Cellular and Molecular Life Sciences (2025) 82:5
https://doi.org/10.1007/s00018-024-05531-6

REVIEW

Lysine and arginine methylation of transcription factors

Benedetto Daniele Giaimo[1] · Francesca Ferrante[1] · Tilman Borggrefe[1]

Received: 24 September 2024 / Revised: 9 November 2024 / Accepted: 26 November 2024

Abstract
Post-translational modifications (PTMs) are implicated in many biological processes including receptor activation, signal transduction, transcriptional regulation and protein turnover. Lysine's side chain is particularly notable, as it can undergo methylation, acetylation, SUMOylation and ubiquitination. Methylation affects not only lysine but also arginine residues, both of which are implicated in epigenetic regulation. Beyond histone-tails as substrates, dynamic methylation of transcription factors has been described. The focus of this review is on these non-histone substrates providing a detailed discussion of what is currently known about methylation of hypoxia-inducible factor (HIF), P53, nuclear receptors (NRs) and RELA. The role of methylation in regulating protein stability and function by acting as docking sites for methyl-reader proteins and via their crosstalk with other PTMs is explored.

Keywords KMT · KDM · PRMT · PTM · Hypoxia · Cell cycle

Introduction

Post-translational modifications (PTMs) of proteins on specific residues provide a sophisticated mechanism for regulating their activity, function and/or localization. Several residues are subjected to be modified, for example phosphorylation occurs on serine (S), threonine (T) and tyrosine (Y) residues. Lysine (K) residues are for example modified by acetylation, methylation, SUMOylation and ubiquitination, while arginine (R) residues are modified by methylation. A lot of research has been devoted to characterize the regulation of PTMs that regulate histones, which constitute the building blocks of the chromatin however, much less is known about PTMs of non-histone proteins. When considering methylation of non-histone proteins such as transcription factors our knowledge is even more scarce. This review explores the role of arginine and lysine methylation in transcription factors, highlighting how these PTMs influence their activity. Additionally, we also discuss arginine and lysine methylation in the context of regulating DNA methyltransferases (DNMTs) activity.

Protein methylation can occur on lysine or arginine residues as a result of the activity of lysine methyltransferases (KMTs) and protein arginine methyltransferases (PRMTs), respectively that use the *S*-adenosyl-L-methionine (SAM) as donor of the methyl group.

KMTs transfer the methyl group from the SAM to the ε-amino group of the lysine of the target protein which can accept up to three methyl groups generating mono-, di- or trimethylation of lysine residues (Kme_1, Kme_2 and Kme_3, respectively; Fig. 1). KMTs can be classified in two different classes (Table 1): One class contains a highly conserved SET [Su(var)3–9, Enhancer of Zeste, and Trithorax] domain and are usually involved in the methylation of lysine residues located in the N-terminal tails of the histones; The members of the other class do not have a SET domain and are involved in the methylation of lysine residues located within the histone globular core, this class is characterized by the highly conserved KMT4 family [1, 2].

PRMTs catalyze the generation of ω-N^G-methylarginine (mono-methylarginine, ωMMA) or ω-N^G,N^G-methylarginine (di-methylarginines, ωDMA; Fig. 1). Importantly, DMA can be either symmetric (ωsDMA) or asymmetric (ωaDMA; Fig. 1). Based on their catalyzed reaction, mammalian PRMTs can be classified in type I, II and III class (Table 1):

✉ Benedetto Daniele Giaimo
Benedetto.Giaimo@biochemie.med.uni-giessen.de

✉ Tilman Borggrefe
Tilman.Borggrefe@biochemie.med.uni-giessen.de

Francesca Ferrante
Francesca.Ferrante@biochemie.med.uni-giessen.de

[1] Institute of Biochemistry, Justus-Liebig-University Giessen, Friedrichstrasse 24, 35392 Giessen, Germany

Published online: 16 December 2024

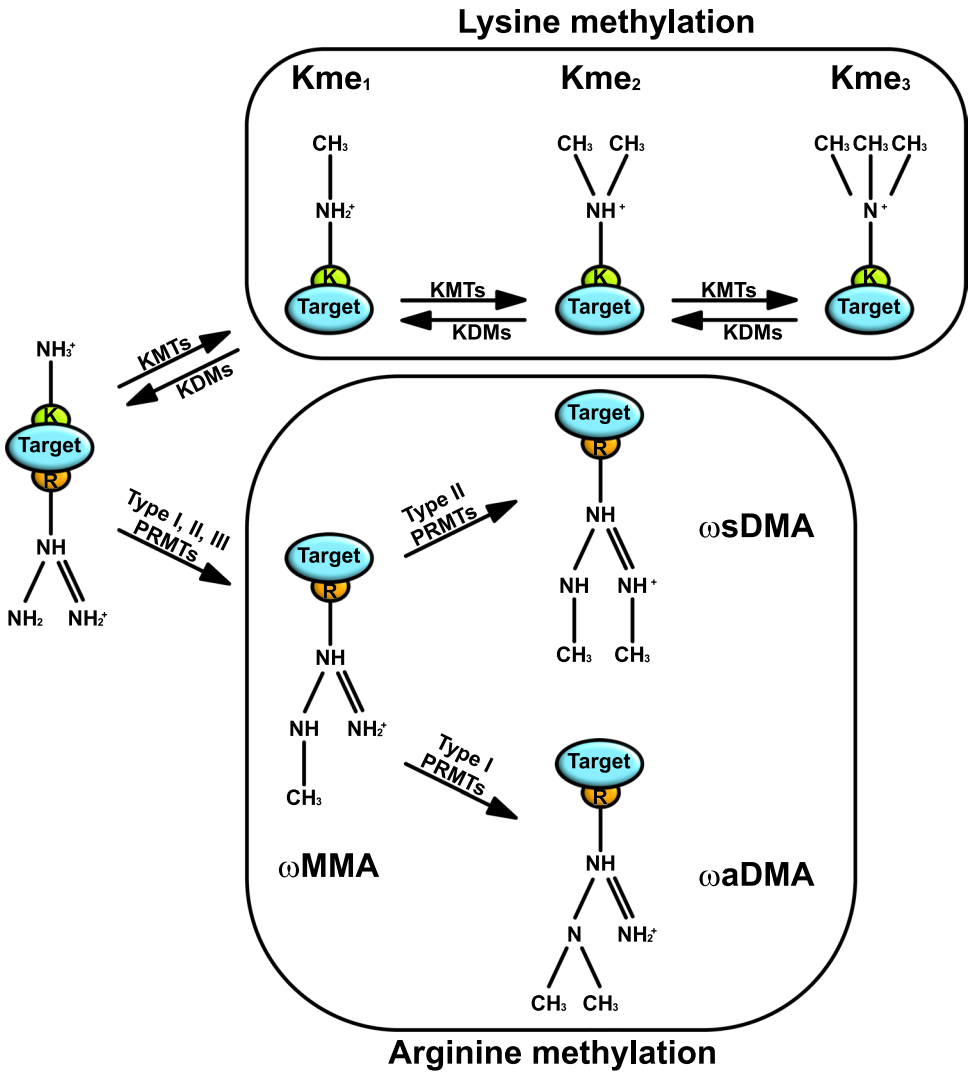

Fig. 1 Schematic representation of lysine (K) and arginine (R) methylation. The NH_3^+ group of lysine (K) residues can be methylated by lysine methyltrasferases (KMTs) or demethylated by lysine demethylases (KDMs). Accordingly, to the degree of methylation, it is possible to distinguish three different methylation states: monomethylation (Kme_1) with only one CH_3 group; dimethylation (Kme_2) with two CH_3 groups; trimethylation (Kme_3) with three CH_3 groups. Arginine (R) residues are methylated by meaning of mono- and dimethylation by protein arginine (R) methyltransferases (PRMTs). Arginine monomethylation (indicated as ωMMA) is catalyzed by Type I (PRMT1, 2, 3, 4, 6 and 8), Type II (PRMT5 and 9) and Type III (PRMT7) PRMTs. Arginine dimethylation can occur as symmetrical (indicated as ωsDMA) or asymmetrical (indicated as ωaDMA): Type I catalyze ωaDMA whereas Type II (PRMT5 and 9) catalyze ωsDMA. Type III PRMT catalyze exclusively ωMMA

Type I (PRMT1, 2, 3, 4, 6 and 8) catalyze ωMMA and ωaDMA; Type II (PRMT5 and 9) catalyze ωMMA and ωsDMA; Type III (PRMT7) catalyze only ωMMA. Most of the PRMTs methylate glycine- and arginine-rich (GAR) motifs [3] however, PRMT4 methylates within proline-, glycine- and methionine-rich (PGM) motifs [4] and PRMT5 catalyzes ωsDMA within both GAR and PGM motifs [5].

For a long time, protein methylation was regarded as a stable modification until the identification of the first lysine demethylase (KDM) KDM1A/LSD1 (lysine demethylase 1A/lysine-specific histone demethylase (1) [6]. KDMs are classified in two groups (Table 2): The LSD family of flavin adenine dinucleotide (FAD)-dependent amine oxidases that includes KDM1A/LSD1 and KDM1B/LSD2 (lysine demethylase 1B/lysine-specific histone demethylase (2); and the jumonji C (JMJC) domain-containing family of KDMs that includes oxygenases that use molecular oxygen as a substrate to promote protein demethylation. While LSD family members catalyze demethylation of mono- and dimethylated lysine residues, JMJC family members can demethylate both mono-, di- and trimethylated lysine residues. The existence of arginine demethylases (RDMs) has been under debate for long time however, more evidences suggest the existence of this enzymatic function. Initial studies have observed Jumonji domain-containing 6 (JMJD6)-mediated arginine demethylation of histone and non-histone proteins both in cell-free and in vitro assays [7–11]. However, two additional studies challenged the conclusion that JMJD6 acts as an arginine demethylase as the authors could not detect such activity [12, 13]. Subsequently, Walport and colleagues observed arginine demethylase activity for KDM3A/JMJD1A (lysine demethylase 3A/Jumonji domain-containing 1A), KDM4E/JMJD2E (lysine demethylase 4E/Jumonji domain-containing 2E), KDM5C/JARID1C [lysine demethylase 5C/Jumonji AT rich interactive (ARID) domain 1C] and KDM6B/JMJD3 (lysine demethylase 4E/Jumonji domain-containing 3) in cell-free assays [13]. Finally, KDM3B/JMJD1B (lysine

Table 1 List of lysine methyltransferases (KMTs) and protein arginine methyltransferases (PRMTs)

	Histone target (s)	Non-histone target (s)	Inhibitor(s)	References
KMTs				
EEF1AKMT4	ND	ND	NP	
KMT1A/SUV39H1	H3K9	ND	F5446	[134]
KMT1B/SUV39H2	H2AXK134, H3K9	ND	OTS186935, OTS193320	[135]
KMT1C/EHMT2/G9A	H1.2K187, H1.4K26, H3K9, H3K18, H3K23, H3K27, H3K56	C/EBPβ, DNMT3A, RUNX3, MEF2D, MYOD1, P53	BIX-01294, UNC0224, UNC0638	[43, 97, 107, 115, 136–140]
KMT1D/EHMT1/GLP	H3K9, H3K18, H3K23, H3K27	DNMT3A, P53	BIX-01294, UNC0224, UNC0638	[43, 115, 136–138, 141]
KMT1E/SETDB1	H3K9	ND	SETDB1-TTD-IN-1	[142]
KMT1F/SETDB2	H3K9	ND	NP	
KMT2A/MLL1	H3K4	ND	MM-401, Win6mer	[143, 144]
KMT2B/MLL2/MLL4/WBP7	H3K4	ND	NP	
KMT2C/MLL3	H3K4	ND	NP	
KMT2D/MLL2/MLL4	H3K4	ND	C1, C16	[145]
KMT2E/MLL5/SETD5B	H3K4	ND	NP	
KMT2F/SETD1A	H3K4, H3K37	ND	Win6mer	[144]
KMT2G/SETD1B	H3K4	ND	NP	
KMT2H/ASH1L	H3K4, H3K36	ND	AS-99	[146]
KMT3A/SETD2	H3K36, H3K37	ND	EPZ-719, EZM0414	[147, 148]
KMT3B/NSD1	H3K36, H4K20	RELA	BT5	[73, 78, 149]
KMT3C/SMYD2	H3K4, H3K36	AR, ERα, P53	AZ505, BAY-598, LLY-507	[25, 57, 58, 69, 150–152]
KMT3D/SMYD1	H3K4	ND	NP	
KMT3E/SMYD3	H3K4, H4K5	ND	BCI-121, EM127, EPZ031686	[153–155]
KMT3F/NSD3	H3K36	ND	13i, BI-9321	[156, 157]
KMT3G/NSD2	H3K36	ND	MR837	[158]
KMT4/DOT1L	H3K79	ND	EPZ004777, Pinometostat, SGC0946	[159–161]
KMT5A/SETD8	H4K20	P53	SPS8I1 – 3, UNC0379	[26, 39, 40, 162, 163]
KMT5B/SUV420H1	H4K20	ND	A-196	[164]
KMT5C/SUV420H2	H4K20	ND	A-196	[164]
KMT6A/EZH2	H3K27, H2BK120	GATA4, RORα, STAT3	DZNep, GSK2816126, Tazemetostat	[63, 88, 89, 119, 165–167]
KMT6B/EZH1	H3K27	ND	UNC1999, Valemetostat	[168, 169]
KMT7/SETD7	H3K4	AR, DNMT1, E2F1, ERα, FOXO3, FXR, GLI3, HIF1α, HIF2α, P53, PDX1, RELA, SOX2, STAT3, YY1, YY2	(R)-PFI-2, Set7_1a	[17–19, 22, 26, 27, 32, 48–50, 54, 55, 67, 68, 72–75, 85, 93, 95, 103, 104, 109, 112, 114, 170–175]
KMT8A/PRDM2	H3K9	ND	NP	
KMT8B/PRDM9	H3K4	ND	MRK-740	[176]

Table 1 (continued)

	Histone target (s)	Non-histone target (s)	Inhibitor(s)	References
KMT8C/PRDM6	H4K20	ND	NP	
KMT8D/PRDM8	H3K9	ND	NP	
KMT8E/MECOM	H3K9	ND	NP	
KMT8F/PRDM16	H3K9	ND	NP	
SETD5	H3K36	ND	NP	
SETD6	H2A.ZK7	E2F1, RELA	NP	[51, 76, 77]
SETMAR	H3K4, H3K36	ND	NP	
PRMTs				
PRMT1	H2AR11, H4R3	AML1/ETO, C/EBPα, E2F1, ERα, FOXO1, GLI1, KLF4, MBD2, MYOD1, NRF2, PR, RELA, RUNX1, STAT3, TWIST1	AMI-1, GSK3368715, MS023	[53, 60, 66, 80, 92, 98–101, 110, 116, 177–185]
PRMT2	H3R8, H4R3	STAT3	NP	[91]
PRMT3	H4R3	HIF1α	GSK3368715, MS023, SGC707	[20, 177, 178, 186]
PRMT4	H3R2, H3R17, H3R26, H3R42, H4R3	PAX7, RELA, SOX2, SOX9	CARM1-IN-4, GSK3368715, MS023, MS049, PRMT4-IN-1	[83, 105, 177, 178, 187–191]
PRMT5	H2AR3, H3R2, H3R8, H4R3	AR, BCL6, E2F1, GATA4, GLI1, HOXA9, MBD2, P53, PAX3, RELA, RORα, SREBP1A	GSK3235025, GSK3326595, Onametostat	[45, 52, 53, 64, 70, 79, 81, 82, 111, 116, 192–199]
PRMT6	H2AR3, H2AR11, H2AR29, H3R2, H3R42, H4R3	FOXO3, STAT3	EPZ020411, GSK3368715, MS023, MS049	[90, 177, 178, 187, 200]
PRMT7	H2AR3, H3R2, H4R3, H4R17, H4R19	ND	SGC3027	[201]
PRMT8	ND	ND	GSK3368715, MS023	[177, 178]
PRMT9	ND	ND	LD2	[202]

Indicated are the histone and the DNA binding proteins known to be methylated by each enzyme including known inhibitors. For simplicity, we do not report all the inhibitors available on the market

ND Not described, *NP* Not published

Table 2 List of lysine demethylases (KDMs)

	Histone target (s)	Non-histone target (s)	Inhibitor (s)	References
KDMs/RDMs				
KDM1A/LSD1	H3K4, H3K9	E2F1, HIF1α, MEF2D, STAT3, OCT4, P53, SOX2, YY2	7c, GSK-LSD1, Iadademstat, Pargyline	[18, 19, 37, 48, 49, 85, 95, 102, 104, 107, 203–205, 128]
KDM1B/LSD2	H3K4, H3K9	ND	7c	[204]
KDM2A	H3K4, H3K36	RELA	Daminozide, KDM2A/7A-IN-1	[73, 78, 206, 207]
KDM2B	H3K4, H3K36	ND	NP	
KDM3A/JMJD1A	H3K9	P53	NP	[23, 24]
KDM3B/JMJD1B	H3K9	ND	P3FI-63	[208]
KDM3C/JMJD1C	H3K9	STAT3	U193D7	[86, 87]
KDM4A/JMJD2A	H3K9, H3K36	ND	5-carboxy-8HQ, IOX1, NCGC00244536, NSC636819	[209–212]
KDM4B/JMJD2B	H3K9, H3K36	ND	NCGC00244536, NSC636819	[211, 212]
KDM4C/JMJD2C	H3K9, H3K36	ND	KDM4C-IN-1, NCGC00244536	[212, 213]
KDM4D/JMJD2D	H3K9, H3K36	ND	KDM4D-IN-1, NCGC00244536	[212, 214]
KDM4E/JMJD2E	ND	ND	3-substituted pyridine 2,4-dicarboxylate	[215]
KDM4F/JMJD2F	ND	ND	NP	
KDM5A/JARID1A	H3K4	ND	KDOAM-25, JQKD82, PBIT, Ryuvidine	[216–219]
KDM5B/JARID1B	H3K4	ND	AS8351, KDOAM-25, PBIT, Ryuvidine	[216, 217, 219, 220]
KDM5C/JARID1C	H3K4	ND	KDOAM-25, PBIT, Ryuvidine	[216, 217, 219]
KDM5D/JARID1D	H3K4	ND	KDOAM-25,	[219]
KDM6A/UTX	H3K27	ND	GSK-J1, GSK-J4	[221]
KDM6B/JMJD3	H3K27	ND	GSK-J1, GSK-J4	[221]
KDM6C/UTY	H3K27	ND	NP	
KDM7A/JHDM1D	H3K9, H3K27, H4K20	ND	Daminozide, KDM2A/7A-IN-1	[206, 207]
KDM7B/PHF8	H3K9, H3K27, H4K20	YY1	Daminozide, iPHF8	[94, 206]
KDM7C/PHF2	H3K9	ND	NP	
KDM8/JMJD5	H3K36	ND	NP	
KDM9	H4K20	ND	NP	
NO66	H3K4, H3K36	ND	NP	

Indicated are the histone and the DNA binding proteins known to be demethylated by each enzyme including known inhibitors. For simplicity, we do not report all the inhibitors available on the market

ND Not described, *NP* Not published

demethylase 3B/Jumonji domain-containing 1B) was shown to have arginine demethylase activity versus histone proteins both in cell-free and in vitro assays [14] and KDM5C/JARID1C to promote arginine demethylation of non-histone proteins in in vitro assays [15]. However more efforts are required to validate the arginine demethylase activity of these enzymes in vivo.

