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Review

Transcription Factor Acetylation and Cell Fate Control: A Molecular Switch in Hematopoiesis and Myogenesis

Pegah Ghavidel[1,2], Yassine Abdelmalki[1,2], Marie-Claude Sincennes[1,2,*]

[1]Centre Armand-Frappier Santé Biotechnologie, Institut National de la Recherche Scientifique, Laval, QC H7V 1B7, Canada
[2]Unité Mixte de Recherche INRS-UQAC en Santé Durable, Chicoutimi, QC G7H 2B1, Canada
*Correspondence: Marie-claude.sincennes@inrs.ca (Marie-Claude Sincennes)

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Abstract

Transcription factor acetylation is a critical yet often overlooked regulator of cell fate. Although traditionally studied in the context of histone modifications, many acetyltransferases and deacetylases also modify transcription factors directly, thereby controlling lineage-specific transcriptional programs. At the molecular level, acetylation fine-tunes transcription factor activity by modulating DNA binding, protein stability, cofactor interactions, and nucleo-cytoplasmic trafficking. These molecular effects frequently intersect with other post-translational modifications, establishing acetylation as a versatile molecular switch of transcriptional output. These molecular effects scale into cellular outcomes that determine identity and plasticity. In pluripotent stem cells, defined acetylation events on core regulators stabilize the pluripotency network and prime lineage-specific enhancers. In hematopoiesis, transcription factor acetylation modulates transitions from stem and progenitor states to committed lineages, while in myogenesis, it governs progenitor differentiation and regenerative capacity. Importantly, differential acetylation of distinct lysine residues can yield context-dependent outcomes, underscoring the precision and adaptability of this modification in controlling cell identity. Recognizing transcription factor acetylation as a central axis of epigenetic regulation reframes our understanding of lineage specification and cellular plasticity. Beyond developmental biology, it provides a mechanistic rationale for therapeutic strategies that target acetylation dynamics, not only altering chromatin states but also reprogramming transcription factor function. This review synthesizes current knowledge of transcription factor acetylation in hematopoietic and myogenic contexts, highlighting its significance as a bridge between molecular mechanisms and cellular identity, and as a promising target in disease intervention.

Keywords: acetylation; transcription factors; gene expression; hematopoiesis; muscle development; stem cells; histone deacetylase inhibitors; chromatin; protein processing; post-translational; acetyltransferases

1. Introduction

Protein acetylation, a reversible post-translational modification involving the transfer of an acetyl group to lysine residues, is a crucial post-translational modification that significantly influences the activity of numerous proteins and plays an essential role in regulating gene transcription. This modification plays a central role in regulating chromatin accessibility, transcription factor function, and gene expression. Acetylation is dynamically controlled by the opposing activities of histone acetyltransferases (HATs) and histone deacetylases (HDACs). With respect to gene expression, acetylation is most often associated with histones, which are the core proteins around which DNA is wrapped to form nucleosomes.

Like histones, transcription factors are also subjected to post-translational modifications, including acetylation, which control their ability to regulate gene expression networks. Transcription factors act as master regulators of cell fate and are often found at the apex of a regulatory hierarchy, controlling downstream gene expression programs crucial for determining cell identity in a particular lineage. Acetylation of transcription factors likely induce conformational changes that substantially modify protein-DNA as well as protein-protein interactions, thus governing the function of transcription factors and their transcriptional input directing cell fate.

In the present review, we aim to discuss the importance of transcription factor acetylation in the control of cell fate. We do not provide an exhaustive list of acetylated transcription factors, but we focus on master regulators of the myogenic and hematopoietic lineage whose function is fine-tuned by acetylation and other post-translational modifications. We also discuss how targeting (de)acetylation of transcription factors could be an attractive therapeutic strategy in cancer and other diseases.

2. Literature Review

2.1 Importance of Acetylation in the Control of Cell Fate

2.1.1 Acetylation of Transcription Factors in Myogenesis

Skeletal muscle formation, known as myogenesis, is a highly intricate biological process that is meticulously orchestrated by a complex network of genetic and epigenetic factors [1]. Acetylation is central to myogenesis as it regulates the function of numerous transcription factors cru-

cially involved at different steps of the myogenic program, from muscle stem cell self-renewal to terminal maturation.

2.1.1.1 PAX Family. PAX (Paired Box) proteins are a family of transcription factors with important roles in embryonic development, organogenesis and cell differentiation. A subset of paired-box transcription factors, namely PAX3, PAX4, PAX6 and PAX7, display the unique ability to recognize two distinct DNA sequences, the homeobox and the paired box. Therefore, they can recognize target genes displaying only a paired box, only a homeobox, or a combination of both [2]. Acetylation can also confer DNA-binding preferences and thus change the repertoire of target genes for a given transcription factor. One striking example is PAX7, the canonical marker of adult muscle stem cells.

PAX7 undergoes post-translational modification via acetylation on two specific lysine residues: K105, located within its paired domain, and K193, which is unique to PAX7 and lies between the paired and homeodomain [3]. Acetylation of these sites, particularly K193, is critical for PAX7 transcriptional activity, as mutations at K193 (K193R) or both sites (K105/193R) significantly reduce PAX7 ability to activate the *Myf5* (Myogenic Factor 5) reporter gene [3]. These acetylation marks directly regulate PAX7 recruitment to chromatin and, more specifically, its binding to DNA via homeobox motifs. It has been demonstrated *in vitro* that mutation of acetylated lysine residues on PAX7 does not change its ability to bind paired boxes [3]. In contrast, while the K105 mutation reduces homeobox binding, the K193 mutation or a combination of both mutations almost completely abolishes it, demonstrating the role of acetylation in specifically recognizing homeoboxes. Strikingly, the ratio of homeobox *versus* paired box-containing PAX7 target genes is significantly different in muscle progenitors compared to other cell types such as the pituitary gland [2], suggesting that acetylation, at least in part, confers cell type specificity for PAX7. Acetylation, mediated by MYST Histone Acetyltransferase 1 (MYST1) and reverted by Sirtuin 2 (SIRT2), promotes PAX7 transcriptional activity and increases binding to homeobox motifs on DNA. Loss of PAX7 acetylation skews muscle stem cells toward symmetric self-renewal and expands the progenitor pool, but impairs differentiation and reduces the regenerative muscle stem cell population after injury [3].

In muscle stem cells, PAX7 is also methylated on multiple N-terminal arginine residues region by the arginine methyltransferase CARM1 [4]. Similarly to acetylation, methylation drives the expression of *Myf5* and drives stem cell commitment. However, while acetylation increases the DNA binding capacity of PAX7 on homeoboxes, methylation does not change DNA binding, but instead enables interaction with Mixed-Lineage Leukemia 1/2 (MLL1/2), promoting the recruitment of the ASH2L:RBBP5:WDR5 (Absent, Small or Homeotic 2-like protein; Retinoblastoma Binding Protein 5; WD repeat domain 5) complex, which mediates histone methylation on PAX7-bound loci. When Coactivator-Associated Arginine Methyltransferase (CARM1) is inhibited or depleted, PAX7 still occupies chromatin, but MLL loading, histone tri-methylation and *Myf5* expression are reduced, indicating that methylation is needed to couple chromatin binding with transcriptional activation. Thus, Together, the data support a cooperative model where acetylation stabilizes PAX7 chromatin binding at specific loci, whereas CARM1-dependent methylation enables coactivator recruitment and transcriptional output, offering a direct route for metabolic cues to influence fate decisions downstream the PAX7 lineage (Fig. 1). Interestingly, in a mouse model of Duchenne muscular dystrophy, defective muscle stem cells exhibit reduced histone H3K4 trimethylation associated with a decrease in PAX7 target gene expression [5], although a defect in PAX7 methylation or acetylation in dystrophic stem cells remains to be been investigated. Additionally, sumoylation of PAX7 at K85 positively regulates PAX7 transcriptional activity in myogenic cells, by an undefined mechanism that does not involve its DNA binding ability [6]. PAX7 expression is turned off during later stages of myogenic differentiation, and sustained expression of PAX7 blocks terminal muscle differentiation. Downregulation of PAX7 is achieved by different molecular mechanisms, one of which is its cleavage on residue D187 by caspase 3 (CASP3) [7]. PAX7 harbors a consensus cleavage site for CASP3, and this cleavage generates two non-functional PAX7 fragments. Accordingly, CASP3 inhibition promotes self-renewal, while its forced expression induces PAX7 cleavage and myogenic differentiation. PAX7 is phosphorylated by CK2 at S201, which prevents CASP3 cleavage [7] and also inhibits PAX7 ubiquitination and proteasomal degradation [8].

Many PAX proteins have been shown to be acetylated on different residues, some of which being conserved across different PAX family members (Fig. 2). PAX3, like PAX7, is a master regulator of myogenesis, particularly during development, and its expression is sustained at the adult stage in a subset of muscle stem cells [9]. In addition to myogenesis, PAX3 is critical for neurogenesis, mediated by neural crest-derived progenitor cells. PAX3 is acetylated at lysine residues K437 and K475, particularly in neural precursors [10]. Acetylation by coactivators like p300/CBP enhances PAX3 ability to activate *Neurog2* and repress *Hes1*, promoting neuronal differentiation over stem cell maintenance. Deacetylation by SIRT1 results in the opposite effect: increased *Hes1* expression and maintenance of stem-like properties [10]. Although these observations were made in neural contexts and their implications for muscle progenitor fate remain to be fully explored, they suggest a general model in which PAX3 acetylation shifts cellular identity by modulating gene expression balance. PAX5 is also acetylated *in vitro* and *in vivo* by p300 in hematopoietic cells [11]. This acetylation takes place within the paired domain of PAX5, on lysine residues

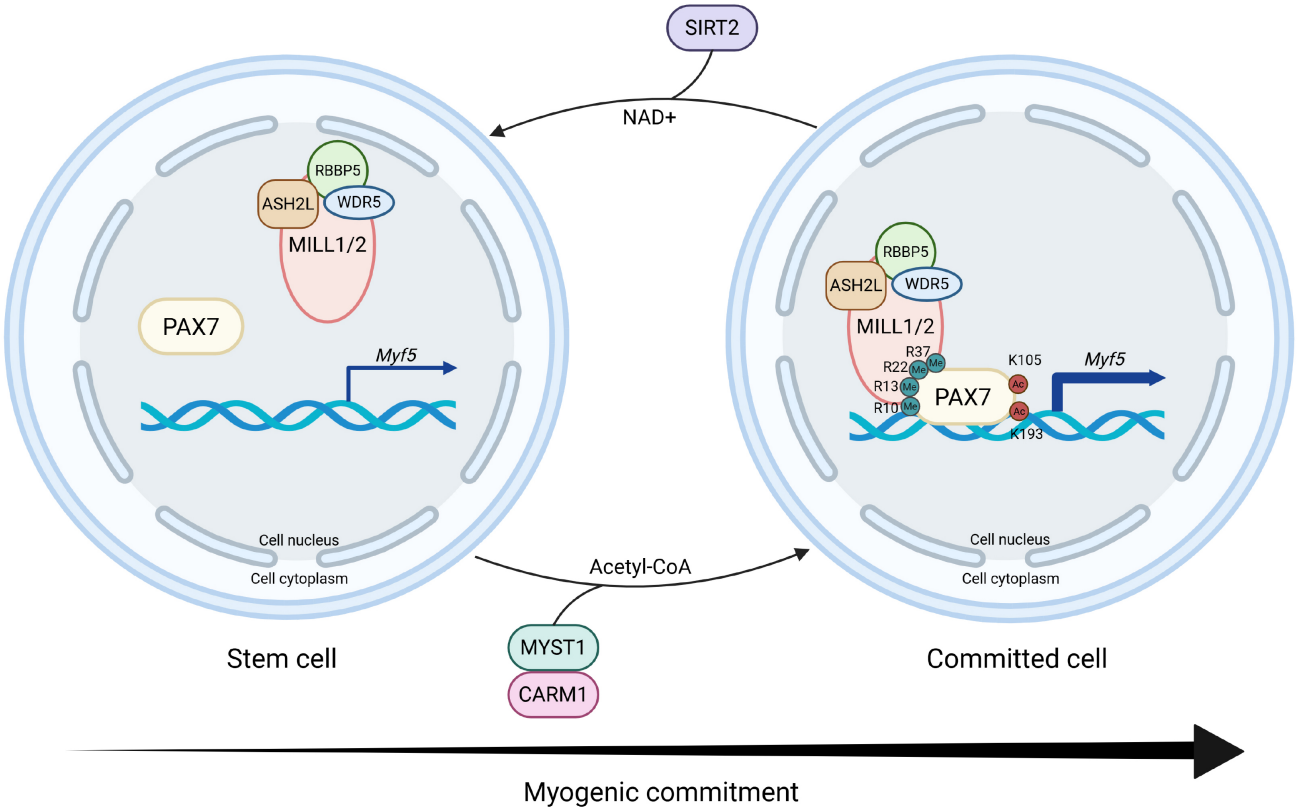

Fig. 1. PAX7 acetylation and methylation drive muscle stem cell commitment. In stem cells, PAX7 is not acetylated and not methylated, precluding its recruitment to target genes such as *Myf5*, and preventing its interaction with the MLL1/2 complex. In more committed stem cells, acetylation (by MYST1) drives PAX7 recruitment to target sequences, while methylation (by CARM1) allows the recruitment of co-activator complexes, driving gene expression. Metabolite availability, such as NAD+ and acetyl-CoA, likely influence myogenic commitment by driving transcription factors post-translational modifications. Created in BioRender.com. Sincennes, M. (2025) https://BioRender.com/tj3ww5h. PAX, Paired Box; MLL1/2, Mixed-Lineage Leukemia 1/2; MYST1, MYST Histone Acetyltransferase 1; CARM1, Coactivator-Associated Arginine Methyltransferase.

that are well conserved amongst other PAX proteins [11], suggesting that acetylation on the paired domain by p300 could be a general mechanism to fine-tune gene expression during cell commitment and differentiation. Mutation of these lysine residues drastically impairs the activation of PAX5 target gene expression in murine pro B cells, such as *Cd19* and *Blnk* [11]. PAX5 is also acetylated on K198 by p300/CBP-associated factor (PCAF), and deacetylation of this residue par SIRT7 is important for B cell differentiation [12]. Deacetylation by SIRT7 has been shown to enhance PAX5 protein stability and to increase PAX5 DNA binding. Thus, unlike PAX3 and PAX7, it seems that acetylation of PAX5 (at least on lysine K198) decreases its ability to activate gene expression during B cell differentiation. Similarly, PAX6 is also negatively regulated by acetylation in neural progenitor cells. PAX6 is acetylated by Lysine Acetyltransferase 2A (KAT2A) (also called GCN5 (General Control Non-repressible 5)) [13]. KAT2A inhibition in zebrafish is accompanied by an increase in PAX6 protein expression in neural stem cells and a phenotype of small eyes. Acetylation by KAT2A enables degradation of PAX6 via the ubiquitin-proteasome system. In that context, three potential acetylation sites have been identified for PAX6: K75, K264 and K270. Only K75 and K264 have been shown to be involved in the regulation of PAX6 protein stability [13]. Overall, acetylation emerges as a conserved yet context-dependent mechanism for fine-tuning PAX transcription factor function. Thus, while acetylation of paired domain lysines appears as a shared regulatory feature among PAX proteins, its functional outcome varies from activating in muscle stem cells (PAX7) to destabilizing or repressing activity in neural and hematopoietic contexts (PAX5, PAX6).

