshi, S.; Mertz, J. A.; Neiss, A.; Normant, E.; O'Meara, M.; Pardo, E.; Poy, F.; Sandy, P.; Supko, J.; Sims, R. J., 3rd; Harmange, J. C.; Taylor, A. M.; Audia, J. E. Identification of a Benzoisoxazoloazepine

Inhibitor (Cpi-0610) of the Bromodomain and Extra-Terminal (Bet) Family as a Candidate for Human Clinical Trials. *J. Med. Chem.* **2016**, *59*, 1330–9.

(239) Ran, X.; Zhao, Y.; Liu, L.; Bai, L.; Yang, C. Y.; Zhou, B.; Meagher, J. L.; Chinnaswamy, K.; Stuckey, J. A.; Wang, S. Structure-Based Design of Gamma-Carboline Analogues as Potent and Specific Bet Bromodomain Inhibitors. *J. Med. Chem.* **2015**, *58*, 4927–39.

(240) Nilsson, L. M.; Green, L. C.; Muralidharan, S. V.; Demir, D.; Welin, M.; Bhadury, J.; Logan, D. T.; Walse, B.; Nilsson, J. A. Cancer Differentiating Agent Hexamethylene Bisacetamide Inhibits Bet Bromodomain Proteins. *Cancer Res.* **2016**, *76*, 2376–83.

(241) Tripathi, S.; Mathur, S.; Deshmukh, P.; Manjula, R.; Padmanabhan, B. A Novel Phenanthridinone Based Scaffold as a Potential Inhibitor of the Brd2 Bromodomain: Crystal Structure of the Complex. *PLoS One* **2016**, *11*, e0156344.

(242) Baud, M. G.; Lin-Shiao, E.; Zengerle, M.; Tallant, C.; Ciulli, A. New Synthetic Routes to Triazolo-Benzodiazepine Analogues: Expanding the Scope of the Bump-and-Hole Approach for Selective Bromo and Extra-Terminal (Bet) Bromodomain Inhibition. *J. Med. Chem.* **2016**, *59*, 1492–500.

(243) Bamborough, P.; Diallo, H.; Goodacre, J. D.; Gordon, L.; Lewis, A.; Seal, J. T.; Wilson, D. M.; Woodrow, M. D.; Chung, C. W. Fragment-Based Discovery of Bromodomain Inhibitors Part 2: Optimization of Phenylisoxazole Sulfonamides. *J. Med. Chem.* **2012**, *55*, 587–96.

(244) Gosmini, R.; Nguyen, V. L.; Toum, J.; Simon, C.; Brusq, J. M.; Krysa, G.; Mirguet, O.; Riou-Eymard, A. M.; Boursier, E. V.; Trotter, L.; Bamborough, P.; Clark, H.; Chung, C. W.; Cutler, L.; Demont, E. H.; Kaur, R.; Lewis, A. J.; Schilling, M. B.; Soden, P. E.; Taylor, S.; Walker, A. L.; Walker, M. D.; Prinjha, R. K.; Nicodeme, E. The Discovery of I-Bet726 (Gsk1324726a), a Potent Tetrahydroquinoline Apo1 up-Regulator and Selective Bet Bromodomain Inhibitor. *J. Med. Chem.* **2014**, *57*, 8111–31.

(245) Jones, M. H.; Hamana, N.; Nezu, J.; Shimane, M. A Novel Family of Bromodomain Genes. *Genomics* **2000**, *63*, 40–5.

(246) Poot, R. A.; Dellaire, G.; Hulsman, B. B.; Grimaldi, M. A.; Corona, D. F.; Becker, P. B.; Bickmore, W. A.; Varga-Weisz, P. D. Huchrac, a Human Iswi Chromatin Remodelling Complex Contains Hacr1 and Two Novel Histone-Fold Proteins. *EMBO J.* **2000**, *19*, 3377–87.

(247) Couture, J. P.; Nolet, G.; Beaulieu, E.; Blouin, R.; Gevry, N. The P400/Brd8 Chromatin Remodeling Complex Promotes Adipogenesis by Incorporating Histone Variant H2a.Z at Ppargamma Target Genes. *Endocrinology* **2012**, *153*, 5796–808.

(248) Bozhenok, L.; Wade, P. A.; Varga-Weisz, P. Wstf-Iswi Chromatin Remodeling Complex Targets Heterochromatic Replication Foci. *EMBO J.* **2002**, *21*, 2231–41.

(249) Poot, R. A.; Bozhenok, L.; van den Berg, D. L.; Steffensen, S.; Ferreira, F.; Grimaldi, M.; Gilbert, N.; Ferreira, J.; Varga-Weisz, P. D. The Williams Syndrome Transcription Factor Interacts with PcnA to Target Chromatin Remodelling by Iswi to Replication Foci. *Nat. Cell Biol.* **2004**, *6*, 1236–44.

(250) Theodoulou, N. H.; Bamborough, P.; Bannister, A. J.; Becher, I.; Bit, R. A.; Che, K. H.; Chung, C. W.; Dittmann, A.; Drewes, G.; Drewry, D. H.; Gordon, L.; Grandi, P.; Leveridge, M.; Lindon, M.; Michon, A. M.; Molnar, J.; Robson, S. C.; Tomkinson, N. C.; Kouzarides, T.; Prinjha, R. K.; Humphreys, P. G. Discovery of I-Brd9, a Selective Cell Active Chemical Probe for Bromodomain Containing Protein 9 Inhibition. *J. Med. Chem.* **2016**, *59*, 1425–39.

(251) Wang, N.; Li, F.; Bao, H.; Li, J.; Wu, J.; Ruan, K. Nmr Fragment Screening Hit Induces Plasticity of Brd7/9 Bromodomains. *ChemBioChem* **2016**, *17*, 1456–63.

(252) Martin, L. J.; Koegl, M.; Bader, G.; Cockcroft, X. L.; Fedorov, O.; Fiegen, D.; Gerstberger, T.; Hofmann, M. H.; Hohmann, A. F.; Kessler, D.; Knapp, S.; Knesl, P.; Kornigg, S.; Muller, S.; Nar, H.; Rogers, C.; Rumpel, K.; Schaaf, O.; Steurer, S.; Tallant, C.; Vakoc, C. R.; Zeeb, M.; Zoephel, A.; Pearson, M.; Boehmelt, G.; McConnell, D. Structure-Based Design of an in Vivo Active Selective Brd9 Inhibitor. *J. Med. Chem.* **2016**, *59*, 4462–75.

- (253) Sun, H.; Liu, J.; Zhang, J.; Shen, W.; Huang, H.; Xu, C.; Dai, H.; Wu, J.; Shi, Y. Solution Structure of Brd7 Bromodomain and Its Interaction with Acetylated Peptides from Histone H3 and H4. *Biochem. Biophys. Res. Commun.* **2007**, *358*, 435–41.
- (254) Yan, K.; You, L.; Degerny, C.; Ghorbani, M.; Liu, X.; Chen, L.; Li, L.; Miao, D.; Yang, X. J. The Chromatin Regulator Brpf3 Preferentially Activates the Hbo1 Acetyltransferase but Is Dispensable for Mouse Development and Survival. *J. Biol. Chem.* **2016**, *291*, 2647–63.
- (255) Feng, Y.; Vlassis, A.; Roques, C.; Lalonde, M. E.; Gonzalez-Aguilera, C.; Lambert, J. P.; Lee, S. B.; Zhao, X.; Alabert, C.; Johansen, J. V.; Paquet, E.; Yang, X. J.; Gingras, A. C.; Cote, J.; Groth, A. Brpf3-Hbo1 Regulates Replication Origin Activation and Histone H3k14 Acetylation. *EMBO J.* **2016**, *35*, 176–92.
- (256) Qin, S.; Jin, L.; Zhang, J.; Liu, L.; Ji, P.; Wu, M.; Wu, J.; Shi, Y. Recognition of Unmodified Histone H3 by the First Phd Finger of Bromodomain-Phd Finger Protein 2 Provides Insights into the Regulation of Histone Acetyltransferases Monocytic Leukemic Zinc-Finger Protein (Moz) and Moz-Related Factor (Morf). *J. Biol. Chem.* **2011**, *286*, 36944–55.
- (257) Alabert, C.; Bukowski-Wills, J. C.; Lee, S. B.; Kustatscher, G.; Nakamura, K.; de Lima Alves, F.; Menard, P.; Mejlvang, J.; Rappsilber, J.; Groth, A. Nascent Chromatin Capture Proteomics Determines Chromatin Dynamics During DNA Replication and Identifies Unknown Fork Components. *Nat. Cell Biol.* **2014**, *16*, 281–93.
- (258) Leachman, N. T.; Brellier, F.; Ferralli, J.; Chiquet-Ehrismann, R.; Tucker, R. P. Atad2b Is a Phylogenetically Conserved Nuclear Protein Expressed During Neuronal Differentiation and Tumorigenesis. *Dev. Growth Differ.* **2010**, *52*, 747–55.
- (259) He, W.; Dorn, D. C.; Erdjument-Bromage, H.; Tempst, P.; Moore, M. A.; Massague, J. Hematopoiesis Controlled by Distinct Tiflgamma and Smad4 Branches of the Tgfbeta Pathway. *Cell* **2006**, *125*, 929–41.
- (260) Dupont, S.; Mamidi, A.; Cordenonsi, M.; Montagner, M.; Zacchigna, L.; Adorno, M.; Martello, G.; Stinchfield, M. J.; Soligo, S.; Morsut, L.; Inui, M.; Moro, S.; Modena, N.; Argenton, F.; Newfeld, S. J.; Piccolo, S. Fam/Uspx, a Deubiquitinating Enzyme Essential for Tgfbeta Signaling, Controls Smad4 Monoubiquitination. *Cell* **2009**, *136*, 123–35.
- (261) Shi, X.; Mihaylova, V. T.; Kuruvilla, L.; Chen, F.; Viviano, S.; Baldassarre, M.; Sperandio, D.; Martinez, R.; Yue, P.; Bates, J. G.; Breckenridge, D. G.; Schlessinger, J.; Turk, B. E.; Calderwood, D. A. Loss of Trim33 Causes Resistance to Bet Bromodomain Inhibitors through Myc- and Tgf-Beta-Dependent Mechanisms. *Proc. Natl. Acad. Sci. U. S. A.* **2016**, *113*, E4558–66.
- (262) Gallouet, A. S.; Ferri, F.; Petit, V.; Parcelier, A.; Lewandowski, D.; Gault, N.; Barroca, V.; Le Gras, S.; Soler, E.; Grosveld, F.; Davidson, I.; Romeo, P. H. Macrophage Production and Activation Are Dependent on Trim33. *Oncotarget* **2017**, *8*, 5111–5122.
- (263) Bloch, D. B.; Nakajima, A.; Gulick, T.; Chiche, J. D.; Orth, D.; de La Monte, S. M.; Bloch, K. D. Sp110 Localizes to the Pml-Sp100 Nuclear Body and May Function as a Nuclear Hormone Receptor Transcriptional Coactivator. *Mol. Cell. Biol.* **2000**, *20*, 6138–46.
- (264) Roscioli, T.; Cliffe, S. T.; Bloch, D. B.; Bell, C. G.; Mullan, G.; Taylor, P. J.; Sarris, M.; Wang, J.; Donald, J. A.; Kirk, E. P.; Ziegler, J. B.; Salzer, U.; McDonald, G. B.; Wong, M.; Lindeman, R.; Buckley, M. F. Mutations in the Gene Encoding the Pml Nuclear Body Protein Sp110 Are Associated with Immunodeficiency and Hepatic Veno-Occlusive Disease. *Nat. Genet.* **2006**, *38*, 620–2.
- (265) Dent, A. L.; Yewdell, J.; Puvion-Dutilleul, F.; Koken, M. H.; de The, H.; Staudt, L. M. Lysp100-Associated Nuclear Domains (Lands): Description of a New Class of Subnuclear Structures and Their Relationship to Pml Nuclear Bodies. *Blood* **1996**, *88*, 1423–6.
- (266) Bloch, D. B.; de la Monte, S. M.; Guigaouri, P.; Filippov, A.; Bloch, K. D. Identification and Characterization of a Leukocyte-Specific Component of the Nuclear Body. *J. Biol. Chem.* **1996**, *271*, 29198–204.
- (267) Saare, M.; Hamarik, U.; Venta, R.; Panarina, M.; Zucchelli, C.; Pihlap, M.; Remm, A.; Kisand, K.; Toots, U.; Moll, K.; Salupere, R.; Musco, G.; Uibo, R.; Peterson, P. Sp140l, an Evolutionarily Recent Member of the Sp100 Family, Is an Autoantigen in Primary Biliary Cirrhosis. *J. Immunol. Res.* **2015**, *2015*, 526518.
- (268) Ferguson, F. M.; Fedorov, O.; Chaikuad, A.; Philpott, M.; Muniz, J. R.; Felletar, I.; von Delft, F.; Heightman, T.; Knapp, S.; Abell, C.; Ciulli, A. Targeting Low-Druggability Bromodomains: Fragment Based Screening and Inhibitor Design against the Baz2b Bromodomain. *J. Med. Chem.* **2013**, *56*, 10183–7.
- (269) Drouin, L.; McGrath, S.; Vidler, L. R.; Chaikuad, A.; Monteiro, O.; Tallant, C.; Philpott, M.; Rogers, C.; Fedorov, O.; Liu, M.; Akhtar, W.; Hayes, A.; Raynaud, F.; Muller, S.; Knapp, S.; Hoelder, S. Structure Enabled Design of Baz2-Icr, a Chemical Probe Targeting the Bromodomains of Baz2a and Baz2b. *J. Med. Chem.* **2015**, *58*, 2553–9.
- (270) Tallant, C.; Valentini, E.; Fedorov, O.; Overvoorde, L.; Ferguson, F. M.; Filippakopoulos, P.; Svergun, D. I.; Knapp, S.; Ciulli, A. Molecular Basis of Histone Tail Recognition by Human Tip5 Phd Finger and Bromodomain of the Chromatin Remodeling Complex Norc. *Structure* **2015**, *23*, 80–92.
- (271) Gu, L.; Frommel, S. C.; Oakes, C. C.; Simon, R.; Grupp, K.; Gerig, C. Y.; Bar, D.; Robinson, M. D.; Baer, C.; Weiss, M.; Gu, Z.; Schapira, M.; Kuner, R.; Sultmann, H.; Provenzano, M.; Cancer, I. P. o. E. O. P.; Yaspo, M. L.; Brors, B.; Korbel, J.; Schlomm, T.; Sauter, G.; Eils, R.; Plass, C.; Santoro, R. Baz2a (Tip5) Is Involved in Epigenetic Alterations in Prostate Cancer and Its Overexpression Predicts Disease Recurrence. *Nat. Genet.* **2015**, *47*, 22–30.
- (272) Hsieh, J. J.; Ernst, P.; Erdjument-Bromage, H.; Tempst, P.; Korsmeyer, S. J. Proteolytic Cleavage of Mll Generates a Complex of N- and C-Terminal Fragments That Confers Protein Stability and Subnuclear Localization. *Mol. Cell. Biol.* **2003**, *23*, 186–94.
- (273) Wang, Z.; Song, J.; Milne, T. A.; Wang, G. G.; Li, H.; Allis, C. D.; Patel, D. J. Pro Isomerization in Mll1 Phd3-Bromo Cassette Connects H3k4me Readout to Cyp33 and Hdac-Mediated Repression. *Cell* **2010**, *141*, 1183–94.
- (274) Fair, K.; Anderson, M.; Bulanova, E.; Mi, H.; Tropshug, M.; Diaz, M. O. Protein Interactions of the Mll Phd Fingers Modulate Mll Target Gene Regulation in Human Cells. *Mol. Cell. Biol.* **2001**, *21*, 3589–97.
- (275) Gue, M.; Sun, J. S.; Boudier, T. Simultaneous Localization of Mll, Af4 and Enl Genes in Interphase Nuclei by 3d-Fish: Mll Translocation Revisited. *BMC Cancer* **2006**, *6*, 20.
- (276) Jacobson, R. H.; Ladurner, A. G.; King, D. S.; Tjian, R. Structure and Function of a Human Tafii250 Double Bromodomain Module. *Science* **2000**, *288*, 1422–5.
- (277) Akai, Y.; Adachi, N.; Hayashi, Y.; Eitoku, M.; Sano, N.; Natsume, R.; Kudo, N.; Tanokura, M.; Senda, T.; Horikoshi, M. Structure of the Histone Chaperone Cia/Asf1-Double Bromodomain Complex Linking Histone Modifications and Site-Specific Histone Eviction. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 8153–8.
- (278) Li, N.; Li, Y.; Lv, J.; Zheng, X.; Wen, H.; Shen, H.; Zhu, G.; Chen, T. Y.; Dhar, S. S.; Kan, P. Y.; Wang, Z.; Shiekhhattar, R.; Shi, X.; Lan, F.; Chen, K.; Li, W.; Li, H.; Lee, M. G. Zmynd8 Reads the Dual Histone Mark H3k4me1-H3k14ac to Antagonize the Expression of Metastasis-Linked Genes. *Mol. Cell* **2016**, *63*, 470–84.
- (279) Savitsky, P.; Krojer, T.; Fujisawa, T.; Lambert, J. P.; Picaud, S.; Wang, C. Y.; Shanle, E. K.; Krajewski, K.; Friedrichsen, H.; Kanapin, A.; Goding, C.; Schapira, M.; Samsonova, A.; Strahl, B. D.; Gingras, A. C.; Filippakopoulos, P. Multivalent Histone and DNA Engagement by a Phd/Brd/Pwpp Triple Reader Cassette Recruits Zmynd8 to K14ac-Rich Chromatin. *Cell Rep.* **2016**, *17*, 2724–2737.
- (280) Gong, F.; Chiu, L. Y.; Cox, B.; Aymard, F.; Clouaire, T.; Leung, J. W.; Cammarata, M.; Perez, M.; Agarwal, P.; Brodbelt, J. S.; Legube, G.; Miller, K. M. Screen Identifies Bromodomain Protein Zmynd8 in Chromatin Recognition of Transcription-Associated DNA Damage That Promotes Homologous Recombination. *Genes Dev.* **2015**, *29*, 197–211.
- (281) Sutherell, C. L.; Tallant, C.; Monteiro, O. P.; Yapp, C.; Fuchs, J. E.; Fedorov, O.; Siejka, P.; Muller, S.; Knapp, S.; Brenton, J. D.; Brennan, P. E.; Ley, S. V. Identification and Development of 2,3-Dihydropyrrolo[1,2-a]Quinazolin-5(1h)-One Inhibitors Targeting

Bromodomains within the Switch/Sucrose Nonfermenting Complex. *J. Med. Chem.* **2016**, *59*, 5095–101.

