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Protein arginine methyltransferases and hepatocellular carcinoma: A review

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ABSTRACT

Hepatocellular carcinoma (HCC) is one of the most frequently diagnosed cancers with a high mortality rate worldwide. The complexity of HCC initiation and progression poses a great challenge to the diagnosis and treatment. An increasing number of studies have focused on the emerging roles of protein arginine methylation in cancers, including tumor growth, invasion, metastasis, metabolism, immune responses, chemotherapy sensitivity, etc. The family of protein arginine methyltransferases (PRMTs) is the most important proteins that mediate arginine methylation. The deregulation of PRMTs' expression and functions in cancers have been gradually unveiled, and many PRMTs inhibitors are in preclinical and clinical investigations now. This review focuses predominantly on the aberrant expression of PRMTs, underlying mechanisms, as well as their potential applications in HCC, and provide novel insights into HCC therapy.

Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent cancers worldwide with a high mortality [1,2]. Though great progress in HCC diagnosis and therapy has been made during the past decades, the survival of HCC patients still remains poor, especially those diagnosed at advanced stage [3]. As a heterogeneous disease, the complexity of HCC initiation and progression poses a great challenge to the diagnosis and treatment. A more comprehensive and thorough understanding of regulatory mechanisms in HCC is of great importance for further investigations.

Protein arginine methylation is a vital post-translational modification that involves multiple biological processes, such as transcription, mRNA splicing and translation, DNA damage, cell fate determination, and signal transduction. The family of protein arginine methyltransferases (PRMTs) is the most important 'writer' to introduce methylation modifications on the arginine residues [4,5]. To date, nine members of the PRMTs family have been identified in humans based on their structures and functions. Increasing evidence has shown the aberrant expression and functions of PRMTs are associated with diverse types of cancers, including hematopoietic diseases, breast cancer, ovarian cancer, colorectal carcinoma, pancreatic cancer, and glioblastoma [6-12]. Over the last decade, the potential role of PRMTs in HCC has been gradually revealed, which may involve different mechanisms.

This review will focus on the roles and underlying mechanisms of PRMTs in HCC. Further, it will underscore the clinical significance of PRMTs in HCC, as well as emerging potential of such druggable targets as novel strategies for HCC therapy.

Overview of PRMTs

There are three different types of methylation modification generated during the process of arginine methylation: (I) asymmetric dimethylarginine (ADMA), (II) symmetric dimethylarginine (SDMA), and (III) monomethyl arginine (MMA) (Fig. 1). The formation of ADMA, SDMA and MMA in mammalian cells is found to be carried out mainly by PRMTs family, although several other proteins showing their functions as arginine methyltransferases, such as the putative arginine

Abbreviations: HCC, hepatocellular carcinoma; PRMT, protein arginine methyltransferase; ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine; MMA, monomethyl arginine; JMJD6, jumonji domain-containing protein 6; HBV, hepatitis B virus; HBx, hepatitis B virus X protein; CARM1, coactivator-associated arginine methyltransferase 1; LXRα, liver X receptor α; NAFLD, nonalcoholic fatty liver disease; TNM, tumor-node-metastasis; HNF4α, hepatocyte nuclear factor 4-alpha; EMT, epithelial-mesenchymal transition; MTDH, metadherin; 3'-UTR, 3'-untranslated region; ccRCC, clear cell renal cell carcinoma.

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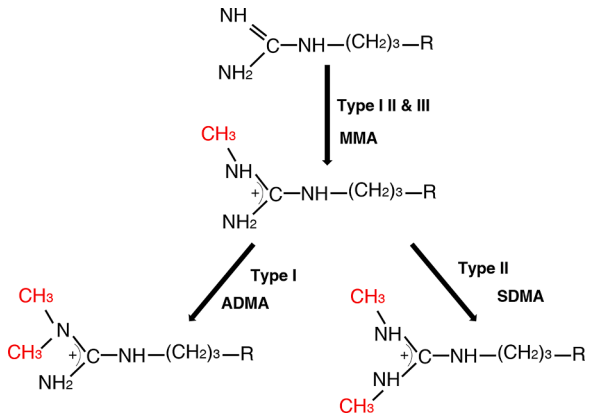

