Research progress on PRMTs involved in epigenetic modification and tumour signalling pathway regulation (Review)

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Abstract. Posttranslational modification (PTM) of proteins is essential for increasing protein diversity and maintaining cellular homeostasis, but uncontrolled modification may lead to tumorigenesis. Arginine methylation is a tumorigenesis-related PTM that affects protein function through protein-protein and protein-nucleic acid interactions. Protein arginine methyltransferases (PRMTs) have vital roles in signalling pathways of tumour-intrinsic and tumour-extrinsic microenvironments. The present review summarizes the modifications and functions of PRMTs in histone methylation and nonhistone methylation, their roles in RNA splicing and DNA damage repair and the currently known functions in tumour metabolism and immunotherapy. In conclusion, this article reviews the latest research progress on the role of PRMTs in tumour signal transduction, providing a theoretical basis for clinical diagnosis and treatment. Targeting PRMTs is expected to provide new directions for tumour therapy.

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1. Introduction

Posttranslational modification (PTM) is critical for protein diversity (1). Modification of proteins at one or more sites may determine protein conformation, subcellular localization, type of interacting protein, and protein stability and activity. The PTM process is catalysed by a variety of enzymes, including enzymes involved in phosphorylation, acetylation, ubiquitination, methylation and hydroxylation; conversely, the process may be reversed by enzymes that antagonize these processes, such as phosphatases, deubiquitinases, deacetylases and demethylases (1).

Protein arginine methylation is a common PTM catalysed by protein arginine methyltransferases (PRMTs) (2). In 1967, Paik and Kim (3) first discovered methylated arginine in a nuclear protein of calf thymocytes. The first member of the PRMT family, PRMT1, was identified in 1996, followed by other members (4). Protein arginine methylation has a role in the maintenance of key cellular processes, such as tissue homeostasis and disease phenotype (2).

2. Classification, structure and function of PRMTs

Based on the number and position of methyl groups on the ω-guanidino nitrogen atom of the protein arginine, arginine methylation modification may be divided into ω-N^G-monomethylarginine (MMA), ω-N^G,N^G-asymmetric dimethylarginine (ADMA) and ω-N^G,N'^G-symmetric dimethylarginine (SDMA). The process by which PRMTs methylate arginine to produce MMA, ADMA and SDMA is provided in Fig. 1. Among them, type I PRMTs include PRMT1-4, -6 and -8, which methylate MMA and ADMA; type II PRMTs include PRMT5 and -9, which methylate MMA and SDMA; and type III PRMTs include PRMT7, which methylates MMA (5). The protein structure, modulation function and chromosomal location of each member of the PRMTs are provided in Fig. 2.

Arginine is a basic amino acid with a positively charged guanidine group containing five potential hydrogen bond donors, which may interact with negatively charged molecules (6). PRMTs transfer the methyl group from S-adenosine methionine (SAM) to the guanidino group of arginine in protein substrates, resulting in S-adenosyl homocysteine and methylated proteins. After methylation of arginine residues, the distance between side chains increases and the molecular configuration changes. At the same time, the addition of methyl groups reduces the number of potential hydrogen bond donors, resulting in enhanced hydrophobicity of methylated arginine, which in turn affects intramolecular and intermolecular interactions, such as protein-to-protein, protein-to-nucleic acid, as well as protein structure and stability, ultimately affecting the biological function of the modified protein (7).

PRMT1 is the most widely studied PRMT enzyme due to its powerful methyl transfer function, accounting for >85% of all modifications of PRMTs (8). The residues M48, E100, E144, E153, M155 and H293 on the active site of PRMT1 are critical for substrate and cofactor interactions (9). Mutations in these active sites weaken or result in the loss of the catalytic activity of PRMT1, leading to ADMA synthesis disorders (10). The interaction between PRMT2 and RB downregulates the activity of E2F through multiple mechanisms, including histone methylation, transcription factor (TF) methylation and RNA splicing (11). PRMT3 is localised in the cytoplasm and its protein structure includes a catalytic core and a zinc finger domain. Of note, zinc finger domains not only help to recognise RNA substrates but also regulate catalytic activity by recruiting interacting proteins (12). PRMT4, also known as coactivator-associated arginine methyltransferase 1 (CARM1), is mainly located in the nucleus and normally promotes transcription. CARM1 consists of a unique N-terminal EVH1 domain (residues 28-140) that binds to a proline-rich sequence that is essential for substrate recognition and catalytic activity (13). PRMT5 is a major type II PRMT consisting of four domains: An N-terminal TIM-barrel domain, an intermediate Rossmann fold, a C-terminal β-barrel subunit and a dimerization arm (14). The conserved F379 residue of PRMT5 methylates the production of SDMA. The F379M mutation not only increased the methylation activity of PRMT5 but also altered product specificity by generating SDMA and ADMA of H4R3. By contrast, both F379G and F379A mutations significantly reduced PRMT5 activity (14). PRMT6, a signature tag for epigenetic transcriptional repression, specifically methylates ADMA of histone H3 (15). PRMT7 is the only type III PRMT, and compared with other types of PRMTs, the protein structure of PRMT7 includes a narrower substrate-binding site, which may lead to catalytic production of MMA (16). PRMT8 is significantly and specifically highly expressed in brain and neuronal tissues. The N-terminal region of PRMT8 is able to bind to the plasma membrane, and there is a substrate binding site in the middle, which is crucial for PRMT8 methylation activity (17). PRMT9 is a recently identified type II PRMT that includes MTase domains and forms a pseudodimer for substrate binding (18).

3. Arginine methylation of histones and nonhistones

Histone methylation and transcriptional regulation. Arginine methylation of histone tails is an epigenetic modification catalysed by PRMTs and regulates gene expression. PRMTs may methylate H2AR3, H2AR29, H3R2, H3R8, H3R17/26/42, H4R3 and H4R17/19, as presented in Fig. 3. Structural analysis indicated that electrostatic interactions have a mechanistic role in the process of substrate methylation catalysed by PRMTs. It has been indicated that PRMT1, -3, -5 and -8 preferentially methylate histone H4, while PRMT4/CARM1 preferentially methylates histone H3 (19). The detailed functions of the PRMT-methylated histones H2A, H3 and H4 are presented in Table I.

PRMT5-7 are able to methylate H2A. Since the first five residues of H2A and H4 are identical, it is likely that most of the methylation of H4R3 also applies to H2AR3 (20). A systematic analysis of the H2A methylation status revealed that H2AR29me2 was specifically enriched in genes inhibited by PRMT6, suggesting that H2AR29me2 is involved in transcriptional repression (21). The haemagglutinin-PRMT5 complex was also able to monomethylate and symmetrically dimethylate bovine histone H2A (22). Chromatin immunoprecipitation revealed that PRMT7 dimethylates H2AR3 and H4R3 and is enriched at target DNA repair genes in parental cells (23). Studies have indicated that PRMTs are able to methylate H2A and mainly take part in transcriptional repression, but the underlying regulatory mechanism remains to be elucidated.

