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ACETYLATION AND SIRTUINS: MOLECULAR MECHANISMS DRIVING METABOLIC FLEXIBILITY

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Abstract. Acetylation is a post-translational modification that alters protein function and plays a crucial role in regulating numerous cellular processes, especially metabolic flexibility, indicating the capacity of cells to modify their metabolic processes following changing energy demands and nutrient availability. Recent mechanistic advances have highlighted the role of mitochondrial sirtuins, such as SIRT3, in controlling acetyl-CoA pools for histone acetylation, directly affecting metabolic flexibility, particularly in the context of aging. Any change in acetylation and deacetylation state leads to the emergence of various metabolic disorders, including neurodegenerative diseases. Moreover, new reports underscore the crosstalk between acetylation and autophagy in the regulation of cancer metabolism, illustrating acetylation's broader regulatory roles. Modulating the activity of enzymes utilizing molecules with inhibitor and activator properties exhibits significant potential for clarifying the cellular functions of acetylation in metabolic sensing and developing therapeutics. This review discusses the enzymes, along with the mechanisms related to acetylation and metabolic flexibility and importantly, it highlights acetylation's influence on both proteostasis and autophagy. Pharmacological modulation of acetyltransferases and deacetylases through selective inhibitors and activators represents a promising therapeutic strategy for metabolic disorders, offering potential for precision medicine approaches. By combining current knowledge on acetylation-mediated metabolic regulation, critical gaps remain, such as the need to clarify sex-specific chromatin dynamics in acetylation. This review highlights critical gaps in understanding tissue-specific acetylation patterns and provides a framework for developing targeted interventions for treating complex metabolic diseases through modulation of the acetylation machinery.

Keywords: *Acetylation, sirtuins, deacetylation, metabolic flexibility, drug development.*

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1. Introduction

The escalating global prevalence of metabolic disorders, including type 2 diabetes, obesity, cardiovascular diseases and neurodegenerative conditions like Parkinson's and Alzheimer's disease, presents a pressing challenge to public health (Atabi *et al*., 2025; Dong *et al*., 2024; Patel & Edison, 2024; Ullah & Tamanna, 2025). Metabolic flexibility describes the cells' ability to utilize different energy substrates, such as glucose, fatty acids and ketones, depending on their availability and energy demands from the diet (Ang *et al*., 2025; Brunetta *et al*., 2022; Kawamura *et al*., 2022). Recent studies have further

emphasized that sedentary behavior directly impairs metabolic flexibility (Garthwaite *et al*., 2024). Mentioned disorders frequently have a basic impairment at their core known as metabolic inflexibility; the inability of cells to adapt their fuel usage in response to fluctuating energy demands and nutrient availability (Swarup *et al*., 2024). An increasing amount of evidence indicates that protein acetylation serves as a principal regulator of this essential metabolic flexibility. Consequently, comprehending the complex interplay between acetylation and metabolic flexibility is essential for formulating innovative therapeutic approaches. Acetylation is a dynamic post-translational modification (PTM) that modifies protein function, stability and localization by neutralizing the positive charge of lysine residues (Figure 1) (Eftekhari *et al*., 2025). This process is strictly controlled by the opposing functions of enzymes: acetyltransferases, which transfer acetyl groups from acetyl-CoA to proteins and deacetylases, which revert the modification. This latter group includes two main families, the histone deacetylases (HDACs) and the NAD^+ - dependent sirtuins (SIRTs) (Hamaidi & Kim, 2022; Soriano-Baguet & Brenner, 2023; X. Wang *et al*., 2024; Zeng *et al*., 2022). The balance between acetylation and deacetylation is crucial for sustaining cellular homeostasis and its disruption is directly linked to the onset of the previously mentioned metabolic diseases (Compton *et al*., 2023; Jiang *et al*., 2023). Specifically, sirtuins are essential energy sensors that connect cellular NAD^+ levels, which are affected by nutrition and exercise, to the deacetylation of important proteins, which in turn controls processes like the tricarboxylic acid cycle (TCA) cycle, glycolysis and fatty acid oxidation (Gibril *et al*., 2024; Lee & Yoon, 2024; Yusri *et al*., 2025). Recently, Wang et al. (2024) elucidated a pivotal role for sirtuins in orchestrating immune-metabolic flexibility, specifically by modulating the acetylation status of FOXO1 and thereby influencing immune cell adaptation to metabolic changes. Furthermore, SIRT3 modulates mitochondrial proteostasis in diabetes through reversible deacetylation of key mitochondrial proteins, maintaining a balanced, functional proteome, suppressing oxidative stress and regulating mitochondrial dynamics and turnover. In diabetic conditions, where SIRT3 expression/activity is often reduced, this regulation is impaired, contributing to disease progression and complications (Liu *et al*., 2015; Sack, 2012; Trinh *et al*., 2024; Wang & Wei, 2020).

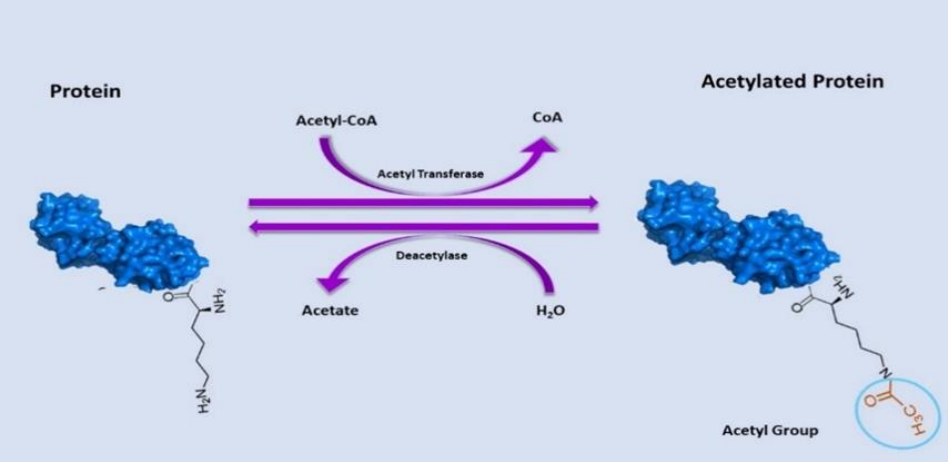

Figure 1. Protein acetylation mechanism. Acetyl transferases transfer the acetyl group from Acetyl Co-enzyme A (Acetyl CoA) to the lysine residue of the proteins. Conversely, deacetylases remove acetyl groups from acetylated lysine, forming acetate as a by-product

In addition, protein lysine acetylation is a well-recognized post-translational modification (PTM) that plays a vital role in regulating protein activity and numerous

cellular pathways. Although classical acetylation events primarily target lysine residues on proteins, emerging evidence has revealed additional non-canonical forms of acetylation, such as modifications occurring on transfer RNAs (tRNAs), that add further complexity to the regulation of cellular homeostasis, particularly under stress conditions (Arif *et al*., 2010; Yang *et al*., 2025; Yao & Huang, 2022). In tRNAs, acetylation primarily occurs at two non-canonical sites: cytidine at position 12 (C12) in the D-arm and N4-acetylcytidine at position 34 (ac4C34), which occupies the wobble position in the anticodon loop (Jin *et al*., 2020; Liu *et al*., 2025). While previous reviews have focused on specific aspects like sirtuins in aging or histone acetylation, a comprehensive synthesis linking the broader cellular acetylation landscape to metabolic flexibility is lacking. This review addresses that gap by summarizing the intricate relationship between acetylation, proteostasis and metabolic flexibility. This integrated approach provides a precise framework for developing novel therapeutics that target metabolic disorders.

2. Post-translational acetylation: Mechanisms and significance

PTM of proteins, such as acetylation, are essential for regulating many cellular processes, including metabolism. Acetylation has significant implications across various biological contexts, including the regulation of gene expression, cell signaling, homeostasis and metabolic control, resulting in implications for health and disease (Y. Wang *et al*., 2020). Protein acetylation primarily occurs in two forms: N-terminal acetylation (Nt-acetylation) and lysine acetylation. N-terminal (Nt-) acetylation is a widespread and often constitutive modification, estimated to occur on over 80% of all human proteins. This reaction is facilitated by one of seven Nt-acetyltransferases (NATs), NatA to NatF and NatH, involving catalytic subunits NAA10 to NAA60 and NAA80. NATs transfer the acetyl group from acetyl coenzyme A (AcCoA) to the free N-terminal α-amino group of target proteins. NatF directly associates with the Golgi membrane for the Nt-acetylation of transmembrane proteins, whereas NatA to NatE associate with ribosomes for cotranslational function (McTiernan *et al*., 2025; Rebowski *et al*., 2020; Ree *et al*., 2024). This type of acetylation profoundly have impacts on protein folding, stability, subcellular localization and complex formation (Calis & Gevaert, 2025; Varland *et al*., 2023). Varland et al. (2023) demonstrated that N-terminal acetylation serves as a potent protective mechanism against protein degradation by preventing the recognition and ubiquitination of proteins by N-degron pathways, thereby enhancing protein stability in human cells. It also functions as a key part of protein quality control, either protecting proteins from degradation or marking them for specific proteolytic pathways (Eldeeb *et al*., 2019). In addition to acetylation at lysine and N-terminal residues, non-lysine acetylation, such as acetylation of cysteine residues, is emerging as a critical redox and metabolic regulatory mechanism. Cysteine acetylation can modulate protein activity, affect the redox state and serve as a reversible switch in response to cellular metabolism and oxidative stress. This highlights the expanding landscape of acetylation, extending regulatory roles well beyond classical substrates and implicating acetylation as a central integrator of metabolic and redox signaling (Keenan *et al*., 2024; McTiernan *et al*., 2025; Percio *et al*., 2024). Lysine acetylation modification, a prominent form of protein modification, affects both histone and non-histone acetylation variations (J.M. Wang *et al*., 2021). In contrast to the widespread nature of Nt-acetylation, the acetylation of internal lysine residues is a highly dynamic and reversible process that acts as a critical regulatory switch (Ali *et al*., 2018; Wang & Lin, 2021). Proteomic studies revealed that non-histone proteins commonly undergo acetylation and influence biological processes such as DNA repair, transcription, signal transduction, cell division, autophagy, protein

folding and metabolism (Zhang *et al*., 2021). Histone acetylation usually takes place in specific lysine residues located in the region of the N-terminal of the core histone where the concentration of basic amino acids is high (Bao & Yang, 2024; Li *et al*., 2020). This process is mediated by lysine acetyltransferases (KATs) and is reversible, regulated by deacetylases (Table 1). Deacetylases are divided into two main subgroups: NAD-dependent sirtuins (SIRTs) (Figure 2) and lysine deacetylases (KDACs), which utilize Zn^{2+} as a cofactor (De Loof *et al*., 2023; Jung *et al*., 2020). Histone deacetylases (HDACs), previously referred to as KDACs, are critical for maintaining genomic integrity, regulating the cell cycle and controlling differentiation, with significant implications for tumorigenesis (Table 2) (Zrimšek *et al*., 2022).

