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Review

Targeting PRMT5 in cancer: Mechanistic insights and clinical progress

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ABSTRACT

Arginine methylation is increasingly recognized as a key regulatory mechanism in cancer, exerting broad influence over chromatin organization, RNA metabolism, and oncogenic signaling. Protein arginine methyltransferase 5 (PRMT5) catalyzes symmetric dimethylation of arginine residues on both histone and non-histone substrates. Through these modifications, PRMT5 modulates transcription, alternative splicing, DNA repair, and apoptosis, which collectively support malignant transformation and disease progression. Elevated expression or hyperactivation of PRMT5 has been documented across multiple cancer types, where it contributes to tumor cell survival, proliferation, metastasis, and therapeutic resistance. Early-generation inhibitors directed against the substrate-binding groove or the S-adenosylmethionine (SAM)-binding pocket demonstrated proof of mechanism but were limited by modest clinical efficacy and dose-limiting toxicities. More recently, methylthioadenosine (MTA)-cooperative inhibitors have shown enhanced selectivity in *MTAP*-deleted tumors by exploiting a synthetic lethal vulnerability, offering new opportunities for precision oncology. Ongoing investigations will be critical to define the therapeutic window of PRMT5 inhibition and to optimize rational combination strategies. This review provides a comprehensive overview of current insights into the oncogenic functions of PRMT5 and highlights emerging therapeutic strategies aimed at improving cancer treatment.

1. Introduction

Aberrant post-translational modifications (PTMs) of proteins play pivotal roles in cancer development and progression by altering gene expression, signaling cascades, and cellular homeostasis. Among various PTMs, arginine methylation has emerged as a key regulatory mechanism in tumorigenesis [1]. Owing to its ability to modify both histone and non-histone proteins, arginine methylation influences a wide range of biological processes including chromatin remodeling, RNA metabolism, and signal transduction [1,2].

Arginine methylation is catalyzed by a family of enzymes known as protein arginine methyltransferases (PRMTs), which transfer methyl groups from S-adenosylmethionine (SAM) to the guanidino nitrogen atoms of arginine residues [3]. The PRMT family is subdivided into three types based on the methylation pattern they catalyze on the arginine guanidino group. Type I PRMTs (PRMT1, 2, 3, 4, 6, and 8) produce ω-NG-monomethylarginine (MMA) as an intermediate, followed by the asymmetric ω-NG, ω-NG-dimethylarginine (ADMA). Type II PRMTs (PRMT5 and 9) also produce MMA as an intermediate but subsequently generate symmetric ω-NG, ω-NG-dimethylarginine (SDMA). Type III PRMT (PRMT7) is distinct in that it catalyzes the formation of MMA without further dimethylation [3,4]. All PRMTs share a conserved SAM-dependent methyltransferase (MTase) domain, which includes a SAM-binding site, a β-barrel for substrate binding, and a dimerization arm essential for enzymatic activity [5]. Despite this conserved domain, individual PRMTs differ in their substrate specificity, subcellular localization, and biological roles (Fig. 1). Methylation of arginine residues affects protein function by reducing hydrogen bonding potential and neutralizing positive charges, thereby influencing protein–protein and protein–RNA interactions, subcellular localization, and complex formation [1,6]. Among PRMTs, PRMT1, CARM1 (PRMT4), and PRMT5 are highly expressed in various cancers and are associated with poor prognosis [1].

Among PRMT enzymes, PRMT5 is particularly important in oncogenesis and has been reported to be overexpressed or hyperactivated across malignancies including lymphoid cancers, glioblastoma, and lung adenocarcinoma [7–9]. PRMT5 localizes to both nuclear and cytoplasmic compartments, and its subcellular localization has important

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biological and clinical implications. Cytoplasmic PRMT5 has been observed in highly proliferative and poorly differentiated cells, whereas nuclear PRMT5 has been observed more frequently in less aggressive and well-differentiated tumor cells [10–12]. Mechanistically, PRMT5 contributes to oncogenesis by repressing tumor suppressor genes such as ST7, PTEN, and TP53BP1 through histone methylation, and by activating oncogenic pathways involving factors like MYC, E2F1, and NF-κB [13,14]. Additionally, PRMT5 regulates alternative splicing of pre-mRNAs involved in apoptosis and cell cycle control, promoting tumor cell survival and adaptation under stress conditions [15,16].

The enzymatic function of PRMT5 depends on its interaction with the methylosome cofactor MEP50 and the utilization of SAM as a methyl donor—features that render PRMT5 amenable to pharmacological inhibition [17,18]. In recent years, selective PRMT5 inhibitors targeting either the SAM-binding pocket or allosteric sites have been developed and entered clinical trials. These agents have shown promising antitumor efficacy, particularly in MTAP-deleted tumors, which exhibit a synthetic lethal dependency on PRMT5 due to the accumulation of methylthioadenosine (MTA), a natural inhibitor of PRMT5 [4,14, 19–21].

In this review, we provide a comprehensive overview of the biological functions of PRMT5 in cancer, outline the current status of PRMT5-targeted therapeutics, and discuss the biological rationale, clinical potential, and future challenges in leveraging PRMT5 inhibition as a precision oncology strategy.

2. Structure and biological functions of PRMT5

2.1. Structure

PRMT5 functions as a multi-subunit complex and assembles into a unique hetero-octameric architecture composed of PRMT5-MEP50 (WDR77) heterodimers [17]. MEP50, a WD-repeat-scaffolding protein, stabilizes the complex and enhances substrate recruitment. This oligomeric arrangement is essential not only for the catalytic activity of PRMT5 but also for mediating interactions with regulatory cofactors such as Blimp1, pICln, RIOK1, and COPR5 [17,22–26]. These cofactors dynamically regulate the subcellular localization, substrate specificity, and functional output of PRMT5 in various cellular contexts.

The catalytic core of PRMT5 adopts a conserved Rossmann fold characteristic of SAM-dependent methyltransferases. Within this domain lies the SAM-binding pocket, which accommodates the methyl donor and facilitates transfer of the methyl group to the guanidino moiety of arginine residues in substrate proteins. PRMT5 also contains a C-terminal β-barrel domain that mediates dimerization and contributes to higher-order complex assembly, whereas the N-terminal TIM barrel domain is involved in substrate recognition and complex integrity [17, 27]. This modular architecture enables PRMT5 to function as a central regulator of arginine methylation across diverse biological processes.

2.2. Biological functions

PRMT5 regulates a wide range of cellular processes–including transcription, RNA splicing, DNA damage response (DDR), and proteasomal degradation–by methylating specific protein substrates (Fig. 2, Table 1). Dysregulated PRMT5 activity has been shown to promote tumorigenesis and metastasis, and its overexpression is frequently associated with poor prognosis across multiple cancer types. Given these diverse roles, PRMT5 functions as a central molecular driver linking epigenetic control to oncogenic signaling. In the following sections, we review major PRMT5 substrates and the resulting biological consequences.

2.2.1. Histone substrates and epigenetic regulation

PRMT5 alters chromatin architecture and regulates transcriptional programs by catalyzing arginine methylation of histone substrates. Through the deposition of symmetric dimethylation marks on histones, PRMT5 mediates both transcriptional repression and activation in a context-dependent manner (Fig. 3A and B). In addition to its role in controlling protein-coding genes, PRMT5 also regulates the transcription of non-coding RNAs, particularly microRNAs, thereby shaping oncogenic and tumor-suppressive networks (Fig. 3C). In the following section, we summarize how PRMT5-driven histone modifications contribute to oncogenic transcriptional programs.

2.2.1.1. Transcriptional repression. PRMT5-mediated histone methylation frequently contributes to the transcriptional silencing of tumor suppressor genes, ultimately driving the initiation and progression of tumorigenesis. Mechanistically, PRMT5 is associated with BRG1 or hBRM, which are core components of the SWI/SNF chromatin remodeling complex, and is recruited to specific gene promoters. At these loci,

