THE ROLE OF THE *PPM1D* GENE IN TUMOR PATHOGENESIS

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The *PPM1D* gene and its protein product (serine-threonine protein phosphatase, PPM1D or Wip1) are involved in regulation of cell's DNA damage response, cell cycle control, and repair. Amplification, overexpression, or mutations of the *PPM1D* gene have a significant impact on cell responses to stress factors and genetic instability as well as impairments of processes of double-strand break repair, nucleotide excision repair, base excision repair, cell cycle, and apoptosis. PPM1D dephosphorylates and thus inactivates p53, proteins that respond to DNA strand integrity damage, cell cycle checkpoint proteins, and apoptotic proteins. This contributes to tumor development, growth, and maintenance of the tumor phenotype. In this review we consider data on the role of the *PPM1D* gene in the formation and maintenance of various oncological processes, including tumors of the mammary glands, ovaries, prostate gland, esophagus, stomach, intestines, liver and pancreas, hemoblastoses, and others.

Keywords: *PPM1D* gene; Mg^{2+}/Mn^{2+}-dependent protein phosphatase 1D; tumor diseases

DOI: 10.18097/PBMCR1495

INTRODUCTION

The *PPM1D* gene (protein phosphatase, Mg^{2+}/Mn^{2+}-dependent 1D, PP2Cδ or IDDGIP) is located on the long arm of chromosome 17 at locus 17q22-23. Its product, the PPM1D protein (Wip1) is a serine-threonine protein phosphatase consisting of 605 amino acid residues. *PPM1D* expression is induced by the wild-type p53 protein in response to adverse external influences; PPM1D is a key regulator of cell's DNA damage response. It should be noted that both the gene and its protein product play an important role in the response of cells to stress factors, regulation of the cell cycle, DNA damage repair and metabolism of tumor cells [1].

Aberrations in genes of the DNA damage response are known mediators of oncogenesis and resistance to chemo- and radiotherapy [2]. Therefore, amplification, overexpression or mutations of the *PPM1D* gene are associated with the formation and course of tumor processes in various organs, as well as with sensitivity to neoplasm therapy and further prognosis of the disease [2]. It should also be noted that, in addition to PPM1D, several other cancer associated genes are located on chromosome 17q: *BRCA1*, *ERBB2*, *NF1*, *RAD51C*, *BRIP1*, and *BIRC5* [3]. Thus, amplification of the *PPM1D* gene, accompanied by its overexpression, may be associated with increased formation of other oncogene proteins. Moreover, truncated variants of the PPM1D protein accumulate 16 times more intensively than the full-length Wip1 variant, even in the absence of damaging factors [4]. This suggests that *PPM1D* deletions contribute to the development of the same effect as amplification of this gene [4].

One of the first studies that identified a new human protein phosphatase PPM1D and its relationship with cancer was conducted by Fiscella et al. [5]. The authors exposed a large number of different cells of animal origin (including myeloid leukemia cells, colon carcinoma, lung carcinoma, fibroblasts, etc.) to ionizing radiation, which resulted in p53-dependent formation of PPM1D mRNA. *PPM1D* transcription was activated rapidly for a short time after exposure to radiation, and the expressed protein was localized in the nucleus. Studying mouse embryos and various animal cells, including mammary gland, uterus, ovaries, adrenal glands, skin and testes at different periods of the cell cycle, the authors found that PPM1D mRNA was universally expressed in all tissues [5].

Subsequently, the relationship between the *PPM1D* gene and oncological processes was confirmed in tumors of the reproductive system, gastrointestinal tract, endocrine glands, hemoblastoses, etc. [6–13]. Thus, consistent study of the *PPM1D* gene and its relationship with tumors is important, since it contributes to the study of the etiology and development of effective treatment of oncological diseases.

The aim of this review was to assess the role of the *PPM1D* gene in oncogenesis and in the development of various types of tumors.

1. THE ROLE OF THE PPM1D GENE IN ONCOGENESIS

The *PPM1D* gene is a negative regulator of the cell's DNA damage response; its protein product (protein phosphatase) dephosphorylates and thus inactivates the p53 protein, proteins that respond to the DNA damage, ATM (ataxia telangiectasia mutated protein), ATR (ataxia telangiectasia mutated and Rad3 related) and DNA-PK (DNA-dependent protein kinase), cell cycle checkpoint proteins (CHEK1, CHEK2, p21), apoptotic proteins (BAX, DAXX), etc. [14]. Under physiological conditions, this leads to resumption of the normal cell cycle and the maintenance of homeostasis. Impaired cell's DNA damage response leads to genetic instability and promotes the accumulation of aberrations and tumor growth.

The *PPM1D* gene regulates three DNA damage repair pathways: double-strand break repair, nucleotide excision repair, and base excision repair [14]. The repair processes required to correct damaged DNA before replication are integral to maintaining genome integrity, preventing mutations, and ensuring normal cell function.