2.1.1.2 MyoD. Myogenic Differentiation 1 (MyoD) is a substrate for HATs such as p300/CBP and PCAF *in vitro* [14]. The primary acetylation sites are K99, K102 and K104, located at the boundary of its basic helix-loop-helix (bHLH) DNA binding/dimerization domain [14,15]. While these lysines are not directly involved in DNA contact, acetylation is hypothesized to induce a conformational change in MyoD that enhances DNA binding. p300/CBP

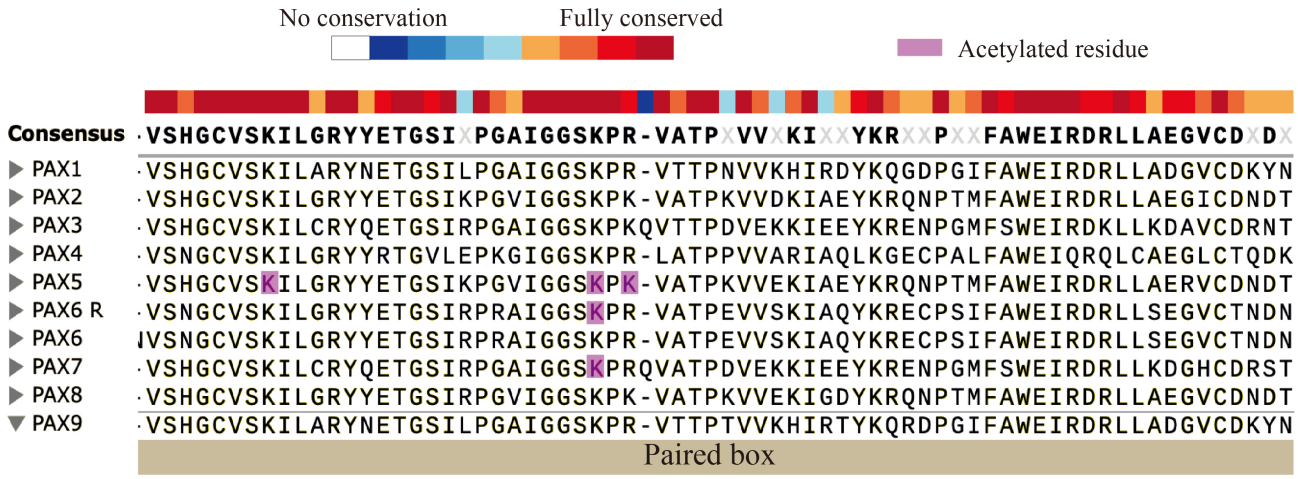

Fig. 2. Multiple members of the PAX family of transcription factors are subjected to acetylation. Multiple sequence alignment of the paired domain from PAX1–PAX9 proteins. The consensus sequence is shown at the top, with conservation indicated by a color scale (red = fully conserved, blue = low conservation). Magenta highlights mark lysine residues reported to be acetylated. The sequence labeled PAX6R corresponds to *Rattus norvegicus* (rat) PAX6, as documented in acetylation studies.

can also acetylate MyoD at these same sites, similarly increasing its transactivating capability [15]. Acetylation of MyoD by PCAF increases its affinity for its DNA target [14]. This effect, observed via electrophoretic mobility shift assay (EMSA), includes an augmented DNA affinity for both MyoD-specific DNA site and for MyoD/E12 heterodimers binding to the E box. K104 is not only acetylated but also methylated: the lysine methyltransferase G9A methylates MyoD on K104, which suppresses MyoD transcriptional activity, represses the myogenic program, promotes MyoD ubiquitination and degradation, thus maintaining an undifferentiated state [16]. Therefore, during myogenic commitment, while PAX7 acetylation and methylation cooperate together to activate target gene expression and stem cell commitment, MyoD is regulated by the antagonism between methylation (inhibiting transcriptional activity and maintaining stemness) and acetylation (driving gene expression and myogenic differentiation). The functional importance of MyoD acetylation has been demonstrated by non-acetylatable MyoD mutants [17]. These mutants show reduced myogenic activity, delayed muscle regeneration *in vivo*, reduced differentiation potential of myoblasts *in vitro*, and reduced ability to activate muscle-specific reporters. In contrast, a K104R substitution (which cannot be methylated or acetylated) has been shown to rescue myogenic differentiation, increase MyoD transcriptional activity (elevated *Myog* and *Tnnt2* expression), and enhance protein stability, reflecting the regulatory weight of K104 [16]. Acetylation of MyoD influences the kinetics and strength of transcription for discrete subsets of genes by regulating chromatin access of MyoD, histone acetylation, and RNA polymerase II recruitment [18]. In undifferentiated myoblasts, MyoD is expressed but maintained in an inactive state through association with histone deacetylase 1 (HDAC1), which maintains MyoD in a deacetylated and transcriptionally repressed form. MyoD and HDAC1 co-occupy the promoters of muscle-specific genes such as *Myog*, thereby repressing their expression. Upon differentiation signals, HDAC1 dissociates from MyoD and is replaced by coactivators like PCAF and p300/CBP [19], which coincides with MyoD acetylation. This acetylation also promotes MyoD interaction with other coactivators (PCAF, p300/CBP, SWI/SNF (Switch/Sucrose Non-Fermentable) (BAF) chromatin remodeling complex) [20] and facilitates recruitment of RNA Polymerase II to muscle gene promoters such as *Myog*, *Ckm*, *Actc1*, *Tnnt1*, *Tnnt2*, *Tncc*, *Tnnc2*, *Mef2a* and *Zfp238* [18]. Because acetylation and methylation are mutually exclusive on the same lysine residue, modifications at K104 operate as an acetyl/methyl switch. G9A methylation likely prevents PCAF-dependent acetylation at K104, thereby blocking MyoD activation and the downstream myogenic program. HDAC inhibitors, such as sodium butyrate or TSA, enhance MyoD acetylation and histone hyperacetylation at MyoD-binding sites, leading to enhanced expression of muscle-specific genes at later stages.

All myogenic regulatory factors (MRFs), as bHLH transcription factors, form heterodimers with ubiquitous E-proteins (e.g., E12, E47) to bind E-box consensus sequences (CANNTG) in the regulatory regions of muscle-specific genes, activating their expression. MyoD-E12 heterodimers, for instance, are known to collaborate with members of the MEF2 family to activate muscle-specific genes and myogenesis [21,22]. Although E-protein transcription factor (E2A) is acetylated to control hematopoiesis, as discussed below, it remains to be demonstrated whether it is also acetylated in myogenic cells and what its impact is on myogenesis.

2.1.1.3 MEF2 Family. In addition to MRFs, the Myocyte Enhancer Factor 2 (MEF2) proteins (MEF2A-D) serve as key orchestrators of muscle cell fate, differentiation, and regeneration. Importantly, MEF2 proteins lack intrinsic myogenic activity but instead strengthen the activity of myogenic bHLH proteins (MRFs), functioning as coactivators. Acetylation is a critical post-translational modification for MEF2 activity. Specifically, Myocyte Enhancer Factor 2C (MEF2C) is acetylated by p300. Six acetylated lysines have been mapped to the transactivation domain of MEF2C. Four of these (K234, K239, K252, and K264) are fully conserved across various MEF2 isoforms and species, suggesting a general, conserved mechanism. Acetylation of K4, located within the MADS box, occurs at the onset of skeletal muscle differentiation and leads to a more stable MEF2/DNA complex [19]. EMSA experiments further revealed that a MEF2C mutant mimicking permanent acetylation (K4Q) exhibited a strongly enhanced DNA-binding activity (at least 7-fold higher), whereas a non-acetylatable mutant (K4R) bound DNA less efficiently. The co-activator p300 is responsible for K4 acetylation and directly enhances MEF2 DNA-binding activity [19]. Furthermore, acetylation of MEF2 is critical for its synergistic cooperation with myogenic bHLH proteins like MyoD. Studies show that the lack of K4 acetylation abolishes this functional interaction, leading to a decrease in myogenic conversion and Myosin heavy chain expression [19]. Overexpression of non-acetylatable MEF2C mutants inhibits myogenic differentiation, underscoring the critical role of acetylation in promoting myogenesis. These mutants display reduced DNA binding activity, reduced capacity to activate gene transcription, inhibition of the synergistic effect with MyoD or myogenin in myogenic conversion assays, and inhibition of myogenic differentiation [19,23]. MEF2C is preferentially acetylated in differentiating myocytes but not in undifferentiated myoblasts [19]. The model proposed is that MEF2 proteins are kept functionally silent in myoblasts by deacetylation, resulting in lower DNA affinity; a shift towards the acetylated form, stabilized by p300, leads to the efficient activation of MEF2 upon differentiation [19,23]. Indeed, in proliferating myoblasts, MEF2 proteins are present but transcriptionally silent due to their association with Class II histone deacetylases (HDACs) (HDAC4, HDAC5, HDAC7, and HDAC9), which bind to MEF2 and repress its activity within the nucleus. Upon differentiation signals, these Class II HDACs dissociate from MEF2, thereby releasing the inhibition on MEF2. This allows MEF2 to associate with HAT coactivators like p300, stimulating MEF2-dependent gene expression. In parallel, MYLK2 phosphorylates MEF2C at T80, a modification that strengthens MEF2C interaction with p300/PCAF and promotes their recruitment to myogenic promoters (e.g. Myog), thereby increasing target gene activation [24]. Moreover, calcium/calmodulin-dependent protein kinase (CaMK) signaling disrupts the repressive MEF2-HDAC4/5 complex (without inhibiting HDAC catalytic activity) and synergizes with p38-MAPK inputs, creating a phosphorylation gate that licenses HAT engagement at MEF2-bound loci [25]. Histone Deacetylase 3 (HDAC3) has also been shown to efficiently deacetylate MEF2D *in vitro* and *in vivo*. Unlike Class II HDACs, HDAC3 directly interacts with the MADS box of MEF2 and associates with MEF2D, MEF2B, and MEF2C. HDAC3 represses MEF2-dependent transcription and inhibits myogenesis. The strong interaction between HDAC3 and MEF2D observed in myoblasts diminishes significantly during differentiation, suggesting a signal-responsive repressive role [26].

2.1.1.4 Targeting Acetylation as a Therapeutic Avenue for Duchenne Muscular Dystrophy. The pivotal role of histone and non-histone acetylation during myogenesis represents an attractive target for drug development for Duchenne muscular dystrophy (DMD), a severe muscle-wasting disease. The therapeutic landscape for both oncology and non-oncology diseases has increasingly recognized the profound impact of targeting protein acetylation through HDAC inhibitors. While it is generally accepted that these inhibitors mediate their action primarily by altering chromatin status, leading to changes in gene expression, it is equally crucial to acknowledge their significant effects through the acetylation status of non-histone proteins, including a wide array of transcription factors. This broader impact offers diverse mechanisms for therapeutic intervention beyond just chromatin remodelling. HDAC inhibitors have been shown to promote myogenesis and skeletal muscle formation both *in vitro* and *in vivo* [27–30]. This is a counterintuitive observation, since global histone acetylation levels normally decrease during myogenic differentiation [31]. This suggests that HDAC inhibitors mediate their effects, at least partly, through non-histone targets. Accordingly, treatment with HDAC inhibitors increases the acetylation of MyoD in myoblasts [32], as well as the acetylation of MEF2 [26]. HDAC inhibitors also enhance muscle regeneration through modifying histone acetylation at specific gene promoters, notably by inducing the expression of the promyogenic gene *Fst* encoding the follistatin protein [30].

The pan-HDAC inhibitor Givinostat has shown significant promise in preclinical studies for Duchenne muscular dystrophy [33]. It has been shown to improve muscle function and histological parameters in murine models of DMD. Given this preclinical success, Givinostat recently received its first approval in the USA for the treatment of DMD, highlighting the direct clinical application of HDAC inhibition in a non-oncology muscle disease and its efficacy in improving muscle function in mouse models [33]. This demonstrates that targeting the acetylation status of proteins involved in myogenesis, including factors like MyoD and MEF2, offers a viable therapeutic strategy

for muscle disorders [33]. Yet, the use of HDAC inhibitors for treating DMD poses challenges that remains to be addressed. First, Givinostat is not a cure for DMD, but instead delays its progression. It is currently not clear whether sustained HDAC inhibition can be tolerated and remain effective in a long-term perspective. Second, the beneficial effects of these inhibitors are limited to the initial stages of the disease in mouse models [34]. Accordingly, clinical trials are currently restricted to young patients at early stages of DMD development. Third, Givinostat is a pan class I and class II HDAC inhibitor, meaning that its oral administration in children is associated to many side effects including diarrhea, abdominal pain and thrombocytopenia. Consequently, the use of Givinostat is restricted to lower dosages that may be less efficient. Developing more specific HDAC inhibitors which would limit toxicity and side effects, while maintaining clinical benefits, is imperative to improve the quality of life of treated DMD patients. Recent work suggests that inhibiting different HDACs, including HDAC6, improves the dystrophic phenotype in mice [35]. Additional research must be performed to precisely decipher the combination of HDACs to be targeted by more specific inhibitors to maximize clinical benefits while causing milder adverse effects.

2.1.2 Acetylation of Transcription Factors in Hematopoiesis

Hematopoiesis, like neurogenesis and myogenesis, represents a robust and well-characterized model for dissecting how transcription factors govern lineage commitment. Hematopoietic stem cells (HSCs), endowed with self-renewal and multilineage differentiation capacities, give rise to a diverse array of blood cells: erythrocytes, granulocytes, monocytes, megakaryocytes, lymphocytes, and dendritic cells through a tightly regulated, hierarchical cascade of fate decisions. These processes are orchestrated by stage-specific transcriptional programs, driven by a core regulatory network of TFs. Several master regulators converge to maintain HSC identity and balance self-renewal with differentiation. Runt-related transcription factor 1 (RUNX1), T-cell acute lymphocytic leukemia protein 1 (TAL1), GATA-binding transcription factors 1 and 2 (GATA1/2), purine-rich box 1 (PU.1), E2A and cellular Myb transcription factor (c-MYB) act not in isolation but as part of an integrated regulatory network [36], frequently assembling into multiprotein complexes and sharing coactivators such as p300 and PCAF, which mediate their acetylation and functional activation. Increasing evidence suggests that post-translational modifications, particularly acetylation, play a crucial role in modulating the activity of these factors by altering their DNA-binding affinity, transcriptional potency, subcellular localization, and protein stability. In addition, a common molecular mechanism seems to regulate hematopoietic transcription factor activity, in which acetylation is associated with increased transcriptional activity, while phosphorylation (often mediated by Ak strain transforming (AKT), Cyclin-dependent kinases (CDKs) and mitogen-activated protein kinases (MAPKs)) primes hematopoietic transcription factors for their ubiquitination (often mediated by STIP1 homology and U-box–containing protein 1 (STUB1) and F-box and WD repeat domain–containing protein 7 (FBXW7))and degradation by the proteasome. This mechanism is exemplified below with the case of RUNX1, E2A and TAL1.

2.1.2.1 RUNX1.

RUNX1 (also known as AML1 (Acute Myeloid Leukemia 1)) is a master transcription factor essential for hematopoiesis, guiding the emergence of HSCs and orchestrating their differentiation into all major blood lineages [37]. Conditional knockout experiments indicate that once HSCs are formed, RUNX1 is dispensable for their maintenance. In contrast, conditional loss of RUNX1 drastically impairs megakaryocytic and lymphoid differentiation, while increasing the number of myeloid progenitors which is associated with a mild myeloproliferative syndrome [37]. A key layer of RUNX1 regulation is acetylation, particularly by the histone acetyltransferase p300 [38]. This modification occurs specifically at two conserved lysine residues, K24 and K43, in the N-terminal region of RUNX1 [39]. Interestingly, acetylation does not regulate the ability of RUNX1 to bind to cofactors, including p300 and Polyomavirus Enhancer-Binding Protein 2 beta subunit (PEBP2β). Acetylation at these sites is essential for RUNX1 DNA-binding activity. Indeed, acetylation significantly enhances RUNX1 sequence-specific DNA-binding and transcriptional activation capacity, while mutation of K24 and K43 abolishes acetylation and severely impairs RUNX1 ability to bind DNA [39]. RUNX1 is also acetylated by KAT6A (MOZ), which also favors myeloid differentiation [40]. In fact, the levels of the RUNX1-KAT6A complex increase during myeloid differentiation. Notably, acetylation of RUNX1 drives its capacity to transactivate the *Csf1* promoter, encoding an essential growth factor for myeloid differentiation, which suggests that acetylation of RUNX1 is important for its capacity to regulate myeloid commitment [39]. In support of these observations, it has been shown that overexpression of p300 or KAT6A increases the capacity of RUNX1 to activate transcription at the myeloperoxidase (*Mpo*) promoter and stimulates myeloid differentiation *in vitro* [40,41].

Acetylation of RUNX1 is also central for its oncogenic potential. While wild-type RUNX1 can efficiently transform fibroblasts, an acetylation-deficient mutant of RUNX1 fails to do so [39]. This has been confirmed in the context of the RUNX1–RUNX1T1 (also called AML1-ETO) fusion protein, derived from the t(8;21) translocation in the context of acute myeloid leukemia. This key oncogenic driver is acetylated by p300 on the same K24 and K43 residues as wild-type RUNX1 [42]. Acetylation of these residues have been detected in cell cultures, in mouse

leukemic cells and also in human acute myeloid leukemia primary samples. However, acetylation of K43, and not K24, is specifically required for the oncogenic activity of the fusion protein. Indeed, the RUNX1–RUNX1T1 fusion protein increases the self-renewal capacity of human HSPCs, while a K43R mutant of RUNX1–RUNX1T1 fails to perform this activity, likely due to its incapacity to activate the expression of key target genes such as *Id1*, *p21* and *Egr1*. Acetylated K43, but not the non-acetylated form, can recruit bromodomain-containing proteins such as the TATA-binding protein-Associated Factors (TAF), partially explaining the molecular mechanism by which acetylation confers oncogenicity for RUNX1–RUNX1T1 [43]. Strikingly, expression of the K43R mutant, or treatment with p300 inhibitors, fails to induce leukemogenesis in mouse models *in vivo* [38,39]. p300 inhibitors significantly increased the median survival of RUNX1–RUNX1T1-expressing mice, providing a potential therapeutic approach for t(8;21) AML and potentially other AML subtypes. This highlights the direct therapeutic potential of targeting the acetylation of a specific transcription factor in a defined cancer context.