Table 1. Summary of KATs, their major histone and non-histone targets and subcellular localization

Family	Enzyme	Histone targets	Non-histone targets	Subcellular localization
MYST (canonical)	KAT6A (MOZ, MYST3)	H3K9, H3K14, H3K23	p53	Nucleus
	KAT6B (MORF, MYST4)	H3K9, H3K14, H3K23	—	Nucleus
	Tip60 (KAT5)	H3K14, H4K5/8/12/16	p53, c-Myc, Rheb, ULK1, Pacer	Nucleus
	KAT8 (MOF, MYST1)	H4K16	p53, Nrf2, TIP5, IRF3, ATP5B	Nucleus, mitochondria
	HBO1 (KAT7, MYST2)	H3K14, H4K5/8/12	ORC2, MCM2, CDC6	Nucleus, cytoplasm
GNAT (canonical)	HAT1 (KAT1)	H2AK5, H4K5, H4K12	CBP, HBO1, AGK, DECR1, ATP5B	Nucleus, cytoplasm, mitochondria
	KAT2A (GCN5)	H3K9, H3K14	c-Myc, PGC-1α, C/EBPα, α-tubulin	Nucleus, cytoplasm
	KAT2B (PCAF)	H3K9, H3K14	p53, c-Myc, FoxP3	Nucleus, cytoplasm
p300/CBP (canonical)	CBP (KAT3A)	H3K18, H3K27	p53, NF-κB, Stat1, Ku70, YAP	Nucleus, cytoplasm
	p300 (KAT3B)	H2A, H2B, H3K12, H3K18, H3K23, H3K27	NF-κB, c-Myc, raptor, androgen receptor, Beclin1, p53	Nucleus, cytoplasm
Non-canonical	TAF1 (KAT4, TFIID complex formation)	H3, H4	—	Nucleus
	ELP3 (KAT9, elongator complex)	H3	α-tubulin	Nucleus, cytoplasm
	GTF3C4 (KAT12, TFIIIC2 complex)	H3	—	Nucleus
	NCOA1 (SRC1, KAT13A)	H3, H4	—	Nucleus
	NCOA2 (SRC2, TIF2, KAT13C)	H3, H4	—	Nucleus
	NCOA3 (SRC3, KAT13B)	H3, H4	—	Nucleus
	CLOCK (KAT13D)	H3K9, H3K14	BMAL1	Nucleus

Source: Keller and Nakamura (2024)

Table 2. Summary of HDACs and their characteristics

Class	Members	Subcellular Localization	Key Substrates	Site-Specific Target
Class I	HDAC1	Nuclear	Histones H3/H4, p53, E2F1	H3K9, H3K14, H4K5, H4K12
	HDAC2	Nuclear	Histones H3/H4, STAT3, YY1	H3K9, H4K5, H4K16
	HDAC3	Nuclear/cytoplasm	Histones, STAT3, RelA	H3K9, H4K5, H4K12
	HDAC8	Nuclear/cytoplasm	SMC3, p53, Cohesin, Non-deacetylase activities	H3K9, H3K14, deacylation, regulation of cohesion
Class IIa	HDAC4	Nuclear and cytoplasm	MEF2, histones, FOXO	H3K9, H3K14, H4K16
	HDAC5	Nuclear and cytoplasm	MEF2, histones, FOXO	H3K9, H3K14, H4K16
	HDAC7	Nuclear and cytoplasm	MEF2, histones, FOXO	H3K9, H3K14, H4K16
	HDAC9	Nuclear and cytoplasm	MEF2, histones, FOXO	H3K9, H3K14, H4K16
Class IIb	HDAC6	Primarily cytoplasm	α-tubulin, HSP90, cortactin	α-tubulin-K40
	HDAC10	Cytoplasm	HSP90	Various lysine residues
Class III	SIRT1	Nuclear/cytoplasm	P53, FOXO, H3/H4	H4K16, p53-K382, H3K9
	SIRT2	Cytoplasm	α-tubulin, FOXO, H4, glucose metabolism	H4K16, α-tubulin-K40, regulation of glucose homeostasis
	SIRT3	Mitochondria	LCAD, AceCS2, SOD2	SOD2-K122, AceCS2-K642
	SIRT4	Mitochondria	GDH, PDH, MCD	GDH-K residues
	SIRT5	Mitochondria	CPS1, HMGCS2, stress response substrates	CPS1-K residues, desuccinylation in stress signaling
	SIRT6	Nuclear	H3, TNF-α, HIF-1α	H3K9, H3K56
	SIRT7	Nuclear	H3, rDNA, PAF53	H3K18, rDNA regulation
Class IV	HDAC11	Nuclear/cytoplasm	Histones, IL-10	H3K9, H3K14
Class III	SIRT1	Nuclear/cytoplasm	P53, FOXO, H3/H4	H4K16, p53-K382, H3K9
	SIRT2	Cytoplasm	α-tubulin, FOXO, H4, glucose metabolism	H4K16, α-tubulin-K40, regulation of glucose homeostasis
	SIRT3	Mitochondria	LCAD, AceCS2, SOD2	SOD2-K122, AceCS2-K642
	SIRT4	Mitochondria	GDH, PDH, MCD	GDH-K residues
	SIRT5	Mitochondria	CPS1, HMGCS2, stress response substrates	CPS1-K residues, desuccinylation in stress signaling
	SIRT6	Nuclear	H3, TNF-α, HIF-1α	H3K9, H3K56
	SIRT7	Nuclear	H3, rDNA, PAF53	H3K18, rDNA regulation
Class IV	HDAC11	Nuclear/cytoplasm	Histones, IL-10	H3K9, H3K14

Source: Cheung et al. (2024); Costanzo et al. (2025); Gautam et al. (2025); Mieland et al. (2025); Nowacka et al. (2025); Reisbitzer et al. (2025); Ren et al. (2025); Yudaev et al. (2025); C. Zhang et al. (2025); Y. Zhang et al. (2025); Zheng et al. (2025); Zhou et al. (2025); Zhu et al. (2025)

It is regulated by the dynamic balance among acetyl-CoA, NAD^+, acetyltransferases and deacetylases, allowing precise control of acetylation levels in cells. Acetyl-CoA supplies the acetyl groups to acetylate both non-histone and histone proteins (Zrimšek *et al*., 2022). Its accumulation in the cytosol can promote protein acetylation and prevent autophagy, which has a detrimental effect on metabolic health (H. Wang *et al*., 2020). In addition to histones, non-histone lysine acetylation targets a wide array of regulatory

proteins, including transcription factors, metabolic enzymes, signaling mediators and structural proteins, greatly expanding the scope of lysine acetylation in cell biology (Encarnacion-Guevara & Gil, 2025; Narita *et al*., 2019; Thomas *et al*., 2024). Recent research demonstrates that non-histone protein acetylation serves as a key modulator of proteostasis in cancer, actively shaping protein stability, controlling degradation mechanisms and enhancing tumor cell resilience to proteotoxic challenges (Crawford & Burslem, 2025; J. Yang *et al*., 2022; Zhao *et al*., 2014). Non-histone acetylation targets various proteins, including transcription factors, metabolic enzymes, signaling molecules and structural proteins, suggesting its potential role in regulating different cellular processes, highlighting its role in maintaining cellular homeostasis and adaptive responses exerts extensive effects on general cellular homeostasis and adaptive responses (Barman *et al*., 2024). Furthermore, lysine acetylation plays a significant role in regulating chromatin structure and gene expression by modifying both histone and non-histone proteins, thereby impacting cellular senescence and contributing to the progression of aging and aging-related disorders (Xu *et al*., 2025). In addition, NAD^+, a critical cofactor for sirtuins, facilitates protein deacetylation by transferring acetyl groups from lysine residues to NAD^+, producing NAM and O-acetyl-ADPr (Ji & Yeo, 2021; Xie *et al*., 2020).

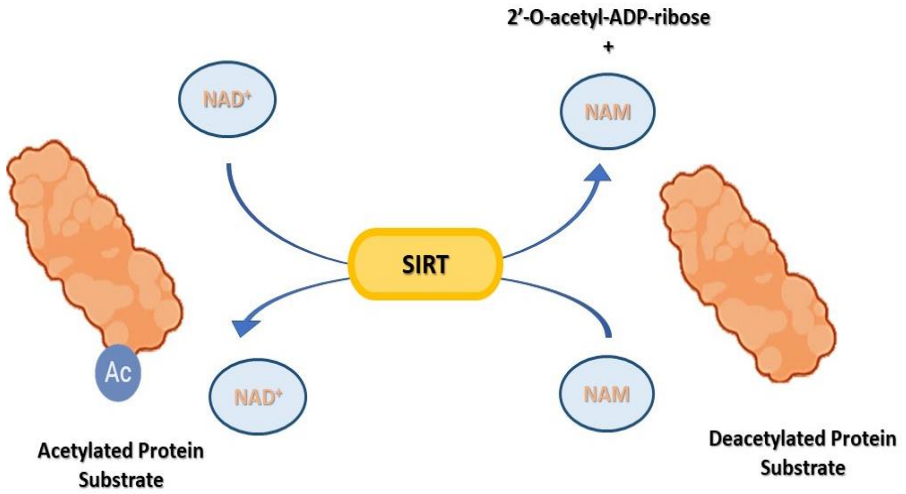

Figure 2. SIRTs catalyze the enzymatic activity model. NAD: nicotinamide adenine dinucleotide, NAM: nicotinamide

