Genome Instability & Disease (2023) 4:305–314
https://doi.org/10.1007/s42764-023-00111-7

REVIEW ARTICLE

The role of protein arginine methylation 5 in DNA damage repair and cancer therapy

Qikun Gao[1] · Ziyi Liu[1] · Jinyang Liu[1] · Xuyang Yan[1] · Junfei Dai[1] · Zixuan Zhang[1] · Rongxiao Li[1] · Shiva Basnet[1] · Changzheng Du[1,2]

Received: 15 June 2023 / Revised: 5 October 2023 / Accepted: 9 October 2023 / Published online: 8 November 2023

Abstract

Protein arginine methylation, a post-translational modification (PTM), is fundamental in regulating protein function and stability. Among the nine protein methyl transferases (PRMT), PRMT5 plays a critical role in promoting oncogenic processes including tumor proliferation, invasiveness, immune escape and DNA damage repair through different signaling pathways. It is also a target in cancer therapy, with numerous inhibitors in clinical trial. In this review, we focus on the biological functions of PRMT5 in DNA damage repair and maintenance of genome stability in cancer, and summarize the development advance of PRMT5 inhibitors in cancer therapy.

Keywords PRMT5 · DNA damage repair · Genome stability

Introduction

Post-translational modification (PTM) is a fundamental protein regulation that realizes or abolishes the function of a protein. Methylation modification on arginine is a common PTM in mammals, catalyzed by the protein arginine methyltransferases (PRMTs) family, which includes nine members from PRMT1 to PRMT9 (Hwang et al., 2021). The methyl groups provided by S-adenosylmethionine (SAM) are transferred by PRMTs to the guanidinium nitrogen atoms of the arginine residue, forming various types of methylated arginine in the substrate protein (Wang et al., 2018). PRMTs are classified into three types depending on the type of methylation modification they catalyze (Fig. 1). PRMT5, a member of the type II PRMT, which consists of 637 amino acids, is gaining increasing attention due to its critical role in cancer and other diseases (Kim & Ronai, 2020; Motolani et al., 2021). PRMT5 catalyzes mono- and symmetric dimethylation modifications on arginine. Its substrate specificity is highly dependent on RGG/RG sequences (PRMT5 target spots), especially the arginine residue, both sides of which are linked to glycine (Gly-Arg-Gly sequence) (Musiani et al., 2019) (Fig. 2). PRMT5 substrates include both histone and non-histone proteins. For histone substrates, particularly the N-terminal histone tails such as H2AR3, H3R2, H3R8, and H4R3, symmetric dimethylation of the aforementioned PRMT5-modified arginines recruits different readers to activate or suppress gene transcription (Kim & Ronai, 2020); for non-histone substrate proteins, methylation of the arginines induce functional alteration in the substrates involving different signaling pathways.

PRMT5 has complicated biological function in cancer cells and plays a critical role in many important cellular processes such as transcription, splicing, translation, metabolism, signal transduction and DNA damage repair (DDR) (Yuan et al., 2021). PRMT5 is not only a star molecule in oncogenesis research, but also a valuable target for cancer therapy with a series of inhibitors in clinical trials or approved by the FDA (Wu et al., 2021). Here, we focused on the role of PRMT5 in responding to DNA damage and maintaining genome stability to better understand its potential in cancer research and therapy.

✉ Changzheng Du
ducz@sustech.edu.cn

[1] Department of Biochemistry, Key University Laboratory of Metabolism and Health of Guangdong, Southern University of Science and Technology, 1088 Xueyuan Road, Shenzhen 518055, China

[2] Digestive Tumor Center, Southern University of Science and Technology Hospital, Shenzhen 518055, China