(282) Pawlowski, R.; Muhl, S. M.; Sulser, T.; Krek, W.; Moch, H.; Schraml, P. Loss of Pbrm1 Expression Is Associated with Renal Cell Carcinoma Progression. *Int. J. Cancer* **2013**, *132*, E11–7.

(283) Sanchez-Tillo, E.; Lazaro, A.; Torrent, R.; Cuatrecasas, M.; Vaquero, E. C.; Castells, A.; Engel, P.; Postigo, A. Zeb1 Represses E-Cadherin and Induces an EMT by Recruiting the Swi/Snf Chromatin-Remodeling Protein Brg1. *Oncogene* **2010**, *29*, 3490–500.

(284) Singh, M.; Popowicz, G. M.; Krajewski, M.; Holak, T. A. Structural Ramification for Acetyl-Lysine Recognition by the Bromodomain of Human Brg1 Protein, a Central ATPase of the Swi/Snf Remodeling Complex. *ChemBioChem* **2007**, *8*, 1308–16.

(285) Lolli, G.; Caflisch, A. High-Throughput Fragment Docking into the Baz2b Bromodomain: Efficient in Silico Screening for X-Ray Crystallography. *ACS Chem. Biol.* **2016**, *11*, 800–7.

(286) Kowenz-Leutz, E.; Pless, O.; Dittmar, G.; Knoblich, M.; Leutz, A. Crosstalk between C/Ebpβ Phosphorylation, Arginine Methylation, and Swi/Snf/Mediator Implies an Indexing Transcription Factor Code. *EMBO J.* **2010**, *29*, 1105–15.

(287) Suh, E. J.; Kabir, M. H.; Kang, U. B.; Lee, J. W.; Yu, J.; Noh, D. Y.; Lee, C. Comparative Profiling of Plasma Proteome from Breast Cancer Patients Reveals Thrombospondin-1 and Brwd3 as Serological Biomarkers. *Exp. Mol. Med.* **2012**, *44*, 36–44.

(288) Zou, J. X.; Revenko, A. S.; Li, L. B.; Gemo, A. T.; Chen, H. W. Ancca, an Estrogen-Regulated AAA+ ATPase Coactivator for Eralpha, Is Required for Coregulator Occupancy and Chromatin Modification. *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 18067–72.

(289) Gonzales, P. A.; Pisitkun, T.; Hoffert, J. D.; Tchapyjnikov, D.; Star, R. A.; Kleta, R.; Wang, N. S.; Knepper, M. A. Large-Scale Proteomics and Phosphoproteomics of Urinary Exosomes. *J. Am. Soc. Nephrol.* **2009**, *20*, 363–79.

(290) Chaikuad, A.; Petros, A. M.; Fedorov, O.; Xu, J.; Knapp, S. Structure-Based Approaches Towards Identification of Fragments for the Low-Druggability Atad2 Bromodomain. *MedChemComm* **2014**, *5*, 1843–1848.

(291) Poncet-Montange, G.; Zhan, Y.; Bardenhagen, J. P.; Petrocchi, A.; Leo, E.; Shi, X.; Lee, G. R. T.; Leonard, P. G.; Geck, D. M. K.; Cardozo, M. G.; Andersen, J. N.; Palmer, W. S.; Jones, P.; Ladbury, J. E. Observed Bromodomain Flexibility Reveals Histone Peptide- and Small Molecule Ligand-Compatible Forms of Atad2. *Biochem. J.* **2015**, *466*, 337–46.

(292) Nakamura, T.; Blechman, J.; Tada, S.; Rozovskaia, T.; Itoyama, T.; Bullrich, F.; Mazo, A.; Croce, C. M.; Geiger, B.; Canaani, E. Huash1 Protein, a Putative Transcription Factor Encoded by a Human Homologue of the Drosophila Ash1 Gene, Localizes to Both Nuclei and Cell-Cell Tight Junctions. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 7284–9.

(293) Gregory, G. D.; Vakoc, C. R.; Rozovskaia, T.; Zheng, X.; Patel, S.; Nakamura, T.; Canaani, E.; Blobel, G. A. Mammalian Ash1 Is a Histone Methyltransferase That Occupies the Transcribed Region of Active Genes. *Mol. Cell. Biol.* **2007**, *27*, 8466–79.

(294) Zeng, L.; Zhang, Q.; Li, S.; Plotnikov, A. N.; Walsh, M. J.; Zhou, M. M. Mechanism and Regulation of Acetylated Histone Binding by the Tandem Phd Finger of Dpf3b. *Nature* **2010**, *466*, 258–62.

(295) Musselman, C. A.; Ramirez, J.; Sims, J. K.; Mansfield, R. E.; Oliver, S. S.; Denu, J. M.; Mackay, J. P.; Wade, P. A.; Hagman, J.; Kutateladze, T. G. Bivalent Recognition of Nucleosomes by the Tandem Phd Fingers of the Chd4 ATPase Is Required for Chd4-Mediated Repression. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 787–92.

(296) Qiu, Y.; Liu, L.; Zhao, C.; Han, C.; Li, F.; Zhang, J.; Wang, Y.; Li, G.; Mei, Y.; Wu, M.; Wu, J.; Shi, Y. Combinatorial Readout of Unmodified H3r2 and Acetylated H3k14 by the Tandem Phd Finger of Moz Reveals a Regulatory Mechanism for Hoxa9 Transcription. *Genes Dev.* **2012**, *26*, 1376–91.

(297) Li, Y.; Wen, H.; Xi, Y.; Tanaka, K.; Wang, H.; Peng, D.; Ren, Y.; Jin, Q.; Dent, S. Y.; Li, W.; Li, H.; Shi, X. A9 Yeats Domain Links

Histone Acetylation to Dot1l-Mediated H3k79 Methylation. *Cell* **2014**, *159*, 558–71.

(298) Luo, Z.; Lin, C.; Shilatifard, A. The Super Elongation Complex (Sec) Family in Transcriptional Control. *Nat. Rev. Mol. Cell Biol.* **2012**, *13*, 543–7.

(299) Wan, L.; Wen, H.; Li, Y.; Lyu, J.; Xi, Y.; Hoshii, T.; Joseph, J. K.; Wang, X.; Loh, Y. E.; Erb, M. A.; Souza, A. L.; Bradner, J. E.; Shen, L.; Li, W.; Li, H.; Allis, C. D.; Armstrong, S. A.; Shi, X. Enl Links Histone Acetylation to Oncogenic Gene Expression in Acute Myeloid Leukaemia. *Nature* **2017**, *543*, 265–269.

(300) Li, Y.; Sabari, B. R.; Panchenko, T.; Wen, H.; Zhao, D.; Guan, H.; Wan, L.; Huang, H.; Tang, Z.; Zhao, Y.; Roeder, R. G.; Shi, X.; Allis, C. D.; Li, H. Molecular Coupling of Histone Crotonylation and Active Transcription by A9 Yeats Domain. *Mol. Cell* **2016**, *62*, 181–93.

(301) Krivtsov, A. V.; Armstrong, S. A. MLL Translocations, Histone Modifications and Leukaemia Stem-Cell Development. *Nat. Rev. Cancer* **2007**, *7*, 823–33.

(302) Wang, D.; Kon, N.; Lasso, G.; Jiang, L.; Leng, W.; Zhu, W. G.; Qin, J.; Honig, B.; Gu, W. Acetylation-Regulated Interaction between P53 and Set Reveals a Widespread Regulatory Mode. *Nature* **2016**, *538*, 118–122.

(303) Gu, W.; Roeder, R. G. Activation of P53 Sequence-Specific DNA Binding by Acetylation of the P53 C-Terminal Domain. *Cell* **1997**, *90*, 595–606.

(304) Kouzarides, T. Acetylation: A Regulatory Modification to Rival Phosphorylation? *EMBO J.* **2000**, *19*, 1176–9.

(305) Kim, S. C.; Sprung, R.; Chen, Y.; Xu, Y.; Ball, H.; Pei, J.; Cheng, T.; Kho, Y.; Xiao, H.; Xiao, L.; Grishin, N. V.; White, M.; Yang, X. J.; Zhao, Y. Substrate and Functional Diversity of Lysine Acetylation Revealed by a Proteomics Survey. *Mol. Cell* **2006**, *23*, 607–18.

(306) Liu, L.; Wang, G.; Song, L.; Lv, B.; Liang, W. Acetylome Analysis Reveals the Involvement of Lysine Acetylation in Biosynthesis of Antibiotics in *Bacillus Amylolyquefaciens*. *Sci. Rep.* **2016**, *6*, 20108.

(307) Kosono, S.; Tamura, M.; Suzuki, S.; Kawamura, Y.; Yoshida, A.; Nishiyama, M.; Yoshida, M. Changes in the Acetylome and Succinylome of *Bacillus Subtilis* in Response to Carbon Source. *PLoS One* **2015**, *10*, e0131169.

(308) Weinert, B. T.; Satpathy, S.; Hansen, B. K.; Lyon, D.; Jensen, L. J.; Choudhary, C. Accurate Quantification of Site-Specific Acetylation Stoichiometry Reveals the Impact of Sirtuin Deacetylase CobB on the *E. Coli* Acetylome. *Mol. Cell. Proteomics* **2017**, *16*, 75910.1074/mcp.M117.067587

(309) Downey, M.; Johnson, J. R.; Davey, N. E.; Newton, B. W.; Johnson, T. L.; Galaang, S.; Seller, C. A.; Krogan, N.; Toczyski, D. P. Acetylome Profiling Reveals Overlap in the Regulation of Diverse Processes by Sirtuins, Gcn5, and Esa1. *Mol. Cell. Proteomics* **2015**, *14*, 162–76.

(310) Konig, A. C.; Hartl, M.; Boersema, P. J.; Mann, M.; Finkemeier, I. The Mitochondrial Lysine Acetylome of Arabidopsis. *Mitochondrion* **2014**, *19* (Pt B), 252–60.

(311) Smith-Hammond, C. L.; Hoyos, E.; Miernyk, J. A. The Pea Seedling Mitochondrial Nepsilon-Lysine Acetylome. *Mitochondrion* **2014**, *19* (Pt B), 154–65.

(312) Smith-Hammond, C. L.; Swatek, K. N.; Johnston, M. L.; Thelen, J. J.; Miernyk, J. A. Initial Description of the Developing Soybean Seed Protein Lys-N(Epsilon)-Acetylome. *J. Proteomics* **2014**, *96*, 56–66.

(313) Xue, B.; Jeffers, V.; Sullivan, W. J.; Uversky, V. N. Protein Intrinsic Disorder in the Acetylome of Intracellular and Extracellular Toxoplasma Gondii. *Mol. Biosyst.* **2013**, *9*, 645–57.

(314) Miao, J.; Lawrence, M.; Jeffers, V.; Zhao, F.; Parker, D.; Ge, Y.; Sullivan, W. J., Jr.; Cui, L. Extensive Lysine Acetylation Occurs in Evolutionarily Conserved Metabolic Pathways and Parasite-Specific Functions During Plasmodium Falciparum Intraerythrocytic Development. *Mol. Microbiol.* **2013**, *89*, 660–75.

(315) Choudhary, C.; Kumar, C.; Gnäd, F.; Nielsen, M. L.; Rehman, M.; Walther, T. C.; Olsen, J. V.; Mann, M. Lysine Acetylation Targets

Protein Complexes and Co-Regulates Major Cellular Functions. *Science* **2009**, *325*, 834–40.

(316) Kim, S. Y.; Sim, C. K.; Zhang, Q.; Tang, H.; Brunmeir, R.; Pan, H.; Karnani, N.; Han, W.; Zhang, K.; Xu, F. An Alternative Strategy for Pan-Acetyl-Lysine Antibody Generation. *PLoS One* **2016**, *11*, e0162528.

(317) Svinkina, T.; Gu, H.; Silva, J. C.; Mertins, P.; Qiao, J.; Fereshtetian, S.; Jaffe, J. D.; Kuhn, E.; Udeshi, N. D.; Carr, S. A. Deep, Quantitative Coverage of the Lysine Acetylome Using Novel Anti-Acetyl-Lysine Antibodies and an Optimized Proteomic Workflow. *Mol. Cell. Proteomics* **2015**, *14*, 2429–40.

(318) Zhu, X.; Liu, X.; Cheng, Z.; Zhu, J.; Xu, L.; Wang, F.; Qi, W.; Yan, J.; Liu, N.; Sun, Z.; Liu, H.; Peng, X.; Hao, Y.; Zheng, N.; Wu, Q. Quantitative Analysis of Global Proteome and Lysine Acetylome Reveal the Differential Impacts of Vpa and Saha on H160 Cells. *Sci. Rep.* **2016**, *6*, 19926.

(319) Rardin, M. J.; Newman, J. C.; Held, J. M.; Cusack, M. P.; Sorensen, D. J.; Li, B.; Schilling, B.; Mooney, S. D.; Kahn, C. R.; Verdin, E.; Gibson, B. W. Label-Free Quantitative Proteomics of the Lysine Acetylome in Mitochondria Identifies Substrates of Sirt3 in Metabolic Pathways. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, 6601–6.

(320) Lundby, A.; Lage, K.; Weinert, B. T.; Bekker-Jensen, D. B.; Secher, A.; Skovgaard, T.; Kelstrup, C. D.; Dmytriiev, A.; Choudhary, C.; Lundby, C.; Olsen, J. V. Proteomic Analysis of Lysine Acetylation Sites in Rat Tissues Reveals Organ Specificity and Subcellular Patterns. *Cell Rep.* **2012**, *2*, 419–31.

(321) Bing, Y.; Zhaobao, W. Effects of Ginkgo Biloba Extract on Free Radical Metabolism of Liver in Mice During Endurance Exercise. *Afr. J. Tradit., Complementary Altern. Med.* **2010**, *7*, 291–5.

(322) Beli, P.; Lukashchuk, N.; Wagner, S. A.; Weinert, B. T.; Olsen, J. V.; Baskcomb, L.; Mann, M.; Jackson, S. P.; Choudhary, C. Proteomic Investigations Reveal a Role for Rna Processing Factor Thrap3 in the DNA Damage Response. *Mol. Cell* **2012**, *46*, 212–25.

(323) Piperno, G.; Fuller, M. T. Monoclonal Antibodies Specific for an Acetylated Form of Alpha-Tubulin Recognize the Antigen in Cilia and Flagella from a Variety of Organisms. *J. Cell Biol.* **1985**, *101*, 2085–94.

(324) Piperno, G.; LeDizet, M.; Chang, X. J. Microtubules Containing Acetylated Alpha-Tubulin in Mammalian Cells in Culture. *J. Cell Biol.* **1987**, *104*, 289–302.

(325) L'Hernault, S. W.; Rosenbaum, J. L. Chlamydomonas Alpha-Tubulin Is Posttranslationally Modified in the Flagella During Flagellar Assembly. *J. Cell Biol.* **1983**, *97*, 258–63.

(326) Fournier, M.; Orpinell, M.; Grauffel, C.; Scheer, E.; Garnier, J. M.; Ye, T.; Chavant, V.; Joint, M.; Esashi, F.; Dejaegere, A.; Gonczy, P.; Tora, L. Kat2a/Kat2b-Targeted Acetylome Reveals a Role for Plk4 Acetylation in Preventing Centrosome Amplification. *Nat. Commun.* **2016**, *7*, 13227.

(327) Masri, S.; Patel, V. R.; Eckel-Mahan, K. L.; Peleg, S.; Forne, I.; Ladurner, A. G.; Baldi, P.; Imhof, A.; Sassone-Corsi, P. Circadian Acetylome Reveals Regulation of Mitochondrial Metabolic Pathways. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, 3339–44.

(328) Simon, G. M.; Cheng, J.; Gordon, J. I. Quantitative Assessment of the Impact of the Gut Microbiota on Lysine Epsilon-Acetylation of Host Proteins Using Gnotobiotic Mice. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 11133–8.

(329) Kim, S. Y.; Sim, C. K.; Tang, H.; Han, W.; Zhang, K.; Xu, F. Acetylome Analysis Identifies Sirt1 Targets in Mrna-Processing and Chromatin-Remodeling in Mouse Liver. *PLoS One* **2015**, *10*, e0140619.

(330) Sol, E. M.; Wagner, S. A.; Weinert, B. T.; Kumar, A.; Kim, H. S.; Deng, C. X.; Choudhary, C. Proteomic Investigations of Lysine Acetylation Identify Diverse Substrates of Mitochondrial Deacetylase Sirt3. *PLoS One* **2012**, *7*, e50545.

(331) Weinert, B. T.; Scholz, C.; Wagner, S. A.; Iesmantavicius, V.; Su, D.; Daniel, J. A.; Choudhary, C. Lysine Succinylation Is a Frequently Occurring Modification in Prokaryotes and Eukaryotes and Extensively Overlaps with Acetylation. *Cell Rep.* **2013**, *4*, 842–51.