2.1. Sirtuins: Structure, function and regulation

SIRTs, members of the class III histone deacetylase enzyme family, are particular enzymes that catalyze PTMs by using NAD^+ as a co-substrate to eliminate acyl groups from lysine residues. This activity influences the function and stability of proteins, controlling physiological processes such as aging, transcription, mitochondrial biogenesis, brain diseases, cardiovascular problems, apoptosis, cancer, genomic stability and metabolic abnormalities. In mammals, seven human SIRT homologs (SIRT1-7) have been identified, each exhibiting diverse enzymatic activity (Park *et al*., 2020). The enzymes share a catalytic core of close similarity, 275 amino acids in size and are classified into five phylogenetic classes (Classes I-V and U-class). While U-class SIRTs are only found in Gram-positive bacteria, there are seven SIRTs encoded in the human genome and located in various cellular compartments: SIRT1, SIRT6 and SIRT7 are nuclear; SIRT2, cytosolic; while SIRT3, SIRT4 and SIRT5 are mitochondrial (Figure 3)

(Heger *et al*., 2019; Pande *et al*., 2020). SIRTs consist of two main domains, including the C-terminal and the N-terminal domain; the C-terminal domain plays a role in the recognition and binding of substrates (Figure 4). The variation observed among individual SIRTs, such as chemical composition, vulnerability to PTMs (commonly phosphorylation) and length, influences their specificity for different substrates. The latter domain exhibits lower conservation and can potentially impact the stability and interaction of SIRTs with other proteins. Furthermore, it could potentially contribute to the control of SIRTs activity. Moreover, the most highly conserved called catalytic domain is the core structure of SIRTs and controls their enzymatic activity. This domain has two subdomains, including the NAD^+-binding site comprising the large subunit and an active site, including a small subunit that has residues that are essential positioning of the acetyl-lysine substrate and the NAD^+ cofactor. The NAD^+ domain often contains the α/β Rossman fold. Additionally, it is found in a small spherical domain equipped with two insertions, one for the helical module and the other for zinc ion binding (Cao *et al*., 2022; Sharma *et al*., 2022; Teixeira *et al*., 2020).

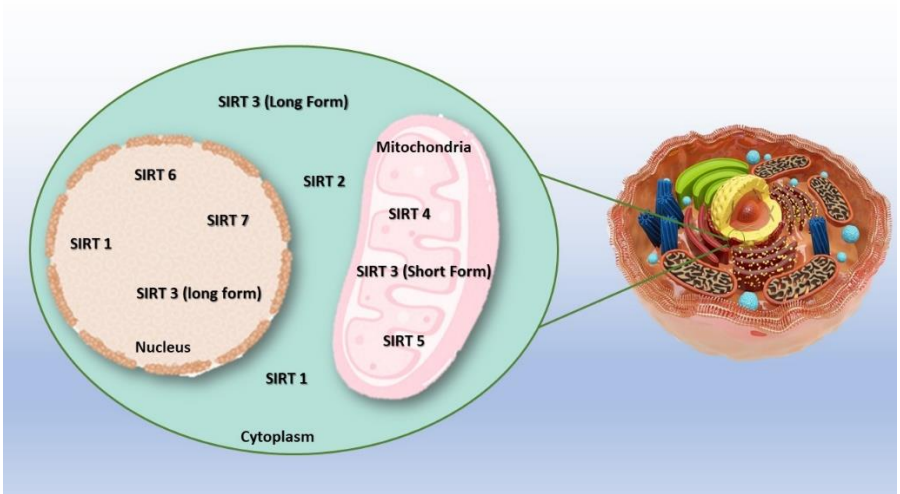

Figure 3. Subcellular location of SIRTs. The SIRT family, specifically SIRT1, SIRT6 and SIRT7, predominantly localizes to the nucleus. Nonetheless, SIRT1 can occasionally be translocated to the cytoplasm. SIRT2 is localized in the cytoplasm. SIRT3-5 is situated within the mitochondria. Under stress conditions, full-length SIRT3 translocates from the cytoplasm to the mitochondria and undergoes cleavage into shorter forms. Full-length human SIRT3 is also present in the nucleus

Recent studies emphasize the dynamic regulation of sirtuins via allosteric mechanisms. Notably, SIRT2 can be inhibited allosterically by compounds such as FLS-359, which do not compete at the active site (Roche *et al*., 2023; Tang *et al*., 2024). The structural flexibility and broad substrate range of SIRT2 complicate drug development and ongoing research focuses on understanding how allosteric modulators control its function, particularly in neurological disease settings. In parallel, SIRT7 has been identified as a significant regulatory sirtuin, particularly in the context of cancer biology. According to recent evidence, SIRT7 promotes thyroid oncogenesis by inducing phosphorylation of key signaling proteins, specifically Akt (Protein Kinase B) and ribosomal protein S6. Through these actions, SIRT7 supports cellular proliferation and survival pathways that are essential for tumor development and progression. In addition to its role in oncogenic signaling, SIRT7 is recognized as a central regulator of genomic stability and gene expression, controlling several fundamental processes including metabolic regulation and cellular stress responses (Fiorentino *et al*., 2025).

Currently, the interactions between activators and inhibitors of the SIRT family are not well understood. In this study, we introduce two activators for SIRT3. Honokiol (HKL) interacts with SIRT3 under two conditions: without and with Carba-NAD. In the absence of Carba-NAD, HKL binds to the flexible cofactor binding loop in a closed conformation, forming hydrogen bonds with Ser162 and Gly163, along with hydrophobic interactions with Pro155 and Leu164. In contrast, in the presence of Carba-NAD, HKL occupies an internal pocket that overlaps with the NAD^+ binding site, establishing hydrogen bonds with Arg158 and van der Waals interactions with Phe294, Phe327, Leu322 and Val324. This interaction stabilizes the closed-loop conformation despite the presence of the nicotinamide moiety of Carba-NAD. Key residues for binding without Carba-NAD include Ser162, Gly163, Pro155 and Leu164, while in the presence of Carba-NAD, key residues include Arg158 (hydrogen bond), Phe294, Phe327, Leu322 and Val324 (van der Waals interactions) (Guan *et al*., 2024) (Figure 4). In addition, the binding of SZC-6 to residues Phe180 and Phe294 is essential (Li *et al*., 2023; D. Zhang *et al*., 2025).

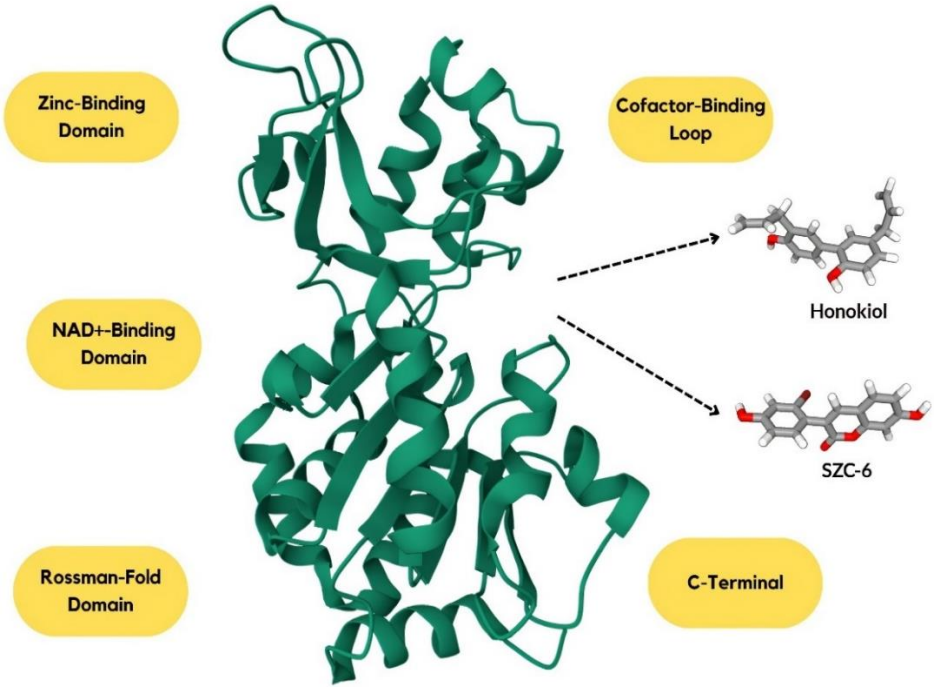

Figure 4. Structural insights into SIRT3 (PDB ID: 5D7N): Honokiol binds to SIRT3's cofactor binding loop in the absence of Carba-NAD, engaging key residues such as Ser162 and Gly163. In the presence of Carba-NAD, Honokiol overlaps with the NAD^+ binding site, stabilizing the closed-loop conformation through interactions with Arg158 and various hydrophobic residues. Additionally, the binding of SZC-6 at residues Phe180 and Phe294 further illustrates crucial interaction dynamics

2.2. Acetylation and sirtuins in metabolic flexibility

Metabolic flexibility is a term that refers to the capacity of the body organism to adjust its metabolic processes in response to varying fuel sources, including carbohydrates and fats, utilization for energy, influenced by variables such as diet, exercise intensity and overall energy requirements (Garthwaite *et al*., 2024; H. Wang *et al*., 2020). It is an essential component of human physiology that significantly contributes to overall health and disease, resulting in lifespan. For instance, skeletal muscle in lean or physically active individuals demonstrates a significant capacity to adjust fuel preference according to nutrient availability and during the short burst of intensive

exercise, the body can use glycogen stores; meanwhile, in long, steady activities, they can burn fat (Conn *et al*., 2024; Miranda-Cervantes *et al*., 2023). Metabolic flexibility has been regulated by pathways that respond to energy and nutrient availability. During nutrient intake, pathways such as the Mammalian Target of Rapamycin (mTOR) and insulin and insulin-like Growth Factor-1 (IGF-1) are activated and the fasting state engages pathways involving AMP-Activated Protein Kinase (AMPK), SIRT deacetylases and PPARγ coactivator 1-α (Garcia & Shaw, 2017).

SIRTs and acetylation are essential for controlling metabolic flexibility. Acetylation may alter the activity, stability and interactions of proteins and enzymes, while the SIRTs act as a counterbalance to acetylation (Nahálková, 2022); together, they play a regulatory role in key metabolic pathways. Dysregulation of acetylation and SIRT activity has been implicated in various diseases, including type II diabetes, cancer, obesity, sepsis, cardiovascular diseases and inflammation (Du *et al*., 2024; Xu *et al*., 2021).