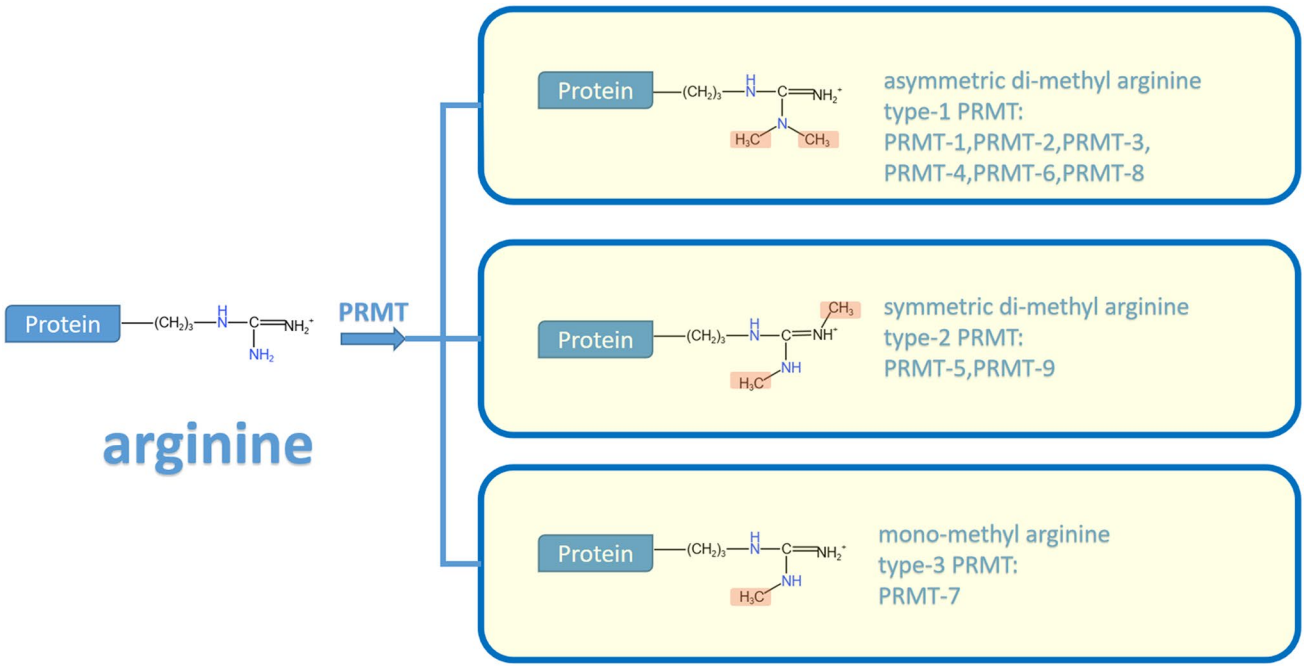

Fig. 1 Classification of PRMT family

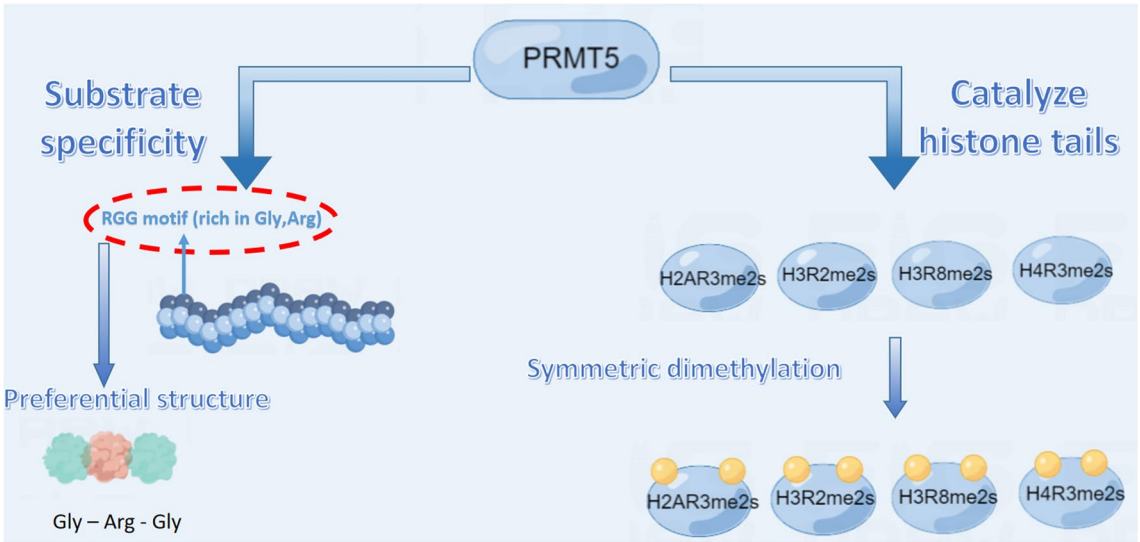

Fig. 2 Substrate specificity of PRMT5

The role of PRMT5 in DNA damage repair and genome stability maintenance

PRMT5 plays a fundamental role in DDR by multiple pathways. By epigenetic regulation, PRMT5 promotes the expression of DDR genes through histone arginine methylation. In prostate cancer, PRMT5 cooperates with partner proteins such as plCln and WDR77 to form an epigenetic activator that upregulates the expression of DDR genes involved in homologous recombination (HR) and non-homologous end joining (NHEJ) pathways, such as KU70/80, RAD51 and BRCA1/2 (Owens et al., 2020). In malignant glioblastoma, PRMT5 promotes the transcription of RNF168, an E3 ligase that activates H2AX and prevents its degradation to enhance the DNA damage response and induce tumor chemoradiation resistance (Du et al., 2019). In addition to double-strand break (DSB) repair, PRMT5