RUNX1 is subjected to numerous post-translational modifications including methylation, ubiquitination and phosphorylation [44] (Fig. 3). Notably, the serine/threonine kinase homeodomain-interacting protein kinase 2 (HIPK2) phosphorylates RUNX1 and p300 [45]. Importantly, phosphorylation of RUNX1 is a prerequisite for the phosphorylation of p300, which stimulates its acetyltransferase activity [45]. Similarly, KAT6A also preferentially interacts with the phosphorylated form of RUNX1 [40], although the specific phosphorylated residues have not been determined. Presumably, the transcriptional potential of RUNX1 is fully achieved by a cascade of events in which HIPK2 phosphorylates RUNX1 on S249 and S276, which induces HIPK2-mediated p300 phosphorylation, stimulates p300 acetyltransferase activity and leads to p300-mediated RUNX1 acetylation.

Ubiquitination of RUNX1 seems to be mutually exclusive with its acetylation. In fact, RUNX1 is ubiquitinated by different E3 ubiquitin ligases including STUB1 and Deltex E3 ubiquitin ligase 2 (DTX2) on multiple lysine residues including K43 [46,47], which is targeted for acetylation by p300. Expression of DTX2 significantly decreases the acetylation levels of RUNX1 and blocks its transactivation capacity on the myeloid-specific *Csf1r* reporter gene [47]. Interestingly, overexpression of DTX2 and STUB1 blocks proliferation of specifically leukemic cells expressing RUNX1 and/or the RUNX1–RUNX1T1 fusion protein, without affecting the growth of other leukemic cells [46, 47]. Accordingly, DTX2 and RUNX1 protein expression are inversely correlated in many leukemic cell lines [47]. Phosphorylation of RUNX1 at S266 and T273, by many members of the Cyclin-Dependent Kinase (CDK) family, provokes the degradation of RUNX1 by the Anaphase-Promoting Complex (APC), which is endowed with E3 ubiquitin ligase activity [48]. Interestingly, phosphorylation on S266/T273 is mutually exclusive with phosphorylation at S249/S276 [48]. Thus, while phosphorylation by CDKs negatively regulate RUNX1 activity and is correlated with a block in its acetylation, phosphorylation by HIPK2 potentiates RUNX1 acetylation and activity.

2.1.2.2 E2A. E2A, a ubiquitous bHLH transcription factor, comprises two isoforms, E12 and E47, and functions as a heterodimerization partner for many cell type-specific bHLH transcription factors, including TAL1 in hematopoiesis and MyoD in myogenesis [49]. In hematopoietic stem cells, E2A sustains quiescence and long-term self-renewal of hematopoietic stem cells, thereby preventing stem-cell exhaustion. In addition, E2A is also indispensable for establishing the lymphoid program [50]. These lineage decisions are enforced through E2A activation domains AD1 and AD3, which engage coactivators and corepressors, ensuring appropriate chromatin and transcriptional states during commitment. Several lines of evidence demonstrated that E2A function is modulated by acetylation. *In vivo* and *in vitro* acetylation assays confirmed that E2A is acetylated by p300/CBP and PCAF in conserved N-terminal lysines, notably K34 and K334, with contributions from K14/K101/K144 and K171-175 [51,52]. Directed mutagenesis showed that removing these acetyl-acceptor sites diminishes E2A acetylation and function, with K34 playing a dominant role [51,52]. Reporter assays demonstrated that acetylation enhances E2A transcriptional output [51]. At the complex level, E2A resides in high-molecular-weight assemblies that co-immunoprecipitate with p300, CBP, and PCAF; co-expression of these HATs increases nuclear retention of E2A [52]. Concordantly, in neonatal bone marrow, double-heterozygous ($E2A^{+/-}$:$p300^{+/-}$) mice display a greater reduction in total and mature B-lineage cells than either single heterozygote. This additive, lineage-restricted effect fades in adulthood, consistent with a stage-specific requirement for p300-mediated E2A acetylation during the perinatal wave of B-lymphopoiesis [52]. Counter-regulation by deacetylation further sharpens this axis; E2A (E47) physically associates with SIRT1, which reverses p300/CBP-driven acetylation; SIRT1 knockdown increases Transcription Factor 3 (TCF3) and E2A protein levels, implicating SIRT1 as a negative regulator of E2A function in early B-cells [53]. Together, these findings support a model in which dynamic acetylation of multiple N-terminal lysines stabilizes E2A within HAT-rich complexes, prolongs its nuclear localization, and amplifies lineage-appropriate transcriptional programs, thereby steering hematopoietic progenitors toward lymphoid fates while restraining alternative lineages. E2A is negatively regulated by a mechanism involving its phosphorylation and degradation. First, E2A is phosphorylated by CDKs on S48 and S154, which negatively regulates its function

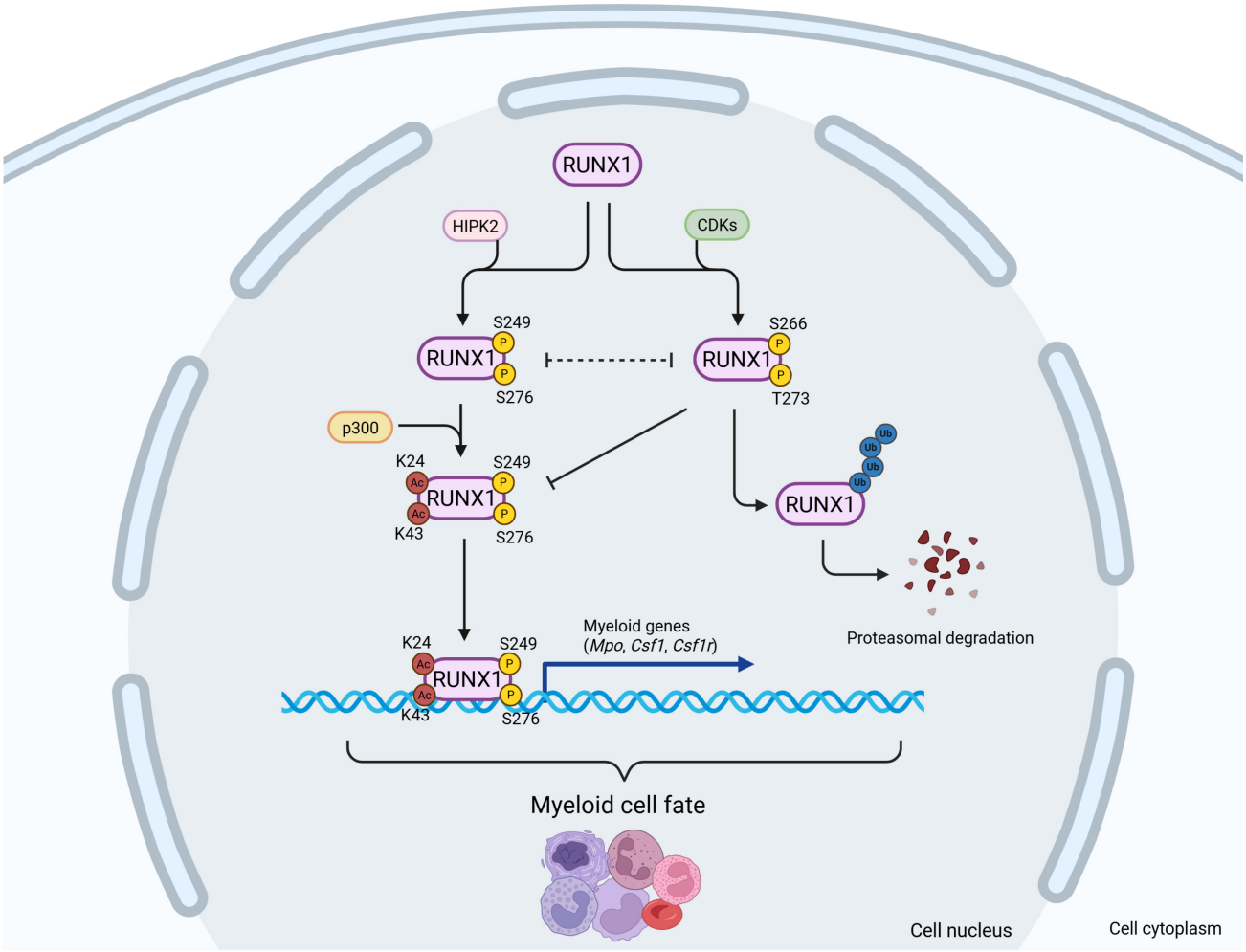

Fig. 3. Interplay between different post-translational modifications: the example of RUNX1. RUNX1 phosphorylation by homeodomain-interacting protein kinase 2 (HIPK2) facilitates p300-dependent acetylation of K24 and K43, which allows RUNX1 recruitment to target genes that drive the myeloid program. In contrast, phosphorylation by cyclin-dependent kinases (CDKs) act negatively on RUNX1 function by driving its ubiquitination and subsequent degradation by the proteasome. Created in BioRender.com. Sincennes, M. (2025) https://BioRender.com/obhlmm6. RUNX1, Runt-related transcription factor 1.

[54]. E2A are ubiquitinated and degraded by the proteasome by a mechanism involving the ubiquitin-conjugating enzyme (E2) UBE2I (also called UbcE2A or Ubc9) as well as the E3 ligase STUB1 [55,56]. Phosphorylation of E2A by ERK1/2 is necessary for its proteasomal degradation, and this process is mediated by NOTCH signaling [57]. Importantly, NOTCH signaling only induces E2A protein degradation in cells expressing ERK1/2. Since NOTCH signaling strongly favors T-cell differentiation over the B-cell lineage, it is possible that E2A proteins are degraded in thymic progenitors by a NOTCH-dependent phosphorylation/ubiquitination mechanism, whereas in B-cell progenitors, E2A proteins are expressed and acetylated to activated gene expression programs driving the B-cell fate. Whether a similar regulatory mechanism exists in myogenesis and in other lineages dependent on E2A activity remains to be determined.

2.1.2.3 TAL1. TAL1 is a key transcription factor in hematopoiesis, where it maintains HSC multipotency while guiding erythroid and megakaryocytic lineage commitment. When mis expressed in lymphoid progenitors, TAL1 is a potent oncogene driving T-cell acute lymphoblastic leukemia [58]. Depending on its interacting partners, TAL1 has the capacity to activate or to repress transcription. This dual role is finely regulated by lysine acetylation. *In vitro* and *in vivo* assays using [^{3}H] acetate labeling identified K221 and K222 as specific targets of KAT2B (P/CAF)-mediated acetylation [59]. This modification enhanced TAL1 binding to E-box elements and increased its transcriptional output. Acetylation of TAL1 does not influence its capacity to interact with p300, KAT2B, or its heterodimerization partner E12. In sharp contrast, acetylation disrupts TAL1 association with the mSin3A-HDAC1 corepressor complex. Expression of KAT2B in erythroid cells, but not a mutant lacking acetyltransferase activity, en-

hances the expression of erythroid-specific genes such as *Hbb* and *Epb4.2*. Thus, acetylation converts TAL1 from a repressive to an activating transcription factor, promoting the expression of erythroid-specific genes and driving erythroid differentiation [59]. TAL1 is also subjected to phosphorylation on different serine residues, some of which being driven by erythropoietin treatment, with various effects on its transcriptional activity. Notably, phosphorylation by AKT1 at T90 [60], which triggers the association between TAL1 and the E3 ligase STUB1, ubiquitination of TAL1 and its degradation by the proteasome [61,62]. Since the kinase AKT1 is activated by the TGFβ pathway, treatment of hematopoietic and leukemic cells with TGFβ leads to the degradation of TAL1 [61]. TGFβ is known to promote terminal differentiation of erythroid cells. Together, these observations suggest a model in which during erythroid commitment, TAL1 is first acetylated to drive the expression of erythroid-specific genes, and is subsequently phosphorylated and ubiquitinated by a TGFβ and AKT1-dependent mechanisms, leading to the degradation of TAL1 to allow terminal erythroid differentiation. Similarly, hypoxia also triggers ubiquitination and proteasomal degradation of TAL1, in a mechanism dependent on MAPK phosphorylation of TAL1 at S122 [63]. Degradation of TAL1 is also induced by NOTCH signaling [62], involved in hematopoietic stem cell self-renewal. Thus, post-translational modifications of TAL1 fine-tune its association with E12/E47, co-activator and co-repressor complexes and E3 ligases, which regulated erythroid cell fate and most likely stemness. Therefore, targeting TAL1 post-translational modifications could be relevant in the context of T-cell acute lymphoblastic leukemia.

2.1.2.4 c-MYB. The transcription factor c-MYB is highly expressed in hematopoietic stem cells, and its expression decreases during differentiation [64]. Accordingly, c-MYB plays a central role in hematopoiesis and is absolutely required for definitive hematopoiesis. In addition, aberrant expression of c-Myb has been associated with different forms of cancers including leukemia. Its transcriptional activity is tightly controlled by post-translational modifications, among which lysine acetylation emerges as a critical regulatory mechanism. Acetylation by the coactivators p300 and CBP targets five conserved lysines (K438, K441, K471, K480, and K485) located within the negative regulatory domain of c-MYB [65,66]. *In vitro* and *in vivo* studies revealed that these acetylation events strongly enhance c-MYB DNA-binding affinity, transactivation potential, and interaction with coactivators such as CBP [65,66]. Site-directed mutagenesis of key lysines, particularly K438 and K441, severely impaired c-MYB acetylation and function, leading to reduced transcriptional output [65,66]. At the physiological level, in a mouse model that compromises the interaction between c-MYB and p300 (mutation M303V in c-MYB), a 10-fold increase in the numbers of hematopoietic stem cells has been observed, with a sharp decrease in mature hematopoietic cells from all lineages (e.g., thrombocytosis, lymphopenia, eosinopenia) [67]. Collectively, these findings position lysine acetylation as a pivotal switch that modulates c-MYB activity and underscore its essential role at the apex of the hematopoietic hierarchy, controlling early steps of stem cell commitment. In addition to acetylation, c-MYB is also subjected to phosphorylation, ubiquitination and sumoylation, although the interplay between all these post-translational modifications have not been directly addressed. However, some of these post-translational modifications take place very closely to the acetylation sites, suggesting that they may be mutually exclusive. In fact, while acetylation of c-MYB in the region between K438 and K485 positively regulates its transcriptional activity, phosphorylation on S528 negatively regulates its activity [68]. However, a mutant that cannot be phosphorylated does not equally impact all target genes, since the expression of the stem cell marker *Cd34* is more strongly affected [69], suggesting that phosphorylation on S528 specifically represses stemness genes, thus controlling hematopoietic cell commitment and differentiation. Accordingly, while c-MYB expression normally maintains myeloblastic cells in an undifferentiated state, co-expression of c-MYB with Nemo-like kinase (NLK), which phosphorylates c-MYB on multiple sites, abrogates this effect [70]. Phosphorylation by lymphocyte adaptor protein (LNK) favors the interaction of c-MYB with the E3 ligase FBXW7, mediating its ubiquitination and degradation by the proteasome [71]. In addition, the negative regulatory domain of c-MYB is also subjected to sumoylation on K499 and K523, which blocks c-MYB transactivation capacity [72–74]. Small Ubiquitin-like Modifier (SUMO) conjugation does not interfere with c-MYB DNA binding. In contrast, the presence of SUMO molecules precludes the recruitment of transcriptional co-activators such as p300 [75]. Blocking c-MYB sumoylation leads to an increase in histone acetylation on the promoters of c-MYB target genes and efficient gene expression. Therefore, it is tempting to speculate that acetylation of c-MYB by p300 and sumoylation are two mutually exclusive post-translational modifications that act as a switch to convert c-MYB transcriptional activity during hematopoietic cell differentiation.

