Emerging role of protein arginine methyltransferase 5 in gastrointestinal cancer (Review)

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Abstract. Gastrointestinal (GI) cancer remains a leading cause of cancer-related mortality worldwide, with epigenetic alterations progressively recognized as key drivers of tumorigenesis and therapeutic resistance. Through its role in facilitating cell proliferation, inhibiting apoptosis, driving epithelial-mesenchymal transition (EMT) and metastasis, reinforcing angiogenesis, inducing metabolic reprogramming, mediating chemoradiotherapy resistance and maintaining cancer stem cell (CSC) properties, protein arginine methyltransferase 5 (PRMT5) has emerged as a key oncogenic regulator among these epigenetic modifiers implicated in GI cancer progression. Elevated PRMT5 expression has been observed in multiple GI cancer subtypes, comprising gastric cancer (GC), colorectal cancer (CRC), hepatocellular carcinoma (HCC) and pancreatic cancer, where PRMT5 markedly contributes to tumorigenesis via symmetric dimethylation of histone (e.g., dimethylation of histone H4 at arginine 3) and non-histone substrates [e.g., AKT1 and sterol regulatory element-binding protein 1a (SREBP1a)]. In GC, PRMT5 activates the PI3K/AKT pathway [e.g., by methylating AKT1 at arginine (R)391 and upregulating c-Myc], facilitating tumor cell proliferation and survival. In CRC, PRMT5-mediated methylation of SMAD4 (e.g., at R361) reinforces TGF-β signaling, facilitating EMT and metastasis, while its interaction with EGFR further amplifies proliferative signals. PRMT5 also upregulates VEGF expression (e.g., via chromatin remodeling at its promoter), stimulating angiogenesis and inhibits ferroptosis (e.g., by suppressing the solute carrier family 7 member 11/glutathione peroxidase 4 axis in HCC), supporting tumor survival. Furthermore, PRMT5 markedly contributes to metabolic reprogramming (e.g., accelerating *de novo* lipogenesis via SREBP1a methylation and glycolysis via epigenetic silencing of F-box and WD repeat domain-containing protein 7), while strengthening DNA repair (e.g., homologous recombination) and CSC self-renewal (e.g., via the β-catenin/IL-8 axis in CRC) to confer therapy resistance. However, PRMT5 inhibitors (e.g., GSK3326595 and JNJ-64619178) demonstrate antitumor effects in preclinical models and methylthioadenosine phosphorylase (MTAP) deletion may serve as a potential biomarker for patient selection. The clinical translation of PRMT5 inhibitors is limited by hematological toxicity, lack of robust predictive biomarkers beyond MTAP and potential resistance from compensatory PRMT family members. It is key to clarify GI cancer-specific PRMT5 mechanisms and potentially develop optimized combination therapies in the future.

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Contents

1. Introduction

Cancer is universally acknowledged as a disease with several diverse aspects involving both genetic and epigenetic alterations throughout its progression (1). Epigenetics is a field of biology that studies heritable changes in gene expression or

cellular phenotype that occur without alterations in the DNA sequence. Mediated by mechanisms such as DNA methylation, histone modifications and non-coding RNA regulation, these changes constitute a hereditary and reversible regulatory layer that modulates gene expression, facilitates interindividual phenotypic variation and can be transmitted to subsequent generations (2). In cancer research, histone methylation, a pivotal post-translational modification (PTM), has garnered increasing attention due to its pivotal role in chromatin remodeling and oncogenesis. Proteins, following synthesis, undergo an array of covalent modifications (collectively termed PTMs), which markedly modulate their functional properties (3,4). The common forms of this process comprise phosphorylation, ubiquitylation, acetylation and methylation (5,6). Among post-translational and nucleic-acid marks, methylation exerts key control over gene activation and silencing, underpinning cancer, aging, dementia and extensive epigenetic regulation (7).

Arginine residues frequently undergo methylation, which is a key PTM catalyzed by the protein arginine methyltransferase (PRMT) family (8). The PRMT family is functionally classified into three types: Type I PRMTs generate monomethylarginine (MMA) and asymmetric dimethylarginine (ADMA); type II PRMTs produce symmetric dimethylarginine (SDMA); and type III PRMTs exclusively catalyze the formation of monomethylarginine (MMA). Through the deposition of these distinct methylation marks (MMA, ADMA and SDMA), PRMTs induce an extensive array of cellular processes, encompassing signal transduction, DNA repair, gene transcription and mRNA splicing (9). Protein arginine methyltransferase 5 (PRMT5) is a type II arginine methyltransferase that symmetrically dimethylates arginine residues on both histone and non-histone substrates (10). By regulating the methylation of these non-histone substrates, PRMT5 serves as a key regulator that modulates fundamental cellular processes, encompassing cell proliferation, migration, differentiation, gene transcription, alternative splicing and Golgi assembly (11). PRMT5 can also undergo auto-methylation (self-methylation) and participate in biological processes such as cell cycle, embryonic development and substrate protein methylation. Among the PRMT family, PRMT5 exerts a direct effect on tumor cell proliferation and differentiation by modulating the expression levels or activity of pivotal genes, comprising p53, Bcl-2, enhancer of zeste homolog 2, Myc and SMAD4 (10,12-15). Several studies have highlighted the role of PRMT5 in regulating tumor progression, encompassing malignancies such as lymphoma, breast cancer and glioblastoma (10,15,16). Previous research also supports its involvement in gastrointestinal (GI) cancer, suggesting PRMT5 as a potential biomarker and therapeutic target (9,11,17-19).