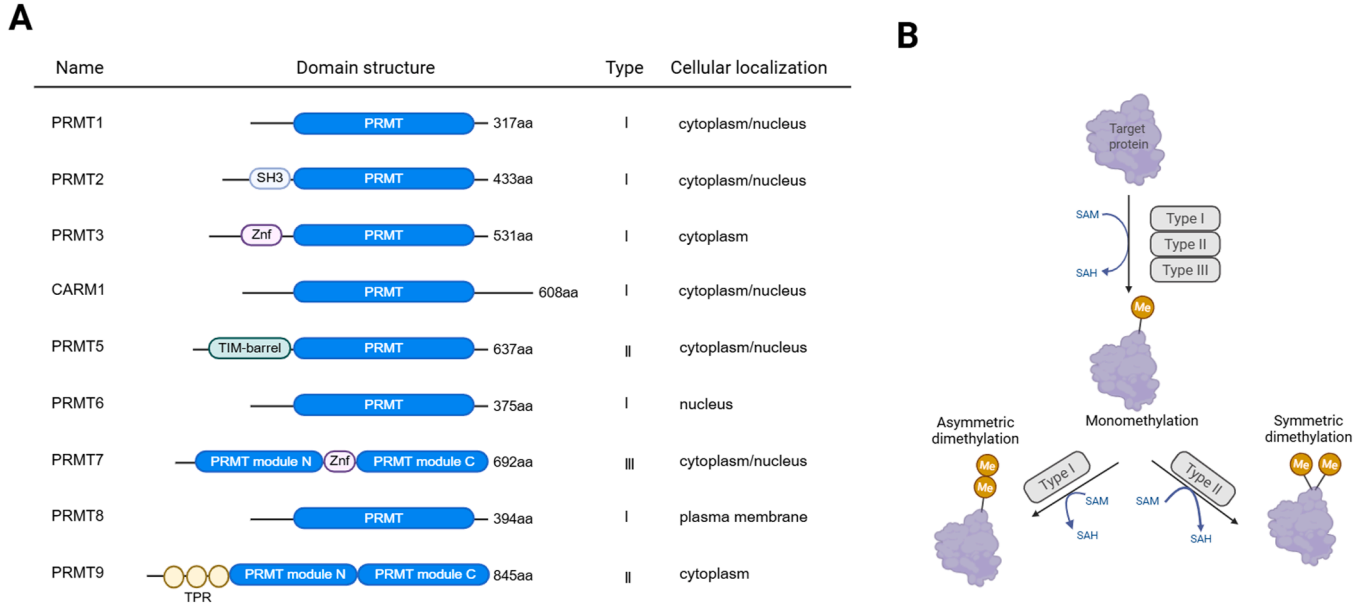

Fig. 1. Classification of PRMT family members. (A) Schematic representation of the nine human protein arginine methyltransferases (PRMTs), illustrating their domain structures, catalytic types, and cellular localization. (B) Catalytic mechanisms of PRMT enzymes.

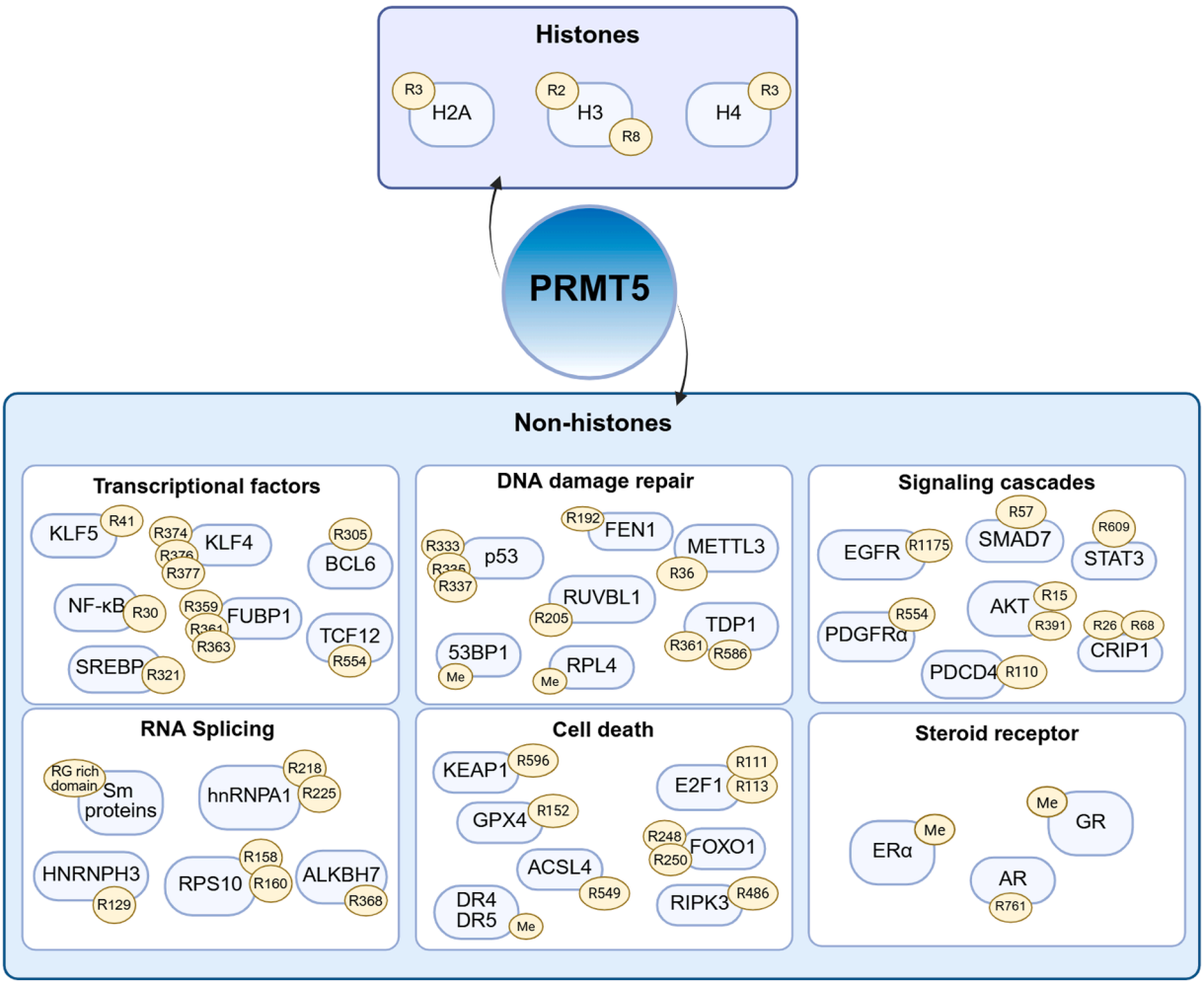

Fig. 2. Substrates of PRMT5. Schematic overview of PRMT5 targets with representative arginine residues subjected to symmetric dimethylation.

PRMT5 catalyzes the symmetric dimethylation of histone H3 at R8 (H3R8me2s) and histone H4 at R3 (H4R3me2s) [28]. These modifications generate a repressive chromatin environment, thereby establishing transcriptional silencing programs that favor tumorigenesis. For example, H3R8me2s antagonizes H3K9 acetylation by maintaining a hypoacetylated state, resulting in silencing of tumor suppressor genes such as ST7 and NM23 [28]. Consistently, elevated H3R8me2s and H4R3me2s marks are detected at the promoters of RB1, RBL1, and RBL2 in chronic lymphocytic leukemia (CLL), and PRMT5 inhibition restores RBL2 expression and tumor suppressor function in CLL cells [8]. In cervical cancer, PRMT5 associates with Snail and the NuRD complex to promote epithelial–mesenchymal transition (EMT). This complex catalyzes H3R2me2s and H4R3me2s modifications at the promoters of E-cadherin and TET1, which leads to transcriptional repression of E-cadherin and hypermethylation of genes [29]. PRMT5-mediated H4R3me2s can also serve as a binding platform for DNMT3A facilitating DNA methyltransferase-dependent silencing of the genes [30]. In gastric cancer, c-Myc has been shown to recruit PRMT5 to the promoters of *PTEN* and *CDKN2C* genes, where PRMT5 deposits repressive H4R3me2s marks; this cooperation enforces silencing of these tumor suppressors and promotes c-Myc-driven oncogenesis [31]. Beyond direct promoter methylation, PRMT5 collaborates with other chromatin-associated factors to shape repressive gene programs. For instance, the N-terminal PHD finger of the chromatin protein PHF1 recognizes PRMT5-catalyzed H4R3me2s, while the C-terminal PHD of PHF1 engages DDB1 in the CRL4B ubiquitin ligase complex. This PHF1–PRMT5–CRL4B axis couples H4R3me2s with H2AK119 monoubiquitination (H2AK119ub1), reinforcing the transcriptional repression of targets like E-cadherin and FBXW7 to facilitate cell growth and migration [32]. In addition, PRMT5 can directly interact with EZH2, which enhances H3K27me3 at the *CDKN2B* promoter and further solidifies silencing of the cell-cycle inhibitor [33](Fig. 3A).

2.2.1.2. Transcriptional activation. Although PRMT5-mediated histone marks at H3R8me2s and H4R3me2s are generally associated with transcriptional repression, in certain oncogenic contexts PRMT5-driven methylation facilitates transcriptional activation of oncogenes. In colorectal cancer, elevated PRMT5 deposits H4R3me2s and H3R8me2s at the promoters of the FGFR3 and EIF4E genes, which correlates with their increased expression and accelerated tumor growth [34]. Similarly, in prostate cancer, PRMT5 is recruited by the transcription factor Sp1 to the androgen receptor (AR) gene promoter, where it dimethylates H4R3. This leads to the upregulation of AR expression and activity, ultimately driving tumorigenesis [35]. In gastric cancer, PRMT5-mediated H3R8me2s modification of the FOXM1 promoter enhances IL-8 transcription, leading to increased tumor-associated angiogenesis [36]. PRMT5 also catalyzes H3R2 symmetric dimethylation (H3R2me2s) that can be associated with transcriptional activation through crosstalk with the WDR5/MLL complex in certain contexts, thereby enhancing H3K4 trimethylation and inducing FOXP1 expression. The resultant increase in *FOXP1* expands cancer stem-cell populations and promotes tumor progression and therapy resistance (Fig. 3B) [37]. In line with this mechanism, PRMT5, in cooperation with the novel cofactor SHARPIN, promotes lung cancer metastasis by catalyzing monomethylation of

Table 1
Summary of PRMT5 substrates and biological function of their methylation by PRMT5s.