Table 1 The targets and regulatory mechanism of PRMT5 in DDR

Gene/Protein	DDR-pathway	Regulatory Mechanism	Biology Outcome
RAD51 RAD51D RAD51AP1 BRCA1 BRCA2	HR *(Owens JL* et al*., 2020)*	PRMT5 and plCln protein co-regulatory gene promoter histone H4R3me2s	Gene expression is upregulated and DDR is increased
NHEJ1 DKAPKs Ku80 XRCC4	NHEJ *(Owens JL* et al*., 2020)*		
BRCA2 *(Du C* et al*., 2021)*	HR	PRMT5 can be epigenetic modulators, regulating FA gene promoter region H3R2me1	Expression of BRCA2 in cancer cells is increased, and DDR is increased
H2AX *(Du C* et al*., 2019)*	DSB recognition	H2AX is phosphorylated into γH2AX when DSB occurs, which can help to recruit DNA repair proteins	The cellular response to DNA damage and DNA repair pathway is increased
BRCA1 *(Wu Y* et al*., 2022)*	HR	PRMT5 methylates ALKBH7 protein, thereby enhancing nuclear translocation of ALKBH5 and demethylating m6A of BRCA1	The mRNA of BRCA1 is stabilized and the ability of cell DDR is enhanced
p65/RelA *(Hwang JW* et al*., 2021)*	Transcriptional factor	PRMT5 methylates the R30 site of the transcription factor p65/RelA	PRMT5 enhances the transactivation of NF-κB and induces the expression of inflammatory SASP components, which plays a key role in DDR activation and cell senescence
HOXA9 *(Hwang JW* et al*., 2021)*	Transcriptional factor	PRMT5 could methylate R140 site of HOXA9 to increase transactivation of it in the E-selectin promoter	HOXA9 is a crucial regulator of the DDR transcriptional program, and the methylation of it can promote DDR
GLI1 *(Hwang JW* et al*., 2021)*	Transcriptional factor	PRMT5 methylates the R990/1018 sites of GLI1 to promote proteasome-dependent degradation of GLI1	Aberrant activation of transcriptional factor GLI1 promotes DNA damage repair. The degradation of GLI1 may affect the DDR process
E2F1 *(Hwang JW* et al*., 2021)*	Transcriptional factor	PRMT5 methylates a certain arginine residues (Arg111/113) of E2F1	When DNA damage creates a stressful environment, PRMT5 decreases the methylation of E2F1, which raises the protein level of E2F1 and encourages the cell to undergo apoptosis
KLF4 *(Hwang JW* et al*., 2021)*	Transcriptional factor	Undergoes methylation at Arg374/376/377 residues by PRMT5	This methylation leads to enhanced stability of KLF4 protein associated with the cellular response to DNA damage
LSm4 *(Hwang JW* et al*., 2021)*	RNA splicing and degradation	PRMT5 can promote the interaction between LSm4 and HAT1-RBBP7	Not clear
Coillin *(*Kannan et al., 2018*)*	RNA metabolism and processing	PRMT5 could methylate coilin to mediates SMN localization in the Cajal body	Chronically low levels of SMN cause increased DSBs, so the methylation of coilin may be conductive to genome stability

Table 1 (continued)

Gene/Protein	DDR-pathway	Regulatory Mechanism	Biology Outcome
TP53BP1	HR *(Clarke TL* et al.*, 2017)*	PRMT5 can directly methylate 53BP1	The stabilization of 53BP1 promotes DDR, thereby promoting cell survival
	NHEJ *(Hwang JW* et al.*, 2021)*	PRMT5 mediates RUVBL1 protein methylation, activation TIP60 acetyltransferase activity, resulting in histone H4K16 acetylation, make 53BP1 break away from double chain	53BP1 breaks away from the DNA double strand, and its inhibitory effect on DNA terminal remodeling is eliminated, which is beneficial to the double-stranded homologous recombination and genome stability
ATM *(Che, Y.* et al.*, 2023)*	DSB response	ATM kinase plays a central role in cellular DSB responses in concert with the tumor suppressors RB1 and TP53. It is known that the overexpression of PRMT5 is related to ATM mutation, but the specific mechanism is still unclear	Overexpression of PRMT5 is associated with mutation of ATM and high instability of DDR genome in MCL
TP53 *(Che, Y.* et al.*, 2023)*		PRMT5 interacts with the p53 protein and methylates its Arg333, Arg353, and Arg337 residues; PRMT5 can also exert control over the translation process of p53 through its regulation of the expression of eIF4E	This methylation affects the p53 protein's ability to bind to a specific promoter, which alters the specificity of p53's control over apoptosis or cell cycle arrest
TDP1 *(Rehman I* et al.*, 2018)*	NER	PRMT5 mediate TDP1 arginine R361 and R586 demethylation, stimulating TDP1 repair function	Top1cc repair favors genome stability
FEN1 *(Guo Z* et al.*, 2010)*	BER	PRMT5 mediate FEN1 symmetrical demethylation of proteins	BER efficiency is improved
CRAF *(Hwang JW* et al.*, 2021)*	Not clear	PRMT5 can regulate degradation of CRAF by methylate R563 site of CRAF substrate	The resistance of aneuploid cells to DNA damage induction is regulated as CRAF is regulated
AKT *(Ghorbani, A.* et al.*, 2015)*		PRMT5 promotes AKT-mediated Ser 83 phosphorylation of ASK1 by methylating R89 site of ASK1 substrate	The activation of AKT can participate in DNA damage signal transduction as the survival branch of DDR
Rad 9 *(Hwang JW* et al.*, 2021)*	Cell cycle arrest	PRMT5 methylates certain arginine residues (Arg172/174/175) of Rad9	The Chk1 signaling pathway is activated and cell cycle checkpoints S/M and G2/M are triggered, preventing cells from dividing and enabling them to repair their DNA
eIF4E *(Lim, J.-H.* et al.*, 2014)*	Translation initiation factor	PRMT5 participates in the interaction between eIF4E and 5′-cap structure of c-Myc or cyclin D1 mRNA	DDR and cell cycle is regulated

