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The Role of PPM1D in Cancer and Advances in Studies of Its Inhibitors

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Abstract

A greater understanding of factors causing cancer initiation, progression and evolution is of paramount importance. Among them, the serine/threonine phosphatase PPM1D, also referred to as wild-type p53-induced phosphatase 1 (Wip1) or protein phosphatase 2C delta (PP2Cδ), is emerging as an important oncoprotein due to its negative regulation on a number of crucial cancer suppressor pathways. Initially identified as a p53-regulated gene, PPM1D has been afterwards found amplified and more recently mutated in many human cancers such as breast cancer. The latest progress in this field further reveals that selective inhibition of PPM1D to delay tumor onset or reduce tumor burden represents a promising anti-cancer strategy. Here, we review the advances in the studies of the PPM1D activity and its relevance to various cancers, and recent progress in development of PPM1D inhibitors and discuss their potential application in cancer therapy. Consecutive research on PPM1D and its relationship with cancer is essential, as it ultimately contributes to the etiology and treatment of cancer.

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Authors' contributions

WD and JL performed the literature search, wrote and edited the manuscript. KD, DJT, BA, QH, WC and ZG performed the literature search and generated the figures. JV and YW conceptualized the paper, wrote and edited the manuscript, and provided overall supervision and co-ordination of manuscript preparation. All authors were involved in writing the manuscript and approved the submitted version.

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Keywords

PPM1D; phosphatase; inhibitor; p53; cancer

Introduction

PPM1D, also known as (PPM1D, PPMID, PP2Cδ or IDDGIP), is a wild-type p53-induced phosphatase 1 (Wip1). The PPM1D gene is located at 17q23. The complete protein encoded by PPM1D (605 amino acids) is a member of the PP2C family of Ser/Thr protein phosphatase and a negative regulator of cellular stress response pathway. The expression of this gene is induced in a p53-dependent manner in response to various environmental threats, and plays an important role in cell stress, cell cycle regulation, DNA damage repair and tumor cell metabolism. At present, PPM1D has been found to be amplified and overexpressed in various tumors and is currently considered to be an oncogene. This article reviews the relationship between PPM1D and cancer as well as advances in studies of its inhibitors as anti-cancer agents.

In 1997, Fiscella M *et al.* exposed a large number of animal-derived cells including myeloid leukemia, lymphoblastoid, colon carcinoma, lung carcinoma, fibroblasts etc. to 6.3 Gy of ionizing radiation, extracted RNA and cDNA, and found a new gene named PPM1D. This gene is induced by ionizing radiation in a p53-dependent manner. It is largely induced in the presence of wild-type p53, but is not sensitive to mutant p53. In addition, their studies demonstrate its homology with type 2C protein phosphatase, including dependence on Mg^{2+} and relative insensitivity to okadaic acid. PPM1D gene transcription is activated rapidly and briefly after ionizing radiation, and the expressed protein is located in the nucleus [1]. Only 3 years later, the structure and expression of mouse PPM1D gene were also determined. PPM1D has been located near p53 gene on chromosome 11. Mouse PPM1D gene consists of 6 exons, spanning 36 kb of DNA length. Compared with human PPM1D (605 amino acids), mouse PPM1D protein is composed of 598 amino acids and their identity and similarity reach 83% and 86%, respectively. The authors observed mouse embryos and various adult tissues including mammary gland, uterus, ovary, adrenal gland, skin and testis in different periods and found that PPM1D mRNA seems to be universally expressed in all tissues and has very high level of expression in testis. Although the expression level fluctuates during development, PPM1D is also expressed at all embryonic stages [2]. In order to further determine the normal biological function of PPM1D in mammalian organisms, the authors obtained $PPM1D^{+/-}$, $PPM1D^{-/-}$ and $PPM1D^{+/+}$ through gene recombination. The body weight, fertility, life span and tumor of the mice were observed for 2 years. The results showed that the male mice with $PPM1D^{-/-}$ genotype had smaller body size, atrophic reproductive organs, reduced fertility and life span, and that their 2-year survival rate was less than 20%, while the survival rate of female mice with $PPM1D^{-/-}$, all $PPM1D^{+/-}$ and $PPM1D^{+/+}$ mice was about 80% in the same period. Moreover, $PPM1D^{-/-}$ male mice also showed increased susceptibility to pathogens and weakened T and B cell functions, resulting in death of all infected $PPM1D^{-/-}$ male mice within 11 days after influenza virus infection, while the survival rate of $PPM1D^{+/-}$ heterozygote mice infected with virus at the same time

was as high as 80%. However, it is noteworthy that PPM1D−/− mice did not show any signs of tumor [3]. Is this just a coincidence?

The NIH Mammalian Gene Collection (MGC) program published related articles in the same year to sequence and verify the complete Open Reading Frame (ORF) clone, which contains a non-redundant set of > 9,000 human and > 6,000 mouse genes. Candidate full ORF clones of another 7,800 individuals and 3,500 mouse genes were also identified [4] and provide a basis for the follow-up research of PPM1D. In the same year Bulavin *et al*. first studied the relationship between PPM1D and tumor. This study measured PPM1D mRNA content in human embryonic fibroblasts, breast cancer cells, ovarian cancer cells, non-small cell lung cancer cells, renal cancer, T lymphocyte leukemia cell lines, etc. and determined the high expression of PPM1D in breast cancer cell lines BT474 and MCF7. This work not only found a breakthrough for the relationship between PPM1D and cancer, but also established the central position of breast cancer in PPM1D and tumor-related research [5]. The research on the relationship between PPM1D and the occurrence and development of tumor has been started since then, and we will make a systematic review for this.