Substrates		Methylation site	Biological function	Ref
Histones	Histone H4	H4R3	Transcriptional regulation (repression/activation)	[28]
	Histone H3	H3R2, H3R8		[28,37]
	Histone H2A	H2AR3		[28]
Non-histones	NF-κB (p65)	R30	Transcriptional regulation, tumor growth and survival	[50]
	BCL6	R305		[53]
	KLF4	R374, R376, R377		[45]
	KLF5	R41		[47]
	SREBP1	R321		[49]
	FUBP1	R359,R361,R363		[52]
	TCF12	R554		[88]
	Sm proteins	RG-rich domain	Regulation of RNA splicing and processing	[15]
	hnRNPA1	R218, R225		[57]
	ALKBH7	R368		[143]
	RPS10	R158, R160		[54]
	p53	R333, R335, R337	DNA damage repair	[58]
	53BP1	/		[60]
	FEN1	R192		[61]
	RUVBL1	R205		[59]
	METTL3	R36		[64]
	TDP1	R361, R586		[65,66]
	RPL4	/		[67]
	KEAP1	R596	Regulation of cell death (Apoptosis, necroptosis, ferroptosis)	[74]
	GPX4	R152		[75]
	ACSL4	R549		[76]
	E2F1	R111, R113		[68]
	DR4, DR5	/		[71]
	RIPK3	R486		[72]
	FOXO1	R248, R250		[73]
	EGFR	R1175	Regulation of cell proliferation, differentiation, and survival	[77]
	PDGFRα	R554		[78]
	AKT	R391, R15		[79,130]
	Smad7	R57		[83]
	STAT3	R609		[84]
	PDCD4	R110		[81]
	CRIP1	R26, R68		[82]
	ERα	/	Regulation of nuclear hormone receptor signaling	[89]
	AR	R761		[90]
	GR	/		[48]

H3R2 (H3R2me1), which subsequently facilitates H3K4me3 deposition at metastasis-related gene loci via recruitment of the MLL complex [38]. Furthermore, under conditions of genotoxic stress, PRMT5 forms a complex with β-catenin and ATM-phosphorylated JDP2. This complex is implicated in deposition of H3R2me1/H3R2me2s at the promoters of genes in the glutathione metabolic pathway, which recruits the WDR5/MLL complex and promotes H3K4 trimethylation. The resulting transcriptional activation enhances glutathione synthesis and antioxidant defenses, helping tumor cells survive under oxidative stress [39].

2.2.1.3. Non-coding RNA silencing. Beyond its effects on protein-coding genes, PRMT5 profoundly reshapes the expression of non-coding RNAs, particularly microRNAs, through the deposition of repressive arginine marks at their promoters. In acute myeloid leukemia (AML), PRMT5 forms a repressor complex with Sp1 that symmetrically dimethylates H4R3 at the MIR29B promoter, leading to silencing of the tumor-suppressive miR-29b. This downregulation, in turn, leads to upregulation of Sp1 and FLT3, forming a feedforward loop that maintains leukemic proliferation [40]. In chronic myeloid leukemia stem cells, PRMT5 deposits H3R8me2s and H4R3me2s at the MIR203 promoter to silence miR-203; this allows continued expression of the oncoprotein BCR-ABL, and creates a self-reinforcing circuit in which BCR-ABL signaling sustains PRMT5 expression and leukemic stem cell self-renewal [41]. Similarly, in B-cell lymphoma, PRMT5-mediated H3R8me2s silences miR-33b, miR-96, and miR-503, thereby increasing the expression of cyclin D1, c-MYC, and PRMT5 itself; collectively, this drives lymphoma cell proliferation and survival [42]. In summary, PRMT5-catalyzed histone methylation often represses microRNA genes that would normally constrain oncogenic signaling pathways, thereby promoting tumor growth and metastasis (Fig. 3C).

2.2.2. Non-histone substrates and functional consequences

PRMT5 exerts extensive regulatory control over numerous non-histone proteins, affecting processes such as transcriptional factor activity, RNA splicing, DNA repair, apoptosis, and signal transduction (Fig. 2). Through these activities, PRMT5 serves as a central hub of post-translational regulation that contributes to both normal physiology and tumorigenesis.

2.2.2.1. Transcriptional factors. Elevated PRMT5 expression or activity in cancer profoundly affects key transcriptional regulators, often by enhancing their stability and transcriptional output via arginine methylation.

PRMT5 symmetrically dimethylates the Krüppel-like factor KLF4 on residues R374, R376, and R377 [43,44]. This modification prevents recognition of KLF4 by the von Hippel–Lindau (VHL) E3 ubiquitin ligase complex, thereby inhibiting its proteasomal degradation. Stabilized KLF4 activates target genes such as the cell-cycle inhibitor p21 (CDKN1A), while concurrently repressing pro-apoptotic genes such as BAX—a dual regulatory effect that collectively favors tumor cell survival [45]. Similarly, PRMT5 methylates KLF5 at R41 which protects KLF5 from GSK3β-mediated phosphorylation and degradation. The stabilized KLF5 drives transcription of oncogenic targets including CCND1, SLUG, and FGFBP1, thereby promoting proliferation, EMT, and survival of malignant cells [46,47]. Additionally, PRMT5 is required for the interaction between glucocorticoid receptor (GR) and heterochromatin protein 1γ (HP1γ). The GR/PRMT5/HP1γ complex promotes the transcription of GR-responsive genes involved in cell migration and

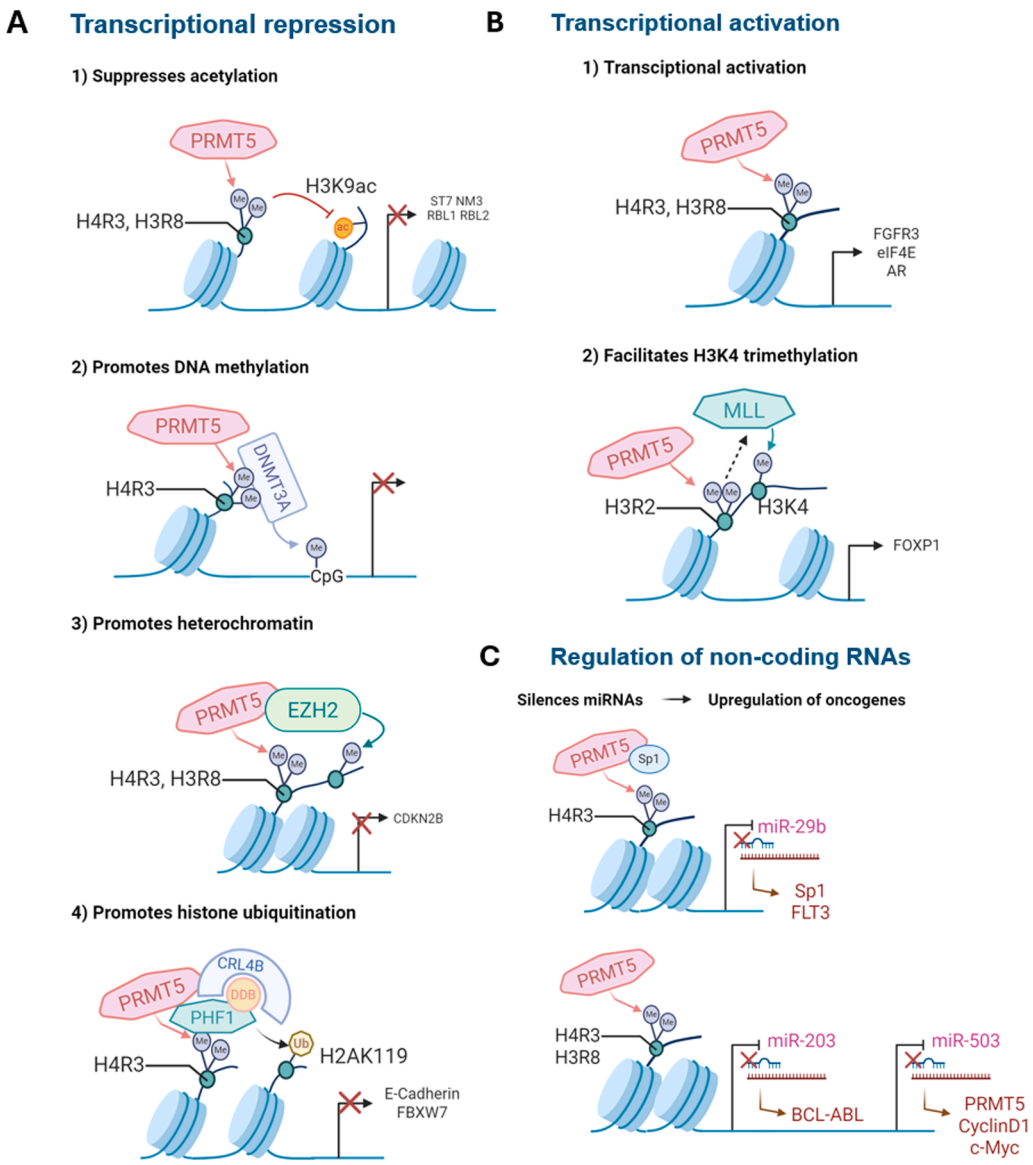

Fig. 3. PRMT5-mediated histone methylation. Schematic depiction of PRMT5-catalyzed histone modifications and their downstream effects: (A) transcriptional repression, (B) transcriptional activation, and (C) regulation of non-coding RNAs.