Post-translationally modified residues represent docking sites for the interaction with proteins that contain domains able to "read" modified residue(s). More domains have been described to recognize methylated lysine and/or arginine: Ankyrin (ANK) repeats, WD40 repeat domain, plant homeodomain (PHD) finger, Tudor domain, proline-tryptophan-tryptophan-proline (PWWP) domain, bromo adjacent homology (BAH) domain, malignant brain tumor (MBT) domain, ATRX-DNMT3A-DNMT3L (ADD) domain, chromodomain (CD) and zinc finger cysteine-tryptophan (zn-CW) domain.

Methylation of transcription factors

Hypoxia-inducible factors (HIFs)

Hypoxia-inducible factors (HIFs) are the key mediators of the hypoxia response, they function as

heterodimers composed of an oxygen (O_2)-sensitive α and an O_2-insensitive β subunit. Under plentiful O_2 concentrations, defined as normoxia, HIFα proteins are hydroxylated by factor inhibiting HIF [FIH; encoded by the *HIF1AN* (hypoxia-inducible factor 1-alpha inhibitor) gene] and by prolyl hydroxylase domain (PHD) proteins and their transcriptional activity is prevented. FIH-mediated hydroxylation of HIFα proteins on asparagine (*N*) residues prevents their interaction with the transcriptional activator KAT3B/EP300 (lysine acetyltransferase 3B/E1A-binding protein 300 kD) while the PHDs-mediated hydroxylation on proline (P) residues leads to their interaction with the von Hippel–Lindau tumor suppressor protein (pVHL) that finally results in the ubiquitin-dependent proteasomal degradation of HIFα proteins. Given that O_2 is the key cofactor for both FIH and PHDs their activity is suppressed under hypoxic conditions leading to stabilization of HIFα proteins and activation of their target genes upon their heterodimerization with the HIFβ subunit(s) [16].

In the recent years, it has become increasingly clear that the regulation of HIF proteins is not exclusively dependent on their hydroxylation and ubiquitination but also on other PTMs, such as lysine methylation. KMT7/SETD7 (lysine methyltransferase 7/SET domain-containing 7) monomethylates HIF1α and HIF2α at highly conserved lysine residues (HIF1αK32me_1 and HIF2αK29me_1, respectively) significantly reducing their transcriptional activity [17]. KMT7/SETD7-dependent methylation of HIF1α reduces its DNA-binding activity without influencing its nuclear translocation, mRNA and protein levels [17]. Notably, the expression of KMT7/SETD7 is reduced under hypoxic conditions leading to a decrease of methylation of HIF1α at K32 [17]. Interestingly, another study found that under hypoxia, the same KMT7/SETD7-mediated methylation on K32 of HIF1α reduces its nuclear stability by promoting increased ubiquitination. This regulation is counteracted by the demethylase activity of KDM1A/LSD1. In fact, overexpression of KDM1A/LSD1 enhances the stabilization of HIF1α and reduces its ubiquitination [18]. However, a second KMT7/SETD7-mediated methylation site has been identified within HIF1α [19]: This dimethylation on K391, that is again counteracted by KDM1A/LSD1, leads to increased pVHL-mediated ubiquitination of HIF1α. In fact, KDM1A/LSD1 reduces HIF1α methylation, which in turn reduces the PHD2-mediated hydroxylation and the pVHL-mediated ubiquitination of HIF1α [19].

The regulation of the hypoxia response encompasses also the asymmetric arginine dimethylation of HIF1α on position 282 (HIF1αR282me_{2a}) which is dependent on PRMT3 [20]. Interestingly, under hypoxia, PRMT3 stabilizes the HIF1α protein preventing its ubiquitination and this methylation is essential for PRMT3-mediated tumorigenesis [20]. Given that hypoxia has been shown to influence the activity of KDM5C/JARID1C finally impacting om the arginine methylation state of ATG1/UNC-51 like autophagy activating kinase 1 (ULK1) [15] it will be important to evaluate whether KDM5C/JARID1C also demethylates arginines of the HIF-proteins.

In summary, these data suggest that under normoxia, KMT7/SETD7-mediated methylation of HIF1α results in

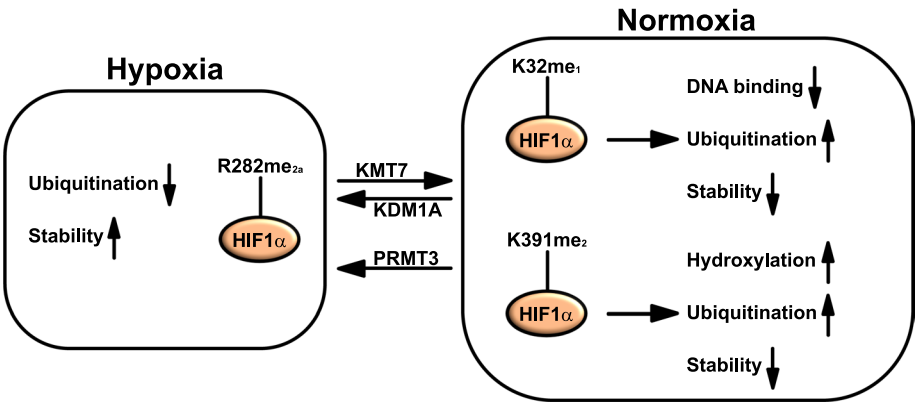

Fig. 2 Regulation of hypoxia-inducible factor 1-alpha (HIF1α) by lysine (K) and arginine (R) methylation. Under plentiful O_2 concentrations (defined as normoxia), KMT7/SETD7 (lysine methyltransferase 7/SET domain-containing 7) catalyzes hypoxia-inducible factor 1-alpha (HIF1α) monomethylation on K32 (HIF1αK32me_1) and dimethylation on K391 (HIF1αK391me_2) resulting in reduced stability of HIF1α as consequence of increased ubiquitination and degradation. K32me_1 also leads to reduced DNA binding of HIF1α while K391me_2 is associated with increased hydroxylation of HIF1α. Both HIF1αK32me_1 and HIF1αK391me_2 are demethylated by KDM1A/LSD1 (lysine demethylase 1A/lysine-specific histone demethylase 1) leading to increased stability of HIF1α. Under hypoxia, protein arginine (R) methyltransferase 3 (PRMT3) catalyzes asymmetrical dimethylation on R282 (HIF1αR282me_{2a}) leading to reduced ubiquitination and as consequence increased stability of the protein. *KDM1A* = *KDM1A/LSD1* lysine demethylase 1A/lysine-specific histone demethylase 1; *KMT7* = *KMT7/SETD7* lysine methyltransferase 7/SET domain-containing 7; *PRMT3* protein arginine methyltransferase 3

increased ubiquitination and degradation (Fig. 2). Under hypoxic conditions, demethylation of HIF1α by KDM1A/LSD1 and PRMT3-mediated methylation of HIF1α lead to its stabilization (Fig. 2).

P53

P53 is a transcription factor which function is to protect cells from genotoxic stresses. P53 is physiologically ubiquitinated by the E3 ubiquitin ligase mouse double minute 2 (MDM2) causing its proteasomal degradation. However, upon DNA damages, P53 is phosphorylated and this prevents its interaction with MDM2 leading to P53 stabilization. As consequence, the stabilization of P53 leads to its tetramerization and this tetramer works as a transcriptional activator of several target genes which function is to promote the reparation of the DNA damages or, alternatively, induce the apoptotic response [21].

P53 is heavily regulated by a wide range of different PTMs and among them lysine methylation plays a significant role. KMT7/SETD7-mediated monomethylation on K372 (P53K372me$_1$) positively regulates the function of P53 [22] while its demethylation is mediated by KDM3A/JMJD1A and leads to reduced expression of pro-apoptotic genes [23, 24]. On the other hand, KMT3C/SMYD2 (lysine methyltransferase 3C/SET and MYND domain-containing 2)-mediated monomethylation on K370 (P53K370me$_1$) reduces the activity of P53 [25, 26]. Interestingly, KMT7/SETD7-mediated P53K372me$_1$ reduces the interaction between P53 and KMT3C/SMYD2 and as a consequence the KMT3C/SMYD2-mediated P53K370me$_1$ finally increasing the transcriptional activity of P53 [25]. Altogether, these observations suggest a competing mechanism between different KMTs to differentially regulate the activity of P53. Of note, KMT7/SETD7-mediated P53K372me1 is a prerequisite for KAT3B/EP300-mediated acetylation of P53 on K373 and K382 [27] which play a positive role in the P53-mediated transcriptional response [28–31]. In line with this, KMT7/SETD7-depleted mouse cells fail to methylate P53 on K369 (corresponding to human 372) and fail to acetylate P53 on K379 [corresponding to human 382 [32]]. Mechanistically, P53K369me$_1$ acts as a docking site for the recruitment of the histone acetyltransferase KAT5/TIP60 (lysine acetyltransferase 5/tat interacting protein 60 kDa) [32] that is known to positively impact on the P53-dependent apoptotic response following genotoxic stress [33, 34]. KMT7/SETD7 regulates P53-dependent transcription also via an indirect mechanism that involves sirtuin 1 (SIRT1). SIRT1 is known to deacetylate P53 reducing its activity [35] however, upon DNA damage, KMT7/SETD7 methylates SIRT1 releasing the SIRT1-P53 interaction finally leading to increased P53-dependent response [36]. The same K370 of P53 is dimethylated (P53K370me$_2$) by an unknown methyltransferase [37] but in contrast to P53K370me$_1$, P53K370me$_2$ plays a positive role in the transcriptional activity of P53 and this occurs via the binding of the coactivator tumor protein P53 binding protein 1 (TP53BP1) to P53K370me$_2$ [37] and the Tudor domain of PHD finger protein 20 (PHF20) [38]. Of note, P53K370me$_2$ is demethylated by KDM1A/LSD1 [37].

Additional lysine residues within P53 are known to be methylated: For example, KMT5A/SETD8 (lysine methyltransferase 5A/SET domain-containing 8) monomethylates P53 on K382 (P53K382me$_1$) reducing its DNA binding and transcriptional activity and KMT5A/SETD8 depletion leads to increased transcriptional activity of P53 in response to DNA damages [26, 39]. Mechanistically, P53K382me$_1$ acts as a docking site for the MBT domains of lethal(3)malignant brain tumor-like protein 1 (L3MBTL1) which depletion leads to increased P53-dependent transcriptional response upon DNA damage [40]. Interestingly, reduction in P53K382me$_1$ is associated with increased acetylation on K382 which supports P53 transcriptional activity [39]. The same residue has been described to be dimethylated (P53K382me$_2$) by unknown KMT(s) and, under these circumstances, to be bound by the methyl reader and coactivator TP53BP1 [41]. P53K382me$_2$ increases upon DNA damages [41] and the positive effect of TP53BP1 on P53 via K382me$_2$ is downmodulated by Tudor-interacting repair regulator (TIRR) which inhibits the interaction between methylated P53 and the Tudor domain of TP53BP1 [42]. P53K382me$_2$ is also bound by the Tudor domain of PHF20 leading to reduced MDM2-mediated P53 ubiquitination finally reducing its degradation and as a consequence increasing stability and activity of P53 [38]. Furthermore, K373 is dimethylated (and probably also monomethylated) by KMT1C/EHMT2/G9A (lysine methyltransferase 1C/euchromatic histone-lysine *N*-methyltransferase 2) and KMT1D/EHMT1/GLP (lysine methyltransferase 1D/euchromatic histone-lysine N-methyltransferase 1/ G9a-like protein 1) and their knockdown results in increased apoptosis suggesting that the KMT1C/EHMT2/G9A- and KMT1D/EHMT1/GLP-mediated methylation of P53 reduces its transcriptional activity [43]. Finally, structural studies suggest KMT2 (lysine methyltransferase 2) family members as possible K methyl writers within P53 [44] however, more efforts are required to support this notion.

Mass-spectrometry studies identified P53 methylation also on arginine residues: R335 and R337 are symmetrically dimethylated (P53R335me$_{2s}$ and P53R337me$_{2s}$), whereas R333 is monomethylated [P53R333me$_1$ [45]]. Arginine methylation of P53 is catalyzed by PRMT5 and this methylation impact on the transcriptional activity of P53 even if with variabilities among its different transcriptional targets

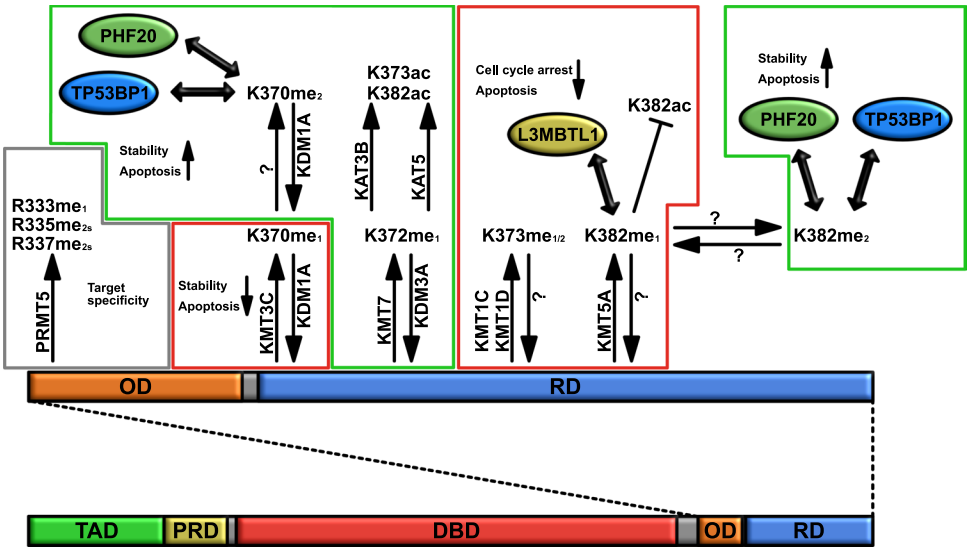

Fig. 3 Regulation of tumor suppressor P53 by lysine (K) and arginine (R) methylation. Lysine (K) methylation of the tumor suppressor P53 occurs at several lysineresidues located within the regulatory domain (RD). KMT3C/SMYD2 (lysine methyltransferase 3C/ SET and MYND domain-containing 2) monomethylates K370 (P53K370me$_1$) leading to reduced activity of P53 and apoptosis. An unknown lysine methyltransferase (KMT) further dimethylates K370 (P53K370me$_2$) which is recognized by Tudor domain-containing proteins [tumor protein P53 binding protein 1 (TP53BP1) or PHD finger protein 20 (PHF20), leading to increased P53 stability and apoptosis. KMT7/SETD7 monomethylates K372 (P53K372me$_1$) and this supports both the KAT3B/EP300 (lysine acetyltransferase 3B/E1A-binding protein 300 kD)-mediated acetylation on K373 and K382 and the KAT5/TIP60 (lysine acetyltransferase 5/tat interacting protein 60 kDa)-mediated acetylation of P53. Furthermore, KMT7/SETD7-mediated P53K372me$_1$ reduces the interaction between P53 and KMT3C/SMYD2 and as consequence it reduces the KMT3C/SMYD2-mediated P53K370me$_1$. As a consequence, P53K372me$_1$ increases stability of P53 and apoptosis. Both P53K370me$_1$ and P53K370me$_2$ are demethylated by KDM1A/LSD1 (lysine demethylase 1A/lysine-specific histone demethylase 1). KMT1C/EHMT2/G9A (lysine methyltransferase 1C/euchromatic histone-lysine N-methyltransferase 2) and KMT1D/EHMT1/GLP (lysine methyltransferase 1D/euchromatic histone-lysine N-methyltransferase 1/G9a-like protein 1) methylate K373 on P53 leading to reduced P53 transcriptional activity and apoptosis. KMT5A/SETD8 (lysine methyltransferase 5A/SET domain-containing 8) monomethylates P53 on K382 (P53K382me$_1$) reducing acetylation on K382 and acting as a docking site for the methyl binding domains (MBT) of lethal(3) malignant brain tumor-like protein 1 (L3MBTL1) finally leading to reduced P53 transcriptional activity, cell cycle arrest and apoptosis. P53K382me$_1$ is further dimethylated (P53K382me$_2$) by unknown KMTs and this post-translation modification (PTM) is further bound by Tudor domain-containing proteins (TP53BP1 or PHF20) increasing stability of P53 and apoptosis. Arginine (R) methylation of P53 occurs on R333 (monomethylation, R333me$_1$), R335 (symmetric dimethylation, R335me$_{2s}$) and R337 (symmetric dimethylation, R337me$_{2s}$) and these methylations regulate the target specificity of P53. Green and red boxes indicate methylation events that play a positive or negative role in the P53-dependent response, respectively. Gray box indicates methylation events that regulate the target specificity of P53 response. *DBD* DNA binding domain; *KAT3B* = *KAT3B/EP300* lysine acetyltransferase 3B/E1A-binding protein 300 kD; *KAT5* = *KAT5/TIP60* lysine acetyltransferase 5/tat interacting protein 60 kDa; *KDM1A* = *KDM1A/LSD1* lysine demethylase 1A/lysine-specific histone demethylase 1; *KDM3A* = *KDM3A/JMJD1A* lysine demethylase 3A/Jumonji domain-containing 1A; *KMT1C* = *KMT1C/EHMT2/G9A* lysine methyltransferase 1C/euchromatic histone-lysine N-methyltransferase 2; *KMT1D* = *KMT1D/EHMT1/GLP* lysine methyltransferase 1D/euchromatic histone-lysine *N*-methyltransferase 1/G9a-like protein 1; *KMT3C* = *KMT3C/SMYD2* lysine methyltransferase 3C/SET and MYND domain-containing 2; *KMT5A* = *KMT5A/SETD8* lysine methyltransferase 5A/SET domain-containing 8; *KMT7* = *KMT7/SETD7* lysine methyltransferase 7/SET domain-containing 7; *L3MBTL1* lethal(3)malignant brain tumor-like protein 1; *OD* oligomerization domain; *PHF20* PHD finger protein 20; *PRD* proline-rich domain; *PRMT5* protein arginine methyltransferase 5; *RD* regulatory domain; *TAD* transcriptional activation domain; *TP53BP1* tumor protein P53 binding protein 1

[45]. In summary, lysine and arginine methylation of P53 has a profound and different impact on the stability, and consequently activity, of P53 based on the specific residues that are modified, on the degree of methylation as well as on the methyl reader protein involved (Fig. 3).

E2F1

Another key tumor suppressor is retinoblastoma protein (pRB) which binds E2F family of transcription factors preventing their activity [46]. E2F family members promote cell cycle as well as apoptosis [47] and are regulated by several different PTMs. Among them, monomethylation on K185 of E2F1 (E2F1K185me$_1$) is dynamically regulated by KMT7/SETD7 and KDM1A/LSD1 [48, 49] and reduces

the stability of E2F1 protein via an ubiquitin-dependent mechanism finally downregulating the proapoptotic activity of E2F1 [48, 50]. Furthermore, E2F1K185me$_1$ crosstalks with other PTMs reducing both acetylation and phosphorylation of E2F1 itself upon DNA damages [48, 50]. In contrast to this, Xie and colleagues observed that KMT7/SETD7-mediated K185me$_1$ of E2F1 stabilizes the protein itself and increases cell death upon DNA damages [49]. The reasons for these discrepancies are not clear but they might depend on the cell type and/or DNA damage agent used in the two different studies [48, 49]. Interestingly, SETD6 (SET domain-containing 6) expression has been shown to be regulated by E2F1 and SETD6 monomethylates E2F1 on K117 [E2F1K117me$_1$ [51]] increasing the DNA binding of E2F1 at the *SETD6* locus finally supporting its expression in a way to establish a positive feedback loop [51].