Breast Cancer

Bulavin *et al*. found that genes encoding PPM1D (17q22/q23) were amplified in human breast tumor cell lines and about 11% of primary breast tumors, most of which carried wild-type p53. Inactivation of p38MAPK (product of mapk14) *in vivo* through overexpression of PPM1D accelerates tumor formation [5–7]. Moreover, a new amplification region of breast cancer was found on chromosome 17q23. In addition to PPM1D, the amplification of ERBB2, RPS6KB1, TBX2 and ZNF217 were also found [7, 8]. Interestingly, PPM1D amplification is related to ERBB2 expression. Some researchers have proposed that PPM1D phosphatase plays a role in MKK6/p38 MAPK signaling pathway to promote ErbB2-driven breast tumor occurrence [9]. Meanwhile, some scholars found that 35% of PPM1D mRNA was up-regulated in invasive breast cancer samples. The overexpression of PPM1D was negatively correlated with the overexpression of p-p38 MAPK, suggesting that PPM1D overexpression eliminated the steady-state balance maintained by p38-p53-PPM1D pathway [10]. Inhibiting BRCA1 expression can effectively reduce PPM1D expression, thus enhancing the activity of p38MAPK and effectively improving cell survival rate [11]. In a cohort study from Brazil, the author tried to find out the relationship between long-term clinical efficacy and gene variation by using gene expression chips of tumor samples from 24 patients with invasive ductal breast cancer, and followed up the patients for at least 5 years. They demonstrated that the up-regulation of B3GNT7, PPM1D, TNKS2, PHB and GTSE1 genes in different breast cancer patients was related to the poor prognosis of patients [12]. Other scholars have introduced next-Generation Sequencing (NGS) into clinical diagnosis, and found that gene mutation including PPM1D may lead to increased risk of bilateral breast cancer (BBC) [13]. Other scholars have evaluated the genetic risk of breast cancer, put forward the important role of single nucleotide polymorphisms (SNPs) in cancer diagnosis, and proposed that PPM1D gene mutation will increase the genetic risk of breast cancer [14]. Kim *et al*. performed NGS analysis on blood samples of patients suspected of having hereditary breast cancer. For patients with PPM1D mutation in blood, routine sequencing was used to check PPM1D mutation in tumor tissue samples. The results showed

that in 719 patients with breast cancer, the mutation rate was less than 0.3%, with truncating mutations in exon 6 as the main mutation, which may be related to previous chemotherapy [15]. Regarding the genetic mutation of breast cancer, Mahdavi *et al.* pointed out that the important reason for the occurrence of genetic breast cancer is the mutation of susceptible genes, including BRCA1, BRCA2, TP53, CHEK2, PTEN, ATM and PPM1D. These mutations are crucial to early onset and the increased risk of familial breast cancer, and lead to 90% of hereditary breast cancer cases [16]. With the rise of research on special types of breast cancer in recent years, triple negative breast cancer (TNBCs) has become the target of conquest. Quist *et al.* have adopted 5 independent cohort studies with a total of 1,168 patients. Four genes EXO1, TP53BP2, FOXM1 and RSU1 have been identified to be related to genomic instability, malignant growth or therapeutic response. In TNBC MC6 cell line, inhibition of PPM1D can increase the sensitivity of the cancer cells to platinum drugs [17]. Our team also conducted relevant research on diabetes-associated breast cancer and observed that high glucose (HG) promotes the expression of PPM1D through PKC-GSK3β and oxidative stress ROS-NF-KB pathway, thus inhibiting p53 function and promoting the proliferation, migration and invasion of breast cancer cells [18].

In another cohort study of clinical trials, 245 patients with invasive breast cancer were observed and analyzed by in situ hybridization and RT-PCR. It was found that breast cancer samples from clinical patients highly expressed estrogen receptor and progesterone receptor, and PPM1D amplification was significantly correlated with HER2, TOP2A and CCND1 amplification [7]. Some researchers have further studied the relationship between estrogen signal transduction and PPM1D expression. MCF7 cells were treated with different concentrations of estradiol (E2) (1, 10, 100 nM) and for 4, 8, 16, 24 hours. The results showed that the expression of PPM1D reached a peak at 16 hours under the treatment of 10 nM E2. Immunoprecipitation technique confirmed the direct binding of estrogen receptor (ER)α to PPM1D promoter. In addition, the cDNA sequence of PPM1D transcribed by adenovirus caused overexpression of PPM1D, inactivating p53 through dephosphorylation and promoting tumor proliferation [19]. Other studies have confirmed that the expression of PPMID in breast cancer can be independent of p53 regulation, and breast cancer can also show malignant process without p53 mutation. In this study, 201 specimens of primary invasive ductal carcinoma were examined. The results of follow-up for 10 years showed that PPM1D (+) itself is a prognostic factor for breast cancer. The expression of PPM1D could reduce the 10-year survival rate of patients from more than 70% to less than 50%, and what's more, the 10-year survival rate of patients with PPM1D(+)p21(−) is lower (nearly 30%) [20].

Esophageal cancer

PPM1D overexpression predicts poor prognosis in esophageal squamous cell carcinoma (ESCC). Li *et al.* studied 101 patients with ESCC and 1: 1 matched control group. Immunohistochemical staining showed that the positive expression of PPM1D protein in tumor tissues of patients with ESCC accounts for 70 cases (69.3%), while the control group accounts for only 15 cases (14.9%), with significant difference. Moreover, the expression of PPM1D mRNA in tumor patients is also significantly higher than that of the control group. The expression of PPM1D in patients with metastatic ESCC is significantly higher than that

in patients with non-metastatic ESCC. COX risk model analysis indicates that lymph node metastasis and high expression of PPM1D are independent prognostic factors of ESCC. Follow-up data show that the 5-year survival rate of patients with high expression of PPM1D in tumors is less than 20%, while that of patients with negative PPM1D is about 50%, suggesting that PPM1D may be a new marker for metastasis and prognosis of ESCC patients [21]. In addition, PPMID was also used to evaluate autophagic effect after paclitaxel treatment of esophageal adenocarcinoma cells [22].