H3 methylation exerts transcriptional activation or transcriptional inhibition by PRMT2, CARM1 and PRMT5-7. For instance, PRMT2 is responsible for generating H3R8me2a. H3R8me2a enrichment at the BCL2 promoter may increase its accessibility to STAT3, promoting Bcl2 gene expression (24). PRMT2 acts as a transcriptional coactivator for oncogenic gene expression programs in glioblastoma multiforme (GBM) pathogenesis. PRMT2-mediated H3R8me2a enrichment at promoters and enhancers is closely associated with known active histone marks and is required for the maintenance of target gene expression (25). CARM1 may methylate H3R17, H3R26 and H3R42 and is recognised by tudor domain containing 3 to function as a coactivator (26). It is necessary that PRMT5 accumulation activates H3R2me1/me2s and recruitment of the WD repeat domain 5 (WDR5)/mixed linage leukemia (MLL) complex to promote H3K4me3, which in turn activates transcription (27-30). Recruitment of PRMT5 to the forkhead box (FOX)P1 promoter may increase H3R2me2s and H3K4me3 (29). The potential interaction of PRMT5-mediated H3R2me1 with MLL complexes (absent, small, or homologous 2 and WDR5) may activate the expression of metastasis-related genes, such as vimentin, snail family transcriptional repressor 1, snail family transcriptional repressor 2 and cadherin 2 (28). Genotoxic stress induces interactions among β-catenin, ATM phosphorylated Jun isomerization protein 2 and PRMT5, promoting redox-related gene transcription. During this process, PRMT5-mediated recruitment of H3R2me1/H3R2me2s to the WDR5/MLL complex leads to transcriptional activation of H3K4me3 and redox-related genes (30). H3R2me2a acts as a repressive mark that antagonises H3K4me3, but H3R2 is also symmetrically dimethylated (H3R2me2s) by PRMT5 and PRMT7 and is present in euchromatic regions (31). Profiling of H3-tail interactors indicated that H3R2me2s excludes binding of RBBP7, a central component of the co-repressor complexes

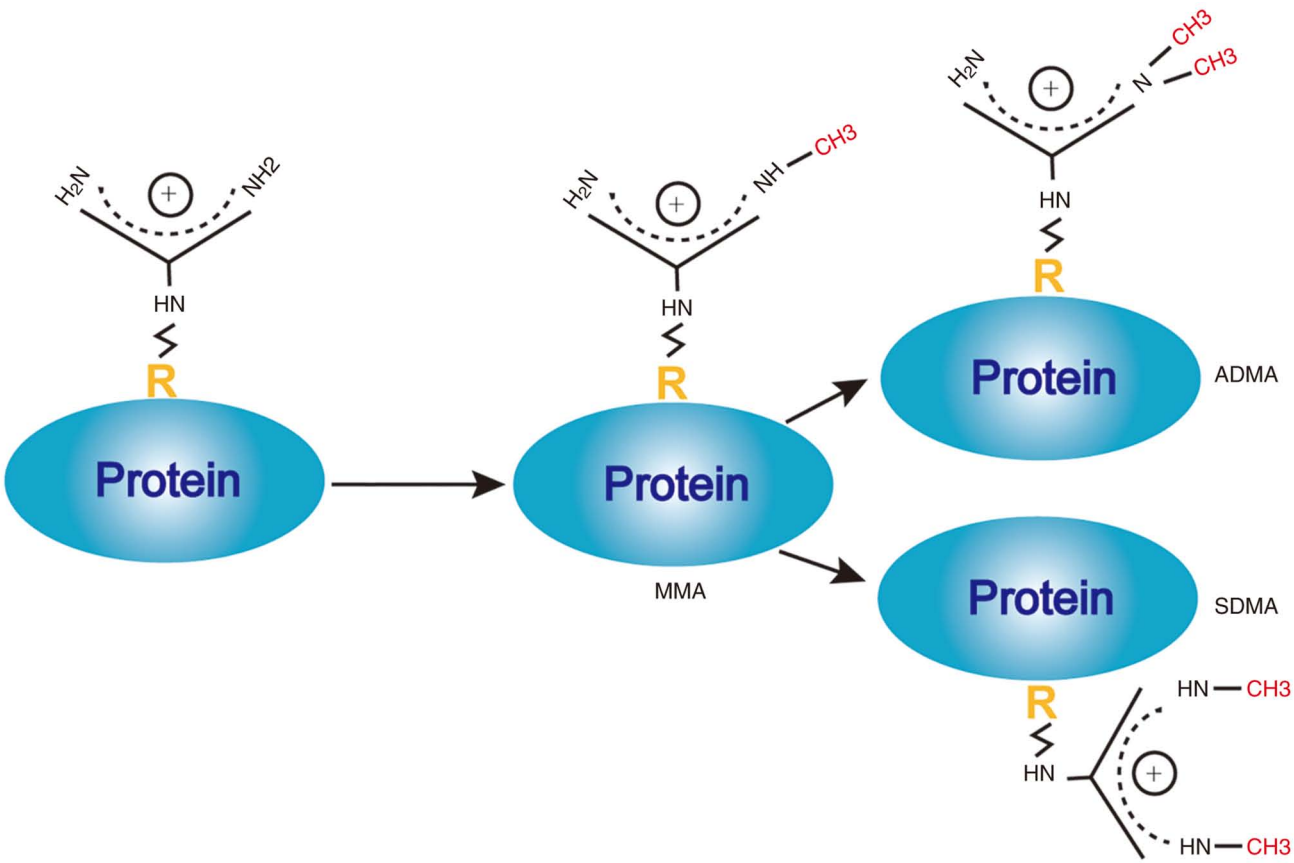

Figure 1. Protein arginine methyltransferases catalyse methylation at arginine to generate MMA, ADMA and SDMA. Arginine residues in the tails of histones may be MMA, ADMA or SDMA. The MMA form of arginine is generally regarded as an intermediate prior to the dimethylated state. This schematic was adapted from the review by Yang and Bedford (169). MMA, ω-N^G-monomethylarginine; ADMA, ω-N^G,N^G-asymmetric dimethylarginine; SDMA, ω-N^G,N'^G-symmetric dimethylarginine.

SIN3 transcription regulator family member A, nucleosome remodeling and deacetylase and polycomb repressive complex 2. Conversely, H3R2me2s may enhance binding of WDR5, which is a common component of the coactivator complexes MLL, nuclear localization signals 1, Ada two-A containing, SET-domain-containing 1A and SET-domain-containing 1B (31). PRMT6-mediated H3R2me2a inhibits transcription by preventing H3K4me3 readers from binding (32). Of note, H3R8me2s and H4R3me2s are mainly considered repressive markers, but they have also been implicated in the transcriptional activation of certain genes, such as fibroblast growth factor receptor (FGFR)3 and eukaryotic initiation factor 4E expression in colorectal cancer (33) and androgen receptor expression in prostate cancer (34). Overall, for the regulation of H3 methylation, the symmetric arginine dimethylation of H3 generally has a role of transcriptional activation, while the asymmetric arginine dimethylation frequently has a role in transcriptional inhibition.

The methylation of H4 also has a key role in regulating the activation and repression of transcription. For instance, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4, the ATPase subunit of the switch/sucrose nonfermentable (SWI/SNF) chromatin remodelling complex, acts as a binder for PRMT1 to methylate H4R3me2a and upregulate epidermal growth factor receptor (EGFR) in colorectal cancer (35). PRMT5-mediated H4R3me2s have been found on promoters of tumour suppressor and cyclin-dependent kinase (CDK) suppressor genes, which silence cancer-cell proliferation (36,37). Menin (MEN1) has an essential role in both repressing and activating gene expression. In MEN1-excised cells, the levels of both PRMT5 binding and H4R3m2s were decreased at the GLI1 promoter (38). MEN1 is a crucial factor for binding of the Sonic Hedgehog ligand to its receptor Patched 1 and subsequent activation of the Hedgehog signalling pathway. Of note, MEN1 mutants have reduced binding to PRMT5 and fail to impart the repressive H4R3m2s mark at the growth arrest specific 1 promoter, resulting in its elevated expression (38,39). Pharmacologic inhibition of Hedgehog signalling significantly reduces the proliferation of insulinoma cells and promotes the expression of Hedgehog signalling targets (39). Zinc finger E-box binding homeobox 1 (ZEB1), a zinc finger TF, is a key factor for epithelial to mesenchymal transition (EMT) (40). PRMT1 impacted the EMT process by mediating the asymmetric dimethylation of H4R3me2as at the ZEB1 promoter to activate its transcription, indicating the essential roles of this epigenetic control in EMT (41). Otherwise, exogenous TGFβ promotes EMT through PRMT5-MEP50 catalysing arginine monomethylation and dimethylation (42). PHD finger protein 1 (PHF1) recognizes H4R3me2s and recruits CUL4Bring E3 ligase through PHF to form a complex, silencing the expression of E-cad and FBXW7 to promote cell growth and migration (43). In addition, in 293 cells, overexpression of PRMT3 may increase the level of H4R3me2a, but the specific