While PRMT5 promotes tumorigenesis across diverse cancer types, its functional impact in GI malignancies is uniquely shaped by tissue-specific contexts. Apart from the canonical roles in cell proliferation and survival observed in lymphomas and breast cancer, PRMT5 in GI cancer markedly regulates angiogenesis, lipid metabolism and cancer stem cell (CSC) maintenance, encompassing processes intrinsically associated with the physiological properties of the digestive system. The present review focuses on these GI-specific mechanisms, emphasizing how PRMT5 intersects with pathways such as TGF-β/SMAD4 [in colorectal cancer (CRC)] and β-catenin/IL-8 [in gastric cancer (GC)] to drive tumor progression in a context-dependent manner. Of note, the present review highlights how PRMT5 functions in GI cancer diverge from those in hematological malignancies and other solid tumors, with particular emphasis on microenvironmental regulation, metabolic adaptation and therapy resistance mechanisms unique to the GI tract.

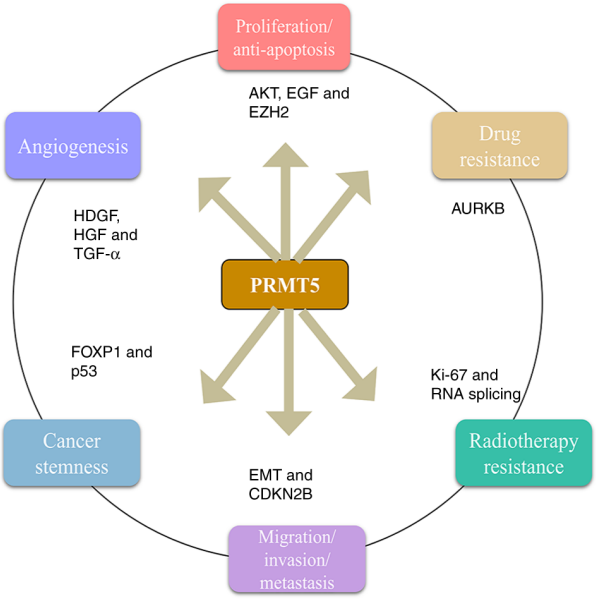

Figure 1. Biological function of PRMT5 in gastrointestinal cancer. PRMT5 regulates the expression levels of AKT, p53 and more through histone methylation modification, and participates in the biological processes of gastrointestinal cancer, encompassing cell-cycle expansion, programmed cell death, neovascularization, motility, tissue penetration and radioresistance. PRMT5, protein arginine methyltransferase 5; EMT, epithelial-mesenchymal transition; HDGF, hepatoma-derived growth factor; HGF, hepatoma growth factor; CDKN2B, CDK inhibitor 2B; AURKB, aurora kinase B; EZH2, enhancer of zeste homolog 2; FOXP1, forkhead box protein P1.

2. Functional contribution of PRMT5 to GI malignancy

Previous studies have revealed a close association between PRMT5 and a diverse spectrum of processes involved in the development of GI carcinoma, encompassing proliferation, apoptosis, metastasis, angiogenesis, chemotherapy/radiotherapy, glycolipid metabolism and the maintenance of CSCs (Fig. 1). The present review provides a summary below of these findings regarding the role of PRMT5 in GI cancer (Table I) (13,17,20-26).

3. Function of PRMT5 in proliferation and apoptosis in GI cancer

PRMT5 serves as a key regulator of cell proliferation and apoptosis in GI malignancies, functioning as an oncogenic driver through both epigenetic and post-translational mechanisms. Increasing research underscores its central role in accelerating tumor progression by modulating key signaling cascades, particularly the PI3K/AKT pathway, which is key to cancer cell survival and tumor growth (24,27,28).

Table I. Role of PRMT5 in gastrointestinal cancer.

First author, year	Cancer type	Role of PRMT5	Target	Biological functions	Mechanisms	Upstream	(Refs.)
Liu *et al*, 2024	CRC	Oncogene	TGF-β	Promotes tumor cell invasion, metastasis, drug resistance and maintains cancer stem cell potential	Triggers SMAD4 methylation at R361 and contributes to the dysregulation of TGF-β signaling	SMAD4	(13)
Zhou *et al*, 2020	LC	Oncogene	β-catenin	Promotes cell proliferation, migration and invasion	Methylation of β-catenin protein	Wnt	(17)
Ge *et al*, 2019	PC	Oncogene	EMT	Promotes cell invasion and metastasis	Methylates transcription factors and regulate EMT	Snai1	(20)
Qin *et al*, 2019	PC	Oncogene	FBW7/c-Myc	Promotes cell proliferation	PRMT5 regulates c-Myc stability post-translationally through FBW7, an E3 ubiquitin ligase governing c-Myc degradation	-	(21)
Zheng *et al*, 2019	LC	Oncogene	HNF4α	Promotes cell differentiation	Targeting PRMT5 activity promotes HNF4α induction in HCC cells	CDKL3	(22)
Liu *et al*, 2020	GC	Oncogene	c-Myc	Promotes cell proliferation and differentiation	Regulates c-Myc	-	(23)
Yan *et al*, 2021	CRC	Oncogene	EGFR	Promotes cell proliferation, migration and invasion	Regulates EGFR signaling cascades	-	(24)
Yin *et al*, 2021	GC	Oncogene	AKT	Promotes cell proliferation, migration and invasion	Activates AKT and decreases apoptosis pathway	PI3K	(25)
Abumustafa *et al*, 2024	CRC	Uncertain	DKK1	Affects cell proliferation, migration and invasion	Affects the Wnt signaling pathway	β-catenin	(26)