2.2.1. Effects of acetylation on metabolic enzymes and pathways

Acetylation can directly affect enzyme activity, enhancing it, such as pyruvate dehydrogenase or acetyl-CoA carboxylase or inhibiting it, as in the case of the glycolytic enzymes (J.M. Wang *et al*., 2021). Secondly, it has the ability to alter the affinity of enzymes to a substrate by modifying their active site, which can result in a change in metabolic reactions (Wagner *et al*., 2023). For example, acetylation of lactate dehydrogenase can influence anaerobic respiration. Thirdly, modifying proteins that have a role in gene expression affects the expression of genes that encode metabolic enzymes, thereby significantly impacting metabolic pathways (Aghayev *et al*., 2023; Rachdaoui *et al*., 2017).

2.2.2. Acetylation and proteostasis

Proteostasis, also known as protein homeostasis, is a highly conserved cellular process important for cell survival across species. The concept involves various cellular mechanisms responsible for protein synthesis, folding, transport and breakdown, ensuring adequate cellular function and protein homeostasis. Aging is associated with the gradual decline of proteostasis and other cellular functions, which, in turn increases the organism's susceptibility to age-related diseases such as Alzheimer's and cardiovascular diseases (Zimmermann *et al*., 2021).

Indeed, acetylation might modulate proteostasis by changing how proteins fold, chaperone activity, autophagy, stability and ubiquitination modification (Aksnes *et al*., 2019; François *et al*., 2023). Omkar and coworkers (2024) demonstrate that acetylation of some specific lysin residues in Ydj1 in yeast prevents its interaction with Ssa1, decreasing protein folding. A study by Barrett and Westerheide (2022) showed the acetylation of heat shock transcription factor via lysine acetyltransferase CBP-1. elegans homolog of mammalian CBP/p300 regulates the heat shock response and protein folding in C. elegans. Moreover, the acetylation of the autoinhibitory loop in p300 facilitates the alleviation of autoinhibition, enabling the enzyme to assume a more active conformation, as reported by Kaypee et al. (2018). Sahbane and Onufriev (2021) demonstrated that the acetylation of the tail of H4 histone significantly compacts and “folds” the intrinsically disordered tail converting it from a random coil configuration into a more globular and compact one.

It has been discovered that lysine acetylation participates in protein homeostasis mainly on the expression levels of transcription factors and molecular chaperones through epigenetic modifications of histone proteins. Acetylation appears to regulate the

expression of chaperone proteins, which are crucial for maintaining proteostasis (Shui *et al*., 2023). Additionally, acetylation of Hsp70 at lysine 126 (K126) significantly diminishes its chaperone activity; this action modifies its interactions with co-chaperones and apoptosis-related proteins, thus hindering its protein folding and cellular protective functions (Sun *et al*., 2019). Besides, several studies in acute pancreatitis have suggested that it plays a critical role in disease progression and represents a promising therapeutic target (Li *et al*., 2025).

Sheehan et al. (2021) investigated that acetylation of ATG9A was shown to affect its interactome associated with the endoplasmic reticulum membrane proteins FAM134B and SEC62 and induced interaction with LC3B autophagy protein recruitment to effect reticulophagy. Acetylation at residue K276 of RB1CC1 also prevents its ubiquitination and thereby degradation but it also prevents this protein from becoming stable and elevated levels of RB1CC1 in cells. Inhibition of CREBBP (an acetyltransferase protein), which blocks the acetylation of RB1CC1 at K276, leads to a reduction in RB1CC1 levels and autophagy activity in breast cancer cells (Yi *et al*., 2023). In addition, the acetylation state of the autophagy-related proteins particularly the ATG7 has been identified as a key regulator of the process as well as the induction of macro-autophagy and LC3-associated micro-autophagy under different cellular and environmental stress conditions (Xu *et al*., 2024).

Varland et al. (2023) discussed that the N-terminal acetylation of proteins achieved by NatC protects from degradation via the Arg/N-degron pathway and the absence of NatC-mediated acetylation leads to reduced stability and raised degradation of various NatC substrate proteins, such as the enzymes UBE2M and UBE2F, which are involved in cullin neddylation. The acetylation of p53 by p300/CBP or PCAF/GCN5 increases the stability of p53 within cells. Cycloheximide chase experiments demonstrated a significant increase in the half-life of p53 following treatment with AceTAG molecules, a chemo-genetic tagging system developed in L.Y. Chen's research group (2024) (Figure 5).

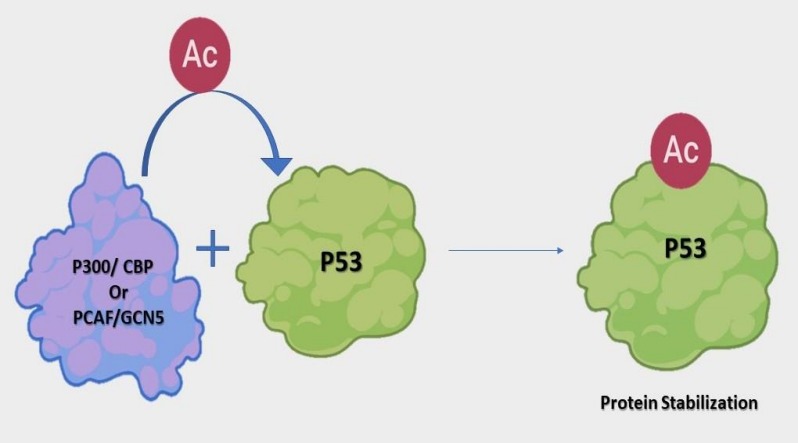

Figure 5. The process of acetylation of p53 by p300/CBP or PCAF/GCN5 led in protein stabilization

Recently, Liu et al. (2014) discussed that the acetylation of USP26 (ubiquitin-specific protease 26) in lysine residue by Tip60 improves the interaction between USP26 and BAG3 (co-chaperone Bcl-2-associated athanogene 3), resulting in increased de-ubiquitination and stabilization of BAG3. The GSDMD (Gasdermin D) is a crucial mediator of pyroptosis, a form of programmed necrotic cell death. Its acetylation at the Lys248 residue facilitates the ubiquitination of GSDMD, especially K27-linked ubiquitination, which promotes GSDMD-dependent pyroptotic cell death. The

deacetylation of GSDMD by HDAC4 inhibits this acetylation-dependent ubiquitination of GSDMD (Xu *et al*., 2023). Moreover, it has been found that the acetylation of MYC (MYC oncogenic transcription factor), which is mainly acetylated via the p300 and GCN5 histone acetyltransferases at various lysine residues (K148/149, K157/158 and K323) exhibits differential effects on its stability, which is dependent on the specific cell type. MYC acetylated at K148/149 or K157/158, which are the primary p300 target sites, exhibited relative instability, with a half-life of approximately 30-37 minutes in both Rat1a fibroblasts and MCF10A mammary epithelial cells, while MYC acetylated at K323 (the primary GCN5 target site) was highly stable with a half-life over 2 hours in Rat1a fibroblasts, but not in MCF10A cells where it had a short half-life of around 30 minutes (Hurd *et al*., 2023). You and coworkers (2023) reported that lysine acetylation has been shown to inhibit polyubiquitin chain elongation. This is not only due to blocking the modification site, but acetylation also inhibits the ubiquitination of other lysine residues. The modification of the protein NAT10 through lysine 2-hydroxyisobutyrylation was found to be significantly upregulated in cancer metastases by Liao et al. (2023).

2.2.3. Sirtuin-mediated deacetylation and its effects on metabolism

SIRTs are essential in regulating metabolism within human cells. It connects cellular energy status with metabolic regulation, influencing insulin sensitivity, fatty acid oxidation and overall metabolic health (Yi *et al*., 2021). For example, Velagapudi and coworkers (2023) demonstrated that SIRT1 binds directly to and deacetylates PCSK9 at specific lysine residues, thereby reducing PCSK9 activity and enhancing LDL-C clearance via the LDLR pathway in human hepatocytes. Additionally, Furukawa et al. (2021) found that the Sirt1 pathway is crucial in mediating the effects of the DPP-4 (Dipeptidyl peptidase-4) inhibitor vildagliptin on FGF21 expression in cardiac fibroblasts, subsequently affecting myocardial energy metabolism. SIRT3 is crucial for regulating endothelial cell metabolism and autophagy during the endothelial-to-mesenchymal transition induced by Angiotensin II. SIRT3 deficiency impairs autophagy, exacerbating the shift towards glycolytic metabolism in endothelial cells during the endothelial-to-mesenchymal transition (EndoMT). SIRT3 modulates this metabolic transition by facilitating the autophagic degradation of the glycolytic enzyme pyruvate kinase M2 (Gao *et al*., 2020). It was reported that SIRT4 ADP-ribosylates and inhibits glutamate dehydrogenase, thereby repressing the entry of carbon into the TCA cycle from glutamine. It also inhibits malonyl-CoA decarboxylase, altering the equilibrium between fatty acid synthesis and oxidation and deacetylates and destabilizes the α-subunit of the mitochondrial trifunctional protein, leading to a reduction in fatty acid oxidation (Betsinger & Cristea, 2019). Moreover, Hu et al. (2020) showed that miR-383 targets and suppresses SIRT1, leading to increased oxidative stress and cell death in diabetes and cardiovascular diseases.

2.2.4. Diseases associated with altered acetylation: Case studies of specific metabolic processes affected

Altered acetylation significantly influences various diseases, including metabolic disorders. Acetylation significantly influences the progression of neurodegenerative diseases through its effects on histone modifications and transcriptional regulation. To understand its effect a study by Yin et al. (2022) tries to explain how acetyl-CoA metabolism, through the action of an enzyme known as ACSS2, contributes to the development of fear memory in mouse and rat models. They found that histone acetylation, regulated by the balance between HATs and HDACs, is crucial in forming

long-term memory. The impaired formation of fear memory was associated with reduced histone acetylation, notably H3K9ac and H4K5ac (Wang *et al*., 2022). Similarly, Gano et al. (2018) on rats showed the expression of SIRT3 protein was decreased during the chronic phase of epilepsy. In contrast, global mitochondrial acetylation increased by 60% in chronically epileptic rats in comparison to controls, which indicates diminished SIRT3 activity in chronic epilepsy. Additionally, in chronically epileptic rats, the acetylation of specific SIRT3 substrates was elevated.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative condition characterized by the gradual deterioration of motor neurons. Research conducted by Rossaert et al. (2019) has indicated that intrinsic metabolic dysregulation could play a role in the development of disease pathology. In a transgenic FUS mouse model that resembles human ALS, notable decreases in global histone acetylation were observed. The changes observed in acetylation were linked to disturbances in metabolic gene expression and modifications in energy homeostasis. Also, the research indicated that prolonged administration of the HDAC inhibitor ACY-738 led to a restoration of global histone acetylation levels. The restoration of acetylation was accompanied by a normalization of metabolic gene expression and a re-establishment of metabolite levels within the spinal cord.

