Role of wild-type p53-induced phosphatase 1 in cancer (Review)

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Received August 5, 2015; Accepted December 16, 2016

DOI: 10.3892/ol.2017.6685

Abstract. Wild-type p53-induced phosphatase (Wip1) is a member of the protein phosphatase type 2C family and is an established oncogene due to its dephosphorylation of several tumor suppressors and negative control of the DNA damage response system. It has been reported to dephosphorylate p53, ataxia telangiectasia mutated, checkpoint kinase 1 and p38 mitogen activated protein kinases, forming negative feedback loops to inhibit apoptosis and cell cycle arrest. Wip1 serves a major role in tumorigenesis, progression, invasion, distant metastasis and apoptosis in various types of human cancer. Therefore, it may be a potential biomarker and therapeutic target in the diagnosis and treatment of cancer. Furthermore, previous evidence has revealed a new role for Wip1 in the regulation of chemotherapy resistance. In the present review, the current knowledge on the role of Wip1 in cancer is discussed, as well as its potential as a novel target for cancer treatment and its function in chemotherapy resistance.

Contents

1. Introduction

Genetic stability ensures the inheritance of the correct genetic information and preserves the function of normal physiological processes. However, cells living in a constantly changing environment are influenced by various stresses, which may alter DNA sequences and induce DNA damage (1). During the evolution of genes, cells have developed a DNA damage response system including cell cycle checkpoints, senescence and apoptosis (2). If that system is not able to repair DNA damage, DNA replication, transcription and recombination may be altered, leading to gene mutation and chromosomal rearrangements or loss, which promotes the development of cancer (3). Wild-type p53-induced phosphatase 1 (Wipl) is an oncogene that negatively regulates the DNA damage response system and serves a role in tumorigenesis, therapy and prognosis in various types of human cancer (4).

Wip1 was originally identified as a target protein in the p53-dependent response to ionizing radiation (5). Wip1 is a serine/threonine protein phosphatase that is encoded by the protein phosphatase magnesium-dependent 1 δ (gene, *PPM1D*) in the 17q22/q24 human chromosomal region, and is a member of the protein phosphatase type 2C (PP2C) family (6). It is 605 amino acids long and consists of a central phosphatase catalytic domain and a non-functional region (7). Wip1 is a monomeric enzyme, similar to other members of the PP2C family, the dephosphorylation of which requires catalysis by bivalent cations, including magnesium and manganese ions (5).

Previous studies have revealed that Wip1 dephosphorylates several key DNA damage response proteins, including p53, ataxia telangiectasia mutated, checkpoint kinase (Chk) 1, Chk2, murine double minute 2 (Mdm2) and p38 mitogen activated protein kinases (p38 MAPK), exercising negative feedback loops that lead to cell cycle arrest, increased tumorigenesis and the inhibition of apoptosis (Fig. 1) (8-12). Among these loops, negative regulation of p53 is vital. *TP53* may be the most important tumor suppressor gene, the mutation or depletion of which is present in ~50% of all human tumors (13). However, Wip1 is not only able to directly dephosphorylate p53 protein at serine 15, but also indirectly inactivate p53 protein through p38 MAPK and Mdm2 (8,14,15), which attenuates the p53 function. Furthermore, dephosphorylation of p53 by Wip1 induces inappropriate re-initiation of mitosis and uncontrolled polyploid progression that may be a potential underlying mechanism of tumor progression (14). Previous studies have identified additional Wip1 targets, including murine double minute X, xeroderma pigmentosum complementation group A and C, nuclear factor kappa B (NF-κB) and DNA methylation, resulting in the promotion of proliferation, inhibition of inflammation and nucleotide excision repair (9,16-19). On the other hand, cytotoxic drugs, including cisplatin and doxorubicin,

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Key words: wild-type p53-induced phosphatase, protein phosphatase magnesium-dependent 1 δ, oncogene, cancer

are able to induce senescence and apoptosis in tumor cells, an effect that is dependent on p53 signaling pathway *in vitro* and *in vivo* (20,21). This indicates that Wip1 phosphatase activity may mediate the cytotoxicity of chemotherapeutic agents via targeting p53. The present review summarizes the regulatory mechanisms and functions of Wip1 as an oncogene in various types of cancer. In addition, the potential role of Wip1 as a tumor biomarker and therapeutic target in these cancer types was investigated.