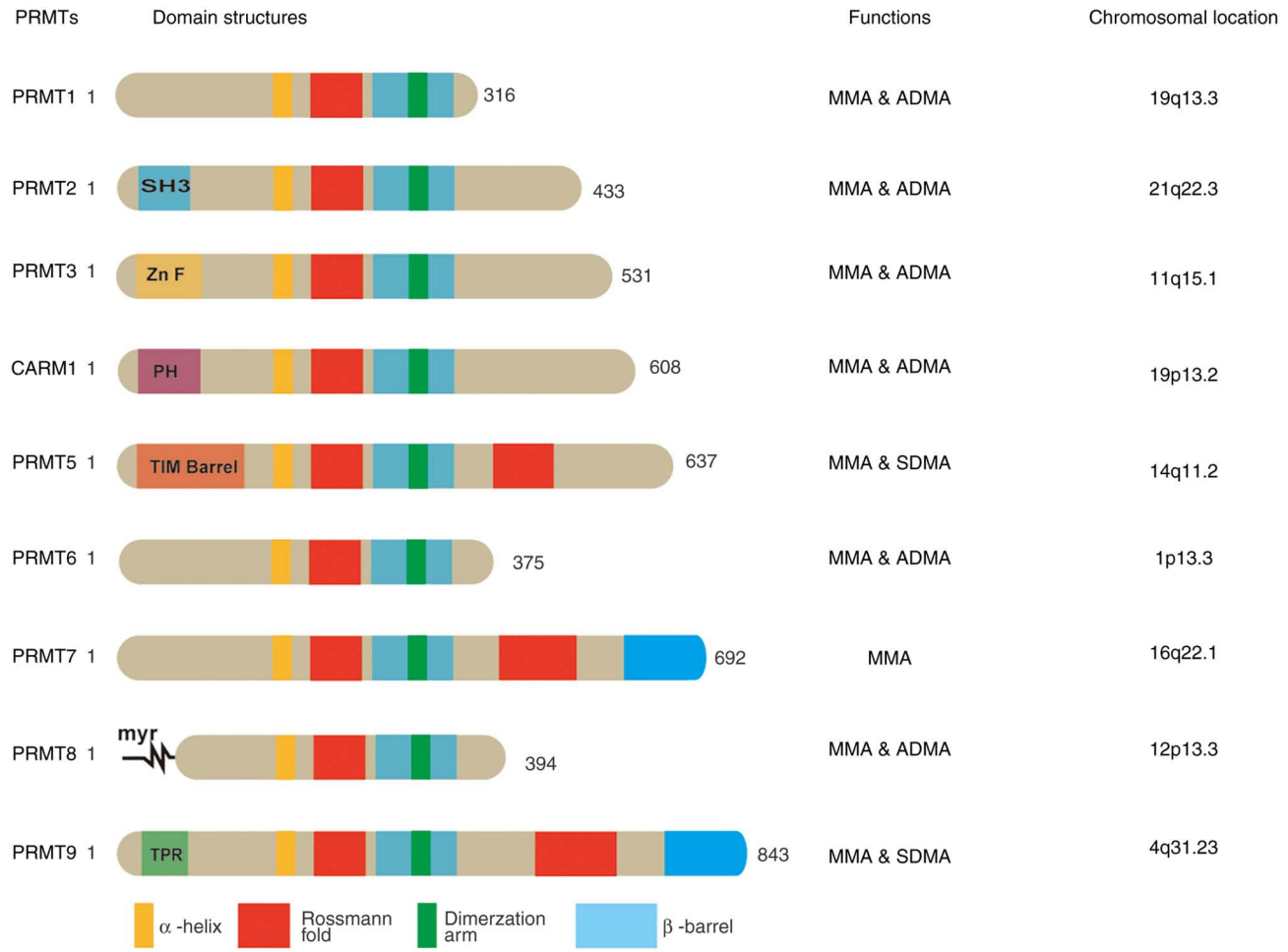

Figure 2. Protein structure, methylation function and chromosomal location of each member of the PRMT family. A total of 9 mammalian PRMTs were identified and these have unique signatures (yellow, red, green and blue) with high sequence similarity. PRMT, protein arginine methyltransferase; MMA, monomethylarginine; ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine; CARM1, coactivator-associated arginine methyltransferase 1; SH3, SH3 domain; ZnF, zinc finger motif; PH, Pleckstrin homology domain; myr, myristoyl; TPR, tetratricopeptide repeat.

mechanism remains to be clarified (44). In conclusion, these findings reveal a novel link between PRMTs and H4, whereby PRMTs epigenetically regulate tumour signalling pathways, revealing them as targets for treating tumours.

Dynamic crosstalk between different histone modification types may affect gene expression. PRMT7 methylates H4R17me1 and allosterically enhances H4R3me2 of PRMT5, which in turn inhibits subsequent H3K4me3, H3Ac and H4Ac (45). Deacetylation of H3K9 by H3R8me2s is a transcriptional repression marker (46), whereas H4R3me2s is associated with H4K5 acetylation and may serve as a transcriptional activation marker (47). Of note, an increasing number of studies have demonstrated the existence of nonlinear crosstalk between different histone modification types, leading to the diversity of protein functions.

PRMTs may also affect protein tail modification by targeting microRNA (miRNA/miR) and regulating tumour gene expression. PRMT5 repressed the transcription of the miR-99 family by symmetrical dimethylation of H4R3, which increased FGFR3 expression and in turn activated Erk1/2 and Akt, leading to cell growth and metastasis in lung cancer (48). PRMT5 knockdown results in miR33b, miR96 and miR503 derepression through loss of repressive complex recruitment targeting miRNA promoters. PRMT5 is overexpressed in B-cell lymphoma and promotes the binding of miR33b, miR96 and miR503 to the 3'-untranslated region of cyclin D1 and c-MYC mRNAs, indirectly leading to enhanced cyclin D1 and c-MYC expression, which reinforces the relevance of PRMT5 in promoting lymphoma cell growth and survival (49).

Methylation of nonhistones. According to the function of non-histones after methylation, PRMTs may be divided into five types, including TFs, RNA-binding proteins (RBPs), DNA damage repair proteins, RNA splicing proteins and functional proteins in cell signalling pathways. The detailed functions of PRMT-methylated nonhistones are provided in Table II.

TFs may combine with RNA polymerase to form a transcription initiation complex, which jointly participates in the process of transcription initiation. E2F-1 may regulate transcription in a methylation-dependent manner (50). PRMT5 and -1 methylate E2F-1 to generate functionally opposite effects. The DNA damage response (DDR) induces E2F-1 methylation by PRMT1, increases E2F-1 expression levels and activates apoptotic gene transcription. Conversely, PRMT5 methylation of E2F-1 is recognised by Tudor domain protein, p100/tudor-SN (TSN), which reduces the E2F-1 half-life and