(332) Gu, S.; Liu, Y.; Zhu, B.; Ding, K.; Yao, T. P.; Chen, F.; Zhan, L.; Xu, P.; Ehrlich, M.; Liang, T.; Lin, X.; Feng, X. H. Loss of Alpha-Tubulin Acetylation Is Associated with Tgf-Beta-Induced Epithelial-Mesenchymal Transition. *J. Biol. Chem.* **2016**, *291*, 5396–405.

(333) Zhong, T.; Ren, F.; Huang, C. S.; Zou, W. Y.; Yang, Y.; Pan, Y. D.; Sun, B.; Wang, E.; Guo, Q. L. Swimming Exercise Ameliorates Neurocognitive Impairment Induced by Neonatal Exposure to Isoflurane and Enhances Hippocampal Histone Acetylation in Mice. *Neuroscience* **2016**, *316*, 378–88.

(334) Tatham, M. H.; Cole, C.; Scullion, P.; Wilkie, R.; Westwood, N. J.; Stark, L. A.; Hay, R. T. A Proteomic Approach to Analyze the Aspirin-Mediated Lysine Acetylome. *Mol. Cell. Proteomics* **2017**, *16*, 310–326.

(335) Scholz, C.; Weinert, B. T.; Wagner, S. A.; Beli, P.; Miyake, Y.; Qi, J.; Jensen, L. J.; Streicher, W.; McCarthy, A. R.; Westwood, N. J.; Lain, S.; Cox, J.; Matthias, P.; Mann, M.; Bradner, J. E.; Choudhary, C. Acetylation Site Specificities of Lysine Deacetylase Inhibitors in Human Cells. *Nat. Biotechnol.* **2015**, *33*, 415–23.

(336) Liu, X.; Liu, S.; Bode, L.; Liu, C.; Zhang, L.; Wang, X.; Li, D.; Lei, Y.; Peng, X.; Cheng, Z.; Xie, P. Persistent Human Borna Disease Virus Infection Modifies the Acetylome of Human Oligodendroglia Cells Towards Higher Energy and Transporter Levels. *Virology* **2015**, *485*, 58–78.

(337) Robinson, P. J.; Rhodes, D. Structure of the '30 Nm' Chromatin Fibre: A Key Role for the Linker Histone. *Curr. Opin. Struct. Biol.* **2006**, *16*, 336–43.

(338) Tweedie-Cullen, R. Y.; Brunner, A. M.; Grossmann, J.; Mohanna, S.; Sichau, D.; Nanni, P.; Panse, C.; Mansuy, I. M. Identification of Combinatorial Patterns of Post-Translational Modifications on Individual Histones in the Mouse Brain. *PLoS One* **2012**, *7*, e36980.

(339) Ma, X. J.; Wu, J.; Altheim, B. A.; Schultz, M. C.; Grunstein, M. Deposition-Related Sites K5/K12 in Histone H4 Are Not Required for Nucleosome Deposition in Yeast. *Proc. Natl. Acad. Sci. U. S. A.* **1998**, *95*, 6693–8.

(340) Garcia, B. A.; Hake, S. B.; Diaz, R. L.; Kauer, M.; Morris, S. A.; Recht, J.; Shabanowitz, J.; Mishra, N.; Strahl, B. D.; Allis, C. D.; Hunt, D. F. Organismal Differences in Post-Translational Modifications in Histones H3 and H4. *J. Biol. Chem.* **2007**, *282*, 7641–55.

(341) Huang, H.; Lin, S.; Garcia, B. A.; Zhao, Y. Quantitative Proteomic Analysis of Histone Modifications. *Chem. Rev.* **2015**, *115*, 2376–418.

(342) Luger, K.; Mader, A. W.; Richmond, R. K.; Sargent, D. F.; Richmond, T. J. Crystal Structure of the Nucleosome Core Particle at 2.8 Å Resolution. *Nature* **1997**, *389*, 251–60.

(343) Udeshi, N. D.; Compton, P. D.; Shabanowitz, J.; Hunt, D. F.; Rose, K. L. Methods for Analyzing Peptides and Proteins on a Chromatographic Timescale by Electron-Transfer Dissociation Mass Spectrometry. *Nat. Protoc.* **2008**, *3*, 1709–17.

(344) Syka, J. E.; Coon, J. J.; Schroeder, M. J.; Shabanowitz, J.; Hunt, D. F. Peptide and Protein Sequence Analysis by Electron Transfer Dissociation Mass Spectrometry. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 9528–33.

(345) Garcia, B. A.; Thomas, C. E.; Kelleher, N. L.; Mizzen, C. A. Tissue-Specific Expression and Post-Translational Modification of Histone H3 Variants. *J. Proteome Res.* **2008**, *7*, 4225–36.

(346) Garcia, B. A.; Pesavento, J. J.; Mizzen, C. A.; Kelleher, N. L. Pervasive Combinatorial Modification of Histone H3 in Human Cells. *Nat. Methods* **2007**, *4*, 487–9.

(347) Phanstiel, D.; Brumbaugh, J.; Berggren, W. T.; Conard, K.; Feng, X.; Levenstein, M. E.; McAlister, G. C.; Thomson, J. A.; Coon, J. J. Mass Spectrometry Identifies and Quantifies 74 Unique Histone H4 Isoforms in Differentiating Human Embryonic Stem Cells. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 4093–8.

(348) Tan, M.; Luo, H.; Lee, S.; Jin, F.; Yang, J. S.; Montellier, E.; Buchou, T.; Cheng, Z.; Rousseaux, S.; Rajagopal, N.; Lu, Z.; Ye, Z.; Zhu, Q.; Wysocka, J.; Ye, Y.; Khochbin, S.; Ren, B.; Zhao, Y. Identification of 67 Histone Marks and Histone Lysine Crotonylation as a New Type of Histone Modification. *Cell* **2011**, *146*, 1016–28.

- (349) Gatta, R.; Mantovani, R. Nf-Y Affects Histone Acetylation and H2a.Z Deposition in Cell Cycle Promoters. *Epigenetics* **2011**, *6*, 526–34.
- (350) Puerta, C.; Hernandez, F.; Lopez-Alarcon, L.; Palacian, E. Acetylation of Histone H2a.H2b Dimers Facilitates Transcription. *Biochem. Biophys. Res. Commun.* **1995**, *210*, 409–16.
- (351) Zheng, Y.; Thomas, P. M.; Kelleher, N. L. Measurement of Acetylation Turnover at Distinct Lysines in Human Histones Identifies Long-Lived Acetylation Sites. *Nat. Commun.* **2013**, *4*, 2203.
- (352) Poplawski, A.; Hu, K.; Lee, W.; Natesan, S.; Peng, D.; Carlson, S.; Shi, X.; Balaz, S.; Markley, J. L.; Glass, K. C. Molecular Insights into the Recognition of N-Terminal Histone Modifications by the Brpf1 Bromodomain. *J. Mol. Biol.* **2014**, *426*, 1661–76.
- (353) Chen, Y.; Zhao, W.; Yang, J. S.; Cheng, Z.; Luo, H.; Lu, Z.; Tan, M.; Gu, W.; Zhao, Y. Quantitative Acetylome Analysis Reveals the Roles of Sirt1 in Regulating Diverse Substrates and Cellular Pathways. *Mol. Cell. Proteomics* **2012**, *11*, 1048–62.
- (354) Garcia, B. A.; Busby, S. A.; Barber, C. M.; Shabanowitz, J.; Allis, C. D.; Hunt, D. F. Characterization of Phosphorylation Sites on Histone H1 Isoforms by Tandem Mass Spectrometry. *J. Proteome Res.* **2004**, *3*, 1219–27.
- (355) Vaquero, A.; Scher, M.; Lee, D.; Erdjument-Bromage, H.; Tempst, P.; Reinberg, D. Human Sirt1 Interacts with Histone H1 and Promotes Formation of Facultative Heterochromatin. *Mol. Cell* **2004**, *16*, 93–105.
- (356) Wisniewski, J. R.; Zougman, A.; Kruger, S.; Mann, M. Mass Spectrometric Mapping of Linker Histone H1 Variants Reveals Multiple Acetylations, Methylations, and Phosphorylation as Well as Differences between Cell Culture and Tissue. *Mol. Cell. Proteomics* **2007**, *6*, 72–87.
- (357) Singh, S. K.; Maeda, K.; Eid, M. M.; Almoftly, S. A.; Ono, M.; Pham, P.; Goodman, M. F.; Sakaguchi, N. Ganp Regulates Recruitment of Aid to Immunoglobulin Variable Regions by Modulating Transcription and Nucleosome Occupancy. *Nat. Commun.* **2013**, *4*, 1830.
- (358) Kamieniarz, K.; Izzo, A.; Dundr, M.; Tropberger, P.; Ozretic, L.; Kirfel, J.; Scheer, E.; Tropel, P.; Wisniewski, J. R.; Tora, L.; Viville, S.; Buettner, R.; Schneider, R. A Dual Role of Linker Histone H1.4 Lys 34 Acetylation in Transcriptional Activation. *Genes Dev.* **2012**, *26*, 797–802.
- (359) Happel, N.; Doenecke, D. Histone H1 and Its Isoforms: Contribution to Chromatin Structure and Function. *Gene* **2009**, *431*, 1–12.
- (360) Sun, J.; Wei, H. M.; Xu, J.; Chang, J. F.; Yang, Z.; Ren, X.; Lv, W. W.; Liu, L. P.; Pan, L. X.; Wang, X.; Qiao, H. H.; Zhu, B.; Ji, J. Y.; Yan, D.; Xie, T.; Sun, F. L.; Ni, J. Q. Histone H1-Mediated Epigenetic Regulation Controls Germline Stem Cell Self-Renewal by Modulating H4k16 Acetylation. *Nat. Commun.* **2015**, *6*, 8856.
- (361) Bernier, M.; Luo, Y.; Nwokolo, K. C.; Goodwin, M.; Dreher, S. J.; Zhang, P.; Parthun, M. R.; Fondufe-Mittendorf, Y.; Ottesen, J. J.; Poirier, M. G. Linker Histone H1 and H3k56 Acetylation Are Antagonistic Regulators of Nucleosome Dynamics. *Nat. Commun.* **2015**, *6*, 10152.
- (362) Karvonen, U.; Janne, O. A.; Palvimo, J. J. Androgen Receptor Regulates Nuclear Trafficking and Nuclear Domain Residency of Corepressor Hdac7 in a Ligand-Dependent Fashion. *Exp. Cell Res.* **2006**, *312*, 3165–83.
- (363) Fu, M.; Wang, C.; Reutens, A. T.; Wang, J.; Angeletti, R. H.; Siconolfi-Baez, L.; Ogryzko, V.; Avantiaggiati, M. L.; Pestell, R. G. P300 and P300/Camp-Response Element-Binding Protein-Associated Factor Acetylate the Androgen Receptor at Sites Governing Hormone-Dependent Transactivation. *J. Biol. Chem.* **2000**, *275*, 20853–60.
- (364) Gaughan, L.; Logan, I. R.; Cook, S.; Neal, D. E.; Robson, C. N. Tip60 and Histone Deacetylase 1 Regulate Androgen Receptor Activity through Changes to the Acetylation Status of the Receptor. *J. Biol. Chem.* **2002**, *277*, 25904–13.
- (365) Fu, M.; Rao, M.; Wu, K.; Wang, C.; Zhang, X.; Hessien, M.; Yeung, Y. G.; Gioeli, D.; Weber, M. J.; Pestell, R. G. The Androgen Receptor Acetylation Site Regulates Camp and Akt but Not Erk-Induced Activity. *J. Biol. Chem.* **2004**, *279*, 29436–49.
- (366) Sun, Y.; Xu, Y.; Roy, K.; Price, B. D. DNA Damage-Induced Acetylation of Lysine 3016 of Atm Activates Atm Kinase Activity. *Mol. Cell. Biol.* **2007**, *27*, 8502–9.
- (367) Bereshchenko, O. R.; Gu, W.; Dalla-Favera, R. Acetylation Inactivates the Transcriptional Repressor Bcl6. *Nat. Genet.* **2002**, *32*, 606–13.
- (368) Nakahata, Y.; Kaluzova, M.; Grimaldi, B.; Sahar, S.; Hirayama, J.; Chen, D.; Guarente, L. P.; Sassone-Corsi, P. The Nad⁺-Dependent Deacetylase Sirt1 Modulates Clock-Mediated Chromatin Remodeling and Circadian Control. *Cell* **2008**, *134*, 329–40.
- (369) Fu, J.; Yoon, H. G.; Qin, J.; Wong, J. Regulation of P-Tefb Elongation Complex Activity by Cdk9 Acetylation. *Mol. Cell. Biol.* **2007**, *27*, 4641–51.
- (370) Zhang, H.; Park, S. H.; Pantazides, B. G.; Karpiuk, O.; Warren, M. D.; Hardy, C. W.; Duong, D. M.; Park, S. J.; Kim, H. S.; Vassilopoulos, A.; Seyfried, N. T.; Johnsen, S. A.; Gius, D.; Yu, D. S. Sirt2 Directs the Replication Stress Response through Cdk9 Deacetylation. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, 13546–51.
- (371) Sabo, A.; Lusic, M.; Cereseto, A.; Giacca, M. Acetylation of Conserved Lysines in the Catalytic Core of Cyclin-Dependent Kinase 9 Inhibits Kinase Activity and Regulates Transcription. *Mol. Cell. Biol.* **2008**, *28*, 2201–12.
- (372) Jang, M. K.; Mochizuki, K.; Zhou, M.; Jeong, H. S.; Brady, J. N.; Ozato, K. The Bromodomain Protein Brd4 Is a Positive Regulatory Component of P-Tefb and Stimulates Rna Polymerase Ii-Dependent Transcription. *Mol. Cell* **2005**, *19*, 523–34.
- (373) Bricambert, J.; Miranda, J.; Benhamed, F.; Girard, J.; Postic, C.; Dentin, R. Salt-Inducible Kinase 2 Links Transcriptional Coactivator P300 Phosphorylation to the Prevention of Chrebp-Dependent Hepatic Steatosis in Mice. *J. Clin. Invest.* **2010**, *120*, 4316–31.
- (374) Marmier, S.; Dentin, R.; Daujat-Chavanieu, M.; Guillou, H.; Bertrand-Michel, J.; Gerbal-Chaloin, S.; Girard, J.; Lotersztajn, S.; Postic, C. Novel Role for Carbohydrate Responsive Element Binding Protein in the Control of Ethanol Metabolism and Susceptibility to Binge Drinking. *Hepatology* **2015**, *62*, 1086–100.
- (375) Lu, Q.; Hutchins, A. E.; Doyle, C. M.; Lundblad, J. R.; Kwok, R. P. Acetylation of Camp-Responsive Element-Binding Protein (Creb) by Creb-Binding Protein Enhances Creb-Dependent Transcription. *J. Biol. Chem.* **2003**, *278*, 15727–34.
- (376) Paz, J. C.; Park, S.; Phillips, N.; Matsumura, S.; Tsai, W. W.; Kasper, L.; Brindle, P. K.; Zhang, G.; Zhou, M. M.; Wright, P. E.; Montminy, M. Combinatorial Regulation of a Signal-Dependent Activator by Phosphorylation and Acetylation. *Proc. Natl. Acad. Sci. U. S. A.* **2014**, *111*, 17116–21.
- (377) Liu, Y.; Dentin, R.; Chen, D.; Hedrick, S.; Ravnksjaer, K.; Schenk, S.; Milne, J.; Meyers, D. J.; Cole, P.; Yates, J., 3rd; Olefsky, J.; Guarente, L.; Montminy, M. A Fasting Inducible Switch Modulates Gluconeogenesis Via Activator/Coactivator Exchange. *Nature* **2008**, *456*, 269–73.
- (378) Cho, S.; Schroeder, S.; Kaehlcke, K.; Kwon, H. S.; Pedal, A.; Herker, E.; Schnoelzer, M.; Ott, M. Acetylation of Cyclin T1 Regulates the Equilibrium between Active and Inactive P-Tefb in Cells. *EMBO J.* **2009**, *28*, 1407–17.
- (379) Safronova, O. S.; Nakahama, K.; Morita, I. Acute Hypoxia Affects P-Tefb through Hdac3 and Hexim1-Dependent Mechanism to Promote Gene-Specific Transcriptional Repression. *Nucleic Acids Res.* **2014**, *42*, 8954–69.
- (380) Wang, C.; Rauscher, F. J., 3rd; Cress, W. D.; Chen, J. Regulation of E2f1 Function by the Nuclear Corepressor Kap1. *J. Biol. Chem.* **2007**, *282*, 29902–9.
- (381) Martinez-Balbas, M. A.; Bauer, U. M.; Nielsen, S. J.; Brehm, A.; Kouzarides, T. Regulation of E2f1 Activity by Acetylation. *EMBO J.* **2000**, *19*, 662–71.
- (382) Zhao, Y.; Tan, J.; Zhuang, L.; Jiang, X.; Liu, E. T.; Yu, Q. Inhibitors of Histone Deacetylases Target the Rb-E2f1 Pathway for Apoptosis Induction through Activation of Proapoptotic Protein Bim. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 16090–5.