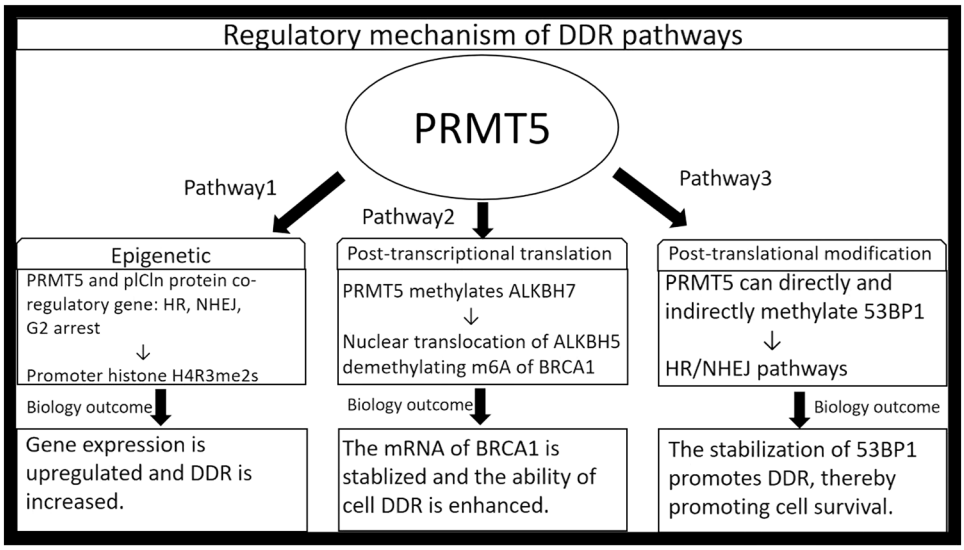

Fig. 3 Regulatory mechanism of PRMT5 to DNA damage repair

also facilitates inter-cross-link damage (ICL) repair through epigenetic regulation (Du et al., 2021). For example, PRMT5 upregulates H3R2me1 in the promoter regions of FA genes, promoting their expression in cancer cells, resulting in cellular resistance to ICL reagents (Du et al., 2021).

Beside histone arginine methylation, PRMT5 also regulates the expression of DDR proteins by targeting RNA, including splicing and RNA m6A modification. PRMT5 has been shown to play an essential role in maintaining splicing fidelity and genome-level stability by methylating Sm proteins (Sachamitr et al., 2021). In PRMT5-deficient hematopoietic stem cells, gene expression is impaired and DDR-related gene splicing is abnormal, exon skipping and intron retention events increase significantly (Tan et al., 2019). For example, loss of PRMT5 leads to abnormal splicing of TIP60 and SUV4-20H2, both of which play critical roles in chromosome remodeling and DDR protein recruitment during DSB repair (Hamard et al., 2018). PRMT5 also promotes BRCA1 expression after doxorubicin treatment in breast cancer, where PRMT5 attenuates m6A methylation of BRCA1 mRNA, thereby enhancing its stability through methylation of RNA demethylase AlkB homolog 5 (ALKBH5) resulting from translocation of ALKBH5 from the nucleus to the cytoplasm for demethylation of its mRNA substrates including BRCA1 (Wu et al., 2022).