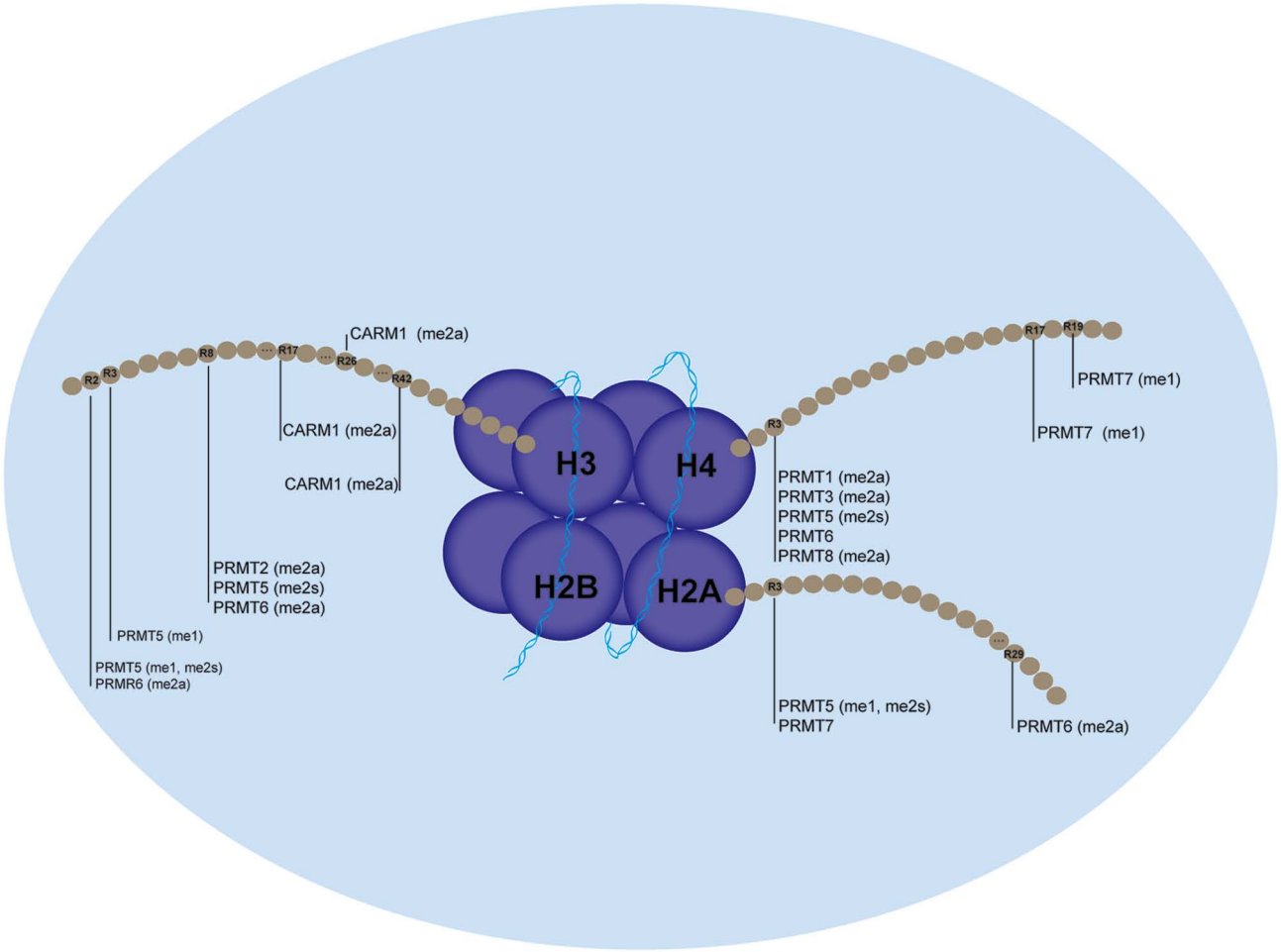

Figure 3. PRMTs methylate arginine on histones H2A, H2B, H3 and H4. PRMT5, PRMT6 and PRMT7 are able to methylate H2A. PRMT2, CARM1, PRMT5 and PRMT6 are able to methylate H3. PRMT1, PRMT3, PRMT5, PRMT6, PRMT7 and PRMT8 can methylate H4. PRMT, protein arginine methyltransferase; CARM1, coactivator-associated arginine methyltransferase 1.

increases cell viability. During cell cycle progression, the binding of E2F-1 to cyclin A masks the PRMT1 methylation of E2F-1, thereby inhibiting apoptosis (50). Sterol regulatory element binding protein 1 (SREBP1) is a TF regulated for *de novo* fatty acid synthesis. PRMT5 methylation of SREBP1 prevents its phosphorylation by glycogen synthase kinase (GSK)3β, but it is subsequently ubiquitinated by F-box and WD repeat domain containing 7 (FBXW7), increasing adipogenesis and promoting tumour growth in hepatocellular carcinoma (HCC) (51). BCL6 is a transcriptional repressor and master regulator of normal germinal centre (GC) formation and GC-derived B-cell lymphomas. PRMT5 methylation of BCL6 at R305 downregulates the activity of BCL6 target genes, inhibiting the growth of diffuse large B-cell lymphoma (52).

ICP27 is an RBP that has a crucial role in the gene expression and replication of herpes simplex virus type 1 (HSV-1) (53). Methylation of ICP27 at residues R138, R148 and R150 by PRMT1 is responsible for the formation of ICP27 nuclear foci, RNA-binding affinity and SRPK interaction. Hypomethylation of ICP27 may significantly inhibit HSV-1 replication, suggesting that PRMT inhibitors have an important role in HSV-2 therapy (53). RNA and transporters compete for binding to nuclear poly(A)-binding protein 1 (PABPN1), but methylation of PABPN1 at R289 reduces the binding capacity between PABPN1 and transporters by ~10-fold, resulting in promotion of the PABPN1-RNA interaction (54). Although eIF4A1 shares >80% sequence similarity with eIF4A2 and -3, only residue R368 of eIF4A1 protein is selectively methylated by PRMT1, whereas other eIF4A isotypes are not (55).

Phosphorylation and ubiquitination are key components of the DDR and arginine methylation is no exception. Deficiency of PRMT1 and PRMT5 leads to spontaneous DNA damage, checkpoint defects and genomic instability in mouse embryonic fibroblasts (56,57). PRMT1 is involved in the methylation of DNA repair proteins, including meiotic recombination 11 (MRE11), p53 binding protein 1, heterogeneous nuclear ribonucleoprotein U like 1, breast cancer 1 (BRCA1) and Separase, which ensure the maintenance of genome stability through homologous recombination (HR) repair and nonhomologous end-joining (NHEJ) (2,58). MRE11 is an essential component of the MRE11-RAD50-NBS1 (MRN) complex that activates the DNA repair pathway. Although methylation of MRE11 does not regulate MRN complex formation, it anchors MRE11 to double-strand breaks (DSBs), preventing nucleases from activating DNA repair. In addition, the TF growth factor independent 1 interacts with PRMT1 and promotes MRE11 methylation (59). Furthermore, CARM1 promotes mitotic arrest deficient 2 like 2 (MAD2L2) silencing

Table I. Role of PRMTs in histone methylation.

Type	Residues	Enzymes	Functions	(Refs.)
H2A	R3me1/me2s	PRMT5	Transcriptional repression	(22)
	R3	PRMT7	DNA repair	(23)
	R29me2a	PRMT6	Transcriptional repression	(21)
H3	R2me1	PRMT5	Transcriptional activation	(28)
	R2me2a	PRMT6	Transcriptional repression	(112,113)
	R2me1/me2s	PRMT5	Transcriptional activation	(29,114)
	R8me2a	PRMT6	Transcriptional repression	(115)
	R8me2a	PRMT2	Transcriptional activation	(24,25)
	R8me2s	PRMT5	Transcriptional activation and repression	(33,34,116,117)
	R17/R26/ R42me2a	CARM1	Transcriptional activation	(26)
	R26me2a	CARM1	Transcriptional repression	(118)
	R3me1	PRMT5	Transcriptional activation	(42)
H4	R3me2a	PRMT1	Transcriptional activation	(35,41,119)
	R3me2a	PRMT3	Transcriptional activation	(44,120)
	R3	PRMT6	Transcriptional activation/ repression	(121,122)
	R3me2s	PRMT5	Transcriptional repression, blocking of SHH pathway, promotion of DNA methylation	(36-39,42,43,123)
	R17me1	PRMT7	Facilitation of PRMT5-mediated H4R3me2s	(124)
	R19me1	PRMT7	Facilitation of PRMT5-mediated H4R3me2s	(124)
	R3me2a	PRMT8	Transcriptional activation	(125)

PRMT, protein arginine methyltransferase; CARM1, coactivator-associated arginine methyltransferase 1; SHH, Sonic hedgehog.

by driving the switch from the SWI/SNF complex to EZH2 by methylating the BAF155 subunit of the SWI/SNF complex on the MAD2L2 promoter. EZH2 inhibition upregulates MAD2L2 to decrease DNA end resection, which increases NHEJ and chromosomal abnormalities, ultimately causing mitotic catastrophe in PARP inhibitor-treated HR-proficient cells (60). PRMT5-deficient HeLa cells are sensitive to radiotherapy and accumulate DNA damage (61). Stress-responsive activator of p300 may be recruited to the p53 complex in the DDR, which recruits PRMT5 and promotes methylation of the p53 oligomerization domain to reduce oligomerization and increase nuclear retention (62), while increasing target expression of p21 and p53-up-regulated modulator of apoptosis (63).