invasion [48]. PRMT5 further contributes to metabolic reprogramming through regulation of sterol regulatory element-binding protein 1 (SREBP1). PRMT5-mediated methylation of SREBP1 at R321 enhances its transcriptional activity, thereby driving lipogenic gene expression and malignant progression in hepatocellular carcinoma (HCC) [49]. In addition, PRMT5 potentiates NF-κB signaling by directly methylating the p65/RelA subunit of NF-κB at R30, which enhances DNA-binding affinity of p65 and promotes robust occupancy at κB elements. This results in increased transcription of inflammatory and tumor-promoting genes such as TNFA, IL8, and NFKBIA, linking PRMT5 activity to chronic inflammation and tumor-supportive microenvironment [50]. In prostate cancer, PRMT5 is required for the interaction between p44 and AR, which facilitates AR-dependent transcriptional activation [51]. Beyond AR signaling, PRMT5-mediated methylation of FUBP1 at R359, R361, and R363 enhances its transcriptional activation of PDK1 and SLC7A11, which in turn promotes tumorigenesis [52].

In B-cell biology, PRMT5 regulates the transcriptional repressor BCL6. PRMT5 symmetrically dimethylates BCL6 at R305, a modification essential for BCL6 to exert its full repressive function. Pharmacological PRMT5 inhibition reduces BCL6 methylation and derepresses BCL6 target genes (e.g., CCR6, BANK1, and CD69), leading to impaired lymphoma cell growth. Notably, dual inhibition of PRMT5 and BCL6 produces synergistic lethality in BCL6-expressing lymphoma models [53].

2.2.2.2. RNA splicing. PRMT5 plays a central role in both spliceosomal assembly and the regulation of alternative splicing. PRMT5-mediated symmetric dimethylation of ribosomal protein S10 (RPS10) at R158 and R160 is required for proper ribosome assembly and efficient protein synthesis, thereby promoting cell proliferation and tumorigenesis [54]. In addition, PRMT5 symmetrically dimethylates the Sm core proteins (SmB/B′, SmD1, SmD3) of small nuclear ribonucleoproteins (snRNPs) [15,55]. These SDMA marks on Sm proteins are recognized by the Tudor domain of the Survival of Motor Neuron (SMN) protein, which facilitates snRNP assembly and spliceosome maturation. Genetic or pharmacological inhibition of PRMT5 disrupts snRNP biogenesis and causes widespread splicing defects.

Beyond its general role in RNA processing, PRMT5 regulates the alternative splicing of both oncogenic and tumor-suppressive transcripts. One prominent example is the MDM4 gene, a negative regulator of p53. PRMT5 activity is required for inclusion of exon 6 in MDM4

mRNA. Upon PRMT5 inhibition or knockdown, exon 6 is skipped, resulting in a truncated MDM4 isoform that lacks the p53-binding domain. This splicing shift effectively unleashes p53 activity, triggering G1 cell-cycle arrest and apoptosis in p53 wild-type cancer cells [56]. PRMT5 also methylates heterogeneous nuclear ribonucleoprotein A1 (hnRNPA1) at R218 and R225, which enhances the role of hnRNPA1 in internal ribosome entry site (IRES)-dependent translation. Through this, PRMT5 selectively increases the cap-independent translation of oncogenic mRNAs such as CCND1, MYC, and HIF1A without altering their mRNA levels. This facilitates proliferation and survival under conditions where cap-dependent translation is compromised [57].

2.2.2.3. DNA damage response. PRMT5 exerts multifaceted roles in the DNA damage response (DDR) by regulating both p53 signaling and DNA repair pathways. It interacts with the p53 cofactor STRAP and thereby catalyzes the symmetric dimethylation of p53 at R333, R335, and R337 [58]. This modification promotes p53 oligomerization and its nuclear retention and enhances the transcriptional activation of target genes such as CDKN1A and PUMA. Importantly, PRMT5-mediated methylation skews p53 activity toward cell-cycle arrest without triggering apoptosis, underscoring its role as a fine-tuner of p53-dependent stress responses.

Beyond p53 regulation, PRMT5 directly modulates several key components of the double-strand break (DSB) repair machinery. It dimethylates RUVBL1, a component of the TIP60 acetyltransferase complex, at R205, which enhances acetyltransferase activity of TIP60. This activation promotes histone H4 acetylation and subsequent ATM kinase activation, facilitating homologous recombination (HR) while antagonizing 53BP1-mediated non-homologous end joining (NHEJ) [59]. Paradoxically, PRMT5 also methylates 53BP1 itself, potentially affecting its recruitment to DNA breaks and thereby influencing the balance between HR and NHEJ [60]. In addition, PRMT5-mediated methylation of FEN1 at R192 is required for recruiting PCNA to DNA repair foci by suppressing FEN1 phosphorylation at S187 [61]. Aberrant PRMT5 activity has been linked to defective checkpoint signaling and accumulation of unrepaired DNA lesions in lymphoma models [62].

PRMT5 driven-DDR activation is also associated with therapy resistance. In ovarian cancer, elevated PRMT5 activity contributes to platinum resistance by promoting transcriptional activation of stress response genes [63]. Similarly, MST4-induced PRMT5 activity drives symmetric dimethylation of METTL3 at R36, which enhances RAD51 recruitment and HR-mediated DSB repair, ultimately conferring cisplatin resistance [64]. PRMT5 also contributes to irinotecan resistance through symmetrically dimethylating TDP1 at R361 and R586. These methylation events enhance the repair of topoisomerase I cleavage complex by promoting XRCC1 foci formation and subsequent DDR pathway activation [65,66]. In HCC, PRMT5-catalyzed dimethylation of RPL14 stabilizes the protein and enhances DNA repair capacity, leading to regorafenib resistance [67].

2.2.2.4. Cell death pathways. PRMT5 exerts complex regulatory effects on apoptosis by modulating transcription factors as well as both the intrinsic and extrinsic apoptotic pathways. One key mechanism involves the transcription factor E2F1, a cell-cycle regulator. PRMT5-mediated symmetric dimethylation of E2F1 at R111 and 113 prevents PRMT1-dependent R109 methylation and recruits the Tudor-domain protein p100/TSN, leading to decreased E2F1 stability and suppression of E2F1-driven apoptosis [68]. Consistent with this, pharmacological inhibition of PRMT5 reduces E2F1 methylation, thereby leading to impaired DNA repair and cell-cycle progression while enhancing apoptosis [69,70]. PRMT5 also rewires the extrinsic apoptosis pathway. By selectively associating with death receptors DR4 and DR5, PRMT5 diverts receptor signaling away from apoptosis and toward activation of the NF-κB signaling pathway. This shift promotes the expression of anti-apoptotic proteins such as Bcl-xL, c-FLIP, and XIAP, thereby protecting cells from TRAIL-induced apoptosis [71]. In addition to suppressing extrinsic cell death, PRMT5 inhibits necroptotic signaling. PRMT5 methylates RIPK3 at R486, a modification that enhances RIPK3 autophosphorylation and ultimately blocks the necroptosis execution [72]. Regulation of the intrinsic apoptosis pathway further highlights the role of PRMT5 in tumor survival. PRMT5-mediated arginine methylation of FOXO1 promotes its nuclear export and subsequent proteasomal degradation [73]. Since nuclear FOXO1 is required for transcription of pro-apoptotic genes like BAX, PRMT5-driven FOXO1 inactivation effectively dampens the intrinsic apoptotic response [99].