Fig. 1. Types of methylation on arginine residues mediated by PRMTs.
MMA is generated by Type I, II and III PRMTs, followed by ADMA produced by Type I PRMTs and SDMA generated by Type II PRMTs.

methyltransferases NDUFAF7 and Mettl23 [13,14]. In addition, recent studies have demonstrated the potential effect of another enzyme, Jumonji domain-containing protein 6 (JMJD6), which was initially identified as a phosphatidylserine receptor, on catalyzing histone arginine demethylation [15,16], and this reaction is dependent on the presence of cofactors, Fe (II) and 2-oxoglutarate (2-OG). Several non-histone proteins have also been found to be targets of JMJD6 for demethylation on their arginine residues, such as tumor necrosis factor receptor-associated factor 6 (TRAF6), heat-shock protein 70 (HSP70), and estrogen receptor α (ERα). However, the role of JMJD6 in demethylating arginine residues remains controversial. Lack of evidence for protein demethylation mediated by JMJD6 directly make us cannot rule out the possibility that JMJD6 may regulate the demethylation of these proteins indirectly. Additionally, many studies did not show the arginine demethylation activity of JMJD6. For instance, in the presence of oxygen, Fe (II) and 2-OG, JMJD6 was incubated with arginine-rich (RS) structural domain, then analyzed by mass spectrometry (MS). The results showed that JMJD6 was unable to produce demethylated arginine histone fragment peptides [17]. Another study on the crystal structure of JMJD6 was also skeptical of its arginine demethylation activity [18]. More studies are expected to further identify the effect of JMJD6 on arginine demethylation.

All nine PRMTs members possess signature motif I, post-I, motif II, post-II (double E loop), motif III, and the conserved THW loop, while several members harbor distinct domains (Fig. 2) [19,20]. PRMTs in human have been divided into three subfamilies according to the type of methylation they catalyze. All type I, II and III PRMTs are capable of generating MMA on one of the terminal guanidino nitrogen atoms. The subsequent formation of ADMA is catalyzed by type I enzymes (PRMT1, PRMT2, PRMT3, PRMT4, PRMT6 and PRMT8), and the generation of SDMA is catalyzed by type II enzymes (PRMT5, PRMT9) [4,19]. PRMT7 is the only type III PRMT specific for only catalyzing monomethyl arginine formation. It has no ability to catalyze SDMA formation directly. The effect of PRMT7 expression on cellular SDMA levels only occurs through the allosteric activation of PRMT5 via PRMT7 other monomethylated sites on the same substrate polypeptide [21].

PRMTs can dynamically regulate chromatin structures, and function as coregulators that co-activate or co-repress gene transcription and expression. As stated, histone H4R3me2a, H3R2me2s, H3R17me2a, H3R26me2a are usually considered as activation marks, while H3R2me2a, H3R8me2a, H3R8me2s, H4R3me2s are repressive marks. Non-histone proteins can also be modified by PRMTs, which may associated with the changes in protein activities, stabilities, expression [22, 19]. For example, ribosomal protein S2 (rpS2) a substrate for PRMT3 in mammals, and PRMT3 is able to inhibit rpS2 ubiquitination to modify the rpS2 protein level in cells [23,24]. PRMTs have an impact on a diverse range of cellular processes, such as cell proliferation and differentiation, transcription, DNA damage and repair, signal transduction, mRNA processing [4,5,19].