Another regulatory pathway of PRMT5 for genome stability is PTM. Several DDR proteins have been identified as substrates for PRMT5, and their symmetrically dimethylated arginine residues regulate their functions, stability, DNA-binding ability, and interaction with other proteins. A typical example is p53, a central protein in the DDR that maintains genome stability, whose R335 and R337 have been dimethylated by PRMT5 (Hwang et al., 2021). Methylated p53 not only enhances its function in DNA damage response and cell cycle arrest, but also promotes the expression of other DDR genes such as the FA family (Du et al., 2016). Similarly, p53-binding protein 1 (53BP1) is also a substrate of PRMT5, whose R1355 has been methylated by PRMT5 (Hwang et al., 2020). 53BP1 functions as a scaffold protein for the recruitment of DDR proteins to damaged chromatin and promotes NHEJ signaling pathways by limiting end resection after a double-strand break (Clarke et al., 2017). Methylated 53BP1 enhances its proteostasis to facilitate DNA repair through the NHEJ pathway, which could be blocked by Src, a kinase that catalyzes inhibitory phosphorylation of PRMT5 at Y324 (Hwang et al., 2020). In addition to DSB repair, PRMT5 also promotes DNA single-stranded damage (SSB) repair ability by methylating critical members involved in base excision repair (BER) and nucleotide excision repair (NER). PRMT5 enhances the efficiency of BER, by mediating symmetric dimethylation of Flap endonuclease 1 (FEN1) at its R192 (Guo et al., 2010), thereby improving cellular resistance to oxidation-induced DNA damage. For the NER process, PRMT5 dimethylates TDP1 at its R361 and R586, increasing its binding affinity to topoisomerase 1 (Top1) to form a complex that repairs damaged single-stranded DNA (Rehman et al., 2018). Arginine methylation of TDP1 also increases the association of XRCC1 with TDP1 in response to camptothecin, a Top1 inhibitor that causes DNA damage (Rehman et al., 2018).

Above all, PRMT5 modulates DDR and maintains genome stability by multiple pathways. We summarized the targets and regulation mechanism of PRMT5 in DDR process, see Table 1 and Fig. 3.

Table 2 The clinical trial of PRMT5 inhibitors

Clinical Trial	NCT Number	Tumor	Drug	Phase	Status	Outcome
A Phase II Window of Opportunity Trial of PRMT5 Inhibitor, GSK3326595, in Early Stage Breast Cancer	NCT04676516	Breast Cancer	GSK3326595	II	Ongoing	NA
An Open-label, Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of GSK3326595 in Participants With Solid Tumors and Non-Hodgkin's Lymphoma (Meteor 1)	NCT02783300	Neoplasms	GSK3326595 and Pembrolizumab	I	Completed	The recommended phase 2 dose is selected as 400 mg QD
Study to Investigate the Safety and Clinical Activity of GSK3326595 and Other Agents to Treat Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML)	NCT03614728	Neoplasms	GSK3326595 and 5-Azacitidine	I, II	Ongoing	NA
AMG 193, Methylthioadenosine (MTA) Cooperative Protein Arginine Methyltransferase 5 (PRMT5) Inhibitor, Alone and in Combination With Docetaxel in Advanced Methylthioadenosine Phosphorylase (MTAP)-Null Solid Tumors (MTAP)	NCT05094336	Advanced MTAP-null Solid Tumors	AMG 193 and Docetaxel	I, II	Ongoing	NA
A Dose Escalation Study Of PF-06939999 In Participants With Advanced Or Metastatic Solid Tumors	NCT03854227	Advanced Solid Tumors and Metastatic Solid Tumors	PF-06939999 and Docetaxel	I	Completed	The recommended dose for expansion is identified as 6 mg QD

Table 2 (continued)

Clinical Trial	NCT Number	Tumor	Drug	Phase	Status	Outcome
A Study of JNJ-64619178, an Inhibitor of PRMT5 in Participants With Advanced Solid Tumors, NHL, and Lower Risk MDS	NCT03573310	Neoplasms, Solid Tumor and Non-Hodgkin Lymphoma	JNJ-64619178	I	Completed	Two provisional recommended phase 2 doses are selected: 1.5 mg intermittently and 1 mg QD
Safety and Tolerability of TNG462 in Patients With MTAP-deleted Solid Tumors	NCT05732831	Locally Advanced Solid Tumor	TNG462	I, II	Not yet recruiting	NA
Safety and Tolerability of TNG908 in Patients With MTAP-deleted Solid Tumors	NCT05275478	Locally Advanced Solid Tumor	TNG908	I, II	Ongoing	NA
A Study to Investigate the Safety and Tolerability of SCR-6920 Capsule in Patients With Advanced Malignant Tumors	NCT05094336	Solid Tumor and Non-Hodgkin Lymphoma	SCR-6920 capsule	I	Recruiting	NA
A Study of PRT811 in Participants With Advanced Solid Tumors, CNS Lymphoma and Gliomas	NCT04089449	Advanced Solid Tumor and Recurrent Glioma	PRT811	I	Completed	PRT811 is particularly effective in uveal melanoma with SF3B1 splicing mutations: one patient achieved SD with 25% tumor regression and another achieved PR with 47% decrease in primary target lesion size. At the 800 mg QD dosing, 27% target lesion decrease of triple negative breast cancer (n = 1) was observed
Phase 1/2 Study of MRTX1719 in Solid Tumors With MTAP Deletion	NCT05245500	Mesothelioma, Non-Small Cell Lung Cancer, Malignant Peripheral Nerve Sheath Tumors, Pancreatic Adenocarcinoma, and others	MRTX1719	I, II	Recruiting	NA