In a model of DNA double-strand breaks induced by etoposide, Gräf et al. [15] identified more than 35 putative PPM1D substrates in human osteosarcoma U2OS cells and another 21 in colorectal cancer HCT116 cells; these substrates were phosphorylated at serine and then glutamine residues. Many PPM1D substrates were associated with chromatin. It was demonstrated that upon acute induction of double-strand breaks, PPM1D dephosphorylated proteins responding to DNA double-strand breaks, primarily ATM, but also ATR and DNA-PK. Thus, the authors concluded that PPM1D inhibited ATM signaling at two levels: by dephosphorylating ATM itself and its substrates (Fig. 1) [15].

Overexpression of *PPM1D* has been shown to suppress nucleotide excision repair. In human osteosarcoma U2OS cells transfected with the human or mouse *PPM1D* gene, nucleotide excision repair was reduced by more than 30% compared to cells transfected with the empty vector. In conditions of ultraviolet DNA damage, PPM1D inhibited the repair proteins XPA (xeroderma pigmentosum complementation group A) and XPC (xeroderma pigmentosum complementation group C), controlled by ATM/ATR kinases. Overexpression of *PPM1D* inhibited repair of cyclobutane-pyrimidine dimers after ultraviolet irradiation [16]. Suppression of base excision repair by PPM1D is associated with inactivation of the nuclear isoform of uracil DNA glycosylase, an enzyme that removes uracil bases that appear in DNA due to cytosine deamination (Fig. 2) [17].

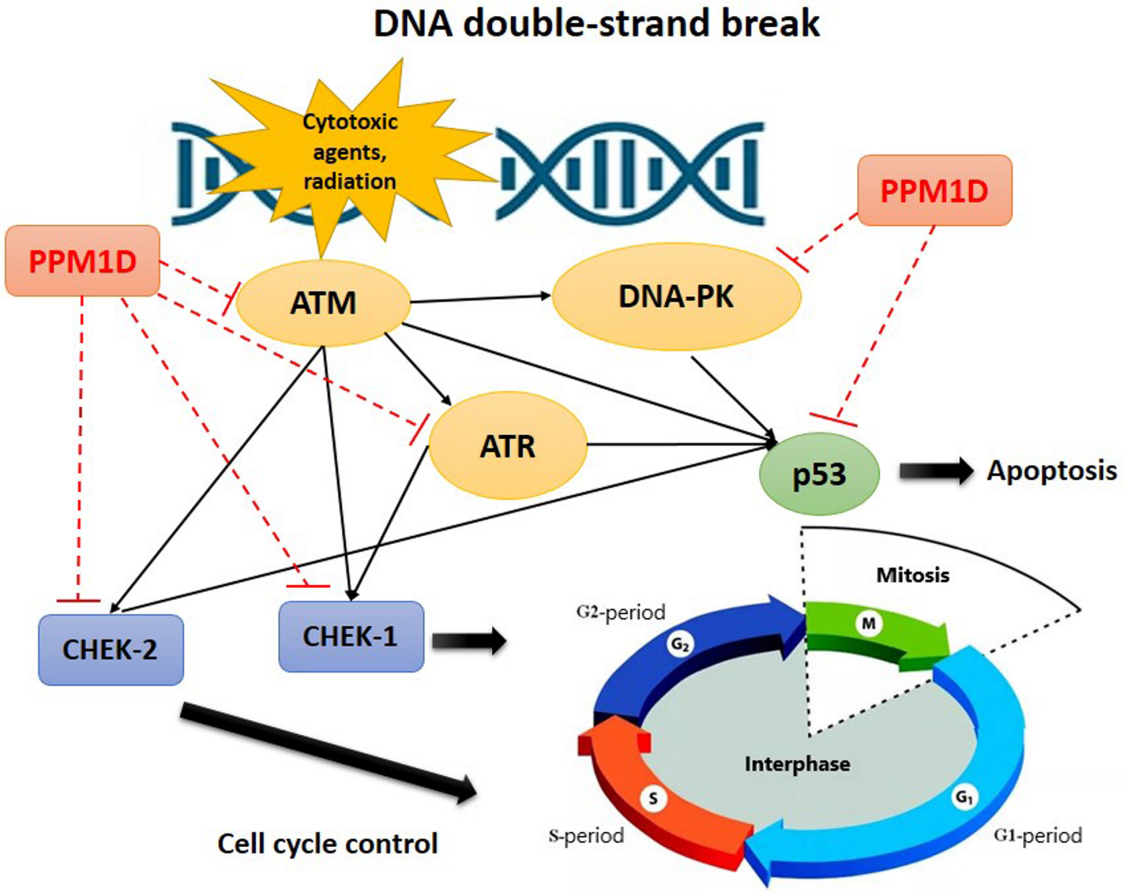

Figure 1. The role of PPM1D in DNA double-strand break repair. Dashed lines show inactivation of PPM1D substrates by dephosphorylation, IR – ionizing radiation.