GC, gastric cancer; CRC, colorectal cancer; LC, liver cancer; PC, pancreatic cancer; HCC, hepatocellular carcinoma; FBW7, F-box and WD repeat domain-containing 7; EMT, epithelial-mesenchymal transition; Snai1, Snail family transcriptional repressor 1; HNF4α, hepatocyte nuclear factor 4 α; CDKL3, CDK-like 3; PRMT5, protein arginine methyltransferase 5; DKK1, Dickkopf-related protein 1.

At the molecular level, PRMT5 promotes the symmetric dimethylation of histone H4 at arginine 3 (H4R3me2s), ultimately giving rise to chromatin remodeling and transcriptional activation of pro-proliferative genes, such as c-Myc and cyclin D1, both of which are pivotal for G_1/S phase transition and sustained cell cycle progression in GI cancer cells (29). Apart from histone modification, PRMT5 directly methylates non-histone proteins, comprising AKT1 at arginine (R)391. This methylation event reinforces AKT1 activity, thereby amplifying downstream proliferative and survival signals (25). Activation of AKT not only fosters metabolic reprogramming and resistance to apoptosis but also potentiates mitogenic signaling in response to extracellular stimuli (30).

PRMT5 is also functionally integrated with receptor tyrosine kinase (RTK)-driven pathways. Upon stimulation by growth factors such as epidermal growth factor (EGF), PRMT5 expression and/or catalytic activity are upregulated, resulting in strengthened transcription of proliferation-associated genes. Mechanistically, this crosstalk reinforces AKT activation, thus establishing a feed-forward loop that drives uncontrolled proliferation of GI tumor cells (28). By contrast, genetic depletion or pharmacological inhibition of PRMT5 disrupts AKT phosphorylation and attenuates signaling through its downstream effectors, such as mTOR and GSK3β, culminating in reduced proliferation and increased susceptibility to apoptotic stimuli (31,32).

Apart from promoting proliferation, PRMT5 exerts anti-apoptotic effects via transcriptional and post-translational regulation of downstream targets and other survival factors (Fig. 2). Clinical studies revealed that PRMT5 is frequently upregulated in multiple GI cancer cases and is associated with aggressive phenotypes and unfavorable prognosis (17,19,20,32,33). In CRC, PRMT5 expression is markedly elevated in tumor tissues compared with that in matched normal

