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Review Article

The biochemical and clinical implications of phosphatase and tensin homolog deleted on chromosome ten in different cancers

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Abstract: Phosphatase and tensin homolog deleted on chromosome ten (PTEN) is widely known as a tumor suppressor gene. It is located on chromosome 10q23 with 200 kb, and has dual activity of both protein and lipid phosphatase. In addition, as a targeted gene in multiple pathways, PTEN has a variety of physiological activities, such as those regulating the cell cycle, inducing cell apoptosis, and inhibiting cell invasion, etc. The PTEN gene have been identified in many kinds of cancers due to its mutations, deletions and inactivation, such as lung cancer, liver cancer, and breast cancer, and they are closely connected with the genesis and progression of cancers. To a large extent, the tumor suppressive function of PTEN is realized through its inhibition of the PI3K/AKT signaling pathway which controls cells apoptosis and development. In addition, PTEN loss has been associated with the prognosis of many cancers, such as lung cancer, liver cancer, and breast cancer. PTEN gene is related to many cancers and their pathological development. On the basis of a large number of related studies, this study describes in detail the structure, regulation, function and classical signal pathways of PTEN, as well as the relationship between various tumors related to PTEN. In addition, some drug studies targeting PTEN/PI3K/AKT/mTOR are also introduced in order to provide some directions for experimental research and clinical treatment of tumors.

Keywords: PTEN, structure, function, pathway, cancer

Introduction

Phosphatase and tensin homolog deleted on chromosome ten (PTEN) are essential for normal cells and are widely concerned and studied tumor suppressor genes [1-3]. PTEN was first discovered in 1997, when the mutation at the 10q23 site on chromosome 10 was studied [4, 5]. In early reports, PTEN was considered as a protein located only in the cytoplasm. Nevertheless, it is now clear that it can exist in the nucleus or cytoplasm [6-9]. In the cytoplasm, PTEN interacts with its cytoplasmic targets to regulate cell growth, proliferation, apoptosis, adhesion, migration and invasion. In the nucleus, PTEN can maintain chromosome stability and DNA double strand break repair, so protecting the completeness of the genome [6, 7, 10]. Because PTEN is very important to many cellular processes, the expression of PTEN is strictly regulated by many cellular mechanisms, which exert effect on the transcriptional, post-transcriptional and post-translational levels [11-13]. Since then, many studies have confirmed that the decrease of PTEN level or activity induces the accumulation of PIP3, and is related to the activation of proto-oncogene AKT, so establishing an important link between PTEN and phosphatidylinositol 3-kinase (PI3K) pathway [14-16]. PI3K/AKT pathway is extremely significant for the growth, proliferation and survival of tumor cells. Many researches have shown that PTEN can regulate PI3K/AKT signal pathway through the dephosphorylation of D3 phosphatidylinositol 3, 4, 5-trisphosphate (PIP3) [17, 18].

It is reported that PTEN inhibits tumorigenesis through different mechanisms. In recent years, it has been found that the mutation, deletion

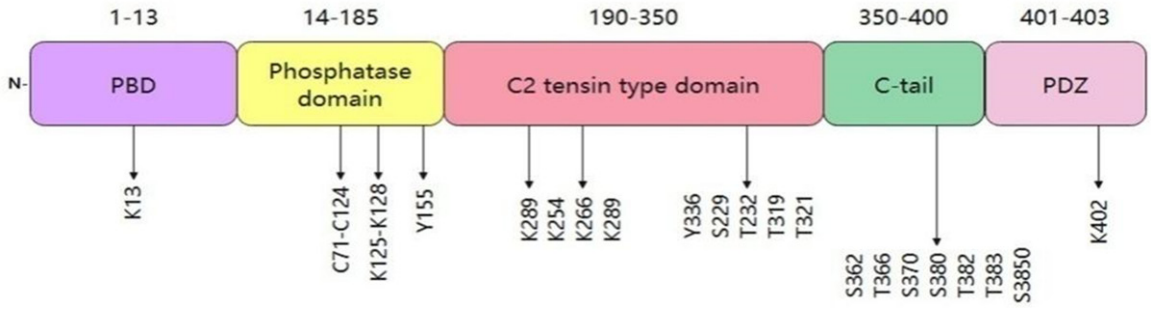

Figure 1. The structure of PTEN gene and occurrence of mutations in exons. Abbreviation: PBD: a p-hosphatidylinositol-4,5-bisphosphate (PtdIns (4,5) P2)-bind-ing domain).

and expression of PTEN gene are closely associated with the development of cancers [19-22]. According to reports, PTEN absence leads to phosphorylation mediated by AKT and the activation of nuclear factor kappa-B (NF-κB) activity, promoting P53 degradation. P53 degradation reduces the apoptotic ability of cells and induces cell cycle progression [23-25]. Inactivation of PTEN also results in MAPK stimulation and activation of mammalian target of rapamycin (mTOR) kinase complex 1 (mTORC1). Apart from the inherent tumor inhibitory function of PTEN, PTEN can also affect the occurrence and development of tumor cells by regulating some information molecules such as focal adhesion kinase (FAK) [26-28], mitogen activated protein kinase (MAPK) [29, 30], hypoxia inducible factor-1 (HIF-1) [31] and vascular endothelial growth factor (VEGF) [32]. In addition, some studies have also emphasized the key function of PTEN in tumor microenvironment, which plays important role in tumor cells, stroma and immune response at different levels, so as to control the occurrence, development and metastasis of the disease [33-35].

As PTEN gene is involved in many kinds of cancers and the pathological process of cancers. In this study, we describe the details of PTEN structure and function and the association between various cancers associated with PTEN on the basis of a myriad of pertinent studies. The aim is to provide a clearer understanding of future revelations.

Information related to PTEN

The structure of PTEN

PTEN is located on chromosome 10q23.3 with a 200 kb and consists of 9 exons and 8 introns, encoding a protein 403 amino acids long with a relative molecular mass of approximately 47 kDa [36]. The amino acid (N) terminus of the protein structure can remove phosphorylate groups from phosphotyrosine, phosphoserine and phosphothreonine on highly acidic substrates, but its catalytic activity is weak [36, 37] (**Figure 1**). In addition, the PTEN structure contains a phosphatase domain, like to protein phosphatases. However, it has an expanded active site that is indispensable to regulating phosphoinositol substrates [38, 39]. PTEN also has a C2 domain that is connected to the phospholipid membrane in vitro. Furthermore, the phosphatase and C2 domains participate in a broad interface, which shows that the C2 domain may be has important impact on in positioning the catalytic domain on the membrane [40].