Table 2 (continued)

Clinical Trial	NCT Number	Tumor	Drug	Phase	Status	Outcome
A Study of PRT543 in Participants With Advanced Solid Tumors and Hematologic Malignancies	NCT03886831	Relapsed/Refractory Advanced Solid Tumors, Diffuse Large B-cell Lymphoma, and others	PRT543	I	Completed	The recommended phase 2 dose is 45 mg 5 times per week. Of the 5 MF patients with spliceosome mutations, 1 MF pt (SF3B1) with anemia and transfusion history experienced a substantial improvement in anemia (hemoglobin increase from 6.0 to ≥ 11.1 g/dL). Three pts with MF exhibited stable disease per IWG for at least 1 year, with 1 MF pt demonstrating improvement in bone marrow reticulin fibrosis (+2–3 to +1–2)
Study of IDE397 in Participants With Solid Tumors Harboring MTAP Deletion	NCT04794699	Solid Tumor	IDE397, Docetaxel, Paclitaxel and others	I	Recruiting	NA

Targeting PRMT5 in cancer therapy

Various PRMT5 inhibitors have been developed and translated into clinical trials (Table 2). Currently, the most commonly used pharmacological approaches for PRMT5 inhibitors include SAM competitive inhibitors, SAM non-competitive inhibitors, and substrate-competitive inhibitors (Fu et al., 2022). In the clinic, PRMT5 inhibitors are classified into two generations according to their target binding site: First-generation inhibitors target the PRMT5 protein directly (e.x. PF0693999) and second-generation inhibitors target the PRMT5-MTA complex (e.x. MRTX1719). Based on the reports from ongoing or finished clinical trials, the therapeutic outcome of PRMT5 inhibitors are encouraging. For example, in a clinical trial organized by MD Anderson Cancer Center, PF-06939999 was proved to dose-dependent and manageable toxicities and 6 mg QD was identified as the recommended monotherapy dose for expansion (NCT03854227). In another multi-center clinical trial, the PRMT5 inhibitor PRT543 showed an excellent anti-inflammation effect and symptom remission rate in selected cancer patients; moreover, a prolonged progression free survival was observed in the patients with refractory myelofibrosis (NCT03886831). With regards to safety, the first-generation inhibitors have been reported to have a high incidence of severe adverse events in clinical trials, including thrombocytopenia, anemia, and gastrointestinal reactions, putting their clinical use at risk (Feustel & Falchook, 2022). In contrast, the second-generation PRMT5 inhibitors were clinically well tolerated and showed acceptable toxicity. The development of second-generation PRMT5 inhibitors is based on the understanding of the enzyme MTAP, which catalyzes the cleavage of methylthioadenosine (MTA) into adenine and 5-methylthioribose-1-phosphate (Bertino et al., 2011). Deletion of MTAP is observed in many cancers, resulting in accumulation of MTA that binds to PRMT5 and attenuates its enzyme activity, leading to lethal synthesis of PRMT5 and MTAP (Kryukov et al., 2016). The second-generation PRMT5 inhibitors mimic MTA to inhibit PRMT5 activity, with optimal clinical effect and acceptable toxicity (Smith et al., 2022). In addition, some marketed drugs and plant-derived natural reagents also have inhibitory effects on PRMT5 (Liu et al., 2022; Prabhu et al., 2023), highlighting their epigenetic and DDR regulatory effects and therapeutic potential in cancer treatment.

In summary, given the importance of PRMT5 for DDR and maintenance of genome stability, deciphering mechanisms underlying PRMT5 expression, activity, and subcellular localization will advance the development of PRMT5-related therapies in cancer. Although many questions remain about PRMT5, such as the upstream activation pathway of PRMT5 and its shuttle mechanism between the cytoplasm and nucleus, we strongly believe that PRMT5 can be profoundly understood with the help of comprehensive research and will transform cancer therapy in the future with increasingly encouraging clinical trial results.

Declarations

Conflict of interest There is no conflict of interests among the authors.

References

Bertino, J. R., Waud, W. R., Parker, W. B., & Lubin, M. (2011). Targeting tumors that lack methylthioadenosine phosphorylase (MTAP) activity: Current strategies. *Cancer Biology & Therapy, 11*(7), 627–632.

Che, Y., Liu, Y., Yao, Y., et al. (2023). Exploiting PRMT5 as a target for combination therapy in mantle cell lymphoma characterized by frequent ATM and TP53 mutations. *Blood Cancer Journal, 13*, 27.