PRMT5 has also been implicated in the regulation of ferroptosis, a form of iron-dependent, regulated necrotic cell death that contributes to therapy resistance. One mechanism involves the dimethylation of KEAP1 at R596, which enhances KEAP1 stability and promotes sustained NRF2 degradation. This leads to reduced expression of NRF2 target genes such as HMOX1, resulting in increased resistance to ferroptotic stress and improved survival under oxidative conditions [74]. Furthermore, PRMT5-mediated methylation of GPX4 at R152 prevents the binding of the Cullin1–FBW7 E3 ligase complex, stabilizing GPX4 and diminishing ferroptotic cell death [75]. PRMT5-mediated methylation of ACSL4 at R549 also facilitates its proteasomal degradation, leading to reduced lipid biosynthesis required for ferroptosis [76]. Finally, pharmacological inhibition of PRMT5 enhances ferroptotic cell death, thereby improving the therapeutic efficacy of chemotherapeutic agents.

2.2.2.5. Oncogenic signaling and immune regulation. PRMT5 modulates diverse growth factor- and cytokine-mediated signaling cascades through arginine methylation of key signaling intermediates, thereby orchestrating oncogenic and immune-regulatory programs. PRMT5 symmetrically dimethylates EGFR at R1175, which enhances EGFR autophosphorylation at Y1173 and potentiates downstream ERK/MAPK signaling [77]. Consequently, PRMT5-mediated EGFR methylation promotes cell proliferation, migration, and invasion, underscoring its role in amplifying tumorigenic signaling. Similarly, PRMT5 methylates PDGFRα at R554, which lies adjacent to a binding site for the E3 ubiquitin ligase Cbl. This modification sterically hinders Cbl binding, thereby preventing PDGFRα ubiquitination and degradation, resulting in prolonged receptor signaling [78]. PRMT5 also promotes activation of the AKT pathway by directly methylating AKT1 at R391 [79] and/or R15 [80]. These modifications facilitate AKT1 membrane translocation and phosphorylation by the upstream kinases PDK1 and mTORC2, leading to sustained activation of the PI3K-AKT-mTOR axis. In addition, PRMT5 dimethylates PDCD4,a tumor suppressor that inhibits eIF4A-dependent translation,at R110. Intriguingly, while elevated PDCD4 levels are generally associated with a favorable prognosis, co-expression of PRMT5 and PDCD4 correlates with more aggressive disease phenotypes. This indicates that PRMT5-mediated methylation functionally converts PDCD4 from a translational repressor into a facilitator of tumor growth [81]. In small cell lung cancer (SCLC), PRMT5 contributes to chemoresistance through activation of the Wnt/β-catenin cascade. Following exposure to cisplatin and etoposide, PRMT5-mediated methylation of CRIP1 at R26 and R68 stabilizes CRIP1 and triggers β-catenin pathway activation, leading to acquisition of a stem-like phenotype and enhanced resistance to therapy [82]. PRMT5 also modulates cytokine signaling, particularly the IL-6/STAT3 pathway. It symmetrically dimethylates SMAD7 at R57, which enhances interaction of SMAD7 with the gp130 subunit of the IL-6 receptor complex. This prevents SMAD7 from blocking gp130, thus ensuring robust JAK2/STAT3 activation in response to IL-6 [83]. In addition, PRMT5 directly methylates STAT3 at R609; this modification is critical for its transcriptional activity of STAT3 and for maintaining tumor growth and cancer stem cell renewal [84].

Beyond cell-intrinsic signaling, PRMT5 plays an important role in shaping the tumor immune microenvironment, particularly through

regulation of immune checkpoint pathways. The mechanisms by which PRMT5 regulates the expression of Programmed Death-Ligand 1 (PD-L1, encoded by CD274) is context-dependent and multifaceted, involving both repressive and activating histone modifications. PRMT5-mediated symmetric dimethylation of H4R3me2s functions as a repressive mark deposited at the CD274 promoter, leading to transcriptional silencing of PD-L1 [85]. Conversely, in breast cancer cells, PRMT5-mediated histone modifications facilitate the recruitment of the WDR4/MLL complex, which promotes H3K4 trimethylation at CD274 promoter, thereby upregulating PD-L1 expression [86]. Similarly, in cervical cancer, PRMT5 enhances STAT1 expression through H3R2me2s modification, which subsequently drives PD-L1 transcription [87]. Furthermore, PRMT5's regulatory influence extends beyond PD-L1 to other inhibitory immune axes. PRMT5-catalyzed symmetric dimethylation of TCF12 at R554 promotes TCF12-driven transcription of fibrinogen-like protein 1 (FGL1), a key immune inhibitory ligand for the LAG-3 receptor. This pathway suppresses effective anti-tumor immunity [88].

In certain contexts, PRMT5 functions as a transcriptional repressor that suppresses oncogenic signaling and is associated with favorable clinical outcomes. In breast cancer, PRMT5 demethylates the DNA-binding domain of estrogen receptor α (ERα), an event associated with improved prognosis. Nuclear localization of PRMT5 strongly correlates with better patient outcomes, and its interaction with ERα is required for the recruitment of ERα corepressors in response to tamoxifen treatment [89]. Similarly, in prostate cancer, PRMT5-mediated symmetric dimethylation of AR at R761 attenuates AR recruitment to target gene promoters in TMPRSS2:ERG fusion–positive prostate cancer cells, thereby restraining AR-driven transcriptional activity [90]. These findings underscore the context-dependent nature of PRMT5 activity, wherein its subcellular localization, binding partners, and substrate specificity collectively determine whether it exerts oncogenic or tumor-suppressive functions.

3. Therapeutic application of PRMT5 inhibitors across cancer types

PRMT5 has been recognized as a vulnerable target across multiple cancer types due to its pivotal role in regulating key cellular processes, including cell cycle progression, apoptosis, and DNA damage repair. Over the past decade, extensive efforts have been devoted to the development of selective PRMT5 inhibitors. Several of these compounds have advanced into clinical evaluation, demonstrating promising anti-tumor activity in both solid and hematologic malignancies. In this section, we provide an overview of the major classes of PRMT5 inhibitors and summarize their pharmacological mechanisms and therapeutic effects in representative cancer types.

3.1. Types of PRMT5 inhibitors

Therapeutic strategies targeting PRMT5 can be broadly classified into four mechanistic categories: substrate-competitive inhibitors, SAM-competitive inhibitors, MTA-cooperative inhibitors, and proteolysis-targeting chimera (PROTAC) degraders. Each class exploits distinct structural or biochemical features of PRMT5, offering complementary avenues for therapeutic intervention.

Substrate-competitive inhibitors block the substrate-binding groove, thereby preventing access of arginine-rich peptide motifs such as glycine–arginine-rich (GAR) sequences found in histones and splicing factors. By mimicking these motifs, they impair substrate methylation while leaving SAM binding intact. EPZ015938 (GSK3326595) and EPZ015666 (GSK3235025) have demonstrated anti-tumor activity by binding the substrate pocket rather than SAM-binding region [84,91,92]. However, the shallow and conformationally flexible nature of the substrate-binding groove has hindered the development of highly potent and selective inhibitors.

SAM-competitive inhibitors occupy the cofactor-binding pocket within the Rossmann fold of PRMT5, directly competing with the methyl donor SAM and thereby blocking methyl transfer to substrates. Although SAM mimetics can efficiently engage the SAM-binding site, their close structural resemblance to the endogenous cofactor often compromises selectivity and increases the risk of off-target interactions [93]. Several agents in this class have advanced through preclinical and clinical development. JNJ-64619178, a dual SAM- and substrate-competitive inhibitor, has demonstrated durable target engagement and antitumor activity in early-phase clinical studies [92,94]. LLY-283 exhibited potent anti-proliferative activity in preclinical glioblastoma and non-small cell lung cancer (NSCLC) models [163]. PRT543 is an orally available, selective PRMT5 inhibitor; it has shown promising antitumor activity in phase 1 studies, particularly in advanced solid tumors and myeloid malignancies [95–97]. PRT382 has demonstrated efficacy in preclinical models of mantle cell lymphoma (MCL) and CLL [98–100]. In addition, PRT811 was designed to penetrate the blood–brain barrier, and has shown therapeutic benefit in glioblastoma and uveal melanoma [101]. PF-06939999 is a potent and selective SAM-competitive PRMT5 inhibitor that suppresses tumorigenesis in NSCLC primarily by disrupting PRMT5-dependent RNA splicing programs [102]. JBI-778 is yet another brain-penetrant SAM-competitive inhibitor currently in early clinical evaluation, aiming to treat primary brain cancers or brain metastases [103].

MTA-cooperative inhibitors represent a novel and highly selective approach that takes advantage of the metabolic vulnerability created by deletion of the MTAP gene, which occurs in approximately 10–15 % of human cancers [104]. MTAP deletion, often co-occurring with CDKN2A loss on chromosome 9p21, leads to accumulation of MTA, a byproduct of polyamine metabolism. MTA is a natural competitive inhibitor of PRMT5 that binds to the SAM pocket, thereby partially suppressing PRMT5 activity in MTAP-deleted cells [105]. As a result, MTAP-deleted cancer cells become hypomorphic for PRMT5 activity and hypersensitive to further pharmacologic inhibition. MTA-cooperative inhibitors are designed to bind preferentially when MTA occupies SAM-binding pocket, stabilizing it in an inactive conformation. This mechanism achieves synthetic lethality in MTAP-deleted tumors while sparing normal MTAP-intact tissues [106]. TNG908, TNG462, MRTX1719, and AMG193 were developed and entered clinical stage in 2022–2023 [20,107–111]. These inhibitors have demonstrated striking selectivity for MTAP-deleted cancer cells, potent efficacy in xenograft models, and encouraging safety profiles with reduced systemic toxicity. Early-phase clinical trials have already begun to report promising activity, highlighting MTA-cooperative inhibition as a transformative paradigm in the development of PRMT5-targeted cancer therapies.