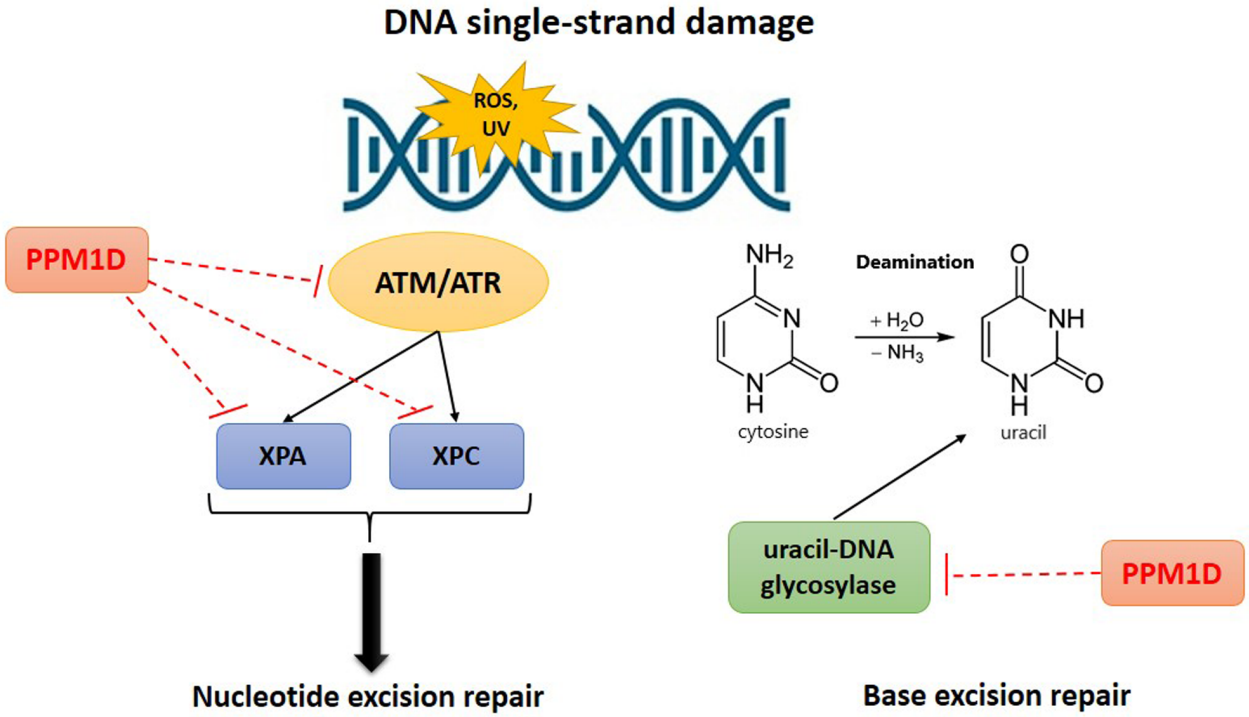

Figure 2. The role of PPM1D in nucleotide excision repair and base excision repair. Dashed lines show inactivation of PPM1D substrates by dephosphorylation, ROS – reactive oxygen species, UV – ultraviolet irradiation.

Other mechanisms of the oncogenic effect of the *PPM1D* gene are associated with its effect on the regulation of the cell cycle and apoptosis. One of the key moments in these processes is the change of p53 protein activity; its mutations lead to disrupted regulation of most important cellular pathways and contribute to neoplastic cell transformation.

It is known that p53 activates PPM1D protein synthesis at the transcription level [14]. In turn, PPM1D dephosphorylates p53 at Ser15 and Ser37, which is critically important post-translational modification needed to stimulate transactivation of p53-sensitive promoters [18].

PPM1D also indirectly inhibits p53 by dephosphorylation of upstream kinases — ATM, ATR [15], as well as CHEK1 (checkpoint kinase 1) and CHEK2 (checkpoint kinase 2) [19], involved in cell cycle control. Inhibition of PPM1D by arsenic trioxide enhances CHEK2/p53-mediated apoptosis [20]. Knockdown of PPM1D promotes activation of the p38 MAPK/p53 signaling pathway in acute myeloid leukemia thus suppressing cell proliferation and promoting apoptosis [21].

PPM1D dephosphorylates E3 ubiquitin ligase, which targets p53 for proteasomal degradation [22]. In a study by Lee et al. [23], downregulation of the tumor suppressor p53 has been found in several types of cancer cells (colon cancer HCT116 cells, non-small cell lung cancer A549 and H460 cells); this is often accompanied by increased activity of PPM1D phosphatase and E3 ubiquitin ligase. The cyclin-dependent kinase inhibitor $p21^{WAF1/CIP1}$ promoted binding of p53 and ubiquitin ligase, and also reduced the stability of the p53 protein through the p53 interaction with PPM1D. Moreover, p21 itself bound on PPM1D with p53/p21/PPM1D trimeric complex formation [23].