On the other side, symmetric arginine methylation of E2F1 is promoted by PRMT5 which predominantly methylates R111 and R113 [E2F1R111me$_{2s}$ and E2F1R113me$_{2s}$ [52, 53]]. Symmetric arginine methylated E2F1 is bound by the Tudor domain of p100-Tudor staphylococcal nuclease (TSN) reducing E2F1 stability and apoptosis [53]. In line with this, a methylation-defective arginine E2F1 mutant is more stable, less ubiquitinated, has a higher transcriptional activity and reduces cell growth compared to its wildtype counterpart and similar results are also observed upon knockdown of PRMT5 [52, 53]. Interestingly, reduced symmetric arginine methylation of E2F1 is detected upon DNA damages and this leads to stabilization of E2F1 and increased apoptosis [52]. Asymmetric arginine methylation of E2F1 has been also described, it occurs on R109 (E2F1R109me$_{2a}$) and is catalyzed by PRMT1 [53]. A methylation-defective R109 mutant of E2F1 or PRMT1 knockdown result in reduced stability of E2F1, reduced transcription of E2F1 target genes and increased cell growth [53]. Interestingly, PRMT1 knockdown leads to reduced apoptosis upon DNA damage [53] while PRMT5 knockdown has the opposite effect [52, 53]. This is explained by the observation that PRMT1-mediated E2F1 methylation prevents the PRMT5-mediated one and binding of CYCLIN A to E2F1 blocks the PRMT1-mediated methylation stimulating the PRMT5-mediated one, keeping cells in cell cycle [53] proposing a competing mechanism for the methylation of E2F1 by the two PRMTs. In summary, these studies reveal that PRMT1-dependent asymmetric arginine methylation of E2F1 prevents its PRMT5-dependent symmetric arginine methylation promoting apoptosis upon DNA damages. CYCLIN A binding to E2F1 prevents asymmetric arginine methylation augmenting symmetric arginine methylation and recruiting p100-TSN which finally leads to cell survival and proliferation.

Nuclear receptors (NRs)

Nuclear receptors (NRs) are the key mediators of hormone signaling. Generally, ligand binding to NRs [for example estrogen receptor alpha (ERα)] in the cytoplasm leads to their nuclear translocation finally activating expression of target genes. Alternatively, some NRs dimerize already in absence of ligand acting as repressor of transcription and ligand binding converts them in transcriptional activators. This is the case for example of retinoic acid receptor alpha (RARα) heterodimerizing with retinoid X receptor (RXR).

ERα is monomethylated on K302 (ERαK302me$_1$) by KMT7/SETD7 [54, 55], having a positive impact on the stability of ERα, on its ligand-dependent transcriptional activity and on its DNA binding [54]. Interestingly, acetylation of the same residue has been proposed to attenuate the ERα transcriptional response [56], suggesting that different PTMs of the same residue within ERα are used in a competitive fashion to modulate its activity. On the other hand, KMT3C/SMYD2-dependent monomethylation of ERα on K266 (ERαK266me$_1$) has a negative impact on gene transcription [57] and is enhanced by the chaperones heat shock protein 90 (HSP90)-P23 [58]. KMT3C/SMYD2 depletion leads to increased DNA binding of ERα associated with increased gene transcription of its target genes upon estradiol (E_2) treatment. However, this depletion has no impact on H3K4me$_2$ while it leads to increased H3K4me$_3$ signal [57]. Of note, ERαK266me$_1$ is demethylated by KDM1A/LSD1 and importantly, it prevents the KAT3B/EP300 and KAT3A/CBP (lysine acetyltransferase 3A/CREB-binding protein)-mediated acetylation of ERα at K266 and K268 [57] which play a positive function in the activity of the receptor [59]. ERα is also asymmetrically dimethylated within its DNA binding domain on R260 (R260me$_{2a}$) by PRMT1 [60]: ERαR260me$_{2a}$ occurs in the cytoplasm, is required for its E_2-induced interaction with SRC and p85, a subunit of the phosphoinositide 3-kinase (PI3K) [60] and this arginine methylation has been suggested to be removed by JMJD6 [9] even if the JMJD6 arginine demethylase activity is still under debate.

Trimethylation at K347 within RARα (RARαK347me$_3$) has a positive impact on its ligand-dependent transcriptional activity facilitating its interaction with both its heterodimeric partner RXR and the transcriptional coactivator KAT2B/PCAF (lysine acetyltransferase 2B/EP300-CBP-associated factor) [61]. Interestingly, in absence of ligand, RARαK347me$_3$ supports its interaction with the corepressor nuclear receptor corepressor 1 (NCoR1) [61]. Two additional monomethylated lysine residues have been identified within RARα: K109 (RARαK109me$_1$) within the DNA-binding domain (DBD) and K171 (RARαK171me$_1$) within the hinge region [62]. Mutational analysis revealed that RARαK109me$_1$ but not RARαK171me$_1$ is required for

ligand-dependent transcriptional activation and surprisingly RARαK109me$_1$ has a stronger impact, compared to RARαK347me$_3$, on the transcriptional activity of RARα [62]. Similarly to RARαK347me$_3$, RARαK109me$_1$ is required for the interaction of RARα with RXR and KAT2B/PCAF [62].

Retinoic acid receptor–related orphan receptor alpha (RORα) is also regulated by methylation of both lysine and arginine residues. KMT6A/EZH2 (lysine methyltransferase 6A/enhancer of zeste homolog 2) monomethylates RORα at K38 (RORαK38me$_1$) creating a docking site that is recognized by the adaptor protein DCAF1 [damage-specific DNA binding protein 1 (DDB1)-cullin4 (CUL4)-associated factor] which bridges RORα to the DDB1/CUL4 E3 ubiquitin ligase complex promoting ubiquitination and proteasomal-dependent degradation of RORα [63]. As a consequence, RORαK38me$_1$ is unstable and this is reflected on its DNA binding and transcriptional activity [63]. Further modifications of RORα include PRMT5-mediated methylation on R37 which acts as a docking site for Itchy E3 ubiquitin protein ligase (ITCH) promoting the ubiquitin-dependent proteasomal degradation of RORα [64].

Lysine monomethylation of progesterone receptor (PR) occurs within the activation function 1 (AF-1) domain at K464 (PRK464me$_1$) and this modification potentially reduces the transactivation activity of the receptor [65]. On the other side, PR is also asymmetrically dimethylated by PRMT1 on R637 (PRR637me$_{2a}$) upon progesterone treatment and PRMT1 expression reduces the stability of PR [66], suggesting that PRMT1-mediated methylation of PR plays a negative role in regulating its stability.

Similarly to PR methylation on K464, KMT7/SETD7-dependent methylation of androgen receptor (AR) at K630 is required for efficient gene induction upon stimulation with the synthetic androgen R1881 positively influencing both its DNA binding and the recruitment of KAT2B/PCAF [67]. A second study could support the notion that KMT7/SETD7-dependent methylation of AR plays a positive role in its transcriptional activity. However, in this case, the authors could detect methylation on K632 but not on K630 [68]; In contrast, Ko and colleagues could detect methylation on K630 but not on K632 [67]. The reason for this discrepancy remains however unclear. KMT3C/SMYD2 interacts with AR and methylates it at unknown residue(s) [69]. KMT3C/SMYD2 increases the stability of AR reducing its ubiquitination and knockdown of KMT3C/SMYD2 reduces its DNA binding and the expression of target genes [69]. Finally, PRMT5-dependent arginine methylation (both ωMMAs and ωsDMA) of AR has also been described and it occurs on R761 leading to reduced DNA binding and expression of its target genes [70].

NF-κB

One of the key mediators of the inflammatory response is the transcription factor nuclear factor 'kappa-light-chain-enhancer' of activated B-cells (NF-κB). NF-κB consists of either homo- or heterodimers of different subunits that include P50, P52, RELA, RELB and C-REL [71]. KMT7/SETD7 monomethylates RELA at K37 (RELAK37me$_1$) and this methylation is required for both DNA binding and induction of a subset of RELA target genes [*tumor necrosis factor alpha* (*TNFα*) and *C-X-C motif chemokine 10* (*CXCL10*)] in response to TNFα or interleukin 1β (IL1β) stimulation [72, 73]. In addition, KMT7/SETD7-dependent monomethylation of RELA at K314 and K315 (RELAK314me$_1$ and RELA K315me$_1$) reduces gene induction upon TNFα stimulation by increasing RELA ubiquitination and as consequence its stability [74]. Interestingly, KAT3B/EP300-mediated acetylation on K310 of RELA reduces its interaction with KMT7/SETD7 and, as a consequence, monomethylation of RELA on K314 and K315 and finally its ubiquitination [75]. K310 of RELA is also monomethylated (RELAK310me$_1$) by SETD6 and this methylation reduces the transcriptional activity of RELA upon stimulation with TNFα and RELA-dependent cell proliferation [76]. Mechanistically, RELAK310me$_1$ acts as a docking site for the recruitment of KMT1D/EHMT1/GLP which promotes H3K9me$_2$ and this interaction is prevented by protein kinase C zeta (PKCζ)-mediated phosphorylation on serine 311 of RELA [76, 77].

Additional methylated lysine residues have been identified within RELA. For example, monomethylation at K218 (RELAK218me$_1$) and dimethylation at K221 (RELAK221me$_2$) are dynamically regulated by KMT3B/NSD1 (lysine methyltransferase 3B/nuclear receptor–binding SET domain-containing protein 1) and KDM2A/JHDM1A (lysine demethylase 2A/JmjC domain-containing histone demethylation protein 1A) in response to TNFα or IL1β stimulation and this methylation has a positive impact on the expression of a subset of RELA target genes and stimulates cell proliferation [73, 78]. Interestingly, IL1β stimulation leads to increased expression of KDM2A/JHDM1A [78] suggesting a possible negative feedback loop that regulates the RELA-dependent response.

PRMT5 symmetrically dimethylates RELA at R30 (RELAR30me$_{2s}$) upon stimulation with IL1β increasing its transcriptional activity [79]. A crystal-structure-based model suggests that RELAR30me$_{2s}$ may increase its DNA binding [79]. R30 of RELA is also asymmetrically dimethylated by PRMT1 reducing its DNA binding activity in response to stimulation with TNFα [80]. Those studies suggest that different arginine methylation, symmetric vs asymmetric, have a different impact on the

RELA-dependent transcriptional response. Another study could show that more arginine residues within RELA are methylated and that those different residues have a different impact on the transcriptional activity of RELA in a gene-specific fashion [81, 82]. Finally, PRMT4-mediated monomethylation of RELA is required for neuronal differentiation from embryonic stem cells (ESCs) however, the exact monomethylated residue(s) have not yet been identified [83].

STAT3

Cytokines like IL6 bind to membrane receptors triggering the activation of Janus kinases (JAKs), which phosphorylate signal transducer and activator of transcription 3 (STAT3) on Y705 (STAT3Y705p). This phosphorylation promotes the homodimerization of STAT3, leading to its release from the receptor, followed by nuclear translocation and activation of target genes [84]. STAT3 is dimethylated on K140 (STAT3K140me$_2$) by KMT7/SETD7 and demethylated by KDM1A/LSD1 [85]. Interestingly, STAT3K140me$_2$ occurs in the nucleus, requires DNA binding, significantly increases upon stimulation with interleukin 6 (IL6) and is required for the induction of only a subset of target genes [85]. In addition to KDM1A/LSD1, also KDM3C/JMJD1C (lysine demethylase 3C/Jumonji domain-containing 1C) is able to demethylate STAT3 on K140 [86, 87]. Mechanistically, KDM3C/JMJD1C-mediated STAT3 demethylation supports the interaction of STAT3 with protein tyrosine phosphatase non-receptor type 6 (PTPN6) and, as a consequence, it reduces STAT3 phosphorylation and activity [86]. Additionally, in colon tumor cells, STAT3 is dimethylated on K49 (STAT3K49me$_2$) by KMT6A/EZH2 and this methylation is required for gene expression, increases upon IL6 stimulation and it is dependent on phosphorylation on Y705 [88]. In glioblastoma cells, KMT6A/EZH2 trimethylates STAT3 on K180 (STAT3K180me$_3$) playing again a positive role in the STAT3-dependent transcriptional response and supporting STAT3Y705p [89].

The activity of STAT3 is also regulated by arginine methylation: PRMT6 asymmetrically dimethylates R729 of STAT3 (STAT3R729me$_{2a}$) and this mark positively correlates with STAT3Y705p [90]. Mechanistically STAT3R729me$_{2a}$ positively influences its interaction with JAK2 and its membrane localization [90]. Importantly, STAT3R729me$_{2a}$ positively correlates with PRMT6 protein levels and STAT3Y705p levels in breast cancer tissues and patients with high levels of STAT3R729me$_{2a}$ have a lower overall survival [90]. Notably, STAT3R729me$_{2a}$ plays an important role also in PRMT6-mediated tumor metastasis and PRMT6 inhibition is able to reduce metastasis [90]. In addition to this, STAT3 is methylated by PRMT2 on R31 and PRMT2 depletion leads to increased STAT3Y705P upon leptin treatment which is known to induce STAT3 signaling [91] suggesting that methylation of R31 within STAT3 plays a negative role on its phosphorylation on Y705. Interestingly, PRMT2 knockout mice are lean, less prone to develop diet-induced obesity and have reduced glycogen stores suggesting that PRMT2-dependent methylation of STAT3 on R31 plays a positive role in obesity [91]. Finally, TNFα-induced protein 8-like protein 1 (TIPE1) inhibits osteosarcoma carcinogenesis and metastatic activity by binding to and inhibiting PRMT1 which is required for the asymmetric dimethylation of STAT3 on R688 (STAT3R688me$_{2a}$), a modification that stimulates the activity of STAT3 itself [92].

Additional examples

Other examples of transcription factors methylated on lysine and/or arginine residues include Yin Yang 1 (YY1), octamer-binding protein 4 (OCT4), runt-related transcription factor 1 (RUNX1) and 3 (RUNX3), myocyte enhancer factor 2D (MEF2D) and GLI proteins.

Yin Yang 1 (YY1) is a zinc-finger transcription factor that acts as both a repressor and an activator of transcription. KMT7/SETD7 monomethylates YY1 on K173 and K411 (YY1K173me$_1$ and YY1K411me$_1$, respectively) promoting its DNA binding and influencing its transcriptional activity [93]. Several additional lysine residues within YY1 have been described to be methylated and importantly, di- and trimethylation on K258 are demethylated by KDM7B/PHF8 (lysine methyltransferase 7B/PHD finger protein 8) [94]. KDM7B/PHF8 depletion as well as K258R mutation within YY1 lead to its reduced DNA binding associated with changes in gene expression [94]]. Similarly to YY1, also its homolog YY2 has been described to be monomethylated on K247 [YY1K247me$_1$ [95]]. This methylation is regulated by KMT7/SETD7 and KDM1A/LSD1 and again it influences DNA binding and transcriptional activity of YY2 [95].

RUNX proteins are members of a family of transcription factors involved in several developmental decisions. The DNA binding RUNX factors heterodimerize with the non-DNA binding protein core-binding factor beta (CBFβ) which function is to stabilize the RUNX/DNA interaction [96]. While RUNX1 is required for hematopoiesis, RUNX2 is needed for osteogenesis and RUNX3 for neurogenesis and other developmental processes [96]. Under hypoxia, RUNX3 is methylated (di- and/or monomethylated) on K129 and K171 by KMT1C/EHMT2/G9A leading to reduced transactivation activity of RUNX3 via inhibition of its interaction with KAT3B/EP300 and CBFβ and reducing, as a consequence, acetylation of RUNX3 itself which is required for its nuclear import [97]. Another member of this family of transcription factor, RUNX1 [also known as acute myeloid leukemia 1 (AML1)], has been described to interact with

and to be methylated on R206 and R210 by PRMT1 [98]. This arginine methylation within RUNX1 prevents its interaction with the transcriptional corepressor SIN3A and methylation-defective arginine mutants of RUNX1 have an increased transcriptional activity compared to their wild type counterpart [98, 99]. Making use of genetic mouse models, it was possible to determine that arginine methylation within RUNX1 has no role for definitive hematopoiesis and steady-state thrombopoiesis but it impacts of the peripheral $CD4^+$ T-cells [99] and increases resistance to apoptosis of hematopoietic stem cells (HSCs) upon genotoxic stress [100]. RUNX1 is also frequently mutated in leukemia and for example, it is fused to the corepressor eight-twenty-one (ETO) generating the oncofusion protein AML1/ETO in acute myeloid leukemia (AML). PRMT1-mediated arginine methylation of AML1/ETO has also been described within the "AML1" portion of the protein and PRMT1 depletion leads to reduced transcription of AML1/ETO targets and compromises the self-renewal ability of AML1/ETO [101].

Mass spectrometry (MS) has identified several methylated lysine residues within the transcription factor OCT4 which is a master transcription factor for ESCs [102]. Monomethylation on K222 of OCT4 (OCT4K222me_1) is regulated by KDM1A/LSD1 which promotes proteasome-independent degradation of OCT4 [102]. Another master transcription factor for stemness, sex-determining region Y protein (SRY)-box transcription factor 2 (SOX2), is methylated on lysine residues. KMT7/SETD7-mediated monomethylation of mouse SOX2 on K119 (SOX2K119me_1; corresponding to human 117) promotes ubiquitination and proteasomal degradation of SOX2 and reduces its transcriptional activity and interaction with KAT3B/EP300 [103]. Mechanistically, SOX2K119me_1 acts as a docking site for the recruitment of the E3 ubiquitin ligase WW domain-containing E3 ubiquitin protein ligase 2 (WWP2) via its E6-AP carboxyl terminus (HECT) domain and interestingly, this methylation counteracts AKT serine/threonine kinase 1 (AKT1)-mediated phosphorylation on T118 which, in contrast to SOX2K119me_1, promotes SOX2 stabilization [103]. KMT7/SETD7 also monomethylates human SOX2 on K42 (SOX2K42me_1) and both methylation sites (human K42 and K117) are demethylated by KDM1A/LSD1 promoting SOX2 stability [104]. In addition, both methylation sites (human K42 and K117) function as docking sites for PHD finger protein 20 like 1 (PHF20L1) which finally protects SOX2 from proteolysis [104]. SOX2 is also methylated on R113 by PRMT4 promoting SOX2 self-association [105].

MEF2D is another good example of lysine methylation of non-histone proteins. MEF2D plays important roles in hematopoiesis as well as muscle and neuronal development [106]. KMT1C/EHMT2/G9A dynamically monomethylates MEF2D on K267 (MEF2DK267me_1) and this methylation is counteracted by KDM1A/LSD1 [107]. Interestingly, MEF2DK267me_1 is reduced during differentiation of C2C12 cells and this reduced methylation is associated with increased DNA binding and transcriptional activity of MEF2D [107].