- (383) Zhang, W.; Bieker, J. J. Acetylation and Modulation of Erythroid Kruppel-Like Factor (Eklf) Activity by Interaction with Histone Acetyltransferases. *Proc. Natl. Acad. Sci. U. S. A.* **1998**, *95*, 9855–60.
- (384) Chen, X.; Bieker, J. J. Unanticipated Repression Function Linked to Erythroid Kruppel-Like Factor. *Mol. Cell. Biol.* **2001**, *21*, 3118–25.
- (385) Kim, M. Y.; Woo, E. M.; Chong, Y. T.; Homenko, D. R.; Kraus, W. L. Acetylation of Estrogen Receptor Alpha by P300 at Lysines 266 and 268 Enhances the Deoxyribonucleic Acid Binding and Transactivation Activities of the Receptor. *Mol. Endocrinol.* **2006**, *20*, 1479–93.
- (386) Ma, Y.; Fan, S.; Hu, C.; Meng, Q.; Fuqua, S. A.; Pestell, R. G.; Tomita, Y. A.; Rosen, E. M. Brcal Regulates Acetylation and Ubiquitination of Estrogen Receptor-Alpha. *Mol. Endocrinol.* **2010**, *24*, 76–90.
- (387) Wang, C.; Fu, M.; Angeletti, R. H.; Siconolfi-Baez, L.; Reuters, A. T.; Albanese, C.; Lisanti, M. P.; Katzenellenbogen, B. S.; Kato, S.; Hopp, T.; Fuqua, S. A.; Lopez, G. N.; Kushner, P. J.; Pestell, R. G. Direct Acetylation of the Estrogen Receptor Alpha Hinge Region by P300 Regulates Transactivation and Hormone Sensitivity. *J. Biol. Chem.* **2001**, *276*, 18375–83.
- (388) Zhao, Y.; Yang, J.; Liao, W.; Liu, X.; Zhang, H.; Wang, S.; Wang, D.; Feng, J.; Yu, L.; Zhu, W. G. Cytosolic Foxo1 Is Essential for the Induction of Autophagy and Tumour Suppressor Activity. *Nat. Cell Biol.* **2010**, *12*, 665–75.
- (389) Jing, E.; Gesta, S.; Kahn, C. R. Sirt2 Regulates Adipocyte Differentiation through Foxo1 Acetylation/Deacetylation. *Cell Metab.* **2007**, *6*, 105–14.
- (390) Hariharan, N.; Maejima, Y.; Nakae, J.; Paik, J.; Depinho, R. A.; Sadoshima, J. Deacetylation of Foxo by Sirt1 Plays an Essential Role in Mediating Starvation-Induced Autophagy in Cardiac Myocytes. *Circ. Res.* **2010**, *107*, 1470–82.
- (391) Tsai, K. L.; Sun, Y. J.; Huang, C. Y.; Yang, J. Y.; Hung, M. C.; Hsiao, C. D. Crystal Structure of the Human Foxo3a-Dbp/DNA Complex Suggests the Effects of Post-Translational Modification. *Nucleic Acids Res.* **2007**, *35*, 6984–94.
- (392) Frescas, D.; Valenti, L.; Accili, D. Nuclear Trapping of the Forkhead Transcription Factor Foxo1 Via Sirt-Dependent Deacetylation Promotes Expression of Glucogenic Genes. *J. Biol. Chem.* **2005**, *280*, 20589–95.
- (393) Dansen, T. B.; Smits, L. M.; van Triest, M. H.; de Keizer, P. L.; van Leenen, D.; Koerkamp, M. G.; Szybowska, A.; Meppelink, A.; Brenkman, A. B.; Yodoi, J.; Holstege, F. C.; Burgering, B. M. Redox-Sensitive Cysteines Bridge P300/Cbp-Mediated Acetylation and Foxo4 Activity. *Nat. Chem. Biol.* **2009**, *5*, 664–72.
- (394) Kwon, H. S.; Lim, H. W.; Wu, J.; Schnolzer, M.; Verdin, E.; Ott, M. Three Novel Acetylation Sites in the Foxp3 Transcription Factor Regulate the Suppressive Activity of Regulatory T Cells. *J. Immunol.* **2012**, *188*, 2712–21.
- (395) Liu, Y.; Wang, L.; Predina, J.; Han, R.; Beier, U. H.; Wang, L. C.; Kapoor, V.; Bhatti, T. R.; Akimova, T.; Singhal, S.; Brindle, P. K.; Cole, P. A.; Albelda, S. M.; Hancock, W. W. Inhibition of P300 Impairs Foxp3(+) T Regulatory Cell Function and Promotes Antitumor Immunity. *Nat. Med.* **2013**, *19*, 1173–7.
- (396) Xiao, Y.; Nagai, Y.; Deng, G.; Ohtani, T.; Zhu, Z.; Zhou, Z.; Zhang, H.; Ji, M. Q.; Lough, J. W.; Samanta, A.; Hancock, W. W.; Greene, M. I. Dynamic Interactions between Tip60 and P300 Regulate Foxp3 Function through a Structural Switch Defined by a Single Lysine on Tip60. *Cell Rep.* **2014**, *7*, 1471–80.
- (397) Kemper, J. K.; Xiao, Z.; Ponugoti, B.; Miao, J.; Fang, S.; Kanamaluru, D.; Tsang, S.; Wu, S. Y.; Chiang, C. M.; Veenstra, T. D. Fxr Acetylation Is Normally Dynamically Regulated by P300 and Sirt1 but Constitutively Elevated in Metabolic Disease States. *Cell Metab.* **2009**, *10*, 392–404.
- (398) Kim, D. H.; Xiao, Z.; Kwon, S.; Sun, X.; Ryerson, D.; Tkac, D.; Ma, P.; Wu, S. Y.; Chiang, C. M.; Zhou, E.; Xu, H. E.; Palvimo, J. J.; Chen, L. F.; Kemper, B.; Kemper, J. K. A Dysregulated Acetyl/Sumo Switch of Fxr Promotes Hepatic Inflammation in Obesity. *EMBO J.* **2015**, *34*, 184–99.
- (399) Ryu, D.; Jo, Y. S.; Lo Sasso, G.; Stein, S.; Zhang, H.; Perino, A.; Lee, J. U.; Zeviani, M.; Romand, R.; Hottiger, M. O.; Schoonjans, K.; Auwerx, J. A Sirt7-Dependent Acetylation Switch of Gabpβ Controls Mitochondrial Function. *Cell Metab.* **2014**, *20*, 856–69.
- (400) Boyes, J.; Byfield, P.; Nakatani, Y.; Ogryzko, V. Regulation of Activity of the Transcription Factor Gata-1 by Acetylation. *Nature* **1998**, *396*, 594–8.
- (401) Hung, H. L.; Lau, J.; Kim, A. Y.; Weiss, M. J.; Blobel, G. A. Creb-Binding Protein Acetylates Hematopoietic Transcription Factor Gata-1 at Functionally Important Sites. *Mol. Cell. Biol.* **1999**, *19*, 3496–505.
- (402) Watamoto, K.; Towatari, M.; Ozawa, Y.; Miyata, Y.; Okamoto, M.; Abe, A.; Naoe, T.; Saito, H. Altered Interaction of Hdac5 with Gata-1 During Mel Cell Differentiation. *Oncogene* **2003**, *22*, 9176–84.
- (403) Delehanty, L. L.; Bullock, G. C.; Goldfarb, A. N. Protein Kinase D-Hdac5 Signaling Regulates Erythropoiesis and Contributes to Erythropoietin Cross-Talk with Gata1. *Blood* **2012**, *120*, 4219–28.
- (404) Geng, H.; Liu, Q.; Xue, C.; David, L. L.; Beer, T. M.; Thomas, G. V.; Dai, M. S.; Qian, D. Z. Hif1α Protein Stability Is Increased by Acetylation at Lysine 709. *J. Biol. Chem.* **2012**, *287*, 35496–505.
- (405) Geng, H.; Harvey, C. T.; Pittsenger, J.; Liu, Q.; Beer, T. M.; Xue, C.; Qian, D. Z. Hdac4 Protein Regulates Hif1α Protein Lysine Acetylation and Cancer Cell Response to Hypoxia. *J. Biol. Chem.* **2011**, *286*, 38095–102.
- (406) Lim, J. H.; Lee, Y. M.; Chun, Y. S.; Chen, J.; Kim, J. E.; Park, J. W. Sirtuin 1 Modulates Cellular Responses to Hypoxia by Deacetylating Hypoxia-Inducible Factor 1α. *Mol. Cell* **2010**, *38*, 864–78.
- (407) Xenaki, G.; Ontikatz, T.; Rajendran, R.; Stratford, I. J.; Dive, C.; Krstic-Demonacos, M.; Demonacos, C. Pcaf Is an Hif-1α Cofactor That Regulates P53 Transcriptional Activity in Hypoxia. *Oncogene* **2008**, *27*, 5785–96.
- (408) Seo, K. S.; Park, J. H.; Heo, J. Y.; Jing, K.; Han, J.; Min, K. N.; Kim, C.; Koh, G. Y.; Lim, K.; Kang, G. Y.; Uee Lee, J.; Yim, Y. H.; Shong, M.; Kwak, T. H.; Kweon, G. R. Sirt2 Regulates Tumour Hypoxia Response by Promoting Hif-1α Hydroxylation. *Oncogene* **2015**, *34*, 1354–62.
- (409) Chen, R.; Xu, M.; Hogg, R. T.; Li, J.; Little, B.; Gerard, R. D.; Garcia, J. A. The Acetylase/Deacetylase Couple Creb-Binding Protein/Sirtuin 1 Controls Hypoxia-Inducible Factor 2 Signaling. *J. Biol. Chem.* **2012**, *287*, 30800–11.
- (410) Dioum, E. M.; Chen, R.; Alexander, M. S.; Zhang, Q.; Hogg, R. T.; Gerard, R. D.; Garcia, J. A. Regulation of Hypoxia-Inducible Factor 2α Signaling by the Stress-Responsive Deacetylase Sirtuin 1. *Science* **2009**, *324*, 1289–93.
- (411) Herrera, J. E.; Sakaguchi, K.; Bergel, M.; Trieschmann, L.; Nakatani, Y.; Bustin, M. Specific Acetylation of Chromosomal Protein Hmg-17 by Pcaf Alters Its Interaction with Nucleosomes. *Mol. Cell. Biol.* **1999**, *19*, 3466–73.
- (412) Tang, X.; Gao, J. S.; Guan, Y. J.; McLane, K. E.; Yuan, Z. L.; Ramratnam, B.; Chin, Y. E. Acetylation-Dependent Signal Transduction for Type I Interferon Receptor. *Cell* **2007**, *131*, 93–105.
- (413) Zhang, K.; Faiola, F.; Martinez, E. Six Lysine Residues on C-Myc Are Direct Substrates for Acetylation by P300. *Biochem. Biophys. Res. Commun.* **2005**, *336*, 274–80.
- (414) Patel, J. H.; Du, Y.; Ard, P. G.; Phillips, C.; Carella, B.; Chen, C. J.; Rakowski, C.; Chatterjee, C.; Lieberman, P. M.; Lane, W. S.; Blobel, G. A.; McMahon, S. B. The C-Myc Oncoprotein Is a Substrate of the Acetyltransferases Hgc5/Pcaf and Tip60. *Mol. Cell. Biol.* **2004**, *24*, 10826–34.
- (415) Faiola, F.; Liu, X.; Lo, S.; Pan, S.; Zhang, K.; Lyman, E.; Farina, A.; Martinez, E. Dual Regulation of C-Myc by P300 Via Acetylation-Dependent Control of Myc Protein Turnover and Coactivation of Myc-Induced Transcription. *Mol. Cell. Biol.* **2005**, *25*, 10220–34.
- (416) Liu, P. Y.; Xu, N.; Malyukova, A.; Scarlett, C. J.; Sun, Y. T.; Zhang, X. D.; Ling, D.; Su, S. P.; Nelson, C.; Chang, D. K.; Koach, J.; Tee, A. E.; Haber, M.; Norris, M. D.; Toon, C.; Rooman, I.; Xue, C.;

Cheung, B. B.; Kumar, S.; Marshall, G. M.; Biankin, A. V.; Liu, T. The Histone Deacetylase Sirt2 Stabilizes Myc Oncoproteins. *Cell Death Differ.* **2013**, *20*, 503–14.

(417) Guarani, V.; Deflorian, G.; Franco, C. A.; Kruger, M.; Phng, L. K.; Bentley, K.; Toussaint, L.; Dequiedt, F.; Mostoslavsky, R.; Schmidt, M. H.; Zimmermann, B.; Brandes, R. P.; Mione, M.; Westphal, C. H.; Braun, T.; Zeiher, A. M.; Gerhardt, H.; Dimmeler, S.; Potente, M. Acetylation-Dependent Regulation of Endothelial Notch Signalling by the Sirt1 Deacetylase. *Nature* **2011**, *473*, 234–8.

(418) Rokudai, S.; Laptenko, O.; Arnal, S. M.; Taya, Y.; Kitabayashi, I.; Prives, C. Moz Increases P53 Acetylation and Premature Senescence through Its Complex Formation with Pml. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, 3895–900.

(419) Wang, Y. H.; Tsay, Y. G.; Tan, B. C.; Lo, W. Y.; Lee, S. C. Identification and Characterization of a Novel P300-Mediated P53 Acetylation Site, Lysine 305. *J. Biol. Chem.* **2003**, *278*, 25568–76.

(420) Drost, J.; Mantovani, F.; Tocco, F.; Elkon, R.; Comel, A.; Holstege, H.; Kerkhoven, R.; Jonkers, J.; Voorhoeve, P. M.; Agami, R.; Del Sal, G. Brd7 Is a Candidate Tumour Suppressor Gene Required for P53 Function. *Nat. Cell Biol.* **2010**, *12*, 380–9.

(421) Abraham, J.; Kelly, J.; Thibault, P.; Benchimol, S. Post-Translational Modification of P53 Protein in Response to Ionizing Radiation Analyzed by Mass Spectrometry. *J. Mol. Biol.* **2000**, *295*, 853–64.

(422) Hofmann, T. G.; Müller, A.; Sirma, H.; Zentgraf, H.; Taya, Y.; Droge, W.; Will, H.; Schmitz, M. L. Regulation of P53 Activity by Its Interaction with Homeodomain-Interacting Protein Kinase-2. *Nat. Cell Biol.* **2002**, *4*, 1–10.

(423) Chen, S.; Seiler, J.; Santiago-Reichert, M.; Felbel, K.; Grummt, I.; Voit, R. Repression of Rna Polymerase I Upon Stress Is Caused by Inhibition of Rna-Dependent Deacetylation of Paf53 by Sirt7. *Mol. Cell* **2013**, *52*, 303–13.

(424) Ma, L.; Gao, J. S.; Guan, Y.; Shi, X.; Zhang, H.; Ayrapetov, M. K.; Zhang, Z.; Xu, L.; Hyun, Y. M.; Kim, M.; Zhuang, S.; Chin, Y. E. Acetylation Modulates Prolactin Receptor Dimerization. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 19314–9.

(425) Andrews, P. G.; Kao, K. R. Wnt/Beta-Catenin-Dependent Acetylation of Pygo2 by Cbp/P300 Histone Acetyltransferase Family Members. *Biochem. J.* **2016**, *473*, 4193–4203.

(426) Kiernan, R.; Bres, V.; Ng, R. W.; Coudart, M. P.; El Messaoudi, S.; Sardet, C.; Jin, D. Y.; Emiliani, S.; Benkirane, M. Post-Activation Turn-Off of Nf-Kappa B-Dependent Transcription Is Regulated by Acetylation of P65. *J. Biol. Chem.* **2003**, *278*, 2758–66.

(427) Chen, L. F.; Mu, Y.; Greene, W. C. Acetylation of Rela at Discrete Sites Regulates Distinct Nuclear Functions of Nf-Kappab. *EMBO J.* **2002**, *21*, 6539–48.

(428) Huang, B.; Yang, X. D.; Zhou, M. M.; Ozato, K.; Chen, L. F. Brd4 Coactivates Transcriptional Activation of Nf-Kappab Via Specific Binding to Acetylated Rela. *Mol. Cell Biol.* **2009**, *29*, 1375–87.

(429) Buerki, C.; Rothgiesser, K. M.; Valovka, T.; Owen, H. R.; Rehrauer, H.; Fey, M.; Lane, W. S.; Hottiger, M. O. Functional Relevance of Novel P300-Mediated Lysine 314 and 315 Acetylation of Rela/P65. *Nucleic Acids Res.* **2008**, *36*, 1665–80.

(430) Yeung, F.; Hoberg, J. E.; Ramsey, C. S.; Keller, M. D.; Jones, D. R.; Frye, R. A.; Mayo, M. W. Modulation of Nf-Kappab-Dependent Transcription and Cell Survival by the Sirt1 Deacetylase. *EMBO J.* **2004**, *23*, 2369–80.

(431) Pickard, A.; Wong, P. P.; McCance, D. J. Acetylation of Rb by Pcaf Is Required for Nuclear Localization and Keratinocyte Differentiation. *J. Cell Sci.* **2010**, *123*, 3718–26.

(432) Wu, Q.; Nie, J.; Gao, Y.; Xu, P.; Sun, Q.; Yang, J.; Han, L.; Chen, Z.; Wang, X.; Lv, L.; Tsun, A.; Shen, J.; Li, B. Reciprocal Regulation of Rorgammat Acetylation and Function by P300 and Hdac1. *Sci. Rep.* **2015**, *5*, 16355.

(433) Lim, H. W.; Kang, S. G.; Ryu, J. K.; Schilling, B.; Fei, M.; Lee, I. S.; Kehasse, A.; Shirakawa, K.; Yokoyama, M.; Schnolzer, M.; Kasler, H. G.; Kwon, H. S.; Gibson, B. W.; Sato, H.; Akassoglou, K.; Xiao, C.; Littman, D. R.; Ott, M.; Verdin, E. Sirt1 Deacetylates Rorgammat and Enhances Th17 Cell Generation. *J. Exp. Med.* **2015**, *212*, 607–17.