On the other hand, PTEN contains a characteristic motif of protein tyrosine phosphatases and bispecific protein phosphatases, which indicates that it is both a protein and lipid phosphatase [5]. The crystal structure of PTEN indicates a separation of the two significant domains, an N-terminal phosphatase domain (residues 7-185) and a C-terminal C2 domain (residues 186-351) [6, 36]. Each of these two domains contains five central β-sheets with one α-helix on one side and four α-helices on another side, similar to the domains conferring specificity to other phosphatases [3, 36]. A short N-terminal (PIP2)-binding domain carries the conserved phosphatase motif HCSSGSSR, which is similar to the catalytic domain of tyrosine phosphatases and serine/threonine phosphatases, with the function to dephosphorylate tyrosine and serine/threonine residues and facilitate PTEN to resist to cancer development [38]. An N-terminal phosphatase domain pro-

motes phospholipid hydrolysis. A C2 domain constituted by two antiparallel β-sheets with two small α-helix strands exerts significant impact on mediating the binding of signal-related proteins to cell membranes [12, 19]. Furthermore, the phosphatase terminus plays indispensable roles in the interaction between a ligand and phosphate head. Nevertheless, three loops, a P loop (H123CKAGKGR130), a WPD loop (residues 88-98), and a TI loop (residues 160-171) include residues participating in catalysis which can control the PIP2 and C2 domains and their interactions [4, 36, 41]. In addition, the C-terminal tail contains a domain with a PEST sequence comprising proline, glutamic acid, serine, and threonine and various phosphorylation sites and a PDZ interaction motif that can bind to lipids [36, 42]. Two natural mutations in the phosphatase domain disrupt the tumor-inhibiting ability of PTEN. The C124S mutation causes dysfunction of PTEN protein and lipid phosphatase activities, while the G129E mutation disrupts only the PTEN lipid phosphatase activity [43-45]. Although the N-terminal phosphatase domain mainly participates in PTEN the physiological activity, most tumor-related PTEN mutations are associated with the C2 domain and C-terminus, indicating that the C-terminal sequence is very important to protect the function of PTEN [46] (**Figure 2**). Papa et al. proved that PTEN homodimerization enhances its lipid phosphatase function stably through the C-terminal tail [47].

The regulation of PTEN

The expression control of PTEN: The expression and function of PTEN are strictly regulated at transcription, post-transcription and post-translation levels [3, 11]. Apart from genetic deletions or somatic mutations in human cancers, these regulatory molecules, which control the expression and function of PTEN, can lead to changes in the level of PTEN, thereby promoting the occurrence and development of tumors in different ways [19, 22, 47]. Epigenetic and transcriptional silencing, as well as disorders in microRNAs (miRNAs) and competitive endogenous RNA (Cerna) systems have been shown to inhibit PTEN expression [15, 16]. Recently, the processing pseudogenes (PTENP1) of PTEN plus pseudogenes are very interested in the regulation of PTEN, and the increased regulation is attracting great interest because it increases the complexity of regulating PTEN expression.

The transcriptional regulation of PTEN: Many molecules directly interact with PTEN promoter and promote or inhibit PTEN transcription. These molecules include early growth response transcription factor 1 (EGR1), peroxisome proliferation activated receptor gamma (PPARγ), activating transcription factor 2 (ATF2) and tumor suppressor p53 [48, 49]. It is reported that P53 upregulates PTEN transcription through functional p53 binding element upstream of PTEN promoter [50, 51]. The transcription of PTEN is suppressed through zinc finger proteins Snail and Slug [52]. Other transcription factors such as Cbf-1 (C-kinetin promoter binding factor-1) and c-Jun, antisense transcripts of NF-KB and PTEN pseudogenes (PTENP1) also interact with PTEN promoter and reduce the transcription of PTEN [53-56]. In addition, it has been reported that several kinds of miRNA, including miR-205, miR-122, and miR-21, bind to the 3' untranslated region of PTEN mRNA, leading to the decrease of PTEN mRNA [11, 15, 57-60].

Post-translational regulation of PTEN: Many post-translational mechanisms can exert effect on the activity and stability of PTEN, including phosphorylation, oxidation, acetylation, ubiquitin, and SUMOylation [1, 61, 62]. The catalytic activity of PTEN can be regulated by phosphorylation at specific points on the C2 and C-Tail domains. Under the help of casein kinase 2 and glycogen synthase kinase 3 (GSK3), the specific serine and threonine residues (Ser380, Thr382, Thr383 and Ser385) at the end of PTEN C are phosphorylated, resulting in a decrease in phosphatase activity [63].

The oxidation of PTEN by hydrogen peroxide promoted the formation of disulfide bonds between Cys124 and Cys71 residues, leading to conformational changes, and then changed the binding sites of PTEN substrates, which bring about the loss of PTEN phosphatase activity [64, 65].

Under the stimulation of growth factors, PCAF acetylates PTEN on lysine residues 125, 128 located in the catalytic site of PTEN, leading to inactivating PTEN and activating PI3K signal pathway. It is reported that CREB can promote