Unlike conventional small molecules that inhibit enzymatic activity, PROTAC degraders promote selective degradation of target proteins through recruitment of E3 ubiquitin ligases, thereby enabling modulation of nonenzymatic and scaffolding functions of PRMT5 [112]. The first PRMT5-targeting PROTAC, MS4322, was developed by conjugating the selective PRMT5 inhibitor EPZ015666 to a VHL E3 ligase ligand, generating a bifunctional molecule that efficiently induces PRMT5 degradation [113]. MS4322 demonstrated comparable efficacy to EPZ015666 in reducing global reduction of SDMA and inhibiting the growth of MCF-7 cells. More recently, YZ-836P, a cereblon (CRBN)-recruiting PROTAC, was developed based on GSK3326595 [114]. YZ-836P effectively induced CRBN-mediated ubiquitination and degradation, demonstrating potent anti-tumor activity in both in vitro and in vivo models of triple-negative breast cancer (TNBC), particularly via modulation of the PRMT5–KLF5 signaling axis.

Collectively, these four mechanistic classes—substrate-competitive, SAM-competitive, MTA-cooperative, and PROTAC degraders—highlight the remarkable versatility of strategies for pharmacologically targeting PRMT5. Each class exploits distinct structural domains or metabolic dependencies of the enzyme, allowing differential modes of inhibition and expanding the therapeutic landscape for clinical application. Building upon this mechanistic foundation, the following section will

discuss how these inhibitors modulate oncogenic signaling and elicit antitumor responses across both hematologic and solid malignancies.

3.2. Lymphoma

PRMT5 is frequently dysregulated in hematologic malignancies and has gained attention as a promising therapeutic target in lymphoid neoplasms. By repressing tumor suppressors such as p53 and promoting the transcriptional activation of oncogenes including MYC and CCND1, PRMT5 contributes to malignant B-cell transformation and lymphoma progression [42,58,62,115].

In diffuse large B-cell lymphoma (DLBCL), which is characterized by high expression of the transcriptional repressor BCL6 [116,117], PRMT5 physically interacts with BCL6 and co-occupies promoters of BCL6 target genes [53]. Through histone modifications and potentially direct regulation of BCL6, PRMT5 enhances the repressive activity of BCL6, thereby silencing genes critical for germinal center B-cell proliferation and survival. Pharmacological inhibition of PRMT5 using GSK591 disrupts the PRMT5–BCL6 complex, reactivates silenced BCL6 target genes, and significantly reduces the viability of DLBCL cells [53]. PRMT5 expression in DLBCL is also positively regulated by B-cell receptor (BCR) signaling. Active BCR signaling increases PRMT5, which in turn facilitates cell-cycle progression and activates the PI3K–AKT pathway, creating a feed-forward pro-survival circuit. Combined inhibition of PRMT5 and AKT induces apoptosis in both established DLBCL cell lines and primary tumor samples and significantly suppresses tumor growth in DLBCL xenograft models [118].

MCL is another B-cell malignancy in which PRMT5 plays a pathogenic role. MCL is associated with poor prognosis and frequent relapse following standard therapy. PRMT5 contributes to MCL progression by epigenetically silencing tumor suppressor genes. For instance, PRMT5 recruits the chromatin remodeler BRG1 to the promoter of ST7, resulting in H4R3me2s deposition and transcriptional repression of ST7, which promotes malignant transformation [119]. Targeting PRMT5 with selective inhibitors has demonstrated strong anti-lymphoma effects in preclinical MCL models. The selective PRMT5 inhibitor PRT382, for example, suppresses the expression of E2F target genes and downregulates signaling through the PI3K–AKT and BCR pathways [120]. Inhibition of AKT activity by PRT382 facilitates the nuclear translocation of FOXO1, thereby activating transcription of the pro-apoptotic gene BAX. Co-treatment with the BCL-2 inhibitor venetoclax amplifies this effect by counteracting BCL2–mediated survival signals, resulting in robust induction of apoptosis through the FOXO1–BAX axis [99].

Mechanisms of resistance to PRMT5 inhibitors in lymphoma are also being actively investigated. Recent single-cell RNA sequencing of MCL patient-derived xenografts has identified upregulation of the mTOR pathway as a potential resistance mechanism. Strikingly, combination treatment with mTOR inhibitor temsirolimus and PRT382 overcame this resistance and significantly prolonged survival in mice bearing resistant MCL xenografts [98]. Genetic lesions commonly found in relapsed/refractory (R/R) MCL, such as mutations or deletions in ATM and TP53, may also influence responses to PRMT5 inhibition. In ATM-deficient MCL cell lines, PRMT5 inhibitors induced accumulation of DNA damage and partially restored p53 activity by altering the splicing of MDM4. This led to the transcriptional activation of p53 target genes and robust induction of apoptosis. Moreover, co-treatment with DNA damage-inducing agents like PARP inhibitors or ATR inhibitors, produced a synthetic lethal effect in ATM-deficient MCL cells, suggesting a promising strategy for aggressive MCL cases harboring DNA repair defects [121].

3.3. Leukemia

PRMT5 is frequently overexpressed in leukemias and correlates with poor clinical outcomes. Both pharmacological and genetic inhibition of PRMT5 have demonstrated therapeutic potential across multiple leukemia subtypes including AML and CLL [40,100,122].

In AML cells, PRMT5 interacts with the transcription factor Sp1 and silences miR-29b through symmetric dimethylation of H4R3, leading to increased expression of FLT3, a kinase critical for leukemic growth. Inhibition of PRMT5 with HLCL-61 reduces FLT3 and Sp1 expression, thereby suppressing leukemic cell proliferation [40]. PRMT5 also catalyzes the methylation of the splicing regulator SRSF1, and loss of PRMT5 results in widespread alternative splicing changes and reduced leukemic cell viability [123]. Additionally, PRMT5 is a direct transcriptional target of the PAFc/MLL1/HOXA9/STAT5 complex in AML, where it mediates H4R3 symmetric dimethylation to sustain progenitor programs and block differentiation. In MLL-rearranged AML models, the PRMT5 inhibitor EPZ015666 induces cell-cycle arrest, differentiation, and reduced proliferation [124]. EPZ015666 also upregulates CDKN1A (p21) and other differentiation markers, particularly in MLL-AF9 fusion AML cells, effectively facilitating cell-cycle exit and cell differentiation [125]. PRT543 disrupts the splicing of genes involved in MYC target regulation and DNA repair in patient samples accompanied by a reduction in global SDMA modifications [96].

In CLL, PRMT5 is aberrantly upregulated due to a disruption of a B cell–specific super-enhancer, leading to MYC-driven transcriptional programs and a stress-response signature that includes impaired DDR. Targeting PRMT5 in CLL has shown encouraging results. EPZ015666 treatment of primary CLL cells and cell lines led to derepression of tumor-suppressive genes such as KLF2, PIK3IP1, and BATF3 and induced apoptotic cell death [122]. Moreover, PRT382 demonstrated superior in vitro cytotoxicity compared to earlier PRMT5 inhibitors and significantly prolonged survival in the Eμ-PRMT5/TCL1 transgenic mouse model of aggressive CLL and Richter's transformation [100]. These findings underscore the role of PRMT5 as a critical dependency in CLL and provide a rationale for clinical trials of PRMT5 inhibitors in R/R CLL, potentially in combination with BTK inhibitors or venetoclax.

3.4. Multiple myeloma

PRMT5 has been identified as a promising therapeutic target in multiple myeloma (MM) [126,127]. PRMT5 is highly expressed in MM cell lines and patient samples and elevated PRMT5 correlates with reduced overall survival and poor prognosis [126,128].

Pharmacological inhibition of PRMT5 has shown encouraging therapeutic efficacy. Treatment with the PRMT5 inhibitor EPZ015666 markedly reduced symmetric dimethylation of TRIM21, an E3 ubiquitin ligase, in MM cell lines [126]. Mechanistically, PRMT5-mediated methylation of TRIM21 suppresses ubiquitination of IKKβ, thereby sustaining NF-κB activation, a key signaling pathway for MM growth and survival. EPZ015666 abrogates this effect by preventing autophagic degradation of IKKβ and subsequent inhibition of NF-κB signaling activity. Another PRMT5 inhibitor, EPZ015938, reduced cell growth and increased apoptosis in both MM cell lines and primary human MM samples harboring diverse molecular defects [127]. Transcriptomic profiling revealed that PRMT5 regulates multiple biological pathways, including alternative splicing, DNA repair, and PI3K/mTOR signaling. Consistently, EPZ015938 treatment reduced ATM and ATR kinase activity, linking its pro-apoptotic effects to impaired DNA repair capacity. Moreover, EPZ015938 also suppressed mTORC1 signaling, and combination treatment with EPZ015938 and the mTOR inhibitor KU-0063794 synergistically reduced MM cell growth, accompanied by increased AMPK activity.