(434) Schroder, S.; Herker, E.; Itzen, F.; He, D.; Thomas, S.; Gilchrist, D. A.; Kaehlcke, K.; Cho, S.; Pollard, K. S.; Capra, J. A.; Schnolzer, M.; Cole, P. A.; Geyer, M.; Bruneau, B. G.; Adelman, K.; Ott, M. Acetylation of Rna Polymerase Ii Regulates Growth-Factor-Induced Gene Transcription in Mammalian Cells. *Mol. Cell* **2013**, *52*, 314–24.

(435) Simonti, C. N.; Pollard, K. S.; Schroder, S.; He, D.; Bruneau, B. G.; Ott, M.; Capra, J. A. Evolution of Lysine Acetylation in the Rna Polymerase Ii C-Terminal Domain. *BMC Evol. Biol.* **2015**, *15*, 35.

(436) Gronroos, E.; Hellman, U.; Heldin, C. H.; Ericsson, J. Control of Smad7 Stability by Competition between Acetylation and Ubiquitination. *Mol. Cell* **2002**, *10*, 483–93.

(437) Simonsson, M.; Heldin, C. H.; Ericsson, J.; Gronroos, E. The Balance between Acetylation and Deacetylation Controls Smad7 Stability. *J. Biol. Chem.* **2005**, *280*, 21797–803.

(438) Hung, J. J.; Wang, Y. T.; Chang, W. C. Sp1 Deacetylation Induced by Phorbol Ester Recruits P300 to Activate 12(S)-Lipoxygenase Gene Transcription. *Mol. Cell Biol.* **2006**, *26*, 1770–85.

(439) Braun, H.; Koop, R.; Ertmer, A.; Nacht, S.; Suske, G. Transcription Factor Sp3 Is Regulated by Acetylation. *Nucleic Acids Res.* **2001**, *29*, 4994–5000.

(440) Ehling, C.; Haussinger, D.; Bode, J. G. Sp3 Is Involved in the Regulation of Socs3 Gene Expression. *Biochem. J.* **2005**, *387*, 737–45.

(441) Ammanamanchi, S.; Freeman, J. W.; Brattain, M. G. Acetylated Sp3 Is a Transcriptional Activator. *J. Biol. Chem.* **2003**, *278*, 35775–80.

(442) Ponugoti, B.; Kim, D. H.; Xiao, Z.; Smith, Z.; Miao, J.; Zang, M.; Wu, S. Y.; Chiang, C. M.; Veenstra, T. D.; Kemper, J. K. Sirt1 Deacetylates and Inhibits Srebp-1c Activity in Regulation of Hepatic Lipid Metabolism. *J. Biol. Chem.* **2010**, *285*, 33959–70.

(443) Paulson, M.; Pisharody, S.; Pan, L.; Guadagno, S.; Mui, A. L.; Levy, D. E. Stat Protein Transactivation Domains Recruit P300/Cbp through Widely Divergent Sequences. *J. Biol. Chem.* **1999**, *274*, 25343–9.

(444) Wang, R.; Cherukuri, P.; Luo, J. Activation of Stat3 Sequence-Specific DNA Binding and Transcription by P300/Creb-Binding Protein-Mediated Acetylation. *J. Biol. Chem.* **2005**, *280*, 11528–34.

(445) Yuan, Z. L.; Guan, Y. J.; Chatterjee, D.; Chin, Y. E. Stat3 Dimerization Regulated by Reversible Acetylation of a Single Lysine Residue. *Science* **2005**, *307*, 269–73.

(446) Ray, S.; Boldogh, I.; Brasier, A. R. Stat3 Nh2-Terminal Acetylation Is Activated by the Hepatic Acute-Phase Response and Required for Il-6 Induction of Angiotensinogen. *Gastroenterology* **2005**, *129*, 1616–32.

(447) Kusan, C.; Ginter, T.; Heinzel, T.; Kramer, O. H. Stat5 Acetylation: Mechanisms and Consequences for Immunological Control and Leukemogenesis. *JAKSTAT* **2013**, *2*, e26102.

(448) Kiernan, R. E.; Vanhulle, C.; Schiltz, L.; Adam, E.; Xiao, H.; Maudoux, F.; Calomme, C.; Burny, A.; Nakatani, Y.; Jeang, K. T.; Benkirane, M.; Van Lint, C. Hiv-1 Tat Transcriptional Activity Is Regulated by Acetylation. *EMBO J.* **1999**, *18*, 6106–18.

(449) Deng, L.; de la Fuente, C.; Fu, P.; Wang, L.; Donnelly, R.; Wade, J. D.; Lambert, P.; Li, H.; Lee, C. G.; Kashanchi, F. Acetylation of Hiv-1 Tat by Cbp/P300 Increases Transcription of Integrated Hiv-1 Genome and Enhances Binding to Core Histones. *Virology* **2000**, *277*, 278–95.

(450) Col, E.; Caron, C.; Seigneurin-Berny, D.; Gracia, J.; Favier, A.; Khochbin, S. The Histone Acetyltransferase, HgcN5, Interacts with and Acetylates the Hiv Transactivator, Tat. *J. Biol. Chem.* **2001**, *276*, 28179–84.

(451) Pagans, S.; Pedal, A.; North, B. J.; Kaehlcke, K.; Marshall, B. L.; Dorr, A.; Hetzer-Egger, C.; Henklein, P.; Frye, R.; McBurney, M. W.; Hruby, H.; Jung, M.; Verdin, E.; Ott, M. Sirt1 Regulates Hiv Transcription Via Tat Deacetylation. *PLoS Biol.* **2005**, *3*, e41.

(452) Lee, J.; Hwang, Y. J.; Boo, J. H.; Han, D.; Kwon, O. K.; Todorova, K.; Kowall, N. W.; Kim, Y.; Ryu, H. Dysregulation of Upstream Binding Factor-1 Acetylation at K352 Is Linked to Impaired Ribosomal DNA Transcription in Huntington's Disease. *Cell Death Differ.* **2011**, *18*, 1726–35.

- (453) Yao, Y. L.; Yang, W. M.; Seto, E. Regulation of Transcription Factor Yy1 by Acetylation and Deacetylation. *Mol. Cell. Biol.* **2001**, *21*, 5979–91.
- (454) Thiagarajan, D.; Vedantham, S.; Ananthakrishnan, R.; Schmidt, A. M.; Ramasamy, R. Mechanisms of Transcription Factor Acetylation and Consequences in Hearts. *Biochim. Biophys. Acta, Mol. Basis Dis.* **2016**, *1862*, 2221–2231.
- (455) Wang, Z.; Yu, T.; Huang, P. Post-Translational Modifications of Foxo Family Proteins (Review). *Mol. Med. Rep.* **2016**, *14*, 4931–4941.
- (456) Park, J. M.; Jo, S. H.; Kim, M. Y.; Kim, T. H.; Ahn, Y. H. Role of Transcription Factor Acetylation in the Regulation of Metabolic Homeostasis. *Protein Cell* **2015**, *6*, 804–13.
- (457) Greene, W. C.; Chen, L. F. Regulation of Nf-Kappab Action by Reversible Acetylation. *Novartis Found. Symp.* **2004**, *259*, 208–17 (discussion 218–25).
- (458) Zhuang, S. Regulation of Stat Signaling by Acetylation. *Cell. Signalling* **2013**, *25*, 1924–31.
- (459) Avallé, L.; Camporeale, A.; Camperi, A.; Poli, V. Stat3 in Cancer: A Double Edged Sword. *Cytokine+* **2017**, *98*, 4210.1016/j.cyto.2017.03.018
- (460) Braunstein, J.; Brutsaert, S.; Olson, R.; Schindler, C. Stats Dimerize in the Absence of Phosphorylation. *J. Biol. Chem.* **2003**, *278*, 34133–40.
- (461) Kumar, A.; Commene, M.; Flickinger, T. W.; Horvath, C. M.; Stark, G. R. Defective Tnf-Alpha-Induced Apoptosis in Stat1-Null Cells Due to Low Constitutive Levels of Caspases. *Science* **1997**, *278*, 1630–2.
- (462) Xu, Y. S.; Liang, J. J.; Wang, Y.; Zhao, X. J.; Xu, L.; Xu, Y. Y.; Zou, Q. C.; Zhang, J. M.; Tu, C. E.; Cui, Y. G.; Sun, W. H.; Huang, C.; Yang, J. H.; Chin, Y. E. Stat3 Undergoes Acetylation-Dependent Mitochondrial Translocation to Regulate Pyruvate Metabolism. *Sci. Rep.* **2016**, *6*, 39517.
- (463) Pejanovic, N.; Hochrainer, K.; Liu, T.; Aerne, B. L.; Soares, M. P.; Anrather, J. Regulation of Nuclear Factor Kappab (Nf-Kappab) Transcriptional Activity Via P65 Acetylation by the Chaperonin Containing Tcp1 (Cct). *PLoS One* **2012**, *7*, e42020.
- (464) Caron, C.; Boyault, C.; Khochbin, S. Regulatory Cross-Talk between Lysine Acetylation and Ubiquitination: Role in the Control of Protein Stability. *BioEssays* **2005**, *27*, 408–15.
- (465) Goel, A.; Janknecht, R. Acetylation-Mediated Transcriptional Activation of the Ets Protein Er81 by P300, P/Caf, and Her2/Neu. *Mol. Cell. Biol.* **2003**, *23*, 6243–54.
- (466) Brooks, C. L.; Gu, W. The Impact of Acetylation and Deacetylation on the P53 Pathway. *Protein Cell* **2011**, *2*, 456–62.
- (467) Rodriguez, M. S.; Desterro, J. M.; Lain, S.; Lane, D. P.; Hay, R. T. Multiple C-Terminal Lysine Residues Target P53 for Ubiquitin-Proteasome-Mediated Degradation. *Mol. Cell. Biol.* **2000**, *20*, 8458–67.
- (468) Luo, J.; Su, F.; Chen, D.; Shiloh, A.; Gu, W. Deacetylation of P53 Modulates Its Effect on Cell Growth and Apoptosis. *Nature* **2000**, *408*, 377–81.
- (469) Liu, X.; Wang, D.; Zhao, Y.; Tu, B.; Zheng, Z.; Wang, L.; Wang, H.; Gu, W.; Roeder, R. G.; Zhu, W. G. Methyltransferase Set7/9 Regulates P53 Activity by Interacting with Sirtuin 1 (Sirt1). *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 1925–30.
- (470) Huang, J.; Perez-Burgos, L.; Placek, B. J.; Sengupta, R.; Richter, M.; Dorsey, J. A.; Kubicek, S.; Opravil, S.; Jenuwein, T.; Berger, S. L. Repression of P53 Activity by Smyd2-Mediated Methylation. *Nature* **2006**, *444*, 629–32.
- (471) Son, M. J.; Kim, W. K.; Park, A.; Oh, K. J.; Kim, J. H.; Han, B. S.; Kim, I. C.; Chi, S. W.; Park, S. G.; Lee, S. C.; Bae, K. H. Set7/9, a Methyltransferase, Regulates the Thermogenic Program During Brown Adipocyte Differentiation through the Modulation of P53 Acetylation. *Mol. Cell. Endocrinol.* **2016**, *431*, 46–53.
- (472) Ivanov, G. S.; Ivanova, T.; Kurash, J.; Ivanov, A.; Chuikov, S.; Gizatullin, F.; Herrera-Medina, E. M.; Rauscher, F., 3rd; Reinberg, D.; Barlev, N. A. Methylation-Acetylation Interplay Activates P53 in Response to DNA Damage. *Mol. Cell. Biol.* **2007**, *27*, 6756–69.
- (473) Yang, X. D.; Tajkhorshid, E.; Chen, L. F. Functional Interplay between Acetylation and Methylation of the Rela Subunit of Nf-Kappab. *Mol. Cell. Biol.* **2010**, *30*, 2170–80.
- (474) Barlev, N. A.; Liu, L.; Chehab, N. H.; Mansfield, K.; Harris, K. G.; Halazonetis, T. D.; Berger, S. L. Acetylation of P53 Activates Transcription through Recruitment of Coactivators/Histone Acetyltransferases. *Mol. Cell* **2001**, *8*, 1243–54.
- (475) Li, A. G.; Piluso, L. G.; Cai, X.; Gadd, B. J.; Ladurner, A. G.; Liu, X. An Acetylation Switch in P53 Mediates Holo-Tfiiid Recruitment. *Mol. Cell* **2007**, *28*, 408–21.
- (476) Wu, Y.; Lin, J. C.; Piluso, L. G.; Dhahbi, J. M.; Bobadilla, S.; Spindler, S. R.; Liu, X. Phosphorylation of P53 by Tafi Inactivates P53-Dependent Transcription in the DNA Damage Response. *Mol. Cell* **2014**, *53*, 63–74.
- (477) Daitoku, H.; Sakamaki, J.; Fukamizu, A. Regulation of Foxo Transcription Factors by Acetylation and Protein-Protein Interactions. *Biochim. Biophys. Acta, Mol. Cell Res.* **2011**, *1813*, 1954–60.
- (478) Sakaguchi, S.; Miyara, M.; Costantino, C. M.; Hafler, D. A. Foxp3+ Regulatory T Cells in the Human Immune System. *Nat. Rev. Immunol.* **2010**, *10*, 490–500.
- (479) van Loosdregt, J.; Brunen, D.; Fleskens, V.; Pals, C. E.; Lam, E. W.; Coffey, P. J. Rapid Temporal Control of Foxp3 Protein Degradation by Sirtuin-1. *PLoS One* **2011**, *6*, e19047.
- (480) Samanta, A.; Li, B.; Song, X.; Bembas, K.; Zhang, G.; Katsumata, M.; Saouaf, S. J.; Wang, Q.; Hancock, W. W.; Shen, Y.; Greene, M. I. Tgf-Beta and Il-6 Signals Modulate Chromatin Binding and Promoter Occupancy by Acetylated Foxp3. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 14023–7.
- (481) Bieniossek, C.; Papai, G.; Schaffitzel, C.; Garzoni, F.; Chaillet, M.; Scheer, E.; Papadopoulos, P.; Tora, L.; Schultz, P.; Berger, I. The Architecture of Human General Transcription Factor Tfiid Core Complex. *Nature* **2013**, *493*, 699–702.
- (482) Muth, V.; Nadaud, S.; Grummt, I.; Voit, R. Acetylation of Taf(I)68, a Subunit of Tif-Ib/Sl1, Activates Rna Polymerase I Transcription. *EMBO J.* **2001**, *20*, 1353–62.
- (483) Boija, A.; Mahat, D. B.; Zare, A.; Holmqvist, P. H.; Philip, P.; Meyers, D. J.; Cole, P. A.; Lis, J. T.; Stenberg, P.; Mannervik, M. Cbp Regulates Recruitment and Release of Promoter-Proximal Rna Polymerase Ii. *Mol. Cell* **2017**, *68*, 491–503 (e5).
- (484) Hsin, J. P.; Manley, J. L. The Rna Polymerase Ii Ctd Coordinates Transcription and Rna Processing. *Genes Dev.* **2012**, *26*, 2119–37.
- (485) Meinhardt, A.; Kamenski, T.; Hoepfner, S.; Baumli, S.; Cramer, P. A Structural Perspective of Ctd Function. *Genes Dev.* **2005**, *19*, 1401–15.
- (486) Zhou, Q.; Li, T.; Price, D. H. Rna Polymerase Ii Elongation Control. *Annu. Rev. Biochem.* **2012**, *81*, 119–43.
- (487) McNamara, R. P.; Bacon, C. W.; D'Orso, I. Transcription Elongation Control by the 7sk Snrnp Complex: Releasing the Pause. *Cell Cycle* **2016**, *15*, 2115–2123.
- (488) Cho, S.; Schroeder, S.; Ott, M. Cycling through Transcription: Posttranslational Modifications of P-Tefb Regulate Transcription Elongation. *Cell Cycle* **2010**, *9*, 1697–705.
- (489) L'Hernault, S. W.; Rosenbaum, J. L. Chlamydomonas Alpha-Tubulin Is Posttranslationally Modified by Acetylation on the Epsilon-Amino Group of a Lysine. *Biochemistry* **1985**, *24*, 473–8.
- (490) Howes, S. C.; Alushin, G. M.; Shida, T.; Nachury, M. V.; Nogales, E. Effects of Tubulin Acetylation and Tubulin Acetyltransferase Binding on Microtubule Structure. *Mol. Biol. Cell* **2014**, *25*, 257–66.
- (491) Tilney, L. G.; Bryan, J.; Bush, D. J.; Fujiwara, K.; Mooseker, M. S.; Murphy, D. B.; Snyder, D. H. Microtubules: Evidence for 13 Protofilaments. *J. Cell Biol.* **1973**, *59*, 267–75.
- (492) Burton, P. R.; Hinkley, R. E.; Pierson, G. B. Tannic Acid-Stained Microtubules with 12, 13, and 15 Protofilaments. *J. Cell Biol.* **1975**, *65*, 227–33.
- (493) Shida, T.; Cueva, J. G.; Xu, Z.; Goodman, M. B.; Nachury, M. V. The Major Alpha-Tubulin K40 Acetyltransferase Alphasat1

Promotes Rapid Ciliogenesis and Efficient Mechanosensation. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 21517–22.

(494) Akella, J. S.; Wloga, D.; Kim, J.; Starostina, N. G.; Lyons-Abbott, S.; Morrisette, N. S.; Dougan, S. T.; Kipreos, E. T.; Gaertig, J. Mec-17 Is an Alpha-Tubulin Acetyltransferase. *Nature* **2010**, *467*, 218–22.

(495) Kalebic, N.; Sorrentino, S.; Perlas, E.; Bolasco, G.; Martinez, C.; Heppenstall, P. A. Alphasat1 Is the Major Alpha-Tubulin Acetyltransferase in Mice. *Nat. Commun.* **2013**, *4*, 1962.