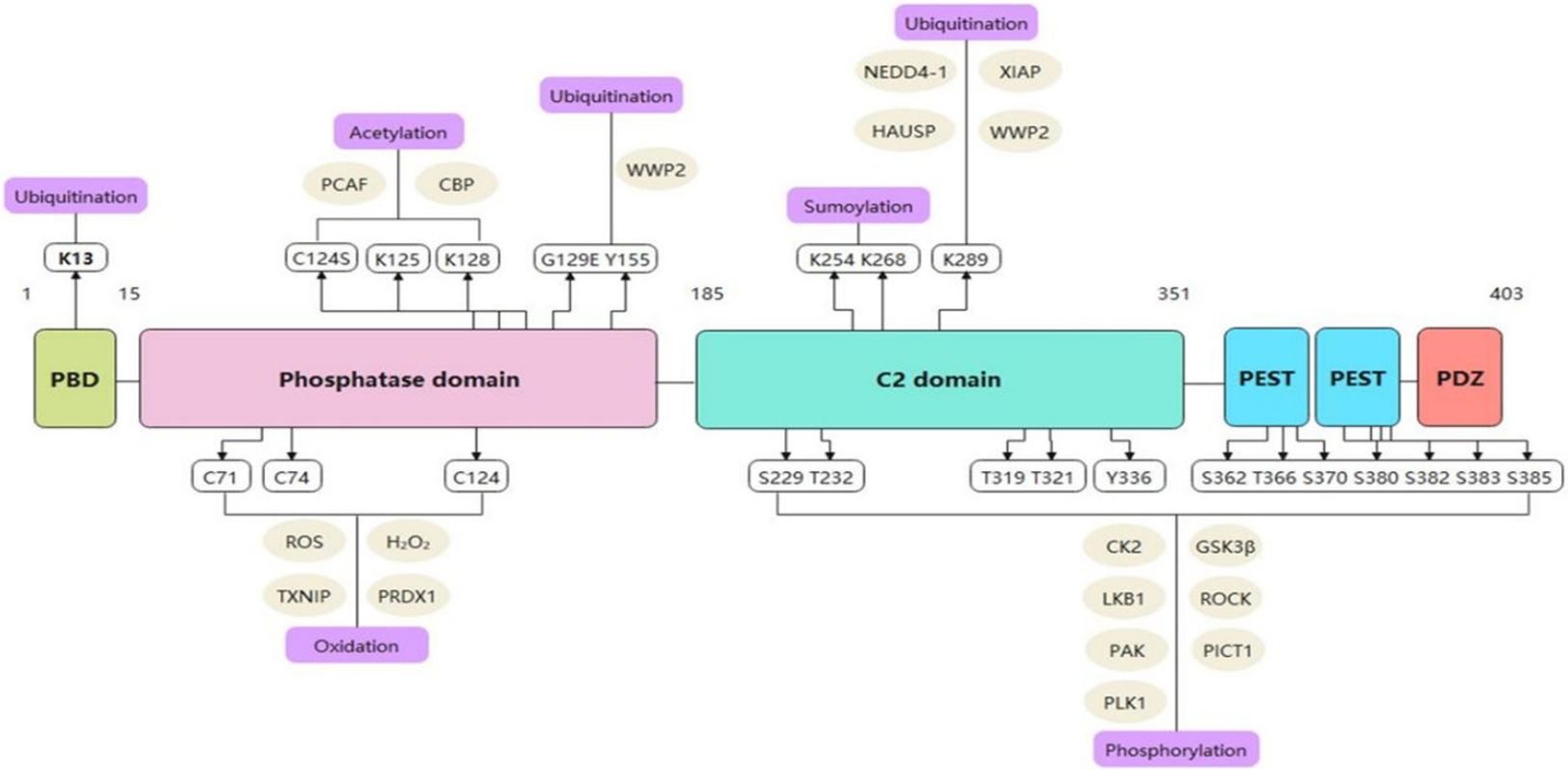

Figure 2. Posttranslational regulation of PTEN at specific sites. Abbreviation: PBD: a phosphatidyli-nositol-4,5-bisphosphate (PtdIns (4,5) P2)-bind-ing domain).

the acetylation of PTEN through the Lys402 in the PTENPDZ binding region [66-68].

Ubiquitin affects the degradation of PTEN. Neural progenitor cells expressing NEDD4-1 can promote the ubiquitination of PTEN [69, 70]. The polyubiquitination of PTEN leads to the decrease of protein stability and the degradation of PTEN through proteasome-mediated decay, while the ubiquitination of PTEN on Lys13 and Lys289 promotes PTEN transport in the nucleus [69, 71].

The connection of ubiquitin-associated modifiers to the protein is also one of the post-translational regulatory mechanisms of PTEN [72]. The SUMOylation of PTEN on Lys266 contributes to PTEN aggregation on the plasma membrane, while the SUMO of PTEN on Lys254 participates in promoting the nuclear localization of PTEN [73, 74].

Typical signal pathways related to PTEN

Under physiological conditions, G protein-coupled receptors (GPCRs) or receptor tyrosine kinase (RTK) (including IGFR, PDGFR, EGFR and c-Met) are stimulated through many molecules, including growth factors, hormones and extracellular matrix (ECM) components to activate PI3K, and then activated PI3K catalyzes the phosphorylation of phosphatidylinositol (4, 5)-diphosphate (PIP2) to PIP3 [75-77]. Subsequently, the production of PIP3 causes proteins containing the PH domain to be attracted to the cell membrane, including AKT and PDK1 [78, 79]. On the cell membrane, PDK1 phosphorylates and activates AKT on Thr308, which in turn activates multiple effect targets, including GSK3, forkhead box O (FoxO) protein and mTORC1 target, thereby regulating various cell processes including apoptosis, proliferation, and metabolism [80-83]. Interestingly, the largest AKT activation needs the other one phosphorylation event on Ser473, which is catalyzed by MTORC2, and mTORC2 also be regulated through PIP3 [84-86]. However, among a variety of substrates, PTEN mainly targets and dephosphorylates PIP3, thus becoming the main passive regulator of PI3K/AKT signal through decreasing the level of PIP3 and restraining the recruitment of subsequent information molecules and AKT activation [14, 87].

The functions of PTEN

The mechanisms by which PTEN controls cellular proliferation, migration, apoptosis, adhesion, and genetic stability impact various cell signal transmission pathways and molecules, forming a complex system.

Regulation of the cell cycle and induction of apoptosis: The PTEN gene exerts important impact on cell migration and cell apoptosis, which suppresses tumorigenicity and cell growth [88, 89]. PTEN expression inhibits SCC-4 cell apoptosis by inducing the PI3K/AKT signaling pathway and increasing the level of the Bcl-2-interacting mediator of cell death [90]. Through its lipid phosphatase activity, PTEN dephosphorylates the 3-phosphoinositide products of PI3K. Moreover, many vital survival kinases, such as PDK1 and AKT, and other proteins that are not kinases can be activated by 3-phosphoinositides. Therefore, PTEN negatively regulates the AKT pathway, and the role of AKT in apoptosis prevention has been well documented [91, 92]. Furthermore, by hydrolyzing PIP3, PTEN antagonizes the activity of PI3K to generate PIP2, which inhibits the activation of downstream signaling molecules and ultimately inhibits cell proliferation, growth and survival [33, 93, 94]. In summary, PTEN can regulate the cell cycle and induce cell death through various signaling pathways.