Beyond apoptosis, PRMT5 inhibition has also been linked to pyroptotic cell death. Treatment with GSK591 or genetic knockdown of PRMT5 induced pyroptosis accompanied by upregulation of caspase-1 expression [129]. Mechanistically, PRMT5 inhibition reduced H4R3me2s levels at the CASP1 promoter, thereby derepressing CASP1 expression. Knockdown of CASP1 abrogated PRMT5 inhibition–induced pyroptosis, confirming its central role in this process. Clinically, patients with high PRMT5 and low CASP1 expression exhibited the poorest

survival outcomes, underscoring the critical contribution of pyroptosis to suppressing MM tumorigenesis. These findings reveal an unexpected mechanism of action for PRMT5 inhibitors in MM and raise the possibility of leveraging inflammatory cell death pathways to combat myeloma.

3.5. Lung cancer

PRMT5 promotes lung cancer development and metastasis by orchestrating multiple oncogenic signaling pathways and epigenetic programs. It has been shown to drive EMT and metastasis of lung cancer cells through activation of the AKT signaling pathway [80,130]. Mechanistically, PRMT5 directly methylates AKT1, with two critical symmetric dimethylation sites identified: R391 and R15. Methylation at R391 and R15 facilitates AKT1 recruitment to the plasma membrane and its subsequent activation by PDK1 and mTORC2. This promotes the expression of EMT-associated transcription factors such as SNAIL, TWIST, and ZEB1, which drive the loss of epithelial markers and gain of mesenchymal traits. Accordingly, treatment with the PRMT5 inhibitor GSK591 significantly reduced lung cancer metastasis in part by decreasing AKT1 methylation and activity [79,131].

In addition, PRMT5 sustains multiple oncogenic pathways in lung cancer. PRMT5 methylates KLF5 at R41, a modification that prevents GSK3β-dependent phosphorylation and subsequent proteasomal degradation, thereby stabilizing KLF5 and maintaining its oncogenic activity. Consequently, PRMT5 inhibition with GSK595 reduces KLF5 expression and significantly impairs tumor growth in preclinical models, highlighting the therapeutic potential of targeting the PRMT5–KLF5 axis in lung cancer [47]. PRMT5 also reinforces Hedgehog signaling by methylating GLI1, the transcriptional effector of the Hedgehog pathway. Methylation of GLI1 by PRMT5 inhibits its ubiquitination, resulting in its accumulation and nuclear retention; this establishes a positive feedback loop wherein GLI1 can transcriptionally upregulate PRMT5 and other pathway components [132]. Furthermore, PRMT5 enhances resistance to extrinsic apoptosis in lung cancer cells by stabilizing the long isoform of c-FLIP (CFLAR-L). PRMT5 methylation of CFLAR-L reduces its ubiquitination and degradation, thereby maintaining high c-FLIP levels which inhibit caspase-8 activation and apoptosis. Elevated c-FLIP also promotes EMT and FoxM1-driven cell-cycle progression, linking PRMT5 activity to both apoptosis evasion and metastasis [133].

PRMT5 is a key modulator of inflammatory signaling in lung tumors as well. It amplifies the IL-6/JAK/STAT3 pathway by methylating Smad7 at R57, which sequesters Smad7 in the gp130 receptor complex and potentiates STAT3 activation [83]. Furthermore, PRMT5-catalyzed methylation of STAT3 at R609 is required for maximal STAT3 transcriptional function and has been tied to the maintenance of lung cancer stem-like cells [84].

From a therapeutic standpoint, PRMT5 inhibition in lung cancer models has demonstrated both direct antitumor effects and immunemodulatory consequences. Treatment with the PRMT5 inhibitor GSK591 led to significant tumor growth suppression; however, it also induced a compensatory upregulation of PD-L1 in tumor cells, potentially attenuating anti-tumor immunity[85]. This suggests that while PRMT5 inhibitors can control tumor growth, they might concurrently enable tumor cells to better escape immune attack. A promising strategy to address this is combining PRMT5 inhibitors with immune checkpoint blockade. Recent studies showed that the MTA-cooperative PRMT5 inhibitor MRTX1719 enhances the efficacy of anti–PD-1 therapy in syngeneic lung cancer models, resulting in superior tumor regression and increased infiltration of $CD8^+$ T cells [134]. Such combination strategies may exploit the tumor-intrinsic vulnerabilities associated with PRMT5 loss while simultaneously mitigating immune escape by maintaining PD-L1 regulation.

Additionally, PRMT5 inhibitors have been shown to disrupt the splicing machinery in lung cancer cells, providing another avenue for therapeutic action. Treatement with JNJ-64619178 led to loss of symmetric dimethylation on Sm proteins (SmD1/D3), indicating spliceosome inhibition, and induced broad antiproliferative effects in both SCLC and NSCLC models [94,135]. Moreover, PRMT5 methylates the tumor suppressor Mxi1, which promotes Mxi1 proteasomal degradation via β-Trcp ligase. Consequently, inhibition of PRMT5 with EPZ015666 stabilizes Mxi1, leading to impaired DNA repair pathways and enhanced radiosensitivity in lung cancer cells [136].

3.6. Breast cancer

Elevated PRMT5 expression is frequently observed in breast cancers and correlates with aggressive disease, therapeutic resistance, and poor patient prognosis [137,138]. The subcellular localization of PRMT5 is also associated with clinical outcomes. Cytoplasmic PRMT5 is predominantly detected in TNBC tissues [12], whereas nuclear PRMT5 correlates with more favorable responses to tamoxifen therapy [89]. These findings suggest that the subcellular localization of PRMT5 may serve as a potential predictive biomarker in breast cancer.

Mechanistically, PRMT5 sustains oncogenic transcriptional programs by stabilizing KLF4 and KLF5, thereby promoting stemness, proliferation, and survival in TNBC [114,139,140]. These transcription factors drive stem cell–like properties and tumor initiation capacity. Therapeutically, this insight has prompted efforts to disrupt the PRMT5–KLF axis. For example, WX2–43 is a small-molecule inhibitor that selectively blocks the interaction between PRMT5 and KLF4, leading to KLF4 destabilization and suppression of the self-renewal of breast cancer stem cells [140]. Likewise, YZ-836P, a PROTAC degrader, effectively reduces PRMT5 protein levels and thereby diminishes KLF5-driven transcription, leading to G1 cell-cycle arrest and induction of apoptosis in TNBC models [114]. Another non-histone target of PRMT5 in breast cancer is PDCD4, a tumor suppressor that inhibits protein translation. PRMT5-mediated methylation of PDCD4 impairs its tumor-suppressive function, contributing to increased tumor cell growth and invasion [141].

PRMT5 also exerts profound effects on the epigenetic and transcriptional landscape of breast cancer. Pharmacological inhibition with EPZ015666 induces apoptosis and cell growth arrest accompanied by reduced symmetric dimethylation at H4R3 in TNBC preclinical models [12]. At the FOXP1 gene locus, PRMT5-catalyzed H3R2me2s serves as a chromatin mark that recruits the WDR5/SET1/MLL complex, thereby facilitating H3K4me3 deposition and active transcription of FOXP1. Upregulation of FOXP1 enhances cancer stemness and contributes to therapeutic resistance [37]. Consistently, circGSK3β is highly expressed in breast cancer cells and enhances PRMT5 expression. Elevated PRMT5 activity, in turn, increases H3K4me3 levels at the CD274 promoter, resulting in PD-L1 upregulation and immune evasion [86]. In the context of EMT and metastasis, PRMT5 cooperates with the transcriptional repressor Slug and the lysine demethylase LSD1. PRMT5 and LSD1 form a complex with Slug at *CDH1* promoters, where PRMT5 deposits H4R3me2s and LSD1 removes H3K4me2 marks. Concurrently, PRMT5/LSD1/Slug can activate mesenchymal genes like VIM through coordinated histone modifications; collectively these alterations drive mesenchymal transition. Targeting both PRMT5 and LSD1 produced a synergistic effect in suppressing breast cancer metastasis in preclinical models, as the combination more effectively restored E-cadherin and reduced vimentin than either agent alone [142].