2. Wip1 in breast cancer

The role of Wip1 in breast cancer is the most studied compared with all other types of human cancer (22). In 28% of primary breast cancer cases, the amplification of the 17q22/q24 chromosomal region has been demonstrated through cytogenetic analysis, a phenomenon that is more common in high-grade breast cancer (23). In addition, a number of studies have identified that the overexpression of Wip1 negatively regulates the p53, p38 MAPK and p16 signaling pathways, which may lead to breast cancer tumorigenesis, proliferation and poor prognosis (24,25). Previous reports have demonstrated that the upregulation of Wip1 may reverse the induction of apoptosis by microRNA (miRNA/miR)-16 and miRNA-34a, which are tumor suppressors of breast cancer (26,27). Therefore, high Wip1 expression levels may be a predisposing factor for breast cancer. Spike and Wahl (28) revealed that Wip1 regulated chemosensitivity by controlling the p53 signaling pathway. Downregulation of Wip1 enhanced the chemosensitivity of breast cancer to adriamycin via targeting wild-type p53 and reducing cell growth and cell survival; however, these effects were not present in cell lines with mutant-type p53 (Table I; Fig. 1) (29,30). Although the occurrence of breast cancer is regulated by various oncogenes, including ErbB2, Wnt1 and breast cancer susceptibility protein type 1 and 2 (22), these results suggested that Wip1 may be considered as a potential biomarker for tumorigenesis and index of prognosis in patients with breast cancer. In addition, decreasing its expression levels may have a therapeutic effect during the chemotherapy of breast cancer with wild-type p53.

3. Wip1 in childhood glioma

Overexpression of Wip1 and gain-of-function mutations of *PPM1D* have been detected in numerous types of pediatric cancer, including glioma (31), neuroblastoma (32) and medulloblastoma (33).

Wip1 in glioma. Zhang *et al* (34) identified that carboxy terminal truncating mutations of *PPM1D* occur in 37.5% of glioma cases, and these gain-of-function *PPM1D* mutants suppressed phosphorylation of Chk2 at threonine 68 and p53 at serine 15, resulting in dysfunction of the DNA damage response network (Table I) (34). This result may be associated with predisposition to and the tumorigenesis of glioma.

Wip1 in neuroblastoma. Overexpression of Wip1 in neuroblastoma may repress p53 function by two signaling pathways, one is the Wip1-p53 pathway, and the other is the Wip1-Mdm2-p53 pathway (35), resulting in tumorigenesis. In addition, a previous report demonstrated that Wip1 was significantly overexpressed in 56% of cancer tissues, and promoted tumor progression to a higher stage, poor prognosis and chemotherapy resistance (Table I) (32). Therefore, these data suggest that the inhibition of Wip1 expression levels may be a potential therapeutic target. GSK2830371 is a Wip1 selective antagonist able to significantly inhibit 96.5% of Wip1 activity in neuroblastoma cell lines, which promotes p53 function and apoptotic responses (32). Furthermore, GSK2830371 had a synergistic effect on the antiproliferative properties of the chemotherapeutic agents adriamycin and carboplatin (32).

Wip1 in medulloblastoma. Previous studies have reported that the amplification and overexpression of Wip1 occurred in 64% of human medulloblastomas, and it is more common in highly aggressive medulloblastomas (36,37). Buss *et al* (37) also identified that high levels of Wip1 expression were associated with increased expression of Mdm2, which may be an underlying mechanism of promoting medulloblastoma growth via targeting p53 (37). In addition, Pfister *et al* (38) demonstrated that the upregulation of Wip1 expression was associated with poor prognosis in medulloblastoma (Table I) (38). Furthermore, the results of a previous study have revealed that Wip1 is able to promote the progression and invasion of aggressive medulloblastoma by regulating C-X-C chemokine receptor type 4 and protein kinase B (Akt; Fig. 1) (33). These data suggest that Wip1 serves an important role in tumorigenesis and cancer progression and may be an indicator for the prognosis of medulloblastoma.

In pediatric types of cancer, overexpression of Wip1 contributes to a number of malignant characteristics, including tumor progression, aggressive phenotype and poor prognosis (32,34,37). In addition, a Wip1 inhibitor may be a promising novel candidate for targeted therapeutic strategies for these severe tumors.