2.1.2.5 GATA Family. GATA-binding protein 1 (GATA1) and GATA2 are master regulators of hematopoiesis, controlling hematopoietic stem cell biology and erythroid lineage differentiation [76]. Loss of either *Gata1* or *Gata2* in mice leads to embryonic lethality associated with profound hematopoietic defects. GATA2 plays a pivotal role in the establishment and maintenance of HSCs, where its high expression ensures stem cell quiescence by promoting self-renewal and survival programs while actively repressing differentiation. GATA1 drives erythroid and megakaryocytic differentiation by activating lineage-specific gene

programs while repressing genes that maintain stemness or promote alternative fates. One of its key roles is to displace GATA2 in a process known as the "GATA switch", thereby silencing stemness-associated genes and promoting terminal erythroid maturation. Multiple lines of evidence establish lysine acetylation as a key regulatory input on GATA1 and GATA2. Acetylation by p300 was first demonstrated for GATA1 to occur on multiple residues (K214, K218, K220) within its DNA-binding domain, leading to increased DNA binding and enhanced transcriptional activity [77]. Accordingly, deleting residues 218–221 diminishes GATA1 transactivation capacity and impairs megakaryocyte differentiation [78]. GATA1 is also acetylated by CBP on two different lysine-rich motifs, which do not influence GATA1 DNA binding but strongly increase its transcriptional activity [79]. In GATA1-deficient erythroid cells, expression of mutant GATA1, in which one motif or the other is deleted, strongly impairs erythroid differentiation *in vitro*, while a double mutant completely abolishes terminal differentiation. These mutants retain their DNA-binding capacity and nuclear localization, but fail to be recruited on erythroid target genes as demonstrated by chromatin immunoprecipitation on multiple erythroid-specific genes including globin genes, *Zfpm1*, *Ahsp* and *Klf1* [80]. Moreover, acetylated GATA1 is specifically recognized by the bromodomain-containing protein bromodomain-containing protein 3 (BRD3) [81]. In erythroid cells, BRD3 co-occupies GATA1-bound promoters and enhancers, independently of the presence of histone acetylation, and is mostly depleted in gene bodies. Pharmacologic inhibition of BRD3 binding inhibits the expression of erythroid genes in a dose-dependent fashion and impairs erythroid differentiation similarly to the phenotype observed with acetylation-defective GATA1 mutants [81]. Together, these results indicate that acetylation is necessary for chromatin engagement of GATA1 and functional activation of target gene expression, strongly supporting a model in which acetylation is a central regulatory mechanism to control GATA1 recruitment to its target genes, at least in erythroid cells.

Moreover, the acetylation of GATA1 also regulates its stability: while it enhances transcriptional activity, it simultaneously flags the protein for ubiquitin-mediated proteasomal degradation [82]. This degradation is acetylation- and phosphorylation-dependent, suggesting a coordinated mechanism in which post-translational modifications couple transcriptional output with protein turnover. Indeed, GATA1 is ubiquitinated and degraded by the proteasome in a MAPK phosphorylation-dependent manner, but it has been suggested that acetylation must be present for degradation to occur [82]. Both acetylation and phosphorylation can occur independently (acetylation is not required for phosphorylation, and vice versa). When GATA1 is solely acetylated, it is transcriptionally active and is not degraded. When it is both acetylated and phosphorylated, then GATA1 is targeted to the ubiquitin-proteasome system. Moreover, the model suggests that phosphorylation takes place preferentially on DNA-bound acetylated GATA1 [82]. In addition, like what has been observed for TAL1, erythropoietin treatment leads to increased GATA1 phosphorylation on multiple amino acid residues, some of which being associated with transcriptional activation, while others being associated with its degradation [82,83]. Together, these findings highlight acetylation as a central regulator of GATA1, linking its ability to activate lineage-specific transcription to its controlled degradation, and ensuring precise regulation of hematopoietic cell fate decisions.

Evidence suggests that acetylation of GATA1 not only drives erythroid maturation, but is also a key mechanism that must be targeted to allow alternative cell fates such as myeloid differentiation. For example, it is well accepted that the antagonism between GATA1 and the transcription factor PU.1 drives erythroid *versus* myeloid cell commitment [84]. GATA1 and PU.1 can bind together and mutually inhibit the activity of each other. In addition, PU.1 directly inhibits GATA1 acetylation *in vitro* and *in vivo*, without altering GATA1 DNA binding capacity [85]. In fact, PU.1 seems to generally repress CBP-mediated acetylation, resulting in a blockade in the acetylation of many erythroid-specific transcription factors, such as GATA1, but also of histone acetylation on erythroid promoters. Therefore, PU.1 targets histone and transcription factor acetylation to drive myeloid differentiation at the expense of an erythroid cell fate. In acute myeloid leukemia, the oncogenic fusion protein RUNX1–RUNX1T1 (AML1-ETO) operates by a similar mechanism to inhibit alternative cell fates such as erythroid lineage commitment by directly blocking GATA1 acetylation [86]. The Nuclear Hormone Receptor 4 (NHR4) domain of RUNX1T1 (ETO) is responsible for mediating this effect, and accordingly, wild-type RUNX1 has no effect on GATA1 acetylation levels. Thus, these studies suggest that blocking the acetylation of GATA1 is a prerequisite to allow myeloid lineage commitment.

Like GATA1, GATA2 is also acetylated at distinct domains, by the action of p300 and KAT2A [87]. Through systematic lysine-to-alanine mutagenesis, six conserved lysine clusters were identified as primary targets of p300. Their acetylation enhances GATA2 DNA-binding affinity, transcriptional activity, and nuclear retention. Importantly, acetylation-defective mutants failed to activate transcription despite retaining partial DNA-binding capacity, highlighting acetylation as a fine-tuner of GATA2 regulatory output. Moreover, in myeloid cells, acetylation was also essential for GATA2 ability to suppress proliferation, linking this post-translational modification to its biological function in hematopoietic regulation [87]. Similarly to GATA1, GATA2 is also phosphorylated by AKT1 and by MAPK, which negatively regulates GATA2 activity, partly by impairing its translocation to the nucleus and its DNA binding activity [88]. Again, a duality between acetylation and

phosphorylation seems to appear as a general mechanism controlling the action of hematopoietic transcription factors.

GATA3 is a lineage gatekeeper in hematopoiesis induced during early T-cell specification. It activates T-lineage specific genes such as the ones encoding the T cell receptor (TCR), CD4, CD8 and IL5, while repressing alternative B-cell and myeloid programs [89]. A decisive layer of regulation is lysine acetylation near the second zinc finger. A conserved basic KRR amino acid triad (K305–R306–R307) located between the two zinc fingers and conserved in GATA1/2 has long been employed as a dominant negative mutant for GATA3 activity [90]. The KRR mutation to alanine residues (AAA) does not affect GATA3 expression, its nuclear localization or its DNA binding function. However, the mutant is capable of blocking GATA3 transcriptional activity [90]. It has later been discovered that this KRR region functions as an acetylation hub that governs coactivator engagement rather than DNA recognition [91]. Biochemical mapping shows that p300 acetylates K305 and neighboring lysines (K293, K347). Pulse-labeling in primary splenocytes confirms physiological acetylation of GATA3 *in vivo* [91]. Converting the KRR motif to alanines reduces acetylation by approximately 75% without altering DNA binding and abolishes GATA3–p300 synergy in reporter assays. A mouse model has been generated in which the hypo-acetylated form (KRR-GATA3) is specifically expressed in the T lineage. These mice present a decrease in Th2 effector genes (IL-4, IL-5) and an imbalance in the proportion of T cells:B cells in the spleen, peripheral blood, lymph nodes and Peyer's patches. This change is mostly due to a defect in T-cell homing, resulting in an impaired immune response in these mice [91]. Together, these findings support a model in which acetylation centered on the KRR motif acts as a molecular rheostat that strengthens coactivator recruitment and enhancer output at lineage-appropriate loci, thereby promoting Th2 differentiation, T cell homing and balanced GATA3-driven cell-fate decisions. In addition to acetylation, GATA3 is subjected to phosphorylation on a motif located very closely to the KRR motif [92]. Phosphorylation on this motif by AKT regulates the recruitment of co-activators and co-repressors on GATA3 target genes and impacts the fate of Th2 cells [92], although the interplay between acetylation and phosphorylation on these two adjacent motifs has not been directly investigated.

Interestingly, the E3 ligase FBXW7 ubiquitinates both GATA2 and GATA3 to promote their proteasomal degradation in a phosphorylation-dependent manner. GATA2 is phosphorylated by CDK1 on T176 [93], while GATA3 is phosphorylated by CDK2 on T156 [94]. Conditional knockout of *Fbxw7* in hematopoietic cells results in increased GATA protein levels, associated to hematopoietic stem cell exhaustion and a predisposition to T cell leukemia [95], while conditional knockout in the T lineage drastically perturbs T cell development [94], suggesting that ubiquitination by FBXW7 during lineage commitment is a key regulatory process to control GATA transcription factor activity, with a profound impact on the hematopoietic cell hierarchy.

2.1.2.6 Myeloid Drivers: PU.1 and C/EBPα. PU.1, a member of the ETS family of transcription factors, is a key regulator of hematopoietic lineage specification, orchestrating the balance between myeloid and lymphoid differentiation while maintaining HSC quiescence under homeostatic and inflammatory conditions. As discussed earlier, GATA1 and PU.1 mutual repression directs hematopoietic cell fate towards the erythroid or myeloid lineage [84]. Beyond transcriptional control, PU.1 activity is finely modulated by post-translational modifications, particularly acetylation. PU.1 is acetylated *in vivo*, and this modification plays a distinct role in its regulatory functions [96,97]. Histone acetyltransferases such as p300 and CBP enhance PU.1's transactivation capacity, with p300 exerting the strongest effect via a direct interaction dependent on residues 7–30 of the N-terminal activation domain [96]. Chromatin immunoprecipitation further confirmed that p300 is recruited alongside PU.1 at endogenous target enhancers, such as the immunoglobulin κ 3′ enhancer, indicating a functional interplay. Mutational analysis revealed that specific lysines within the DNA-binding domain (notably K170/171 and K206/208) are required for full transcriptional activation, cofactor recruitment, and repression of lineage-inappropriate genes [96]. Acetylation-deficient PU.1 mutants retained some transactivation ability but lost repressive functions, particularly on the *c-myc* promoter, due to impaired interaction with the mSin3A corepressor [97]. Notably, these mutants failed to inhibit erythroid differentiation or suppress β-globin expression in erythroid progenitor cells, and were unable to induce apoptosis or downregulate survival genes such as *Myc* and *Bcl2*, underscoring the role of acetylation in PU.1-mediated lineage restriction and growth control [97]. Thus, acetylation of PU.1 is essential for inhibiting the erythroid program while promoting myeloid cell fate. Paradoxically, HDAC inhibition by trichostatin A increased PU.1 acetylation but repressed its transcriptional activity on inflammatory gene promoters like *Il1b* and *Csf2ra*, suggesting that hyperacetylation disrupts functional protein–protein interactions or the composition of transcriptional complexes. Altogether, these findings highlight a nuanced role for acetylation in fine-tuning PU.1's transcriptional output, not only by enhancing coactivator function but also by regulating lineage fidelity, repression of alternate fate programs, and control of proliferation and apoptosis in hematopoietic progenitors.

C/EBPα is a master regulator of myeloid lineage commitment and differentiation, particularly of granulopoiesis. C/EBPα is acetylated by p300 [98–100] and GCN5 [101, 102]. Acetylation takes place at multiple lysine residues,

many of which being located within the DNA-binding and the leucine zipper domains. Acetylation does not seem to affect C/EBPα protein expression or cellular localization. However, acetylation perturbs the capacity of C/EBPα to bind DNA and thus negatively regulates C/EBPα activity [103]. Infection of myeloid cells with acetylation-mimetic mutants of C/EBPα leads to defects in granulocytic differentiation *ex vivo* [101]. During myeloid differentiation, GCN5 expression is progressively decreased, leading to deacetylation of C/EBPα, and presumably to an increase in its transcriptional activity. Acetylation of C/EBPα is also regulated by interaction with PU.1 [100], suggesting that the interplay between different acetylated transcription factors controls myeloid lineage differentiation. C/EBPα negatively regulated by sumoylation, which promotes its ubiquitination and proteasome degradation [104]. Sumoylation also hinders the recruitment of the SWI/SNF chromatin remodeling complex on C/EBPα target genes, The E3 ligase FBXW7 is responsible for ubiquitinating C/EBPα to promote adipogenic cell fate [105], but whether this holds true in the hematopoietic system remains to be determined. It is interesting to note that acetylation of specific lysine residues of C/EBPα has been associated with an increase in transcriptional activity [98,99], in contrast to most acetylation sites being involved in inhibiting C/EBPα function. Acetylation of C/EBPα by p300 and its deacetylation by SIRT1 are important for the expression of mitochondrial genes and regulate mitochondrial respiration [98]. By maintaining a delicate balance between self-renewal and quiescence, this acetylation-sensitive transcriptional network ensures the preservation of stem cell integrity and responsiveness to differentiation cues.

2.1.3 Acetylation of Transcription Factors in Neurogenesis and Pluripotency

Neurogenesis is the process by which neural stem cells (NSCs) differentiate into neurons. Upon activation, NSCs enter the cell cycle, proliferate and commit into neuroblasts, which differentiate into neurons (reviewed in [106]). While transcription factor acetylation appears to be a general mechanism controlling hematopoietic and myogenic cell fate, there are fewer examples of transcription factor acetylation in the control of neurogenesis. For example, NEUROD1 has been shown to be acetylated by p300 in pancreatic cells [107], but the relevance of this acetylation in the context of neurogenesis has yet to be examined. Acetylation of two paired-box transcription factors, PAX3 and PAX6, has been documented in the context of neurogenesis. PAX3 acetylation acts as a molecular switch controlling the balance between stem cell maintenance and neurogenic commitment. Notably, PAX3 acetylation mediates its capacity to drive the expression of two of its target genes: *Hes1*, involved in stem cell self-renewal; and *Neurog2*, associated with neurogenic commitment. When PAX3 is deacetylated, *Hes1* expression is favored and stem cell maintenance is the preferred output [10]. In contrast, acetylation of PAX3 promotes neuronal differentiation at the expense of stemness, by driving the expression of *Neurog2* [10]. In addition to PAX3, PAX6 acetylation also controls the balance between neural stem cell self-renewal and differentiation, by a distinct mechanism. Acetylation of PAX6 by KAT2A promotes PAX6 proteasomal degradation in zebrafish [13]. On the opposite, KAT2A inhibition leads to increased PAX6 protein levels and to increased proliferation of neural stem cells, while blocking their differentiation [13].

One family of transcription factors, the SRY-related HMG-box (SOX) family, plays crucial roles in various developmental processes, including cell differentiation and stem cell maintenance. There are 20 SOX proteins in humans, which are widely expressed in embryonic as well as adult tissues. They are extensively regulated by acetylation on multiple lysine residues, with SOX2 acetylation being largely studied and serving as a paradigm for other SOX family members. Acetylation of SOX proteins occurs both at conserved lysines within the HMG-box (e.g., SOX2 K97/K105/K111, SOX4 K95, SOX9 K61), where it generally supports transcriptional activity, and at unique sites outside the HMG-box, such as SOX9 K253/K398, where the precise contribution is less clear (Fig. 4). In addition, acetylation in localization signals (SOX2 K75 in the nuclear export signal (NES) and SRY K136 in the nuclear localization signal (NLS)) regulates stability and nuclear transport. In muscle cells, SOX4 is acetylated on K95 by KAT5 (originally named TIP60) [108]. This acetylation mark is critical for myoblast differentiation, as a mutated SOX4 on the acetylation site cannot rescue myogenic differentiation defects observed *in vitro* upon SOX4 knockdown. Acetylation of SOX4 is important to mediate its transcriptional activity and to regulate the expression of target genes involved in cell signaling, migration and adhesion, such as *Cald1* [108]. KAT5 also acetylates SOX9 on K61, K253 and K398 [109]. KAT5 potentiates the transcriptional activity of SOX9 during chondrogenesis, however this enhanced activity does not seem to be dependent on direct acetylation of SOX9 [109].

