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Chapter

The Role of Protein Arginine Methyltransferase 1 in Gastrointestinal Cancers

Jin Zou, Wei Shen, Yu Zhang and Shibo Ying

Abstract

Mammals can produce nine kinds of arginine methylation enzymes that can be divided into three types (I, II, and III) according to their catalytic activity. Arginine methyltransferase 1 (PRMT1), as the first discovered arginine methyltransferase type I, has been reported to be involved in cell signal transduction, DNA damage repair, RNA transcription and other processes. Its imbalance or abnormal expression is also involved in cancer metastasis. PRMT1 is highly expressed in gastrointestinal tumors and promotes tumor biomarkers expression, chemotherapy resistance and tumorigenicity to promote cancer progression, while downregulation of PRMT1 expression can inhibit the migration and invasion of related tumor cells or promote tumor cells apoptosis and inhibit the progression of cancer. Therefore, PRMT1 may be a cancer therapeutic target. In this paper, arginine methylase 1 expression in various types of gastrointestinal tumors, the tumorigenic mechanism and the role of PRMT1 in tumorigenesis and development were reviewed.

Keywords: PRMT1, gastrointestinal cancers, arginine methylation

1. Introduction

1.1 Protein arginine methylation

Arginine methylation is a common type of protein posttranslational modification (PTM) that preserves arginine's positive charge but reduces its hydrogen bonding capacity because each methyl group removes a hydrogen atom. Moreover, methylation increases the hydrophobicity of the side chain, thus facilitating the interaction with the aromatic ring [1]. Arginine methylation leads to changes in gene expression by altering the nucleoprotein-DNA interaction. Arginine can occur monomethylation (MMA), symmetric dimethylation (SDMA) and asymmetric dimethylation (ADMA) under the catalysis of different protein arginine methylases (PRMTs). At present, the methyl arginine identified in eukaryotes mainly occurs in three types: $\omega\text{-}N^G$-methylarginine (MMA), $\omega\text{-}N^G,N^G$-asymmetric dimethyl arginine (aDMA) and $\omega\text{-}N^G,N^{‘G}$-symmetric dimethyl arginine (sDMA) [2, 3]. Protein arginine methylation affects many important biological pathways and plays a key role in DNA damage signal transduction, pre-mRNA splicing, mRNA translation, cell signal transduction and cell fate determination [3].

1.2 Protein arginine methyltransferase

PRMT catalyzes the transfer of methyl from s-adenosine methionine (SAM) to arginine arc nitrogen atoms to produce s-adenosine homocysteine and methylarginine in histones and non-histones [3]. PRMT of histone methylation and histones, according to their different catalytic activities, can be divided into type I (PRMT1, PRMT2, PRMT3, PRMT4/CARM1, PRMT6 and PRMT8), type II (PRMT5 and PRMT9) and type III (PRMT7). PRMT is a highly conserved gene product that plays a major role in normal body development and disease. In most cases, the expression of PRMT was upregulated. Maladjustment or abnormal expression of PRMT influences the development of cancer, especially the overexpression of PRMT1, PRMT4 and PRMT5, which has been confirmed in many malignant tumors [4, 5]. PRMT is associated with a variety of diseases, such as tumors, cardiovascular diseases, viral infections, and autoimmune diseases [6]. Studies have shown that PRMT can be a potentially interesting therapeutic target [5].

1.3 Protein arginine methyltransferase 1

As arginine methylation is closely related to various tumors, more and more researchers are beginning to study the relationship between PRMT and cancer, especially PRMT1. PRMT1, PRMT3, PRMT6 and PRMT8 were all highly expressed in arginine methyltransferase, but the expression of PRMT1 was significantly upregulated [7]. PRMT1 was the first arginine methylase discovered and is the major type I enzyme in mammals [8, 9]; furthermore, PRMT1 is responsible for monomethylation and more than 80% of ADMA modifications [5]. As PRMT1 activity was lost, the MMA and SDMA levels increased significantly [10]. The expression of PRMT1 in cancer cells of various tissues was significantly higher than that in nonneoplastic cells [11], and the expression level in embryonic nerve tissues was the highest [12]. PRMT1 has been found to be overexpressed or abnormally spliced in malignant tumors such as those of the breast, prostate, lung, colon, bladder and leukemia. Previous studies have also found that PRMT1 is an Important adjustment factor of epithelial-mesenchymal transition (EMT) [13, 14]. In contrast to the PRMT5 symmetrical methylated histone H4R3me2s involved in transcriptional inhibition, the PRMT1 asymmetrically methylated histone H4R3me2a recruits the p300/cAMP-binding-protein (p300/CBP) related factor complex, enhances histone H3 acetylation in lysines 9 and 14, promotes transcription factors binding, and participates in transcriptional activation [3, 7]. H4R3 methylation causes p300 to acetylate the H4 tail, while PRMT1 inhibits acetylation of the H4 tail [15]. Studies have shown that only PRMT1 and EGFR 2 (D2) coincubated with colon cancer methylation screening tests produced strong methylation signals *in vitro* [16]. PRMT3 overexpression does not regulate HBV transcription, while PRMT1 overexpression leads to HBV transcriptional inhibition [17]. This paper mainly describes the role of PRMT1 in gastrointestinal tumorss.