Intriguingly, most recently Yokoyama *et al.* analyzed 157 cases of physiologically normal oesophageal epithelia (PNE), 12 cases of esophageal epithelial dysplasia and 519 cases of esophageal squamous cell carcinoma. It was found that smoking and drinking contributed the most to gene mutation, and age itself was also a risk factor. People over the age of 76 are more likely to develop esophageal cancer. The comparative analysis of normal esophageal epithelium and esophageal carcinoma indicated that the increase of TP53 gene expression and the decrease of *PPM1D* and *NOTCH1* gene expression were statistically significant. Compared to the mutations of esophageal cancer, the normal esophageal epithelia has obvious overrepresentation of NOTCH1 and PPM1D mutations. These mutations can be acquired before late puberty (as early as infancy) and increase significantly with heavy smoking and drinking [23].

Colon cancer

DNA damage can increase PPM1D content and initiate ATM/CHK2, ATR/CHK1 as well as p38-MAPK-induced p53 inhibition to facilitate damage repair. Kleiblova *et al.* found that PPM1D gene mutation exists in colon cancer, which lead to the persistent suppression of p53 and the occurrence of tumors [24]. Oliva *et al.* also confirmed that overexpression of PPM1D inhibited CHK2's ability to detect and repair cell cycle damage in colon cancer cells, leading to malignant progression of cancer [25]. Some scholars have pointed out that PPM1D can activate downstream p38MAPK and JNK signaling pathways independent of p53 in colon cancer cells [26].

Li, Wang, Bai and Peng *et al.* analyzed the expression of PPM1D protein and mRNA in colorectal cancer and normal tissues. Their results show unanimously that PPM1D protein and mRNA levels in colorectal cancer tissues are significantly higher than those in normal control group and are correlated with lymph node metastasis, Dukes stage, histological grade, 5 year survival rate and liver metastasis [27–30]. Studies on the related mechanisms indicate that p53-dependent PPM1D-KPNA2-AKT/GSK-3beta pathway and NF-kappa B-PPM1D-mTOR-P21 pathway are new pathways for molecular regulation of colon cancer [28, 29]. Using lentiviral shRNA to reduce the expression of PPM1D in RKO cells, Yin *et al.* demonstrated that inhibition of PPM1D expression effectively inhibited the proliferation and colony formation, and that the cell cycle arrested at the G0/G1 phase and a large number of tumor cells accumulated in G1 phase [31]. Moreover, Suman *et al.* demonstrated that the deletion of PPM1D inhibited the development of radiation-induced intestinal tumors [32].

Apart from interfering with the development of colon cancer, PPM1D also contributes to the drug resistance of colon cancer. Xia added 50 nmo/L PPM1D siRNA to 5-FU, oxaliplatin

and doxorubicin-induced drug resistance model, successfully reducing IC50 of 5-FU-, oxaliplatin- and doxorubicin-resistant strains from 56.88 to 25.32 μmol/L, 43.60 to 18.74 μmol/L, 2.13 to 0.88 μmol/L, respectively [33]. P53-negative tumors are more likely to develop resistance to antineoplastic drugs. However, some scholars have found that overexpression of PPM1D in p53-negative tumors makes them sensitive to chemotherapeutics and protects normal tissues from side effects of anticancer therapy [34].

Hematological Tumors

In clonal hematopoiesis of leukemia, mutations in *TP53* and *PPM1D* seem to lead to clonal growth, which may result in subsequent malignant tumors [35]. In the early stage of tumorigenesis, CDK6 promotes tumorigenesis through regulating transcriptional response in a stage-specific manner. In hematopoietic stem cells, CDK6 inhibits the function of p53 gene by binding to PPM1D [36]. Coombs *et al.* found that myelodysplastic syndrome was related to mutation of PPM1D and that chemotherapy could cause mutation of PPM1D and TP53. However, for the treatment of hematological tumors, patients with PPM1D mutation are more likely to need growth factor therapy [37]. Xie et al. focused on TCGA database to study gene mutations of tumors in the blood system. Seventy-seven specific mutations were found through analysis of blood source-related genes in 2728 individuals. Among them, PPM1D mutations were associated with hematological diseases such as myelodysplastic syndrome, leukemia and lymphoma [38]. Previous studies indicated that PPM1D gene was amplified and overexpressed in leukemia. Kamada *et al.* found that PPM1D expression increased in nucleus and cytoplasm of human promyelocytic leukemia cell line HL-60 when it differentiated into neutrophils. PPM1D inhibitor can increase the proportion of HL-60 differentiating into neutrophils, and also induce G1 cell cycle arrest in HL-60 cells. Their results suggest that PPM1D may be a potential therapeutic target for hematopoietic diseases, including leukemia [39]. Other researchers have confirmed that arsenic trioxide (ATO) can activate Chk2/p53 and p38MAPK/p53 pathways by inhibiting the function of PPM1D, leading to apoptosis of acute promyelocytic leukemia cells. Its role has been verified by using PPM1D siRNA [40].

Thyroid cancer

Pekova *et al.* studied 113 children's thyroid samples, including 30 benign lesions and 83 thyroid cancer samples. Mutant genes in thyroid cancer were identified by Next Generation Gene Sequencing, and mutations were found in genes including PPM1D [41]. Another study included 301 thyroid patients, including 119 males and 182 females, with a median age of 34 years. Analysis with PCR and Sanger sequencing revealed that EIF1AX, PPM1D and CHEK2 are the three most important new mutation genes [42, 43].

Sarcoma

Osteosarcoma (OS) is a primary malignant bone tumor with high incidence. After analyzing the expression of PPM1D in 18 pairs of osteosarcoma tissues and control tissues, Long *et al.* found that the expression of PPM1D in osteosarcoma was significantly higher than that in control tissues, and that PPM1D mRNA was highly expressed in U2OS and MG63 cells

[44]. A miRNA microarray analysis of cancer tissues and adjacent non-cancer tissues from 62 OS patients showed that 29 miRNA were up-regulated and 26 miRs were down-regulated, of which miR-499a-5p was down-regulated the most. In addition, expression levels of PPM1D mRNA and protein in osteosarcoma tissue are higher than those in non-cancerous tissue. Targetscan predicts that PPM1D is regulated by miR-499a-5p. In order to further confirm the regulatory relationship between miR-499a-5p and PPM1D, they transfected miR-499a-5p mimics into osteosarcoma cell MG-63, and found that it can down-regulate the expression of PPM1D mRNA and protein through Akt/GSK-3β signaling, thus inhibiting tumor cell proliferation [45]. Stole *et al.* also found that the intervention of PPM1D can reduce the cell viability of Ewing sarcoma, showing the target effect of PPM1D in Ewing sarcoma treatment [46].