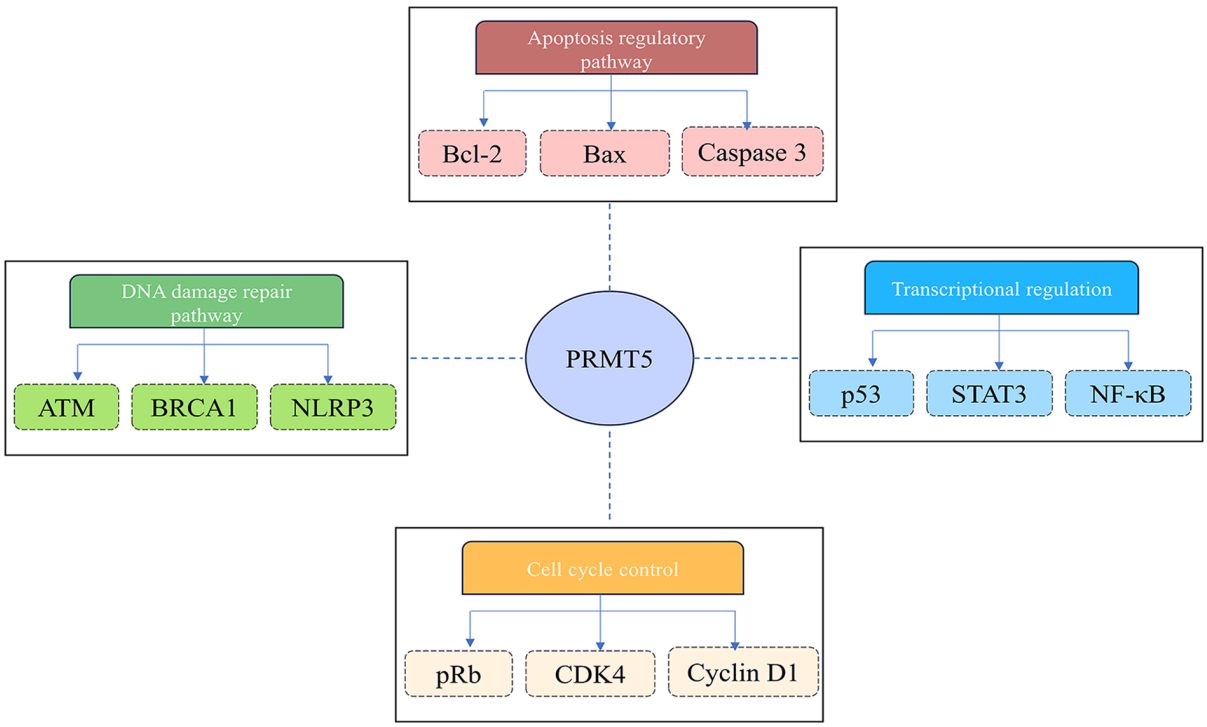

Figure 2. Downstream region of PRMT5. Apoptosis regulatory pathway: core genes comprise Bcl-2, Bax and Caspase 3, which collectively participate in the regulation of the initiation and execution of apoptosis. Transcriptional regulation pathway: Comprising pivotal molecules such as p53, STAT3, NF-κB, ATM, BRCA1 and NLRP3, these genes are involved in signal transduction and expression regulation of multifarious cellular functions through transcriptional regulation. Cell cycle control pathway: The paramount components are pRb, CDK4 and cyclin D1, which jointly mediate the regulation of cell cycle progression. The DNA damage repair pathway regulates ATM, BRCA1, and NLRP3 to maintain genome stability through coordinated damage sensing, repair, and inflammatory responses. PRMT5, protein arginine methyltransferase 5; ATM, Ataxia-telangiectasia mutated; NLRP3, NLR family pyrin domain containing 3; pRB, retinoblastoma protein.

mucosa and high PRMT5 levels are associated with lymph node metastasis and poor overall survival. Co-expression of PRMT5 and EZH2 further stratifies a subset of patients with CRC with markedly poor prognosis (8). Similarly, in hepatocellular carcinoma (HCC), PRMT5 upregulation is prevalent and associated with increased tumor aggressiveness and recurrence. Based on functional studies, PRMT5 knockdown impairs HCC cell proliferation and induces apoptosis, whereas forced overexpression rescues these phenotypes (22).

In summary, PRMT5 drives GI tumor progression by synergistically activating the PI3K/AKT pathway via histone modification and direct methylation of AKT1. This facilitates transcriptional upregulation of pro-proliferative genes while inhibiting apoptotic signaling, collectively sustaining aberrant cell survival and proliferation.

4. Functional contribution of PRMT5 in the migration, invasion and metastasis of GI cancer

PRMT5 acts as a key regulator in cell proliferation. PRMT5 also regulates tumor migration. Furthermore, it affects tumor invasion and metastasis (34). Tumor epithelial-mesenchymal transition (EMT) involves the loss of epithelial polarity, tight junctions and intercellular adhesion, coupled with the acquisition of invasive and migratory properties, thereby facilitating the transformation of epithelial cells into mesenchymal-like cells. Metastasis is a multistep process that involves a sequential cascade encompassing primary tumor invasion, intravasation into the vasculature or lymphatic system, survival during hematogenous transit, extravasation, and ultimately, colonization of distant organs (35). PRMT5 also serves a key role in EMT by downregulating epithelial markers, such as E-cadherin, and upregulating mesenchymal markers, such as N-cadherin, thereby facilitating the acquisition of mesenchymal traits in GI cancer cells and strengthening their migratory and invasive potential. Furthermore, notable findings suggested that PRMT5 serves a notable role in the migration and invasion of HCC cells. Silencing PRMT5 markedly decreased the migratory and invasive abilities of HCC cells (22). In CRC, PRMT5 regulates the CDK inhibitor 2B, thereby affecting the migration and invasion of colorectal malignant neoplastic cells (10). Collectively, these findings implicate PRMT5 as a driver oncogene that propels EMT and metastatic dissemination in GI malignancies.

5. Functional contribution of PRMT5 to neovascularization in GI malignancies

Angiogenesis represents a notable hallmark of tumor growth and metastasis, serving as a key mechanism to sustain the metabolic demands of proliferating cancer cells (36). Increasing research revealed that PRMT5 contributes markedly to the transcriptional modulation of several angiogenesis-related factors in GI cancer (37,38). Of note, PRMT5 has been reported to strengthen the expression level of vascular EGF (VEGF), which is a key mediator of angiogenesis that promotes

endothelial cell proliferation, migration and tube formation. Mechanistically, PRMT5-mediated symmetric H4R3me2s within the VEGF promoter facilitates local chromatin relaxation, thereby elevating transcription factor accessibility and upregulating VEGF expression in the tumor microenvironment (39).

Apart from VEGF, previous studies have implicated PRMT5 in the broader regulation of pro-angiogenic signaling networks (37). For instance, PRMT5 may influence the expression or activity of fibroblast growth factor (FGF) family members, which are known to control diverse processes comprising cell proliferation, survival and migration through their cognate RTKs (40). Nonetheless, direct evidence linking PRMT5 to the transcriptional or post-translational regulation of FGF ligands or receptors in GI cancers remains limited and warrants further investigation.