Acetylation of SOX2 is involved in the maintenance of embryonic stem (ES) cell pluripotency but is also important for reprogramming somatic cells into induced pluripotent stem cells [110,111]. In ES cells, SOX2 is acetylated by p300/CBP on multiple lysine residues, the majority of which being located within the DNA-binding domain of SOX2 (the HMG-box) [111]. SOX2 can be deacetylated by SIRT1 [110] and HDAC4 [112]. Acetylation on K97, K105, and K111 residues promotes the interaction between SOX2 and transcriptional cofactors from the steroid receptor coactivator (SRC) family, which likely maintains ES cell pluripotency by driving self-renewal [113]. On the other hand, acetylation of K75 located in the NES strengthens SOX2 interaction with Chromosome Region Mainte-

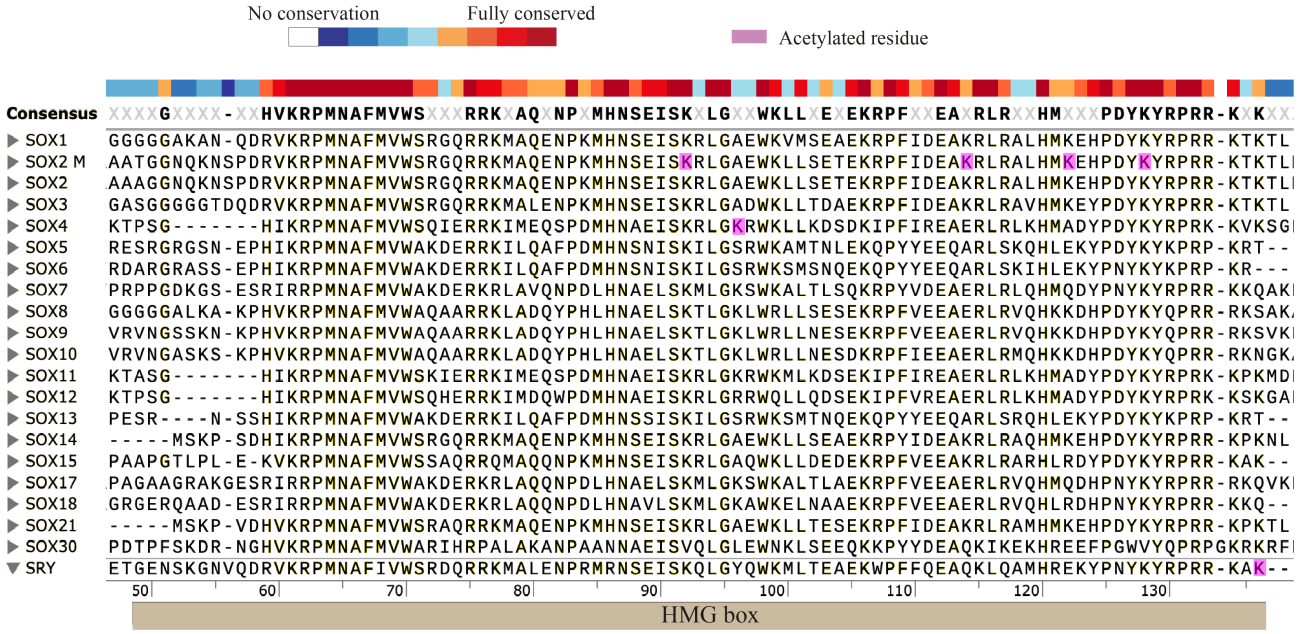

Fig. 4. Multiple members of the SRY-related HMG-box (SOX) family of transcription factors are subjected to acetylation. Multiple sequence alignment of the HMG box domain from SOX1-SOX21 and SRY proteins. The consensus sequence is shown at the top, with conservation indicated by a color scale (red = fully conserved, blue = low conservation). Magenta highlights mark lysine residues reported to be acetylated. The sequence labelled SOX2 M corresponds to *Mus musculus* (mouse) SOX2, as documented in acetylation studies.

nance 1 (CRM1), a nuclear export receptor [111]. Acetylation of K75 thus promotes nuclear export and proteasomal degradation of SOX2 thereby lowering nuclear SOX2 and biasing toward differentiation. It is interesting to note that SRY, another member of the SOX family, is acetylated by p300 in its NLS (on K136), which promotes its nuclear retention [114]. This indicates that acetylation of transcription factors in their NES and NLS is a common mechanism to control nuclear/cytoplasmic shuttling of transcription factors, notably SOX family members.

A second regulatory hub (K115–T116/118–K117–K119), where methylation and phosphorylation directly intersect with acetylation. Methylation of K119 by SET domain–containing protein 7 (SET7) represses SOX2 activity and licenses WW domain–containing E3 ubiquitin protein ligase 2 (WWP2)-dependent ubiquitination and degradation, while AKT phosphorylation of the neighboring threonine 116 in human and T118 in mouse embryonic stem cells (ESCs) antagonizes K119me and blocks Ubiquitin Protein Ligase E3 Component N-Recognin 5 (UBR5)-mediated ubiquitination at K115, thereby stabilizing SOX2 [115,116]. Within this same cluster, K117 and K119 are subjected to acetylation in vitro by p300/CBP [111], which positions acetylation to potentially compete sterically or electrostatically with K115 ubiquitination and K119 methylation. However, there is no direct evidence that K117ac or K119ac per se increase SOX2 stability, so these should be treated as competitive marks rather than proven stabilizers. Together, these modifications define an acetylation-centered switch that directs SOX2 fate. First, K75 acetylation promotes CRM1-dependent export and proteasomal turnover, lowering nuclear SOX2 and thereby permitting differentiation. Second, SET7-mediated K119 methylation earmarks SOX2 for ubiquitylation and degradation, reinforcing differentiation. Third, AKT phosphorylation at T116/118 antagonizes K119 methylation and K115 ubiquitylation, stabilizing a nuclear, transcription-competent pool of SOX2 that supports stemness/self-renewal. Acetylation at K117 or K119 could, in principle, compete with nearby degradative marks, but current evidence does not demonstrate a direct stabilizing effect of these acetylation marks in cells. Together, these findings highlight acetylation as a versatile and context-dependent mechanism that fine-tunes SOX family function.

It is interesting to note that defects in acetylation and deacetylation are commonly associated to neurological disorders and neurodegenerative conditions. For example, in amyotrophic lateral sclerosis (ALS), Alzheimer's and Huntington's diseases, histone acetyltransferase activity is decreased and the availability of acetyl donors in the brain is also diminished. This dual inhibition results in profound changes in histone acetylation [117]. These alterations play a key role in disease etiology by drastically changing gene expression patterns, leading to neuronal death, impaired memory and cognitive decline. The protective role of HDAC inhibition in Alzheimer's disease

is well documented in cellular and animal models [118] and undoubtedly represent a promising therapeutic avenue for neurocognitive disorders. Similarly, HDAC inhibitors were proven effective in mouse models of ALS [119], and selective HDAC3 inhibitors improve the phenotype of Huntington's disease in mice [120]. However, as observed for the treatment of DMD, using HDAC inhibitors in the treatment of neurological diseases brings significant challenges relative to toxicity and side effects. An additional barrier that comes into play when treating neurological disorders is brain permeability of HDAC inhibitors, which limits drug delivery. In addition, the specific implication of individual HDACs in mediating neuroprotective effects remains to be clarified. Importantly, HAT activators, with the example of N-(4-Chloro-3-trifluoromethyl-phenyl)-2-ethoxy-6-pentadecyl-ben-zamide (CTPB), are being developed and tested as an alternative to HDAC inhibitors with the hope of restoring acetylation in neurodegenerative diseases [117]. Such compounds have been shown to efficiently cross the blood-brain barrier and may be more specific compared to HDAC inhibitors. Although the acetylation of non-histone proteins and transcription factors (alpha-tubulin, Tau, p53, NK-kB) is impaired in neurodegenerative diseases such as Alzheimer's [118], their involvement in disease etiology, as well as their attractiveness as therapeutic targets, remains to be determined. More recently, acetylation defects have been associated with neurodevelopmental disorders such as Rett syndrome, Fragile X syndrome and autistic spectrum disorder (ASD), as well as with epilepsy and anxiety [121]. Moreover, missense variants in *HDAC3* have been associated with a rare neurodevelopmental disorder [122], while some cases of intellectual disability syndromes are caused by *HDAC4* haploinsufficiency [123]. The HDAC inhibitor valproic acid is commonly used for treating epilepsy and is currently tested in clinical trials as a therapeutic option for anxiety. Furthermore, it has been proposed that HDAC inhibition might mitigate ASD symptoms [121] and ameliorate the phenotype of Tuberous Sclerosis Complex (TSC) disorder in mice [124]. Although it is too early to understand how non-histone and transcription factor acetylation contribute to the etiology of these diseases, it becomes clear that acetylation of histones and non-histone proteins have the potential of becoming attractive therapeutic targets for neurological diseases.

2.2 Pleiotropic Molecular Roles of Transcription Factor Acetylation in the Control of Gene Expression

Acetylation was shown to directly increase DNA-binding affinity for numerous transcription factors, including MyoD, MEF2, RUNX1 and c-MYB, as discussed in the previous sections. In addition, as exemplified by PAX7, acetylation can fine-tune DNA binding capacity to favor recruitment to a subset of target genes, for fine-tuning lineage commitment. However, although most transcription factors are positively regulated by acetylation, in some cases, acetylation impairs transcriptional activity. For example, most Forkhead transcription factor family members are negatively regulated by acetylation. Forkhead box O1 (FOXO1) has been shown to be acetylated by CBP and deacetylated by SIRT1 [125] and SIRT2 [126,127]. A mutant FOXO1 that cannot be acetylated displays increased transactivation potential [125], which is mediated by a higher affinity for DNA [128]. Similarly, FOXO4 transcriptional activity is decreased by CBP-mediated acetylation [129,130]. FOXO3 is also deacetylated by sirtuins [131,132], which increases FOXO3 DNA binding and enhances the expression of its target genes, notably *Cdkn1b*, *Sod2* and *Bcl2l11* [132]. Similarly, acetylation of FOXA1 by p300 seems to reduce FOXA1 affinity for DNA probes *in vitro* [133]. In addition to increasing DNA binding, it has been proposed that deacetylation of Forkhead family members favors their nuclear localization [134].

Similar to transcriptional activators, transcriptional repressors can also be subjected to acetylation. For example, the transcriptional repressor GFI1, a cell fate determinant involved in hematopoietic stem cell function and in T cell lymphomagenesis, is acetylated in mammalian cells, which prevents its interaction with p53 and leads to a de-repression of p53 pro-apoptotic target genes [135]. Acetylation also controls the function of the transcriptional repressor Zinc finger E-box–binding homeobox 1 (ZEB1), an important regulator of T cell differentiation, also involved in the regulation of epithelial-mesenchymal transition in cancer cells. Acetyl-mimetic and acetyl-deficient ZEB1 mutants were generated and demonstrated that acetylation of ZEB1 preferentially leads to a repression of epithelial genes, thus promoting tissue invasion and metastasis [136].

In addition to controlling DNA-binding affinity and sequence recognition, acetylation of transcription factors can also influence their protein stability or their capacity to mediate protein-protein interactions, as discussed below and represented in Fig. 5.

Bromodomains are recognized "readers" of lysine acetylation, and they are well characterized to bind acetylated histone tails to transduce the signal to modulate gene expression. Strikingly, bromodomains can also bind to non-histone proteins that are acetylated. This is the case for the transcription factor MyoD, for which acetylation is specifically recognized by the bromodomain of CBP. Mutants of MyoD that cannot be acetylated fail to recruit CBP to activate muscle-specific genes [20]. Similarly, acetylation of the RUNX1–RUNX1T1 fusion protein creates a docking site for bromodomain-containing proteins such as TAFs, which initiates transcription [43]. Finally, the bromodomain of BRD3 recognizes acetylated GATA1 to promote erythroid cell fate [81].

Depending on the cellular context, acetylation can positively or regulate protein stability. As discussed earlier, acetylation simultaneously enhances GATA1 transcriptional activation and mediates its degradation by the

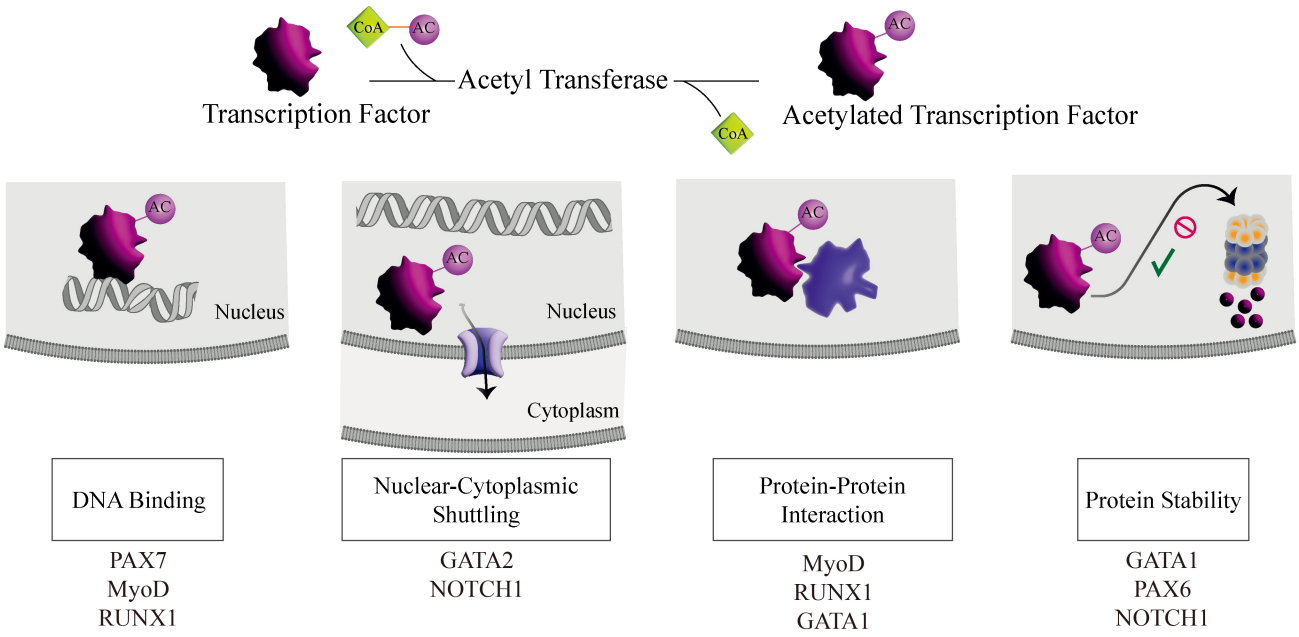

Fig. 5. Functional consequences of transcription factor acetylation. Acetylation of transcription factors, catalyzed by histone acetyltransferases (HATs) such as p300/CBP or PCAF, can regulate multiple aspects of their activity beyond histone modification. The addition of acetyl groups to lysine residues alters the conformation, charge, and protein-protein interactions of transcription factors, leading to distinct functional outcomes. These include: (1) DNA binding, changes in acetylation can enhance or reduce transcription factor affinity for target gene promoters/enhancers (e.g., PAX7, MyoD, RUNX1); (2) Nuclear-cytoplasmic shuttling, acetylation may influence the subcellular localization of transcription factors, enabling export to or retention within the nucleus (e.g., GATA2, NOTCH1); (3) Protein-protein interactions, acetylation can promote or disrupt interactions with coactivators, corepressors, or other transcription factors, modulating gene regulatory networks (e.g., MyoD, RUNX1, GATA1); and (4) Protein stability, acetylation can protect transcription factors from ubiquitin-mediated proteasomal degradation or, in some cases, target them for turnover (e.g., GATA1, PAX6, NOTCH1). These modifications integrate upstream signalling cues into transcriptional responses, influencing cell fate decisions in normal development and disease. PCAF, p300/CBP-associated factor; PAX, Paired Box; MyoD, Myogenic Differentiation 1; GATA2, GATA-binding protein 2; NOTCH1, Notch homolog 1.

ubiquitin-proteasome pathway [82]. Similarly, acetylation of PAX6 induces its degradation by the ubiquitin-proteasome system [13]. In contrast, the NOTCH family of transcription factors is stabilized by acetylation. The Notch family (NOTCH1-4) mediates a highly conserved, cell-cell signaling system that shapes cell-fate decisions, differentiation, proliferation, and tissue patterning. Upon ligand binding, NOTCH receptors are cleaved by proteolysis to release the Notch intracellular domain (NICD), which translocates to the nucleus and activates target genes such as the well-characterized *HES* and *HEY* (Hairy/Enhancer-of-split related with YRPW motif) genes. Notably, among the four paralogs, acetylation of NOTCH1 and NOTCH3 has emerged as a context-dependent modulator of signaling output and, consequently, of cell fate. Reversible acetylation of the Notch1 intracellular domain (NICD1) is a key post-translational mechanism that calibrates signaling amplitude, duration, and subcellular routing, with direct consequences for cell fate. Acetylation of conserved lysines (K1774, K1780, K1781, K1782) by p300 and PCAF prolongs NICD1 half-life and augments transcriptional output, whereas the NAD^+-dependent deacetylase SIRT1 binds NICD1 and removes these acetylation marks to promote turnover [137]. In endothelial cells, loss of SIRT1 sensitizes the pathway to the Delta-like ligand 4 (DLL4) ligand, elevates HES/HEY target expression, and reduces vascular branching in zebrafish and mice [137]. Acetylation also dictates nuclear topology; NICD1 has been shown to localize to the nucleolus, a process that is dependent on acetylation and deacetylation by SIRT1 [138]. Finally, in Notch1-driven leukemias, HDAC3 shapes NICD1 acetylation and stability; HDAC3 loss or inhibition reduces Notch target expression despite stabilizing NICD1, and an HDAC3-insensitive NICD1 variant is more stable yet less transcriptionally competent, underscoring that productive lineage outcomes depend on chromatin context and cofactor engagement, not stability alone [139]. In contrast to NOTCH1, where acetylation generally stabilizes NICD and prolongs signaling, NOTCH3 carries conserved RBP-Jκ–associated module (RAM)-domain lysines (K1692, K1731) whose acetylation by p300 has the opposite effect [140]. Acetylated NOTCH3 is preferentially

ubiquitinated and degraded, shortening Notch3 intracellular domain (N3IC) half-life and dampening transcriptional output (e.g., at the pTα promoter). HDAC1 reverses this by deacetylating N3IC. Accordingly, a non-acetylatable mutant (K1692R/K1731R) is more stable, more transcriptionally active, and enhances T-cell proliferation, whereas HDACi treatment in NOTCH3-transgenic mice enforces hyperacetylation, reduces NOTCH3 levels, and $CD4^+CD8^+$ double-positive thymocyte pools, and stops NOTCH3-driven T-cell acute lymphoblastic leukemia [140]. Thus, acetylation serves as a positive regulator of NOTCH1 signaling but a negative regulator of NOTCH3 by regulating their protein stability, leading to divergent cell-fate outcomes.