Inhibition of cell invasion: It has been widely shown that the protein phosphatase activity of PTEN has important effect on its ability to inhibit cell invasion [91, 92, 95, 96]. The epithelial-mesenchymal transition (EMT) is considered to be one of the key factors of cell invasion and metastasis. Downregulation of PTEN can activate the PI3K/AKT pathway, thus promoting the invasion ability of cancer cells and facilitating the EMT [96]. Upregulation of PTEN can inhibit the EMT and tumor cell invasion. This effect may be realized by the downregulation of the Hedgehog (Hh) signaling pathway. Ecadherin and β-catenin can enhance cell-cell adhesion, and their decreased expression is connected to cancer cells invasion and metastasis [97]. The overexpression of PTEN is positively related to the expression of B-catenin cells and negatively correlated with the expression of cadherin and vimentin, indicating that B-catenin is

related to the EMT and may be involved in the assembly of adhesion connections during the EMT [98]. Therefore, PTEN can suppress the EMT by downregulating the Hh signaling pathway, thus inhibiting cell invasion.

Regulation of tumor drug resistance: PTEN suppresses tumors by inhibiting tumor proliferation induced by P13K/AKT pathway activation [99]. Moreover, evidence has shown that PI3K inhibitors can enhance the sensitivity of NSCLC cells with high levels of phosphorylated AKT to medically induced cellular apoptosis [100]. Recent evidence suggests that activated AKT/PKB causes cell resistance to drug-induced apoptosis by phosphorylating downstream targets [101]. Furthermore, PTEN also regulates both the antitumor effect of the anaphase-promoting complex (APC) and its regulatory factor Ecadherin in the nucleus independent of its lipid phosphatase activity [91]. Through the aforementioned mechanisms, PTEN can regulate tumor drug resistance.

Others functions: Many other vital functions of PTEN have been verified. For example, lipid phosphatase activity of PTEN on cell membranes has been established, but PTEN also exhibits nuclear functions. Centrosome stabilization requires PTEN binding to centromeric protein C1 (CENP-C1), while DNA repair protein RAD51-mediated DNA double-strand break (DSB) repair requires PTEN nuclear localization [91, 102]. Additionally, PTEN can regulate cellular migration, adhesion, and stretching through regulating FAK activity by dephosphorylation and can modulate membrane channels [93]. In addition, studies have demonstrated that PTEN deficiency can also increase cell activity. In summary, PTEN has a nuclear function, controls cell migration, adhesion and stretching, and regulates cell activity.

The roles of PTEN in some cancers

As mentioned above, PTEN is a vital gene in cell growth, development, mobility, apoptosis, signal transduction and other cellular processes, processes that contribute greatly to its tumor suppressor function. The detailed mechanism and effect of PTEN in cancers are presented in **Table 1**. PTEN is able to control cell apoptosis and survival by restraining the PI3K/AKT pathway because of its lipid phosphatase activity [103, 104]. PTEN is a phosphatase for phosphoinositol lipids, which are regulated to be critically involved in cellular adhesion and tumor metastasis [105]. PTEN has been demonstrated that dephosphorylize the FAK regulating cell migration. The function of PTEN disorders and its FAK substrate are significantly associated with multiple cancers [33, 106, 107]. Furthermore, as a dual protein and lipid phosphatase, PTEN interrupts downstream AKT activation by dephosphorylating the secondary messenger produced by PI3K, thus affecting tumorigenesis [108, 109].

In addition, PTEN gene mutations have been widely demonstrated is related to cancers; specifically, loss of post-translational expression results in abnormal cells proliferation, apoptosis, movement, and adhesion. The details of these effects are listed in **Table 2**. Different parts of PTEN are associated with the development of cancers. For example, the P-loop (residues 123-130) contains four mutated residues, His123, Lys125, Gly127, and Lys128, which are important for identifying changes in the loop [110] and reducing protein activity by approximately 50-60%. The TI loop has four conserved residues: Val166, Thr167, Ile168 and Gln171. These amino acids are related to the C2 domain and the phosphatase domain. Thr167 and Gln171 are frequently mutated residues in the TI loop, and these mutations lead to 60-75% dysfunction. Mutation to the His93 residue in the WPD loop has the same effect on protein activity, reducing PTEN function by approximately 75%. In addition, frequent mutations at the D5 site may lead to the occurrence of cancer [36]. Chromosome 10q heterozygosity was reported in cases of endometrial cancer [111, 112]. It has also been indicated that PTEN is much more likely to be mutated than other genes, including Kras and p53 [113]. Different mutant amino acid residues are mutated in each loop, with each being critical for reducing protein activity.

PTEN mutations, or partial deletions, are common in all types of tumors. Abnormalities in cell proliferation, adhesion, migration, and apoptosis resulting from loss of PTEN post-translational regulation are usually associated with cancer occurrence, development, and metastasis. Therefore, PTEN and its functionally related proteins are promising new anti-