Upregulation of key DNA repair genes is the main mechanism of chemotherapy and radiation therapy resistance in tumour cells (64). PRMT5 may promote the survival of tumour cells in the context of genetic damage; therefore, the combination of PRMT5 inhibitors and chemotherapy may be a new strategy to treat cancer resistance. In patients with BRCA1-mutated breast cancer, the HR repair pathway is missing, so the cells rely mainly on PARP-mediated DSB repair. Therefore, Olaparib treatment is effective (65). However, the majority of patients with triple-negative breast cancer (TNBC) do not have BRCA1 mutations and targeting PRMT5 inhibition is similar to HR deficiency in BRCA1 mutations; therefore, targeting PRMT5 inhibition is beneficial for improving patient outcomes (66). Regulator of chromosome condensation 1 (RCC1), as a guanylate exchange factor of RAN, localises in the nucleus and binds to chromatin to regulate DNA damage repair. The methylation of RCC1 at R214 by PRMT6 is necessary for RCC1 to bind to chromatin and activate RAN (67). Inhibition of PRMT6 reduces the tumorigenicity of the cells in GBM and improves the effects of radiation therapy on GBM growth in mice (67).

Interactions between different posttranslational modifications are critical for the DNA damage response. Arginine methylation has an essential role in maintaining genome stability, and arginine methylation and ubiquitination crosstalk control DNA end resection and HR repair (68). Mass spectrometry analysis of PRMT1-interacting proteins revealed that ubiquitin specific peptidase 11 (USP11) has a key role in the early stage of DSB repair by regulating the activity of the

Table II. Role of PRMTs in nonhistone methylation.

Type	Enzymes	Substrate	Function	(Refs.)
TFs	PRMT1	TWIST1	Activation of EMT	(126,127)
	PRMT1	TAF15	Affects TAF15 cellular localization and expression of TAF15-targeted genes	(128)
	PRMT1	RUNX1	Enhanced transcription activity to maintain the peripheral T-cell count	(129)
	PRMT1	FOXO1	Enhanced cell apoptosis and gluconeogenesis	(130)
	PRMT1/5	E2F-1	Transcriptional activation promotes apoptosis; increased cell viability	(50,78)
	PRMT1	C/EBPα	Promotes cyclin D1 expression	(131)
	PRMT1	SMAD7	Facilitates the dissociation of Smad7 from type I receptors	(55)
	PRMT5	SREBP1	Increases adipogenesis and tumour growth in hepatocellular carcinoma	(51)
	PRMT5	BCL6	Inhibits the activity of BCL6 target genes	(52)
RBPs	PRMT1	PABPN1	Reduces the affinity of PABPN1 for transportin, promotes the PABPN1-RNA interaction	(54,132)
	PRMT1	ICP27	Nuclear foci-like structure formation, RNA-binding affinity and SRPK interactions of ICP27	(53)
	PRMT5	hnRNPA1	Promotes hnRNPA1 interaction with ITAD, accompanied by translation of cyclin D1 and c-MYC	(93)
DNA damage response	PRMT1	53BP1	Interaction with single- and double-stranded DNA	(133)
	PRMT1	MRE11	Induction of the intra-S-phase checkpoint defect	(134)
	PRMT1	BRCA1	Influences the interaction of BRCA1 with specific promoters or proteins	(135)
	PRMT1/3/6	TOP3B	Translational regulation	(136)
	PRMT6	RCC1	Chromatin binds and activates RAN	(67)
RNA splicing	PRMT5	Sm proteins	Assembles into snRNPs	(137)
	PRMT5	SRSF1	Differential binding of SRSF1 to its alternative pre-mRNA splicing targets	(75)
	PRMT5	TIP60/KAT	Ensuring error-free HR DNA repair and maintaining genomic integrity	(57)
	PRMT1	RBM15	Aberrant RNA splicing	(138)
	PRMT9	SF3B2	Maintains splicing fidelity	(79)
	PRMT1	EZH2	Regulates stability and promotes breast cancer metastasis	(139)
Signalling pathways	PRMT1	ERα	Activates the cytoplasmic signalling	(140)
	PRMT1	EGFR	Activates the EGFR signalling pathway	(141)
	PRMT5	P65	Activates NF-κB	(82)
	PRMT5	TRIM21	Activates NF-κB	(83)
	PRMT5	SKI	Altered TGFβ signalling-mediated transcriptional regulation	(86)
	PRMT3	HIF1α	Activation of the HIF1/VEGF signalling pathway	(88)

TF, transcription factor; RBP, RNA binding protein; PRMT, protein arginine methyltransferase; EMT, epithelial to mesenchymal transition. TWIST1, twist family bHLH transcription factor 1; TAF15, TATA-box binding protein associated factor 15; RUNX1, RUNX family transcription factor 1; FOXO1, forkhead box O1; E2F-1, E2F transcription factor 1; C/EBPα, CCAAT enhancer binding protein α; SMAD7, SMAD family member 7; SREBP1, Sterol regulatory element binding protein 1; BCL6, BCL6 transcription repressor; PABPN1, poly(A)-binding protein 1; ICP27, infected cell protein 27; hnRNPA1, heterogeneous nuclear ribonucleoprotein A1; 53BP1, p53 binding protein 1; MRE11, meiotic recombination 11; BRCA1, breast cancer 1; TOP3B, DNA topoisomerase III beta; RCC1, regulator of chromosome condensation 1; RAN, ras-related nuclear protein; SRSF1, serine and arginine rich splicing factor 1; TIP60, Tat interactive protein 60kDa; KAT5, lysine acetyltransferase 5; RNM15, RNA binding motif protein 15; SF3B2, splicing factor 3b subunit 2; EZH2, enhancer of zeste 2 polycomb repressive complex 2 subunit; ERα, estrogen receptor alpha; EGFR, epidermal growth factor receptor; TRIM21, tripartite motif containing 21; TGFβ, transforming growth factor beta; HIF1α, hypoxia inducible factor 1 subunit alpha; VEGF, vascular endothelial growth factor.

PRMT1-MRE11 pathway. USP11 is a substrate of PRMT1 and methylation of USP11 promotes DNA end resection and DSB repair of DNA through HR. PRMT1 is also a ubiquitinated protein that acts as a target of de-ubiquitination to regulate the binding and methylation of PRMT1 to MRE11 (68).