2.3 Conformational Changes Mediated by Acetylation

Addition of one or multiple acetyl groups to a protein can directly alter the protein structure and can alternatively change its DNA or protein binding affinity. Since acetylation of histones is known to introduce a negative charge that diminishes their affinity for DNA, one could expect that the same observation applies to transcription factors. This is the case for FOXO transcription factors, for which acetylation negatively regulates DNA binding. Acetylation of FOXO1 takes place in the DNA binding domain and likely neutralizes positive charges that are involved in DNA contact [128,141].

However, as discussed in the previous sections, many transcription factors have increased affinity for DNA when acetylated, which is counterintuitive. The two first examples to be documented are the acetylation of p53 and GATA1, which strikingly stimulates DNA binding [77, 142]. In EMSA assays, not only acetylated GATA1 displayed increased recognition of its target DNA sequence, but in addition, the mobility of the protein-DNA complex was altered, suggesting a conformational change. Indeed, while two different GATA1-DNA complexes were observed for the non-acetylated GATA1, only the slowly migrating complex was observed for acetylated GATA1. Furthermore, the complex involving acetylated GATA1 migrated slightly faster compared to the non-acetylated one, an observation that was even more striking when the DNA sequence contained two GATA1 binding sites instead of one [77].

For p53, acetylation takes on multiple sites including a region of 30 amino acids located at the C-terminal of the protein, which is well characterized to regulate sequence-specific DNA binding by p53. Indeed, the C-terminal region mediates intramolecular interactions with the DNA binding domain, preventing DNA binding. This intramolecular « tail-core » interaction must be disrupted to allow DNA sequence recognition. This can be achieved using an antibody that binds to the C-terminal domain of p53 [143], and presumably by acetylation of the C-terminal tail [142]. Similar mechanisms have been suggested for the E2 promoter–binding factor (E2F) family of transcription factors, in which acetylation, occuring in a helix adjacent to the DNA-binding domain, could induce a conformational change that would facilitate access to DNA [144]. In addition to the C-terminal tail, p53 is acetylated within its DNA-binding domain at K120, which specifically mediates the expression of pro-apoptotic target genes such as *Bax*, without affecting the expression of genes involved in cell cycle arrest. Thus, acetylation confers DNA binding specificity for p53. Crystal structures have been generated for acetylated or non-acetylated p53, in complex with different DNA sequences (*Bax* responsive element or consensus p53 responsive element) [145]. It has been demonstrated that acetylation of K120 increases the flexibility of the L1 loop of p53, which enables different DNA-binding modes for acetylated p53 compared to the non-acetylated form. The proposed model suggests that non-acetylated p53 forms a similar complex regardless of its binding to *Bax* recognition sequence or consensus sequence. However, acetylated p53 bound on *Bax* responsive element triggers a conformational change both in the protein and in DNA, while only a protein conformational change (and not a DNA conformational change) is observed when acetylated p53 is bound to a consensus response element [145]. Together, these observations confirm that acetylation can induce conformational changes that determine the architecture of promoter-bound transcriptional complexes on DNA.

Recent advances in deep learning tools to predict 3D protein structure will undoubtedly contribute to better deciphering how single amino acid modifications impact intramolecular protein conformation and their capacity to mediate protein-DNA and protein-protein interactions. Such prediction tools were recently employed to model how adding acetyl groups to Krüppel-like factors (KLFs) impacts their capacity to mediate protein-protein interactions with known binding partners [146]. Notably, it was found that acetylation of KLF1, KLF5 and KLF6 displaces existing intermolecular interactions with protein partners such as CBP, WWP1, activating transcription factor 3 (ATF3) and c-Jun (Jun proto-oncogene), while forming new binding interfaces, resulting in more stable interactions. In contrast, the interaction between KLF4 and p300 is destabilized by acetylation, confirming previous observations. Depending on the cellular context, KLFs can act as transcriptional activators or repressors and can exhibit tumor suppressive or oncogenic functions. The authors propose a model in which acetylation modulates the strength of interaction with transcriptional co-activators and co-repressors, thus fine-tuning the capacity of KLFs to control key processes such as proliferation and apoptosis [146]. This dynamic interplay can determine whether KLF act as tumor suppressors or promote oncogenesis, depending on the cellular context.

3. Conclusions

The action of HAT and HDAC inhibitors extends significantly to non-histone proteins, particularly transcription factors, where their acetylation status directly impacts protein function, including stability, enzyme activity, subcellular localization, and interactions with DNA or other proteins. Acetylation influences diverse cellular processes, including differentiation, proliferation, and stress responses. The studies summarized here show that acetylation can have either activating or repressive effects depending on the transcription factor and cellular context. Importantly, dysregulated acetylation is implicated in human disease, including malignancies, and neuromuscular disorders such as Duchenne muscular dystrophy, where impaired acetylation of transcription factors contributes to defective muscle regeneration. As a result, targeting acetylation and its regulators holds significant therapeutic potential.

Author Contributions

MCS developed the overall concept. PG, YA and MCS conducted the literature search and wrote the manuscript. PG and MCS integrated and refined key highlights. PG and MCS designed and created the figures. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used ChatGpt-5.0 in order to check spell and grammar. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

References

[1] Sincennes MC, Brun CE, Rudnicki MA. Concise Review: Epigenetic Regulation of Myogenesis in Health and Disease. Stem Cells Translational Medicine. 2016; 5: 282–290. https://doi.org/10.5966/sctm.2015-0266.

[2] Mayran A, Pelletier A, Drouin J. Pax factors in transcription and epigenetic remodelling. Seminars in Cell & Developmental Biology. 2015; 44: 135–144. https://doi.org/10.1016/j.semcdb.2015.07.007.

[3] Sincennes MC, Brun CE, Lin AYT, Rosembert T, Datzkiw D, Saber J, *et al*. Acetylation of PAX7 controls muscle stem cell self-renewal and differentiation potential in mice. Nature Communications. 2021; 12: 3253. https://doi.org/10.1038/s41467-021-23577-z.

[4] Kawabe YI, Wang YX, McKinnell IW, Bedford MT, Rudnicki MA. Carm1 regulates Pax7 transcriptional activity through MLL1/2 recruitment during asymmetric satellite stem cell divisions. Cell Stem Cell. 2012; 11: 333–345. https://doi.org/10.1016/j.stem.2012.07.001.

[5] Chang NC, Sincennes MC, Chevalier FP, Brun CE, Lacaria M, Segalés J, *et al*. The Dystrophin Glycoprotein Complex Regulates the Epigenetic Activation of Muscle Stem Cell Commitment. Cell Stem Cell. 2018; 22: 755–768.e6. https://doi.org/10.1016/j.stem.2018.03.022.

[6] Luan Z, Liu Y, Stuhlmiller TJ, Marquez J, García-Castro MI. SUMOylation of Pax7 is essential for neural crest and muscle development. Cellular and Molecular Life Sciences: CMLS. 2013; 70: 1793–1806. https://doi.org/10.1007/s00018-012-1220-1.

[7] Dick SA, Chang NC, Dumont NA, Bell RAV, Putinski C, Kawabe Y, *et al*. Caspase 3 cleavage of Pax7 inhibits self-renewal of satellite cells. Proceedings of the National Academy of Sciences of the United States of America. 2015; 112: E5246–E5252. https://doi.org/10.1073/pnas.1512869112.

[8] González N, Moresco JJ, Cabezas F, de la Vega E, Bustos F, Yates JR, 3rd, *et al*. Ck2-Dependent Phosphorylation Is Required to Maintain Pax7 Protein Levels in Proliferating Muscle Progenitors. PloS One. 2016; 11: e0154919. https://doi.org/10.1371/journal.pone.0154919.

[9] Dumont NA, Bentzinger CF, Sincennes MC, Rudnicki MA. Satellite Cells and Skeletal Muscle Regeneration. Comprehensive Physiology. 2015; 5: 1027–1059. https://doi.org/10.1002/cphy.c140068.

[10] Ichi S, Boshnjaku V, Shen YW, Mania-Farnell B, Ahlgren S, Sapru S, *et al*. Role of Pax3 acetylation in the regulation of Hes1 and Neurog2. Molecular Biology of the Cell. 2011; 22: 503–512. https://doi.org/10.1091/mbc.E10-06-0541.

[11] He T, Hong SY, Huang L, Xue W, Yu Z, Kwon H, *et al*. Histone acetyltransferase p300 acetylates Pax5 and strongly enhances Pax5-mediated transcriptional activity. The Journal of Biological Chemistry. 2011; 286: 14137–14145. https://doi.org/10.1074/jbc.M110.176289.

[12] Gamez-Garcia A, Espinosa-Alcantud M, Bueno-Costa A, Alari-Pahissa E, Marazuela-Duque A, Thackray JK, *et al*. A SIRT7-dependent acetylation switch regulates early B cell differentiation and lineage commitment through Pax5. Nature Immunology. 2024; 25: 2308–2319. https://doi.org/10.1038/s41590-024-01995-7.

[13] Dong Z, He W, Lin G, Chen X, Cao S, Guan T, *et al*. Histone acetyltransferase KAT2A modulates neural stem cell differentiation and proliferation by inducing degradation of the transcription factor PAX6. The Journal of Biological Chemistry. 2023; 299: 103020. https://doi.org/10.1016/j.jbc.2023.103020.

[14] Sartorelli V, Puri PL, Hamamori Y, Ogryzko V, Chung G, Nakatani Y, *et al*. Acetylation of MyoD directed by PCAF is necessary for the execution of the muscle program. Molecular Cell. 1999; 4: 725–734. https://doi.org/10.1016/s1097-2765(00)80383-4.

[15] Polesskaya A, Duquet A, Naguibneva I, Weise C, Vervisch A, Bengal E, *et al*. CREB-binding protein/p300 activates MyoD by acetylation. The Journal of Biological Chemistry. 2000; 275: 34359–34364. https://doi.org/10.1074/jbc.M003815200.

[16] Ling BMT, Bharathy N, Chung TK, Kok WK, Li S, Tan YH, *et al*. Lysine methyltransferase G9a methylates the transcription factor MyoD and regulates skeletal muscle differentiation. Proceedings of the National Academy of Sciences of the United States of America. 2012; 109: 841–846. https://doi.org/10.1073/pnas.1111628109.

[17] Duquet A, Polesskaya A, Cuvellier S, Ait-Si-Ali S, Héry P, Pritchard LL, *et al*. Acetylation is important for MyoD function in adult mice. EMBO Reports. 2006; 7: 1140–1146. https://doi.org/10.1038/sj.embor.7400820.

[18] Di Padova M, Caretti G, Zhao P, Hoffman EP, Sartorelli V. MyoD acetylation influences temporal patterns of skeletal muscle gene expression. The Journal of Biological Chemistry. 2007; 282: 37650–37659. https://doi.org/10.1074/jbc.M707309200.

[19] Angelelli C, Magli A, Ferrari D, Ganassi M, Matafora V, Parise F, *et al*. Differentiation-dependent lysine 4 acetylation enhances MEF2C binding to DNA in skeletal muscle cells. Nucleic Acids Research. 2008; 36: 915–928. https://doi.org/10.1093/nar/gkm1114.

[20] Polesskaya A, Naguibneva I, Duquet A, Bengal E, Robin P, Harel-Bellan A. Interaction between acetylated MyoD and the bromodomain of CBP and/or p300. Molecular and Cellular Biology. 2001; 21: 5312–5320. https://doi.org/10.1128/MCB.21.16.5312-5320.2001.

[21] Mal A, Sturniolo M, Schiltz RL, Ghosh MK, Harter ML. A role for histone deacetylase HDAC1 in modulating the transcriptional activity of MyoD: inhibition of the myogenic program. The EMBO Journal. 2001; 20: 1739–1753. https://doi.org/10.1093/emboj/20.7.1739.

[22] Sabourin LA, Rudnicki MA. The molecular regulation of myogenesis. Clinical Genetics. 2000; 57: 16–25. https://doi.org/10.1034/j.1399-0004.2000.570103.x.

[23] Ma K, Chan JKL, Zhu G, Wu Z. Myocyte enhancer factor 2 acetylation by p300 enhances its DNA binding activity, transcriptional activity, and myogenic differentiation. Molecular and Cellular Biology. 2005; 25: 3575–3582. https://doi.org/10.1128/MCB.25.9.3575-3582.2005.

[24] Al Madhoun AS, Mehta V, Li G, Figeys D, Wiper-Bergeron N, Skerjanc IS. Skeletal myosin light chain kinase regulates skeletal myogenesis by phosphorylation of MEF2C. The EMBO Journal. 2011; 30: 2477–2489. https://doi.org/10.1038/emboj.2011.153.

[25] Lu J, McKinsey TA, Nicol RL, Olson EN. Signal-dependent activation of the MEF2 transcription factor by dissociation from histone deacetylases. Proceedings of the National Academy of Sciences of the United States of America. 2000; 97: 4070–4075. https://doi.org/10.1073/pnas.080064097.

[26] Grégoire S, Xiao L, Nie J, Zhang X, Xu M, Li J, *et al*. Histone deacetylase 3 interacts with and deacetylates myocyte enhancer factor 2. Molecular and Cellular Biology. 2007; 27: 1280–1295. https://doi.org/10.1128/MCB.00882-06.

[27] Hagiwara H, Saito F, Masaki T, Ikeda M, Nakamura-Ohkuma A, Shimizu T, *et al*. Histone deacetylase inhibitor trichostatin A enhances myogenesis by coordinating muscle regulatory factors and myogenic repressors. Biochemical and Biophysical Research Communications. 2011; 414: 826–831. https://doi.org/10.1016/j.bbrc.2011.10.036.

[28] Ikeda K, Ito A, Imada R, Sato M, Kawabe Y, Kamihira M. In vitro drug testing based on contractile activity of C2C12 cells in an epigenetic drug model. Scientific Reports. 2017; 7: 44570. https://doi.org/10.1038/srep44570.

[29] Minetti GC, Colussi C, Adami R, Serra C, Mozzetta C, Parente V, *et al*. Functional and morphological recovery of dystrophic muscles in mice treated with deacetylase inhibitors. Nature Medicine. 2006; 12: 1147–1150. https://doi.org/10.1038/nm1479.

[30] Iezzi S, Di Padova M, Serra C, Caretti G, Simone C, Maklan E, *et al*. Deacetylase inhibitors increase muscle cell size by promoting myoblast recruitment and fusion through induction of follistatin. Developmental Cell. 2004; 6: 673–684. https://doi.org/10.1016/s1534-5807(04)00107-8.

[31] Asp P, Blum R, Vethantham V, Parisi F, Micsinai M, Cheng J, *et al*. Genome-wide remodeling of the epigenetic landscape during myogenic differentiation. Proceedings of the National Academy of Sciences of the United States of America. 2011; 108: E149–E158. https://doi.org/10.1073/pnas.1102223108.

[32] Iezzi S, Cossu G, Nervi C, Sartorelli V, Puri PL. Stage-specific modulation of skeletal myogenesis by inhibitors of nuclear deacetylases. Proceedings of the National Academy of Sciences of the United States of America. 2002; 99: 7757–7762. https://doi.org/10.1073/pnas.112218599.

[33] Lamb YN. Givinostat: First Approval. Drugs. 2024; 84: 849–856. https://doi.org/10.1007/s40265-024-02052-1.

[34] Mozzetta C, Consalvi S, Saccone V, Tierney M, Diamantini A, Mitchell KJ, *et al*. Fibroadipogenic progenitors mediate the ability of HDAC inhibitors to promote regeneration in dystrophic muscles of young, but not old Mdx mice. EMBO Molecular Medicine. 2013; 5: 626–639. https://doi.org/10.1002/emmm.201202096.

[35] Osseni A, Ravel-Chapuis A, Belotti E, Scionti I, Gangloff YG, Moncollin V, *et al*. Pharmacological inhibition of HDAC6 improves muscle phenotypes in dystrophin-deficient mice by downregulating TGF-β via Smad3 acetylation. Nature Communications. 2022; 13: 7108. https://doi.org/10.1038/s41467-022-34831-3.

[36] Calvanese V, Mikkola HKA. The genesis of human hematopoietic stem cells. Blood. 2023; 142: 519–532. https://doi.org/10.1182/blood.2022017934.