Table 1. The mechanisms and effects of PTEN in different cancers

Disease	Mechanism	Effect	References
Lung Cancer	PI3K/AKT signaling pathway↓	regulating the proliferation and apoptosis of tumor cells, leading to cell malignant transformation, tumor cell migration and adhesion, angiogenesis and extracellular matrix degradation	[100, 114]
	HDAC inhibitors ↓	regulating a variety of genes and pathways in tumor cells and enhancing the anti-tumor effects of other anti-tumor drugs and radiotherapy	[116-119]
	SHCBP1↓	a key role in the apoptosis of lung cancer cells	[115]
Ovarian Cancer	miRNA-200a↓	Inhibiting proliferation and invasion of ovarian cancer cells	[123]
	miRNA-205↑	Promoting proliferation and invasion of OC cells and inhibiting angiogenesis	[122]
	miRNA-552↓	Inhibiting the proliferation and metastasis of OC	[59]
	PI3K pathway↓	enhanced apoptosis and radiation sensitivity	[125]
Epithelial Ovarian Cancer	miR-21↑	EOC tumor development and poor prognosis	[124]
Liver cancer	PRL-3↓→AKT pathway↓	Inhibiting the aggressive progression of HCC	[134, 135]
	miR-21↑	Triggering cell death in liver cancer cells	[136, 137]
Colon Cancer	PI3K/AKT/NF-κB pathway↓	inhibiting colon cancer progression	[106]
	AR↓	inhibiting the proliferation of colon cancer cells	[108]
	microRNA-26b↓	Inhibiting the invasiveness, migration and stem cell-like phenotype of colorectal cancer	[139]
Breast Cancer	AKT, NF-κB↑→P53 degradation↑	reducing the apoptotic ability of cells and induces cell cycle progression	[141]
	MiR-142-5p↑→PTEN↓	Inhibiting the invasion of breast cancer cells	[148]
Gastric Cancer	miR-718↓	Inhibiting the proliferation and invasion of gastric cancer cells	[153]
	PI3K signaling pathway↑	inducing drug resistance by inducing the expression of multi-drug resistance protein-1	[154-156]
	phosphorylation and activation of SRC kinase↑	resistance to chemotherapy drugs such as trastuzumab	[160]
Prostate Cancer	PLce, miR-20b→PTEN↓	inhibiting tumor cell proliferation	[164-168]
Pancreatic Cancer	JARID1B↓	Inhibiting cancer cell proliferation and tumor growth	[169]
	PI3K/AKT signaling pathway	Inhibiting tumor cell proliferation	[172-174]
Esophageal Cancer	the phosphorylation of AKT↓	Affecting the development of cancer cells	[175]
	JARID1B↓	Inhibiting the proliferation of esophageal carcinoma cells and tumor growth	[169, 176]
	miR-93-5p↓	Inhibiting the proliferation of receptor cancer cells	[177]
Endometrial Carcinoma	miR-205→PTEN/AKT↓	Inhibiting tumor cell apoptosis	[178]

Abbreviations: HDAC: histone deacetylase inhibitors; SHCBP1: SH2-binding protein 1; OC: Ovarian cancer; EOC: epithelial ovarian cancer; HCC: hepatocellular carcinoma; PRL-3: regenerating liver-3; AR: aldose reductase; PLCe: Phospholipase Ce; JARID1B: Jumonji AT-rich interactive domain 1B; PI3K: phosphatidylinositol 3-kinase.

Table 2. The effect of genetic mutations on cancers

Disease	Part	Effect	References
Cancer	Entire loss	Abnormal cell proliferation, apoptosis, migration, and adhesion	[6, 36]
	P-loop	identifying changes in the loop and reduce protein activity	[110]
	Ti ring	functional loss and occurrence of cancer	[36]
Lung cancer	Entire loss	poor prognosis and resistance to EGFR and TKIs	[116]
Ovarian cancer	Entire loss	inducing tubal cancer and subsequently to involve the ovaries; producing serous borderline tumors of FTE and endometriosis carcinoma	[125]
Liver Cancer	Entire loss	high malignant potential/poor prognosis	[134]
		poor cell differentiation	[133]
Breast Cancer	Entire loss	overgrowth, proliferation, survival, and metabolism of tumor cells	[3, 141-147]
Gastric Cancer	Entire loss	tumor resistance	[150-152]
Prostate Cancer	Entire loss	changes in a variety of genes and pathways that affect the progression of cancer	[167, 168]
Esophageal Cancer	Gene mutation	Stability decline, leading to the development of endometrial cancer	[113]

Abbreviations: EGFR: epidermal growth factor receptor; TKIs: tyrosine kinase inhibitors; FTE: fallopian tube epithelium; PI3K: phosphatidylinositol 3-kinase.

cancer drugs, and the potential of PTEN use in gene therapy and other therapeutics should be fully explored.

PTEN and lung cancer

As a tumor suppressor, PTEN inhibitory effects are largely realized through its lipid phosphatase activity that inhibits PI3K/AKT activation, as the PI3K/AKT signaling pathway regulates proliferation and migration of tumor cells. However, PTEN is often mutated in cancer, and this change to PTEN leads to malignant transformation, tumor cells migration and adhesion, extracellular matrix degradation and angiogenesis [100, 114]. Furthermore, PTEN expression is regulated by SH2-binding protein 1 (SHCBP1) downregulation, as silencing SHCBP1 can lead to significant increase in PTEN expression. This suggests that SHCBP1 may be upregulated in lung cancer and may have an important role in the apoptosis of tumor cells; this role is related to the expression of PTEN [115]. In addition, histone deacetylase (HDAC) inhibitors can regulate a variety of genes and pathways in tumor cells and enhance the antitumor effects of other antitumor drugs and radiotherapy; therefore, HDAC inhibitors have shown strong anticancer effects [116]. More importantly, the target of HDACs is PTEN, and HDAC inhibition upregulates the expression of PTEN [117-119]. The expression of PTEN can affect the expression of HDACs and SHCBPI, and then affect lung cancer cells, suggesting that PTEN may be an effective therapeutic target for lung cancer. In lung cancer, PTEN deficiency is related to poor prognosis and resistance to EGFR and other tyrosine kinase inhibitors (TKIs), such as erlotinib. However, suberoylanilide hydroxamic acid (SAHA) can upregulate PTEN expression and increase tumor cell apoptosis [116], thus alleviating erlotinib resistance. However, the specific molecular mechanism remains to be determined.

PTEN and ovarian cancer (OC)

It is reported the absence of PTEN is linked to ovarian cancer. The loss of PTEN in tubal epithelial cells is sufficient to induce tubal cancer and subsequently involves the ovaries. Furthermore, homozygous PTEN deletion produces borderline serous tumors of the fallopian tube epithelium (FTE) and endometriosis-associated carcinoma, which are similar to human precursor lesions [120].