The role of PRMTs in benign liver diseases

The main risk factors for HCC are chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), heavy alcohol intake, and excess body weight. PRMTs have been reported to be involved in benign liver diseases, such as viral hepatitis, alcoholic liver disease (ALD), and non-alcoholic fatty liver disease (NAFLD). In the context of virus infection, PRMT1, the first protein arginine methyltransferase identified in the end of 1990s that accounting for approximately 85% of all cellular PRMT activity, overexpression of which inhibits HBV transcription via histone 4 (H4) methylation in HepG2 cells and the binding of HBx to PRMT1 might abolish the inhibitory effect of PRMT1 on HBV transcription [25-27]. PRMT5 has been reported to suppress HBV replication partially through mediating symmetrically demethylation of H4 at position R3 (H4R3me2s) on the cccDNA minichromosome [28]. PRMT6 seems to be a potential susceptibility gene for HBV-related HCC in a pilot two-phase genome-wide association study (GWAS) [29]. Besides, PRMTs also play a role in hepatic metabolism. PRMT1-mediated arginine methylation of

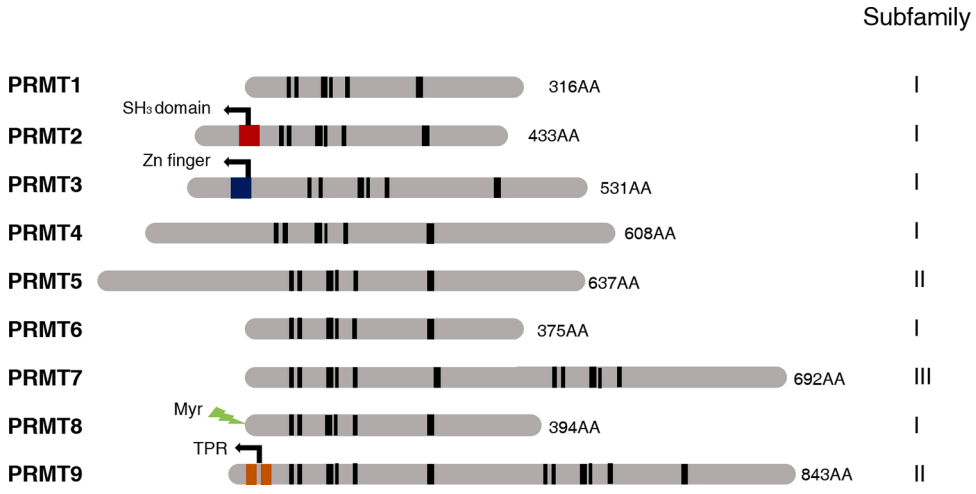

Fig. 2. The mammalian PRMTs.
All PRTMs possess conserved signature motifs I (VLD/EVGXGXG), post-I (V/IXG/AXD/E), motif II (F/I/VDI/L/K), post-II (double E loop), motif III (LR/KXXG), and THW loop (in black bars). Other motifs include SH3 domain, Zn Finger domain, myristoylation motif (Myr), tetratricopeptide repeats (TPR).

Table 1
The expression and clinical relevance of PRMTs in HCC.

PRMTs	Expression in HCC tissues	Prognostic values (high vs low)	Correlation with clinical characteristics	References
PRMT1	Increased	Poor	Microvascular invasion, tumor differentiation, tumor size, portal vein tumor thrombus (PVTT), small lesions	[39,40, 55]
PRMT2	Increased	Poor	Tumor size, histological grade, tumor-node-metastasis (TNM) stage	[41]
PRMT3	N.A	N.A	N.A	N.A
PRMT4	Decreased	N.A	N.A	[46]
PRMT5	Increased	Poor	Tumor size, UICC pathological stage, α-fetoprotein (AFP), tumor differentiation, microscopic hepatic invasion	[42–44]
PRMT6	Decreased	N.A	Age, vascular invasion, intraoperative rupture	[47]
PRMT7	N.A	N.A	N.A	N.A
PRMT8	N.A	N.A	N.A	N.A
PRMT9	Increased	Poor	Hepatitis B virus antigen (HBsAg), vascular invasion, tumor differentiation, TNM stage	[45]

FoxO1 contributes to the increase in hepatic glucose production in mouse models of genetic PRMT1 haploinsufficiency and transient depletion of hepatic PRMT1 in diabetic db/db mice. In the mouse models of alcohol induced liver injury, PRMT1 protect hepatocytes from oxidative stress response [30,31]. PRMT3 is involved in hepatic lipogenesis by interacting with LXRα, and palmitic acid treatment induces PRMT3 translocation to the nucleus accompanied by increased transcriptional activity of LXRα in mouse models of NAFLD [32-34]. PRMT6 promotes fasting-induced activation of the gluconeogenic program dependent on CRTC2, and couples glucose availability with mitochondria biogenesis by mediating SIRT7 methylation [35,36]. Furthermore, PRMT5 knockdown boosts the expression of PPARα and PGC-1α in mouse models fed with high-fat diet, with a concomitant increase in hepatic mitochondrial biogenesis, indicating its effect on redox reactions [37]. These studies indicate that distinct PRMTs perform distinct roles in distinct benign liver diseases that may progress to HCC.