Activation of the PI3K/AKT signaling axis in endothelial cells serves a key role in facilitating angiogenesis, particularly by supporting cell survival, migration and morphogenesis. PRMT5 has been reported to modulate this pathway through arginine methylation of specific substrates, which may in turn exert profound influences on endothelial cell behavior throughout vessel formation (25,27,28). Although these findings indicate a potential mechanistic association between PRMT5 activity and endothelial activation, the precise downstream effectors remain incompletely defined. Furthermore, while PRMT5 has been implicated in regulating VEGF expression and may intersect with FGF signaling, the extent to which it drives angiogenesis in GI malignancies by regulating VEGF and FGF pathways, encompassing the possibilities of coordinated regulation and synergy, remains speculative and warrants further research.

To conclude, current research supports a multifunctional role for PRMT5 in facilitating angiogenesis in GI cancer, primarily via VEGF upregulation and potential modulation of FGF-associated signals and endothelial PI3K/AKT activity. Nonetheless, few studies have directly investigated the coordinated actions among PRMT5, VEGF and FGF in tumor neovascularization, which represents a notable knowledge gap and thus, a promising direction for future research.

6. Functional impact of PRMT5 on chemo- and radio-resistance in GI malignancies

An extensive spectrum of heritable genomic and epigenomic aberrations underpin reduced efficacy of chemotherapy and radiotherapy, driving treatment resistance in cancer (41). In GI malignancies, emerging research now provides direct insights into the role of PRMT5 in chemo- and radio-resistance, revealing functional contributions mediated through DNA repair reinforcement, metabolic reprogramming and ferroptosis inhibition (42-44).

In CRC, high PRMT5 expression is associated with markedly worse 5-year disease-free survival in patients receiving adjuvant chemotherapy, which is a clinical association driven by strengthened homologous recombination and non-homologous end joining via histone and non-histone methylation, sustained Fanconi anemia pathway activity and suppression of the ring finger protein 168-H2A histone family member X axis (45). In pancreatic ductal adenocarcinoma, PRMT5 forms a positive feedback loop with c-Myc and sustains the Warburg effect through glycolytic enzyme regulation and the ubiquitin protein ligase E3 component N-recognin 7-PRMT5 axis, thereby facilitating gemcitabine resistance; PRMT5 inhibition not only abrogates this feedback loop, but also exerts a synergistic effect with CDK4/6 or cell division cycle 7 blockers to induce replication stress and cell cycle arrest (18). In HCC and esophageal squamous cell carcinoma (ESCC), stanniocalcin 2 (STC2)-activated PRMT5 suppresses ferroptosis via H4R3me2s-dependent repression of pro-ferroptosis genes and upregulation of the solute carrier family 7 member 11 (SLC7A11)/glutathione peroxidase 4 axis (HCC) or activating transcription factor 4-driven solute carrier family 3 member 2/SLC7A11 axis (ESCC); by contrast, PRMT5 inhibition restores radiosensitivity in these malignancies, accompanied by increased reactive oxygen species and lipid peroxidation (46,47).

In summary, these GI-specific findings establish PRMT5 as a direct contributor to treatment resistance, operating through convergent mechanisms that strengthen DNA repair, maintain metabolic adaptation and block ferroptosis. These findings underscore its notable potential as a therapeutic target; nevertheless, comprehensive validation in larger patient cohorts and exploration of combination strategies are key to translating these insights into ameliorated therapeutic efficacy for GI malignancies in the future.

7. Functional impact of PRMT5 on glycolipid metabolic reprogramming within GI malignancies

Dysregulated metabolic networks encompassing glucose, lipid and amino acid metabolism are defining features of cancer, which can markedly facilitate the bioenergetic and biosynthetic demands of rapidly proliferating tumor cells (48,49). Metabolic reprogramming is a well-recognized defining feature of malignant transformation, enabling cancer cells to remodel metabolic pathways to sustain persistent proliferation and survival (12,50). By promoting biomass accumulation and redox homeostasis key to neoplastic growth, the coordinated upregulation of aerobic glycolysis and *de novo* lipogenesis (DNL) among notable metabolic reprogramming events serves as a key driver of tumor initiation, malignant progression and therapeutic resistance in GI malignancies (51).

In particular, PRMT5 promotes DNL through multifaceted post-translational mechanisms in the context of lipid metabolism. A key mechanism involves PRMT5 directly symmetrically dimethylating nuclear sterol regulatory element-binding protein 1a (SREBP1a) at R321, which reinforces the transcriptional activity and stability of SREBP1a by preventing phosphorylation-dependent ubiquitination and proteasomal degradation. This methylation event potentiates SREBP1a-mediated transcription of lipogenic genes, such as fatty acid synthase, acetyl-CoA carboxylase α, ATP citrate lyase and stearoyl-CoA desaturase 1, thereby accelerating lipid synthesis and tumor progression in HCC (52). Apart from regulating its substrates, the PTM of PRMT5 fine-tunes its lipogenic function. Of note, desuccinylation of PRMT5 at lysine 387 (K387) reinforces its methyltransferase activity by accelerating octameric complex formation with methylosome protein 50, while simultaneously inhibiting STIP1 homology

and U-box containing protein 1-mediated ubiquitination and degradation (53). This desuccinylation switch amplifies PRMT5-dependent SREBP1a methylation, ultimately inducing increased intracellular accumulation of triglycerides, fatty acids and cholesterol (54). Furthermore, PRMT5-mediated symmetric dimethylation of Ras-GTPase-activating protein SH3 domain-binding protein 2 (G3BP2) at R468 reinforces G3BP2 protein stability via USP7-dependent deubiquitination, thereby fostering lipid droplet biogenesis in malignant cells (55).