Lung cancer

Yang *et al.* performed immunohistochemical determination of PPM1D in 60 non-small cell lung cancer (NSCLC) tissues and 20 normal lung tissues, and found PPM1D expression in 38 lung cancer tissues, but negative expression in normal tissues. This difference is related to tumor size (3 cm as the boundary) and differentiation degree. It was also observed that the expression of PPM1D was negatively correlated with the expression of p38MAPK, p53 and p16 [47]. Zhao *et al.* also observed this phenomenon. Among 117 cases of NSCLC, 81 cases expressed PPM1D, but there was no expression or only weak expression in 15 normal lung tissues. The data of follow-up for more than 6 years show that the 6-year survival rate of lung cancer patients with high PPM1D expression is less than 20%, while the survival rate of lung cancer patients with low PPM1D expression is more than 40%. COX risk model regression analysis shows that the difference in survival rate is mainly related to PPM1D protein expression, lymph nodes metastasis and pathological stage [48]. Yang also observed a significant increase in PPM1D mRNA expression in NSCLC tissues, which is significantly correlated with tumor grade, tumor size T stage, clinical stage, and lymph node metastasis [49], suggesting PPM1D has independent evaluation significance for lung cancer [49–51].

Not only can PPM1D be expressed in lung cancer tissues, but it can also mediate the regulation of amyloid protein-binding protein 2 (APPBP2) on lung cancer tissues as an intermediate molecule of pathway. Gong *et al.* observed an ectopic expression of APPBP2, PPM1D and SPOP in human NSCLC tissues. The results suggest that APPBP2 promotes the progression of NSCLC by regulating PPM1D and SPOP signaling pathways [52].

In view of the significance of PPM1D in the prognosis of lung cancer, researchers began to study the intervention of PPM1D. Gu *et al.* studied the role of mir-16 in lung cancer and confirmed that PPM1D was the target gene of mir-16 in lung cancer cell line A459. Transfection of mir-16 mimics significantly inhibited the expression of wild-type PPM1D, and reduced the proliferation of A459 cells and promoted cell apoptosis [53]. PPM1D snRNA treatment in A459 and H1299 cells could also reduce the proliferation of tumor cells and induce cell cycle arrest in G0/G1 phase [54].

Ovarian cancer

Previous studies have confirmed that PPM1D gene amplification is closely related to ovarian cancer [55, 56]. Phroah *et al.* studied 3236 patients with ovarian cancer and found that 0.37% of them had chimeric mutations in PPM1D. However, PPM1D mutation was detected in the blood of 1827 patients after chemotherapy. The authors believe that these PPM1D mutations are related to chemotherapy, but not to the susceptibility of primary tumors [57]. Akbari *et al.* observed 1,295 cases of ovarian cancer and concluded that in the absence of a family history of cancer, PPM1D chimeric mutation could make women more susceptible to ovarian cancer [58].

Feng *et al.* transfected PPM1D siRNA into ovarian cancer cell SKOV3 and found that after PPM1D was inhibited, the percentage of tumor cell apoptosis increased, the expression of P53 increased, and the Bax/bcl2 ratio also increased [59]. However, Yin *et al.* have reached the opposite conclusion. Inhibition of PPM1D expression with shRNA increased the proliferation, migration and invasion ability of Hey A8 and A2780 cells. Moreover, overexpression of PPM1D can inhibit proliferation, migration and invasion of ovarian cancer cells in SKOV3 and OVCA433 cells and mouse metastatic tumor models. At the same time, they substantiated that PPM1D can inhibit ovarian cancer metastasis through negative regulation of p-ATM, p-Akt and Snail. This mechanism is independent of the previous regulatory mechanism involving p53, and may provide new ideas for the treatment of ovarian cancer [60]. Furthermore, Hirata *et al.* confirmed that miR-21, which located at the same gene position 17q23–25 as PPM1D may also participate in the pathogenesis of ovarian cancer [61].

PPM1D not only can be used as a gene target for ovarian cancer, but also plays an important role in relieving drug resistance of ovarian cancer. Ali proposed a tumor drug resistance mechanism model. In sensitive cells, cisplatin (CDDP) induces PPM1D nuclear rejection and proteasome degradation, thus allowing CDDP to induce Chk1 and p53 activation and eventually initiate cell apoptosis. However, in chemoresistant cells, Akt activation and overexpression stabilize PPM1D, leading to sustained PPM1D expression and nuclear localization, which inhibits Chk1 and p53 activity and reduces apoptosis, thus contributing to CDDP resistance in cancer cells. PPM1D, as a target molecule of AKT, plays an important role in eliminating chemotherapeutic drug resistance [62, 63]. Tsuyoshi confirmed that Saikosaponin-d (Ssd) can induce cancer cell death and sensitize chemoresistant cancer cells to anti-cancer drugs by down-regulating PPM1D and increasing the phosphorylation of checkpoint protein kinase (Chk) 1, cell division cycle 25C (Cdc25c) and cyclin dependent kinase 1 (Cdk1) [64].

Pancreatic cancer

The study of PPM1D in pancreatic cancer is relatively few. Wu *et al.* found that the expression of PPM1D protein and mRNA in human pancreatic cancer tissues was significantly higher than that in normal pancreas. The expression of PPM1D in pancreatic cancer tissues was related to tumor size (2cm as the boundary), case classification, lymph node metastasis and vascular invasion. Further mechanism study showed that the expression

of PPM1D mRNA and protein in PANC-1 and MIA Paca-2 cell lines was higher. High expression of PPM1D can significantly promote the proliferation, invasion and migration of cancer cells through wnt/beta-catenin pathway. Down-regulation of PPM1D expression with PPM1D siRNA significantly increased aspp2 and p38MAPK/p53, and promoted apoptosis of cancer cells. Experiments in nude mice also confirmed that PPM1D siRNA could significantly reduce tumors, suggesting that PPM1D is a carcinogenic gene of pancreatic cancer [65]. Other studies indicated the independent predictive effect of PPM1D on pancreatic cancer patients and that the 3-year survival rate of patients with high PPM1D expression was 0%, while the 10-year survival rate of patients with low PPM1D expression was 10% [66].