Expression and clinical significance of PRMTs in HCC

As shown in Table 1, the deregulation of PRMTs expression is often observed in HCC. The expression of PRMT1, PRMT2, and PRMT5 in HCC tissues is significantly higher than that in matched nontumor tissues both at transcription and protein levels [38-44]. Additionally, compared with in matched noncancerous tissues, the expression of PRMT9 is higher in HCC tissues at protein level, whereas there is no difference at transcription level [45]. The expression of PRMT4 at protein level and the expression of PRMT6 at both levels has been found to be downregulated in human HCC tissues [46-48]. Intriguingly, in a model of DEN-induced HCC, the expression of PRMT4 is elevated in the early stage of hepatocarcinogenesis, which suggests that PRMT4 may play different roles in different stages of HCC initiation and progression [49]. However, this phenomenon is only observed in animal models, and more explorations should be conducted in human.

Importantly, the aberrant expression of some PRMTs have been demonstrated to be associated with the prognosis and clinicopathological features of patients with HCC. PRMT1 has been considered as a prognostic biomarker for HCC, as its overexpression is strongly correlated with poor prognosis in cohorts of HCC patients from different regions and adverse clinicopathological features, such as microvascular invasion presence, worse tumor differentiation, lager tumor volumes and more portal vein tumor thrombus (PVTT) [39,40]. Besides, it is also an independent risk factor for both disease-free survival and overall survival of HCC patients [40]. High PRMT2 expression is related to larger tumor size, poor histological grade, advanced tumor-node-metastasis (TNM) stage, as well as shorter survival time [41]. Similarly, the elevated expression of PRMT5 also has a positive correlation with poor prognosis and aggressive clinicopathological characters, including worse tumor differentiation, more frequent microvascular invasion, larger tumor size and higher serum α-fetoprotein levels [43,44,50]. Zhang et al. have shown that PRMT9 expression level has a relationship with HBsAg, vascular invasion, tumor differentiation, and TNM stage, and patients with positive PRMT9 expression have shorter survival time than those with negative PRMT9 expression [45]. These findings suggest that PRMTs might act as potential prognostic biomarkers for HCC patients.

The role of PRMTs in HCC malignant phenotypes

Sustaining proliferation, activation of invasion and metastasis have been considered as hallmarks of cancer cells [51]. Several previous studies have revealed the roles that PRMTs play in HCC. PRMT1 inhibition results in reduced HNF4α expression and hepatocyte proliferation, thus promoting alcohol-induced HCC progression, which suggests that PRMT1 seems to perform a protective role in the context of alcohol-induced HCC [52,53,31]. Nevertheless, PRMT1 functions as an oncogene in other contexts of HCC. PRMT1 promotes HCC proliferation, invasion and metastasis via activating STAT3 signaling, and STAT3 inhibitor can reverse the effects mediated by PRMT1 [40]. Epithelial-mesenchymal transition (EMT) has been considered as a vital program involved in cancer cell metastasis [54]. PRMT1 is able to drive EMT program in HCC cells through TGF-β1/Smad pathway, as its overexpression increases the expression of mesenchymal markers (Vimentin, Snail and N-cadherin) and decreases the expression of epithelial marker E-cadherin [55]. PRMT2 has been reported to facilitate HCC growth and inhibit cell apoptosis by regulating BCL2 expression. Mechanically, PRMT2 overexpression results in H3R8 asymmetric methylation (H3R8me2a) enrichment at the BCL2 promoter, which increases its accessibility to STAT3 and promotes BCL2 gene expression [41]. PRMT5 promotes HCC proliferation through affecting cell cycle partially by decreasing BTG2 expression. The regulation of BTG2 expression by PRMT5 is related to ERK phosphorylation, as treatment with a selective ERK1/2 inhibitor remarkably reverses the effect of PRMT5 on BTG2 expression [42]. Besides, when glucose induction in HCC cells, PRMT5 competitively interacts with CDK4 at R24 to drive G1/S cell cycle progression and tumor growth [56]. Subcellular localization of PRMT5 is also pivotal for HCC growth and metastasis. In the process of metadherin (MTDH)-mediated HCC metastasis, PRMT5 translocates from the nucleus to the cytoplasm, accompanied by nucleus localization of β-catenin, thus activating the WNT-β-catenin signaling pathway [57]. PRMT6 functions as a suppressor in HCC, and it methylates CRAF at R100 that decreases its RAS binding potential, then its downstream MEK/ERK signaling is inhibited [47]. Moreover, PRMT9 has been shown to enhance HCC invasion and metastasis by inducing EMT through PI3K/Akt/GSK-3b/Snail signaling [45].