In Huntington's disease, Narayan and coworkers (2020) reported a significant increase in histone H4 acetylation (AcH4) levels in the sensory cortex, motor cortex and middle temporal gyrus of post-mortem Huntington's disease brain samples compared to controls. Moreover, Beaver and teammates (2020) discussed the disruption of acetylation homeostasis, particularly the imbalance between HAT Tip60 and HDAC2, which constitutes an early pathogenic event that results in transcriptional dysregulation of synaptic genes and subsequent neuronal dysfunction in various neurodegenerative disorders on *Drosophila* models (fruit fly).

Abnormal acetylation profoundly impacts on metabolism in various diseases, including diabetes and NAFLD. One of the most widely used diabetes drugs, metformin, has been shown to exert part of its therapeutic effect by modulating acetylation. Specifically, metformin inhibits p300/CBP activity, thereby reducing the acetylation of histones and other proteins involved in metabolic regulation (Marmorstein & Zhou, 2014). Additionally, Kerr and teammates (2020) conducted a study using rats with type 2 diabetes. They indicated that energetic dysfunction in diabetic hearts was linked to reduced mitochondrial respiration and ATP synthesis rates and this reduction in mitochondrial function was related to elevated acetylation of mitochondrial proteins in the hearts of individuals with Type 2 Diabetes. Chen et al. (2021) reported that the Sirtuin3 rs28365927 variant leads to a decreased acetylation state that impairs mitochondrial function and elevates oxidative stress. This results in heightened susceptibility to non-alcoholic fatty liver disease and exacerbating liver injury in affected individuals in the Chinese Han population.

In cancer, dysregulated acetylation promotes tumor progression and metastasis. High acetylation, primarily via the N4-acetylcysteine (ac4C) modification facilitated by the acetyltransferase NAT10, correlates with various diseases. Elevated NAT10 expression correlated with unfavorable lymph node metastasis, prognosis and distant metastasis in colorectal cancer patients. NAT10 facilitated tumor growth, suppressed apoptosis and increased proliferation, invasion and migration of colorectal cancer cells (Jin *et al*., 2022). Also, acetylation levels of CLIC1 at K131 were significantly elevated in primary cervical cancer tissues relative to adjacent normal tissues. Acetylation of CLIC1, resulting in its stabilization, enhances multiple malignant characteristics of

cervical cancer cells, such as elevated proliferation, migration and invasion, observed in both in vitro and in vivo studies (W. Wang *et al*., 2021).

Furthermore, acetylation plays a crucial role in regulating both histone and non-histone proteins within the heart, influencing cellular energy metabolism, contractility and the response to stress. Certain proteins, including LCAD/SCAD and β-HAD, along with transcription factors such as GATA4 and MEF2C, are recognized for undergoing acetylation modifications, which subsequently influence their roles in fatty acid oxidation and the hypertrophic response. Studies have shown that during times of metabolic stress, particularly in the context of obesity and type 2 diabetes, there is an increase in non-enzymatic acetylation, which is attributed to increased levels of acetyl-CoA. The process of hyperacetylation affects protein activity, resulting in compromised mitochondrial function and diminished fatty acid oxidation, both of which play a direct role in cardiac dysfunction (Dubois-Deruy *et al*., 2022). Heart failure represents the ultimate outcome of various metabolic cardiovascular conditions. In the context of heart failure, it is commonly noted that there is a widespread increase in protein acetylation, which is often attributed to the reduced activity of deacetylases like SIRT3 and SIRT6 (Cao *et al*., 2022; Saiyang *et al*., 2021).

2.3. Therapeutic implications

2.3.1. Potential of targeting acetylation/deacetylation for metabolic disorders

Modulating acetylation and deacetylation is a promising therapeutic approach against metabolic disorders. Several proteins involved in this process, including acetyltransferase, HDACs and SIRTs, have been identified as potential therapeutic targets.

2.3.1.1. Histone deacetylases

HDACs are considered epigenetic enzymes because they regulate transcriptional activation and chromatin remodeling by removing acetyl groups from the epsilon-amino groups of lysine residues in histonic and nonhistonic proteins. Deacetylation itself plays a critical role in gene expression, protein stability and cellular function. Based on differences in structure, function and cellular localization, HDACs are classified into four classes: class I, class II, class III and class IV. They are implicated in various biological processes and diseases, making them promising therapeutic targets.

HDACs are required for fungal growth and virulence by regulating non-histone proteins' deacetylation, such as the molecular chaperone Hsp90. The interaction of HDACs with Hsp90 plays a significant function in antifungal drug resistance. For this purpose, Li and coworkers (2022) developed a dual inhibitor. While it showed a selective inhibition of fungal HDACs and Hsp90 and compared to human counterparts, it showed remarkable synergistic antifungal activity against azole-resistant *Candida albicans* both in vitro and in vivo.

HDAC8 is a zinc-dependent histone deacetylase that facilitates the deacetylation of non-histone proteins. According to the recent DrugBank website (https://go.drugbank.com/), HDAC8 inhibitors include 4-(dimethylamino)-N-[7-(hydroxyamino)-7-oxoheptyl]benzamide, Abexinostat, Acetyldinaline, Alteminostat, Belinostat, Bufexamac, CG-200745, Citarinostat, CUDC-101, Entinostat, Fimepinostat, Givinostat, Mocetinostat, Nanatinostat, OBP-801, Panobinostat, Pracinostat, R-306465, Ricolinostat, Romidepsin, Scriptaid, Tacedinaline, Tefinostat, Trichostatin A, Tucidinostat, Valproic acid and Vorinostat. HDAC8 is implicated in cancer development,

making its inhibitors a promising candidate for anticancer therapy. In this context, Nurani et al. (2024) used machine learning and screened a library of compounds and identified a non-hydroxamic acid HDAC8 inhibitor features a 1,2,4-triazole-3-thione scaffold that coordinates with the zinc ion in the HDAC8 active site and interactions with key residues such as His143, His180 and Tyr306 further contribute to its inhibitory activity against HDAC8 which was found by binding mode analysis. Today, extensive computational studies, such as machine learning and molecular simulations, are used to identify inhibitors and investigate molecular movements across various biological topics, offering many advantages, including time savings (Ebrahimi & Alijanianzadeh, 2024; Ebrahimi *et al*., 2022). Additionally, sixteen HDAC inhibitors, derived from the clinical candidate quisinostat, an anticancer drug currently under consideration, were fabricated by Stopper and coworkers (2025) to investigate their potencies for therapeutic intervention against cancer and malaria, as well as to further elucidate the structure-activity relationships associated with HDAC inhibition. Inhibition of HDACs may result in the reactivation of tumor-suppressor genes, induction of cell cycle arrest or apoptosis and disruption of interactions between non-histone proteins and oncogenic client proteins. Also, HDAC inhibitors can potentially counteract resistance to anaplastic lymphoma kinase (ALK) inhibitors such as crizotinib. The combination of HDAC and ALK inhibitors has demonstrated efficacy in addressing resistance. To address this, a series of novel benzimidazole derivatives were designed and synthesized based on the structures of reported orally available ALK and HDAC inhibitors, specifically pracinostat and the findings suggested a novel dual ALK/HDAC inhibitors, compounds 3b and 3c, that demonstrated significant in vitro and in vivo anti-tumor activities (K.L. Wang *et al*., 2024). Additionally, ZG compounds, a hybrid molecule combining a vitamin D receptor agonist with an HDAC inhibitor, have been developed to improve anticancer effectiveness (Sarmadi *et al*., 2024). It has been reported that co-treatment of Salubrinal (eukaryotic translation initiation factor 2A kinase inhibitor), GSK429286A (a Rho-associated coiled-coil kinase inhibitor), BX-912(PDK1 inhibitor) and Mirin (MRE11 inhibitor) inhibitors with the HDAC inhibitor SAHA demonstrated a significant synergistic effect in suppressing the growth of multiple solid tumor cell lines (Hao *et al*., 2024). HDAC10 induces autophagy in cancer cells in response to cytotoxic chemotherapy, thereby enhancing cancer cell survival. Moreover, HDAC10 represents a novel target for drug development, as it serves as a biomarker indicating poor prognosis in pediatric neuroblastoma cases, so investigators designed selective inhibitors that may be utilized in cancer chemotherapy to address drug resistance associated with HDAC10. Consequently, they synthesized six compounds of acetylated phenylthioketone inhibitors, posing positively charged para- and meta-substituted amino groups (Goulart Stollmaier *et al*., 2024). Another HDAC10 inhibitor is piperidine-4-acrylhydroxamates, which is characterized by Zeyen and lab mates (2022) and was accomplished by targeting the acidic gatekeeper residue Glu274 of HDAC10 with a basic piperidine moiety, which mimics the interaction of the polyamine substrate of HDAC10. Ren et al. (2021) found that a dual inhibitor of HDAC and STAT3 may demonstrate a synergistic effect and greater efficacy against solid tumors than HDAC inhibitors used in isolation; therefore, a series of novel pterostilbene (PTE) derivatives were synthesized by integrating the hydroxamic acid fragment, recognized as a pharmacophore for HDAC inhibition, into the PTE scaffold. Tetrahydro-β-carboline (THβC) is another scaffold with natural advantages that benefit drug development. By incorporating a typical aliphatic linker and the zinc-binding hydroxamic acid group, a common motif in HDAC inhibitors, into this scaffold, potent and selective HDAC inhibitors, specifically targeting HDAC1, have been manufactured (Shi *et al*., 2024). Also, romidepsin was found to be helpful as a method to

address the chemotherapy resistance resulting from the loss of p53 function in B-cell precursor acute lymphoblastic leukemia (Cox *et al*., 2024). Moreover, hydrophobic tagging is a novel approach to targeted protein degradation, presenting an alternative to PROTACs (Proteolysis-Targeting Chimeras). This process utilizes the cellular unfolded protein response, wherein hydrophobic regions on the surfaces of partially unfolded proteins are identified and subsequently degraded; hence, Feller and Hansen (2023) developed a series of hydrophobically tagged HDAC inhibitors as a proof-of-concept to investigate the potential of hydrophobic tagging for the targeted degradation of HDACs, particularly HDAC1, as an alternative to traditional HDAC inhibition. The soft drug approach entails integrating ester groups that can undergo hydrolysis by esterases, producing less potent carboxylic acid metabolites. This may restrict the systemic distribution of the active HDAC inhibitor. Therefore, researchers synthesized methyl ester HDAC inhibitors as derivatives of the approved HDAC inhibitor vorinostat (Figure 6) (Seitz *et al*., 2024).