One further example is represented by GLI3, one of the key transcriptional mediator of the Hedgehog (HH) signaling pathway. GLI3 is proteolytically cleaved in absence of HH signals acting as a transcriptional repressor however, in presence of HH signaling, it is stabilized and functions as a transcriptional activator [108]. The full-length but not the proteolytically processed GLI3 protein is monomethylated on K436 and K595 (GLI3K436me_1 and GLI3K595me_1) by KMT7/SETD7 [109]]. This methylation promotes the HH-mediated gene expression via two different mechanisms: Methylation on K436 increases GLI3 protein stability while methylation on K595 promotes its DNA binding [109]. Interestingly, methylation of GLI3 has a positive effect on both proliferation and migration of lung cancer cells [109]. Another member of the GLI family, GLI1, is asymmetrically dimethylated on R597 by PRMT1 and this methylation plays a positive role in the GLI1 transcriptional activity by promoting its DNA binding ability finally increasing its oncogenic activity [110]. Finally, GLI1 is also symmetrically dimethylated on R515, R990 and R1018 by PRMT5 and these methylation events (with exclusion of R515) stabilize the GLI1 protein inhibiting its ITCH/NUMB-mediated ubiquitination [111].

Methylation of DNA methyltransferases (DNMTs)

Methylation of the DNA base cytosine is a key determinant in regulating gene expression and is mediated by DNA methyltransferases (DNMTs). There are five human DNMTs isoforms: DNMT1, DNMT3A and DNMT3B but not DNMT2 and DNMT3L have DNMT catalytic activity. DNMT1 is required for maintenance of DNA methylation and is responsible of post-replicative copy of DNA methylation patterns from parental strands into newly synthesized DNA. On the other side, DNMT3A and DNMT3B are the so-called de novo DNMTs which are responsible to establish new methylation patterns. The epigenetic information represented by methylated DNA is subsequently read via the methyl-DNA binding domain (MBD) which bridges methylated DNA to corepressors such as histone deacetylases (HDACs).

DNMT1 is monomethylated on K142 (DNMT1K142me_1) by KMT7/SETD7 and this methylation promotes the proteasome-dependent degradation of DNMT1 [50, 112]. Interestingly, KMT7-SETD7-mediated DNMT1K142me_1 is prevented by AKT1-mediated phosphorylation at S143, a mark that increases the stability of DNMT1 [113]. Additionally, KMT7/SETD7 and KDM1A/LSD1 dynamically regulate the

methylation state of DNMT1 on K1096 and KDM1A/LSD1 depletion in ESCs leads to growth and differentiation defects associated with DNA hypomethylation and reduced DNMT1 protein levels [114].

KMT1C/EHMT2/G9A and KMT1D/EHMT1/GLP dimethylate human DNMT3A on K47 creating a docking site that is recognized by the chromodomain of M-phase phosphoprotein 8 (MPP8) [115]. Given that KMT1D/EHMT1/GLP auto-methylates at K205 and that this methylated site is again bound by the chromodomain of MPP8 and given that MPP8 can dimerize, this suggest a simple model to explain how H3K9 methylation and DNA methylation are established in combination together on chromatin [115].

The methyl-DNA binding reader MBD2 is methylated on R residues by PRMT1 and PRMT5 reducing its interaction both with HDACs and methylated DNA [116], suggesting that not only methylation of DNMTs but also of methyl DNA readers can contribute to heterochromatin regulation.

Translational aspects

Since the regulation of transcription factors is also dysregulated in pathological conditions like cancer, the search for inhibitors of methyltransferase or demethylase is a logical next step. We briefly mention a few examples and the reader is referred to other reviews focusing on this topic [117].

Tazemetostat is an inhibitor of KMT6A/EZH2 and recently entered clinical trials. Tazemetostat is an orally bioavailable potent and selective SAM competitive KMT6A/EZH2 inhibitor. In preclinical models Tazemetostat is potentially effective in the context of non-Hodgkin lymphoma [118], malignant rhabdoid tumors [119] and synovial sarcoma [120]. Based on these results, Tazemetostat has been used in a phase-II study for the treatment of malignant pleural mesothelioma patients characterized by BAP1 [breast cancer 1 (BRCA1) associated protein 1] inactivation [121] showing a good tolerability to the drug. The promising efficacy of Tazemetostat has been further marked in relapsed/refractory follicular lymphomas and diffuse large B-cell lymphomas [122–125].

Inhibition of KMT4/DOT1L (lysine methyltransferase 4/disrupter of telomeric silencing 1-like) deserved also attention in more clinical trials. Pinometostat has been used in a phase 1 study mainly focused on acute leukemia patients characterized by mixed lineage leukemia (*MLL*) gene rearrangements [(MLL-r), 11q23 translocations; [126]]. This study could demonstrate that even if the drug was well tolerated, only 2 out of the 51 patients enrolled in the study showed a complete remission [126]. A second phase I study conducted on MLL-r children supported again the safety of the drug however no drug response was observed [127].

Furthermore, KDM1A/LSD1 inhibitors have been tested in clinical trials, for example Iadademstat has been used in combination with azacytidine for the treatment of AML patients showing a manageable safety with promising efficacy [128]. In addition, the KDM1A/LSD1 inhibitor TAK-418 has been tested for tolerability, pharmacokinetics and pharmacodynamics in Kabuki syndrome patients with promising results [129].

Perspectives

Methylation, compared to other PTMs such as phosphorylation and ubiquitination, tends to be relatively slow and stable. A key aspect in regard to mechanism for methylation of lysine residues is that methylation prevents ubiquitination of the same lysine residue and as consequence protein turnover. Alternatively, it is also possible that methylation on a lysine residue supports ubiquitination of a different lysine residue supporting protein turnover. It will be interesting to investigate whether this also affects local concentration of proteins as for example often suggested for nuclear condensates with specialized functions such as transcriptional repression or microscopically visible nuclear speckles. Arginine methylation is frequently identified in proteomic studies as affecting RNA-binding proteins involved in post-transcriptional regulation. It will be interesting to explore whether arginine methylated transcription factors play a role not only in transcriptional regulation but also in processes like splicing and/or nuclear export.

By now we know that methylation of transcription factors can regulate their stability/turnover as well the binding to their interaction partners. Those partners can be enzymes that regulate both chromatin structure as well as PTMs within the transcription factors themselves. Alternatively, interaction partners can be readers of PTMs or scaffold and architectural proteins. In this case, PTMs of transcription factors can modulate gene transcription by a several different mechanisms regulating even chromatin looping giving finally gene specificity. In addition, environmental factors such as oxygen levels profoundly affect methylation states, as observed for HIF transcription factors. This in turn affects development and differentiation.

Aberrant transcription factor methylation can be caused by mutations and/or aberrant activity of writers, readers and erasers leading to diseases such as cancer but also genetic diseases. In future, the development of methyl-specific antibodies is are needed as tools to properly investigate and understand the link between aberrant methylation of transcription factors and pathological conditions.

Such methylation-specific antibodies could also be useful reagents for clinical diagnostics. In parallel, the development of specific small molecule inhibitors especially of writers and erasers could be also extremely valuable not only to understand the molecular mechanism but also for clinical applications.

In addition, it remains to be seen how extremely high oxygen levels, that is hyperoxia, affect methylation states of transcription factors. Hyperoxia could affect the expression levels of writers, erasers and readers, but also could affect enzymatic activities especially of the demethylases as for example the activity of the O_2-dependent JMJC domain-containing family of KDMs. Based on this, it has been shown that hyperoxia influences the expression of KMT6A/EZH2 [130] however, it is unknown whether this hyperoxia-induced KMT6A/EZH2 downregulation impacts on the methylation of HIF proteins.

Similarly to proteomic approaches investigating kinases or E3 ubiquitin ligases, it would be attractive to perform loss-of-function of the different enzymes involved in controlling lysine and arginine methylation. This can be combined with subsequent pan-methyl-lysine or pan-methyl-arginine antibodies immunoaffinity purification and mass-spectrometry [131–133], in order to identify the specific sites that are regulated by each individual enzyme. This could significantly accelerate the discovery of new methylation substrates. High quality antibodies recognizing specific methylated residues of transcription factors are urgently needed to better study the role of lysine/arginine methylation of transcription factors for example making use of genomic approaches such as chromatin immunoprecipitation followed by deep sequencing (ChIP-Seq).

In addition, more efforts are definitely required to further characterize the arginine demethylase activity of RDM proteins and their activity in regard to transcription factors as substrates with obvious potential clinical implications.

The development of highly specific inhibitors versus KMTs, PRMTs and KDMs as well as methyl-binding readers is crucial not only to study the function of arginine/lysine methylation of transcription factors but also for their possible clinical use to treat diseases characterized by alteration of arginine/lysine methylation of transcription factors.

Acknowledgements We would like to apologize to the colleagues whose work we did not cite due to space limitations.

Author contributions All authors contributed to the study conception and design. Figures and Tables preparation and analysis were performed by BDG. The manuscript was written by all authors. All authors read and approved the final manuscript.

Funding Open Access funding enabled and organized by Projekt DEAL. This work was funded by a research grant of the University Medical Center Giessen and Marburg (UKGM) to F.F. and T.B. and to the LOEWE research cluster iCANx to T.B.

Data availability Not applicable.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

References

1. Jenuwein T, Laible G, Dorn R, Reuter G (1998) SET domain proteins modulate chromatin domains in eu- and heterochromatin. Cell Mol Life Sci 54(1):80–93. https://doi.org/10.1007/s000180050127
2. Dillon SC, Zhang X, Trievel RC, Cheng X (2005) The SET-domain protein superfamily: protein lysine methyltransferases. Genome Biol 6(8):227. https://doi.org/10.1186/gb-2005-6-8-227
3. Boffa LC, Karn J, Vidali G, Allfrey VG (1977) Distribution of NG, NG,-dimethylarginine in nuclear protein fractions. Biochem Biophys Res Commun 74(3):969–976. https://doi.org/10.1016/0006-291x(77)91613-8
4. Cheng D, Cote J, Shaaban S, Bedford MT (2007) The arginine methyltransferase CARM1 regulates the coupling of transcription and mRNA processing. Mol Cell 25(1):71–83. https://doi.org/10.1016/j.molcel.2006.11.019
5. Branscombe TL, Frankel A, Lee JH, Cook JR, Yang Z, Pestka S, Clarke S (2001) PRMT5 (Janus kinase-binding protein 1) catalyzes the formation of symmetric dimethylarginine residues in proteins. J Biol Chem 276(35):32971–32976. https://doi.org/10.1074/jbc.M105412200
6. Shi Y, Lan F, Matson C, Mulligan P, Whetstine JR, Cole PA, Casero RA, Shi Y (2004) Histone demethylation mediated by the nuclear amine oxidase homolog LSD1. Cell 119(7):941–953. https://doi.org/10.1016/j.cell.2004.12.012
7. Chang B, Chen Y, Zhao Y, Bruick RK (2007) JMJD6 is a histone arginine demethylase. Science 318(5849):444–447. https://doi.org/10.1126/science.1145801
8. Liu W, Ma Q, Wong K, Li W, Ohgi K, Zhang J, Aggarwal A, Rosenfeld MG (2013) Brd4 and JMJD6-associated anti-pause enhancers in regulation of transcriptional pause release. Cell 155(7):1581–1595. https://doi.org/10.1016/j.cell.2013.10.056
9. Poulard C, Rambaud J, Hussein N, Corbo L, Le Romancer M (2014) JMJD6 regulates ERalpha methylation on arginine. PLoS One 9(2):e87982. https://doi.org/10.1371/journal.pone.0087982

10. Gao WW, Xiao RQ, Peng BL, Xu HT, Shen HF, Huang MF, Shi TT, Yi J, Zhang WJ, Wu XN, Gao X, Lin XZ, Dorrestein PC, Rosenfeld MG, Liu W (2015) Arginine methylation of HSP70 regulates retinoid acid-mediated RARbeta2 gene activation. Proc Natl Acad Sci USA 112(26):E3327-3336. https://doi.org/10.1073/pnas.1509658112
11. Lawrence P, Conderino JS, Rieder E (2014) Redistribution of demethylated RNA helicase A during foot-and-mouth disease virus infection: role of Jumonji C-domain containing protein 6 in RHA demethylation. Virology 452–453:1–11. https://doi.org/10.1016/j.virol.2013.12.040
12. Webby CJ, Wolf A, Gromak N, Dreger M, Kramer H, Kessler B, Nielsen ML, Schmitz C, Butler DS, Yates JR 3rd, Delahunty CM, Hahn P, Lengeling A, Mann M, Proudfoot NJ, Schofield CJ, Bottger A (2009) Jmjd6 catalyses lysyl-hydroxylation of U2AF65, a protein associated with RNA splicing. Science 325(5936):90–93. https://doi.org/10.1126/science.1175865
13. Walport LJ, Hopkinson RJ, Chowdhury R, Schiller R, Ge W, Kawamura A, Schofield CJ (2016) Arginine demethylation is catalysed by a subset of JmjC histone lysine demethylases. Nat Commun 7:11974. https://doi.org/10.1038/ncomms11974
14. Li S, Ali S, Duan X, Liu S, Du J, Liu C, Dai H, Zhou M, Zhou L, Yang L, Chu P, Li L, Bhatia R, Schones DE, Wu X, Xu H, Hua Y, Guo Z, Yang Y, Zheng L, Shen B (2018) JMJD1B demethylates H4R3me2s and H3K9me2 to facilitate gene expression for development of hematopoietic stem and progenitor cells. Cell Rep 23(2):389–403. https://doi.org/10.1016/j.celrep.2018.03.051
15. Li J, Zhang T, Ren T, Liao X, Hao Y, Lim JS, Lee JH, Li M, Shao J, Liu R (2022) Oxygen-sensitive methylation of ULK1 is required for hypoxia-induced autophagy. Nat Commun 13(1):1172. https://doi.org/10.1038/s41467-022-28831-6
16. Collier H, Albanese A, Kwok CS, Kou J, Rocha S (2023) Functional crosstalk between chromatin and hypoxia signalling. Cell Signal 106:110660. https://doi.org/10.1016/j.cellsig.2023.110660
17. Liu X, Chen Z, Xu C, Leng X, Cao H, Ouyang G, Xiao W (2015) Repression of hypoxia-inducible factor alpha signaling by Set7-mediated methylation. Nucl Acids Res 43(10):5081–5098. https://doi.org/10.1093/nar/gkv379
18. Kim Y, Nam HJ, Lee J, Park DY, Kim C, Yu YS, Kim D, Park SW, Bhin J, Hwang D, Lee H, Koh GY, Baek SH (2016) Methylation-dependent regulation of HIF-1alpha stability restricts retinal and tumour angiogenesis. Nat Commun 7:10347. https://doi.org/10.1038/ncomms10347
19. Lee JY, Park JH, Choi HJ, Won HY, Joo HS, Shin DH, Park MK, Han B, Kim KP, Lee TJ, Croce CM, Kong G (2017) LSD1 demethylates HIF1alpha to inhibit hydroxylation and ubiquitin-mediated degradation in tumor angiogenesis. Oncogene 36(39):5512–5521. https://doi.org/10.1038/onc.2017.158
20. Zhang X, Wang K, Feng X, Wang J, Chu Y, Jia C, He Q, Chen C (2021) PRMT3 promotes tumorigenesis by methylating and stabilizing HIF1alpha in colorectal cancer. Cell Death Dis 12(11):1066. https://doi.org/10.1038/s41419-021-04352-w
21. Chen X, Zhang T, Su W, Dou Z, Zhao D, Jin X, Lei H, Wang J, Xie X, Cheng B, Li Q, Zhang H, Di C (2022) Mutant p53 in cancer: from molecular mechanism to therapeutic modulation. Cell Death Dis 13(11):974. https://doi.org/10.1038/s41419-022-05408-1
22. Chuikov S, Kurash JK, Wilson JR, Xiao B, Justin N, Ivanov GS, McKinney K, Tempst P, Prives C, Gamblin SJ, Barlev NA, Reinberg D (2004) Regulation of p53 activity through lysine methylation. Nature 432(7015):353–360. https://doi.org/10.1038/nature03117
23. Ramadoss S, Guo G, Wang CY (2017) Lysine demethylase KDM3A regulates breast cancer cell invasion and apoptosis by targeting histone and the non-histone protein p53. Oncogene 36(1):47–59. https://doi.org/10.1038/onc.2016.174
24. Ramadoss S, Sen S, Ramachandran I, Roy S, Chaudhuri G, Farias-Eisner R (2017) Lysine-specific demethylase KDM3A regulates ovarian cancer stemness and chemoresistance. Oncogene 36(11):1537–1545. https://doi.org/10.1038/onc.2016.320
25. Huang J, Perez-Burgos L, Placek BJ, Sengupta R, Richter M, Dorsey JA, Kubicek S, Opravil S, Jenuwein T, Berger SL (2006) Repression of p53 activity by Smyd2-mediated methylation. Nature 444(7119):629–632. https://doi.org/10.1038/nature05287
26. Zhu J, Dou Z, Sammons MA, Levine AJ, Berger SL (2016) Lysine methylation represses p53 activity in teratocarcinoma cancer cells. Proc Natl Acad Sci USA 113(35):9822–9827. https://doi.org/10.1073/pnas.1610387113
27. Ivanov GS, Ivanova T, Kurash J, Ivanov A, Chuikov S, Gizatullin F, Herrera-Medina EM, Rauscher F 3rd, Reinberg D, Barlev NA (2007) Methylation-acetylation interplay activates p53 in response to DNA damage. Mol Cell Biol 27(19):6756–6769. https://doi.org/10.1128/MCB.00460-07
28. Mujtaba S, He Y, Zeng L, Yan S, Plotnikova O, Sachchidanand SR, Zeleznik-Le NJ, Ronai Z, Zhou MM (2004) Structural mechanism of the bromodomain of the coactivator CBP in p53 transcriptional activation. Mol Cell 13(2):251–263. https://doi.org/10.1016/s1097-2765(03)00528-8
29. Gu W, Roeder RG (1997) Activation of p53 sequence-specific DNA binding by acetylation of the p53 C-terminal domain. Cell 90(4):595–606. https://doi.org/10.1016/s0092-8674(00)80521-8
30. Barlev NA, Liu L, Chehab NH, Mansfield K, Harris KG, Halazonetis TD, Berger SL (2001) Acetylation of p53 activates transcription through recruitment of coactivators/histone acetyltransferases. Mol Cell 8(6):1243–1254. https://doi.org/10.1016/s1097-2765(01)00414-2
31. Luo J, Li M, Tang Y, Laszkowska M, Roeder RG, Gu W (2004) Acetylation of p53 augments its site-specific DNA binding both in vitro and in vivo. Proc Natl Acad Sci USA 101(8):2259–2264. https://doi.org/10.1073/pnas.0308762101
32. Kurash JK, Lei H, Shen Q, Marston WL, Granda BW, Fan H, Wall D, Li E, Gaudet F (2008) Methylation of p53 by Set7/9 mediates p53 acetylation and activity in vivo. Mol Cell 29(3):392–400. https://doi.org/10.1016/j.molcel.2007.12.025
33. Sykes SM, Mellert HS, Holbert MA, Li K, Marmorstein R, Lane WS, McMahon SB (2006) Acetylation of the p53 DNA-binding domain regulates apoptosis induction. Mol Cell 24(6):841–851. https://doi.org/10.1016/j.molcel.2006.11.026
34. Tang Y, Luo J, Zhang W, Gu W (2006) Tip60-dependent acetylation of p53 modulates the decision between cell-cycle arrest and apoptosis. Mol Cell 24(6):827–839. https://doi.org/10.1016/j.molcel.2006.11.021
35. Vaziri H, Dessain SK, Ng Eaton E, Imai SI, Frye RA, Pandita TK, Guarente L, Weinberg RA (2001) hSIR2(SIRT1) functions as an NAD-dependent p53 deacetylase. Cell 107(2):149–159. https://doi.org/10.1016/s0092-8674(01)00527-x
36. Liu X, Wang D, Zhao Y, Tu B, Zheng Z, Wang L, Wang H, Gu W, Roeder RG, Zhu WG (2011) Methyltransferase Set7/9 regulates p53 activity by interacting with Sirtuin 1 (SIRT1). Proc Natl Acad Sci USA 108(5):1925–1930. https://doi.org/10.1073/pnas.1019619108
37. Huang J, Sengupta R, Espejo AB, Lee MG, Dorsey JA, Richter M, Opravil S, Shiekhattar R, Bedford MT, Jenuwein T, Berger SL (2007) p53 is regulated by the lysine demethylase LSD1. Nature 449(7158):105–108. https://doi.org/10.1038/nature06092
38. Cui G, Park S, Badeaux AI, Kim D, Lee J, Thompson JR, Yan F, Kaneko S, Yuan Z, Botuyan MV, Bedford MT, Cheng JQ, Mer G (2012) PHF20 is an effector protein of p53 double lysine methylation that stabilizes and activates p53. Nat Struct Mol Biol 19(9):916–924. https://doi.org/10.1038/nsmb.2353