Glioma

Dodgshum *et al.* observed PPM1D mutation in a 3-year-old patient with glioblastoma multiforme [67]. The deletion of Rb gene inactivation of p38MAPK through PPM1D is a new biological behavior of glioma [68]. Wang *et al.* found that PPM1D is expressed in glioma cell line U87-MG. After silencing PPM1D and treating the cell with TMZ, they showed that PPM1D gene silencing can better inhibit TMZ-induced cell proliferation and induce cell apoptosis and cell cycle arrest, and that PIK3R1/AKT pathway plays a role in various functions of glioma cells [69].

Gastric Cancer

It has been reported that PPM1D is highly expressed in glands of gastric cancer tissues, while almost no PPM1D is expressed in normal gastric mucosa. High expression of PPM1D is associated with lymph node metastasis, distant metastasis and vascular invasion. Survival analysis showed that the 5-year survival rate of patients with PPM1D positive expression is about 40%, while that of patients with PPM1D negative expression is over 70%. Therefore, the expression of PPM1D in cancer tissues could be used as an indicator of poor prognosis of gastric cancer patients [70]. Fuku *et al.* proposed that the expression of PPM1D in human gastric cancer tissues is related to the size of tumors and the dephosphorylation of Chk2. In addition, carrying out experiments in HEK293 and MKN-74 gastric cancer cells, the authors suggest that ionizing radiation (IR) can induce PPM1D up-regulation and inhibition of CHK2, leading to down-regulation of p53. This pathway provides a new way for the treatment of gastric cancer [71].

Nasopharyngeal Carcinoma

The expression of PPM1D in nasopharyngeal carcinoma is significantly higher than that in normal tissues. Its positive expression is significantly correlated with T stage, lymph node metastasis, clinical stage, tumor differentiation and radiotherapy response. The 5-year survival rate of PPM1D positive patients is less than 40%, while that of PPM1D negative patients is more than 60%. Transfection of PPM1D siRNA into nasopharyngeal carcinoma CNE2 cells significantly reduces the proliferation, invasion and migration of tumor cells, increases apoptosis, and promotes protein expressions of p53 and p16. It is suggested that

PPM1D may participate in the development of nasopharyngeal carcinoma by regulating p53-p16 pathway [72].

Liver Cancer

The expression of PPM1D in hepatocellular carcinoma is significantly higher than that in normal liver tissues. Immunohistochemistry showed that PPM1D protein is highly expressed in hepatocellular carcinoma tissues, but hardly expressed in normal tissues. The expression of PPM1D in hepatocellular carcinoma is associated with family history, tumor size, alpha-fetoprotein (α-FP), TNM stage and recurrence. However, it is not significantly correlated with age, gender, portal vein invasion, lymph node metastasis, hepatitis B virus (HBV) infection and alcohol intake. The 3-year survival rate of patients with high expression of PPM1D is 0%, while that of patients with low expression of PPM1D is close to 40%. These results suggest that high expression of PPM1D is associated with poor clinical prognosis of patients with hepatocellular carcinoma [73]. Wang *et al.* reported that microRNA-29c was down-regulated in hepatocellular carcinoma tissues in 50.6% patients of 255 cases, while PPM1D was up-regulated in 45.4% of these tissues, and the down-regulation of microRNA-29c was negatively correlated with the up-regulation of PPM1D. Ectopic overexpression of microRNA-29c significantly inhibited cell proliferation and induced apoptosis of HepG2 cells and G1 cell cycle arrest. In contrast, knockdown of miR-29c greatly enhanced the proliferation of HepG2 cells and inhibited cell apoptosis. These studies confirmed that the target of biological effect of miR-29c is PPM1D, and proposed that miR-29c can be used as an intervention target for liver cancer [74]. In addition, other scholars have proposed that the synergistic anticancer effect of miR-29a and arsenic trioxide may provide new opportunities for the treatment of liver cancer by reducing the dose and side effects of arsenic trioxide [75].

Renal Carcinoma and Bladder Cancer

The expression of PPM1D protein and mRNA in human renal cell carcinoma is significantly higher than that in normal kidney tissues. The high expression of PPM1D is related to the depth of invasion T stage, Fuhrman grade, lymph node metastasis and distant metastasis. PPM1D shRNA can inhibit the proliferation, migration and invasion of 786-O and RLC-310 renal cancer cells, while overexpression of PPM1D promotes the growth and invasion of these cells *in vitro*. Survival analysis showed that the 5-year survival rate of patients with high expression of PPM1D in renal cell carcinoma was 0%, while that of patients with low expression of PPM1D was more than 20%. Regression analysis showed that the depth of T3+T4, Fuhrman grade of G3-G4, distant metastasis and high expression of PPM1D are risk factors for poor prognosis of renal cancer patients [76, 77].

Wang *et al.* transfected PPM1D ShRNA into 5367 and T24 cells via lentiviral vectors. shRNA-mediated PPM1D knockdown significantly inhibited cell growth and colony formation in bladder cancer cell lines 5637 and T24, increased the proportion of G0/G1 phase cells, and decreased the proportion of S and G2 phase cells. These results suggest that PPM1D is a target molecule for bladder cancer treatment [78]. In the treatment of advanced or metastatic bladder cancer, cisplatin resistance often occurs. Lin *et al.* found that

overexpression of HIPK2 in bladder cancer TR4 cells can sensitize chemoresistant bladder cancer cells to cisplatin by regulating the expression of PPM1D [79].