[37] Deltcheva E, Nimmo R. RUNX transcription factors at the interface of stem cells and cancer. The Biochemical Journal. 2017; 474: 1755–1768. https://doi.org/10.1042/BCJ20160632.

[38] Wang L, Huang G, Zhao X, Hatlen MA, Vu L, Liu F, *et al*. Post-translational modifications of Runx1 regulate its activity in the cell. Blood Cells, Molecules & Diseases. 2009; 43: 30–34. https://doi.org/10.1016/j.bcmd.2009.03.005.

[39] Yamaguchi Y, Kurokawa M, Imai Y, Izutsu K, Asai T, Ichikawa M, *et al*. AML1 is functionally regulated through p300-mediated acetylation on specific lysine residues. The Journal of Biological Chemistry. 2004; 279: 15630–15638. https://doi.org/10.1074/jbc.M400355200.

[40] Kitabayashi I, Aikawa Y, Nguyen LA, Yokoyama A, Ohki M. Activation of AML1-mediated transcription by MOZ and inhibition by the MOZ-CBP fusion protein. The EMBO Journal. 2001; 20: 7184–7196. https://doi.org/10.1093/emboj/20.24.7184.

[41] Kitabayashi I, Yokoyama A, Shimizu K, Ohki M. Interaction and functional cooperation of the leukemia-associated factors AML1 and p300 in myeloid cell differentiation. The EMBO Journal. 1998; 17: 2994–3004. https://doi.org/10.1093/emboj/17.11.2994.

[42] Wang L, Gural A, Sun XJ, Zhao X, Perna F, Huang G, *et al*. The leukemogenicity of AML1-ETO is dependent on site-specific lysine acetylation. Science (New York, N.Y.). 2011; 333: 765–769. https://doi.org/10.1126/science.1201662.

[43] Xu Y, Man N, Karl D, Martinez C, Liu F, Sun J, *et al*. TAF1

plays a critical role in AML1-ETO driven leukemogenesis. Nature Communications. 2019; 10: 4925. https://doi.org/10.1038/s41467-019-12735-z.

[44] Goyama S, Huang G, Kurokawa M, Mulloy JC. Posttranslational modifications of RUNX1 as potential anticancer targets. Oncogene. 2015; 34: 3483–3492. https://doi.org/10.1038/onc.2014.305.

[45] Aikawa Y, Nguyen LA, Isono K, Takakura N, Tagata Y, Schmitz ML, *et al*. Roles of HIPK1 and HIPK2 in AML1- and p300-dependent transcription, hematopoiesis and blood vessel formation. The EMBO Journal. 2006; 25: 3955–3965. https://doi.org/10.1038/sj.emboj.7601273.

[46] Yonezawa T, Takahashi H, Shikata S, Liu X, Tamura M, Asada S, *et al*. The ubiquitin ligase STUB1 regulates stability and activity of RUNX1 and RUNX1-RUNX1T1. The Journal of Biological Chemistry. 2017; 292: 12528–12541. https://doi.org/10.1074/jbc.M117.785675.

[47] Yonezawa T, Takahashi H, Hao Y, Furukawa C, Tsuchiya A, Zhang W, *et al*. The E3 ligase DTX2 inhibits RUNX1 function by binding its C terminus and prevents the growth of RUNX1-dependent leukemia cells. The FEBS Journal. 2023; 290: 5141–5157. https://doi.org/10.1111/febs.16914.

[48] Biggs JR, Peterson LF, Zhang Y, Kraft AS, Zhang DE. AML1/RUNX1 phosphorylation by cyclin-dependent kinases regulates the degradation of AML1/RUNX1 by the anaphase-promoting complex. Molecular and Cellular Biology. 2006; 26: 7420–7429. https://doi.org/10.1128/MCB.00597-06.

[49] Murre C. Helix-loop-helix proteins and the advent of cellular diversity: 30 years of discovery. Genes & Development. 2019; 33: 6–25. https://doi.org/10.1101/gad.320663.118.

[50] Greenbaum S, Zhuang Y. Regulation of early lymphocyte development by E2A family proteins. Seminars in Immunology. 2002; 14: 405–414. https://doi.org/10.1016/s1044532302000751.

[51] Hyndman BD, Thompson P, Denis CM, Chitayat S, Bayly R, Smith SP, *et al*. Mapping acetylation sites in E2A identifies a conserved lysine residue in activation domain 1 that promotes CBP/p300 recruitment and transcriptional activation. Biochimica et Biophysica Acta. 2012; 1819: 375–381. https://doi.org/10.1016/j.bbagrm.2011.11.013.

[52] Bradney C, Hjelmeland M, Komatsu Y, Yoshida M, Yao TP, Zhuang Y. Regulation of E2A activities by histone acetyltransferases in B lymphocyte development. The Journal of Biological Chemistry. 2003; 278: 2370–2376. https://doi.org/10.1074/jbc.M211464200.

[53] Wang Z, Zhang C, Warden CD, Liu Z, Yuan YC, Guo C, *et al*. Loss of SIRT1 inhibits hematopoietic stem cell aging and age-dependent mixed phenotype acute leukemia. Communications Biology. 2022; 5: 396. https://doi.org/10.1038/s42003-022-03340-w.

[54] Chu C, Kohtz DS. Identification of the E2A gene products as regulatory targets of the G1 cyclin-dependent kinases. The Journal of Biological Chemistry. 2001; 276: 8524–8534. https://doi.org/10.1074/jbc.M008371200.

[55] Kho CJ, Huggins GS, Endege WO, Hsieh CM, Lee ME, Haber E. Degradation of E2A proteins through a ubiquitin-conjugating enzyme, UbcE2A. The Journal of Biological Chemistry. 1997; 272: 3845–3851. https://doi.org/10.1074/jbc.272.6.3845.

[56] Huang Z, Nie L, Xu M, Sun XH. Notch-induced E2A degradation requires CHIP and Hsc70 as novel facilitators of ubiquitination. Molecular and Cellular Biology. 2004; 24: 8951–8962. https://doi.org/10.1128/MCB.24.20.8951-8962.2004.

[57] Nie L, Xu M, Vladimirova A, Sun XH. Notch-induced E2A ubiquitination and degradation are controlled by MAP kinase activities. The EMBO Journal. 2003; 22: 5780–5792. https://doi.org/10.1093/emboj/cdg567.

[58] Porcher C, Chagraoui H, Kristiansen MS. SCL/TAL1: a multifaceted regulator from blood development to disease. Blood. 2017; 129: 2051–2060. https://doi.org/10.1182/blood-2016-12-754051.

[59] Huang S, Qiu Y, Shi Y, Xu Z, Brandt SJ. P/CAF-mediated acetylation regulates the function of the basic helix-loop-helix transcription factor TAL1/SCL. The EMBO Journal. 2000; 19: 6792–6803. https://doi.org/10.1093/emboj/19.24.6792.

[60] Palamarchuk A, Efanov A, Maximov V, Aqeilan RI, Croce CM, Pekarsky Y. Akt phosphorylates Tal1 oncoprotein and inhibits its repressor activity. Cancer Research. 2005; 65: 4515–4519. https://doi.org/10.1158/0008-5472.CAN-05-0751.

[61] Terme JM, Lhermitte L, Asnafi V, Jalinot P. TGF-beta induces degradation of TAL1/SCL by the ubiquitin-proteasome pathway through AKT-mediated phosphorylation. Blood. 2009; 113: 6695–6698. https://doi.org/10.1182/blood-2008-07-166835.

[62] Nie L, Wu H, Sun XH. Ubiquitination and degradation of Tal1/SCL are induced by notch signaling and depend on Skp2 and CHIP. The Journal of Biological Chemistry. 2008; 283: 684–692. https://doi.org/10.1074/jbc.M704981200.

[63] Tang T, Arbiser JL, Brandt SJ. Phosphorylation by mitogen-activated protein kinase mediates the hypoxia-induced turnover of the TAL1/SCL transcription factor in endothelial cells. The Journal of Biological Chemistry. 2002; 277: 18365–18372. https://doi.org/10.1074/jbc.M109812200.

[64] Wang X, Angelis N, Thein SL. MYB - A regulatory factor in hematopoiesis. Gene. 2018; 665: 6–17. https://doi.org/10.1016/j.gene.2018.04.065.

[65] Sano Y, Ishii S. Increased affinity of c-Myb for CREB-binding protein (CBP) after CBP-induced acetylation. The Journal of Biological Chemistry. 2001; 276: 3674–3682. https://doi.org/10.1074/jbc.M006896200.

[66] Tomita A, Towatari M, Tsuzuki S, Hayakawa F, Kosugi H, Tamai K, *et al*. c-Myb acetylation at the carboxyl-terminal conserved domain by transcriptional co-activator p300. Oncogene. 2000; 19: 444–451. https://doi.org/10.1038/sj.onc.1203329.

[67] Sandberg ML, Sutton SE, Pletcher MT, Wiltshire T, Tarantino LM, Hogenesch JB, *et al*. c-Myb and p300 regulate hematopoietic stem cell proliferation and differentiation. Developmental Cell. 2005; 8: 153–166. https://doi.org/10.1016/j.devcel.2004.12.015.

[68] Aziz N, Miglarese MR, Hendrickson RC, Shabanowitz J, Sturgill TW, Hunt DF, *et al*. Modulation of c-Myb-induced transcription activation by a phosphorylation site near the negative regulatory domain. Proceedings of the National Academy of Sciences of the United States of America. 1995; 92: 6429–6433. https://doi.org/10.1073/pnas.92.14.6429.

[69] Miglarese MR, Richardson AF, Aziz N, Bender TP. Differential regulation of c-Myb-induced transcription activation by a phosphorylation site in the negative regulatory domain. The Journal of Biological Chemistry. 1996; 271: 22697–22705. https://doi.org/10.1074/jbc.271.37.22697.

[70] Kanei-Ishii C, Ninomiya-Tsuji J, Tanikawa J, Nomura T, Ishitani T, Kishida S, *et al*. Wnt-1 signal induces phosphorylation and degradation of c-Myb protein via TAK1, HIPK2, and NLK. Genes & Development. 2004; 18: 816–829. https://doi.org/10.1101/gad.1170604.

[71] Kanei-Ishii C, Nomura T, Takagi T, Watanabe N, Nakayama KI, Ishii S. Fbxw7 acts as an E3 ubiquitin ligase that targets c-Myb for nemo-like kinase (NLK)-induced degradation. The Journal of Biological Chemistry. 2008; 283: 30540–30548. https://doi.org/10.1074/jbc.M804340200.

[72] Dahle Ø, Andersen TØ, Nordgård O, Matre V, Del Sal G, Gabrielsen OS. Transactivation properties of c-Myb are critically dependent on two SUMO-1 acceptor sites that are conjugated in a PIASy enhanced manner. European Journal of

Biochemistry. 2003; 270: 1338–1348. https://doi.org/10.1046/j.1432-1033.2003.03504.x.

[73] Sramko M, Markus J, Kabát J, Wolff L, Bies J. Stress-induced inactivation of the c-Myb transcription factor through conjugation of SUMO-2/3 proteins. The Journal of Biological Chemistry. 2006; 281: 40065–40075. https://doi.org/10.1074/jbc.M609404200.

[74] Bies J, Markus J, Wolff L. Covalent attachment of the SUMO-1 protein to the negative regulatory domain of the c-Myb transcription factor modifies its stability and transactivation capacity. The Journal of Biological Chemistry. 2002; 277: 8999–9009. https://doi.org/10.1074/jbc.M110453200.

[75] Molvaersmyr AK, Saether T, Gilfillan S, Lorenzo PI, Kvaløy H, Matre V, *et al*. A SUMO-regulated activation function controls synergy of c-Myb through a repressor-activator switch leading to differential p300 recruitment. Nucleic Acids Research. 2010; 38: 4970–4984. https://doi.org/10.1093/nar/gkq245.

[76] Katsumura KR, Bresnick EH, GATA Factor Mechanisms Group. The GATA factor revolution in hematology. Blood. 2017; 129: 2092–2102. https://doi.org/10.1182/blood-2016-09-687871.

[77] Boyes J, Byfield P, Nakatani Y, Ogryzko V. Regulation of activity of the transcription factor GATA-1 by acetylation. Nature. 1998; 396: 594–598. https://doi.org/10.1038/25166.

[78] Visvader JE, Crossley M, Hill J, Orkin SH, Adams JM. The C-terminal zinc finger of GATA-1 or GATA-2 is sufficient to induce megakaryocytic differentiation of an early myeloid cell line. Molecular and Cellular Biology. 1995; 15: 634–641. https://doi.org/10.1128/MCB.15.2.634.

[79] Hung HL, Lau J, Kim AY, Weiss MJ, Blobel GA. CREB-Binding protein acetylates hematopoietic transcription factor GATA-1 at functionally important sites. Molecular and Cellular Biology. 1999; 19: 3496–3505. https://doi.org/10.1128/MCB.19.5.3496.

[80] Lamonica JM, Vakoc CR, Blobel GA. Acetylation of GATA-1 is required for chromatin occupancy. Blood. 2006; 108: 3736–3738. https://doi.org/10.1182/blood-2006-07-032847.

[81] Lamonica JM, Deng W, Kadauke S, Campbell AE, Gamsjaeger R, Wang H, *et al*. Bromodomain protein Brd3 associates with acetylated GATA1 to promote its chromatin occupancy at erythroid target genes. Proceedings of the National Academy of Sciences of the United States of America. 2011; 108: E159–E168. https://doi.org/10.1073/pnas.1102140108.

[82] Hernandez-Hernandez A, Ray P, Litos G, Ciro M, Ottolenghi S, Beug H, *et al*. Acetylation and MAPK phosphorylation cooperate to regulate the degradation of active GATA-1. The EMBO Journal. 2006; 25: 3264–3274. https://doi.org/10.1038/sj.emboj.7601228.

[83] Zhao W, Kitidis C, Fleming MD, Lodish HF, Ghaffari S. Erythropoietin stimulates phosphorylation and activation of GATA-1 via the PI3-kinase/AKT signaling pathway. Blood. 2006; 107: 907–915. https://doi.org/10.1182/blood-2005-06-2516.

[84] Burda P, Laslo P, Stopka T. The role of PU.1 and GATA-1 transcription factors during normal and leukemogenic hematopoiesis. Leukemia. 2010; 24: 1249–1257. https://doi.org/10.1038/leu.2010.104.

[85] Hong W, Kim AY, Ky S, Rakowski C, Seo SB, Chakravarti D, *et al*. Inhibition of CBP-mediated protein acetylation by the Ets family oncoprotein PU.1. Molecular and Cellular Biology. 2002; 22: 3729–3743. https://doi.org/10.1128/MCB.22.11.3729-3743.2002.

[86] Choi Y, Elagib KE, Delehanty LL, Goldfarb AN. Erythroid inhibition by the leukemic fusion AML1-ETO is associated with impaired acetylation of the major erythroid transcription factor GATA-1. Cancer Research. 2006; 66: 2990–2996. https://doi.org/10.1158/0008-5472.CAN-05-2944.

[87] Hayakawa F, Towatari M, Ozawa Y, Tomita A, Privalsky ML, Saito H. Functional regulation of GATA-2 by acetylation. Journal of Leukocyte Biology. 2004; 75: 529–540. https://doi.org/10.1189/jlb.0603389.

[88] Towatari M, May GE, Marais R, Perkins GR, Marshall CJ, Cowley S, *et al*. Regulation of GATA-2 phosphorylation by mitogen-activated protein kinase and interleukin-3. The Journal of Biological Chemistry. 1995; 270: 4101–4107. https://doi.org/10.1074/jbc.270.8.4101.

[89] Bacha R, Pedersen S, Ismail R, Alwisi N, Al-Mansoori L. GATA3: Orchestrating cellular fate through differentiation and proliferation. Biochimica et Biophysica Acta. Molecular Cell Research. 2025; 1872: 119893. https://doi.org/10.1016/j.bbamcr.2024.119893.

[90] Smith VM, Lee PP, Szychowski S, Winoto A. GATA-3 dominant negative mutant. Functional redundancy of the T cell receptor alpha and beta enhancers. The Journal of Biological Chemistry. 1995; 270: 1515–1520. https://doi.org/10.1074/jbc.270.4.1515.

[91] Yamagata T, Mitani K, Oda H, Suzuki T, Honda H, Asai T, *et al*. Acetylation of GATA-3 affects T-cell survival and homing to secondary lymphoid organs. The EMBO Journal. 2000; 19: 4676–4687. https://doi.org/10.1093/emboj/19.17.4676.

[92] Hosokawa H, Tanaka T, Endo Y, Kato M, Shinoda K, Suzuki A, *et al*. Akt1-mediated Gata3 phosphorylation controls the repression of IFNγ in memory-type Th2 cells. Nature Communications. 2016; 7: 11289. https://doi.org/10.1038/ncomms11289.