2. PRMT1 in cancers

2.1 PRMT1 in esophageal cancer

In 2015, Virendra Singh et al. reported for the first time that PRMT1 was involved in the transition from low to high degree of tumor formation in esophageal cancer (EC) When ESCC was poorly differentiated, moderately differentiated and then well differentiated, the expression of PRMT1 decreased [7]. PRMT1 was found

in 89.5% of ESCC patients and in only 46.3% of adjacent normal tissues, and the expression level of PRMT1 in ESCC cell lines was significantly upregulated compared with that in normal esophageal epithelial cell lines [18]. The overexpression of PRMT1 led to the proliferation of OV6 + ECA109 and TE1 cells, while the down-regulation of PRMT1 reduced the tumorigenicity and tumor growth of OV6+ cells. Xenotransplantation of NOD/SCID mice showed that PRMT1 expression enhanced the tumorigenicity of OV6 + ESCC cells *in vivo* [18]. Further studies showed that PRMT1 inhibited H3K9 methylation by catalyzing H4R3me2a methylation and promoted acetylation of H3 lysine residues, which enhanced chromatin activity and resulted in increased ESCC transcription [7]. PRMT1 upregulated histone H4R3me2a expression, promoted TIC markers, stem cell-like properties, chemotherapy resistance, and oncogenic expression, and increased PRMT1 expression in ECSS samples. In addition, RNA-seq transcriptome analysis showed that PRMT1 overexpression led to activation of the Wnt/β-catenin and Notch signaling pathways [18]. In conclusion, as a new effector, the PRMT1 expression level is closely related to abnormal clinicopathological features and poor patient prognosis, and PRMT1 may be a reliable diagnostic and therapeutic target for esophageal cancer.

2.2 PRMT1 in gastric carcinoma

Currently, PRMT1 and FOXO1 are mainly expressed in the nucleus of gastric cancer (GC) cell lines, and FOXO1 expression is correlated with the PRMT1 level. PRMT1 may regulate chemotherapy sensitivity and apoptosis of GC cells by activating the tumor suppressors FOXO1 and BAD [19]. Interestingly, PRMT1 inhibited drug resistance and nuclear accumulation of p-FOXO1 and p-BAD in GC cell lines, and the recurrence rate of GC in patients with low expression of PRMT1 after adjuvant chemotherapy was significantly higher than GC in patients with high expression of PRMT1. Cisplatin and 5-flu-orouracil sensitivities were inhibited by RNA interference with PRMT1 downregulation in GC cells [19]. After that, other studies suggested that PRMT1 overexpression in GC cells had the effect of "migration-proliferation", which could promote the migration and invasion and inhibit the proliferation of tumor cells, while PRMT1 knockdown had the opposite effect [13]. PRMT1 is a novel regulator of EMT that is reported to enhance migration and invasion by Hippo signaling and promote EMT. PRMT1 can reduce the expression of E-cadherin, the epithelial marker of GC, and increase the expression of the interstitial markers N-cadherin, Vimentin, Snail and Catenin [13]. In conclusion, evaluating the expression of PRMT1 in GC is an effective predictor of poor prognosis and recurrence after adjuvant chemotherapy. However, in view of its dual functions, caution should be taken prior to utilizing PRMT1 as a potential drug target for GC.

2.3 PRMT1 in colorectal cancer

Colorectal cancer (CRC) is a common malignant tumor in the gastrointestinal tract. PRMT1 is overexpressed in colorectal adenoma, carcinoma and adenocarcinoma, and the expression level of PRMT1 in colon cancer samples is higher than normal colon and rectal samples [20]. Compared with normal tissue, the expression of the PRMT1-v1 variant was significantly increased in colon cancer tissue and increased as normal tissue progressed to adenoma and eventually to cancer. In other words, the higher the degree of malignancy, the higher the expression of the variant. The Cox proportional hazard regression model and Kaplan–Meier method showed that patients with high expression of PRMT1-v1 variants had a higher probability of recurrence or death and a lower survival probability [21]. After PRMT1 was knocked out, the proliferation of HCT116 cells was significantly inhibited, and the apoptosis