Clarke, T.L/, Sanchez-Bailon. M.P., Chiang, K., Reynolds, J.J., Herrero-Ruiz, J., Bandeiras, T.M., Matias, P.M., Maslen, S.L., Skehel, J.M., Stewart, G.S., Davies C.C. (2017). PRMT5-Dependent methylation of the TIP60 coactivator RUVBL1 is a key regulator of homologous recombination. *Mol Cell*, *65*(5)**:** 900–916 e907.

Du, C., Hansen, L.J., Singh, S.X., Wang, F., Sun, R., Moure, C.J., Roso, K., Greer. P.K., Yan, H., He, Y. (2019). A PRMT5-RNF168-SMURF2 axis controls H2AX proteostasis. *Cell Reports*, *28*(12)**:** 3199–3211 e3195.

Du, C., Li, S. W., Singh, S. X., Roso, K., Sun, M. A., Pirozzi, C. J., Yang, R., Li, J. L., & He, Y. (2021). Epigenetic regulation of fanconi anemia genes implicates PRMT5 blockage as a strategy for tumor chemosensitization. *Molecular Cancer Research, 19*(12), 2046–2056.

Du, W., Amarachintha, S., Erden, O., Wilson, A., & Pang, Q. (2016). The Fanconi anemia pathway controls oncogenic response in hematopoietic stem and progenitor cells by regulating PRMT5-mediated p53 arginine methylation. *Oncotarget, 7*(37), 60005–60020.

Feustel, K., & Falchook, G. S. (2022). Protein arginine methyltransferase 5 (PRMT5) inhibitors in oncology clinical trials: A review. *J Immunother Precis Oncol, 5*(3), 58–67.

Fu, S., Zheng, Q., Zhang, D., Lin, C., Ouyang, L., Zhang, J., & Chen, L. (2022). Medicinal chemistry strategies targeting PRMT5 for cancer therapy. *European Journal of Medicinal Chemistry, 244*, 114842.

Ghorbani, A., Jeddi-Tehrani, M., Saidpour, A., Safa, M., Bayat, A. A., & Zand, H. (2015). PI3K/AKT and Mdm2 activation are associated with inhibitory effect of cAMP increasing agents on

DNA damage-induced cell death in human pre-B NALM-6 cells. *Archives of Biochemistry and Biophysics, 566*, 58–66.

Guo, Z., Zheng, L., Xu, H., Dai, H., Zhou, M., Pascua, M. R., Chen, Q. M., & Shen, B. (2010). Methylation of FEN1 suppresses nearby phosphorylation and facilitates PCNA binding. *Nature Chemical Biology, 6*(10), 766–773.

Hamard, P. J., Santiago, G. E., Liu, F., Karl, D. L., Martinez, C., Man, N., Mookhtiar, A. K., Duffort, S., Greenblatt, S., Verdun, R. E., & Nimer, S. D. (2018). PRMT5 regulates DNA repair by controlling the alternative splicing of histone-modifying enzymes. *Cell Reports, 24*(10), 2643–2657.

Hwang, J. W., Cho, Y., Bae, G. U., Kim, S. N., & Kim, Y. K. (2021). Protein arginine methyltransferases: Promising targets for cancer therapy. *Experimental & Molecular Medicine, 53*(5), 788–808.

Hwang, J. W., Kim, S. N., Myung, N., Song, D., Han, G., Bae, G. U., Bedford, M. T., & Kim, Y. K. (2020). PRMT5 promotes DNA repair through methylation of 53BP1 and is regulated by Src-mediated phosphorylation. *Commun Biol, 3*(1), 428.

Kannan, A., Bhatia, K., Branzei, D., & Gangwani, L. (2018). Combined deficiency of Senataxin and DNA-PKcs causes DNA damage accumulation and neurodegeneration in spinal muscular atrophy. *Nucleic Acids Research, 46*(16), 8326–8346.

Kim, H., & Ronai, Z. A. (2020). PRMT5 function and targeting in cancer. *Cell Stress, 4*(8), 199–215.

Kryukov, G. V., Wilson, F. H., Ruth, J. R., Paulk, J., Tsherniak, A., Marlow, S. E., Vazquez, F., Weir, B. A., Fitzgerald, M. E., Tanaka, M., Bielski, C. M., Scott, J. M., Dennis, C., Cowley, G. S., Boehm, J. S., Root, D. E., Golub, T. R., Clish, C. B., Bradner, J. E., … Garraway, L. A. (2016). MTAP deletion confers enhanced dependency on the PRMT5 arginine methyltransferase in cancer cells. *Science, 351*(6278), 1214–1218.

Lim, J. H., Lee, Y. M., Lee, G., et al. (2014). PRMT5 is essential for the eIF4E-mediated 5'-cap dependent translation. *Biochemical and Biophysical Research Communications, 452*(4), 1016–1021.