RNA splicing is critical for regulating tumour phenotypes (69,70). Therefore, splicing factors must be tightly controlled genetically and epigenetically to ensure splicing fidelity. It is also important to note that protein arginine methylation usually occurs on the splicing component and that RBPs are required for pre-RNA splicing (71,72). In addition, proteome-wide analysis revealed that the enrichment of arginine-methylated proteins was associated with the control of RNA splicing, trafficking and degradation (73,74). Serine and arginine rich splicing factor 1 (SRSF1) is the substrate and effector of PRMT5 (73,75). Knockdown of PRMT5 resulted in differential binding of SRSF1 to alternative pre-mRNA splicing targets, leading to a decrease in the interaction of SRSF1 with other proteins (73). PRMT5 regulates methylation of the RGG/RG motif in RNA-binding motif protein X and forms a higher-order complex with SRSF1, and splicing generates the short isoform of MDM4 (75). PRMT5 knockdown or inhibition induces aberrant MDM4 splicing, which initiates p53-mediated cell cycle- and apoptosis-related genes, finally promoting tumour growth (76). Furthermore, activation of PRMT5 is critical for sensitivity to CDK4/6 inhibitors, and regulation of the PRMT5-MDM4 axis by palbociclib leads to loss of drug resistance in melanoma (77). By indirectly suppressing PRMT5 activity, palbociclib alters the pre-mRNA splicing of MDM4, a negative regulator of p53, leading to decreased MDM4 protein expression and subsequent p53 activation. In turn, p53 induces p21, leading to inhibition of CDK2, the main kinase substituting for CDK4/6 and a key driver of resistance to palbociclib. Loss of the ability of palbociclib to regulate the PRMT5-MDM4 axis leads to resistance. Importantly, combining palbociclib with the PRMT5 inhibitor GSK3326595 enhances the efficacy of palbociclib in treating naive and resistant models and delays the emergence of resistance. Tat interactive protein 60kDa (TIP60)/lysine acetyltransferase 5 (KAT5) is a histone lysine acetyltransferase that drives the HR of DNA and is regulated by PRMT5-mediated alternative splicing. In response to DNA damage, PRMT5 promotes alternative splicing of the pre-mRNA of TIP60/KAT to the TIP60a isoform (with high H4 lysine acetylase activity), thereby ensuring HR repair of DNA and maintaining genome integrity (57). In addition to PRMT5 methylation altering transcriptional activity, E2F1 is also involved in alternative splicing after PRMT5 methylation. Methylation of E2F1 promotes the recruitment of p100/TSN and small nuclear ribonucleoprotein, which regulates alternative splicing of E2F1 targets (78). PRMT9 is present in the splicing factor (SF)3B2 and -4 complex and methylates SF3B2. Methylated SF3B2 is recognised by the SMN Tudor domain and has an important role in maintaining splicing fidelity (79).

Methylation of arginine-specific proteins may modify the structure or activity of the protein, alter the interaction between specific molecules and then affect tumour cell signalling pathways. Recent cancer-related studies on the role of PRMTs are summarized in Table III. In TNBC, PRMT1 regulates the EGFR and the Wnt signalling pathways (80). Type I PRMT inhibitors decrease breast cancer cell proliferation and have anti-tumour activity. These inhibitors display synergistic interactions with certain chemotherapies used to treat TNBC, as well as erlotinib, an EGFR inhibitor. Therefore, targeting PRMT1 in combination with these chemotherapies may improve existing treatments for TNBC (80). Inhibition of PRMT5, the predominant type II PRMT, produces synergistic cancer-cell growth inhibition when combined with GSK3368715, which is a potent and reversible type I PRMT inhibitor (81). Of note, deletion of the methylthioadenosine phosphorylase gene (MTAP) results in accumulation of the metabolite 2-methylthioadenosine, an endogenous inhibitor of PRMT5, and is associated with sensitivity to GSK3368715. Overall, the MTAP status may serve as a biomarker for patient selection (81). NF-κB has an important role in tumorigenesis and PRMT5 activates NF-κB through methylation of the p65 subunit (82). Although TNFα-induced intracellular signalling pathways have been well studied, the TRAIL signalling pathway remains to be fully elucidated. PRMT5, a novel TRAIL receptor-binding protein, contributes to TRAIL-induced activation of inhibitor of κB kinase (IKK) and NF-κB, leading to induction of several NF-κB target genes (83). PRMT5 methylation of TRIM21 induces selective autophagy, which inhibits TRIM21-dependent monoubiquitination and degradation of IKKβ and activates the NF-κB signalling pathway. Thus, PRMT5 inhibition blocks the NF-κB signalling pathway (84). SKI is a transcriptional repressor that interacts with SMAD and may be methylated by the PRMT5-methylosome protein 50 (MEP50)-SHANK-associated RH domain interactor (SHARPIN) complex, altering transcriptional regulation of the TGFβ signalling pathway (52). In HCC, PRMT9 activates the PI3K/Akt/GSK3β/Snail signalling pathway to regulate Snail, increasing cell migration and invasion through EMT (85). SHARPIN, an adaptor for the linear ubiquitin chain assembly complex, has an important role in the NF-κB signalling pathway. Activated PRMT5 controls the expression of SRY-box transcription factor 10 and melanocyte inducing transcription factor and inhibition of the transcriptional corepressor SKI by SHARPIN-dependent arginine demethylation, contributing to the occurrence of melanomagenesis (86). The expression of PRMT3 is upregulated in colorectal cancer and may stabilise the protein structure of c-MYC, and PRMT3 promotes the expression of c-MYC by interacting with c-MYC through the SAM-dependent MTase-PRMT domain (87). PRMT3 methylates hypoxia-inducible factor (HIF)1α at R282 and stabilizes the structure of HIF1α, while activating the HIF1/VEGFA signalling pathway to promote tumorigenesis (88). PRMT1, -5 and -7 regulate glioma-associated oncogene 1 (GLI1) and GLI2 activity (89). Methylation of GLI1 by PRMT1 upregulates its activity and promotes target gene expression. PRMT5 methylates GLI1 in the cytoplasm and increases GLI1 protein stability. Conversely, nuclear PRMT5 interacts with MENIN to inhibit the expression of growth arrest-specific protein 1, which facilitates Hedgehog ligand binding to Patched and indirectly downregulates GLI1 activity. PRMT7 methylates GLI2 to upregulate its activity through GLI2 dissociation and fusion inhibitors (89). PRMT1 expression is upregulated and promotes tumour cell growth in pancreatic ductal adenocarcinoma (PDAC). PRMT1 promotes β-catenin expression by binding -699 to -874 bp and -1,191 to -1,413 bp of the β-catenin

Table III. Roles of different PRMTs in cancer.

PRMTs	Cancer type	Expression	Biological mechanism	Function	(Refs.)
PRMT1	Colorectal cancer	High	Activation of EGFR signalling by EGFR methylation	Oncogenic	(35)
		High	Promotion of tumour growth by regulation of E2F-1	Oncogenic	(50)
	Breast cancer	High	Modulation of EMT and cellular senescence through regulation of ZEB1	Oncogenic	(41)
		High	Methylation of EZH2 and regulation of its stability	Oncogenic	(139)
		High	Activation of cyclin D1 expression by methylation of C/EBPα	Oncogenic	(131)
		High	Regulation of IGF-1 signalling by methylation of ERα	Oncogenic	(142)
	Pancreatic cancer	High	Promotion of β-catenin expression by binding the β-catenin promoter	Oncogenic	(90)
		High	Stabilisation of BCL2 mRNA by methylation of HSP70	Oncogenic	(143)
	Lung	High	Promotion of EMT by methylation of Twist1	Oncogenic	(126)
	HNC	High	Promotion of proliferation and migration	Oncogenic	(144)
	ESCC	High	Promotion of the growth and migration by activating Hedgehog signalling	Oncogenic	(145)
PRMT2	Hepatocellular carcinoma	High	Acceleration of tumorigenesis by activating Bcl2 via H3R8 methylation	Oncogenic	(24)
	Glioblastoma	High	Promotion of oncogenic activation and tumorigenesis by methylation of H3R8	Oncogenic	(25)
	Breast cancer	High	Splice variants of PRMT2 modulate ERα signalling	Oncogenic	(146)
PRMT3	Colorectal cancer	High	Promotion of tumorigenesis through regulating c-MYC stabilization	Oncogenic	(87)
		High	Promotion of tumorigenesis by methylating and stabilizing HIF1α	Oncogenic	(88)
	Pancreatic cancer	High	Increase of ABCG2 expression by methylation of hnRNPA1	Oncogenic	(92)
		High	Induction of metabolic reprogramming	Oncogenic	(107)
PRMT4	Ovarian cancer	High	Activation of Wnt/β-catenin and neoplastic transformation	Oncogenic	(147)
	Breast cancer	High	Upregulation of cyclin E1 led to the promotion of S-phase entry	Oncogenic	(148)
		High	Enhancement of tumour progression and metastasis by methylation of BAF155	Oncogenic	(149)
		High	Promotion of invasion and metastasis by regulation of LSD1 stability	Oncogenic	(150)
		-	Block of tumour cell proliferation and induction of differentiation through ERα-regulated genes	Tumour suppressive	(151)
	Pancreatic cancer	Low	Inhibition of glutamine metabolism and tumour growth by methylation of MDH1	Tumour suppressive	(152)
	Liver cancer	Low	Regulation of glucose metabolism by GAPDH methylation	Tumour suppressive	(152)
PRMT5	Lung cancer	High	SHARPIN-PRMT5-H3R2me1 axis activates transcription of metastasis-related genes	Oncogenic	(28)
		High	Enhancement of localization to the surface membrane by Enolase-1 methylation	Oncogenic	(153)
		High	Promotion of tumour cell proliferation by regulation of AKT	Oncogenic	(154)

Table III. Continued.