(496) Misawa, T.; Takahama, M.; Kozaki, T.; Lee, H.; Zou, J.; Saitoh, T.; Akira, S. Microtubule-Driven Spatial Arrangement of Mitochondria Promotes Activation of the Nlrp3 Inflammasome. *Nat. Immunol.* **2013**, *14*, 454–60.

(497) Nagai, T.; Ikeda, M.; Chiba, S.; Kanno, S.; Mizuno, K. Furry Promotes Acetylation of Microtubules in the Mitotic Spindle by Inhibition of Sirt2 Tubulin Deacetylase. *J. Cell Sci.* **2013**, *126*, 4369–80.

(498) Kramer, O. H.; Mahboobi, S.; Sellmer, A. Drugging the Hdac6-Hsp90 Interplay in Malignant Cells. *Trends Pharmacol. Sci.* **2014**, *35*, 501–9.

(499) Scroggins, B. T.; Robzyk, K.; Wang, D.; Marcu, M. G.; Tsutsumi, S.; Beebe, K.; Cotter, R. J.; Felts, S.; Toft, D.; Karnitz, L.; Rosen, N.; Neckers, L. An Acetylation Site in the Middle Domain of Hsp90 Regulates Chaperone Function. *Mol. Cell* **2007**, *25*, 151–9.

(500) Kovacs, J. J.; Murphy, P. J.; Gaillard, S.; Zhao, X.; Wu, J. T.; Nicchitta, C. V.; Yoshida, M.; Toft, D. O.; Pratt, W. B.; Yao, T. P. Hdac6 Regulates Hsp90 Acetylation and Chaperone-Dependent Activation of Glucocorticoid Receptor. *Mol. Cell* **2005**, *18*, 601–7.

(501) Jimenez-Canino, R.; Lorenzo-Diaz, F.; Jaisser, F.; Farman, N.; Giraldez, T.; Alvarez de la Rosa, D. Histone Deacetylase 6-Controlled Hsp90 Acetylation Significantly Alters Mineralocorticoid Receptor Subcellular Dynamics but Not Its Transcriptional Activity. *Endocrinology* **2016**, *157*, 2515–32.

(502) Nishioka, C.; Ikezoe, T.; Yang, J.; Takeuchi, S.; Koeffler, H. P.; Yokoyama, A. Ms-275, a Novel Histone Deacetylase Inhibitor with Selectivity against Hdac1, Induces Degradation of Flt3 Via Inhibition of Chaperone Function of Heat Shock Protein 90 in Aml Cells. *Leuk. Res.* **2008**, *32*, 1382–92.

(503) Weingarten, M. D.; Lockwood, A. H.; Hwo, S. Y.; Kirschner, M. W. A Protein Factor Essential for Microtubule Assembly. *Proc. Natl. Acad. Sci. U. S. A.* **1975**, *72*, 1858–62.

(504) Witman, G. B.; Cleveland, D. W.; Weingarten, M. D.; Kirschner, M. W. Tubulin Requires Tau for Growth onto Microtubule Initiating Sites. *Proc. Natl. Acad. Sci. U. S. A.* **1976**, *73*, 4070–4.

(505) Wang, Y.; Mandelkow, E. Tau in Physiology and Pathology. *Nat. Rev. Neurosci.* **2016**, *17*, 22–35.

(506) Goedert, M.; Jakes, R. Mutations Causing Neurodegenerative Tauopathies. *Biochim. Biophys. Acta, Mol. Basis Dis.* **2005**, *1739*, 240–50.

(507) Cohen, T. J.; Guo, J. L.; Hurtado, D. E.; Kwong, L. K.; Mills, I. P.; Trojanowski, J. Q.; Lee, V. M. The Acetylation of Tau Inhibits Its Function and Promotes Pathological Tau Aggregation. *Nat. Commun.* **2011**, *2*, 252.

(508) Min, S. W.; Cho, S. H.; Zhou, Y.; Schroeder, S.; Haroutunian, V.; Seeley, W. W.; Huang, E. J.; Shen, Y.; Masliah, E.; Mukherjee, C.; Meyers, D.; Cole, P. A.; Ott, M.; Gan, L. Acetylation of Tau Inhibits Its Degradation and Contributes to Tauopathy. *Neuron* **2010**, *67*, 953–66.

(509) Morris, M.; Knudsen, G. M.; Maeda, S.; Trinidad, J. C.; Ioanoviciu, A.; Burlingame, A. L.; Mucke, L. Tau Post-Translational Modifications in Wild-Type and Human Amyloid Precursor Protein Transgenic Mice. *Nat. Neurosci.* **2015**, *18*, 1183–9.

(510) Hwang, A. W.; Trzeciakiewicz, H.; Friedmann, D.; Yuan, C. X.; Marmorstein, R.; Lee, V. M.; Cohen, T. J. Conserved Lysine Acetylation within the Microtubule-Binding Domain Regulates Map2/Tau Family Members. *PLoS One* **2016**, *11*, e0168913.

(511) Cohen, T. J.; Constance, B. H.; Hwang, A. W.; James, M.; Yuan, C. X. Intrinsic Tau Acetylation Is Coupled to Auto-Proteolytic Tau Fragmentation. *PLoS One* **2016**, *11*, e0158470.

(512) Cohen, T. J.; Friedmann, D.; Hwang, A. W.; Marmorstein, R.; Lee, V. M. The Microtubule-Associated Tau Protein Has Intrinsic Acetyltransferase Activity. *Nat. Struct. Mol. Biol.* **2013**, *20*, 756–62.

(513) Noack, M.; Leyk, J.; Richter-Landsberg, C. Hdac6 Inhibition Results in Tau Acetylation and Modulates Tau Phosphorylation and Degradation in Oligodendrocytes. *Glia* **2014**, *62*, 535–47.

(514) Xiong, Y.; Zhao, K.; Wu, J.; Xu, Z.; Jin, S.; Zhang, Y. Q. Hdac6 Mutations Rescue Human Tau-Induced Microtubule Defects in *Drosophila*. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, 4604–9.

(515) Tracy, T. E.; Gan, L. Acetylated Tau in Alzheimer's Disease: An Instigator of Synaptic Dysfunction Underlying Memory Loss: Increased Levels of Acetylated Tau Blocks the Postsynaptic Signaling Required for Plasticity and Promotes Memory Deficits Associated with Tauopathy. *BioEssays* **2017**, *39*, 1600224.10.1002/bies.201600224.

(516) Sohn, P. D.; Tracy, T. E.; Son, H. I.; Zhou, Y.; Leite, R. E.; Miller, B. L.; Seeley, W. W.; Grinberg, L. T.; Gan, L. Acetylated Tau Destabilizes the Cytoskeleton in the Axon Initial Segment and Is Mislocalized to the Somatodendritic Compartment. *Mol. Neurodegener.* **2016**, *11*, 47.

(517) Tracy, T. E.; Sohn, P. D.; Minami, S. S.; Wang, C.; Min, S. W.; Li, Y.; Zhou, Y.; Le, D.; Lo, I.; Ponnusamy, R.; Cong, X.; Schilling, B.; Ellerby, L. M.; Haganir, R. L.; Gan, L. Acetylated Tau Obstructs Kibra-Mediated Signaling in Synaptic Plasticity and Promotes Tauopathy-Related Memory Loss. *Neuron* **2016**, *90*, 245–60.

(518) Cook, C.; Carlomagno, Y.; Gendron, T. F.; Dunmore, J.; Scheffel, K.; Stetler, C.; Davis, M.; Dickson, D.; Jarpe, M.; DeTure, M.; Petrucelli, L. Acetylation of the Kxgs Motifs in Tau Is a Critical Determinant in Modulation of Tau Aggregation and Clearance. *Hum. Mol. Genet.* **2014**, *23*, 104–16.

(519) Thomas, S. N.; Funk, K. E.; Wan, Y.; Liao, Z.; Davies, P.; Kuret, J.; Yang, A. J. Dual Modification of Alzheimer's Disease Phf-Tau Protein by Lysine Methylation and Ubiquitylation: A Mass Spectrometry Approach. *Acta Neuropathol.* **2012**, *123*, 105–17.

(520) Funk, K. E.; Thomas, S. N.; Schafer, K. N.; Cooper, G. L.; Liao, Z.; Clark, D. J.; Yang, A. J.; Kuret, J. Lysine Methylation Is an Endogenous Post-Translational Modification of Tau Protein in Human Brain and a Modulator of Aggregation Propensity. *Biochem. J.* **2014**, *462*, 77–88.

(521) Anderson, K. A.; Hirschey, M. D. Mitochondrial Protein Acetylation Regulates Metabolism. *Essays Biochem.* **2012**, *52*, 23–35.

(522) Weinert, B. T.; Wagner, S. A.; Horn, H.; Henriksen, P.; Liu, W. R.; Olsen, J. V.; Jensen, L. J.; Choudhary, C. Proteome-Wide Mapping of the *Drosophila* Acetylome Demonstrates a High Degree of Conservation of Lysine Acetylation. *Sci. Signaling* **2011**, *4*, ra48.

(523) Wang, Q.; Zhang, Y.; Yang, C.; Xiong, H.; Lin, Y.; Yao, J.; Li, H.; Xie, L.; Zhao, W.; Yao, Y.; Ning, Z.-B.; Zeng, R.; Xiong, Y.; Guan, K.-L.; Zhao, S.; Zhao, G.-P. Acetylation of Metabolic Enzymes Coordinates Carbon Source Utilization and Metabolic Flux. *Science* **2010**, *327*, 1004–7.

(524) Zhao, S.; Xu, W.; Jiang, W.; Yu, W.; Lin, Y.; Zhang, T.; Yao, J.; Zhou, L.; Zeng, Y.; Li, H.; Li, Y.; Shi, J.; An, W.; Hancock, S. M.; He, F.; Qin, L.; Chin, J.; Yang, P.; Chen, X.; Lei, Q.; Xiong, Y.; Guan, K.-L. Regulation of Cellular Metabolism by Protein Lysine Acetylation. *Science* **2010**, *327*, 1000–4.

(525) Berg, J. M.; Tymoczko, J. L.; Stryer, L. *Biochemistry*, 7th ed.; W.H. Freeman: New York, 2012; pp xxxii, 1054; 132 pp.

(526) He, W.; Newman, J. C.; Wang, M. Z.; Ho, L.; Verdin, E. Mitochondrial Sirtuins: Regulators of Protein Acylation and Metabolism. *Trends Endocrinol. Metab.* **2012**, *23*, 467–76.

(527) Lombard, D. B.; Alt, F. W.; Cheng, H. L.; Bunkenborg, J.; Streeper, R. S.; Mostoslavsky, R.; Kim, J.; Yancopoulos, G.; Valenzuela, D.; Murphy, A.; Yang, Y.; Chen, Y.; Hirschey, M. D.; Bronson, R. T.; Haigis, M.; Guarente, L. P.; Farese, R. V.; Weissman, S.; Verdin, E.; Schwer, B. Mammalian Sir2 Homolog Sirt3 Regulates Global Mitochondrial Lysine Acetylation. *Mol. Cell. Biol.* **2007**, *27*, 8807–14.

(528) Lin, S. J.; Defossez, P. A.; Guarente, L. Requirement of Nad and Sir2 for Life-Span Extension by Calorie Restriction in *Saccharomyces Cerevisiae*. *Science* **2000**, *289*, 2126–8.

- (529) Lin, S. J.; Kaeberlein, M.; Andalis, A. A.; Sturtz, L. A.; Defossez, P. A.; Culotta, V. C.; Fink, G. R.; Guarente, L. Calorie Restriction Extends *Saccharomyces Cerevisiae* Lifespan by Increasing Respiration. *Nature* **2002**, *418*, 344–8.
- (530) Lin, S. J.; Ford, E.; Haigis, M.; Liszt, G.; Guarente, L. Calorie Restriction Extends Yeast Life Span by Lowering the Level of Ndh. *Genes Dev.* **2004**, *18*, 12–6.
- (531) Bitterman, K. J.; Anderson, R. M.; Cohen, H. Y.; Latorre-Esteves, M.; Sinclair, D. A. Inhibition of Silencing and Accelerated Aging by Nicotinamide, a Putative Negative Regulator of Yeast Sir2 and Human Sirt1. *J. Biol. Chem.* **2002**, *277*, 45099–107.
- (532) Anderson, R. M.; Bitterman, K. J.; Wood, J. G.; Medvedik, O.; Sinclair, D. A. Nicotinamide and Pnc1 Govern Lifespan Extension by Calorie Restriction in *Saccharomyces Cerevisiae*. *Nature* **2003**, *423*, 181–5.
- (533) Palacios, O. M.; Carmona, J. J.; Michan, S.; Chen, K. Y.; Manabe, Y.; Iij, J. L.; Goodyear, L. J.; Tong, Q. Diet and Exercise Signals Regulate Sirt3 and Activate Ampk and Pgc-1alpha in Skeletal Muscle. *Aging* **2009**, *1*, 771–83.
- (534) Ahn, B. H.; Kim, H. S.; Song, S.; Lee, I. H.; Liu, J.; Vassilopoulos, A.; Deng, C. X.; Finkel, T. A Role for the Mitochondrial Deacetylase Sirt3 in Regulating Energy Homeostasis. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 14447–14452.
- (535) Hirschey, M.; Shimazu, T.; Goetzman, E.; Jing, E.; Schwer, B.; Lombard, D.; Grueter, C.; Harris, C.; Biddinger, S.; Ilkayeva, O.; Stevens, R.; Li, Y.; Saha, A.; Ruderman, N.; Bain, J.; Newgard, C.; Farese, R., Jr.; Alt, F.; Kahn, C.; Verdin, E. Sirt3 Regulates Mitochondrial Fatty Acid Oxidation Via Reversible Enzyme Deacetylation. *Nature* **2010**, *464*, 121–125.
- (536) Caton, P. W.; Holness, M. J.; Bishop-Bailey, D.; Sugden, M. C. Pparalpha-Lxr as a Novel Metabolostatic Signalling Axis in Skeletal Muscle That Acts to Optimize Substrate Selection in Response to Nutrient Status. *Biochem. J.* **2011**, *437*, 521–30.
- (537) Hallows, W. C.; Yu, W.; Smith, B. C.; Devries, M. K.; Ellinger, J. J.; Someya, S.; Shortreed, M. R.; Prolla, T.; Markley, J. L.; Smith, L. M.; Zhao, S.; Guan, K. L.; Denu, J. M. Sirt3 Promotes the Urea Cycle and Fatty Acid Oxidation During Dietary Restriction. *Mol. Cell* **2011**, *41*, 139–49.
- (538) Tauriainen, E.; Luostarinen, M.; Martonen, E.; Finckenberg, P.; Kovalainen, M.; Huotari, A.; Herzig, K. H.; Lecklin, A.; Mervaala, E. Distinct Effects of Calorie Restriction and Resveratrol on Diet-Induced Obesity and Fatty Liver Formation. *J. Nutr. Metab.* **2011**, *2011*, 525094.
- (539) Alhazzazi, T. Y.; Kamarajan, P.; Joo, N.; Huang, J. Y.; Verdin, E.; D'Silva, N. J.; Kapila, Y. L. Sirtuin-3 (Sirt3), a Novel Potential Therapeutic Target for Oral Cancer. *Cancer* **2011**, *117*, 1670–8.
- (540) Garland, P. B.; Shepherd, D.; Yates, D. W. Steady-State Concentrations of Coenzyme a, Acetyl-Coenzyme a and Long-Chain Fatty Acyl-Coenzyme a in Rat-Liver Mitochondria Oxidizing Palmitate. *Biochem. J.* **1965**, *97*, 587–94.
- (541) Paik, W. K.; Pearson, D.; Lee, H. W.; Kim, S. Nonenzymatic Acetylation of Histones with Acetyl-CoA. *Biochim. Biophys. Acta, Nucleic Acids Protein Synth.* **1970**, *213*, 513–22.
- (542) Schwer, B.; Eckersdorff, M.; Li, Y.; Silva, J.; Fermin, D.; Kurtev, M.; Giallourakis, C.; Comb, M.; Alt, F.; Lombard, D. Calorie Restriction Alters Mitochondrial Protein Acetylation. *Aging Cell* **2009**, *8*, 60410.1111/j.1474-9726.2009.00503.x
- (543) Hirschey, M.; Aouizerat, B.; Jing, E.; Shimazu, T.; Grueter, C.; Collins, A.; Stevens, R.; Lam, M.; Muehlbauer, M.; Schwer, B.; Gao, B.; Bass, N.; Alt, F.; Deng, C.-X.; Kakar, S.; Newgard, C.; Farese, R., Jr.; Kahn, C.; Verdin, E. Sirt3 Deficiency and Mitochondrial Protein Hyperacetylation Accelerate the Development of the Metabolic Syndrome. *Mol. Cell* **2011**, *44*, 177.
- (544) Fritz, K. S.; Galligan, J. J.; Hirschey, M. D.; Verdin, E.; Petersen, D. R. Mitochondrial Acetylome Analysis in a Mouse Model of Alcohol-Induced Liver Injury Utilizing Sirt3 Knockout Mice. *J. Proteome Res.* **2012**, *11*, 1633–43.
- (545) Picklo, M. J., Sr. Ethanol Intoxication Increases Hepatic N-Lysyl Protein Acetylation. *Biochem. Biophys. Res. Commun.* **2008**, *376*, 615–9.
- (546) Scott, I.; Webster, B. R.; Chan, C. K.; Okonkwo, J. U.; Han, K.; Sack, M. N. Gcn5-Like Protein 1 (Gcn5l1) Controls Mitochondrial Content through Coordinated Regulation of Mitochondrial Biogenesis and Mitophagy. *J. Biol. Chem.* **2014**, *289*, 2864–72.
- (547) Fan, J.; Shan, C.; Kang, H. B.; Elf, S.; Xie, J.; Tucker, M.; Gu, T. L.; Aguiar, M.; Lonning, S.; Chen, H.; Mohammadi, M.; Britton, L. M.; Garcia, B. A.; Aleckovic, M.; Kang, Y.; Kaluz, S.; Devi, N.; Van Meir, E. G.; Hitosugi, T.; Seo, J. H.; Lonial, S.; Gaddh, M.; Arellano, M.; Khoury, H. J.; Khuri, F. R.; Boggon, T. J.; Kang, S.; Chen, J. Tyr Phosphorylation of Pdp1 Toggles Recruitment between Acat1 and Sirt3 to Regulate the Pyruvate Dehydrogenase Complex. *Mol. Cell* **2014**, *53*, 534–48.
- (548) Jing, E.; Emanuelli, B.; Hirschey, M. D.; Boucher, J.; Lee, K. Y.; Lombard, D.; Verdin, E. M.; Kahn, C. R. Sirtuin-3 (Sirt3) Regulates Skeletal Muscle Metabolism and Insulin Signaling Via Altered Mitochondrial Oxidation and Reactive Oxygen Species Production. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 14608–13.
- (549) Finley, L. W.; Carracedo, A.; Lee, J.; Souza, A.; Egia, A.; Zhang, J.; Teruya-Feldstein, J.; Moreira, P. I.; Cardoso, S. M.; Clish, C. B.; Pandolfi, P. P.; Haigis, M. C. Sirt3 Opposes Reprogramming of Cancer Cell Metabolism through Hif1alpha Destabilization. *Cancer Cell* **2011**, *19*, 416–28.
- (550) Cimen, H.; Han, M. J.; Yang, Y.; Tong, Q.; Koc, H.; Koc, E. C. Regulation of Succinate Dehydrogenase Activity by Sirt3 in Mammalian Mitochondria. *Biochemistry* **2010**, *49*, 304–11.
- (551) Bao, J.; Scott, I.; Lu, Z.; Pang, L.; Dimond, C. C.; Gius, D.; Sack, M. N. Sirt3 Is Regulated by Nutrient Excess and Modulates Hepatic Susceptibility to Lipotoxicity. *Free Radical Biol. Med.* **2010**, *49*, 1230–1237.
- (552) Hallows, W.; Lee, S.; Denu, J. Sirtuins Deacetylate and Activate Mammalian Acetyl-CoA Synthetases. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 10230–5.
- (553) Schwer, B.; Bunkenborg, J.; Verdin, R. O.; Andersen, J. S.; Verdin, E. Reversible Lysine Acetylation Controls the Activity of the Mitochondrial Enzyme Acetyl-CoA Synthetase 2. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 10224–9.
- (554) Shimazu, T.; Hirschey, M.; Hua, L.; Dittenhafer-Reed, K. E.; Schwer, B.; Lombard, D.; Li, Y.; Bunkenborg, J.; Alt, F. W.; Denu, J. M.; Jacobson, M. P.; Verdin, E. Sirt3 Deacetylates Mitochondrial 3-Hydroxy-3-Methylglutaryl CoA Synthase 2, Increases Its Enzymatic Activity and Regulates Ketone Body Production. *Cell Metab.* **2010**, *12*, 654–661.
- (555) Shulga, N.; Wilson-Smith, R.; Pastorino, J. G. Sirtuin-3 Deacetylation of Cyclophilin D Induces Dissociation of Hexokinase Ii from the Mitochondria. *J. Cell Sci.* **2010**, *123*, 894–902.
- (556) Kim, H. S.; Patel, K.; Muldoon-Jacobs, K.; Bisht, K. S.; Aykin-Burns, N.; Pennington, J. D.; van der Meer, R.; Nguyen, P.; Savage, J.; Owens, K. M.; Vassilopoulos, A.; Ozden, O.; Park, S. H.; Singh, K. K.; Abdulkadir, S. A.; Spitz, D. R.; Deng, C. X.; Gius, D. Sirt3 Is a Mitochondria-Localized Tumor Suppressor Required for Maintenance of Mitochondrial Integrity and Metabolism During Stress. *Cancer Cell* **2010**, *17*, 41–52.
- (557) Someya, S.; Yu, W.; Hallows, W. C.; Xu, J.; Vann, J. M.; Leeuwenburgh, C.; Tanokura, M.; Denu, J. M.; Prolla, T. A. Sirt3 Mediates Reduction of Oxidative Damage and Prevention of Age-Related Hearing Loss under Caloric Restriction. *Cell* **2010**, *143*, 802–812.
- (558) Qiu, X.; Brown, K.; Hirschey, M. D.; Verdin, E.; Chen, D. Calorie Restriction Reduces Oxidative Stress by Sirt3-Mediated Sod2 Activation. *Cell Metab.* **2010**, *12*, 662–667.
- (559) Tao, R.; Coleman, M. C.; Pennington, J. D.; Ozden, O.; Park, S.-H.; Jiang, H.; Kim, H.-S.; Flynn, C. R.; Hill, S.; Hayes McDonald, W.; Olivier, A. K.; Spitz, D. R.; Gius, D. Sirt3-Mediated Deacetylation of Evolutionarily Conserved Lysine 122 Regulates Mnsod Activity in Response to Stress. *Mol. Cell* **2010**, *40*, 893–904.