The role of PRMTs in HCC immune responses

HCC is a type of inflammation-associated cancer, in which local and systemic immune responses play an important role [58,59]. Increasing evidence has shown the significance of PRMTs in immune response [60, 61]. For example, PRMT1 is essential for proliferation, activation, and differentiation of human and mouse peripheral B cells. PRMT5 negatively modulates cGAS-mediated antiviral immune response by blocking the DNA binding capability of cGAS in mice [62,63]. We have

mentioned above that PRMT1 might be a protector in alcohol-associated HCC, but in the perspective of immunology, PRMT1-dependent macrophage IL-6 secretion has been identified to be an important mechanism of alcohol-induced HCC progression. PRMT1 knockout results in the decrease in both IL-10 and IL-6 cytokines expression and tumor growth in mice of DEN-induced HCC [64]. The polymorphism rs975484 in the PRMT1 gene promoter regulates the expression of some immune checkpoint genes in HCC, such as PD-L1 and PD-L2, which indicates the polymorphism of the gene may be linked to immunotherapy of HCC [65]. Furthermore, PRMT5 inhibition induces lymphocytes infiltration and the expression of several MHC II molecule family components, including H2-Ab1, H2-Aa, and Cd74, which might enhance the anti-tumor immune responses [66].

The role of PRMTs in HCC metabolism

Metabolism reprogramming has been recognized as an emerging hallmark of cancer [51,67]. The liver plays a critical part in coordinating a variety of metabolic activities. Metabolic abnormalities are involved in both HCC initiation and malignant progression [68,69]. Recently, more and more studies have recognized the functions of PRMTs in HCC metabolism. PRMT4 has been reported to be correlated with glucose abnormality in HCC, it methylates GAPDH at R234 to inhibit its catalytic activity and Warburg effect, thus delaying HCC growth [46]. It has been demonstrated that PRMT5 is strongly correlated with metabolism regulation in cancers [70-72]. In HCC, PRMT5 enhances lipid biosynthesis and HCC growth by induce methylation of SREBP1α both *in vivo* and *in vitro*. PRMT5 promotes SREBP1α transcriptional activity through mediating its symmetrically dimethylation at R321. Moreover, PRMT5-induced methylation of SREBP1α induced by PRMT5 prevented its phosphorylation at S430 by GSK3β, followed by disassociation from Fbw7 (FBXW7) and evasion from degradation via ubiquitin-proteasome pathway [73]. PRMT6 is another member of PRMTs family that has been shown to be associated with metabolism deregulation of HCC. The interaction between PRMT6 and CRAF regulates aerobic glycolysis by altering ERK-mediated nuclear relocalization of PKM2. PRMT6 methylates BAG5 at R15 and R24 to promote the degradation of its interacting partner HSC70, an identified autophagy player. Under oxygen or nutrient-derived conditions, PRMT6 is downregulated to induce autophagy in HCC and PRMT6 expression negatively correlates with enhanced autophagic flux in cells. [74,75].