4. Wip1 in ovarian clear cell carcinoma

A previous study identified that the amplification and overexpression of the *PPM1D* gene occurred in ≥40% of cases of ovarian clear cell carcinoma, which is higher compared with other ovarian tumor subtypes (39). A gene knockdown study revealed the viability of ovarian clear cell carcinoma cell lines depended on the phosphatase activity of Wip1, indicating that the Wip1 and *PPM1D* genes may be drivers of ovarian clear cell carcinoma (40). Another previous study reported that Wip1 is able to negatively regulate the Chk1 and p53 signaling pathway, resulting in tumorigenesis (41). However, cisplatin mediates tumor cell DNA damage and apoptotic function through these signaling pathways, suggesting that Wip1 may be responsible for the cisplatin resistance of ovarian clear cell carcinoma (41). In addition, a recent study demonstrated that Akt confers cisplatin resistance in part through the regulation of *PPM1D* protein stability, preventing its proteasomal degradation and consequently increasing its half-life (Table I) (42). Accumulating evidence has indicated that Wip1 is directly associated with tumor cell survival and chemoresistance (43). Due to its late diagnosis and the development of chemoresistance, ovarian clear cell carcinoma is characterized by the poorest prognosis among ovarian types of cancer (44).

Table I. Roles of Wip1 in various types of cancer.

Cancer type	Overexpression/ mutation level, %	Targets	Tumorigenesis	Differentiation	Chemoresistance	Prognosis
Breast	28	p53, p16, p38 MAPK	+	+	+	+
Glioma	37.5	Chk2, p53	+	ND	ND	ND
Neuroblastoma	56	Mdm2, p53	+	+	+	+
Medulloblastoma	64	Mdm2, p53, CXCR4, AKT	+	+	ND	+
Ovarian clear cell carcinoma	40	Chk1, p53	+	ND	+	+
Liver	65	P53	+	+	ND	+
Bladder	ND	P53	+	ND	+	ND
Kidney	67	ND	+	+	ND	+
Nasopharyngeal carcinoma	69	ND	+	+	ND	+

Wip1, wild-type p53-induced phosphatase 1; P38 MAPK, p38 mitogen activated protein kinases; Chk1, checkpoint kinase 1; Chk2, checkpoint kinase 2; Mdm2, murine double minute 2; CXCR4, C-X-C chemokine receptor type 4; AKT, protein kinase B; +, positive correlation; ND, no data available.

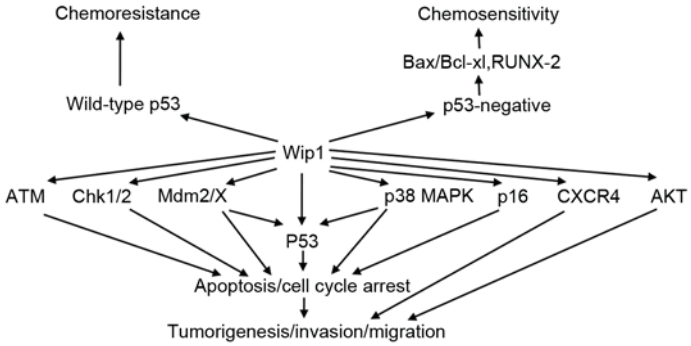

Figure 1. Targets and functional consequences of Wip1 signaling. Wip1 directly dephosphorylates target proteins including ATM, Chk1/2, Mdm2/X, p53, p38 MAPK, p16, CXCR4 and AKT, resulting in inhibition of apoptosis and cell cycle arrest, which promotes tumorigenesis, invasion and migration. Wip1 leads to chemoresistance in tumor cell with wild-type p53. However, Wip1 increases chemosensitivity in p53-negative tumor cells by regulating Bax/Bcl-xl and RUNX-2. P38 MAPK, p38 mitogen activated protein kinases; Chk1/2, checkpoint kinase 1/2; Mdm2/X, murine double minute 2/X; CXCR4, C-X-C chemokine receptor type 4; AKT, protein kinase B; Bax, B-cell lymphoma-2 associated X protein; Bcl-xl, B-cell lymphoma-xl; RUNX-2, runt-related transcription factor-2; ATM, ataxia telangiectasia mutated; Wip1, wild-type p53-induced phosphatase 1.

Therefore, Wip1 expression levels may be a biomarker of diagnosis and index of prognosis. In addition, targeting Wip1 may improve therapeutic outcomes in ovarian clear cell carcinoma.