- (560) Chen, Y.; Zhang, J.; Lin, Y.; Lei, Q.; Guan, K. L.; Zhao, S.; Xiong, Y. Tumour Suppressor Sirt3 Deacetylates and Activates Manganese Superoxide Dismutase to Scavenge Ros. *EMBO Rep.* **2011**, *12*, 534–41.
- (561) Candido, E. P.; Reeves, R.; Davie, J. R. Sodium Butyrate Inhibits Histone Deacetylation in Cultured Cells. *Cell* **1978**, *14*, 105–13.
- (562) Vidali, G.; Boffa, L. C.; Mann, R. S.; Allfrey, V. G. Reversible Effects of Na-Butyrate on Histone Acetylation. *Biochem. Biophys. Res. Commun.* **1978**, *82*, 223–7.
- (563) Yoshida, M.; Hoshikawa, Y.; Koseki, K.; Mori, K.; Beppu, T. Structural Specificity for Biological Activity of Trichostatin A, a Specific Inhibitor of Mammalian Cell Cycle with Potent Differentiation-Inducing Activity in Friend Leukemia Cells. *J. Antibiot.* **1990**, *43*, 1101–6.
- (564) Yoshida, M.; Kijima, M.; Akita, M.; Beppu, T. Potent and Specific Inhibition of Mammalian Histone Deacetylase Both in Vivo and in Vitro by Trichostatin A. *J. Biol. Chem.* **1990**, *265*, 17174–9.
- (565) Richon, V. M.; Emiliani, S.; Verdin, E.; Webb, Y.; Breslow, R.; Rifkind, R. A.; Marks, P. A. A Class of Hybrid Polar Inducers of Transformed Cell Differentiation Inhibits Histone Deacetylases. *Proc. Natl. Acad. Sci. U. S. A.* **1998**, *95*, 3003–7.
- (566) Gottlicher, M.; Minucci, S.; Zhu, P.; Kramer, O. H.; Schimpf, A.; Giavara, S.; Sleeman, J. P.; Lo Coco, F.; Nervi, C.; Pelicci, P. G.; Heinzel, T. Valproic Acid Defines a Novel Class of Hdac Inhibitors Inducing Differentiation of Transformed Cells. *EMBO J.* **2001**, *20*, 6969–78.
- (567) Mottamal, M.; Zheng, S.; Huang, T. L.; Wang, G. Histone Deacetylase Inhibitors in Clinical Studies as Templates for New Anticancer Agents. *Molecules* **2015**, *20*, 3898–941.
- (568) Subramanian, S.; Bates, S. E.; Wright, J. J.; Espinoza-Delgado, I.; Piekarz, R. L. Clinical Toxicities of Histone Deacetylase Inhibitors. *Pharmaceuticals* **2010**, *3*, 2751–2767.
- (569) Xu, W. S.; Parmigiani, R. B.; Marks, P. A. Histone Deacetylase Inhibitors: Molecular Mechanisms of Action. *Oncogene* **2007**, *26*, 5541–52.
- (570) Takai, N.; Desmond, J. C.; Kumagai, T.; Gui, D.; Said, J. W.; Whittaker, S.; Miyakawa, I.; Koeffler, H. P. Histone Deacetylase Inhibitors Have a Profound Antigrowth Activity in Endometrial Cancer Cells. *Clin. Cancer Res.* **2004**, *10*, 1141–9.
- (571) Gui, C. Y.; Ngo, L.; Xu, W. S.; Richon, V. M.; Marks, P. A. Histone Deacetylase (Hdac) Inhibitor Activation of P21waf1 Involves Changes in Promoter-Associated Proteins, Including Hdac1. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 1241–6.
- (572) Lusic, M.; Marcello, A.; Cereseto, A.; Giacca, M. Regulation of Hiv-1 Gene Expression by Histone Acetylation and Factor Recruitment at the Ltr Promoter. *EMBO J.* **2003**, *22*, 6550–61.
- (573) Falkenberg, K. J.; Johnstone, R. W. Histone Deacetylases and Their Inhibitors in Cancer, Neurological Diseases and Immune Disorders. *Nat. Rev. Drug Discovery* **2014**, *13*, 673–91.
- (574) Butler, K. V.; Kalin, J.; Brochier, C.; Vistoli, G.; Langley, B.; Kozikowski, A. P. Rational Design and Simple Chemistry Yield a Superior, Neuroprotective Hdac6 Inhibitor, Tubastatin A. *J. Am. Chem. Soc.* **2010**, *132*, 10842–6.
- (575) Balasubramanian, S.; Ramos, J.; Luo, W.; Sirisawad, M.; Verner, E.; Buggy, J. J. A Novel Histone Deacetylase 8 (Hdac8)-Specific Inhibitor Pci-34051 Induces Apoptosis in T-Cell Lymphomas. *Leukemia* **2008**, *22*, 1026–34.
- (576) Kaerberlein, M.; McVey, M.; Guarente, L. The Sir2/3/4 Complex and Sir2 Alone Promote Longevity in *Saccharomyces Cerevisiae* by Two Different Mechanisms. *Genes Dev.* **1999**, *13*, 2570–80.
- (577) Howitz, K. T.; Bitterman, K. J.; Cohen, H. Y.; Lamming, D. W.; Lavu, S.; Wood, J. G.; Zipkin, R. E.; Chung, P.; Kisielewski, A.; Zhang, L. L.; Scherer, B.; Sinclair, D. A. Small Molecule Activators of Sirtuins Extend *Saccharomyces Cerevisiae* Lifespan. *Nature* **2003**, *425*, 191–6.
- (578) Wood, J. G.; Rogina, B.; Lavu, S.; Howitz, K.; Helfand, S. L.; Tatar, M.; Sinclair, D. Sirtuin Activators Mimic Caloric Restriction and Delay Ageing in Metazoans. *Nature* **2004**, *430*, 686–9.
- (579) Walle, T.; Hsieh, F.; DeLegge, M. H.; Oatis, J. E., Jr.; Walle, U. K. High Absorption but Very Low Bioavailability of Oral Resveratrol in Humans. *Drug Metab. Dispos.* **2004**, *32*, 1377–82.
- (580) Erdogan, C. S.; Morup-Lendal, M.; Dalggaard, L. T.; Vang, O. Sirtuin 1 Independent Effects of Resveratrol in Ins-1e Beta-Cells. *Chem.-Biol. Interact.* **2017**, *264*, 52–60.
- (581) Mercken, E. M.; Mitchell, S. J.; Martin-Montalvo, A.; Minor, R. K.; Almeida, M.; Gomes, A. P.; Scheibye-Knudsen, M.; Palacios, H. H.; Licata, J. J.; Zhang, Y.; Becker, K. G.; Khraiwesh, H.; Gonzalez-Reyes, J. A.; Villalba, J. M.; Baur, J. A.; Elliott, P.; Westphal, C.; Vlasuk, G. P.; Ellis, J. L.; Sinclair, D. A.; Bernier, M.; de Cabo, R. Srt2104 Extends Survival of Male Mice on a Standard Diet and Preserves Bone and Muscle Mass. *Aging Cell* **2014**, *13*, 787–96.
- (582) Mitchell, S. J.; Martin-Montalvo, A.; Mercken, E. M.; Palacios, H. H.; Ward, T. M.; Abulwerdi, G.; Minor, R. K.; Vlasuk, G. P.; Ellis, J. L.; Sinclair, D. A.; Dawson, J.; Allison, D. B.; Zhang, Y.; Becker, K. G.; Bernier, M.; de Cabo, R. The Sirt1 Activator Srt1720 Extends Lifespan and Improves Health of Mice Fed a Standard Diet. *Cell Rep.* **2014**, *6*, 836–43.
- (583) Chauhan, D.; Bandi, M.; Singh, A. V.; Ray, A.; Raje, N.; Richardson, P.; Anderson, K. C. Preclinical Evaluation of a Novel Sirt1Modulator Srt1720 in Multiple Myeloma Cells. *Br. J. Haematol.* **2011**, *155*, 588–98.
- (584) Beher, D.; Wu, J.; Cumine, S.; Kim, K. W.; Lu, S. C.; Atangan, L.; Wang, M. Resveratrol Is Not a Direct Activator of Sirt1 Enzyme Activity. *Chem. Biol. Drug Des.* **2009**, *74*, 619–24.
- (585) Pacholec, M.; Bleasdale, J. E.; Chrunk, B.; Cunningham, D.; Flynn, D.; Garofalo, R. S.; Griffith, D.; Griffior, M.; Loulakis, P.; Pabst, B.; Qiu, X.; Stockman, B.; Thanabal, V.; Varghese, A.; Ward, J.; Withka, J.; Ahn, K. Srt1720, Srt2183, Srt1460, and Resveratrol Are Not Direct Activators of Sirt1. *J. Biol. Chem.* **2010**, *285*, 8340–51.
- (586) Hubbard, B. P.; Gomes, A. P.; Dai, H.; Li, J.; Case, A. W.; Considine, T.; Riera, T. V.; Lee, J. E.; E, S. Y.; Lamming, D. W.; Pentelute, B. L.; Schuman, E. R.; Stevens, L. A.; Ling, A. J.; Armour, S. M.; Michan, S.; Zhao, H.; Jiang, Y.; Sweitzer, S. M.; Blum, C. A.; Disch, J. S.; Ng, P. Y.; Howitz, K. T.; Rolo, A. P.; Hamuro, Y.; Moss, J.; Perni, R. B.; Ellis, J. L.; Vlasuk, G. P.; Sinclair, D. A. Evidence for a Common Mechanism of Sirt1 Regulation by Allosteric Activators. *Science* **2013**, *339*, 1216–9.
- (587) Lakshminarasimhan, M.; Rauh, D.; Schutkowski, M.; Steegborn, C. Sirt1 Activation by Resveratrol Is Substrate Sequence-Selective. *Aging* **2013**, *5*, 151–4.
- (588) Napper, A. D.; Hixon, J.; McDonagh, T.; Keavey, K.; Pons, J. F.; Barker, J.; Yau, W. T.; Amouzegh, P.; Flegg, A.; Hamelin, E.; Thomas, R. J.; Kates, M.; Jones, S.; Navia, M. A.; Saunders, J. O.; DiStefano, P. S.; Curtis, R. Discovery of Indoles as Potent and Selective Inhibitors of the Deacetylase Sirt1. *J. Med. Chem.* **2005**, *48*, 8045–54.
- (589) Mai, A.; Massa, S.; Lavu, S.; Pezzi, R.; Simeoni, S.; Ragno, R.; Mariotti, F. R.; Chiani, F.; Camilloni, G.; Sinclair, D. A. Design, Synthesis, and Biological Evaluation of Sirtinol Analogues as Class Iii Histone/Protein Deacetylase (Sirtuin) Inhibitors. *J. Med. Chem.* **2005**, *48*, 7789–95.
- (590) McCarthy, A. R.; Pirrie, L.; Hollick, J. J.; Ronseaux, S.; Campbell, J.; Higgins, M.; Staples, O. D.; Tran, F.; Slawin, A. M.; Lain, S.; Westwood, N. J. Synthesis and Biological Characterisation of Sirtuin Inhibitors Based on the Tenovins. *Bioorg. Med. Chem.* **2012**, *20*, 1779–93.
- (591) He, X.; Nie, H.; Hong, Y.; Sheng, C.; Xia, W.; Ying, W. Sirt2 Activity Is Required for the Survival of C6 Glioma Cells. *Biochem. Biophys. Res. Commun.* **2012**, *417*, 468–72.
- (592) Luthi-Carter, R.; Taylor, D. M.; Pallos, J.; Lambert, E.; Amore, A.; Parker, A.; Moffitt, H.; Smith, D. L.; Runne, H.; Gokce, O.; Kuhn, A.; Xiang, Z.; Maxwell, M. M.; Reeves, S. A.; Bates, G. P.; Neri, C.; Thompson, L. M.; Marsh, J. L.; Kazantsev, A. G. Sirt2 Inhibition

Achieves Neuroprotection by Decreasing Sterol Biosynthesis. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 7927–32.

(593) Riepsamen, A.; Wu, L.; Lau, L.; Listijono, D.; Ledger, W.; Sinclair, D. A.; Homer, H. Correction: Nicotinamide Impairs Entry into and Exit from Meiosis I in Mouse Oocytes. *PLoS One* **2015**, *10*, e0130058.