PPM1D plays an important role in tumor phenotype maintenance. PPM1D regulates the PI3K/Akt signaling pathway, which is involved in the survival and growth of tumor cells by controlling the activity of tumor suppressor proteins, including p53 [24]. PPM1D promotes tumor cell proliferation through p21 and mTOR (mechanistic target of rapamycin or mammalian target of rapamycin), which are downstream targets of p53, as well as through NF-κB, a positive transcriptional regulator of the PPM1D protein phosphatase [7].

The main mechanisms of PPM1D influence on oncogenesis are shown in Figure 3.

2. BREAST CANCER

There is a relationship between the *PPM1D* gene and breast cancer [1]. Analysis of tumor material from 245 patients with invasive breast cancer who underwent surgery followed by adjuvant anthracycline-based chemotherapy showed overexpression and amplification of *PPM1D* in 25% and 6% of cases, respectively [25]. In turn, *PPM1D* amplification is associated with overexpression of *ERBB2*, which encodes the human epidermal growth factor receptor 2 (HER2) [25]. *ERBB2* overexpression is observed in approximately 20% of invasive

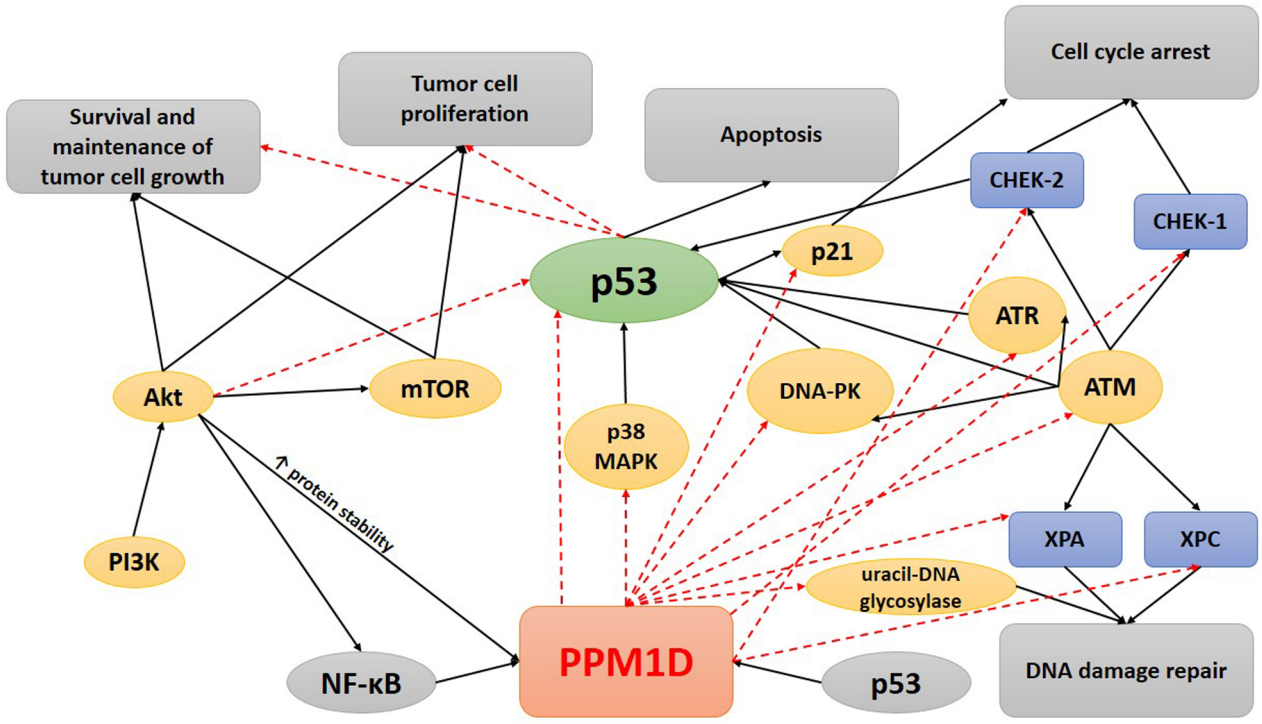

Figure 3. The role of PPM1D in oncogenesis. Dashed lines show the inactivation of PPM1D substrates by dephosphorylation.

breast cancers and is associated with a poor prognosis in the absence of specialized therapy. HER2-positive breast cancer tends to have a more aggressive course compared to other types of breast cancer and is less responsive to hormonal therapy [26]. HER2 has been shown to promote early metastasis in breast cancer via suppression of the p38-MK2-Hsp27 signaling pathway. p38 MAPK and the p38-MK2-Hsp27 signaling pathway are also affected by PPM1D. Inhibition of this phosphatase results in suppression of tumor cell dissemination both *in vitro* and in mouse models of HER2-positive breast cancer [27].