39. Shi X, Kachirskaia I, Yamaguchi H, West LE, Wen H, Wang EW, Dutta S, Appella E, Gozani O (2007) Modulation of p53 function by SET8-mediated methylation at lysine 382. Mol Cell 27(4):636–646. https://doi.org/10.1016/j.molcel.2007.07.012
40. West LE, Roy S, Lachmi-Weiner K, Hayashi R, Shi X, Appella E, Kutateladze TG, Gozani O (2010) The MBT repeats of L3MBTL1 link SET8-mediated p53 methylation at lysine 382 to target gene repression. J Biol Chem 285(48):37725–37732. https://doi.org/10.1074/jbc.M110.139527
41. Kachirskaia I, Shi X, Yamaguchi H, Tanoue K, Wen H, Wang EW, Appella E, Gozani O (2008) Role for 53BP1 Tudor domain recognition of p53 dimethylated at lysine 382 in DNA damage signaling. J Biol Chem 283(50):34660–34666. https://doi.org/10.1074/jbc.M806020200
42. Parnandi N, Rendo V, Cui G, Botuyan MV, Remisova M, Nguyen H, Drane P, Beroukhim R, Altmeyer M, Mer G, Chowdhury D (2021) TIRR inhibits the 53BP1-p53 complex to alter cell-fate programs. Mol Cell 81 (12):2583–2595 e2586. https://doi.org/10.1016/j.molcel.2021.03.039
43. Huang J, Dorsey J, Chuikov S, Zhang X, Jenuwein T, Reinberg D, Berger SL (2010) G9a and Glp methylate lysine 373 in the tumor suppressor p53. J Biol Chem 285(13):9636–9641. https://doi.org/10.1074/jbc.M109.062588
44. Li Y, Zhao L, Tian X, Peng C, Gong F, Chen Y (2020) Crystal Structure of MLL2 Complex Guides the Identification of a Methylation Site on P53 Catalyzed by KMT2 Family Methyltransferases. Structure 28 (10):1141–1148 e1144. https://doi.org/10.1016/j.str.2020.07.002
45. Jansson M, Durant ST, Cho EC, Sheahan S, Edelmann M, Kessler B, La Thangue NB (2008) Arginine methylation regulates the p53 response. Nat Cell Biol 10(12):1431–1439. https://doi.org/10.1038/ncb1802
46. Munro S, Carr SM, La Thangue NB (2012) Diversity within the pRb pathway: is there a code of conduct? Oncogene 31(40):4343–4352. https://doi.org/10.1038/onc.2011.603
47. Putzer BM, Engelmann D (2013) E2F1 apoptosis counterattacked: evil strikes back. Trends Mol Med 19(2):89–98. https://doi.org/10.1016/j.molmed.2012.10.009
48. Kontaki H, Talianidis I (2010) Lysine methylation regulates E2F1-induced cell death. Mol Cell 39(1):152–160. https://doi.org/10.1016/j.molcel.2010.06.006
49. Xie Q, Bai Y, Wu J, Sun Y, Wang Y, Zhang Y, Mei P, Yuan Z (2011) Methylation-mediated regulation of E2F1 in DNA damage-induced cell death. J Recept Signal Transduct Res 31(2):139–146. https://doi.org/10.3109/10799893.2011.552914
50. Montenegro MF, Sanchez-Del-Campo L, Gonzalez-Guerrero R, Martinez-Barba E, Pinero-Madrona A, Cabezas-Herrera J, Rodriguez-Lopez JN (2016) Tumor suppressor SET9 guides the epigenetic plasticity of breast cancer cells and serves as an early-stage biomarker for predicting metastasis. Oncogene 35(47):6143–6152. https://doi.org/10.1038/onc.2016.154
51. Kublanovsky M, Ulu GT, Weirich S, Levy N, Feldman M, Jeltsch A, Levy D (2023) Methylation of the transcription factor E2F1 by SETD6 regulates SETD6 expression via a positive feedback mechanism. J Biol Chem 299(10):105236. https://doi.org/10.1016/j.jbc.2023.105236
52. Cho EC, Zheng S, Munro S, Liu G, Carr SM, Moehlenbrink J, Lu YC, Stimson L, Khan O, Konietzny R, McGouran J, Coutts AS, Kessler B, Kerr DJ, Thangue NB (2012) Arginine methylation controls growth regulation by E2F–1. EMBO J 31(7):1785–1797. https://doi.org/10.1038/emboj.2012.17
53. Zheng S, Moehlenbrink J, Lu YC, Zalmas LP, Sagum CA, Carr S, McGouran JF, Alexander L, Fedorov O, Munro S, Kessler B, Bedford MT, Yu Q, La Thangue NB (2013) Arginine methylation-dependent reader-writer interplay governs growth control by E2F–1. Mol Cell 52(1):37–51. https://doi.org/10.1016/j.molcel.2013.08.039
54. Subramanian K, Jia D, Kapoor-Vazirani P, Powell DR, Collins RE, Sharma D, Peng J, Cheng X, Vertino PM (2008) Regulation of estrogen receptor alpha by the SET7 lysine methyltransferase. Mol Cell 30(3):336–347. https://doi.org/10.1016/j.molcel.2008.03.022
55. Dhayalan A, Kudithipudi S, Rathert P, Jeltsch A (2011) Specificity analysis-based identification of new methylation targets of the SET7/9 protein lysine methyltransferase. Chem Biol 18(1):111–120. https://doi.org/10.1016/j.chembiol.2010.11.014
56. Wang C, Fu M, Angeletti RH, Siconolfi-Baez L, Reutens AT, Albanese C, Lisanti MP, Katzenellenbogen BS, Kato S, Hopp T, Fuqua SA, Lopez GN, Kushner PJ, Pestell RG (2001) Direct acetylation of the estrogen receptor alpha hinge region by p300 regulates transactivation and hormone sensitivity. J Biol Chem 276(21):18375–18383. https://doi.org/10.1074/jbc.M100800200
57. Zhang X, Tanaka K, Yan J, Li J, Peng D, Jiang Y, Yang Z, Barton MC, Wen H, Shi X (2013) Regulation of estrogen receptor alpha by histone methyltransferase SMYD2-mediated protein methylation. Proc Natl Acad Sci U S A 110(43):17284–17289. https://doi.org/10.1073/pnas.1307959110
58. Obermann WMJ (2018) A motif in HSP90 and P23 that links molecular chaperones to efficient estrogen receptor alpha methylation by the lysine methyltransferase SMYD2. J Biol Chem 293(42):16479–16487. https://doi.org/10.1074/jbc.RA118.003578
59. Kim MY, Woo EM, Chong YT, Homenko DR, Kraus WL (2006) Acetylation of estrogen receptor alpha by p300 at lysines 266 and 268 enhances the deoxyribonucleic acid binding and transactivation activities of the receptor. Mol Endocrinol 20(7):1479–1493. https://doi.org/10.1210/me.2005-0531
60. Le Romancer M, Treilleux I, Leconte N, Robin-Lespinasse Y, Sentis S, Bouchekioua-Bouzaghou K, Goddard S, Gobert-Gosse S, Corbo L (2008) Regulation of estrogen rapid signaling through arginine methylation by PRMT1. Mol Cell 31(2):212–221. https://doi.org/10.1016/j.molcel.2008.05.025
61. Huq MD, Tsai NP, Khan SA, Wei LN (2007) Lysine trimethylation of retinoic acid receptor-alpha: a novel means to regulate receptor function. Mol Cell Proteom 6(4):677–688. https://doi.org/10.1074/mcp.M600223-MCP200
62. Huq MD, Ha SG, Wei LN (2008) Modulation of retinoic acid receptor alpha activity by lysine methylation in the DNA binding domain. J Proteome Res 7(10):4538–4545. https://doi.org/10.1021/pr800375z
63. Lee JM, Lee JS, Kim H, Kim K, Park H, Kim JY, Lee SH, Kim IS, Kim J, Lee M, Chung CH, Seo SB, Yoon JB, Ko E, Noh DY, Kim KI, Kim KK, Baek SH (2012) EZH2 generates a methyl degron that is recognized by the DCAF1/DDB1/CUL4 E3 ubiquitin ligase complex. Mol Cell 48(4):572–586. https://doi.org/10.1016/j.molcel.2012.09.004
64. Im H, Baek HJ, Yang E, Kim K, Oh SK, Lee JS, Kim H, Lee JM (2023) ROS inhibits RORalpha degradation by decreasing its arginine methylation in liver cancer. Cancer Sci 114(1):187–200. https://doi.org/10.1111/cas.15595
65. Chung HH, Sze SK, Woo AR, Sun Y, Sim KH, Dong XM, Lin VC (2014) Lysine methylation of progesterone receptor at activation function 1 regulates both ligand-independent activity and ligand sensitivity of the receptor. J Biol Chem 289(9):5704–5722. https://doi.org/10.1074/jbc.M113.522839
66 Malbeteau L, Poulard C, Languilaire C, Mikaelian I, Flamant F, Le Romancer M, Corbo L (2020) PRMT1 is critical for the transcriptional activity and the stability of the progesterone receptor. iScience 23(6):101236. https://doi.org/10.1016/j.isci.2020.101236

67. Ko S, Ahn J, Song CS, Kim S, Knapczyk-Stwora K, Chatterjee B (2011) Lysine methylation and functional modulation of androgen receptor by Set9 methyltransferase. Mol Endocrinol 25(3):433–444. https://doi.org/10.1210/me.2010-0482
68. Gaughan L, Stockley J, Wang N, McCracken SR, Treumann A, Armstrong K, Shaheen F, Watt K, McEwan IJ, Wang C, Pestell RG, Robson CN (2011) Regulation of the androgen receptor by SET9-mediated methylation. Nucl Acids Res 39(4):1266–1279. https://doi.org/10.1093/nar/gkq861
69. Li J, Hong Z, Zhang J, Zheng S, Wan F, Liu Z, Dai B (2024) Lysine methyltransferase SMYD2 enhances androgen receptor signaling to modulate CRPC cell resistance to enzalutamide. Oncogene 43(10):744–757. https://doi.org/10.1038/s41388-024-02945-1
70. Mounir Z, Korn JM, Westerling T, Lin F, Kirby CA, Schirle M, McAllister G, Hoffman G, Ramadan N, Hartung A, Feng Y, Kipp DR, Quinn C, Fodor M, Baird J, Schoumacher M, Meyer R, Deeds J, Buchwalter G, Stams T, Keen N, Sellers WR, Brown M, Pagliarini RA (2016) ERG signaling in prostate cancer is driven through PRMT5-dependent methylation of the Androgen Receptor. Elife. https://doi.org/10.7554/eLife.13964
71. Zinatizadeh MR, Schock B, Chalbatani GM, Zarandi PK, Jalali SA, Miri SR (2021) The nuclear factor kappa B (NF-kB) signaling in cancer development and immune diseases. Gen Dis 8(3):287–297. https://doi.org/10.1016/j.gendis.2020.06.005
72. Ea CK, Baltimore D (2009) Regulation of NF-kappaB activity through lysine monomethylation of p65. Proc Natl Acad Sci USA 106(45):18972–18977. https://doi.org/10.1073/pnas.0910439106
73. Lu T, Yang M, Huang DB, Wei H, Ozer GH, Ghosh G, Stark GR (2013) Role of lysine methylation of NF-kappaB in differential gene regulation. Proc Natl Acad Sci USA 110(33):13510–13515. https://doi.org/10.1073/pnas.1311770110
74. Yang XD, Huang B, Li M, Lamb A, Kelleher NL, Chen LF (2009) Negative regulation of NF-kappaB action by Set9-mediated lysine methylation of the RelA subunit. EMBO J 28(8):1055–1066. https://doi.org/10.1038/emboj.2009.55
75. Yang XD, Tajkhorshid E, Chen LF (2010) Functional interplay between acetylation and methylation of the RelA subunit of NF-kappaB. Mol Cell Biol 30(9):2170–2180. https://doi.org/10.1128/MCB.01343-09
76. Levy D, Kuo AJ, Chang Y, Schaefer U, Kitson C, Cheung P, Espejo A, Zee BM, Liu CL, Tangsombatvisit S, Tennen RI, Kuo AY, Tanjing S, Cheung R, Chua KF, Utz PJ, Shi X, Prinjha RK, Lee K, Garcia BA, Bedford MT, Tarakhovsky A, Cheng X, Gozani O (2011) Lysine methylation of the NF-kappaB subunit RelA by SETD6 couples activity of the histone methyltransferase GLP at chromatin to tonic repression of NF-kappaB signaling. Nat Immunol 12(1):29–36. https://doi.org/10.1038/ni.1968
77. Chang Y, Levy D, Horton JR, Peng J, Zhang X, Gozani O, Cheng X (2011) Structural basis of SETD6-mediated regulation of the NF-kB network via methyl-lysine signaling. Nucl Acids Res 39(15):6380–6389. https://doi.org/10.1093/nar/gkr256
78. Lu T, Jackson MW, Wang B, Yang M, Chance MR, Miyagi M, Gudkov AV, Stark GR (2010) Regulation of NF-kappaB by NSD1/FBXL11-dependent reversible lysine methylation of p65. Proc Natl Acad Sci USA 107(1):46–51. https://doi.org/10.1073/pnas.0912493107
79. Wei H, Wang B, Miyagi M, She Y, Gopalan B, Huang DB, Ghosh G, Stark GR, Lu T (2013) PRMT5 dimethylates R30 of the p65 subunit to activate NF-kappaB. Proc Natl Acad Sci USA 110(33):13516–13521. https://doi.org/10.1073/pnas.1311784110
80. Reintjes A, Fuchs JE, Kremser L, Lindner HH, Liedl KR, Huber LA, Valovka T (2016) Asymmetric arginine dimethylation of RelA provides a repressive mark to modulate TNFalpha/NF-kappaB response. Proc Natl Acad Sci USA 113(16):4326–4331. https://doi.org/10.1073/pnas.1522372113
81. Harris DP, Bandyopadhyay S, Maxwell TJ, Willard B, DiCorleto PE (2014) Tumor necrosis factor (TNF)-alpha induction of CXCL10 in endothelial cells requires protein arginine methyltransferase 5 (PRMT5)-mediated nuclear factor (NF)-kappaB p65 methylation. J Biol Chem 289(22):15328–15339. https://doi.org/10.1074/jbc.M114.547349
82. Harris DP, Chandrasekharan UM, Bandyopadhyay S, Willard B, DiCorleto PE (2016) PRMT5-mediated methylation of NF-kappaB p65 at Arg174 is required for endothelial CXCL11 gene induction in response to TNF-alpha and IFN-gamma costimulation. PLoS One 11(2):e0148905. https://doi.org/10.1371/journal.pone.0148905
83. Niu H, Xiao J, Ma Z, Chen L (2020) Prmt4-mediated methylation of NF-kappaB is critical for neural differentiation of embryonic stem cells. Biochem Biophys Res Commun. https://doi.org/10.1016/j.bbrc.2020.02.072
84 Ma Z, Zhou F, Jin H, Wu X (2024) Crosstalk between CXCL12/CXCR4/ACKR3 and the STAT3 Pathway. Cells. https://doi.org/10.3390/cells13121027
85. Yang J, Huang J, Dasgupta M, Sears N, Miyagi M, Wang B, Chance MR, Chen X, Du Y, Wang Y, An L, Wang Q, Lu T, Zhang X, Wang Z, Stark GR (2010) Reversible methylation of promoter-bound STAT3 by histone-modifying enzymes. Proc Natl Acad Sci USA 107(50):21499–21504. https://doi.org/10.1073/pnas.1016147107
86. Yin Y, Yang X, Wu S, Ding X, Zhu H, Long X, Wang Y, Zhai S, Chen Y, Che N, Chen J, Wang X (2022) Jmjd1c demethylates STAT3 to restrain plasma cell differentiation and rheumatoid arthritis. Nat Immunol 23(9):1342–1354. https://doi.org/10.1038/s41590-022-01287-y
87. Long X, Zhang S, Wang Y, Chen J, Lu Y, Hou H, Lin B, Li X, Shen C, Yang R, Zhu H, Cui R, Cao D, Chen G, Wang D, Chen Y, Zhai S, Zeng Z, Wu S, Lou M, Chen J, Zou J, Zheng M, Qin J, Wang X (2024) Targeting JMJD1C to selectively disrupt tumor T(reg) cell fitness enhances antitumor immunity. Nat Immunol 25(3):525–536. https://doi.org/10.1038/s41590-024-01746-8
88. Dasgupta M, Dermawan JK, Willard B, Stark GR (2015) STAT3-driven transcription depends upon the dimethylation of K49 by EZH2. Proc Natl Acad Sci USA 112(13):3985–3990. https://doi.org/10.1073/pnas.1503152112
89. Kim E, Kim M, Woo DH, Shin Y, Shin J, Chang N, Oh YT, Kim H, Rheey J, Nakano I, Lee C, Joo KM, Rich JN, Nam DH, Lee J (2013) Phosphorylation of EZH2 activates STAT3 signaling via STAT3 methylation and promotes tumorigenicity of glioblastoma stem-like cells. Cancer Cell 23(6):839–852. https://doi.org/10.1016/j.ccr.2013.04.008
90. Chen Q, Hu Q, Chen Y, Shen N, Zhang N, Li A, Li L, Li J (2023) PRMT6 methylation of STAT3 regulates tumor metastasis in breast cancer. Cell Death Dis 14(10):655. https://doi.org/10.1038/s41419-023-06148-6
91. Iwasaki H, Kovacic JC, Olive M, Beers JK, Yoshimoto T, Crook MF, Tonelli LH, Nabel EG (2010) Disruption of protein arginine *N*-methyltransferase 2 regulates leptin signaling and produces leanness in vivo through loss of STAT3 methylation. Circ Res 107(8):992–1001. https://doi.org/10.1161/CIRCRESAHA.110.225326
92. Yang M, Zhang Y, Liu G, Zhao Z, Li J, Yang L, Liu K, Hu W, Lou Y, Jiang J, Liu Q, Zhao P (2022) TIPE1 inhibits osteosarcoma tumorigenesis and progression by regulating PRMT1 mediated STAT3 arginine methylation. Cell Death Dis 13(9):815. https://doi.org/10.1038/s41419-022-05273-y
93. Zhang WJ, Wu XN, Shi TT, Xu HT, Yi J, Shen HF, Huang MF, Shu XY, Wang FF, Peng BL, Xiao RQ, Gao WW, Ding JC, Liu W (2016) Regulation of transcription factor yin yang 1 by