PRMTs	Cancer type	Expression	Biological mechanism	Function	(Refs.)
	Breast cancer	High	Critical regulator of breast cancer stem cells via histone methylation and Foxp1 expression	Oncogenic	(29)
		High	PRMT5/WDR77 complex regulates alternative splicing through ZNF326	Oncogenic	(155)
		High	Increase of sensitivity to chemotherapeutics by governing stemness	Oncogenic	(156)
	Prostate cancer	High	Promotion of pICln-dependent androgen receptor transcription	Oncogenic	(157)
	Gastric cancer	High	PRMT5-dependent transcriptional repression of c-MYC target genes	Oncogenic	(158)
		High	Mediation of epigenetic silencing of IRX1 contributes to tumorigenicity and metastasis	Oncogenic	(159)
	AML	High	Genetic deletion or small-molecule inhibition	Oncogenic	(36)
		High	Gene activation and repression via histone arginine methylation	Oncogenic	(117)
	HCC	High	Promotion of invasive activity of tumour cells by regulation of MMP2	Oncogenic	(160)
		High	Promotion of tumour cell proliferation by inhibiting BTG2 expression via the ERK signalling pathway	Oncogenic	(161)
	Melanoma	High	Regulation of MDM4 via alternative splicing result in response to CDK4/6 inhibitors	Oncogenic	(77)
	Lymphoma	High	Activation of WNT/β-catenin and AKT/GSK3β signalling	Oncogenic	(162)
	DLBCL	High	PRMT5 is upregulated by B-cell receptor signalling and forms a positive feedback loop with PI3K/AKT	Oncogenic	(163)
	Bladder cancer	High	Promotion of cancer growth through inhibiting NF-κB-dependent apoptosis	Oncogenic	(164)
PRMT6	Lung cancer	High	Activation of tumour-associated macrophages via interaction with ILF2	Oncogenic	(165)
	Endometrial cancer	High	Activation of AKT/mTOR signalling	Oncogenic	(166)
PRMT7	Breast cancer	High	Promotion of tumour cell invasion through the induction of MMP9 expression	Oncogenic	(167)
	NSCLC	High	Contribution to tumour cell metastasis by the interaction with HSPA5 and EEF2	Oncogenic	(168)
PRMT9	HCC	High	Promotion of tumour cell invasion and metastasis by activating PI3K/Akt/GSK-3β/Snail signalling	Oncogenic	(85)

AML, acute myeloid leukemia; HNC, head and neck cancer; DLBCL, diffuse large B-cell lymphoma; ESCC, esophageal squamous cell carcinoma; NSCLC, non-small cell lung carcinoma; HCC, hepatocarcinoma; PRMT, protein arginine methyltransferase; EGFR, epidermal growth factor receptor; E2F-1, E2F transcription factor 1; EMT, epithelial to mesenchymal transition; ZEB1, Zinc finger E-box binding homeobox 1; EZH2, enhancer of zeste 2 polycomb repressive complex 2 subunit; C/EBPα, CCAAT enhancer binding protein alpha; IGF-1, IGF like family member 1; ERα, estrogen receptor alpha; BCL2, BCL2 apoptosis regulator; HSP70, heat shock protein 70; ABCG2, ATP binding cassette subfamily G member 2; hnRNPA1, heterogeneous nuclear ribonucleoprotein A1; BAF155, SWI/SNF related, matrix associated, actin dependent regulator of chromatin subfamily c member 1; LSD1, lysine demethylase 1; MDH1, malate dehydrogenase 1; SHARPIN, SHANK-associated RH domain interactor; WDR77, WD repeat domain 77; ZNF326, zinc finger protein 326; IRX1, iroquois homeobox 1; MMP2, matrix metallopeptidase 2; BTG2, BTG anti-proliferation factor 2; ILF2, interleukin enhancer binding factor 2.

promoter (90). Tumour suppressor protein von Hippel-Lindau interacts with PRMT3 and then forms a protein complex with Auxin response factor and regulates the methylation of p53 (91). PRMT3 protein expression is upregulated in patients with gemcitabine (GEM)-resistant pancreatic cancer. ATP binding cassette subfamily G member 2 (ABCG2) is a newly discovered target of PRMT3, and PRMT3 overexpression increases the methylation of heterogeneous nuclear ribonucleoprotein A1 (hnRNPA1) at R31, resulting in enhanced RNA-binding activity of hnRNPA1 and increased expression of ABCG2 mRNA. Therefore, PRMT3 methylates the RNA recognition motif of hnRNPA1 to promote the binding of hnRNPA1 and ABCG2 to enhance the resistance of pancreatic cancer to GEM (92). PRMT5 methylation of hnRNPA1 promotes the interaction of hnRNPA1 with internal ribosome entry site (IRES) RNA to promote IRES-dependent translation of cyclin D1 and c-MYC (93). The PRMT type 1 inhibitor MS023 is a potent inducer of colon cancer-cell differentiation with a wide therapeutic window. This finding may lead to the development of clinically effective anti-cancer drugs based on the mechanism of cancer cell differentiation (94).

4. Participation in tumour immunity

PRMTs can modulate Toll-like receptor and interferon (IFN) activation at multiple levels to modulate immune responses (95). PRMT5 expression was observed to be negatively associated with antitumor immunity. After PRMT5 inhibition, the number of infiltrating immune cells increased and antitumour immunity was enhanced in immunocompetent mice (96). PRMT5 promotes antitumour immunity through two different intertumoral pathways. First, PRMT5-mediated interferon gamma inducible protein 16 (IFI16)/IFI204 methylation attenuates dsDNA-induced TANK binding kinase 1 (TBK1)-interferon regulatory factor 3 (IRF3) activation and chemokine production. dsDNA induced activation of TBK1-IRF3, as reflected by the levels of STING phosphorylation, dimerization and polymerization. PRMT5 methylation of IFI16/IFI204 impacts cyclic GMP-AMP synthase-stimulator of interferon genes (STING) signalling. Ectopically expressed IFI204 in B16 cells activated TBK1-IRF3 signalling and increased the expression of IFNB1 and C-C motif chemokine ligand 5 following dsDNA treatment. IFI204Mt1 (R12A) expression increased STING dimerization and polymerization following dsDNA stimuli, suggesting a critical role of IFI204 methylation on Arg12 in the dsDNA-stimulated STING pathway activation. PRMT5-mediated IFI16/IFI204 methylation attenuates dsDNA-induced TBK1-IRF3 activation and type I interferon and chemokine production. In addition, NLR family CARD domain containing 5, a master regulator of inflammasomes and antigen presentation pathways, was inversely correlated with PRMT5 expression. PRMT5 inhibits immune cell recruitment and activation as well as tumour recognition, thereby influencing tumour immune evasion. Likewise, inhibition of PRMT5 is expected to enhance the response of cold tumours to immune checkpoint therapy (96). MS023, a type I PRMT inhibitor, causes splicing of modulatory drugs, treatment alterations with intron retention and exon skipping, and these alterations result in substantial enrichment of major histocompatibility complex I-binding peptides. Of note, a fairly large proportion (up to 43%) of these putative neoantigens are immunogenic, resulting in neoantigen-specific CD8+ T-cell activation (97).