PPM1D phosphatase inactivation inhibits breast tumorigenesis via activation of the p53 and p16(Ink4a)-p19(Arf) signaling pathways with subsequent signaling to the p38 MAPK mitogen-activated protein kinase, which suppresses *in vitro* transformation of mouse embryonic fibroblasts by oncogenes. In mice bearing murine mammary tumor virus (MMTV) oncogenes driven by the *ERBB2* promoter, *in vivo* deletion of PPM1D impaired mammary carcinogenesis. At the same time, a decrease in p16 and p19 expression due to methylation-induced gene silencing or p38 MAPK inactivation correlated with the tumor growth process [28]. The study by Inoue et al. [8] has shown that *PPMID* expression in breast invasive ductal carcinoma may be independent of p53 regulation, and the tumor itself is capable of malignant growth without p53 mutation. The authors found that PPM1D protein levels can be regulated by *PPM1D* amplification independent of the *TP53* gene status. Moreover, an increase in the nuclear protein level of PPM1D and a decrease in the level of the intracellular protein-inhibitor of cyclin-dependent kinase 1A p21 were associated with the worst prognosis of the disease and suggested a loss of p53 function [8].

In a cohort study conducted by Canevari et al. [29], it was demonstrated that activation of the *B3GNT7*, *PPM1D*, *TNKS2*, *PHB*, and *GTSE1* genes in patients with invasive ductal breast cancer caused the development of distant metastases within 5 years after surgery [29]. In a study using next-generation sequencing (NGS) technology, it was found that mutation of the *PPM1D* gene led to an increased risk of bilateral breast cancer. The results showed that in 719 patients with breast cancer, the mutation rate was less than 0.3%, but deletions in exon 6 prevailed. These mutations, which may have arisen as a result of chemotherapy, are critical in the early development of the tumor and account for 90% of cases of hereditary breast cancer [30].

3. OVARIAN AND PROSTATE TUMORS

PM1D gene mutations are associated with an increased risk of ovarian cancer [31]. Akbari et al. [31] compared the frequency of PPM1D mutations in leukocytes of 1295 patients with ovarian cancer and 834 control group women. The authors found a truncating mutation (a mutation leading to the synthesis of a shorter version of the protein) in 20 patients compared to 1 control woman (odds ratio [OR] = 13.07; 95% confidence interval [CI] = 1.75 to 97.55; $p<0.001$). Moreover, the mortality rate of patients during

12 years of observation was higher in the case of mutations in the *PPM1D* gene than in those without it (OR = 2.02; 95% CI = 1.21 to 3.39; p = 0.007). In addition, three out of 20 women with a history of *PPM1D* mutation had breast cancer (OR = 6.69; 95% CI = 1.86 to 24.11; p = 0.007) [31]. This suggests that mosaic PPM1D mutations increase the risk of breast and ovarian cancer in women without an aggravated family history.

It was shown that 0.37% (12 out of 3236) of patients with epithelial ovarian cancer had mosaic *PPM1D* mutations in lymphocyte DNA [32]. It was suggested that the presence of mutations in the *PPM1D* gene could be associated with chemotherapy of patients [32]. Similar conclusions were made by Swisher et al. [6]; they performed massively parallel sequencing to quantify mutations in peripheral blood mononuclear cells in 686 women with primary (n=412, including 326 patients without chemotherapy and 86 treated) and recurrent ovarian cancer (n=274). Mosaic mutations in *PPM1D* were statistically significantly more common in patients who received chemotherapy (p<0.001). The presence of *PPM1D* mutations in patients with recurrent ovarian cancer was also associated with the number of previous chemotherapy regimens: in 21 of 138 women (15.2%) after 1 regimen versus 35 of 130 women (26.9%) after 2 regimens (p = 0.02). For further evaluation of the impact of chemotherapy on the presence or frequency of somatic mosaic mutations, deep sequencing of paired mononuclear cell samples was performed using biomaterial of 13 patients at diagnosis and then at relapse. In the first case, the studied mutations in *PPM1D* were either not detected or were present in significantly lower quantities than in the second. However, it should be noted that in 3 patients, *PPM1D* mutations were observed in a high proportion of reads (30–37%) at diagnosis and did not increase after chemotherapy [6].

Increased expression and amplification of the *PPM1D* gene directly correlated with a poor prognosis in hormone-dependent malignancies. Treatment of human breast carcinoma ZR-75-1 cells with different concentrations of estradiol (E2) (1 nM, 10 nM, 100 nM) for 4 h, 8 h, 16 h, and 24 h, *PPM1D* expression peaked at 16 h (10 nM E2). Immunoprecipitation assay confirmed direct binding of estrogen receptor (ER) α to the *PPM1D* promoter [33].