SET7/9-mediated lysine methylation. Sci Rep 6:21718. https://doi.org/10.1038/srep21718
94. Wu XN, Li JY, He Q, Li BQ, He YH, Pan X, Wang MY, Sang R, Ding JC, Gao X, Wu Z, Liu W (2024) Targeting the PHF8/YY1 axis suppresses cancer cell growth through modulation of ROS. Proc Natl Acad Sci USA 121(2):e2219352120. https://doi.org/10.1073/pnas.2219352120
95. Wu XN, Shi TT, He YH, Wang FF, Sang R, Ding JC, Zhang WJ, Shu XY, Shen HF, Yi J, Gao X, Liu W (2017) Methylation of transcription factor YY2 regulates its transcriptional activity and cell proliferation. Cell Discov 3:17035. https://doi.org/10.1038/celldisc.2017.35
96. Collins A, Littman DR, Taniuchi I (2009) RUNX proteins in transcription factor networks that regulate T-cell lineage choice. Nat Rev Immunol 9(2):106–115. https://doi.org/10.1038/nri2489
97. Lee SH, Hyeon DY, Yoon SH, Jeong JH, Han SM, Jang JW, Nguyen MP, Chi XZ, An S, Hyun KG, Jung HJ, Song JJ, Bae SC, Kim WH, Hwang D, Lee YM (2021) RUNX3 methylation drives hypoxia-induced cell proliferation and antiapoptosis in early tumorigenesis. Cell Death Differ 28(4):1251–1269. https://doi.org/10.1038/s41418-020-00647-1
98. Zhao X, Jankovic V, Gural A, Huang G, Pardanani A, Menendez S, Zhang J, Dunne R, Xiao A, Erdjument-Bromage H, Allis CD, Tempst P, Nimer SD (2008) Methylation of RUNX1 by PRMT1 abrogates SIN3A binding and potentiates its transcriptional activity. Genes Dev 22(5):640–653. https://doi.org/10.1101/gad.1632608
99. Mizutani S, Yoshida T, Zhao X, Nimer SD, Taniwaki M, Okuda T (2015) Loss of RUNX1/AML1 arginine-methylation impairs peripheral T cell homeostasis. Br J Haematol 170(6):859–873. https://doi.org/10.1111/bjh.13499
100. Matsumura T, Nakamura-Ishizu A, Muddineni S, Tan DQ, Wang CQ, Tokunaga K, Tirado-Magallanes R, Sian S, Benoukraf T, Okuda T, Asou N, Matsuoka M, Osato M, Suda T (2020) Hematopoietic stem cells acquire survival advantage by loss of RUNX1 methylation identified in familial leukemia. Blood 136(17):1919–1932. https://doi.org/10.1182/blood.2019004292
101. Shia WJ, Okumura AJ, Yan M, Sarkeshik A, Lo MC, Matsuura S, Komeno Y, Zhao X, Nimer SD, Yates JR 3rd, Zhang DE (2012) PRMT1 interacts with AML1-ETO to promote its transcriptional activation and progenitor cell proliferative potential. Blood 119(21):4953–4962. https://doi.org/10.1182/blood-2011-04-347476
102. Dan S, Song Y, Duan X, Pan X, Chen C, She S, Su T, Li J, Chen X, Zhou Y, Chen W, Zhang X, Pan X, Wang YJ, Kang B (2021) LSD1-mediated demethylation of OCT4 safeguards pluripotent stem cells by maintaining the transcription of PORE-motif-containing genes. Sci Rep 11(1):10285. https://doi.org/10.1038/s41598-021-89734-y
103. Fang L, Zhang L, Wei W, Jin X, Wang P, Tong Y, Li J, Du JX, Wong J (2014) A methylation-phosphorylation switch determines Sox2 stability and function in ESC maintenance or differentiation. Mol Cell 55(4):537–551. https://doi.org/10.1016/j.molcel.2014.06.018
104. Zhang C, Hoang N, Leng F, Saxena L, Lee L, Alejo S, Qi D, Khal A, Sun H, Lu F, Zhang H (2018) LSD1 demethylase and the methyl-binding protein PHF20L1 prevent SET7 methyltransferase-dependent proteolysis of the stem-cell protein SOX2. J Biol Chem 293(10):3663–3674. https://doi.org/10.1074/jbc.RA117.000342
105. Zhao HY, Zhang YJ, Dai H, Zhang Y, Shen YF (2011) CARM1 mediates modulation of Sox2. PLoS ONE 6(10):e27026. https://doi.org/10.1371/journal.pone.0027026
106. Zhang P, Lu R (2024) The molecular and biological function of MEF2D in leukemia. Adv Exp Med Biol 1459:379–403. https://doi.org/10.1007/978-3-031-62731-6_17
107. Choi J, Jang H, Kim H, Lee JH, Kim ST, Cho EJ, Youn HD (2014) Modulation of lysine methylation in myocyte enhancer factor 2 during skeletal muscle cell differentiation. Nucl Acids Res 42(1):224–234. https://doi.org/10.1093/nar/gkt873
108. Lemos T, Merchant A (2022) The hedgehog pathway in hematopoiesis and hematological malignancy. Front Oncol 12:960943. https://doi.org/10.3389/fonc.2022.960943
109. Fu L, Wu H, Cheng SY, Gao D, Zhang L, Zhao Y (2016) Set7 mediated Gli3 methylation plays a positive role in the activation of Sonic Hedgehog pathway in mammals. Elife. https://doi.org/10.7554/eLife.15690
110. Wang Y, Hsu JM, Kang Y, Wei Y, Lee PC, Chang SJ, Hsu YH, Hsu JL, Wang HL, Chang WC, Li CW, Liao HW, Chang SS, Xia W, Ko HW, Chou CK, Fleming JB, Wang H, Hwang RF, Chen Y, Qin J, Hung MC (2016) Oncogenic functions of Gli1 in pancreatic adenocarcinoma are supported by Its PRMT1-mediated methylation. Cancer Res 76(23):7049–7058. https://doi.org/10.1158/0008-5472.CAN-16-0715
111. Abe Y, Suzuki Y, Kawamura K, Tanaka N (2019) MEP50/PRMT5-mediated methylation activates GLI1 in Hedgehog signalling through inhibition of ubiquitination by the ITCH/NUMB complex. Commun Biol 2:23. https://doi.org/10.1038/s42003-018-0275-4
112. Esteve PO, Chin HG, Benner J, Feehery GR, Samaranayake M, Horwitz GA, Jacobsen SE, Pradhan S (2009) Regulation of DNMT1 stability through SET7-mediated lysine methylation in mammalian cells. Proc Natl Acad Sci USA 106(13):5076–5081. https://doi.org/10.1073/pnas.0810362106
113. Esteve PO, Chang Y, Samaranayake M, Upadhyay AK, Horton JR, Feehery GR, Cheng X, Pradhan S (2011) A methylation and phosphorylation switch between an adjacent lysine and serine determines human DNMT1 stability. Nat Struct Mol Biol 18(1):42–48. https://doi.org/10.1038/nsmb.1939
114. Wang J, Hevi S, Kurash JK, Lei H, Gay F, Bajko J, Su H, Sun W, Chang H, Xu G, Gaudet F, Li E, Chen T (2009) The lysine demethylase LSD1 (KDM1) is required for maintenance of global DNA methylation. Nat Genet 41(1):125–129. https://doi.org/10.1038/ng.268
115. Chang Y, Sun L, Kokura K, Horton JR, Fukuda M, Espejo A, Izumi V, Koomen JM, Bedford MT, Zhang X, Shinkai Y, Fang J, Cheng X (2011) MPP8 mediates the interactions between DNA methyltransferase Dnmt3a and H3K9 methyltransferase GLP/G9a. Nat Commun 2:533. https://doi.org/10.1038/ncomms1549
116. Tan CP, Nakielny S (2006) Control of the DNA methylation system component MBD2 by protein arginine methylation. Mol Cell Biol 26(19):7224–7235. https://doi.org/10.1128/MCB.00473-06
117. Rugo HS, Jacobs I, Sharma S, Scappaticci F, Paul TA, Jensen-Pergakes K, Malouf GG (2020) The promise for histone methyltransferase inhibitors for epigenetic therapy in clinical oncology: a narrative review. Adv Ther 37(7):3059–3082. https://doi.org/10.1007/s12325-020-01379-x
118. Knutson SK, Kawano S, Minoshima Y, Warholic NM, Huang KC, Xiao Y, Kadowaki T, Uesugi M, Kuznetsov G, Kumar N, Wigle TJ, Klaus CR, Allain CJ, Raimondi A, Waters NJ, Smith JJ, Porter-Scott M, Chesworth R, Moyer MP, Copeland RA, Richon VM, Uenaka T, Pollock RM, Kuntz KW, Yokoi A, Keilhack H (2014) Selective inhibition of EZH2 by EPZ-6438 leads to potent antitumor activity in EZH2-mutant non-Hodgkin lymphoma. Mol Cancer Ther 13(4):842–854. https://doi.org/10.1158/1535-7163.MCT-13-0773
119. Knutson SK, Warholic NM, Wigle TJ, Klaus CR, Allain CJ, Raimondi A, Porter Scott M, Chesworth R, Moyer MP, Copeland RA, Richon VM, Pollock RM, Kuntz KW, Keilhack H (2013) Durable tumor regression in genetically altered malignant rhabdoid tumors by inhibition of methyltransferase EZH2. Proc Natl Acad Sci USA 110(19):7922–7927. https://doi.org/10.1073/pnas.1303800110

120. Kawano S, Grassian AR, Tsuda M, Knutson SK, Warholic NM, Kuznetsov G, Xu S, Xiao Y, Pollock RM, Smith JS, Kuntz KK, Ribich S, Minoshima Y, Matsui J, Copeland RA, Tanaka S, Keilhack H (2016) Preclinical evidence of anti-tumor activity induced by ezh2 inhibition in human models of synovial sarcoma. PLoS One 11(7):e0158888. https://doi.org/10.1371/journal.pone.0158888
121. Zauderer MG, Szlosarek PW, Le Moulec S, Popat S, Taylor P, Planchard D, Scherpereel A, Koczywas M, Forster M, Cameron RB, Peikert T, Argon EK, Michaud NR, Szanto A, Yang J, Chen Y, Kansra V, Agarwal S, Fennell DA (2022) EZH2 inhibitor tazemetostat in patients with relapsed or refractory, BAP1-inactivated malignant pleural mesothelioma: a multicentre, open-label, phase 2 study. Lancet Oncol 23(6):758–767. https://doi.org/10.1016/S1470-2045(22)00277-7
122. Izutsu K, Ando K, Nishikori M, Shibayama H, Goto H, Kuroda J, Kato K, Imaizumi Y, Nosaka K, Sakai R, Abe M, Hojo S, Nakanishi T, Rai S (2024) Tazemetostat for relapsed/refractory B-cell non-Hodgkin lymphoma with EZH2 mutation in Japan: 3-year follow-up for a phase II study. Int J Hematol 120(5):621–630. https://doi.org/10.1007/s12185-024-03834-9
123. Morschhauser F, Tilly H, Chaidos A, Phillips T, Ribrag V, Campbell P, Ghandi Laurent D, Jurczak W, McKay P, Opat S, Radford J, Rajarethinam A, Yang J, Howell H, Newberry KJ, Adib D, Salles G (2019) Interim update from a phase 2 multicenter study of tazemetostat, an EZH2 inhibitor, in patients with relapsed or refractory follicular lymphoma. Hematol Oncol 37:154–156. https://doi.org/10.1002/hon.111_2629
124. Ribrag V, Morschhauser F, McKay P, Salles GA, Batlevi CL, Schmitt A, Tilly H, Cartron G, Thieblemont C, Fruchart C, Gribben JG, Lamy T, Le Gouill S, Bouabdallah R, Dickinson M, Opat S, Adib D, Blakemore SJ, Larus J, Johnson P (2018) Interim results from an ongoing phase 2 multicenter study of tazemetostat, an EZH2 inhibitor, in patients with relapsed or refractory (R/R) diffuse large B-Cell lymphoma (DLBCL). Blood 132:4196
125. Italiano A, Soria JC, Toulmonde M, Michot JM, Lucchesi C, Varga A, Coindre JM, Blakemore SJ, Clawson A, Suttle B, McDonald AA, Woodruff M, Ribich S, Hedrick E, Keilhack H, Thomson B, Owa T, Copeland RA, Ho PTC, Ribrag V (2018) Tazemetostat, an EZH2 inhibitor, in relapsed or refractory B-cell non-Hodgkin lymphoma and advanced solid tumours: a first-in-human, open-label, phase 1 study. Lancet Oncol 19(5):649–659. https://doi.org/10.1016/S1470-2045(18)30145-1
126. Stein EM, Garcia-Manero G, Rizzieri DA, Tibes R, Berdeja JG, Savona MR, Jongen-Lavrenic M, Altman JK, Thomson B, Blakemore SJ, Daigle SR, Waters NJ, Suttle AB, Clawson A, Pollock R, Krivtsov A, Armstrong SA, DiMartino J, Hedrick E, Lowenberg B, Tallman MS (2018) The DOT1L inhibitor pinometostat reduces H3K79 methylation and has modest clinical activity in adult acute leukemia. Blood 131(24):2661–2669. https://doi.org/10.1182/blood-2017-12-818948
127. Shukla NWC, O'Brien MM, Silverman LB, Brown P, Cooper TM, Thomson B, Blakemore SJ, Daigle S, Suttle B, Waters NJ, Krivstov AV, Armstrong SA, Ho PT, Gore L (2016) Final report of phase 1 study of the DOT1L inhibitor, pinometostat (EPZ-5676), in children with relapsed or refractory MLL-r acute leukemia. Blood 128(22):2780
128. Salamero O, Molero A, Perez-Simon JA, Arnan M, Coll R, Garcia-Avila S, Acuna-Cruz E, Cano I, Somervaille TCP, Gutierrez S, Arevalo MI, Xaus J, Buesa C, Limon A, Faller DV, Bosch F, Montesinos P (2024) Iadademstat in combination with azacitidine in patients with newly diagnosed acute myeloid leukaemia (ALICE): an open-label, phase 2a dose-finding study. Lancet Haematol 11(7):e487–e498. https://doi.org/10.1016/S2352-3026(24)00132-7
129. Yin W, Arkilo D, Khudyakov P, Hazel J, Gupta S, Quinton MS, Lin J, Hartman DS, Bednar MM, Rosen L, Wendland JR (2021) Safety, pharmacokinetics and pharmacodynamics of TAK-418, a novel inhibitor of the epigenetic modulator lysine-specific demethylase 1A. Br J Clin Pharmacol 87(12):4756–4768. https://doi.org/10.1111/bcp.14912
130. Zhu Y, Fu J, Yang H, Pan Y, Yao L, Xue X (2015) Hyperoxia-induced methylation decreases RUNX3 in a newborn rat model of bronchopulmonary dysplasia. Respir Res 16(1):75. https://doi.org/10.1186/s12931-015-0239-x
131. Berryhill CA, Hanquier JN, Doud EH, Cordeiro-Spinetti E, Dickson BM, Rothbart SB, Mosley AL, Cornett EM (2023) Global lysine methylome profiling using systematically characterized affinity reagents. Sci Rep 13(1):377. https://doi.org/10.1038/s41598-022-27175-x
132. Carlson SM, Gozani O (2014) Emerging technologies to map the protein methylome. J Mol Biol 426(20):3350–3362. https://doi.org/10.1016/j.jmb.2014.04.024
133. Li WJ, He YH, Yang JJ, Hu GS, Lin YA, Ran T, Peng BL, Xie BL, Huang MF, Gao X, Huang HH, Zhu HH, Ye F, Liu W (2021) Profiling PRMT methylome reveals roles of hnRNPA1 arginine methylation in RNA splicing and cell growth. Nat Commun 12(1):1946. https://doi.org/10.1038/s41467-021-21963-1
134. Lu C, Yang D, Klement JD, Oh IK, Savage NM, Waller JL, Colby AH, Grinstaff MW, Oberlies NH, Pearce CJ, Xie Z, Kulp SK, Coss CC, Phelps MA, Albers T, Lebedyeva IO, Liu K (2019) SUV39H1 represses the expression of cytotoxic T-lymphocyte effector genes to promote colon tumor immune evasion. Cancer Immunol Res 7(3):414–427. https://doi.org/10.1158/2326-6066.CIR-18-0126
135. Vougiouklakis T, Saloura V, Park JH, Takamatsu N, Miyamoto T, Nakamura Y, Matsuo Y (2018) Development of novel SUV39H2 inhibitors that exhibit growth suppressive effects in mouse xenograft models and regulate the phosphorylation of H2AX. Oncotarget 9(61):31820–31831. https://doi.org/10.18632/oncotarget.25806
136. Kubicek S, O'Sullivan RJ, August EM, Hickey ER, Zhang Q, Teodoro ML, Rea S, Mechtler K, Kowalski JA, Homon CA, Kelly TA, Jenuwein T (2007) Reversal of H3K9me2 by a small-molecule inhibitor for the G9a histone methyltransferase. Mol Cell 25(3):473–481. https://doi.org/10.1016/j.molcel.2007.01.017
137. Chang Y, Zhang X, Horton JR, Upadhyay AK, Spannhoff A, Liu J, Snyder JP, Bedford MT, Cheng X (2009) Structural basis for G9a-like protein lysine methyltransferase inhibition by BIX-01294. Nat Struct Mol Biol 16(3):312–317. https://doi.org/10.1038/nsmb.1560
138. Liu F, Chen X, Allali-Hassani A, Quinn AM, Wasney GA, Dong A, Barsyte D, Kozieradzki I, Senisterra G, Chau I, Siarheyeva A, Kireev DB, Jadhav A, Herold JM, Frye SV, Arrowsmith CH, Brown PJ, Simeonov A, Vedadi M, Jin J (2009) Discovery of a 2,4-diamino-7-aminoalkoxyquinazoline as a potent and selective inhibitor of histone lysine methyltransferase G9a. J Med Chem 52(24):7950–7953. https://doi.org/10.1021/jm901543m
139. Pless O, Kowenz-Leutz E, Knoblich M, Lausen J, Beyermann M, Walsh MJ, Leutz A (2008) G9a-mediated lysine methylation alters the function of CCAAT/enhancer-binding protein-beta. J Biol Chem 283(39):26357–26363. https://doi.org/10.1074/jbc.M802132200
140. Ling BM, Bharathy N, Chung TK, Kok WK, Li S, Tan YH, Rao VK, Gopinadhan S, Sartorelli V, Walsh MJ, Taneja R (2012) Lysine methyltransferase G9a methylates the transcription factor MyoD and regulates skeletal muscle differentiation. Proc Natl Acad Sci USA 109(3):841–846. https://doi.org/10.1073/pnas.1111628109
141. Vedadi M, Barsyte-Lovejoy D, Liu F, Rival-Gervier S, Allali-Hassani A, Labrie V, Wigle TJ, Dimaggio PA, Wasney GA, Siarheyeva A, Dong A, Tempel W, Wang SC, Chen X, Chau I, Mangano TJ, Huang XP, Simpson CD, Pattenden SG, Norris JL,