Other than lipogenesis, PRMT5 markedly modulates glycolytic metabolism in GI cancer. In pancreatic cancer, PRMT5 promotes aerobic glycolysis through epigenetic silencing of the tumor suppressor F-box and WD repeat domain-containing 7 (FBW7), ultimately inducing c-Myc stabilization and subsequent upregulation of glycolytic enzymes encompassing glucose transporter 1, hexokinase 2 and lactate dehydrogenase A (18,56). This molecular axis reinforces the Warburg effect, thereby facilitating lactate production and biosynthetic precursor generation. PRMT5 has also been implicated in the regulation of pyruvate kinase M2 activity, further contributing markedly to glycolytic flux in tumor cells (21).

From a therapeutic perspective, the dependency of GI cancer on PRMT5-mediated metabolic reprogramming may be effectively exploited through targeted therapeutic approaches. Pharmacological inhibition of PRMT5 methyltransferase activity restores SREBP1a ubiquitination, suppresses lipogenesis and attenuates tumor growth in preclinical models (52). Furthermore, strategies aimed at disrupting the sirtuin 7-PRMT5 interaction or accelerating PRMT5 K387 succinylation represent novel metabolic-targeting approaches distinct from direct methyltransferase inhibition (53).

Collectively, the evidence establishes PRMT5 as a central nexus integrating glycolytic and lipogenic pathways in GI malignancies through substrate methylation (SREBP1a and G3BP2) and transcriptional regulation (FBW7/c-Myc axis) (21). Further elucidation of PRMT5 PTMs and metabolic interactomes may reveal additional therapeutic targets for metabolic intervention in GI cancer.

8. Functional contribution of PRMT5 to CSCs within GI malignancies

Previous studies suggest that CSCs sustain malignant expansion through self-renewal and limitless proliferation (57,58). CSCs can enter a dormant state that persists for extended periods of time, thereby contributing markedly to therapeutic resistance and eventual relapse even after standard therapy eliminates the bulk tumor population (57,59). Therefore, even after standard therapy eradicates the majority of tumor cells, malignant disease retains a high propensity for relapse. While PRMT5 has been notably demonstrated to maintain the proliferative and self-renewal capacities of breast CSCs and glioblastoma stem cells through mechanisms involving forkhead box protein P1 upregulation and p53 modulation (60-62), recent studies demonstrated that PRMT5 also serves as a key regulator of stemness in GI malignancies, although its specific mechanisms in CSC populations remain incompletely characterized (9,63).

Fundamentally, PRMT5 is key to maintaining normal intestinal stem cells by sustaining histone H3 lysine 27 acetylation levels at stemness gene loci (leucine-rich repeat-containing G-protein coupled receptor 5 and olfactomedin 4), establishing a mechanistic basis for its oncogenic potential (64). In GC, PRMT5 promotes malignant progression by activating the β-catenin/IL-8 axis and elevating chemoresistance (23,65), whereas in CRC, it drives stemness through interaction with minichromosome maintenance complex component 7 and activation of EMT-associated pathways, which are associated with poor therapeutic outcomes (45).

Nevertheless, despite these advances in understanding the general oncogenic functions of PRMT5, its direct regulation of CSC-specific traits, such as sphere formation capacity, asymmetric division and tumor initiation in GI malignancies, remains insufficiently validated and warrants systematic investigation in the future.

9. Potential clinical application of PRMT5

Increasing research identifies PRMT5 as a rational therapeutic target in GI malignancies, due to its central role in accelerating proliferation, metabolic reprogramming and CSC maintenance (17,66,67). In GC, PRMT5 promotes tumor progression through metabolic adaptation and sustains stemness phenotypes, supporting its mechanistic relevance in GI tumor biology.

Early preclinical studies established that PRMT5 inhibition, particularly when mediated by S-adenosylmethioninecompetitive inhibitors, such as GSK3326595, impairs the growth of hematological and solid tumor models (Fig. 3), comprising colorectal and gastric cell lines (33). More recently, first-in-human phase I data for JNJ-64619178 confirmed that PRMT5 inhibition is feasible in advanced cancer types, with GI tumor subsets included in the dose-escalation cohorts (68). Synthetic lethality arising from methylthioadenosine phosphorylase (MTAP) deletion represents a key biomarker strategy; MTAP-null tumors become reliant on PRMT5, as illustrated in genome-wide CRISPR screens (69), providing a rationale for patient selection.