Prostate Cancer

The expression of PPM1D in prostate cancer is significantly higher than that in benign prostatic hyperplasia (BPH) control group, and the expression of PPM1D is related to Gleason score, T stage and lymph node infiltration. Kaplan-Meier curve analysis showed that the 10-year survival rate of PPM1D positive prostate cancer patients was about 50%, while that of PPM1D negative prostate cancer patients was more than 90%. COX risk model regression analysis showed that the difference of survival rate was mainly related to PPM1D protein expression, Gleason score and T stage. In order to further study the mechanism of PPM1D in prostate cancer, Jiao *et al.* transfected prostate cancer cell lines CP-3 and LNCaP with PPM1D siRNA and found that PPM1D knockdown inhibits the proliferation, migration and invasion of PC-3 and LNCaP cells [80]. Song *et al.* reported that PPM1D protein expression in prostate cancer LNCaP cells increased significantly after exposure to irradiation. LNCaP cells were continuously exposed to 10Gy radiation for 2–4 hours, p53 content was reduced, p38-p, c-Jun-p, JNK-p, ATR-p, MKK4-p were all inhibited, while PPM1D inhibitor CCT00793 could reverse the inhibition of the above molecules. Further studies have confirmed that PPM1D directly interacts with BAX and dephosphorylates it. Overexpression of PPM1D and BAX in BAX deficient cells can greatly reduce cell apoptosis, reflecting the downregulation of BAX activity by PPM1D [81].

In addition to the various tumors mentioned above, a large number of studies have shown that PPM1D inhibition can also become a new way to treat oral cancer/laryngeal cancer [82], neuroblastoma [83, 84] and melanoma [85].

PPM1D Inhibition as a promising strategy for cancer treatment

PPM1D is amplified and overexpressed in a number of human tumors. Based on Mouse genetic studies and data from RNAi-mediated depletion of PPM1D in cancer cell lines, PPM1D was proposed as an attractive pharmacological target [86–88]. Recently, significant progress has been made in the design of PPM1D inhibitors. On the basis of the PPM1D p53 substrate, peptide inhibitors were designed and further developed to produce a cyclic thioether peptide, which has an in vitro Ki of 110 nM against PPM1D [89]. In spite of a valuable tool compound, the two phosphoric acid moieties on the peptide strictly limit cell entry and the binding of PPM1D. Hence, peptide-based inhibitors have not been further studied to determine their antiproliferative effect. As an alternative to rational design, some labs have screened and developed small molecule inhibitors of Wip1 phosphatase [18, 90–92]. Nevertheless, the majority of these compounds lack the efficacy, target specificity or bioavailability required to encourage further research. Here, we summarize the currently available proof-of-principle small molecule inhibitors and attempt to give a prospect on PPM1D targeted therapeutic strategies in the future.

M321237 and CCT-007093

Compound M321237 was identified through screening chemical libraries based on its ability to repress PPM1D protein phosphatase activity in vitro [93]. Cell viability assay demonstrated that M321237 sensitizes breast cancer MCF-7 cells to doxorubicin. *In vivo* studies showed that M321237 reduced tumor volumes in xenograft models; nonetheless, the selectivity of M321237 to PPM1D was never validated.

Similar screening methods resulted in identification of CCT007093, which has an *in vitro* PPM1D protein phosphatase IC50 value of only 8.4 μM [92]. CCT007093 suppresses cell viability in p53-proficient tumor cells carrying amplified *PPM1D* [92]. Alternatively, CCT007093 inhibits UV-induced apoptosis in skin keratinocytes through blocking activation of JNK, suggesting that the inhibitor is less specific to WIP1 [94]. Additionally, CCT007093 was shown to inhibit cell proliferation irrespective of the presence of WIP1 in U2OS cells, confirming its off-target effect [95]. In addition, CCT007093 treatment does not affect levels of p53-pS15 and γH2AX, both of which are well-established substrates of WIP1 [95]. Finally, CCT-007093 is a strong Michael acceptor that may produce adverse irreversible target inhibition [92]. These data indicate that CCT007093 does not impede WIP1 in cells and emphasize the urgent need to verify the specificity of small molecule inhibitors in cell models, including the CRISPR/Cas9-mediated target gene knockout.

SPI-001 and SL-176

Compared with aforementioned compounds, small molecule perhydrophenanthrene SPI-001 and its analogue SL-176 were identified as non-competitive inhibitors of recombinant WIP1 (IC50 = 110 and 86.9 nM, respectively) [91, 96]. In addition, the specificity of SPI-001 to PPM1D protein phosphatase was determined to be about 50 times higher than that of another PP2C phosphatase PPM1A [91]. Both SPI-001 and SL-176 inhibit the proliferation in human breast cancer MCF7 cells overexpressing wild-type (WT) PPM1D in a dose-dependent manner [96]. In human colorectal cancer HCT-116 cells expressing truncated PPM1D, SPI-001 treatment does not affect cell proliferation, nonetheless combination treatment with SPI-001 and doxorubicin enhances cell growth inhibition by increasing p53 phosphorylation at Ser15 [97]. In summary, SPI-001 and SL-176 are promising lead compounds but further analysis is needed to test their specificity, efficiency and pharmacokinetics in organismal levels [91].

GSK2830371

A particularly intriguing PPM1D protein phosphatase inhibitor with high selectivity was identified recently by combining biochemical and biophysical screens, which employed suppression of PPM1D enzymatic activity and high-affinity binding as readouts, respectively [90]. Firstly, a number of capped amino acids (CAA) were identified (in vitro IC50: 10–20 nM) [90]. The lead CAA compounds are characterized as non-competitive, allosteric PPM1D inhibitors, which bind to a conformationally flexible flap domain that is implicated in substrate conjugation. This is a non-conserved sequence among homologous PPM1D phosphatase family members, assuming that it provides selectivity for PPM1D inhibitors.