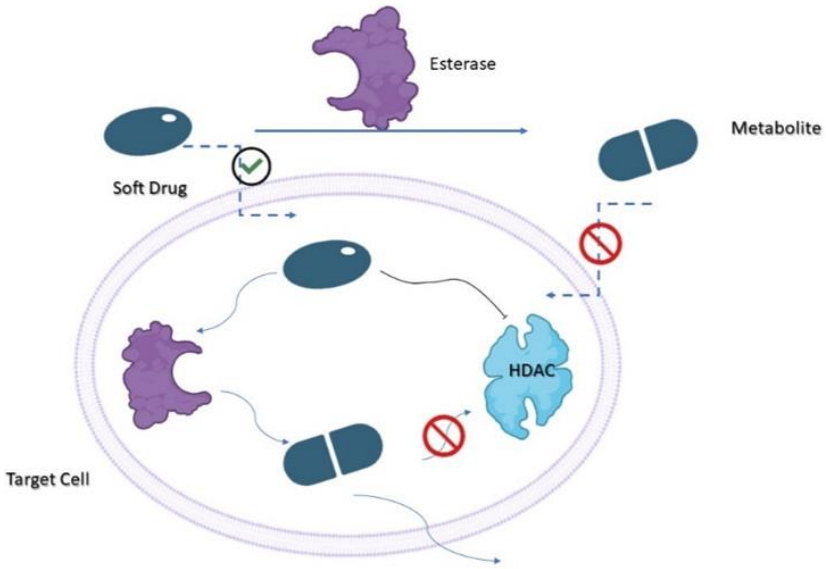

Figure 6. Principle of soft drug. The active soft drug inhibits its target protein (HDAC) and is subsequently converted into an inactive metabolite. The metabolite of the soft medication is either less effective against the target or incapable of penetrating into the cell membranes, hence inhibiting systemic adverse effects

HDAC6 is another key player in tumorigenesis, metastasis and tau-mediated toxicity in Alzheimer's disease. Hence, a group of scientists designed a new class of inhibitors combining quinone moieties, specifically naphthoquinone and menadione, as the CAP group with various zinc-binding groups, including hydroxamic acid, benzamide and mercaptoacetamide that demonstrated anticancer and neuroprotective effects (Guardigni *et al*., 2024). HDAC4 is also identified as a target in neurodegenerative diseases, notably Huntington's disease and various cancer types. Class IIa HDACs, such as HDAC4, represent a well-researched protein family with multiple inhibitors developed. For instance, researchers recently synthesized a series of cyclic peptides based on the SMRT-motif 1 sequence, which plays a role in the interaction between the corepressor SMRT and HDAC4 to enhance the binding properties and inhibition of the catalytic domain of HDAC4 (cHDAC4) in comparison to the linear SM1 peptide (Lill *et al*., 2024). Overexpression of HDAC2 has been demonstrated to reduce dendritic spine density, synapse quantity, synaptic plasticity and memory formation, positioning it as a possible target for cancer and neurodegenerative diseases. Therefore, a series of 8-

substituted quinoline-2-carboxamide derivatives were fabricated as novel HDAC inhibitors (Zhao *et al*., 2023). HDAC6, as mentioned earlier, is associated with tau-mediated toxicity in Alzheimer's disease, further highlighting its therapeutic relevance (Guardigni *et al*., 2024).

HDACs regulate cardiac hypertrophy and fibrosis, which are prevalent in heart failure. Inhibiting class I and class IIb HDACs (HDAC1, HDAC2, HDAC3, HDAC6) is considered a promising therapeutic approach for preventing and improving cardiac hypertrophy and suppressing autophagic flux, which can be beneficial in heart failure. To improve this problem, Se-SAHA, a selenium derivative of suberoylanilide hydroxamic acid (SAHA), was synthesized and characterized and showed efficient inhibition in overexpression of HDAC1 and HDAC6, induced by isoproterenol, was observed in both in vitro and in vivo models of heart failure (Cheng *et al*., 2024).

Given the diversity of chemical scaffolds and selectivity profiles, numerous HDAC inhibitors have been synthesized and characterized. These include quinoline derivatives, hydroxamic acids, benzimidazoles, triazole-thiones and hybrid molecules that target specific HDAC isoforms such as HDAC1, HDAC2, HDAC6 and HDAC10. Reported compounds demonstrate nanomolar to low micromolar inhibitory activity, with some exhibiting dual-targeting properties; for instance, combined inhibition of HDACs along with STAT3 or ALK. Taken together, these studies highlight the structural diversity and therapeutic potential of HDAC inhibitors in neurodegenerative disorders, cancer and cardiovascular diseases. Besides, these findings emphasize the structural versatility of HDAC inhibitors and provide a framework for understanding their translational potential.

2.3.1.2. Acetyltransferases

Overactive acetyltransferases may cause excessive acetylation of proteins, which could contribute to metabolic disorders. P300 and CBP are essential transcriptional co-activators that play significant roles in various cellular processes. Their malfunctioning has been associated with multiple human diseases, such as cancer, Huntington's disease and cardiac disease. Yang and coworkers discovered potent, highly selective small molecule inhibitors of p300 and CBP HAT exhibiting desirable drug-like properties utilizing an AI-enhanced drug discovery framework (Yang *et al*., 2020). Another research group used HAT-12 as a template molecule, modified and improved binding at the p300 active site to investigate a prospective therapy for idiopathic pulmonary fibrosis (Hwang *et al*., 2020). P300 has been identified as a significant contributor to liver fibrosis by promoting the transcription of genes associated with fibrosis, resulting in enhanced collagen synthesis and fibrosis progression. Since EP300/CBP HAT activity is associated with several human diseases, such as cancer, inflammatory disorders, fibrosis and neurodegenerative diseases, Wilson et al. (2020) improved the potency of a lead compound by substituting the indole scaffold of the lead compound with an aminopyridine scaffold resulted in enhanced potency, solubility and bioavailability. A study was conducted on synthesizing and examining various second-generation naphthoquinone compounds as small-molecule inhibitors of arylamine NAT1 since NAT1 expression attenuates mitochondrial function, indicating its potential as a drug target in mitochondrial dysfunction diseases (Choudhury *et al*., 2024).

To enhance the understanding of N-terminal acetylation's roles, especially concerning cytoskeletal dynamics, actin function and cellular processes, studying inhibitors may be useful in both in vitro and in vivo studies to clarify the roles and effects of NAA80 and actin acetylation. Hence, researchers systematically optimized the peptide component of a bisubstrate-based NAA80 inhibitor, which comprises coenzyme A (CoA)

conjugated to the N-terminus of a tetrapeptide amide through an acetyl linker (Myklebust *et al*., 2023).

NatD increases oncogene expression by upregulating protein arginine methyltransferase 5 in colorectal cancer cells; inhibition of NatD may have therapeutic implications. Therefore, the first series of potent and selective bisubstrate inhibitors for NatD was accompanied by structural and mechanistic insights regarding their binding and selectivity by Deng and teammates (2021). KAT6A (MOZ) has been identified as a novel target for leukemia treatment. Its histone acetyltransferase activity is crucial for the self-renewal of hematopoietic stem cells and mutations or translocations of KAT6A have been identified as significant contributors to leukemia development; for this reason, compounds derived from N-(2-oxoethyl) sulfanilamide serve as inhibitors of KAT6A has been fabricated by modifying the structure of the known KAT6A inhibitor CTX-0124143 involves replacing the N-N bond with an N-C bond through an isostere strategy (Duan *et al*., 2023). In order to differentiate between the catalytic function of HAT1 and its structural contribution within protein complexes and assess HAT1 as a viable target for cancer therapy, new riboflavin analogs were synthesized and found to inhibit cancer cell growth in vitro and demonstrated on-target activity by decreasing H4K12 acetylation in cells (Gaddameedi *et al*., 2023).

Activation of p300/CBP enhances histone acetylation, which correlates with gene activation and plays a crucial role in neuronal development, neuronal differentiation and dendritic branching and arborization. It has been suggested that utilizing activators may be advantageous for disorders associated with abnormal histone acetylation. For this reason, researchers functionalized a small molecule activator, TTK21, which was conjugated to a glucose-derived carbon nanosphere (CSP) to create CSP-TTK21 (AS *et al*., 2024).

Several classes of acetyltransferase inhibitors have been developed, targeting enzymes such as NAT1, HAT1, p300/CBP, NAA80, NatD and KAT6A. These compounds include scaffold-optimized small molecules, bisubstrate analogs and structure-based derivatives, many of which demonstrate nanomolar activity and selective inhibition. Together, they demonstrate how acetyltransferases can be used therapeutically to treat fibrosis, cancer, hematologic malignancies and mitochondrial dysfunction; hence, these results highlight the potential of acetyltransferase inhibitors as adaptable therapeutics.