The protein product of the *PPM1D* gene, magnesium-dependent protein phosphatase 1-delta, plays an important role in increasing the resistance of ovarian and cervical cancer cells to drug therapy. Resistance to cisplatin is associated with activation of the oncogenic serine/threonine kinase Akt, which regulates the level of PPM1D protein and increases its content in chemorefractory cells. Next, PPM1D inactivates the p53 protein through its dephosphorylation (Ser 15), which significantly reduces its pro-apoptotic activity [34].

At the same time, it was found that the PPM1D protein, through a p53-independent signaling pathway, suppressed invasion, migration, epithelial-mesenchymal transition and metastasis in serous ovarian carcinoma through negative regulation of the protein kinases p-ATM (phosphorylated ATM — ataxia telangiectasia mutated, phosphorylated protein), p-Akt (phosphorylated protein kinase B), and zinc finger protein Snail [35].

Jiao et al. [36] have shown that PPM1D is actively synthesized in prostate cancer tissues and cell lines. The PPM1D level in prostate cancer tissues obtained after radical prostatectomy was significantly higher than in benign prostatic hyperplasia tissue. In addition, PPM1D synthesis directly correlated with the Gleason score (p = 0.022), T stage (p = 0.015), and the presence of lymph node metastases (p = 0.016) [36]. The presence of increased PPM1D expression is associated with a high risk of recurrence and low survival [36].

An association of mutations in the *PPM1D* gene with prostate cancer has been recognized [37]. Assessment of their prevalence in leukocytes by sequencing the coding region of exon 6 in 462 patients with early and/or familial/hereditary prostate cancer, revealed the presence of truncated genetic variants of *PPM1D* and nonsynonymous mutations in germ cells [37]. In addition, the same missense variant (c.1607G>A, p.Arg536Lys), which was absent in men from the control group, was detected in three patients [37]. Hereditary mutations and their association with clinical features and treatment response in patients with early-onset prostate cancer were studied. A total of 62 germline mutations in 45 genes were confirmed in 22 patients, one of which was *PPM1D* [13]. The incidence rate was 8.3% (2/24) [13].

4. ESOPHAGEAL, STOMACH, AND INTESTINAL CANCERS

Good evidence exists that *PPM1D* is involved in the development and progression of a wide range of neoplasms, including gastrointestinal tract tumors [10, 38]. *PPM1D* overexpression is associated with a poor prognosis in esophageal squamous cell carcinoma [10]. An immunohistochemical study has shown that among 101 patients with this disease showed increased formation of the PPM1D protein in tumor tissues occurred in 70 out of 101 cases (69.3%). In addition, the PPM1D level was directly associated with the TNM stage (International Classification of Malignant Neoplasms: T — size and extent of the primary tumor, N — lymph node involvement, M — presence of metastases), tumor differentiation and the presence of lymph node metastases (p<0.01), but was not associated with the gender and age of patients. Notably, *PPM1D* expression in patients with metastatic esophageal squamous cell carcinoma

was significantly higher than in patients with the non-metastatic form ($p<0.01$). Follow-up data showed that the 5-year survival rate of patients with *PPM1D* overexpression in tumors was less than 20% [10]. Smoking and alcohol consumption are predisposing factors for *PPM1D* gene mutations. In addition, the number of mutations of this gene demonstrated age-dependent increase: people over 76 years old were more prone to develop esophageal cancer [38].

Immunohistochemical data obtained in 800 patients with gastric cancer before chemotherapy showed that PPM1D levels were significantly higher in tumor cells than in adjacent normal tissue (48% vs. 9.5%; $p<0.001$). There was a direct association between PPM1D overexpression and lymph node metastases, distant metastases, and vascular invasion. Patients with PPM1D overexpression had significantly lower 5-year survival rates compared to the group of patients without PPM1D expression (41% vs. 72%; $p = 0.0012$). These results suggest that PPM1D overexpression may be an indicator of poor prognosis in patients with gastric cancer [39]. A relationship was demonstrated between PPM1D formation and tumor size ($p = 0.0497$), as well as with the process of CHEK2 dephosphorylation ($p = 0.0213$), a serine-threonine kinase involved in DNA repair. Activation of PPM1D at the protein level was detected in MKN-74 gastric cancer cells exposed to ionizing radiation. In this case, the mechanism of cell cycle regulation was disrupted due to CHEK2 inhibition. However, the proteasome inhibitor Z-Leu-Leu-Leu (ZLLL) effectively increased the level of PPM1D both in the presence and absence of ionizing radiation, thus suggesting posttranslational modulation of PPM1D protein expression [40].