Regulatory mechanisms underlying PRMTs deregulation in HCC

Posttranslational modifications are of great significance in regulation of PRMTs, such as phosphorylation and ubiquitylation [4]. For instance, the methyltransferase activity of PRMT4 is suppressed by phosphorylation at Serine 228 (S228), and phosphorylation at S217 promotes PRMT4 cytoplasmic localization to impair its enzymatic activity [76, 77]. PRMT1 can be polyubiquitylated for proteasome degradation by FBXL17 at Lysine 117(K117) [78]. Noteworthy, the activity and function of PRMTs can be regulated by automethylation, a special type of posttranslational modification mediated by themselves. Automethylation of PRMT4 at R551 has an impact on transcription and pre-mRNA splicing modulated by itself [79]. PRMT6 automethylation at R35 enhances its stability, while R58 automethylation of PRMT8 attenuates its activity by influencing R73 automethylation [80,81]. In the context of HCV infection, upregulation of protein phosphatase 2A (PP2A) has been reported to modulates NS3 helicase activity via inhibiting PRMT1 enzymatic activity [82]. Notably, the stability of PRMT4 is regulated by the SKP2-containing SCF (SKP1-cullin1-F-box protein) E3 ubiquitin ligase in the nucleus, but not in the cytoplasm. Under glucose deprivation induced autophagy, the activation of AMPKα2, reduction of SKP2, and subsequent upregulation of CARM1, are observed in the nucleus of HCC cells, suggesting a potential role of nuclear AMPK-SKP2-CARM1 signaling in the induction of autophagy in HCC cells [83,84]. Moreover, the activity of PRMT5 is regulated by phosphorylation at Threonine 80 (T80) by RhoA-associated protein kinase (ROK) and myosin phosphatase (MP). PRMT5-specific SDMA modification on arginine residues of histone 2A (H2A) and H4 is considered as a repressing gene expression mark, which can be increased by silencing of myosin phosphatase target subunit-1 (MYPT1), and it leads to a global change in the expression of genes associated with cell growth, proliferation and death [85].

Besides, the role of specific lncRNAs (long non-coding RNA) and miRNAs (microRNAs) in the regulation of PRMTs' expression has also been investigated. MiR-503 suppresses the expression of PRMT1 by target 3'-untranslated region (3'-UTR) of PRMT1 mRNA, thus remarkably inhibiting invasion and migration in HCC cells [86]. MiR24-2 targeting 3'UTR of PRMT7 mRNA to inhibit the translational ability and the methylation of H4R3 mediated by PRMT7, which promotes liver cancer stem cells malignant progression [87]. Amplification of LINC01138 promotes HCC proliferation, invasion and metastasis through physically interacting with PRMT5 and protecting it from degradation by ubiquitin-proteasome pathway in HCC [88].

It has been recently demonstrated that PRMT5 can be regulated by MYC, a vital oncogene driving the genesis of many human cancers, in HCC. The level of urinary SDMA is increased in a MYC-dependent manner in DEN-induced HCC mouse model and patients with HCC, and PRMT5 is identified as a direct MYC target gene [66,89].

Applications of PRMT inhibitors in HCC

Unlike the irreversibility of genetic mutations, reversibility of epigenetic modifications shed light to cancer therapy [90,91]. Since the first PRMT inhibitor generated in 2004, AMI-1, which inhibits all type I PRMTs, the development and application of PRMTs inhibitors has undergone great progress in the past less than two decades [92]. Recently, many selective and potent PRMT inhibitors targeting PRMT3 (SGC707), PRMT4 (TP-064, EZM2302), PRMT5 (GSK591, LLY-283), PRMT6 (EPZ020411), and PRMT7 (SGC3027) with membrane permeability have been developed. Their efficacy in cellular and animal models have highlighted the therapeutic and pharmacological potential [93,94]. For instance, in breast cancers, PRMT4 inhibitor (TP-064) treatment inhibits a subset of multiple myeloma cell lines proliferation by affecting cell cycle [95]. A recent study has shown that the pharmacological inhibition of PRMT1 by a novel potent inhibitor DCPT1061 suppresses clear cell renal cell carcinoma (ccRCC) cell proliferation and sensitizes ccRCC to sunitinib treatment. Combination of DCPT1061 and sunitinib exhibited a striking anti-proliferative effect in ccRCC cell models and xenograft animal models [96].