Despite these advances, therapeutic translation remains at an early stage. Dose-limiting hematological toxicity, including anemia, neutropenia, and thrombocytopenia, has been observed in early-phase clinical trials of PRMT5 inhibitors (GSK3326595, JNJ-64619178 and PRT543), reflecting the physiological roles of PRMT5 in normal tissues (68,70,71). Furthermore, the absence of validated predictive biomarkers aside from MTAP status, as well as potential resistance mechanisms (comprising compensatory upregulation of alternative arginine methyltransferases), poses challenges for extensive implementation. Combination strategies are under active investigation: In HCC, PRMT5 inhibition (GSK591) synergizes with programmed cell death-ligand 1 (PD-L1) blockade to strengthen $CD8^+$ T-cell-mediated antitumor immunity (72), whereas in microsatellite-stable CRC, PRMT5 inhibition combined with chemotherapy (irinotecan) induces a deficient mismatch repair-like state that sensitizes tumors to immune checkpoint blockade via, cGMP-AMP synthase-stimulator of interferon genes activation (43). In ESCC, the PRMT5 inhibitor GSK3326595 effectively reverses STC2 upregulation-induced

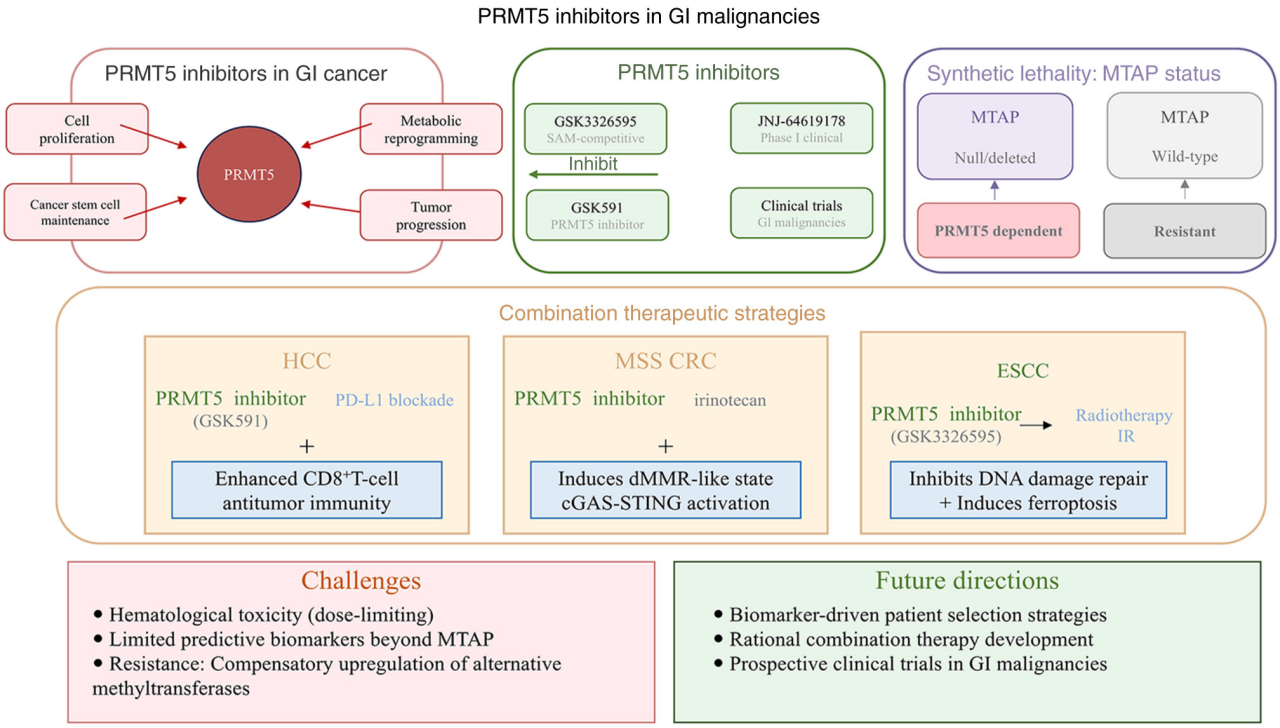

Figure 3. Mechanisms and combination therapeutic strategies of PRMT5 inhibitors in GI malignancies. HCC: PRMT5 inhibitor (GSK591) combined with PD-L1 blockade reinforces CD8+ T-cell antitumor immunity. CRC: PRMT5 inhibition plus irinotecan induces a dMMR-like state and activates the cGAS-STING pathway. ESCC: PRMT5 inhibitor (GSK3326595) combined with radiotherapy inhibits DNA damage repair and induces ferroptosis, reversing radio-resistance. PRMT5, protein arginine methyltransferase 5; PD-L1, programmed cell death-ligand 1; HCC, hepatocellular carcinoma; CRC, colorectal cancer; ESCC, esophageal squamous cell carcinoma; cGAS-STING, cGMP-AMP synthase-stimulator of interferon genes; dMMR, deficient mismatch repair; MTAP, methylthioadenosine phosphorylase; MSS, microsatellite stable; GI, gastrointestinal; IR, ionizing radiation.

radio-resistance, exhibits synergistic effects with anti-PD-L1 therapy, reinforces CD8+ T-cell infiltration and function, and demonstrates radiosensitizing efficacy across multiple ESCC cell lines (73). These rational combinations represent a tangible pathway to translate PRMT5 targeting from preclinical concept to potential clinical utility in GI malignancies in the future.