The peptide properties of these lead compounds led to poor cell permeability and consequently stimulated the further exploration of structure-activity relationship that produces GSK2830371. It has an *in vitro* IC50 of 6 nM against PPM1D and *in vivo* activity against a B-cell lymphoma xenograft model, despite a fairly aggressive oral treatment regimen (150 mg/kg, three times a day for two weeks) [90]. It is noteworthy that GSK2830371 also rapidly reduces the level of PPM1D protein in cancer cells through a mechanism that has not been fully described. Moreover, cell proliferation studies showed that GSK2830371 effectively inhibited the proliferation of cancer cells carrying PPM1D amplification while retaining WT p53, e.g. some breast cancer, neuroblastoma, and hematological cancer cell lines [84, 90, 95, 98, 99]. Notably, U2OS-PPM1D-KO cells knocked out by CRISPR/Cas9 did not respond to GSK2830371, which further confirmed its specificity to PPM1D at the cellular level [95]. Inhibition of PPM1D by GSK2830371 up-regulates expression of p53 target genes such as CDKN1A, PUMA, and BAX, leading to cell cycle arrest, but is not enough to induce cell death [90, 95, 98, 100]. Of note, these studies also indicate that GSK2830371 is orally bioavailable. Nevertheless, the relatively low stability in blood could limit its clinical application. Further optimization of GSK2830371 is expected to develop a small molecule PPM1D inhibitor with better pharmacokinetic properties.

Compound 23

Recently, we identified a 1,5-diheteroarylpenta-1,4-dien-3-one (Compound 23, or C23) as an effective PPM1D protein phosphatase inhibitor via cell based screening assay for growth inhibition and activity of a series of curcumin mimics [18]. In structure, CCT007093 and these compounds have a similar central pentacarbon monoketone linker and two same aromatic terminal rings. These curcumin mimics are structurally different from CCT007093 in that they have a distinctive nitrogen containing moiety in the terminal heteroaromatic rings. The growth inhibition assay demonstrated that C23 has a remarkable cytotoxicity on MCF-7 cells (IC50: 0.98 μM) but not MCF-12A cells compared to CCT007093. The docking simulation for binding mode of C23 to the PPM1D phosphatase domain shows that C23 is buried into the catalytic site consisting of Asp105, Arg110, Arg243, Arg258, Arg259, Gln265, Phe268, Asp314, Arg364, Asp366, and Asn367. The carbonyl oxygen atom and the nitrogen atom in C23 heteroaromatic ring form two hydrogen bonds with side chains of Arg258 and Asp105, which leads to a stable binding model of C23. In addition, C23 has a good selectivity versus two other Ser/Thr phosphatases, i.e. PP2Cβ and PP2A.

In addition to the direct inhibition of PPM1D phosphatase activity, C23 suppresses high glucose induction of PPM1D expression through heat shock protein 27 (HSP27) induction and subsequent inhibition of ROS/NF-kB pathway. The water solubility and bioavailability of C23 are still insufficient. To improve its aqueous solubility and bioavailability, we developed PLGANPs of C23, which could significantly inhibit the growth of breast cancer MCF-7 xenografts in diabetic nude mice. We suggest that C23 can be developed as a unique therapeutic agent for breast cancer patients with diabetes.

Conclusions and future perspectives

PPM1D phosphatase is an important negative regulator of p53 pathway and DNA damage response. Overexpressed PPM1D damages p53 function and promotes tumorigenesis, generally in concert with activation of other oncogenes. Amplification, overexpression or mutation of PPM1D are closely related to many human tumors. In contrast, loss of PPM1D dramatically postpones cancer development in mice and depletion of PPM1D by genetic approach reactivates p53 and hinders proliferation in p53-proficient cancers. Until recently, the selective inhibition of PPM1D phosphatase is still a main challenge, and the lack of specific small molecule inhibitors limits the development of wip1 as a pharmacological target for cancer treatment. Because the structure of PPM1D is still unknown, the potential inhibitors of PPM1D have been identified through high throughput screening of a large number of chemical libraries. In the past decade, several compounds have been developed to antagonize the activity of PPM1D; nonetheless, only two of these inhibitors i.e., GSK2830371 and C23, shows high specificity to PPM1D and encouraging results in preclinical analysis. Notably, GSK2830371 is bioavailable by oral administration, and its ability to inhibit the growth of cancer cells *in vivo* has been confirmed in xenograft models. At the same time, GSK2830371 is promptly inactivated in plasma, limiting its further clinical application. The water solubility and bioavailability of C23 still need to be improved. Thus, further development of GSK2830371 and C23 derivatives with better pharmacokinetic properties is extremely desirable. In addition, solving the three-dimensional structure of PPM1D can stimulate the development of more specific inhibitors. The existing studies show that the inhibition of PPM1D will be the most effective in cancers with WT p53 and amplification or mutations of PPM1D. Therefore, it is important to determine the status of TP53 and PPM1D in tumor for predicting the treatment outcome of PPM1D inhibitors. Although mice are well tolerated to loss of PPM1D, there is new evidence that a lack of PPM1D in the immune system induces an inflammatory environment [101]. In view of these newly discovered physiological effects of PPM1D, it is important to address the potential side effects of temporary suppression of PPM1D during treatment interventions.

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Highlights

- PPM1D, an oncoprotein, negatively regulates several cancer suppressor pathways
- PPM1D has been found amplified and mutated in many human cancers
- Selective inhibition of PPM1D represents a promising anti-cancer strategy
- Recent progress in PPM1D's relevance to cancers and development of PPM1D inhibitors