5. Wip1 in liver cancer

miR-29c belongs to the miR-29 family, which are established tumor suppressors (45). A previous study demonstrated that miR-29c is downregulated in liver cancer and may affect the apoptosis, tumorigenesis, and prognosis of tumor cells (46). Previous studies have revealed that the overexpression of miR-29c inhibits cancer cell proliferation and metastasis, as well as inducing cell cycle arrest (47,48). Wip1 was also revealed to be significantly upregulated in hepatocellular carcinoma and may contribute to the development of this cancer (49). Wang *et al* (49) were the first to investigate the association between Wip1 and miR-29c, revealing an inverse correlation. In addition, the overexpression of Wip1 may suppress miR-29c-induced apoptosis and cell cycle arrest via dephosphorylating wild-type p53 (49). Although mutations of *p53* occur in ~50% of human cancer cases, this rate is <30% for liver cancer cases, the majority of which express *wild-type p53* (50). These findings suggest that Wip1 and miR-29c serve roles in the development of hepatocellular carcinoma. Furthermore, a previous study demonstrated that Wip1 was overexpressed in hepatocellular carcinoma tissues, compared with in non-cancerous tissues, and high Wip1 expression levels were associated with a more advanced tumor-node-metastasis stage, as well as being a significantly independent prognostic factor (51). Therefore, Wip1 not only participates in tumorigenesis but also indicates poor prognosis in liver cancer.

6. Wip1 in bladder cancer

Amplification and overexpression of Wip1 were also identified in bladder cancer (52). Wang *et al* (53) demonstrated that RNA

interference of *PPM1D* inhibited bladder cancer cell proliferation and tumorigenesis in mice, potentially through targeting of the p53, p38 MAPK and Akt signaling pathways. This indicates that targeting *PPM1D* may be a potential therapeutic strategy for the treatment of bladder cancer. Furthermore, Lin *et al* (54) revealed that the level of Wip1 expression in cisplatin-resistant bladder cancer was high compared with the control tumor tissue (54). In addition, loss of homeodomain-interacting protein kinase-2 enhanced Wip1 expression, which subsequently increased tumor cell viability in cell lines with wild-type p53 during cisplatin treatment (54). These results suggest that Wip1 upregulation decreases the tumor response to cisplatin, resulting in tumor cell-survival and resistance to apoptosis that is induced by chemotherapeutic drugs. Therefore, Wip1 may lead to chemotherapy resistance in bladder cancer. Conversely, previous studies have revealed that chemotherapy resistance induced by Wip1 is dependent on the presence of wild-type p53; however, in p53-negative cell lines, Wip1 sensitizes tumor cells to chemotherapeutic drugs by regulating the B-cell lymphoma-2 associated X protein:B-cell lymphoma-extra large ratio and runt related transcription factor-2 and protects normal tissues (Fig. 1) (55,56). Therefore, Wip1 inhibition is a potential therapeutic target in bladder cancer with preserved wild-type p53, but the reverse effect may occur in p53-negative tumors; however, this remains to be elucidated.

7. Wip1 in kidney cancer

Two previous studies demonstrated that Wip1 is amplified and overexpressed in kidney cancer, the pathological types of which included clear cell type, granule cell type and papillary cell type (57,58). These reports revealed that Wip1 expression levels are correlated with the clinical characteristics of kidney cancer, including lymph node metastasis, distant metastasis, Fuhrman grade, clinical stage and pathological differentiation (57,58). In addition, these studies also identified that patients with high levels of Wip1 expression had significantly lower survival rates than those with low levels of Wip1 expression, and the downregulation of Wip1 promoted apoptosis and decreased migration and invasion in kidney cancer cell lines (Table I) (57,58). These results indicate that Wip1 may serve an important role in the tumorigenesis and the progression of kidney cancer.

8. Wip1 in nasopharyngeal carcinoma

Sun *et al* (59) also observed the tumorigenic action of Wip1 in nasopharyngeal carcinoma, leading to a more aggressive grade, distant metastasis and a poorer prognosis (Table I). Therefore, all the aforementioned evidence suggests that Wip1 overexpression promotes tumorigenesis in a number of solid tumors and indicates that Wip1 is a potential molecular target for tumor therapy.

9. Conclusion

Wip1 has received increasing attention since it was first identified in 1997 (5). A number of studies have demonstrated that Wip1 negatively regulates various signaling pathways and feedback loops, particularly p53-induced mechanisms, resulting in tumorigenesis of multiple tissues and organs. In addition, Wip1 expression serves a critical role in the progression, migration, invasion and apoptosis of cancer. As an oncogene, its expression levels indicate a poor prognosis of disease. Therefore, Wip1 may act as a potential tumor biomarker, therapeutic target and index of prognosis in various types of cancer.

In conclusion, a number of studies have demonstrated that Wip1 is an attractive chemotherapeutic target. Its overexpression and amplification increases chemotherapy resistance in tumors with wild-type p53, but the reverse of this effect is observed in p53-negative tumor cells. However, the underlying mechanisms by which Wip1 affects chemotherapy remain to be investigated.

Acknowledgements

The present study was supported by the Capital Health Research and Development of Special Grants (grant no. 2011-2002-05).

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