Liu, S., Liu, Z., Piao, C., Zhang, Z., Kong, C., Yin, L., & Liu, X. (2022). Flavokawain A is a natural inhibitor of PRMT5 in bladder cancer. *Journal of Experimental & Clinical Cancer Research, 41*(1), 293.

Motolani, A., Martin, M., Sun, M., Lu, T. (2021). The structure and functions of PRMT5 in human diseases. *Life (Basel)*, *11*(10).

Musiani, D., Bok, J., Massignani, E., Wu, L., Tabaglio, T., Ippolito, M.R., Cuomo, A., Ozbek, U., Zorgati. H., Ghoshdastider, U., Robinson, R.C., Guccione, E., Bonaldi, T. (2019). Proteomics profiling of arginine methylation defines PRMT5 substrate specificity. *Sci Signal*, *12*(575).

Owens, J.L., Beketova, E., Liu, S., Tinsley, S.L., Asberry, A.M., Deng, X., Huang, J., Li, C., Wan, J., Hu, C.D. (2020). PRMT5 Cooperates with pICln to Function as a Master Epigenetic Activator of DNA Double-Strand Break Repair Genes. *iScience*, *23*(1): 100750.

Prabhu, L., Martin, M., Chen, L., Demir, O., Jin, J., Huang, X., Motolani, A., Sun, M., Jiang, G., Nakshatri, H., Fishel, M. L., Sun, S., Safa, A., Amaro, R. E., Kelley, M. R., Liu, Y., Zhang, Z. Y., & Lu, T. (2023). Inhibition of PRMT5 by market drugs as a novel cancer therapeutic avenue. *Genes Dis, 10*(1), 267–283.

Rehman, I., Basu, S. M., Das, S. K., Bhattacharjee, S., Ghosh, A., Pommier, Y., & Das, B. B. (2018). PRMT5-mediated arginine methylation of TDP1 for the repair of topoisomerase I covalent complexes. *Nucleic Acids Research, 46*(11), 5601–5617.

Sachamitr, P., Ho, J. C., Ciamponi, F. E., Ba-Alawi, W., Coutinho, F. J., Guilhamon, P., Kushida, M. M., Cavalli, F. M. G., Lee, L., Rastegar, N., Vu, V., Sánchez-Osuna, M., Coulombe-Huntington, J., Kanshin, E., Whetstone, H., Durand, M., Thibault, P., Hart, K., Mangos, M., … Dirks, P. B. (2021). PRMT5 inhibition disrupts splicing and stemness in glioblastoma. *Nature Communications, 12*(1), 979.

Smith, C. R., Aranda, R., Bobinski, T. P., Briere, D. M., Burns, A. C., Christensen, J. G., Clarine, J., Engstrom, L. D., Gunn, R. J., Ivetac, A., Jean-Baptiste, R., Ketcham, J. M., Kobayashi, M., Kuehler, J., Kulyk, S., Lawson, J. D., Moya, K., Olson, P., Rahbaek, L., … Marx, M. A. (2022). Fragment-based discovery of MRTX1719, a synthetic lethal inhibitor of the PRMT5*MTA complex for the treatment of MTAP-deleted cancers. *Journal of Medicinal Chemistry, 65*(3), 1749–1766.

Tan DQ, Li Y, Yang C, Li J, Tan SH, Chin DWL, Nakamura-Ishizu A, Yang H, Suda T. (2019) PRMT5 Modulates Splicing for Genome Integrity and Preserves Proteostasis of Hematopoietic Stem Cells. *Cell Reports*, *26*(9): 2316–2328 e2316.

Wang, Y., Hu, W., & Yuan, Y. (2018). Protein arginine methyltransferase 5 (PRMT5) as an anticancer target and its inhibitor discovery. *Journal of Medicinal Chemistry, 61*(21), 9429–9441.

Wu, Q., Schapira, M., Arrowsmith, C. H., & Barsyte-Lovejoy, D. (2021). Protein arginine methylation: From enigmatic functions to therapeutic targeting. *Nature Reviews. Drug Discovery, 20*(7), 509–530.

Wu, Y., Wang, Z., Han, L., Guo, Z., Yan, B., Guo, L., Zhao, H., Wei, M., Hou, N., Ye, J., Wang, Z., Shi, C., Liu, S., Chen, C., Chen, S., Wang, T., Yi, J., Zhou, J., Yao, L., … Zhang, J. (2022). PRMT5 regulates RNA m6A demethylation for doxorubicin sensitivity in breast cancer. *Molecular Therapy, 30*(7), 2603–2617.

Yuan, Y., & Nie, H. (2021). Protein arginine methyltransferase 5: A potential cancer therapeutic target. *Cellular Oncology (dordrecht), 44*(1), 33–44.