An increase in PPM1D mRNA and protein expression is also associated with the development of colorectal cancer [41]. PPM1D levels were significantly higher in colorectal cancer tissues (85% (102/120)) compared to normal surrounding tissues (30% (36/120)) ($p<0.05$). A similar trend was observed for PPM1D mRNA expression (1.113±0.018 vs. 0.658±0.036, respectively, $p<0.05$). PPM1D protein levels were not associated with age, gender, or tumor site, but were associated with lymph node metastases, Dukes' stage, and liver metastases [41].

In vitro study showed that in HCT15 colorectal cancer cells, PPM1D overexpression resulted in suppression of CHEK2 activity in the G2/M phase of the cell cycle upon DNA damage and promoted malignant progression of cancer [42]. Bai et al. [7] found that the transcription factor NF-κB served as a positive regulator of PPM1D mRNA formation in colorectal cancer cells. In turn, PPM1D promoted colorectal cancer cell proliferation through p21 and mTOR proteins, the p53 downstream targets [7]. The study by Wang et al. [43] demonstrated another pathway of PPM1D influence on colorectal cancer cell proliferation and migration. This protein interacted with KPNA2 (karyopherin subunit alpha 2), possibly in a p53-dependent manner, via the AKT/GSK-3β signaling pathway [43].

5. LIVER AND PANCREATIC CANCERS

Increased PPM1D mRNA expression serves as a prognostic marker for hepatocellular carcinoma [44]. The level of PPM1D mRNA and protein was statistically significantly higher in tumor tissue compared to normal tissue. Moreover, PPM1D expression in hepatocellular carcinoma is associated with family history, tumor size, alpha-fetoprotein (α-FP) level, and cancer stage. The three-year survival rate of patients with high PPM1D mRNA expression is 0%, while in patients with low expression it is close to 40% [44]. These results suggest that high PPM1D mRNA expression is associated with poor clinical prognosis [45]. This pattern was confirmed in the study by Yu et al. [12]. In addition, the authors found that high PPM1D mRNA expression was associated with tumor cell infiltration by monocytes, tumor-associated M1 and M2 macrophages, dendritic cells, T helpers, and regulatory T lymphocytes [12].

The *PPM1D* gene and its protein product also play a role in the development and pathogenesis of pancreatic cancer [45]. PPM1D is overexpressed in human pancreatic cancer tissues and cell lines MIA PaCa-2 and PANC-1, and the protein level is directly related to tumor growth and metastasis. PPM1D promotes tumor cell migration and invasion through activation of the Wnt/β-catenin signaling pathway and suppression of apoptosis-stimulating p53 protein 2 (ASPP2); this results in decreased ASPP2 levels in pancreatic cancer tissues. In addition, PPM1D suppresses tumor cell apoptosis through inhibition of the p38 MAPK/p53 pathway due to the dephosphorylation of p38 MAPK. PPM1D promotes pancreatic cancer growth *in vivo* [45].

6. HEMATOLOGICAL TUMORS

Overexpression of the *PPM1D* gene is associated with most hematological malignancies [9, 46, 47]. In the study by Silver et al. [9], 77 specific mutations characteristic of hematological tumors were found in 2728 people. Among them, *PPM1D* mutations were associated with myelodysplastic syndrome, leukemia, and lymphoma [9].

The majority of them, identified in blood and bone marrow samples of patients with hematological malignancies, were located in exon 6. It should be noted that mutations arise as a result of tumor treatment by agents, including platinum drugs, topoisomerase I and II inhibitors, and radiation

therapy [46]. Myelodysplastic syndrome was found to be associated with overexpression of *PPM1D*, as well as with mutations in *PPM1D* and *TP53* that arose after chemotherapy [47]. Mutations in the *PPM1D* gene were found in 20% of patients with acute myeloid leukemia and myelodysplastic syndrome that developed after therapy with alkylating agents [4]. Cell lines overexpressing *PPM1D* proliferate and outcompete normal cells after exposure to cytotoxic agents that damage DNA. This effect is mediated primarily by increased resistance to apoptosis. Moreover, heterozygous hematopoietic cells with mutant *PPM1D* outperformed their wild-type counterparts *in vivo* after exposure to cisplatin and doxorubicin [4].

PPM1D expression was found to be increased in the human promyelocytic leukemia cell line HL-60 upon induction of differentiation into neutrophils [48]. A PPM1D inhibitor could increase the proportion of HL-60 cells that transformed into neutrophils and also delayed cells in the G1 phase of the cell cycle. These results suggest that PPM1D may be a potential therapeutic target in diseases associated with hematopoiesis disorders [48].