rate was increased. Treating HCT116 cells with downregulated PRMT1 with sodium propionate inhibited the mTOR signaling pathway to induce cell apoptosis, thereby inhibiting cell growth and proliferation [20]. PRMT1 methylates epidermal growth factor receptor (EGFR) in the extracellular region of the endoplasmic reticulum/ Golgi body, enhancing ligand binding and receptor activation before transport to the cell membrane. PRMT1 mainly methylates the EGFR extracellular domain at R198 and R200; enhances the binding to EGF and the subsequent receptor dimerization and signal transduction activation; enhances the receptor function of CRC cells; promotes the growth of EGFR-dependent cells; and reduces cell resistance to cetuximab. When PRMT1 is knocked out, the EGFR methylation signal is reduced [16]. In conclusion, PRMT1 can be considered a useful therapeutic marker for the treatment of CRC, and the development of new methods to downregulate the expression of PRMT1 is of great significance for the prognosis and treatment of CRC.

2.4 PRMT1 in hepatocellular carcinoma

Increasing evidence shows that PRMT1 expression in clinical hepatocellular carcinoma (HCC) samples and cell lines is significantly higher than adjacent normal liver tissue, and high PRMT1 expression is closely related to poor prognosis and recurrence of HCC. PRMT1 upregulation in HCC cell lines promoted cell proliferation, colony formation and migration *in vitro*, while the knockdown of the PRMT1 gene inhibited that role [14, 22]. Bingshou Li et al. found that the high expression of PRMT1 was associated with the low expression of miR-503. MiR-503 can inhibit the invasion and migration of HCC cells by targeting the 3'-UTR of the PRMT1 gene, resulting in downregulation of the mRNA and protein expression of PRMT1 [23]. Further studies found that PRMT1 knockdown resulted in increased hepatocyte proliferation and decreased Hnf4a expression. In the absence of PRMT1, JMJD6 causes the Hnf4a promoter to undergo arginine demethylation, leading to the significant downregulation of Hnf4a expression and the promotion of hepatocyte proliferation. Knockout of JMJD6 restored Hnf4a expression and inhibited hepatocyte proliferation in PRMT1-knockout mice [24]. In addition, PRMT1 can also increase STAT3 phosphorylation through high expression and activate the STAT3 signaling pathway to promote *in vitro* and *in vivo* metastasis of HCC cells, while cryptotanshinone, a STAT3 inhibitor, inhibits STAT3 phosphorylation and inhibits HCC proliferation and migration [22]. Similar to PRMT1 in GC, PRMT1 is also associated with EMT in liver cancer. The expression of PRMT1 downregulated TGF-β1, p-Smad2 and p-Smad3; significantly reduced expression of the interstitial markers Vimentin, Snail and N-cadherin; and upregulated the expression of the epithelial marker E-cadherin. PRMT1 overexpression leads to the opposite effect. Therefore, PRMT1 may promote EMT in HCC cells through the TGF-β1/Smad pathway [14]. PRMT1 is also a negative adjustment factor of HBV transcription. Studies have shown that overexpression of PRMT1 in HepG2 cells results in inhibition of 60% HBV transcription, and low expression of PRMT1 significantly increased HBV transcription by 1.6-fold. *In vivo* animal models, PRMT1 activity was further reduced in HBV-replicating cells. HBx binding to PRMT1 may facilitate HBV replication [17]. In conclusion, PRMT1 may be a new therapeutic target for liver cancer prognosis, which is of great significance for improving therapeutic strategies for HCC patients.

2.5 PRMT1 in pancreatic cancer

In 2018, Zhibin Lin et al. found that PRMT1 was abnormally upregulated in permanent pancreatic cancer (PC) cell lines and human pancreatic tumors compared with nonneoplastic pancreatic epithelial tissues, but the effect of PRMT1