PTEN is regulated by various microRNAs, which play vital roles in OC. Studies have suggested that PTEN serves as a target gene for miRNA-200a, miR-205, and miR-552 [120-122]. MIR-205 participates in the positive feedback of cell proliferation and invasion, and contributes to cell proliferation and invasion through inhibiting PTEN expression [121]. Furthermore, exosomal miR-205 can inhibit angiogenesis through silencing PTEN, thereby activating the downstream AKT pathway, indicating a new mechanism by which exosomal miR-205 is related to OC metastasis [122]. miR-552 can also directly activate PTEN expression by interacting with the 3'-UTR of its mRNA, promoting

the proliferation and metastasis of OC. More importantly, PTEN siRNA disrupted the apparent ability of miR-552 to induce the growth and metastasize between OC cells, compared to its effect on control cells. Moreover, miR-552 may be a good prognostic biomarker for patients with OC [59]. The miR-200a can directly bind to PTEN and negatively regulate the mRNA expression of PTEN in SKOV3 or OVCAR3 cells. By inhibiting PTEN expression, miRNA-200a contributes to the proliferation and invasion of OC cells [123]. In human epithelial ovarian cancer (EOC), there may be an intercommunication between miR-21 and PTEN [124]. On the one hand, miR-21 was overexpressed in clinical EOC tumors and EOC cell lines. On the other hand, PTEN gene expression was significantly decreased. These findings indicate that the overexpression of miR-21 and the downregulation of PTEN can regulate EOC cells. Furthermore, downregulation of PTEN may contribute to miR-21 expression [124].

In terms of drug resistance and radiotherapy, studies have found that PTEN, which inhibits the function of PI3K at the molecular level, is upregulated by paeonol and inhibits the activation of the PI3K pathway [125]. This inhibition may be the cause of an increased apoptosis rate and enhanced radiation sensitivity, which can support the development of barriers to radiotherapy resistance in OC [125].

Overall, PTEN is regulated by various microRNAs, which play vital roles in OC, and the absence of PTEN is associated with the occurrence of OC. PTEN can also lead to apoptosis and increased radiotherapy sensitivity, contributing to the formation of a barrier to radiotherapy resistance in OC. As suggested, PTEN is a very important regulatory gene in OC.

PTEN and liver cancer

As a negative regulator of the EGFR/PI3K/AKT signaling pathway, loss and mutation of PTEN often occur in liver cancer [126]. A progenitor cell mechanism may be associated with the PTEN mutations observed in human liver cancer and high malignant potential/poor prognosis [126]. Twenty-nine percent of HCC tissues lost cytoplasmic PTEN, and 25% of HCC tissues lost all expression of PTEN. In HCC tissues, PTEN expression was significantly reducing than that in adjacent nonneoplastic tissues [127, 128], and its downregulation was associated with poor differentiation [129, 130]. High levels of reactive oxygen species (ROS) are associated with tumorigenesis in PTEN-deficient mouse models [131]. Moreover, the deletion and downregulation of PTEN were significantly associated with the overexpression of fatty acid synthase (FAS) and histological grade of HCC. In addition, PTEN deficiency is related to poor prognosis in patients with advanced HCC. When FAS is overexpressed, the situation worsens [132].

In liver cancer cells, both the expression and the tumor suppressive ability of PTEN are significant [132]. Notably, the expression density of PTEN is connected with the development of liver cancer. This phenomenon may protect of the body itself in the case where tumor cells further express PTEN in adjacent cancer tissues under high-pressure conditions [133]. PTEN can act as a negative switch of the AKT pathway, thereby promoting the aggressive progression of hepatocellular carcinoma (HCC) by activating the AKT pathway [134]. On the other hand, the level and activity of PTEN in liver cancer are changed by various complex mechanisms. For instance, the expression of PI3K is negatively connected to the expression of PTEN. PI3K overexpression may be closely correlated with the formation of tumors. The anticancer effect of PTEN depends on the extent of its negative regulation of PI3K signaling [135]. In addition, phosphatase in regenerating liver-3 (PRL-3) can enhance the phosphorylation level of PTEN to reduce the PTEN level. Through this negative regulation of PTEN expression, PRL-3 may activate the PI3K/AKT signaling pathway, which promotes HCC progression [134]. PTEN serves as the downstream target of miR-21, and ectopic miR-21-mediated downregulation of PTEN and highly upregulated miR-21 expression were evident in hepatocellular carcinoma cell lines. PTEN is involved with miR-21 triggering of liver cancer cell death [136, 137].

In summary, the expression of PTEN is closely connected with the occurrence and development of liver cancer, and its mechanism is related to various other mechanisms, such as those associated with the AKT pathway, PI3K, PRL-3, and miR-21. Deletions and mutations are frequent in liver cancer. PTEN is associated with the prognosis and drug resistance of

liver cancer, making it a potential diagnostic and prognostic marker.

PTEN and colon cancer

In terms of the association between PTEN variations and cancers, a considerable proportion of patients with colon cancer (34.3%) showed PTEN expression deficiency [138]. In terms of mechanisms, it has been revealed that PTEN inhibits colon cancer progression through restraining paxillin expression downstream of the PI3K/AKT/NF-κB pathway [106]. In addition, PTEN expression can be regulated by aldose reductase (AR). Studies have shown that AR inhibition can inhibit PTEN phosphorylation induced by growth factors, thereby activating PTEN and increasing the expression of this protein in tumor cells, thus inhibiting colon cancer cells proliferation [108]. Furthermore, inhibition of PTEN increases the expression of microRNA-26b and contributes to the invasiveness, migration and stem cell-like phenotype of colorectal cancer (CRC) [139]. In summary, PTEN deficiency is closely associated with the occurrence of colon cancer, and this gene can affect PI3K/AKT/NF-κB, AR and miR-26b to inhibit colon cancer, and therefore, PTEN may be a new prognostic biomarker or therapeutic target.

PTEN and breast cancer

Breast cancer is the most frequent cancer in women and PTEN gene is strongly linked to it [140]. First, PTEN deficiency leads to the overgrowth, survival, proliferation, and metabolism of tumor cells [3]. It causes AKT-mediated phosphorylation and increased NF-κB activity, thereby promoting P53 degradation. Then, P53 degradation reduces the apoptotic ability of cells and induces cell cycle progression [141]. Heterozygosity disorders in chromosome 10q23 are evident in advanced sporadic tumors, including breast cancer [58, 142-144].