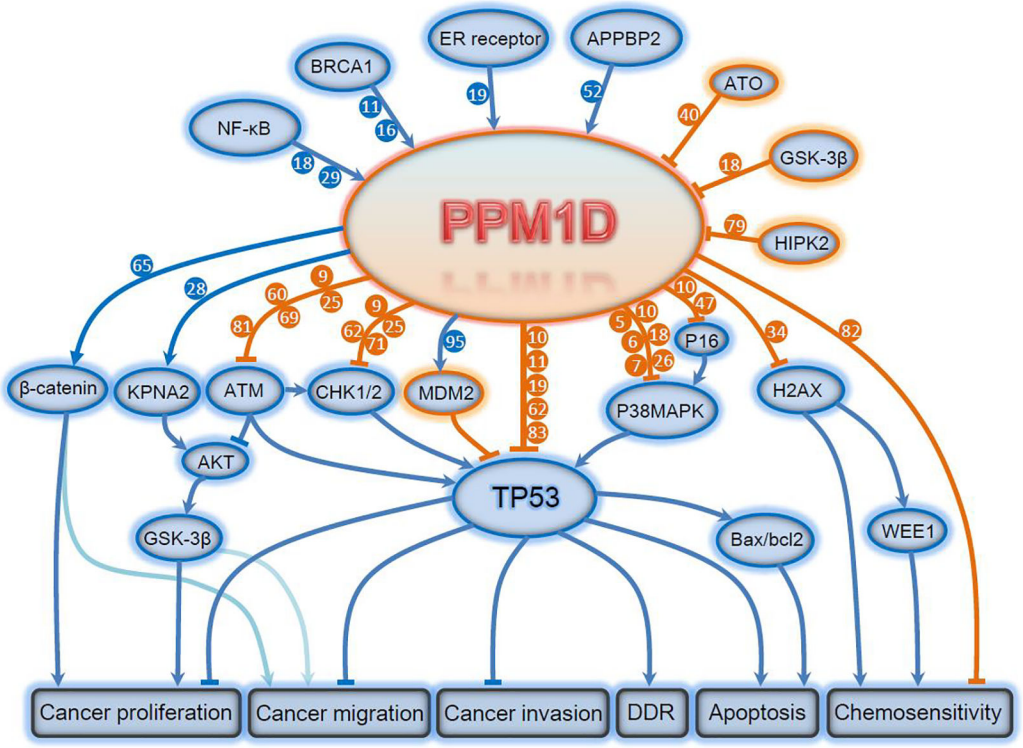


Figure 1. Targets and functional consequences of PPM1D signaling.

The expression and function of PPM1D is regulated by upstream NF-kB, BRCA1, ER receptor, APPBP2, etc. PPM1D phosphatase directly dephosphorylates target proteins including KPNA2, ATM, Chk1/2, Mdm2, p53, p38 MAPK, p16, H2AX and p16, leading to inhibition of apoptosis and promotion of tumorigenesis, invasion, migration and chemoresistance. AKT, AKT Serine/Threonine Kinase; APPBP2, Amyloid Beta Precursor Protein Binding Protein 2; ATM, Ataxia Telangiectasia Mutated; ATO, Arsenic Trioxide; BAX, BCL2 Associated X; BCL2, BCL2 Apoptosis Regulator; BRCA1, BRCA1 DNA Repair Associated; CHK1/2, Checkpoint Kinase 1/2; DDR, DNA Damage Response; ER, Estrogen Receptor; GSK-3β, Glycogen Synthase Kinase 3 Beta; H2AX, H2A Histone Family Member X; HIPK2, Homeodomain Interacting Protein Kinase 2; KPNA2, Karyopherin Subunit Alpha 2; MDM2, Murine Double Minute 2; NF-κB, Nuclear Factor Kappa B; P38 MAPK, P38 Mitogen Activated Protein Kinases; PPM1D, Protein Phosphatase, Mg2+/Mn2+ Dependent 1D; TP53, Tumor Protein P53; WEE1, WEE1 G2 Checkpoint Kinase.

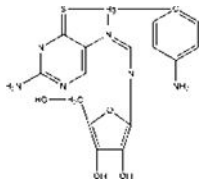
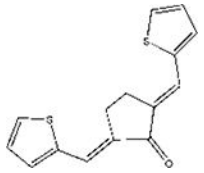
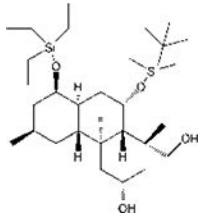
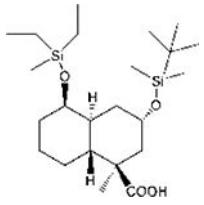
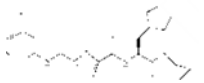
Table 1

PPM1D in cancers

Cancer type	Amplification	mRNA upregulation	Protein upregulation	Mutation	Reference
Breast cancer	+	+	+	+	5–7,10–11,13
Esophageal cancer	−	+	+	+	21,22,23
Colon cancer	−	+	+	+	24,26,27
Hematological tumor	+	−	−	+	35,37,39
Thyroid cancer	−	−	−	+	41,42
sarcoma	−	+	+	−	44,45
Lung cancer	−	+	+	+	48,49,53
Ovarian cancer	+	+	+	+	56,57,58,59,61
Pancreatic cancer	−	+	+	−	65
glioma	+	+	−	+	67,69
Gastric cancer	−	−	+	−	70,71
Nasopharyngeal carcinoma	−	+	+	−	72
Liver cancer	−	+	+	−	73,74,75
Renal carcinoma	−	+	+	−	76
Bladder cancer	−	+	+	−	77,
Prostate cancer	−	+	+	−	80,81
Oral cancer	−	−	+	−	82
neuroblastoma	−	+	+	−	83,84
melanoma	−	+	+	−	85

Table 2

PPM1D inhibitors

Compound name	Structure	IC50 cell proliferation	IC50 phosphatase activity	Animal study	Animal model	Shortcomings	Reference
M321237		–	0.5μM /MCF7	+	Transgenic mice/ Xenograft	selectivity	93
CCT007093		–	8.4μM /MCF7	+	Knockout mice	selectivity	94
SPI-001		26.9μM /MCF7	86.9 nM /MCF7	–	–	Need more test	91,96
SL-176		7.4μM /MCF7	110 nM /MCF7	–	–	Need more test	96
GSK2830371		–	6.0 nM /MCF7	+	Xenograft	Low stability in blood	90,98

Compound name	Structure	IC50 cell proliferation	IC50 phosphatase activity	Animal study	Animal model	Shortcomings	Reference
C23		0.98μM /MCF7	–	+	Xenograft	Water solubility and bioavailability	18