Importantly, a growing number of PRMT inhibitors are in clinical trials, further indicating the possibility of clinical applications of these PRMT inhibitors, especially PRMT5 inhibitors for their efficacy in hematological diseases. GSK3368715, a PRMT5 inhibitor, is in Phase I clinical trial for relapsed or refractory diffuse large B cell lymphoma and selected solid tumors with deletion of the methylthioadenosine phosphorylase (MTAP) gene (NCT03666988) [97]. Besides, GSK3326595 and JNJ-64619178, another two small molecule inhibitors targeting PRMT5, have also be in clinical trials for hematological diseases and some solid tumors now (NCT02783300, NCT03614728, CT03573310) [98].

Here, we focus our attention on applications of PRMT inhibitors in HCC. Despite the great advances in PRMT inhibitors development, their applications in the field of HCC remains limited. MS023, a type I PRMT inhibitor, has been found to impair tumorigenesis in HCC mouse models [41]. Moreover, Zheng et al. have found that targeting PRMT5 activity by DW14800 treatment, a novel potent PRMT5 inhibitor that binds to the substrate binding site of PRMT5 with high activity against PRMT5, is able to inhibit HCC malignancy. DW14800 treatment decreases the occupation of H4R3me2s on the promoter of HNF4α to promote HNF4α expression, thus resulting in the reduced abilities of proliferation and

Table 2
The role of PRMTs in HCC.

PRMTs	Subcellular localization	Substrates or relevant signalings	Effects in HCC	References
PRMT1	Cytoplasm, nucleus	HNF4α	A protector in alcohol-induced HCC	[52,53, 100]
		STAT3 signaling	Promotes proliferation, invasion, metastasis	[40]
		TGF-β1/Smad pathway	Drives EMT program	[55]
		IL-6-STAT3	Immune environment formation in alcohol-induced HCC	[64]
PRMT2	Cytoplasm, nucleus	H3R8me2a at the BCL2 promoter	Promotes proliferation, and inhibits apoptosis	[41]
PRMT3	Cytoplasm	N.A	N.A	N.A
PRMT4	Cytoplasm, nucleus	GAPDH at R234	Inhibits Warburg effect and tumor growth	[46]
		Nuclear AMPK-SKP2-CARM1	Induces autophagy in HCC cells	[83]
PRMT5	Cytoplasm, nucleus	ERK-BTG2	Promotes proliferation	[42]
		CDK4 at R24	Promotes proliferation	[56]
		WNT-β-catenin	Promotes metastasis	[43]
		SREBP1α at R321	Promotes lipid biosynthesis and tumor growth	[73]
PRMT6	Nucleus	CRAF at R100	Inhibits tumor-initiation, metastasis, and therapy resistance	[47]
		ERK-PKM2	Inhibits aerobic glycolysis	[74]
		HSC70	Inhibits autophagy	[75]
PRMT7	Cytoplasm, nucleus	N.A	N.A	N.A
PRMT8	Membrane	N.A	N.A	N.A
PRMT9	Cytoplasm	PI3K/Akt/GSK-3b/Snail	Promotes invasion and metastasis	[45]

invasion in HCC [99]. In another recent study, Luo et al. have noticed that PRMT5 inhibitor treatment, GSK3326595, increase the infiltration of CD45.1+leukocytes, natural killer (NK) cells, CD4+T cells, CD8+T cells, dendritic cells (DC) and monocytes in HCC tumors of mouse models. Combination of GSK3326595 with anti-PD-1 immune checkpoint (ICT) therapy significantly improved therapeutic effects in HCC, which provides a novel strategy to attenuate the resistance of 'immune-cold' tumor to ICT [66].