Transgenic mice overexpressing *PPM1D* had tumors phenotypically and genetically similar to tumors in mice with dysfunctional p53 protein [3]. T cell lymphoblastic lymphoma was the most common malignancy observed in animals (55%), followed by adenocarcinomas (24%), leukemias (12%), and other solid tumors, including neuroblastoma [3]. The development of T cell lymphomas in mice overexpressing PPM1D was associated with a deletion of the tumor suppressor gene *Pten* (encodes the protein tyrosine phosphatase enzyme PTEN) and impaired p53 function. In addition, *PPM1D* transgenic mice frequently have mutations in the human transmembrane receptor protein Notch1 gene [3]; they are periodically observed in T-cell acute lymphoblastic lymphoma [3]. A truncated variant of the *PPM1D* gene reduced the self-renewal of hematopoietic stem cells and promoted the development of aggressive acute myeloid leukemia after exposure to ionizing radiation [49].

7. OTHER TYPES OF TUMORS

The *PPM1D* gene plays an important role in the development and progression of non-small cell lung cancer [51]. Kaplan-Meier survival analysis and proportional hazards (Cox regression) models showed that PPM1D mRNA expression was significantly increased in tumor tissue compared to healthy tissues ($p<0.001$) and was associated with the grade of malignancy ($p = 0.006$), size ($p = 0.017$), clinical stage ($p = 0.001$), and lymph node metastasis ($p = 0.002$). PPM1D overexpression is associated with poor prognosis in patients with non-small cell lung cancer ($p<0.001$) [50]. The presence of the PPM1D protein in non-small cell lung cancer tissues was also detected in 63.3% (38/60) and its absence in normal lung tissue (0/20; $p<0.01$). In addition, increased PPM1D formation was associated with tumor size and differentiation ($p = 0.008$ and $p = 0.03$, respectively). An inverse correlation has been found between PPM1D expression and the expression levels of p38MAPK, p53, and p16 ($r = -0.284$, -0.352, and -0.348, respectively), which control apoptosis and the cell cycle [51]. Another signaling pathway involved in the development of non-small cell lung cancer is the Wip1-p38-MK2-HSP27 cascade [52].

In 113 pediatric thyroid tissue samples (30 benign and 83 malignant neoplasms), mutations in various genes, including *PPM1D*, were identified by sequencing [53]. *PPM1D* overexpression was confirmed in clinical papillary thyroid carcinoma tissue samples [11]. Knockdown of *PPM1D* in thyroid cancer cell lines suppressed proliferation, migration, and invasion, but promoted cell apoptosis [11]. The protein levels of phosphorylated p38 mitogen-activated protein kinase (MAPK), p53, and Bax were increased in *PPM1D* knockdown cells, while inhibition of p38 phosphorylation restored cell migration, proliferation, and apoptosis. Thus, the PPM1D protein is involved in the regulation of the p38 MAPK and p53 signaling pathway, contributing to the progression of thyroid cancer [11].

CONCLUSIONS

Amplification, overexpression, or mutations of the *PPM1D* gene can stimulate uncontrolled cell growth, thereby leading to tumor malignancy. The *PPM1D* gene is an attractive therapeutic target due to its prevalence in many types of cancer and its oncogenic potential. Screening of patients and detection of *PPM1D* mutations may be relevant in cancer patients before planning cytostatic treatment and may have implications for the selection of new targeted agents.

FUNDING

The authors declare no external sources of funding.

COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any research involving humans or the use of animals as objects.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Received: 10. 07. 2024.
Revised: 07. 09. 2024.
Accepted: 19. 09. 2024.

РОЛЬ ГЕНА *PPM1D* В ПАТОГЕНЕЗЕ ОПУХОЛЕЙ

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Ген *PPM1D* и его белковый продукт (серин-треониновая протеинфосфатаза, PPM1D или Wip1) принимают участие в регуляции ответов клетки на повреждение ДНК, контроле клеточного цикла и репарации. Амплификация, сверхэкспрессия или мутации гена *PPM1D* приводят к изменению реакции клетки на воздействие стрессовых факторов и генетической нестабильности. Нарушаются процессы восстановления двухцепочечных разрывов, эксцизионная репарация нуклеотидов и эксцизионное восстановление азотистых оснований, клеточный цикл и апоптоз. PPM1D путём дефосфорилирования инактивирует белок p53, белки, реагирующие на нарушение целостности цепей ДНК, белки контрольных точек клеточного цикла, апоптотические белки. Это способствует развитию опухоли, её росту и сохранению опухолевого фенотипа. В обзоре представлены данные о роли гена *PPM1D* в формировании и поддержании различных онкологических процессов — опухолей молочных желез, яичников, предстательной железы, пищевода, желудка, кишечника, печени и поджелудочной железы, гемобластозов и других.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: ген *PPM1D*; Mg^{2+}/Mn^{2+}-зависимая протеинфосфатаза 1D; опухолевые заболевания

Финансирование. Авторы заявляют об отсутствии внешних источников финансирования.

Поступила в редакцию: 10.07.2024; после доработки: 07.09.2024; принята к печати: 19.09.2024.