Controlling PRMT5 activity is a promising strategy for cancer therapy when host immunity against tumours occurs in a FOXP3-dependent manner (98). Arginine methylation occurs frequently at R27, R51 and R146 of FOXP3, but pharmacological inhibition of PRMT5 by DS-437 may reduce T-regulatory cell (Treg) functions and inhibits the methylation of FOXP3. Furthermore, DS-437 significantly enhanced the anti-tumour effects of anti-erbB2/neu monoclonal antibody targeted therapy in BALB/c mice, which bore CT26Her2 tumours, by inhibiting Treg function and induction of tumour immunity (98). Of note, FOXP3 also undergoes methylation on R48 and R51 by interacting with PRMT1. The inhibition of arginine methylation confers gene expression profiles representing type I helper T cells to FOXP3+ T cells, which resulted in attenuated suppressive activity (99). Otherwise, knockout of PRMT1 may enhance anti-programmed cell death receptor-1 immunotherapy in MC38-derived tumours in isogenic C57BL/6 mice (100). Of note, the PRMT1 polymorphism rs975484 modulates programmed cell death ligand-1 (PD-L1) and PD-L2 levels and serves as a predictor of immune checkpoint blockade efficiency in HCC (101). CARM1 was identified as a negative regulator of tumour-specific T cells in B16F10 melanoma-resistant C57BL/6 mice (102).

Furthermore, studies have indicated that type I PRMT inhibitors may enhance the effect of immunotherapy. PT1001B enhances antitumor immunity, and combining it with anti-PD-L1 checkpoint inhibitors provides a potential strategy to overcome anti-PD-L1 resistance in PDAC (103). MS023 treatment significantly improved anti-PD1 therapy in C57BL/6 tumour-bearing mice (104). Therefore, further studies are needed to determine the effect of PRMT inhibition, not only on tumour cells, but also on other cell types in the tumour microenvironment, including immune cells and stromal cells.

5. Participation in metabolic reprogramming

Metabolic reprogramming is an important process by which cancer cells adapt to high energy demands and supplement biosynthetic needs, and numerous cancers switch their tumour cell metabolism to the glycolytic pathway under oxygen-rich conditions. Therefore, inhibition of metabolic reprogramming by modulating different metabolic pathways in tumours provides a new strategy for cancer therapy (105,106).

In pancreatic cancer, PRMT3 may methylate GAPDH at R248 to enhance cancer glycolysis and mitochondrial respiration. PRMT3-overexpressing cancer cells were addicted to GAPDH-mediated metabolism and sensitive to the inhibition of GAPDH and mitochondrial respiration. Both intermediates in the glycolytic pathway and the tricarboxylic acid cycle are enriched in PRMT3-expressed cells. In addition, these cells exhibit an increased extracellular acidification rate and oxygen consumption rate. Double blockade of GAPDH and mitochondrial respiration will be a novel strategy for the treatment of PRMT3-overexpressing pancreatic cancer (107). Esophageal squamous cell carcinoma (ESCC) is associated

with elevated asymmetric and systemic arginine dimethylarginine. PRMT1, PRMT5, ornithine decarboxylase 1 and nitric oxide (NO) synthase 2 are overexpressed, and arginase 1, arginase 2 and dimethylarginine dimethylaminohydrolase 1 are downregulated in tumours compared to adjacent tissues. Arginine bioavailability increased and citrulline decreased along with ESCC advancement. In short, metabolic reprogramming in ESCC manifests as alterations in the L-arginine/NO pathway (108). In HCC, PRMT3 mediates ADMA modification of lactate dehydrogenase A (LDHA) at R112. LDHA-R112K-mutant-expressing cells exhibited a decrease in LDH activity, HCC cell glycolysis and proliferation (109). In chronic myeloid leukemia (CML), loss of PRMT7 resulted in reduced expression of glycine decarboxylase, leading to the reprograming of glycine metabolism to generate methylglyoxal, which is detrimental to leukemia stem cells (LSCs). These findings link histone arginine methylation with glycine metabolism, while suggesting PRMT7 as a potential therapeutic target for the eradication of LSCs in CML (109).

6. Methylation profiles of PRMTs

Despite the relevance of PRMTs for signal transduction, metabolism, transcription and other cellular phenotypes, the methylation profiles of protein arginine remain understudied. The function of PRMTs under physiological and pathological conditions often depends on methyltransferase activity. Therefore, comprehensively revealing the substrates of PRMTs is the key to exploring their functions and underlying molecular mechanisms.

Combining two newly developed methylation sequencing methods, immunoaffinity purification and high pH strong cation exchange, may improve the coverage of protein methylation and reveal new PRMT1 targets (110). After knockout of PRMT1, 127 arginine methylation sites on 78 proteins were significantly changed. In contrast, only one lysine methylation site was significantly changed after PRMT1 knockdown, indicating that amino acid methylation was not affected by PRMT1 knockdown. In PRMT1-knockout cells, 114 MMA sites were found to be significantly altered on proteins enriched in the mRNA metabolic process. A high-confidence list of 18 PRMT1 substrates and 12 methylation sites scavenged by other PRMTs in the absence of PRMT1 activity was found through integrative analysis of MMA and DMA. Most importantly, the methylation site hnRNPA1 R206 switched from ADMA to SDMA after PRMT1 knockout (110).

High-resolution mass spectrometry combined with SILAC technology was used to analyse the arginine methylation regulated by PRMT7 in 293 cells (111). A total of 1,031 MMA sites of 513 proteins were detected and a two-fold decrease in monomethylation levels at 297 arginine sites in 174 proteins was found, termed the PRMT7 methylome. During this process, the methylation of 176 MMA sites in 108 proteins disappeared completely. After treatment with the PRMT7-specific inhibitor SGC3027, 503 MMA sites of 274 proteins were more than two-fold reduced, and ~60% of PRMT7-regulated substrates were also inhibited. The same method was also used to identify the methylated substrates of PRMT4 and -5, representing type I and II PRMTs, respectively. The PRMT4 methyl group (two-fold decrease) includes 301 proteins with 660 methylation sites, while the PRMT5 methyl group (two-fold decrease) includes 244 proteins with 429 methylation sites. PRMT4 substrates, such as mediator complex subunit 12, SWI/SNF related, matrix associated, actin dependent regulator of chromatin subfamily c member 1 and E1A binding protein p300, and PRMT5 substrates, such as FUS RNA binding protein, hnRNPA1 and survival of motor neuron 1, have also been identified. Most importantly, PRMT4, -5 and -7 coregulate alternative splicing in an enzyme-dependent manner and share a number of RNA splicing factors, such as hnRNPA1; furthermore, hnRNPA1 arginine methylation is required for the growth of various cancer cells (116). Taken together, the methylation profiles of PRMTs indicated that hnRNAPA1 has a role of co-RNA splicing factor in various arginine methylation modification processes and may also promote the transformation of ADMA to SDMA. Further study of its mechanism will reveal the types of arginine methylation.

7. Future outlook

While much important progress has been made in research on PRMT function, the complexity and significance of gene post-transcriptional processing determine the diversity of the PRMT regulatory mechanisms. The regulatory effect of PRMTs on the function of RBP clearly exemplifies the important regulatory role of arginine methylation in post-transcriptional processing. Although numerous important advances have been made in the study of PRMTs regulating the function of RBP, various questions remain to be answered in the field of cancer, such as how a single arginine methylation site determines the function of specific proteins, how different PRMT family members synergistically regulate the occurrence of specific substrate methylation and how arginine methylation modifications are recognized and removed. In addition, the sequence characteristic of the target RNA directly affected by RBP and how arginine methylation regulates the interaction between RBP and its target RNA at the genome-wide level are also key questions to be solved. In addition, PRMTs directly methylate numerous proteins to control their subcellular localization, protein-protein interactions, stability or activity. Many of these contribute to oncogenic transformation, and thus, evaluation of potential PRMT inhibitors is warranted. What remains to be established is how the inhibition of arginine methylation may be integrated with immunotherapeutic approaches to achieve a maximal, long-lasting therapeutic effect.

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Authors' contributions

KW, CN and HL were involved in the conception of the review. KW wrote the manuscript and performed the literature search. KW and LF reviewed and edited the final manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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