Kireev DB, Tripathy A, Edwards A, Roth BL, Janzen WP, Garcia BA, Petronis A, Ellis J, Brown PJ, Frye SV, Arrowsmith CH, Jin J (2011) A chemical probe selectively inhibits G9a and GLP methyltransferase activity in cells. Nat Chem Biol 7(8):566–574. https://doi.org/10.1038/nchembio.599

142. Uguen M, Deng Y, Li F, Shell DJ, Norris-Drouin JL, Stashko MA, Ackloo S, Arrowsmith CH, James LI, Liu P, Pearce KH, Frye SV (2023) SETDB1 triple tudor domain ligand, (R, R)-59, promotes methylation of Akt1 in cells. ACS Chem Biol 18(8):1846–1853. https://doi.org/10.1021/acschembio.3c00280
143. Cao F, Townsend EC, Karatas H, Xu J, Li L, Lee S, Liu L, Chen Y, Ouillette P, Zhu J, Hess JL, Atadja P, Lei M, Qin ZS, Malek S, Wang S, Dou Y (2014) Targeting MLL1 H3K4 methyltransferase activity in mixed-lineage leukemia. Mol Cell 53(2):247–261. https://doi.org/10.1016/j.molcel.2013.12.001
144. Alicea-Velazquez NL, Shinsky SA, Loh DM, Lee JH, Skalnik DG, Cosgrove MS (2016) Targeted disruption of the interaction between WD-40 repeat protein 5 (WDR5) and mixed lineage leukemia (MLL)/SET1 family proteins specifically inhibits MLL1 and SETd1A methyltransferase complexes. J Biol Chem 291(43):22357–22372. https://doi.org/10.1074/jbc.M116.752626
145. Yu Q, Liao Z, Liu D, Xie W, Liu Z, Liao G, Wang C (2020) Small molecule inhibitors of the prostate cancer target KMT2D. Biochem Biophys Res Commun 533(3):540–547. https://doi.org/10.1016/j.bbrc.2020.09.004
146. Rogawski DS, Deng J, Li H, Miao H, Borkin D, Purohit T, Song J, Chase J, Li S, Ndoj J, Klossowski S, Kim E, Mao F, Zhou B, Ropa J, Krotoska MZ, Jin Z, Ernst P, Feng X, Huang G, Nishioka K, Kelly S, He M, Wen B, Sun D, Muntean A, Dou Y, Maillard I, Cierpicki T, Grembecka J (2021) Discovery of first-in-class inhibitors of ASH1L histone methyltransferase with anti-leukemic activity. Nat Commun 12(1):2792. https://doi.org/10.1038/s41467-021-23152-6
147. Alford JS, Lampe JW, Brach D, Chesworth R, Cosmopoulos K, Duncan KW, Eckley ST, Kutok JL, Raimondi A, Riera TV, Shook B, Tang C, Totman J, Farrow NA (2022) Conformational-design-driven discovery of EZM0414: a selective, potent SETD2 inhibitor for clinical studies. ACS Med Chem Lett 13(7):1137–1143. https://doi.org/10.1021/acsmedchemlett.2c00167
148. Lampe JW, Alford JS, Boriak-Sjodin PA, Brach D, Cosmopoulos K, Duncan KW, Eckley ST, Foley MA, Harvey DM, Motwani V, Munchhof MJ, Raimondi A, Riera TV, Tang C, Thomenius MJ, Totman J, Farrow NA (2021) Discovery of a first-in-class inhibitor of the histone methyltransferase SETD2 suitable for preclinical studies. ACS Med Chem Lett 12(10):1539–1545. https://doi.org/10.1021/acsmedchemlett.1c00272
149. Huang H, Howard CA, Zari S, Cho HJ, Shukla S, Li H, Ndoj J, Gonzalez-Alonso P, Nikolaidis C, Abbott J, Rogawski DS, Potopnyk MA, Kempinska K, Miao H, Purohit T, Henderson A, Mapp A, Sulis ML, Ferrando A, Grembecka J, Cierpicki T (2020) Covalent inhibition of NSD1 histone methyltransferase. Nat Chem Biol 16(12):1403–1410. https://doi.org/10.1038/s41589-020-0626-6
150. Nguyen H, Allali-Hassani A, Antonysamy S, Chang S, Chen LH, Curtis C, Emtage S, Fan L, Gheyi T, Li F, Liu S, Martin JR, Mendel D, Olsen JB, Pelletier L, Shatseva T, Wu S, Zhang FF, Arrowsmith CH, Brown PJ, Campbell RM, Garcia BA, Barsyte-Lovejoy D, Mader M, Vedadi M (2015) LLY-507, a cell-active, potent, and selective inhibitor of protein-lysine methyltransferase SMYD2. J Biol Chem 290(22):13641–13653. https://doi.org/10.1074/jbc.M114.626861
151. Ferguson AD, Larsen NA, Howard T, Pollard H, Green I, Grande C, Cheung T, Garcia-Arenas R, Cowen S, Wu J, Godin R, Chen H, Keen N (2011) Structural basis of substrate methylation and inhibition of SMYD2. Structure 19(9):1262–1273. https://doi.org/10.1016/j.str.2011.06.011
152. Eggert E, Hillig RC, Koehr S, Stockigt D, Weiske J, Barak N, Mowat J, Brumby T, Christ CD, Ter Laak A, Lang T, Fernandez-Montalvan AE, Badock V, Weinmann H, Hartung IV, Barsyte-Lovejoy D, Szewczyk M, Kennedy S, Li F, Vedadi M, Brown PJ, Santhakumar V, Arrowsmith CH, Stellfeld T, Stresemann C (2016) Discovery and characterization of a highly potent and selective aminopyrazoline-based in vivo probe (BAY-598) for the protein lysine methyltransferase SMYD2. J Med Chem 59(10):4578–4600. https://doi.org/10.1021/acs.jmedchem.5b01890
153. Peserico A, Germani A, Sanese P, Barbosa AJ, Di Virgilio V, Fittipaldi R, Fabini E, Bertucci C, Varchi G, Moyer MP, Caretti G, Del Rio A, Simone C (2015) A SMYD3 small-molecule inhibitor impairing cancer cell growth. J Cell Physiol 230(10):2447–2460. https://doi.org/10.1002/jcp.24975
154. Parenti MD, Naldi M, Manoni E, Fabini E, Cederfelt D, Talibov VO, Gressani V, Guven U, Grossi V, Fasano C, Sanese P, De Marco K, Shtil AA, Kurkin AV, Altieri A, Danielson UH, Caretti G, Simone C, Varchi G, Bartolini M, Del Rio A (2022) Discovery of the 4-aminopiperidine-based compound EM127 for the site-specific covalent inhibition of SMYD3. Eur J Med Chem 243:114683. https://doi.org/10.1016/j.ejmech.2022.114683
155. Mitchell LH, Boriack-Sjodin PA, Smith S, Thomenius M, Rioux N, Munchhof M, Mills JE, Klaus C, Totman J, Riera TV, Raimondi A, Jacques SL, West K, Foley M, Waters NJ, Kuntz KW, Wigle TJ, Scott MP, Copeland RA, Smith JJ, Chesworth R (2016) Novel oxindole sulfonamides and sulfamides: EPZ031686, the first orally bioavailable small molecule SMYD3 inhibitor. ACS Med Chem Lett 7(2):134–138. https://doi.org/10.1021/acsmedchemlett.5b00272
156. Bottcher J, Dilworth D, Reiser U, Neumuller RA, Schleicher M, Petronczki M, Zeeb M, Mischerikow N, Allali-Hassani A, Szewczyk MM, Li F, Kennedy S, Vedadi M, Barsyte-Lovejoy D, Brown PJ, Huber KVM, Rogers CM, Wells CI, Fedorov O, Rumpel K, Zoephel A, Mayer M, Wunberg T, Bose D, Zahn S, Arnhof H, Berger H, Reiser C, Hormann A, Krammer T, Corcokovic M, Sharps B, Winkler S, Haring D, Cockcroft XL, Fuchs JE, Mullauer B, Weiss-Puxbaum A, Gerstberger T, Boehmelt G, Vakoc CR, Arrowsmith CH, Pearson M, McConnell DB (2019) Fragment-based discovery of a chemical probe for the PWWP1 domain of NSD3. Nat Chem Biol 15(8):822–829. https://doi.org/10.1038/s41589-019-0310-x
157. Kim S, Hwang I, Kim SH, Chung HW, Ji MJ, Moon S, Park HM, Kong G, Hur W (2023) Identification of novel class inhibitors of NSD3 methyltransferase showing a unique, bivalent binding mode in the SET domain. Chem Biol Drug Des 102(3):500–513. https://doi.org/10.1111/cbdd.14249
158. Ferreira de Freitas R, Liu Y, Szewczyk MM, Mehta N, Li F, McLeod D, Zepeda-Velazquez C, Dilworth D, Hanley RP, Gibson E, Brown PJ, Al-Awar R, James LI, Arrowsmith CH, Barsyte-Lovejoy D, Min J, Vedadi M, Schapira M, Allali-Hassani A (2021) Discovery of small-molecule antagonists of the PWWP domain of NSD2. J Med Chem 64(3):1584–1592. https://doi.org/10.1021/acs.jmedchem.0c01768
159. Yu W, Chory EJ, Wernimont AK, Tempel W, Scopton A, Federation A, Marineau JJ, Qi J, Barsyte-Lovejoy D, Yi J, Marcellus R, Iacob RE, Engen JR, Griffin C, Aman A, Wienholds E, Li F, Pineda J, Estiu G, Shatseva T, Hajian T, Al-Awar R, Dick JE, Vedadi M, Brown PJ, Arrowsmith CH, Bradner JE, Schapira M (2012) Catalytic site remodelling of the DOT1L methyltransferase by selective inhibitors. Nat Commun 3:1288. https://doi.org/10.1038/ncomms2304
160. Daigle SR, Olhava EJ, Therkelsen CA, Basavapathruni A, Jin L, Boriack-Sjodin PA, Allain CJ, Klaus CR, Raimondi A, Scott MP, Waters NJ, Chesworth R, Moyer MP, Copeland RA, Richon VM, Pollock RM (2013) Potent inhibition of DOT1L as treatment of

MLL-fusion leukemia. Blood 122(6):1017–1025. https://doi.org/10.1182/blood-2013-04-497644
161. Daigle SR, Olhava EJ, Therkelsen CA, Majer CR, Sneeringer CJ, Song J, Johnston LD, Scott MP, Smith JJ, Xiao Y, Jin L, Kuntz KW, Chesworth R, Moyer MP, Bernt KM, Tseng JC, Kung AL, Armstrong SA, Copeland RA, Richon VM, Pollock RM (2011) Selective killing of mixed lineage leukemia cells by a potent small-molecule DOT1L inhibitor. Cancer Cell 20(1):53–65. https://doi.org/10.1016/j.ccr.2011.06.009
162. Ma A, Yu W, Li F, Bleich RM, Herold JM, Butler KV, Norris JL, Korboukh V, Tripathy A, Janzen WP, Arrowsmith CH, Frye SV, Vedadi M, Brown PJ, Jin J (2014) Discovery of a selective, substrate-competitive inhibitor of the lysine methyltransferase SETD8. J Med Chem 57(15):6822–6833. https://doi.org/10.1021/jm500871s
163. Blum G, Ibanez G, Rao X, Shum D, Radu C, Djaballah H, Rice JC, Luo M (2014) Small-molecule inhibitors of SETD8 with cellular activity. ACS Chem Biol 9(11):2471–2478. https://doi.org/10.1021/cb500515r
164. Bromberg KD, Mitchell TR, Upadhyay AK, Jakob CG, Jhala MA, Comess KM, Lasko LM, Li C, Tuzon CT, Dai Y, Li F, Eram MS, Nuber A, Soni NB, Manaves V, Algire MA, Sweis RF, Torrent M, Schotta G, Sun C, Michaelides MR, Shoemaker AR, Arrowsmith CH, Brown PJ, Santhakumar V, Martin A, Rice JC, Chiang GG, Vedadi M, Barsyte-Lovejoy D, Pappano WN (2017) The SUV4-20 inhibitor A-196 verifies a role for epigenetics in genomic integrity. Nat Chem Biol 13(3):317–324. https://doi.org/10.1038/nchembio.2282
165. Tan J, Yang X, Zhuang L, Jiang X, Chen W, Lee PL, Karuturi RK, Tan PB, Liu ET, Yu Q (2007) Pharmacologic disruption of Polycomb-repressive complex 2-mediated gene repression selectively induces apoptosis in cancer cells. Genes Dev 21(9):1050–1063. https://doi.org/10.1101/gad.1524107
166. McCabe MT, Ott HM, Ganji G, Korenchuk S, Thompson C, Van Aller GS, Liu Y, Graves AP, Della Pietra A, 3rd, Diaz E, LaFrance LV, Mellinger M, Duquenne C, Tian X, Kruger RG, McHugh CF, Brandt M, Miller WH, Dhanak D, Verma SK, Tummino PJ, Creasy CL (2012) EZH2 inhibition as a therapeutic strategy for lymphoma with EZH2-activating mutations. Nature 492 (7427):108–112.https://doi.org/10.1038/nature11606
167. He A, Shen X, Ma Q, Cao J, von Gise A, Zhou P, Wang G, Marquez VE, Orkin SH, Pu WT (2012) PRC2 directly methylates GATA4 and represses its transcriptional activity. Genes Dev 26(1):37–42. https://doi.org/10.1101/gad.173930.111
168. Yamagishi M, Hori M, Fujikawa D, Ohsugi T, Honma D, Adachi N, Katano H, Hishima T, Kobayashi S, Nakano K, Nakashima M, Iwanaga M, Utsunomiya A, Tanaka Y, Okada S, Tsukasaki K, Tobinai K, Araki K, Watanabe T, Uchimaru K (2019) Targeting excessive EZH1 and EZH2 activities for abnormal histone methylation and transcription network in malignant lymphomas. Cell Rep 29 (8):2321–2337 e2327. https://doi.org/10.1016/j.celrep.2019.10.083
169. Konze KD, Ma A, Li F, Barsyte-Lovejoy D, Parton T, Macnevin CJ, Liu F, Gao C, Huang XP, Kuznetsova E, Rougie M, Jiang A, Pattenden SG, Norris JL, James LI, Roth BL, Brown PJ, Frye SV, Arrowsmith CH, Hahn KM, Wang GG, Vedadi M, Jin J (2013) An orally bioavailable chemical probe of the lysine methyltransferases EZH2 and EZH1. ACS Chem Biol 8(6):1324–1334. https://doi.org/10.1021/cb400133j
170. Li G, Li D, Wu C, Li S, Chen F, Li P, Ko CN, Wang W, Lee SM, Lin L, Ma DL, Leung CH (2022) Homocysteine-targeting compounds as a new treatment strategy for diabetic wounds via inhibition of the histone methyltransferase SET7/9. Exp Mol Med 54(7):988–998. https://doi.org/10.1038/s12276-022-00804-1
171. Calnan DR, Webb AE, White JL, Stowe TR, Goswami T, Shi X, Espejo A, Bedford MT, Gozani O, Gygi SP, Brunet A (2012) Methylation by Set9 modulates FoxO3 stability and transcriptional activity. Aging (Albany NY) 4(7):462–479. https://doi.org/10.18632/aging.100471
172. Barsyte-Lovejoy D, Li F, Oudhoff MJ, Tatlock JH, Dong A, Zeng H, Wu H, Freeman SA, Schapira M, Senisterra GA, Kuznetsova E, Marcellus R, Allali-Hassani A, Kennedy S, Lambert JP, Couzens AL, Aman A, Gingras AC, Al-Awar R, Fish PV, Gerstenberger BS, Roberts L, Benn CL, Grimley RL, Braam MJ, Rossi FM, Sudol M, Brown PJ, Bunnage ME, Owen DR, Zaph C, Vedadi M, Arrowsmith CH (2014) (R)-PFI-2 is a potent and selective inhibitor of SETD7 methyltransferase activity in cells. Proc Natl Acad Sci USA 111(35):12853–12858. https://doi.org/10.1073/pnas.1407358111
173. Maganti AV, Maier B, Tersey SA, Sampley ML, Mosley AL, Ozcan S, Pachaiyappan B, Woster PM, Hunter CS, Stein R, Mirmira RG (2015) Transcriptional activity of the islet beta cell factor Pdx1 is augmented by lysine methylation catalyzed by the methyltransferase Set7/9. J Biol Chem 290(15):9812–9822. https://doi.org/10.1074/jbc.M114.616219
174. Xie Q, Hao Y, Tao L, Peng S, Rao C, Chen H, You H, Dong MQ, Yuan Z (2012) Lysine methylation of FOXO3 regulates oxidative stress-induced neuronal cell death. EMBO Rep 13(4):371–377. https://doi.org/10.1038/embor.2012.25
175. Balasubramaniyan N, Ananthanarayanan M, Suchy FJ (2012) Direct methylation of FXR by Set7/9, a lysine methyltransferase, regulates the expression of FXR target genes. Am J Physiol Gastrointest Liver Physiol 302(9):G937-947. https://doi.org/10.1152/ajpgi.00441.2011
176. Allali-Hassani A, Szewczyk MM, Ivanochko D, Organ SL, Bok J, Ho JSY, Gay FPH, Li F, Blazer L, Eram MS, Halabelian L, Dilworth D, Luciani GM, Lima-Fernandes E, Wu Q, Loppnau P, Palmer N, Talib SZA, Brown PJ, Schapira M, Kaldis P, O'Hagan RC, Guccione E, Barsyte-Lovejoy D, Arrowsmith CH, Sanders JM, Kattar SD, Bennett DJ, Nicholson B, Vedadi M (2019) Discovery of a chemical probe for PRDM9. Nat Commun 10(1):5759. https://doi.org/10.1038/s41467-019-13652-x
177. Eram MS, Shen Y, Szewczyk M, Wu H, Senisterra G, Li F, Butler KV, Kaniskan HU, Speed BA, Dela Sena C, Dong A, Zeng H, Schapira M, Brown PJ, Arrowsmith CH, Barsyte-Lovejoy D, Liu J, Vedadi M, Jin J (2016) A Potent, selective, and cell-active inhibitor of human type i protein arginine methyltransferases. ACS Chem Biol 11(3):772–781. https://doi.org/10.1021/acschembio.5b00839
178. Fedoriw A, Rajapurkar SR, O'Brien S, Gerhart SV, Mitchell LH, Adams ND, Rioux N, Lingaraj T, Ribich SA, Pappalardi MB, Shah N, Laraio J, Liu Y, Butticello M, Carpenter CL, Creasy C, Korenchuk S, McCabe MT, McHugh CF, Nagarajan R, Wagner C, Zappacosta F, Annan R, Concha NO, Thomas RA, Hart TK, Smith JJ, Copeland RA, Moyer MP, Campbell J, Stickland K, Mills J, Jacques-O'Hagan S, Allain C, Johnston D, Raimondi A, Porter Scott M, Waters N, Swinger K, Boriack-Sjodin A, Riera T, Shapiro G, Chesworth R, Prinjha RK, Kruger RG, Barbash O, Mohammad HP (2019) Anti-tumor activity of the type I PRMT inhibitor, GSK3368715, synergizes with PRMT5 inhibition through MTAP loss. Cancer Cell 36 (1):100–114 e125. https://doi.org/10.1016/j.ccell.2019.05.014
179. Cheng D, Yadav N, King RW, Swanson MS, Weinstein EJ, Bedford MT (2004) Small molecule regulators of protein arginine methyltransferases. J Biol Chem 279(23):23892–23899. https://doi.org/10.1074/jbc.M401853200
180. Yamagata K, Daitoku H, Takahashi Y, Namiki K, Hisatake K, Kako K, Mukai H, Kasuya Y, Fukamizu A (2008) Arginine methylation of FOXO transcription factors inhibits their phosphorylation by Akt. Mol Cell 32(2):221–231. https://doi.org/10.1016/j.molcel.2008.09.013