[93] Nakajima T, Kitagawa K, Ohhata T, Sakai S, Uchida C, Shibata K, *et al*. Regulation of GATA-binding protein 2 levels via ubiquitin-dependent degradation by Fbw7: involvement of cyclin B-cyclin-dependent kinase 1-mediated phosphorylation of THR176 in GATA-binding protein 2. The Journal of Biological Chemistry. 2015; 290: 10368–10381. https://doi.org/10.1074/jbc.M114.613018.

[94] Kitagawa K, Shibata K, Matsumoto A, Matsumoto M, Ohhata T, Nakayama KI, *et al*. Fbw7 targets GATA3 through cyclin-dependent kinase 2-dependent proteolysis and contributes to regulation of T-cell development. Molecular and Cellular Biology. 2014; 34: 2732–2744. https://doi.org/10.1128/MCB.01549-13.

[95] Matsuoka S, Oike Y, Onoyama I, Iwama A, Arai F, Takubo K, *et al*. Fbxw7 acts as a critical fail-safe against premature loss of hematopoietic stem cells and development of T-ALL. Genes & Development. 2008; 22: 986–991. https://doi.org/10.1101/gad.1621808.

[96] Bai Y, Srinivasan L, Perkins L, Atchison ML. Protein acetylation regulates both PU.1 transactivation and Ig kappa 3' enhancer activity. Journal of Immunology (Baltimore, Md.: 1950). 2005; 175: 5160–5169. https://doi.org/10.4049/jimmunol.175.8.5160.

[97] Kihara-Negishi F, Suzuki M, Yamada T, Sakurai T, Oikawa T. Impaired repressor activity and biological functions of PU.1 in MEL cells induced by mutations in the acetylation motifs within the ETS domain. Biochemical and Biophysical Research Communications. 2005; 335: 477–484. https://doi.org/10.1016/j.bbrc.2005.07.098.

[98] Zaini MA, Müller C, de Jong TV, Ackermann T, Hartleben G, Kortman G, *et al*. A p300 and SIRT1 Regulated Acetylation Switch of C/EBPα Controls Mitochondrial Function. Cell Reports. 2018; 22: 497–511. https://doi.org/10.1016/j.celrep.2017.12.061.

[99] Ceseña TI, Cardinaux JR, Kwok R, Schwartz J. CCAAT/enhancer-binding protein (C/EBP) beta is acetylated at multiple lysines: acetylation of C/EBPbeta at lysine 39 modulates its ability to activate transcription. The Journal of Biological Chemistry. 2007; 282: 956–967. https://doi.org/10.1074/jbc.M511451200.

[100] Joo M, Park GY, Wright JG, Blackwell TS, Atchison ML, Christman JW. Transcriptional regulation of the

cyclooxygenase-2 gene in macrophages by PU.1. The Journal of Biological Chemistry. 2004; 279: 6658–6665. https://doi.org/10.1074/jbc.M306267200.

[101] Bararia D, Kwok HS, Welner RS, Numata A, Sárosi MB, Yang H, *et al*. Acetylation of C/EBPα inhibits its granulopoietic function. Nature Communications. 2016; 7: 10968. https://doi.org/10.1038/ncomms10968.

[102] Wiper-Bergeron N, Salem HA, Tomlinson JJ, Wu D, Haché RJG. Glucocorticoid-stimulated preadipocyte differentiation is mediated through acetylation of C/EBPbeta by GCN5. Proceedings of the National Academy of Sciences of the United States of America. 2007; 104: 2703–2708. https://doi.org/10.1073/pnas.0607378104.

[103] Xu M, Nie L, Kim SH, Sun XH. STAT5-induced Id-1 transcription involves recruitment of HDAC1 and deacetylation of C/EBPbeta. The EMBO Journal. 2003; 22: 893–904. https://doi.org/10.1093/emboj/cdg094.

[104] Chung SS, Ahn BY, Kim M, Choi HH, Park HS, Kang S, *et al*. Control of adipogenesis by the SUMO-specific protease SENP2. Molecular and Cellular Biology. 2010; 30: 2135–2146. https://doi.org/10.1128/MCB.00852-09.

[105] Bengoechea-Alonso MT, Ericsson J. The ubiquitin ligase Fbxw7 controls adipocyte differentiation by targeting C/EBPalpha for degradation. Proceedings of the National Academy of Sciences of the United States of America. 2010; 107: 11817–11822. https://doi.org/10.1073/pnas.0913367107.

[106] Liu H, Song N. Molecular Mechanism of Adult Neurogenesis and its Association with Human Brain Diseases. Journal of Central Nervous System Disease. 2016; 8: 5–11. https://doi.org/10.4137/JCNSD.S32204.

[107] Qiu Y, Guo M, Huang S, Stein R. Acetylation of the BETA2 transcription factor by p300-associated factor is important in insulin gene expression. The Journal of Biological Chemistry. 2004; 279: 9796–9802. https://doi.org/10.1074/jbc.M307577200.

[108] Jang SM, Kim JW, Kim CH, An JH, Johnson A, Song PI, *et al*. KAT5-mediated SOX4 acetylation orchestrates chromatin remodeling during myoblast differentiation. Cell Death & Disease. 2015; 6: e1857. https://doi.org/10.1038/cddis.2015.190.

[109] Hattori T, Coustry F, Stephens S, Eberspaecher H, Takigawa M, Yasuda H, *et al*. Transcriptional regulation of chondrogenesis by coactivator Tip60 via chromatin association with Sox9 and Sox5. Nucleic Acids Research. 2008; 36: 3011–3024. https://doi.org/10.1093/nar/gkn150.

[110] Mu WL, Wang YJ, Xu P, Hao DL, Liu XZ, Wang TT, *et al*. Sox2 Deacetylation by Sirt1 Is Involved in Mouse Somatic Reprogramming. Stem Cells (Dayton, Ohio). 2015; 33: 2135–2147. https://doi.org/10.1002/stem.2012.

[111] Baltus GA, Kowalski MP, Zhai H, Tutter AV, Quinn D, Wall D, *et al*. Acetylation of sox2 induces its nuclear export in embryonic stem cells. Stem Cells (Dayton, Ohio). 2009; 27: 2175–2184. https://doi.org/10.1002/stem.168.

[112] Seo Y, Kim DK, Park J, Park SJ, Park JJ, Cheon JH, *et al*. A Comprehensive Understanding of Post-Translational Modification of Sox2 via Acetylation and *O*-GlcNAcylation in Colorectal Cancer. Cancers. 2024; 16: 1035. https://doi.org/10.3390/cancers16051035.

[113] Huang Y, Duan X, Wang Z, Sun Y, Guan Q, Kang L, *et al*. An acetylation-enhanced interaction between transcription factor Sox2 and the steroid receptor coactivators facilitates Sox2 transcriptional activity and function. The Journal of Biological Chemistry. 2021; 297: 101389. https://doi.org/10.1016/j.jbc.2021.101389.

[114] Thevenet L, Méjean C, Moniot B, Bonneaud N, Galéotti N, Aldrian-Herrada G, *et al*. Regulation of human SRY subcellular distribution by its acetylation/deacetylation. The EMBO Journal. 2004; 23: 3336–3345. https://doi.org/10.1038/sj.emboj.7600352.

[115] Fang L, Zhang L, Wei W, Jin X, Wang P, Tong Y, *et al*. A methylation-phosphorylation switch determines Sox2 stability and function in ESC maintenance or differentiation. Molecular Cell. 2014; 55: 537–551. https://doi.org/10.1016/j.molcel.2014.06.018.

[116] Wang Z, Kang L, Zhang H, Huang Y, Fang L, Li M, *et al*. AKT drives SOX2 overexpression and cancer cell stemness in esophageal cancer by protecting SOX2 from UBR5-mediated degradation. Oncogene. 2019; 38: 5250–5264. https://doi.org/10.1038/s41388-019-0790-x.

[117] Selvi BR, Cassel JC, Kundu TK, Boutillier AL. Tuning acetylation levels with HAT activators: therapeutic strategy in neurodegenerative diseases. Biochimica et Biophysica Acta. 2010; 1799: 840–853. https://doi.org/10.1016/j.bbagrm.2010.08.012.

[118] Lu X, Wang L, Yu C, Yu D, Yu G. Histone Acetylation Modifiers in the Pathogenesis of Alzheimer's Disease. Frontiers in Cellular Neuroscience. 2015; 9: 226. https://doi.org/10.3389/fncel.2015.00226.

[119] Rossaert E, Pollari E, Jaspers T, Van Hellepute L, Jarpe M, Van Damme P, *et al*. Restoration of histone acetylation ameliorates disease and metabolic abnormalities in a FUS mouse model. Acta Neuropathologica Communications. 2019; 7: 107. https://doi.org/10.1186/s40478-019-0750-2.

[120] Suelves N, Kirkham-McCarthy L, Lahue RS, Ginés S. A selective inhibitor of histone deacetylase 3 prevents cognitive deficits and suppresses striatal CAG repeat expansions in Huntington's disease mice. Scientific Reports. 2017; 7: 6082. https://doi.org/10.1038/s41598-017-05125-2.

[121] Tseng CEJ, McDougle CJ, Hooker JM, Zürcher NR. Epigenetics of Autism Spectrum Disorder: Histone Deacetylases. Biological Psychiatry. 2022; 91: 922–933. https://doi.org/10.1016/j.biopsych.2021.11.021.

[122] Yoon JG, Lim SK, Seo H, Lee S, Cho J, Kim SY, *et al*. De novo missense variants in HDAC3 leading to epigenetic machinery dysfunction are associated with a variable neurodevelopmental disorder. American Journal of Human Genetics. 2024; 111: 1588–1604. https://doi.org/10.1016/j.ajhg.2024.06.015.

[123] Williams SR, Aldred MA, Der Kaloustian VM, Halal F, Gowans G, McLeod DR, *et al*. Haploinsufficiency of HDAC4 causes brachydactyly mental retardation syndrome, with brachydactyly type E, developmental delays, and behavioral problems. American Journal of Human Genetics. 2010; 87: 219–228. https://doi.org/10.1016/j.ajhg.2010.07.011.

[124] Basu T, O'Riordan KJ, Schoenike BA, Khan NN, Wallace EP, Rodriguez G, *et al*. Histone deacetylase inhibitors restore normal hippocampal synaptic plasticity and seizure threshold in a mouse model of Tuberous Sclerosis Complex. Scientific Reports. 2019; 9: 5266. https://doi.org/10.1038/s41598-019-41744-7.

[125] Daitoku H, Hatta M, Matsuzaki H, Aratani S, Ohshima T, Miyagishi M, *et al*. Silent information regulator 2 potentiates Foxo1-mediated transcription through its deacetylase activity. Proceedings of the National Academy of Sciences of the United States of America. 2004; 101: 10042–10047. https://doi.org/10.1073/pnas.0400593101.

[126] Jing E, Gesta S, Kahn CR. SIRT2 regulates adipocyte differentiation through FoxO1 acetylation/deacetylation. Cell Metabolism. 2007; 6: 105–114. https://doi.org/10.1016/j.cmet.2007.07.003.

[127] Wang F, Tong Q. SIRT2 suppresses adipocyte differentiation by deacetylating FOXO1 and enhancing FOXO1's repressive interaction with PPARgamma. Molecular Biology of the Cell. 2009; 20: 801–808. https://doi.org/10.1091/mbc.e08-06-0647.

[128] Matsuzaki H, Daitoku H, Hatta M, Aoyama H, Yoshimochi K, Fukamizu A. Acetylation of Foxo1 alters its DNA-binding

ability and sensitivity to phosphorylation. Proceedings of the National Academy of Sciences of the United States of America. 2005; 102: 11278–11283. https://doi.org/10.1073/pnas.0502738102.

[129] Fukuoka M, Daitoku H, Hatta M, Matsuzaki H, Umemura S, Fukamizu A. Negative regulation of forkhead transcription factor AFX (Foxo4) by CBP-induced acetylation. International Journal of Molecular Medicine. 2003; 12: 503–508.

[130] van der Horst A, Tertoolen LGJ, de Vries-Smits LMM, Frye RA, Medema RH, Burgering BMT. FOXO4 is acetylated upon peroxide stress and deacetylated by the longevity protein hSir2(SIRT1). The Journal of Biological Chemistry. 2004; 279: 28873–28879. https://doi.org/10.1074/jbc.M401138200.

[131] Brunet A, Sweeney LB, Sturgill JF, Chua KF, Greer PL, Lin Y, *et al*. Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase. Science (New York, N.Y.). 2004; 303: 2011–2015. https://doi.org/10.1126/science.1094637.

[132] Wang F, Nguyen M, Qin FXF, Tong Q. SIRT2 deacetylates FOXO3a in response to oxidative stress and caloric restriction. Aging Cell. 2007; 6: 505–514. https://doi.org/10.1111/j.1474-9726.2007.00304.x.

[133] Kohler S, Cirillo LA. Stable chromatin binding prevents FoxA acetylation, preserving FoxA chromatin remodeling. The Journal of Biological Chemistry. 2010; 285: 464–472. https://doi.org/10.1074/jbc.M109.063149.

[134] Frescas D, Valenti L, Accili D. Nuclear trapping of the forkhead transcription factor FoxO1 via Sirt-dependent deacetylation promotes expression of glucogenetic genes. The Journal of Biological Chemistry. 2005; 280: 20589–20595. https://doi.org/10.1074/jbc.M412357200.

[135] Petrusca DN, Toscani D, Wang FM, Park C, Crean CD, Anderson JL, *et al*. Growth factor independence 1 expression in myeloma cells enhances their growth, survival, and osteoclastogenesis. Journal of Hematology & Oncology. 2018; 11: 123. https://doi.org/10.1186/s13045-018-0666-5.

[136] Perez-Oquendo M, Manshouri R, Tian Y, Fradette JJ, Rodriguez BL, Kundu ST, *et al*. ZEB1 Is Regulated by K811 Acetylation to Promote Stability, NuRD Complex Interactions, EMT, and NSCLC Metastasis. Molecular Cancer Research: MCR. 2023; 21: 779–794. https://doi.org/10.1158/1541-7786.MCR-22-0503.

[137] Guarani V, Deflorian G, Franco CA, Krüger M, Phng LK, Bentley K, *et al*. Acetylation-dependent regulation of endothelial Notch signalling by the SIRT1 deacetylase. Nature. 2011; 473: 234–238. https://doi.org/10.1038/nature09917.

[138] Saini N, Bheeshmachar G, Sarin A. Sirtuin1 meditated modification of Notch1 intracellular domain regulates nucleolar localization and activation of distinct signaling cascades. Frontiers in Cell and Developmental Biology. 2022; 10: 988816. https://doi.org/10.3389/fcell.2022.988816.

[139] Ferrante F, Giaimo BD, Bartkuhn M, Zimmermann T, Close V, Mertens D, *et al*. HDAC3 functions as a positive regulator in Notch signal transduction. Nucleic Acids Research. 2020; 48: 3496–3512. https://doi.org/10.1093/nar/gkaa088.

[140] Palermo R, Checquolo S, Giovenco A, Grazioli P, Kumar V, Campese AF, *et al*. Acetylation controls Notch3 stability and function in T-cell leukemia. Oncogene. 2012; 31: 3807–3817. https://doi.org/10.1038/onc.2011.533.

[141] Brent MM, Anand R, Marmorstein R. Structural basis for DNA recognition by FoxO1 and its regulation by posttranslational modification. Structure (London, England: 1993). 2008; 16: 1407–1416. https://doi.org/10.1016/j.str.2008.06.013.

[142] Gu W, Roeder RG. Activation of p53 sequence-specific DNA binding by acetylation of the p53 C-terminal domain. Cell. 1997; 90: 595–606. https://doi.org/10.1016/s0092-8674(00)80521-8.

[143] Hupp TR, Sparks A, Lane DP. Small peptides activate the latent sequence-specific DNA binding function of p53. Cell. 1995; 83: 237–245. https://doi.org/10.1016/0092-8674(95)90165-5.

[144] Martínez-Balbás MA, Bauer UM, Nielsen SJ, Brehm A, Kouzarides T. Regulation of E2F1 activity by acetylation. The EMBO Journal. 2000; 19: 662–671. https://doi.org/10.1093/emboj/19.4.662.

[145] Vainer R, Cohen S, Shahar A, Zarivach R, Arbely E. Structural Basis for p53 Lys120-Acetylation-Dependent DNA-Binding Mode. Journal of Molecular Biology. 2016; 428: 3013–3025. https://doi.org/10.1016/j.jmb.2016.06.009.

[146] Jha K, Kumar A, Bhatnagar K, Patra A, Bhavesh NS, Singh B, *et al*. Modulation of Krüppel-like factors (KLFs) interaction with their binding partners in cancers through acetylation and phosphorylation. Biochimica et Biophysica Acta. Gene Regulatory Mechanisms. 2024; 1867: 195003. https://doi.org/10.1016/j.bbagrm.2023.195003.