In addtion, a recent meta-analysis demonstrated that hypermethylation of the PTEN promoter is considered to be among the most important mechanisms for inactivating PTEN in ductal carcinoma in situ (DCIS) and invasive ductal carcinoma of the breast, suggesting that the inactivation of PTEN is involved in the early stage of breast neoplasia [145, 146]. In terms of PTEN and cancer prognosis, it has also been previously reported that tumor cells with loss of PTEN function lead to poor prognoses [147]. The inactivation of PTEN was significantly associated with a decrease in 5-year overall survival and disease-free survival rates in breast tumor patients. PTEN reduction was significantly correlated with tumor volume increases, estrogen progesterone receptor (ER)/progesterone receptor (PR) negativity, axillary lymph node metastasis positivity, and advanced stage and local recurrence of breast cancer, indicating a worsening prognosis [145].

Some researches have also demonstrated that the level of PTEN mRNA in breast cancer tissue is significantly decreased. The expression level of mIR-142-5p was positively and negatively correlated with PTEN, and the PTEN level was related to tumor size and metastasis [148].

PTEN and gastric cancer (GC)

Scientists found that the expression of PTEN decreased gradually as GC progressed [93]. The expression of PTEN in primary tumors was obviously lower than that in adjacent non-tumor tissues [149]. Therefore, the decrease or loss of PTEN expression is a dynamic process in gastric cancer progression and the level of PTEN can be considered as an indicator for the diagnosis of GC pathological status [150-152].

In terms of prognosis, PTEN and miR-718 have been identified as prognostic factors for GC. MiR-718 can promote the proliferation and invasion of GC cells through targeting PTEN mRNA [153]. Thus, PTEN is a prognostic risk factor for poor prognosis of GC. These findings are helpful for studying the progress and treatment of GC. In addition, tumor resistance is mainly caused by the inactivation of PTEN and subsequent activation of the AKT pathway [154-156]. To date, many mechanisms have been proven for the specific role of PTEN in endowing tumor cells with chemotherapy drug resistance. First, through inducing the expression of multidrug resistance protein 1 (MRP1), the PI3K signaling pathway is activated, especially PI3K3a and PAKT, which induces PTEN-induced drug resistance [157-159]. In addition, reduced expression of PTEN in cancer cells can lead to increased phosphorylation and activation of SRC kinase, leading to resistance to chemotherapy drugs such as trastuzumab [160].

In conclusion, the dysfunction of PTEN in GC leads to multiple processes. PTEN level not only can be used as a diagnostic indicator of GC pathological status but also as a risk factor for the poor prognosis in patients with GC. PTEN also has an inseparable relationship with drug resistance and is a promising potential therapeutic factor for cancers. However, further research is needed to study how PTEN regulates the interactions between these processes, interaction dynamics, and homeostasis under pathological conditions.

PTEN and prostate cancer

PTEN mutations can cause alterations in various genes and pathways that affect the development of prostate cancer, which may be significant to the individualized treatment of prostate cancer. Thus, drugs directed at lipid metabolism pathways may be targeted to PTEN-mutant prostate cancer in the development of new treatments for patients. As patients with PTEN mutations may be more sensitive to docetaxel and because these patients need early intervention to prolong their survival, docetaxel chemotherapy may be the most effective treatment [161]. In addition, advanced disease and poor prognosis are associated with PTEN mutations, and known mechanisms of ectopic PTEN effects include PTEN deletion, dysregulated transcription, and epigenetic modification [162, 163]. In general, the disease progression of various cancer types is related to low PTEN expression levels [164-166], indicating the importance of PTEN mutation in disease progression. Furthermore, PTEN is associated with two oncogenes: phospholipase Ce (PLCe) and miR-20b in prostate cancer. PLCe expression downregulates PTEN expression in cancer cell lines and inhibits tumor cell proliferation by the PTEN/AKT signaling pathway [167], while miR-20b can restrain PTEN expression through directly combine with the 3'-UTR of PTEN mRNA [168].

PTEN has a strong link with oncogenes, but the mechanisms remain unclear. Reduced expression of PTEN is often related to the progression of many types of cancers and is one of the important potential mechanisms by which PTEN mutations are associated with cancer progression. However, the determination of the mechanisms and verification of gene mutations in cancer needs further molecular biological and clinical experimental research, and the characterization of the relationship between PTEN mutations and specific events in prostate cancer requires data from larger samples to produce the most accurate results.

PTEN and pancreatic cancer

PTEN is an essential factor in regulating the development of pancreatic cancer cells. PTEN plays a vital role in Jumonji AT-rich interactive domain 1B (JARID1B)-promoted cell and tumor proliferation. JARID1B may affect the activation of PTEN by regulating the methylation of lysine 4 on histone H3 (H3K4), thus promoting PC cell proliferation and tumor growth [169]. Moreover, studies have indicated that miR-486 can facilitate the proliferation of CAPAN-2 human pancreatic cancer cells through targeting PTEN. The tumor suppressor gene PTEN is the regulatory target gene of miR-486 [170]. At the protein level, miR-486 can negatively regulate the expression of PTEN. Moreover, PTEN gene overexpression disrupts the proliferation of miR-486 mimics because miR-486 is functionally targeted by PTEN in CAPAN-2 cells [171]. Furthermore, PTEN can be downregulated to target NF-κB and cMyc in pancreatic cancer cell lines through the activation of the PI3K/AKT signaling pathway, thereby playing an inhibitory role in pancreatic cancer [172]. Furthermore, PTEN is related to the regulation of pancreatic cancer cell angiogenesis, which may be related to chemotherapy resistance and tumor recurrence [173, 174]. In conclusion, there is still a lack of effective diagnostic markers, drug targets, and treatment strategies to successfully treat PC. PTEN acts mainly on JARID1B and miR-486 in pancreatic cancer, both of which are potential therapeutic targets.

PTEN and esophageal cancer (EC)

Studies on EC have suggested that the downregulation of PTEN in EC is due to the hypermethylation of its promoter region [175]. The downregulation of PTEN can inhibit the phosphorylation of AKT in EC cells, while long intergenic nonprotein-coding RNA 184 (LINC00-184) can activate AKT phosphorylation, thus positively regulating PTEN gene methylation [175]. Furthermore, other studies have shown other factors that affect PTEN and thus the development of cancer cells. For example,

JARID1B can promote the proliferation of esophageal carcinoma cells and tumor growth after activating PTEN [169, 176]. miR-93-5p may affect the expression of p21 and Cyclin D1, downstream proteins of PTEN in the PTEN/PI3K/AKT pathway, so contributed to cancer cells proliferation [177].