2.3.2. Current and emerging sirtuin-based therapies

Sirtuin-based therapies demonstrate considerable potential for addressing various conditions associated with metabolism, aging and neurodegeneration. SIRT activators have gained considerable interest recently because of their possible therapeutic advantages. It has been found that activation of SIRT1 can be beneficial by enhancing mitochondrial health and function, antioxidant defenses, alleviating oxidative damage and having neuroprotective effects; as a consequence, Khan et al. (2024) conducted a study on the effectiveness of silibinin, a flavonoid derived from the seeds of milk thistle, as a SIRT1 activator and found the neuroprotective potential in diabetic neuropathy through triggering, furthermore, Liu and lab mates (2022) designed a high-throughput molecular docking strategy to evaluate a virtual compound library to identify and experimentally validate multiple novel potential SIRT1 activators. SIRT3 functions as a principal deacetylase within mitochondria, significantly influencing mitochondrial activity and plays vital roles in regulating oxidative stress, catabolism, ATP production within mitochondria and protection against cardiac hypertrophy and other cardiovascular

diseases. Its levels decrease with age, associated with rotator cuff degeneration and chondrocyte senescence; based on this, scientists experiment to activate the SIRT3 utilizing SIRT3 gene delivery employing AAV2 (adeno-associated virus 2) vectors and a pharmacological SIRT3 activator known as honokiol and mitigate degeneration of the rotator cuff fibrocartilage associated with aging and enhance the healing of rotator cuff injuries in aged mice, the other group employed structure-based screening to identify potential SIRT3 activators that target a specific binding pocket, referred to as pocket L, on SIRT3, in addition, Li and coworkers (2023) introduced novel small-molecule activator of SIRT3 called SZC-6 (3-(2-bromo-4-hydroxyphenyl)-7-hydroxy-2H-chromen-2-one) which inhibited the proliferation and differentiation of cardiac fibroblasts via SIRT3 activation (Peng *et al*., 2024; Xie *et al*., 2023).

SIRT1 contributes to the preservation of endothelial function and the maintenance of cardiovascular health. Since CMV infection and ox-LDL treatment were observed to decrease SIRT1 levels in brain microvascular endothelial cells, Ye et al. (2023) found utilizing SRT1720, a SIRT1 agonist, significantly reduced the increased IL-1β levels caused by CMV infection and ox-LDL treatment; a study reported that SIRT1720 substantially suppresses the proliferation of both mice and human bladder cancer organoids. It also inhibits the progression of mouse in situ bladder cancer and human PDX bladder cancer (Tan *et al*., 2021). Another study on the effect of SRT1720 noticed that activating the Sirt1/PGC1α pathway in neuroinflammation in Parkinson's disease enhanced cell viability and decreased apoptosis (Y. Yang *et al*., 2022). Another research group used curcumin as an activator and their results indicated that curcumin treatment enhanced SIRT1-mediated autophagy signaling on day seven post-stroke in comparison to the vehicle control group (Teertam *et al*., 2023); also reported that it has a role in upregulating SIRT3 in both in vivo and in vitro models of diabetic cardiomyopathy (Zhang *et al*., 2024). A selective SIRT1 activator called “SRT2104” was studied for its effects on cardiac electrophysiology and arrhythmias since SIRT1 is associated with protection against cardiovascular diseases, including myocardial infarction, ischemia-reperfusion injury and hypertension and noted that SRT2104 markedly decreased both the occurrence and duration of aconitine-induced ventricular tachycardia (VT) and ventricular fibrillation (VF) in murine models (Ma *et al*., 2024); also the efficacy of SRT2104 was observed to be decreased osteoarthritis progression regarding the control group in osteoarthritis progression in a mouse model and could potentially indicate a novel therapeutic strategy for it (Miyaji *et al*., 2021). Its antidepressant impact on a mouse model of depression provoked by chronic unpredictable mild stress was observed to diminish CUMS-induced depressive-like behaviors through the modulation of neuroinflammation and the alteration of microglial polarization towards the M2 phenotype (Duan *et al*., 2020).

Besides, SIRT6 is significantly expressed in the heart and is essential for protecting blood vessels and the heart from endothelial dysfunction, atherosclerosis, cardiac hypertrophy, myocardial fibrosis and heart failure so scientists explored the efficacy of xanthenone, a recently identified activator of the angiotensin-converting enzyme 2 and angiotensin 1-7 axis, treatment and observed a significant increase in SIRT6 expression which was related to cardioprotective effects against via experiments induced myocardial infarction in rats (Abdel-Nasser *et al*., 2023).

SIRTFOOD®SHOT is a dietary supplement developed by the Swiss company System-Biologie AG. Haslberger et al. (2021) conducted a study to evaluate its usefulness and observed several findings: a notably enhanced expression of sirtuins SIRT1 and SIRT3; an increased quantity of mtDNA suggests enhanced mitochondrial activity, correlating with improved energy metabolism; variations in the expression levels of

particular microRNAs and an enhancement in advantageous gut microbiota in comparison to a placebo group (Haslberger *et al*., 2021).

Perampanel, a pharmaceutical agent for epilepsy produced by Eisai Pharmaceutical Co. Ltd., has been documented to exert neuroprotective effects by boosting SIRT1 expression and stimulating the SIRT1/PGC-1α signaling pathway (Jiang *et al*., 2021).

Nicotinamide mononucleotide has been considered an intermediate and predecessor to NAD^+. Hence, its administration will increase concentrations of NAD^+ in aged animals to activate SIRT1 in the neurovascular unit. It has been noted that its supplementation enhances neurovascular rejuvenation in aged mice via several mechanisms, such as mitochondrial protection, SIRT1 activation and anti-apoptotic and anti-inflammatory effects (Kiss *et al*., 2020).

Jin et al. (2023) investigated the mechanism by which resveratrol, which is a natural compound known as SIRT7 activator, increases the deacetylase activity of SIRT7 through AMPK-mediated phosphorylation of SIRT7; they explored the mechanism of RSV protects skin from radiation-induced damage and emphasizes the potential of RSV as a radioprotective agent in clinical settings.

SRT1460 is involved in regulating various diseases, including inhibiting cell growth and survival in pancreatic cancer. It also plays a role in treating type 2 diabetes by activating Sirt1. It was shown to decrease the infarct area of the heart caused by myocardial ischemia/reperfusion (I/R) injury in rats (Chini *et al*., 2016; Milne *et al*., 2007; Zhao & Yu, 2021).

One of the most researched polyphenols that occurs naturally in a variety of plants is quercetin. Nevertheless, clinical application is hindered by its limited bioavailability, necessitating the development of derivatives with superior pharmacological qualities. It has been shown to upregulate the SIRT1 activity both in vivo and in vitro (Howitz *et al*., 2003). Peredo-Escárcega and teammates (2015) demonstrated that combining quercetin and resveratrol effectively improves various aspects of metabolic syndrome by elevating SIRT1 and SIRT2 expression in vivo. Furthermore, Heger et al. (2019) identified scaffolds for designing SIRT6 inhibitors by examining the impact of a variety of polyphenols extracted from the root bark of Morus nigra, including quercetin and rutin derivatives, on SIRT6 activity, they found diquercetin and 2-chloro-1,4-naphtoquinone-quercetin, as promising inhibitors. They also report that 2-Chloro-1,4-naphtoquinone-quercetin has inhibitory effect on SIRT2 as well. According to molecular docking experiments, 2-chloro-1,4-naphtoquinone-quercetin prefers to bind into the substrate binding site, while quercetin prefers the binding site of the nicotinamide (NAM) moiety. Overall, in vitro research and molecular modeling results show that 2-chloro-1,4-naphthoquinone-quercetin competes with the acetylated substrate in the catalytic region of SIRT6, while quercetin competes with nicotinamide adenine dinucleotide (NAD^+). Interestingly a structural and functional analysis of quercetin and its derivatives as modulators of Sirt6 has been carried out and revealed that quercetin acts as a low-potency activator of SIRT6 while inhibiting other SIRT isoforms. Moreover, the structural analyses demonstrated that the catechol moiety of quercetin functions as a link when it binds to the isoform-specific acyl binding channel of SIRT6. They discovered that, although they have minor variations, activators and inhibitors bind nearly identically. Activators contain unsaturated, planar C-rings, whereas inhibitors often have saturated C-rings and bind in a tilted orientation. Isoquercetin was also found to be a more selective Sirt6 activator because of its sugar moiety, which inhibits binding to other sirtuin isoforms (You *et al*., 2019).

Sirtuin inhibition represents a significant focus of investigation within the domain of metabolic disorders and other diseases. To begin with, Wu and teammates (2024)

developed cyclic tripeptide inhibitors targeting human SIRT3. They used the cyclic structure in these compounds to potentially improve binding affinity to sirtuin active sites compared to linear peptides. In previous studies, SIRT5 is strongly induced in microglia after ischemic stroke, promotes neuroinflammation and neuronal damage and was identified as a desuccinylating agent for annexin-A1 (ANXA1), inhibiting its membrane recruitment and extracellular release, which ultimately resulted in neuronal cell injury following ischemic stroke. Therefore, researchers examined the application of MC3482, a selective inhibitor of SIRT5, as a prospective therapeutic agent for ischemic stroke (Xia *et al*., 2024). Additionally, another research group developed several potent SIRT5 inhibitors using 3-thioureidopropanoic acid derivatives and structure-activity relationship (SAR) they fund that compounds with aromatic heterocycles had improved biochemical properties compared to with phenyl rings and compounds with aminoethyl linker showed comparable or better inhibitory activity compared to allyl linker (Yang *et al*., 2021). On the other side, SIRT1 inhibitors are under investigation as potential therapeutic agents for a range of diseases, especially human immunodeficiency virus, cancer, neurodegenerative disorders such as Huntington's Disease, Parkinson's Disease and Alzheimer's Disease; so researchers have developed a dual-purpose molecule benzoxazine-based carbon-11 labeled compound as a novel PET tracer for neuroimaging and inhibition and imidazole and imidazothiazole scaffolds exhibited significant inhibitory activity, despite their structural resemblance to known SIRT1 activators; furthermore, a series of N-acylhydrazone (NAH) derivatives and their cyclic analogs (pyrazolines) have been synthesized as inhibitors, besides a new class of SIRT1 with a benzoxazine scaffold was introduced by Spinck et al. (2021) (Lipson *et al*., 2023, 2024; Y. Wang *et al*., 2024). SIRT2 inhibition demonstrates potential as a therapeutic approach for treating multiple cancer types. Inhibiting SIRT2 can regulate and modulate cellular processes such as energy expression, DNA repair and cell cycle control; in this respect, a series of 7-aroyl [1,2,4] triazolo[1,5-a] pyrimidine derivatives (compounds 4a-e) were synthesized via a three-component condensation reaction and post-modified analogs of these derivatives were generated by altering the active functional groups of the bicyclic structure (Marchenko *et al*., 2024). Due to the involvement of SIRT4 in essential cellular processes associated with metabolism, aging and cancer, several compounds containing N-(5-((4-nitrophenyl)sulfonyl)thiazol-2-yl)acetamide, (3,4-dihydro-4-oxopyrimidine-2-yl)thio/(3,4-dihydro-4-oxoquinazoline-2-yl)thio moieties and 5-chloro-2-thio-1H-benzo[d]imidazole groups (Pannek *et al*., 2024).