PRMT5 activity has been linked to several mechanisms of therapy resistance in breast cancer, including chemotherapy resistance and evasion of ferroptosis. PRMT5 symmetrically dimethylates ALKBH7 at R368, which promotes the formation and nuclear translocation of an ALKBH5–ALKBH7 complex [143]. Inside the nucleus, ALKBH5 removes m6A methylation from mRNAs, including the transcript of the DNA repair gene BRCA1. By facilitating ALKBH5 activity, PRMT5 ultimately increases BRCA1 expression, enhancing DNA repair and reducing the efficacy of doxorubicin-induced DNA damage. Consequently, PRMT5 inhibition sensitizes tumors to doxorubicin by downregulating BRCA1

expression [143]. In line with this, PRMT5 inhibition has been shown to synergize with DNA-damaging agents; for example, GSK3326595 sensitized breast cancer cells to etoposide and cisplatin by down-regulating PI3K/AKT signaling and DNA repair pathways [79]. Similarly, PRMT5 inhibition also augmented DNA damage and potentiated the antitumor efficacy of PARP inhibitor Olaparib in a BRCA1-mutated TNBC patient-derived xenograft model [144]. EPZ015666 also exhibited synergistic effect with the EGFR inhibitor Erlotinib in an EGFR-high TNBC model [12]. Enhanced PRMT5 activity leads to ferroptosis resistance by dimethylation of KEAP1 and subsequent suppression of NRF2-dependent anti-oxidant defenses. Importantly, pharmacological inhibition of PRMT5 with GSK3326595 reverses this phenotype, restoring ferroptosis and potentiates the anti–PD-1 therapy in TNBC preclinical models [74].

3.7. Glioblastoma

PRMT5 is markedly upregulated in high-grade gliomas including glioblastoma multiforme (GBM), and its expression inversely correlates with patient survival [9]. Functional studies demonstrate that PRMT5 is essential for the survival of GBM cells, although its effects differ between differentiated tumor cells and glioma stem cell (GSC) populations. Differentiated GBM cells depend on PRMT5 for viability and undergo apoptosis upon its inhibition. By contrast, inhibition of PRMT5 in GSCs induces cellular senescence, characterized by G1/S cell-cycle arrest associated with upregulation of p27Kip1 and reduced phosphorylation of Rb [145]. PRMT5 also represses the PTEN promoter by depositing symmetric dimethylation at H3R8 and H4R3, resulting in reduced PTEN expression and enhanced PI3K/AKT signaling, a key pathway for tumor initiation and progression. Based on this mechanism, pharmacologic PRMT5 inhibition increases sensitivity to Trametinib, a MEK1/2 inhibitor, by suppressing Trametinib-induced HER3-AKT activation and promoting apoptosis. Second-generation PRMT5 inhibitors, such as CMP5, CMP12, HLCL-65, and HLCL-66, also show anti-GBM efficacy consistent with this signaling axis [146].

Beyond signaling regulation, PRMT5 exerts oncogenic effects through splicing control. By methylating snRNP proteins, PRMT5 maintains spliceosome integrity, with transcripts involved in cell-cycle regulation being particularly sensitive [147]. Inhibition with LLY-283 reduces SDMA marks on SmB/B', disrupting spliceosome assembly and leading to aberrant splicing of key transcripts. These splicing alterations leads to proteome dysregulation and loss of essential proteins for cell proliferation [148]. Additionally, PRMT5-dependent methylation of hnRNP A1 modulates IRES-dependent translation of oncogenes such as cyclin D1 and c-MYC [147]. EPZ015666 disrupts cell-cycle progression by inducing G2/M accumulation and reducing S-phase entry, suppressing GBM growth both in vitro and in vivo [57]. From a therapeutic perspective, PRMT5 inhibition has been shown to synergize with mTOR blockade. Inhibition of PRMT5 reduces hnRNP A1-mediated IRES translation of cyclin D1 and c-MYC, enhancing apoptotic responses when combined with mTOR inhibitors. Consistent with this, EPZ015666 demonstrated synergy with the mTOR kinase inhibitor PP242, producing significant anti-GBM effects in preclinical models [149].

4. Ongoing clinical development of PRMT5 inhibitors

The clinical translation of PRMT5 inhibitors has evolved significantly, moving from early broad-spectrum inhibitors to more targeted synthetic lethal approaches. Ongoing clinical trials of PRMT5 inhibitors are summarized in Table 2.

The most dynamic area of current PRMT5 drug development lies in MTA-cooperative inhibitors such as AMG193, MRTX1719, and TNG462 [20,21,150,151]. Early phase 1 results for AMG193 and MRTX1719 have provided proof-of-mechanism, demonstrating robust reductions in symmetric arginine dimethylation within patient tumors and preliminary evidence of antitumor activity. Importantly, these agents have so far demonstrated improved tolerability profiles, particularly with respect to hematological toxicity, compared to the first-generation PRMT5 inhibitors. For example, dose-limiting toxicities such as thrombocytopenia and anemia, which were common with SAM-competitive inhibitors, appear less severe with MTA-cooperative compounds, likely due to their selectivity for MTAP-null tumor cells. As a result, these trials are now expanding into histology-specific cohorts—including lung cancer, mesothelioma, pancreatic cancer, and others with high rates of MTAP deletion—and investigating rational combination strategies with immune checkpoint inhibitors or KRAS-targeted agents [134,152,153]. In addition, the CNS-penetrant agent TNG908 is being evaluated in glioblastoma and other brain tumors, while TNG462 has been optimized to further refine potency and pharmacokinetic properties [21,111].

By contrast, inhibitors targeting the substrate or SAM-binding pockets—such as GSK3326595, JNJ-64619178, PRT811, and PRT543—have yielded valuable biological insights but shown more limited clinical activity as monotherapies. For instance, GSK3326595 advanced to phase I/II testing in myelodysplastic syndromes and AML, where only modest clinical benefit was observed and trials were ultimately terminated due to limited efficacy [154]. Similarly, JNJ-64619178 completed early-phase studies in solid tumors and lymphomas, showing occasional disease stabilization but insufficient activity to support broad clinical expansion. PRT543 has demonstrated pharmacodynamic activity and disease stabilization in adenoid cystic carcinoma and myeloid neoplasms, whereas PRT811—a brain-penetrant compound—remains in clinical evaluation for gliomas and uveal melanoma [95,96,155]. Although clinical efficacy signals from these programs have been modest, they provide critical pharmacological benchmarks and continue to explore niches—particularly CNS malignancies—where MTA-cooperative inhibitors may be less effective.

Table 2
Ongoing clinical trials of PRMT5 inhibitors.

Drug	Company	Phase	Indication	NCT identifier	Ref
AMG193	Amgen	I/II	Advanced Solid Tumors with MTAP deficiency	NCT05094336	[150]
AZD3470	AstraZeneca	I/II	Relapsed/Refractory Haematologic Malignancies	NCT06137144	[156]
BAY 3713372	Bayer	I	MTAP-deleted Solid Tumors	NCT06914128	
BGB−58067	BeiGene	Ia/b	Advanced Solid Tumors with MTAP deficiency	NCT06589596	[157]
GSK3326595	GlaxoSmithKline	I/II	AML, MDS	NCT03614728	[154]
JNJ−64619178	Janssen Pharmaceuticals	I	NHL, MDS, advanced solid tumors	NCT03573310	[158–161]
PRT543	Prelude Therapeutics	I	r/r Advanced solid tumors, r/rDLBCL, r/r myelodysplasia, r/r adenoid cystic carcinoma, r/r MCL, r/r AML	NCT03886831	[95,96]
PRT811	Prelude Therapeutics	I	Advanced solid tumor, Recurrent glioma, CNS lymphoma	NCT04089449	[155]
MRTX1719	Mirati Therapeutics	I/II	Mesothelioma, NSCLC, Malignant peripheral nerve sheath tumors, PDAC, advanced solid tumors, Recurrent glioblastoma	NCT05245500 NCT06883747	[20]
SCR−6920	Jiangsu Simcere Pharmaceutical	I	advanced solid tumors and relapsed/refractory non-Hodgkin lymphoma(NHL).	NCT05528055	[162]
TNG908	Tango Therapeutics	I/II	MTAP-deleted solid tumors	NCT05275478	[21]
TNG462	Tango Therapeutics	I/II	MTAP-deleted Solid Tumors	NCT05732831	[151]

5. Conclusion

PRMT5 has emerged as a multifaceted oncogenic driver that integrates epigenetic regulation, RNA processing, and cellular signaling in cancer. Recent advances, particularly MTA-cooperative inhibitors have shown synthetic lethal effects in MTAP-deleted cancers, underscoring the potential of precision medicine approaches. Despite this progress, challenges such as therapeutic resistance, toxicity, and limited brain penetration remain. Future success will rely on rational drug combinations, biomarker-driven patient selection, and optimized delivery strategies. Ultimately, PRMT5 inhibition offers a promising therapeutic avenue, exemplifying how mechanistic insights into epigenetic enzymes can be harnessed for precision oncology.

CRediT authorship contribution statement

Inah Hwang: Writing – review & editing, Writing – original draft, Supervision. **Jiye Kim:** Writing – review & editing, Writing – original draft. **Joohyun Lee:** Writing – review & editing, Writing – original draft.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors used ChatGPT(version GPT-5) to assist in English editing. After using the tool, all authors thoroughly reviewed and revised the content as necessary and take full responsibility for the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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