In summary, while preclinical and early clinical data support continued investigation of PRMT5 in GI malignancies, robust biomarker-driven patient selection and mitigation of on-target toxicity are prerequisites in realizing its clinical potential. Prospective studies incorporating rational combinations will be key to defining the therapeutic utility of PRMT5.

10. Discussion

Although PRMT5 has been extensively implicated in a diverse spectrum of malignancies, such as lymphoma, breast cancer and glioblastoma, its role in GI cancer exhibits both shared and context-specific features. For instance, while PRMT5 promotes cell proliferation and survival via AKT pathway activation across multiple cancer types, its impact on GI tumorigenesis is also shaped by pathways such as TGF-β/SMAD4 in CRC and β-catenin/IL-8 in GC. Although the precise role of PRMT5 in GI CSCs remains to be fully elucidated, emerging evidence suggests that PRMT5 markedly contributes to the maintenance of stemness properties, potentially driving therapy resistance and tumor recurrence. These context-dependent functions highlight the necessity for GI cancer-specific research. The present review highlighted that PRMT5 is frequently upregulated in diverse GI malignancies compared with that in normal tissues, where it markedly contributes to tumorigenesis and progression. These context-specific functions underscore the necessity for further investigation tailored to the GI tumor microenvironment.

PRMT5 serves as a key regulator involved in multiple aspects of GI cancer development, encompassing apoptosis, invasion and migration, metastasis, angiogenesis, resistance to radiochemotherapy, glycolysis/lipid metabolism and the maintenance of CSCs. PRMT5 operates through an intricate network of molecular players and signaling cascades in GI malignancies. As suggested by these findings, PRMT5 is markedly elevated in GC tissues and is associated with adverse impacts on the clinical outcomes of patients with GC. PRMT5 has been reported to be upregulated in GC tissues, where it is associated with adverse clinical outcomes. As demonstrated by the aforementioned findings, the AKT/VEGF/nuclear SREBP1a axis markedly contributes to gastric tumor expansion and dissemination by strengthening glycolytic flux and angiogenesis (23). Furthermore, previous studies reported that PRMT5 can activate the E2F transcription factors (74) and EMT process (35) to strengthen neoplastic expansion and metastatic dissemination while attenuating programmed cell death in gastric carcinoma.

Although the precise mechanisms by which PRMT5 drives tumorigenesis vary across cancer types, previous studies on colorectal and hepatic cancer highlights its role in pivotal processes, such as TGF-β signaling, EMT and epigenetic

silencing. For instance, PRMT5-mediated methylation of SMAD4 licenses TGF-β signaling, fostering CRC dissemination via transcriptional upregulation of hepatocyte nuclear factor 4 α (29). In GC, PRMT5-dependent transcriptional repression of c-Myc target genes promotes GC progression (23). To conclude, PRMT5 regulates the post-transcriptional regulation of oncogenes and tumor suppressor genes, which in turn markedly contributes to the development of GI carcinoma.

Despite increasing preclinical evidence, the therapeutic targeting of PRMT5 presents notable challenges. First, PRMT5 is involved in normal physiological processes, particularly in hematopoietic and stem cell compartments, which may underlie the myelosuppressive toxicity observed in early-phase clinical trials. Furthermore, off-target effects or functional compensation by other PRMT family members (for example, PRMT1 or PRMT7) may limit efficacy or promote resistance. Additionally, the identification of robust, predictive biomarkers aside from MTAP deletion is key to patient stratification. Ongoing efforts to develop isoform-selective inhibitors or rational combination strategies, such as with immunotherapy or metabolic modulators, may be advantageous in overcoming these limitations and unlocking the clinical potential of PRMT5-targeted approaches in GI cancer.

As the present review demonstrates, PRMT5 contributes immensely to GI carcinogenesis through its role in regulating the expression and processing of key transcripts involved in oncogenic signaling, encompassing AKT, VEGF and EMT-related pathways. Ongoing studies continue to delineate its biological roles and underlying mechanisms. Although PRMT5 has been explored as a potential biomarker in an array of cancer types, its diagnostic specificity and sensitivity in GI cancer subtypes require further validation in future research. Similarly, while PRMT5 inhibitors have demonstrated preliminary promise in preclinical models, particularly in combination settings or MTAP-null tumors, research in this area remains in its early stages and faces notable challenges.

11. Conclusion

PRMT5 serves a key role in the development and progression of GI cancer. Nonetheless, several aspects of its function remain to be fully elucidated. Future research should concentrate on its role within the tumor ecosystem, the regulatory mechanisms controlling its activity and the development of effective and safe therapeutic strategies, comprising the identification of reliable biomarkers for patient stratification.

While PRMT5 serves a central role in the initiation and progression of GI cancer, numerous questions remain unanswered regarding its regulatory mechanisms, tumor microenvironment interactions and therapeutic applicability. The function of PRMT5 in the tumor microenvironment, the molecular processes controlling PRMT5 activity, clinical use and screening of certain inhibitors should be the principal topics in future research. PRMT5 represents an emerging therapeutic target for cancer research in the future.

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Authors' contributions

JS and ZL conceptualized the present review. RZ devised the methodology and prepared the original draft. YL was responsible for data validation, figure and table generation, and assisted with critical revision of the manuscript. WW, FZ and XF reviewed and edited the manuscript. JS and ZL obtained funding. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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