Plant-derived inhibitors, in comparison to synthetic inhibitors, have advantages including better safety profile, chemo-protecting activity, extended biological activities and abundant availability. To this point, Sinha and teammates (2019) conducted a comprehensive study combining in silico and in vitro to investigate the plant-derived inhibitors against SIRTs in triple-negative breast cancer. By screening 21 plant-derived inhibitors, they found sulforaphane effectively inhibited the SIRT1 and SIRT5, kaempferol showed high inhibition to the SIRT3 and apigenin inhibited SIRT6 successfully.

While selisistat (EX-527) shows no inhibition against SIRT4-7, it is a strong and selective inhibitor for SIRT1 compared to SIRT2-3. Selisistat is an indole inhibitor found through high-throughput screening (HTS) (Zhao *et al*., 2013). In order to find more effective derivatives that could potentially provide better therapeutic outcomes for patients with conditions like Huntington's disease and endometriosis, Hasan and Al-hamashi (2024) identified two promising compounds from a library of 100 small molecules by in silico virtual screening; compound 1, which demonstrated stronger binding affinity than EX-527 for SIRT1 and SIRT2 and compound 8 that exhibited better

binding with SIRT3. Wu et al. (2020) investigated whether EX-527 might reduce allergic airway inflammation and whether the protective effects were mediated by mTOR activation-driven autophagy suppression. They also studied the connection between mTOR signaling and SIRT1 suppression in allergic asthma and they found EX-527 suppressed SIRT1 expression and demonstrated therapeutic effects on allergen-induced airway inflammation through mTOR-mediated autophagy in an asthma model. Through virtual screening of 1.0 million compounds and structure-based design, Purushotham's team (2022) developed two series of novel compounds (benzimidazole monopeptides and pyrazolyl methylidenes of rhodanine carboxylic acids) as SIRT1 inhibitors. Their study identified that compounds require an aromatic moiety with a polar group to interact with pocket-C for inhibitory action and another aromatic ring at the substrate-binding site with small substitutions (like methoxy, nitro or di-fluoro) on the phenyl ring to improve stability and selectivity.

Interestingly, Troelsen et al. (2021) aimed to selectively target and inhibit SIRT3 with an innovative strategy by incorporating mitochondria-targeting peptide sequences into inhibitor structures, rather than relying solely on enzyme recognition for selectivity. As a result, they successfully achieved selective SIRT3 inhibition through mitochondrial targeting rather than enzyme recognition alone.

From a translational perspective, developing sirtuin-based modulators is a quickly developing field combining novel therapeutic approaches with molecular pharmacology. Several sirtuin activators and inhibitors have been discovered, including synthetic inhibitors, small-molecule agonists and natural compounds (such as resveratrol, silibinin and curcumin), demonstrating the adaptability of sirtuins as pharmacological targets with wide-ranging therapeutic potential. Lastly, these findings indicate that improving selectivity, reducing resistance mechanisms and extending clinical translation are important future initiatives.

2.3.3. Challenges and opportunities in drug development

Both the HDAC family, which comprises 18 members and is organized into four classes (I, II, III and IV) and acetyltransferases, including histone acetyltransferases and non-histone acetyltransferases, are characterized by unique functions and tissue distributions (Zhu *et al*., 2024). The presence of diversity complicates the development of selective inhibitors. Also, they have overlapping functions, complicating the prediction of the effects resulting from the inhibition of a specific enzyme without influencing others (Dushanan *et al*., 2022).

Several inhibitors exhibit a lack of specificity, resulting in the inhibition of multiple enzymes and consequently causing undesirable side effects such as hydroxamic acid-based HDAC inhibitors; hence developing new selective inhibitors would diminish the adverse effects (Cianferotti *et al*., 2021). In addition, cancer cells may confer resistance to inhibitors by multiple mechanisms, for example, the upregulation of compensatory pathways or mutations in target proteins. Comprehending and addressing these resistance mechanisms is essential for effective treatment (König & Hansen, 2024; Yang *et al*., 2024).

Computational methods and high-throughput screening can accelerate drug discovery and improve the design of selective inhibitors. These approaches help target specific isoforms, reducing off-target effects and enhancing therapeutic outcomes. Developing the targeted delivery of HDAC inhibitor strategies to specific tissues or cells may improve their therapeutic efficacy, specificity, bioavailability and reduce systemic toxicity (Elmezayen & Kemal, 2021; Peterson *et al*., 2023).

While all those challenges mentioned above apply to SIRT modulators; the complexity of the SIRT family, with issues of selectivity, cofactor dependence and resistance mechanisms, sets significant challenges. However, advancements in combination therapies, drug design and biomarker development provide promising opportunities for effective treatments (Wu *et al*., 2024; Van Scoyk *et al*., 2023).

2.4. Future directions

Advancements in emerging technologies for studying acetylation and SIRTs enhance our comprehension of these essential biological processes and their relevance to health and disease but yet many challenges remain. Mass spectrometry is an effective analytical method for identifying and quantifying proteins and their PTMs, such as acetylation (Bolla *et al*., 2021; Fiorentino *et al*., 2023, 2021). It allows acetylome analysis, identification of acetylated proteins and precise acetylation sites. Techniques including tandem mass tags (TMT) and isobaric tags for relative and absolute quantitation facilitate quantitative comparisons of acetylation levels under varying conditions or treatments (Fuller *et al*., 2024; van de Kooij *et al*., 2023; B. Wang *et al*., 2024). For example, Arias-Alvarado et al. (2021) utilized high-resolution mass spectrometry to ascertain the individual lysine residues that were acetylated on histone peptides and simultaneously quantified the turnover rates of acetyl-CoA and acetylated histones in vivo.

Fluorescence resonance Energy Transfer is a technique used in the study of protein-protein interactions and conformational changes in live cells and helps in designing biosensors to monitor SIRT activity in real time (Bischoff *et al*., 2023; Chen *et al*., 2023; N. Chen *et al*., 2024; Gao *et al*., 2023; Szewczyk *et al*., 2023). Analyzing the acetylation pattern in tumor cells compared to adjacent stromal cells through single-cell RNA sequencing (scRNA-seq) and single-cell proteomics provides insights into mechanisms underlying tumor resistance and progression (Chang *et al*., 2024; Z. Chen *et al*., 2024; Yu *et al*., 2024). Further understanding of the role of SIRTs in disease processes and responses to therapy has also been provided with the help of sophisticated in vivo imaging techniques like PET and MRI, together with the development of probes detecting SIRT activity or acetylation status (Chattopadhyay *et al*., 2020).

The functions of specific SIRT genes and their implications in cellular processes and disease models can be investigated by knocking out or modifying these genes. Therefore, CRISPR can be utilized to introduce specific mutations in acetylation sites to evaluate their functional significance. Ultimately, computational models predict the influence of acetylation on protein function and interactions, thereby informing experimental design, which can lead to enhancing the drug discovery process and addressing the challenges linked to conventional methods (Björnson *et al*., 2023; Carrico *et al*., 2023; Liu *et al*., 2023; Pandit *et al*., 2024; Phillips *et al*., 2024; Su *et al*., 2024).

Studying the condition and activity of enzymes and proteins utilizing the mentioned techniques results in personalized medication, to start; examining the acetylation status of proteins in a patient's tumor may assist in identifying potential therapeutic targets and guiding treatment decisions and based on a patient's unique molecular profile can enhance therapeutic efficacy and overcome resistance mechanisms. Developing biomarkers can assist either in predicting patient responses to specific therapies or monitoring treatment efficacy and guiding dose adjustments (Ji *et al*., 2023; Kronfol *et al*., 2020).

3. Conclusion

Acetylation has emerged as a burgeoning characteristic of many general cellular processes; however, much remains to be elucidated regarding metabolic flexibility, including the overall mechanisms and their tissue-specific roles. However, major gaps exist in defining specific mechanisms, substrates and condition-specific roles for nonhistone acetylation. In this review, we summarized the functions of SIRTs in metabolism and their cellular localization, as well as enzymes that play a crucial role in the acetylation of proteins. Dysregulation of acetylation and deacetylation has been associated with several metabolic diseases, such as cancer, obesity and diabetes (Williams *et al*., 2020); hence, in order to help investigators, this review gathered several recently emerged modulator compounds of HDACs, acetyltransferases and SIRTs. Despite the numerous modulators reported to date, certain underdeveloped areas require additional research; no Sirt2, Sirt4 or Sirt7 activators have been reported. The proposed Sirt1 activators SRT1720 and SRT2104 demonstrate isoform selectivity, high potency and biological activity in preclinical and early clinical trials (Bolla *et al*., 2021; Yee Ng *et al*., 2013). The discovery of HDAC enzymes, such as HDAC 10, plays an important role in cancer progression and drug resistance, leading to the fabrication of drugs that target these enzymes to reactivate the activity of genes that suppress tumors and trigger cell death. Despite advancements in developing HAT inhibitors, there is still a concern about these compounds' selectivity; many inhibitors may unintentionally affect multiple targets, inducing off-target effects that diminish the therapeutic efficacy. Although most investigations conducted in vitro have given promising results, it is quite important to perform in vivo studies to determine their safety and efficiency within the organism. The equilibrium between HAT and HDAC activities is important for cellular homeostasis. However, the determinants of this balance remain poorly understood. As observed in various disease states, outcomes of disturbances in the HAT-HDAC balance further require studies to elucidate potential therapeutic approaches. Acetylation regulates proteostasis by affecting protein folding and stability, interaction with chaperones and ubiquitin systems. Recent works have revealed that acetylation controls the activity of proteins directly involved in proteostasis, including p53, Hsp70 and proteins related to autophagy. Emerging technologies, such as mass spectrometry, advanced imaging techniques and cryo-electron microscopy, have helped scientists obtain high-resolution structures of small proteins and enhance their understanding of acetylation and SIRT activity in health and disease. These methodologies facilitate the identification of acetylated proteins, elucidate protein-protein interactions and enable monitoring of enzymatic activity in real-time.

In summary, this review highlighted the importance of studies on histone deacetylases and acetyltransferases and their regulatory roles in proteostasis maintenance and promotion of metabolic flexibility. It also noted the critical need for developing selective inhibitors and personalized therapeutic strategies to improve treatment outcomes for age-related diseases and cancer.

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