Conclusions and future prospects

Primary liver cancer ranks as the sixth most frequently diagnosed cancer and the third leading cause of cancer death worldwide in 2020, and HCC accounts for 75%-85% of these cases [2]. Posttranslational modification of HCC is a rapidly growing and emerging area of research, contributing to our comprehensive understanding of the pathophysiological and molecular mechanisms underlying HCC tumorigenesis and progression. Many studies have reported the distinct roles of PRMTs in benign liver diseases that may progress to HCC, which indicates targeting PRMTs might play a role in HCC prevention. More importantly, above studies have also demonstrated that the deregulation of PRMTs expression or functions are involved in HCC, suggesting their potential as prognostic markers for HCC. PRMTs regulates but not limited to HCC growth, invasion, metastasis, immune response, and metabolism both dependent or independent on arginine methylation (Table 2) (Fig. 3). Therefore, it is worth considering several PRMTs as potential targets for HCC. Furthermore, the expression and activity of PRMTs can be regulated at transcriptional, posttranscriptional, and posttranslational levels. As mentioned in the review, studies on PRMTs in HCC are limited. There has been lack of investigations on the role of PRMTs in different context of HCC. In addition, previous studies have reported the alternative splicing, subcellular localization and the scope of isoforms within some PRMTs, whether they have an effect on HCC remains to be explored [94].

The feasibility of the class of enzymes associated with arginine modification for drug development, coupled with the rapid development of emerging biological technologies, is revealing novel opportunities for HCC therapy. To date, the PRMTs inhibitors are predominantly utilized in hematological diseases, and adverse effects and efficacy of most PRMTs inhibitors to be further confirmed. The next decades will focus on the development and discovery of more specific and selective PRMT

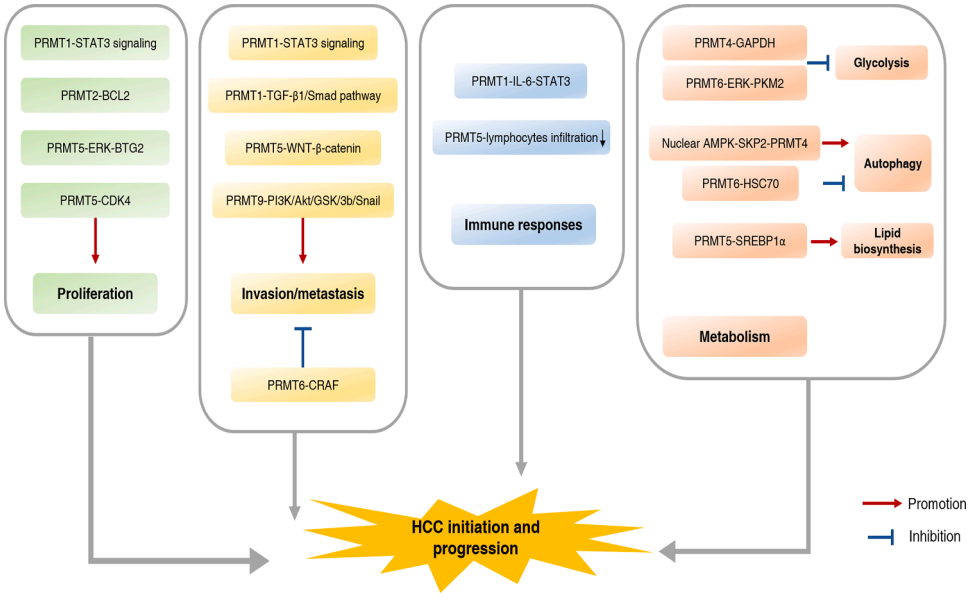

Fig. 3. The role of PRMTs in HCC.

inhibitors useful for treating specific cancers. The utility of these compounds, together with the analysis of PRMTs' functions will help to resolve the different and overlapping functions of these epigenetic enzymes in HCC. Furthermore, it is also important to develop more PRMT inhibitors with safety and efficacy for clinical applications, as well as conduct intensive clinical trials on existing drugs.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Author contributions

Yu Lei, Ping Han, and Dean Tian contribute to conception and writing.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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