(594) Rumpf, T.; Schiedel, M.; Karaman, B.; Roessler, C.; North, B. J.; Lehotzky, A.; Olah, J.; Ladwein, K. I.; Schmidt-kunz, K.; Gajer, M.; Pannek, M.; Steegborn, C.; Sinclair, D. A.; Gerhardt, S.; Ovadi, J.; Schutkowski, M.; Sippl, W.; Einsle, O.; Jung, M. Selective Sirt2 Inhibition by Ligand-Induced Rearrangement of the Active Site. *Nat. Commun.* **2015**, *6*, 6263.

(595) Erburu, M.; Munoz-Cobo, I.; Diaz-Perdigon, T.; Mellini, P.; Suzuki, T.; Puerta, E.; Tordera, R. M. Sirt2 Inhibition Modulate Glutamate and Serotonin Systems in the Prefrontal Cortex and Induces Antidepressant-Like Action. *Neuropharmacology* **2017**, *117*, 195–208.

(596) Heltweg, B.; Gatbonton, T.; Schuler, A. D.; Posakony, J.; Li, H.; Goehle, S.; Kolipara, R.; Depinho, R. A.; Gu, Y.; Simon, J. A.; Bedalov, A. Antitumor Activity of a Small-Molecule Inhibitor of Human Silent Information Regulator 2 Enzymes. *Cancer Res.* **2006**, *66*, 4368–77.

(597) Lancelot, J.; Caby, S.; Dubois-Abdesselem, F.; Vanderstraete, M.; Trolet, J.; Oliveira, G.; Bracher, F.; Jung, M.; Pierce, R. J. Schistosoma Mansonii Sirtuins: Characterization and Potential as Chemotherapeutic Targets. *PLoS Neglected Trop. Dis.* **2013**, *7*, e2428.

(598) Lara, E.; Mai, A.; Calvanese, V.; Altucci, L.; Lopez-Nieva, P.; Martinez-Chantar, M. L.; Varela-Rey, M.; Rotili, D.; Nebbioso, A.; Roperio, S.; Montoya, G.; Oyarzabal, J.; Velasco, S.; Serrano, M.; Witt, M.; Villar-Garea, A.; Imhof, A.; Mato, J. M.; Esteller, M.; Fraga, M. F. Salermide, a Sirtuin Inhibitor with a Strong Cancer-Specific Proapoptotic Effect. *Oncogene* **2009**, *28*, 781–91.

(599) Cui, H.; Kamal, Z.; Ai, T.; Xu, Y.; More, S. S.; Wilson, D. J.; Chen, L. Discovery of Potent and Selective Sirtuin 2 (Sirt2) Inhibitors Using a Fragment-Based Approach. *J. Med. Chem.* **2014**, *57*, 8340–57.

(600) Salo, H. S.; Laitinen, T.; Poso, A.; Jarho, E.; Lahtela-Kakkonen, M. Identification of Novel Sirt3 Inhibitor Scaffolds by Virtual Screening. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2990–5.

(601) Alhazzazi, T. Y.; Kamarajan, P.; Xu, Y.; Ai, T.; Chen, L.; Verdin, E.; Kapila, Y. L. A Novel Sirtuin-3 Inhibitor, Lc-0296, Inhibits Cell Survival and Proliferation, and Promotes Apoptosis of Head and Neck Cancer Cells. *Anticancer Res.* **2016**, *36*, 49–60.

(602) Dekker, F. J.; Haisma, H. J. Histone Acetyl Transferases as Emerging Drug Targets. *Drug Discovery Today* **2009**, *14*, 942–8.

(603) Marmorstein, R. Structure and Function of Histone Acetyltransferases. *Cell. Mol. Life Sci.* **2001**, *58*, 693–703.

(604) Marcu, M. G.; Jung, Y. J.; Lee, S.; Chung, E. J.; Lee, M. J.; Trepel, J.; Neckers, L. Curcumin Is an Inhibitor of P300 Histone Acetyltransferase. *Med. Chem.* **2006**, *2*, 169–74.

(605) Arif, M.; Pradhan, S. K.; Thanuja, G. R.; Vedamurthy, B. M.; Agrawal, S.; Dasgupta, D.; Kundu, T. K. Mechanism of P300 Specific Histone Acetyltransferase Inhibition by Small Molecules. *J. Med. Chem.* **2009**, *52*, 267–77.

(606) Sun, Y.; Jiang, X.; Chen, S.; Price, B. D. Inhibition of Histone Acetyltransferase Activity by Anacardic Acid Sensitizes Tumor Cells to Ionizing Radiation. *FEBS Lett.* **2006**, *580*, 4353–6.

(607) Lau, O. D.; Kundu, T. K.; Soccio, R. E.; Ait-Si-Ali, S.; Khalil, E. M.; Vassilev, A.; Wolffe, A. P.; Nakatani, Y.; Roeder, R. G.; Cole, P. A. Hats Off: Selective Synthetic Inhibitors of the Histone Acetyltransferases P300 and Pcaf. *Mol. Cell* **2000**, *5*, 589–95.

(608) Gao, X. N.; Lin, J.; Ning, Q. Y.; Gao, L.; Yao, Y. S.; Zhou, J. H.; Li, Y. H.; Wang, L. L.; Yu, L. A Histone Acetyltransferase P300 Inhibitor C646 Induces Cell Cycle Arrest and Apoptosis Selectively in Aml1-Eto-Positive Aml Cells. *PLoS One* **2013**, *8*, e55481.

(609) Lasko, L. M.; Jakob, C. G.; Edalji, R. P.; Qiu, W.; Montgomery, D.; Digiammarino, E. L.; Hansen, T. M.; Risi, R. M.; Frey, R.; Manaves, V.; Shaw, B.; Algire, M.; Hessler, P.; Lam, L. T.; Uziel, T.; Faivre, E.; Ferguson, D.; Buchanan, F. G.; Martin, R. L.; Torrent, M.; Chiang, G. G.; Karukurichi, K.; Langston, J. W.; Weinert, B. T.;

Choudhary, C.; de Vries, P.; Van Drie, J. H.; McElligott, D.; Kesicki, E.; Marmorstein, R.; Sun, C.; Cole, P. A.; Rosenberg, S. H.; Michaelides, M. R.; Lai, A.; Bromberg, K. D. Discovery of a Selective Catalytic P300/Cbp Inhibitor That Targets Lineage-Specific Tumours. *Nature* **2017**, *550*, 128–132.

(610) Montgomery, D. C.; Sorum, A. W.; Guasch, L.; Nicklaus, M. C.; Meier, J. L. Metabolic Regulation of Histone Acetyltransferases by Endogenous Acyl-CoA Cofactors. *Chem. Biol.* **2015**, *22*, 1030–9.

(611) Feldman, J. L.; Baeza, J.; Denu, J. M. Activation of the Protein Deacetylase Sirt6 by Long-Chain Fatty Acids and Widespread Deacetylation by Mammalian Sirtuins. *J. Biol. Chem.* **2013**, *288*, 31350–6.

(612) Shirakawa, K.; Wang, L.; Man, N.; Maksimoska, J.; Sorum, A. W.; Lim, H. W.; Lee, I. S.; Shimazu, T.; Newman, J. C.; Schroder, S.; Ott, M.; Marmorstein, R.; Meier, J.; Nimer, S.; Verdin, E. Salicylate, Diflunisal and Their Metabolites Inhibit Cbp/P300 and Exhibit Anticancer Activity. *eLife* **2016**, *5*, 10.7554/eLife.11156

(613) Min, S. W.; Chen, X.; Tracy, T. E.; Li, Y.; Zhou, Y.; Wang, C.; Shirakawa, K.; Minami, S. S.; Defensor, E.; Mok, S. A.; Sohn, P. D.; Schilling, B.; Cong, X.; Ellerby, L.; Gibson, B. W.; Johnson, J.; Krogan, N.; Shamloo, M.; Gestwicki, J.; Masliah, E.; Verdin, E.; Gan, L. Critical Role of Acetylation in Tau-Mediated Neurodegeneration and Cognitive Deficits. *Nat. Med.* **2015**, *21*, 1154–62.

(614) Zeng, L.; Li, J.; Muller, M.; Yan, S.; Mujtaba, S.; Pan, C.; Wang, Z.; Zhou, M. M. Selective Small Molecules Blocking Hiv-1 Tat and Coactivator Pcaf Association. *J. Am. Chem. Soc.* **2005**, *127*, 2376–7.

(615) Mujtaba, S.; He, Y.; Zeng, L.; Farooq, A.; Carlson, J. E.; Ott, M.; Verdin, E.; Zhou, M. M. Structural Basis of Lysine-Acetylated Hiv-1 Tat Recognition by Pcaf Bromodomain. *Mol. Cell* **2002**, *9*, 575–86.

(616) Dorr, A.; Kiermer, V.; Pedal, A.; Rackwitz, H. R.; Henklein, P.; Schubert, U.; Zhou, M. M.; Verdin, E.; Ott, M. Transcriptional Synergy between Tat and Pcaf Is Dependent on the Binding of Acetylated Tat to the Pcaf Bromodomain. *EMBO J.* **2002**, *21*, 2715–23.

(617) Nishiyama, A.; Mochizuki, K.; Mueller, F.; Karpova, T.; McNally, J. G.; Ozato, K. Intracellular Delivery of Acetyl-Histone Peptides Inhibits Native Bromodomain-Chromatin Interactions and Impairs Mitotic Progression. *FEBS Lett.* **2008**, *582*, 1501–7.

(618) Miyoshi, S.; Ooike, S.; Iwata, K.; Hikawa, H.; Sugaraha, K. Antitumor Agent. Patent WO2009084693A1, 2009.

(619) Filippakopoulos, P.; Qi, J.; Picaud, S.; Shen, Y.; Smith, W. B.; Fedorov, O.; Morse, E. M.; Keates, T.; Hickman, T. T.; Felletar, I.; Philpott, M.; Munro, S.; McKeown, M. R.; Wang, Y.; Christie, A. L.; West, N.; Cameron, M. J.; Schwartz, B.; Heightman, T. D.; La Thangue, N.; French, C. A.; Wiest, O.; Kung, A. L.; Knapp, S.; Bradner, J. E. Selective Inhibition of Bet Bromodomains. *Nature* **2010**, *468*, 1067–73.

(620) Grayson, A. R.; Walsh, E. M.; Cameron, M. J.; Godec, J.; Ashworth, T.; Ambrose, J. M.; Aserlind, A. B.; Wang, H.; Evan, G. I.; Kluk, M. J.; Bradner, J. E.; Aster, J. C.; French, C. A. Myc, a Downstream Target of Brd-Nut, Is Necessary and Sufficient for the Blockade of Differentiation in Nut Midline Carcinoma. *Oncogene* **2014**, *33*, 1736–42.

(621) Nicodeme, E.; Jeffrey, K. L.; Schaefer, U.; Beinke, S.; Dewell, S.; Chung, C. W.; Chandwani, R.; Marazzi, I.; Wilson, P.; Coste, H.; White, J.; Kirilovsky, J.; Rice, C. M.; Lora, J. M.; Prinjha, R. K.; Lee, K.; Tarakhovsky, A. Suppression of Inflammation by a Synthetic Histone Mimic. *Nature* **2010**, *468*, 1119–23.

(622) Zhu, H.; Bengsch, F.; Svoronos, N.; Rutkowski, M. R.; Bitler, B. G.; Allegrezza, M. J.; Yokoyama, Y.; Kossenkova, A. V.; Bradner, J. E.; Conejo-Garcia, J. R.; Zhang, R. Bet Bromodomain Inhibition Promotes Anti-Tumor Immunity by Suppressing Pd-L1 Expression. *Cell Rep.* **2016**, *16*, 2829–37.

(623) Korb, E.; Herre, M.; Zucker-Scharff, I.; Darnell, R. B.; Allis, C. D. Bet Protein Brd4 Activates Transcription in Neurons and Bet Inhibitor Jq1 Blocks Memory in Mice. *Nat. Neurosci.* **2015**, *18*, 1464–73.

(624) Anand, P.; Brown, J. D.; Lin, C. Y.; Qi, J.; Zhang, R.; Artero, P. C.; Alaiti, M. A.; Bullard, J.; Alazem, K.; Margulies, K. B.; Cappola, T.

- P.; Lemieux, M.; Plutzky, J.; Bradner, J. E.; Haldar, S. M. Bet Bromodomains Mediate Transcriptional Pause Release in Heart Failure. *Cell* **2013**, *154*, 569–82.
- (625) Conrad, R. J.; Ott, M. Therapeutics Targeting Protein Acetylation Perturb Latency of Human Viruses. *ACS Chem. Biol.* **2016**, *11*, 669–80.
- (626) Winter, G. E.; Buckley, D. L.; Paulk, J.; Roberts, J. M.; Souza, A.; Dhe-Paganon, S.; Bradner, J. E. Drug Development. Phthalimide Conjugation as a Strategy for in Vivo Target Protein Degradation. *Science* **2015**, *348*, 1376–81.
- (627) Liu, Z.; Wang, P.; Chen, H.; Wold, E. A.; Tian, B.; Brasier, A. R.; Zhou, J. Drug Discovery Targeting Bromodomain-Containing Protein 4. *J. Med. Chem.* **2017**, *60*, 4533.
- (628) Roe, J. S.; Mercan, F.; Rivera, K.; Pappin, D. J.; Vakoc, C. R. Bet Bromodomain Inhibition Suppresses the Function of Hematopoietic Transcription Factors in Acute Myeloid Leukemia. *Mol. Cell* **2015**, *58*, 1028–39.
- (629) Lockwood, W. W.; Zejnullahu, K.; Bradner, J. E.; Varmus, H. Sensitivity of Human Lung Adenocarcinoma Cell Lines to Targeted Inhibition of Bet Epigenetic Signaling Proteins. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 19408–13.
- (630) Shi, J.; Wang, Y.; Zeng, L.; Wu, Y.; Deng, J.; Zhang, Q.; Lin, Y.; Li, J.; Kang, T.; Tao, M.; Rusinova, E.; Zhang, G.; Wang, C.; Zhu, H.; Yao, J.; Zeng, Y. X.; Evers, B. M.; Zhou, M. M.; Zhou, B. P. Disrupting the Interaction of Brd4 with Diacetylated Twist Suppresses Tumorigenesis in Basal-Like Breast Cancer. *Cancer Cell* **2014**, *25*, 210–25.
- (631) Lamonica, J. M.; Deng, W.; Kadauke, S.; Campbell, A. E.; Gamsjaeger, R.; Wang, H.; Cheng, Y.; Billin, A. N.; Hardison, R. C.; Mackay, J. P.; Blobel, G. A. Bromodomain Protein Brd3 Associates with Acetylated Gata1 to Promote Its Chromatin Occupancy at Erythroid Target Genes. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, E159–68.
- (632) Berthon, C.; Raffoux, E.; Thomas, X.; Vey, N.; Gomez-Roca, C.; Yee, K.; Taussig, D. C.; Rezai, K.; Roumier, C.; Herait, P.; Kahatt, C.; Quesnel, B.; Michallet, M.; Recher, C.; Lokiec, F.; Preudhomme, C.; Dombret, H. Bromodomain Inhibitor Otx015 in Patients with Acute Leukaemia: A Dose-Escalation, Phase I Study. *Lancet Haematol* **2016**, *3*, e186–95.
- (633) Odore, E.; Lokiec, F.; Cvitkovic, E.; Bekradda, M.; Herait, P.; Bourdel, F.; Kahatt, C.; Raffoux, E.; Stathis, A.; Thieblemont, C.; Quesnel, B.; Cunningham, D.; Riveiro, M. E.; Rezai, K. Phase I Population Pharmacokinetic Assessment of the Oral Bromodomain Inhibitor Otx015 in Patients with Haematologic Malignancies. *Clin. Pharmacokinet.* **2016**, *55*, 397–405.
- (634) Theodoulou, N. H.; Tomkinson, N. C.; Prinjha, R. K.; Humphreys, P. G. Clinical Progress and Pharmacology of Small Molecule Bromodomain Inhibitors. *Curr. Opin. Chem. Biol.* **2016**, *33*, 58–66.
- (635) Chen, P.; Chaikuad, A.; Bamborough, P.; Bantscheff, M.; Bountra, C.; Chung, C. W.; Fedorov, O.; Grandi, P.; Jung, D.; Lesniak, R.; Lindon, M.; Muller, S.; Philpott, M.; Prinjha, R.; Rogers, C.; Selenski, C.; Tallant, C.; Werner, T.; Willson, T. M.; Knapp, S.; Drewry, D. H. Discovery and Characterization of Gsk2801, a Selective Chemical Probe for the Bromodomains Baz2a and Baz2b. *J. Med. Chem.* **2016**, *59*, 1410–24.
- (636) Theodoulou, N. H.; Tomkinson, N. C.; Prinjha, R. K.; Humphreys, P. G. Progress in the Development of Non-Bet Bromodomain Chemical Probes. *ChemMedChem* **2016**, *11*, 477–87.
- (637) Sabari, B. R.; Tang, Z.; Huang, H.; Yong-Gonzalez, V.; Molina, H.; Kong, H. E.; Dai, L.; Shimada, M.; Cross, J. R.; Zhao, Y.; Roeder, R. G.; Allis, C. D. Intracellular Crotonyl-CoA Stimulates Transcription through P300-Catalyzed Histone Crotonylation. *Mol. Cell* **2015**, *58*, 203–15.
- (638) Hirschey, M. D.; Zhao, Y. Metabolic Regulation by Lysine Malonylation, Succinylation, and Glutarylation. *Mol. Cell. Proteomics* **2015**, *14*, 2308–15.
- (639) Weinert, B. T.; Iesmantavicius, V.; Moustafa, T.; Scholz, C.; Wagner, S. A.; Magnes, C.; Zechner, R.; Choudhary, C. Acetylation Dynamics and Stoichiometry in *Saccharomyces Cerevisiae*. *Mol. Syst. Biol.* **2014**, *10*, 716.