upregulation on tumor cells is controversial. In PANC-1 and SW1990 cells, PRMT1 overexpression did not affect the proliferation or invasion of PC cells [25]. Interestingly, the latest research data show that PRMT1 has a protumor effect and that inhibiting PRMT1 inhibits tumor growth *in vivo* and *in vitro*. PRMT1 expression is upregulated in human pancreatic ductal adenocarcinoma (PDAC) and promotes the growth and carcinogenesis of PC cells both *in vivo* and *in vitro* and is associated with higher tumor grade, higher invasivity, and poorer prognosis [26, 27]. PRMT1 downregulation significantly inhibited tumor proliferation and invasion *in vitro* and *in vivo*. Further studies found that ZEB1 expression in PC cells was closely related to PRMT1 expression, that ZEB1 expression was inhibited in PC cells downregulated by PRMT1, and that overexpression of ZEB1 reversed the antitumor effect of PRMT1 downregulation [25]. PRMT1 may act as a positive regulator of β-catenin, increasing the cellular β-catenin levels. The overexpression of exogenous PRMT1 in PC cells promoted the growth of tumor cells and increased the β-catenin levels after treatment with lithium chloride. PRMT1 expression downregulation inhibited the growth and tumorigenicity of pancreatic cancer cells and inhibited the increase in β-catenin protein under lithium chloride treatment [27]. PRMT1 overexpression enhances HSP70 binding and BCL-2 mRNA stability through the gold-rich element in the 3'-UTR, thereby increasing BCL-2 protein expression and protecting cancer cells from cell stress and treatment-induced apoptosis. The PRMT1 inhibitors DB75 and TC-E5003 reduce PRMT1-mediated protein arginine methylation, thereby inhibiting PRMT1 enzyme activity but not its expression level [26]. The levels of total Gli1 and methylated Gli1 were positively correlated with PRMT1 protein levels in human PDAC specimens. PRMT1 methylates the oncogenic transcription factor Gli1 in R597 to enhance transcriptional activity by enhancing the binding of Gli1 to its target gene promoter, while disruption of Gli1 methylation weakens the oncogenic function of Gli1 and sensitizes PDAC cells to gemcitabine therapy [28]. Downregulation PRMT1 was associated with the PD-L1 downregulation. The inhibitor PT1001B enhanced the inhibition of anti-PD-L1 on tumor cell proliferation and enhanced the induction of tumor cell apoptosis. Therefore, the combination of a protein arginine methyltransferase inhibitor (PD-1) and anti-programmed death ligand-1 (PD-L1) can effectively inhibit the progression of PC [29]. In conclusion, PRMT1 may serve as a potential biomarker for pancreatic cancer.

3. Conclusion

Protein arginine methylation affects many important biological pathways, such as DNA damage signal transduction, pre-mRNA splicing, mRNA translation, and cell signal transduction [3]. More and more evidences have shown that arginine methyltransferase is involved in various physiological and pathological processes in humans, especially in malignant tumors. Studies have found that PRMT1 is involved in the development and diseases of the nervous system and plays an important role in neurodegenerative diseases [30]. PRMT1 also promotes asthma by regulating asthma-related pri-let-7i and pri-miR-423 [31]. PRMT1-v2 activated the gluconeogenic program in hepatocytes via interactions with PGC1α, a key transcriptional coactivator regulating gluconeogenesis [32]. PRMT1 is involved in the progression of lung cancer by regulating the high expression of FEN1 [33]. PRMT1 can also promote the metastasis of breast cancer by regulating the expression of EZH2 [34]. In glioma cells, upregulation of PRMT1 can promote the growth and metastasis of glioma cells, and downregulation of PRMT1 can also produce opposite inhibition [35]. PRMT1, as the main type I enzyme in mammals [8, 9], is responsible for arginine mono methylation and more than 80% asymmetric methylation modifications [5].

In gastrointestinal tumors, PRMT1 expression has been proved to be upregulated, and its imbalance or abnormal expression is involved in the occurrence and development of cancer. Current research evidence shows that PRMT1 plays a tumorigenic role in gastrointestinal tumors. PRMT1 upregulation can promote the growth and proliferation of EC cells [1, 2], CRC cells [6, 7, 9], and PC cells [15–19]. In GC cells, PRMT1 upregulation promotes tumor cell migration, invasion and mesenchymal transformation of epithelial cells and inhibits GC cell proliferation [3, 5]. In HCC cells, PRMT1 is upregulated to promote tumor cell proliferation, migration, invasion and mesenchymal transformation of epithelial cells [10–14]. However, PRMT1 knockdown or deletion may have the opposite effect. Therefore, PRMT1 may be used as a new potential tumor biomarker and target for prognosis therapy. At present, many PRMT1 inhibitors, such as AMI-1, MS023 and GSK3368715, have entered the first phase of clinical trials, trying to open up a new way of cancer treatment [1, 36]. The latest animal experimental results show that the growth rate of HT-29 tumor cell line after xenotransplantation is slowed down under the treatment of the inhibitor MS023 [37]. Of course, there are some new inhibitors of PRMT1 under study. The latest research results show that the inhibitor TC-E-5003 has a good inhibitory effect on lung cancer and breast cancer and can also be used as an antitumor drug [38]. However, the role of PRMT1 in prognostic therapy needs to be further studied.

Acknowledgements

Conflict of interest

The authors declare no conflicts of interest.

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