181. Zuo ZY, Yang GH, Wang HY, Liu SY, Zhang YJ, Cai Y, Chen F, Dai H, Xiao Y, Cheng MB, Huang Y, Zhang Y (2022) Klf4 methylated by Prmt1 restrains the commitment of primitive endoderm. Nucl Acids Res 50(4):2005–2018. https://doi.org/10.1093/nar/gkac054
182. Liu Q, Zhang XL, Cheng MB, Zhang Y (2019) PRMT1 activates myogenin transcription via MyoD arginine methylation at R121. Biochim Biophys Acta Gene Regul Mech 1862(10):194442. https://doi.org/10.1016/j.bbagrm.2019.194442
183. Avasarala S, Van Scoyk M, Karuppusamy Rathinam MK, Zerayesus S, Zhao X, Zhang W, Pergande MR, Borgia JA, DeGregori J, Port JD, Winn RA, Bikkavilli RK (2015) PRMT1 Is a novel regulator of epithelial-mesenchymal-transition in non-small cell lung cancer. J Biol Chem 290(21):13479–13489. https://doi.org/10.1074/jbc.M114.636050
184. Liu LM, Sun WZ, Fan XZ, Xu YL, Cheng MB, Zhang Y (2019) Methylation of C/EBPalpha by PRMT1 inhibits its tumor-suppressive function in breast cancer. Cancer Res 79(11):2865–2877. https://doi.org/10.1158/0008-5472.CAN-18-3211
185. Liu X, Li H, Liu L, Lu Y, Gao Y, Geng P, Li X, Huang B, Zhang Y, Lu L (2016) Methylation of arginine by PRMT1 regulates Nrf2 transcriptional activity during the antioxidative response. Biochim Biophys Acta 1863(8):2093–2103. https://doi.org/10.1016/j.bbamcr.2016.05.009
186. de Jong LM, Zhang Z, den Hartog Y, Sijsenaar TJP, Martins Cardoso R, Manson ML, Hankemeier T, Lindenburg PW, Salvatori DCF, Van Eck M, Hoekstra M (2022) PRMT3 inhibitor SGC707 reduces triglyceride levels and induces pruritus in Western-type diet-fed LDL receptor knockout mice. Sci Rep 12(1):483. https://doi.org/10.1038/s41598-021-04524-w
187. Shen Y, Szewczyk MM, Eram MS, Smil D, Kaniskan HU, de Freitas RF, Senisterra G, Li F, Schapira M, Brown PJ, Arrowsmith CH, Barsyte-Lovejoy D, Liu J, Vedadi M, Jin J (2016) Discovery of a potent, selective, and cell-active dual inhibitor of protein arginine methyltransferase 4 and protein arginine methyltransferase 6. J Med Chem 59(19):9124–9139. https://doi.org/10.1021/acs.jmedchem.6b01033
188. Liu C, Li Y, Liu Z, Cao C, Lin M, Chen X, Yuan M, Fan Y, Gu X, Wang L, Yang F, Ye F, Jin J (2024) Structure-based discovery of potent CARM1 inhibitors for colorectal cancer therapy. Eur J Med Chem 269:116288. https://doi.org/10.1016/j.ejmech.2024.116288
189. Iannelli G, Milite C, Marechal N, Cura V, Bonnefond L, Troffer-Charlier N, Feoli A, Rescigno D, Wang Y, Cipriano A, Viviano M, Bedford MT, Cavarelli J, Castellano S, Sbardella G (2022) Turning Nonselective inhibitors of type I protein arginine methyltransferases into potent and selective inhibitors of protein arginine methyltransferase 4 through a deconstruction-reconstruction and fragment-growing approach. J Med Chem 65(17):11574–11606. https://doi.org/10.1021/acs.jmedchem.2c00252
190. Kawabe Y, Wang YX, McKinnell IW, Bedford MT, Rudnicki MA (2012) Carm1 regulates Pax7 transcriptional activity through MLL1/2 recruitment during asymmetric satellite stem cell divisions. Cell Stem Cell 11(3):333–345. https://doi.org/10.1016/j.stem.2012.07.001
191. Ito T, Yadav N, Lee J, Furumatsu T, Yamashita S, Yoshida K, Taniguchi N, Hashimoto M, Tsuchiya M, Ozaki T, Lotz M, Bedford MT, Asahara H (2009) Arginine methyltransferase CARM1/PRMT4 regulates endochondral ossification. BMC Dev Biol 9:47. https://doi.org/10.1186/1471-213X-9-47
192. Gerhart SV, Kellner WA, Thompson C, Pappalardi MB, Zhang XP, Montes de Oca R, Penebre E, Duncan K, Boriack-Sjodin A, Le B, Majer C, McCabe MT, Carpenter C, Johnson N, Kruger RG, Barbash O (2018) Activation of the p53-MDM4 regulatory axis defines the anti-tumour response to PRMT5 inhibition through its role in regulating cellular splicing. Sci Rep 8(1):9711. https://doi.org/10.1038/s41598-018-28002-y
193. Chan-Penebre E, Kuplast KG, Majer CR, Boriack-Sjodin PA, Wigle TJ, Johnston LD, Rioux N, Munchhof MJ, Jin L, Jacques SL, West KA, Lingaraj T, Stickland K, Ribich SA, Raimondi A, Scott MP, Waters NJ, Pollock RM, Smith JJ, Barbash O, Pappalardi M, Ho TF, Nurse K, Oza KP, Gallagher KT, Kruger R, Moyer MP, Copeland RA, Chesworth R, Duncan KW (2015) A selective inhibitor of PRMT5 with in vivo and in vitro potency in MCL models. Nat Chem Biol 11(6):432–437. https://doi.org/10.1038/nchembio.1810
194. Brehmer D, Beke L, Wu T, Millar HJ, Moy C, Sun W, Mannens G, Pande V, Boeckx A, van Heerde E, Nys T, Gustin EM, Verbist B, Zhou L, Fan Y, Bhargava V, Safabakhsh P, Vinken P, Verhulst T, Gilbert A, Rai S, Graubert TA, Pastore F, Fiore D, Gu J, Johnson A, Philippar U, Morschhauser B, Walker D, De Lange D, Keersmaekers V, Viellevoye M, Diels G, Schepens W, Thuring JW, Meerpoel L, Packman K, Lorenzi MV, Laquerre S (2021) Discovery and pharmacological characterization of JNJ-64619178, a novel small-molecule inhibitor of PRMT5 with potent antitumor activity. Mol Cancer Ther 20(12):2317–2328. https://doi.org/10.1158/1535-7163.MCT-21-0367
195. Lu X, Fernando TM, Lossos C, Yusufova N, Liu F, Fontan L, Durant M, Geng H, Melnick J, Luo Y, Vega F, Moy V, Inghirami G, Nimer S, Melnick AM, Lossos IS (2018) PRMT5 interacts with the BCL6 oncoprotein and is required for germinal center formation and lymphoma cell survival. Blood 132(19):2026–2039. https://doi.org/10.1182/blood-2018-02-831438
196. Bandyopadhyay S, Harris DP, Adams GN, Lause GE, McHugh A, Tillmaand EG, Money A, Willard B, Fox PL, Dicorleto PE (2012) HOXA9 methylation by PRMT5 is essential for endothelial cell expression of leukocyte adhesion molecules. Mol Cell Biol 32(7):1202–1213. https://doi.org/10.1128/MCB.05977-11
197. Wu TF, Yao YL, Lai IL, Lai CC, Lin PL, Yang WM (2015) Loading of PAX3 to mitotic chromosomes is mediated by arginine methylation and associated with waardenburg syndrome. J Biol Chem 290(33):20556–20564. https://doi.org/10.1074/jbc.M114.607713
198. Chen M, Yi B, Sun J (2014) Inhibition of cardiomyocyte hypertrophy by protein arginine methyltransferase 5. J Biol Chem 289(35):24325–24335. https://doi.org/10.1074/jbc.M114.577494
199. Liu L, Zhao X, Zhao L, Li J, Yang H, Zhu Z, Liu J, Huang G (2016) Arginine methylation of SREBP1a via PRMT5 promotes de novo lipogenesis and tumor growth. Cancer Res 76(5):1260–1272. https://doi.org/10.1158/0008-5472.CAN-15-1766
200. Choi S, Jeong HJ, Kim H, Choi D, Cho SC, Seong JK, Koo SH, Kang JS (2019) Skeletal muscle-specific Prmt1 deletion causes muscle atrophy via deregulation of the PRMT6-FOXO3 axis. Autophagy 15(6):1069–1081. https://doi.org/10.1080/15548627.2019.1569931
201. Szewczyk MM, Ishikawa Y, Organ S, Sakai N, Li F, Halabelian L, Ackloo S, Couzens AL, Eram M, Dilworth D, Fukushi H, Harding R, Dela Sena CC, Sugo T, Hayashi K, McLeod D, Zepeda C, Aman A, Sanchez-Osuna M, Bonneil E, Takagi S, Al-Awar R, Tyers M, Richard S, Takizawa M, Gingras AC, Arrowsmith CH, Vedadi M, Brown PJ, Nara H, Barsyte-Lovejoy D (2020) Pharmacological inhibition of PRMT7 links arginine monomethylation to the cellular stress response. Nat Commun 11(1):2396. https://doi.org/10.1038/s41467-020-16271-z
202. Dong H, He X, Zhang L, Chen W, Lin YC, Liu SB, Wang H, Nguyen LXT, Li M, Zhu Y, Zhao D, Ghoda L, Serody J, Vincent B, Luznik L, Gojo I, Zeidner J, Su R, Chen J, Sharma R, Pirrotte P, Wu X, Hu W, Han W, Shen B, Kuo YH, Jin J, Salhotra A, Wang J, Marcucci G, Luo YL, Li L (2024) Targeting PRMT9-mediated arginine methylation suppresses cancer stem cell maintenance and elicits cGAS-mediated anticancer immunity. Nat Cancer 5(4):601–624. https://doi.org/10.1038/s43018-024-00736-x

203. Metzger E, Wissmann M, Yin N, Muller JM, Schneider R, Peters AH, Gunther T, Buettner R, Schule R (2005) LSD1 demethylates repressive histone marks to promote androgen-receptor-dependent transcription. Nature 437(7057):436–439. https://doi.org/10.1038/nature04020
204. Niwa H, Watanabe C, Sato S, Harada T, Watanabe H, Tabusa R, Fukasawa S, Shiobara A, Hashimoto T, Ohno O, Nakamura K, Tsuganezawa K, Tanaka A, Shirouzu M, Honma T, Matsuno K, Umehara T (2022) Structure-activity relationship and in silico evaluation of *cis*- and trans-PCPA-derived inhibitors of LSD1 and LSD2. ACS Med Chem Lett 13(9):1485–1492. https://doi.org/10.1021/acsmedchemlett.2c00294
205. Wang Z, Long QY, Chen L, Fan JD, Wang ZN, Li LY, Wu M, Chen X (2017) Inhibition of H3K4 demethylation induces autophagy in cancer cell lines. Biochim Biophys Acta Mol Cell Res 1864(12):2428–2437. https://doi.org/10.1016/j.bbamcr.2017.08.005
206. Rose NR, Woon EC, Tumber A, Walport LJ, Chowdhury R, Li XS, King ON, Lejeune C, Ng SS, Krojer T, Chan MC, Rydzik AM, Hopkinson RJ, Che KH, Daniel M, Strain-Damerell C, Gileadi C, Kochan G, Leung IK, Dunford J, Yeoh KK, Ratcliffe PJ, Burgess-Brown N, von Delft F, Muller S, Marsden B, Brennan PE, McDonough MA, Oppermann U, Klose RJ, Schofield CJ, Kawamura A (2012) Plant growth regulator daminozide is a selective inhibitor of human KDM2/7 histone demethylases. J Med Chem 55(14):6639–6643. https://doi.org/10.1021/jm300677j
207. Gerken PA, Wolstenhulme JR, Tumber A, Hatch SB, Zhang Y, Muller S, Chandler SA, Mair B, Li F, Nijman SMB, Konietzny R, Szommer T, Yapp C, Fedorov O, Benesch JLP, Vedadi M, Kessler BM, Kawamura A, Brennan PE, Smith MD (2017) Discovery of a highly selective cell-active inhibitor of the histone lysine demethylases KDM2/7. Angew Chem Int Ed Engl 56(49):15555–15559. https://doi.org/10.1002/anie.201706788
208. Kim YY, Gryder BE, Sinniah R, Peach ML, Shern JF, Abdelmaksoud A, Pomella S, Woldemichael GM, Stanton BZ, Milewski D, Barchi JJ Jr, Schneekloth JS Jr, Chari R, Kowalczyk JT, Shenoy SR, Evans JR, Song YK, Wang C, Wen X, Chou HC, Gangalapudi V, Esposito D, Jones J, Procter L, O'Neill M, Jenkins LM, Tarasova NI, Wei JS, McMahon JB, O'Keefe BR, Hawley RG, Khan J (2024) KDM3B inhibitors disrupt the oncogenic activity of PAX3-FOXO1 in fusion-positive rhabdomyosarcoma. Nat Commun 15(1):1703. https://doi.org/10.1038/s41467-024-45902-y
209. Hu Q, Chen J, Zhang J, Xu C, Yang S, Jiang H (2016) IOX1, a JMJD2A inhibitor, suppresses the proliferation and migration of vascular smooth muscle cells induced by angiotensin II by regulating the expression of cell cycle-related proteins. Int J Mol Med 37(1):189–196. https://doi.org/10.3892/ijmm.2015.2393
210. Feng T, Li D, Wang H, Zhuang J, Liu F, Bao Q, Lei Y, Chen W, Zhang X, Xu X, Sun H, You Q, Guo X (2015) Novel 5-carboxy-8-HQ based histone demethylase JMJD2A inhibitors: introduction of an additional carboxyl group at the C-2 position of quinoline. Eur J Med Chem 105:145–155. https://doi.org/10.1016/j.ejmech.2015.09.013
211. Chu CH, Wang LY, Hsu KC, Chen CC, Cheng HH, Wang SM, Wu CM, Chen TJ, Li LT, Liu R, Hung CL, Yang JM, Kung HJ, Wang WC (2014) KDM4B as a target for prostate cancer: structural analysis and selective inhibition by a novel inhibitor. J Med Chem 57(14):5975–5985. https://doi.org/10.1021/jm500249n
212. Duan L, Rai G, Roggero C, Zhang QJ, Wei Q, Ma SH, Zhou Y, Santoyo J, Martinez ED, Xiao G, Raj GV, Jadhav A, Simeonov A, Maloney DJ, Rizo J, Hsieh JT, Liu ZP (2015) KDM4/JMJD2 histone demethylase inhibitors block prostate tumor growth by suppressing the expression of AR and BMYB-regulated genes. Chem Biol 22(9):1185–1196. https://doi.org/10.1016/j.chembiol.2015.08.007
213. Letfus V, Jelic D, Bokulic A, Petrinic Grba A, Kostrun S (2020) Rational design, synthesis and biological profiling of new KDM4C inhibitors. Bioorg Med Chem 28(1):115128. https://doi.org/10.1016/j.bmc.2019.115128
214. Fang Z, Wang TQ, Li H, Zhang G, Wu XA, Yang L, Peng YL, Zou J, Li LL, Xiang R, Yang SY (2017) Discovery of pyrazolo[1,5-a]pyrimidine-3-carbonitrile derivatives as a new class of histone lysine demethylase 4D (KDM4D) inhibitors. Bioorg Med Chem Lett 27(14):3201–3204. https://doi.org/10.1016/j.bmcl.2017.05.002
215. Thalhammer A, Mecinovic J, Loenarz C, Tumber A, Rose NR, Heightman TD, Schofield CJ (2011) Inhibition of the histone demethylase JMJD2E by 3-substituted pyridine 2,4-dicarboxylates. Org Biomol Chem 9(1):127–135. https://doi.org/10.1039/c0ob00592d
216. Sayegh J, Cao J, Zou MR, Morales A, Blair LP, Norcia M, Hoyer D, Tackett AJ, Merkel JS, Yan Q (2013) Identification of small molecule inhibitors of Jumonji AT-rich interactive domain 1B (JARID1B) histone demethylase by a sensitive high throughput screen. J Biol Chem 288(13):9408–9417. https://doi.org/10.1074/jbc.M112.419861
217. Mitsui E, Yoshida S, Shinoda Y, Matsumori Y, Tsujii H, Tsuchida M, Wada S, Hasegawa M, Ito A, Mino K, Onuki T, Yoshida M, Sasaki R, Mizukami T (2019) Identification of ryuvidine as a KDM5A inhibitor. Sci Rep 9(1):9952. https://doi.org/10.1038/s41598-019-46346-x
218. Ohguchi H, Park PMC, Wang T, Gryder BE, Ogiya D, Kurata K, Zhang X, Li D, Pei C, Masuda T, Johansson C, Wimalasena VK, Kim Y, Hino S, Usuki S, Kawano Y, Samur MK, Tai YT, Munshi NC, Matsuoka M, Ohtsuki S, Nakao M, Minami T, Lauberth S, Khan J, Oppermann U, Durbin AD, Anderson KC, Hideshima T, Qi J (2021) Lysine demethylase 5A is required for MYC driven transcription in multiple myeloma. Blood Cancer Discov 2(4):370–387. https://doi.org/10.1158/2643-3230.BCD-20-0108
219. Tumber A, Nuzzi A, Hookway ES, Hatch SB, Velupillai S, Johansson C, Kawamura A, Savitsky P, Yapp C, Szykowska A, Wu N, Bountra C, Strain-Damerell C, Burgess-Brown NA, Ruda GF, Fedorov O, Munro S, England KS, Nowak RP, Schofield CJ, La Thangue NB, Pawlyn C, Davies F, Morgan G, Athanasou N, Muller S, Oppermann U, Brennan PE (2017) Potent and selective KDM5 inhibitor stops cellular demethylation of H3K4me3 at transcription start sites and proliferation of MM1S myeloma cells. Cell Chem Biol 24(3):371–380. https://doi.org/10.1016/j.chembiol.2017.02.006
220. Cao N, Huang Y, Zheng J, Spencer CI, Zhang Y, Fu JD, Nie B, Xie M, Zhang M, Wang H, Ma T, Xu T, Shi G, Srivastava D, Ding S (2016) Conversion of human fibroblasts into functional cardiomyocytes by small molecules. Science 352(6290):1216–1220. https://doi.org/10.1126/science.aaf1502
221. Kruidenier L, Chung CW, Cheng Z, Liddle J, Che K, Joberty G, Bantscheff M, Bountra C, Bridges A, Diallo H, Eberhard D, Hutchinson S, Jones E, Katso R, Leveridge M, Mander PK, Mosley J, Ramirez-Molina C, Rowland P, Schofield CJ, Sheppard RJ, Smith JE, Swales C, Tanner R, Thomas P, Tumber A, Drewes G, Oppermann U, Patel DJ, Lee K, Wilson DM (2012) A selective jumonji H3K27 demethylase inhibitor modulates the proinflammatory macrophage response. Nature 488(7411):404–408. https://doi.org/10.1038/nature11262