In conclusion, the downregulation of PTEN in EC is due to the hypermethylation at its promoter region. However, the relationship between the regulation of glucose metabolism by LINC00184 and EC cell tumors remains unclear and requires further study. On the other hand, both JARID1B and miR-93-5p can promote the proliferation of cancer cells by affecting PTEN, making them potential therapeutic targets to cure EC.

PTEN and endometrial carcinoma

Deficiency of the phosphatase and catalytic activities of the PTEN protein has been associated with various types of cancer, including endometrial cancer (EDC). Mutant PTEN is less stable than normal PTEN. Substrate binding sites in PTEN are abrogated when PTEN is mutated, leading to the development of endometrial cancer [113]. Furthermore, the miRNAs associated with PTEN are often dysregulated in human cancers. Among these miRNAs, miR-205 can directly regulate the expression of PTEN in endometrial tumor cells and result in cell apoptosis inhibition. As an oncogene, miR-205 restrains apoptosis through targeting the PTEN/AKT pathway. Thus, the increasing expression of miR-205 in cancer cells may have essential effect on EDC progression [178].

In terms of prognosis, it has been shown that PTEN is associated with clinicopathological factors and prognosis in EDC patients. The decrease in PTEN expression is associated with poor prognosis. By contrast, EDC patients with high level of PTEN had low malignant tumor levels, diminished proliferative activity and a better prognosis [179]. In summary, the dysregulation and loss of PTEN expression are related to endometrial cancer and prognosis, which is a potential factor for cancer treatment.

Drugs of targeting the PTEN/PI3K/AKT/mTOR axis

The overall active role of PI3K/AKT/mTOR signaling pathway in cell growth and development makes it possible for small molecule inhibitors of PI3K, AKT or mTOR to target the treatment of PTNE deficient cancer [180-183]. As the most common abnormal regulatory pathway in tumors, this pathway has attracted more and more attention because of its potential in targeted therapy of many kinds of malignant tumors. In this context, a variety of inhibitors for this pathway are mainly targeted at PI3Ks, AKT and mTOR [181, 184-186]. PI3K inhibitors include LY294002 [187], wortmannin [188], curcumin [189], BLY719 [190], BKM120 [191], idelalisib [192], copanlisib [193], etc. AKT inhibitors include perifosine [194], celecoxib [195], GSK690693 [196], deguelin [197], MK-2206 [198], etc. mTOR inhibitors include RAD-001 (everolimus) [199], CCI-779 (temsirolimus) [200], AP23573 (deforolimus) [201] and so on.

The mTOR-based inhibitors temsirolimus and everolimus, as well as PI3K-based inhibitors idelalisib and copanlisib, have been approved by the Food and Drug Administration for clinical anticancer treatment [192, 193, 199, 200, 202]. Curcumin (NCT03211104, NCT03980509), perifosine (NCT01048580, NCT01224730), celecoxib (NCT03896113, NCT02429427), GSK690693 (NCT00666081), MK-2206 (NCT01147211, NCT01240928), AP23573 (NCT00704054, NCT00122343) have entered the clinical experimental research in the treatment of tumors. However, LY294002, Wortmannin [186] and deguelin are still in the stage of experimental research [187, 203].

Although the most effective anti-tumor effect of PTEN is the passive regulation of PI3K/mTOR/AKT carcinogenic signal pathway, but further tumor inhibition functions have been reported, such as chromosome integrity and DNA repair [10, 74]. At present, some small molecular inhibitors have been experimentally explored as a potential treatment by pharmacological inhibition of PTEN. For example, bpv (phen), bpv (pic), bpv (HOpic), bpv (pis), Vo-OHpic, the effect of this inhibitor on PTEN can be reversed by reductant, just like the inhibition of PTEN by ROS [204-206]. SF1670, an inhibitor targeting PTEN, has been found that SF1670 restrains cells apoptosis and inflammation by inhibiting PTEN and activating AKT, thus preventing intervertebral disc degeneration [207]. It has also been found that SF1670 protects PC12 cells from cell death induced by oxygen-glucose deprivation by restraining PTEN [208].

However, there are few studies on the mechanism of SF1670 inhibiting PTEN in tumor.

On the PI3K/AKT/mTOR axis, PTEN plays important tumor inhibitory role through regulating transcription, translation, cell cycle progression, inducing cell death, stimulating angiogenesis and stem cell self-renewal [17, 34, 94, 164, 209]. From this point of view, it can be considered that it is of great benefit to strengthen the research and development of PTEN activators in the future. However, PTEN inhibition is considered as a potential treatment. Most pathological conditions depend on the direct negative regulation of PIP3 phosphatase activity on the signal of PI3K/AKT/mTOR pathway. The evidence shows that PTEN protein phosphatase activity and non-catalytic PTEN activity exert significant function on physiological and pathological processes. Whether it is feasible to selectively inhibit the activity of small molecular PTEN lipoprotein phosphatase or protein phosphatase remains to be discussed.

Perspectives and future directions

PTEN has been extensively studied by scholars as a tumor factor. PTEN inhibits tumorigenesis by various mechanisms, including phosphatase-dependent and independent activities, subcellular localization and protein-protein interactions, affecting many physiological and pathological processes, including growth, development, survival, DNA repair and cells movement [3, 11, 61, 210]. To date, considerable progress has been made in the study of PTEN mutation and deficiency in cancers, and knowledge of anticancer mechanisms, prognoses and drug resistance in different cancer types has advanced. In terms of the mechanism of cancer inhibition, the PI3K/AKT pathway has been widely and frequently mentioned. However, there are still a few cancers for which PTEN has been rarely studied, and more extensive research is needed. As a vital tumor suppressor gene, the main function of PTEN is to control apoptosis and regulate the cycle of cancer cells. Apart from the inherent tumor inhibitory function of PTEN, some researches have also emphasized the key function of PTEN in regulating tumor microenvironment. It acts on cancer cells, stroma and immune response at different levels, thereby promoting the occurrence, development and metastasis of the diseases [1, 35, 211-215]. In view of the fact that PTEN is an important target with a variety of biological functions in tumors, the future drug research on PTEN will be of great significance to the treatment and prognostic diagnosis of tumors. Although, in the PTEN/PI3K/AKT/mTOR axis, targeted PI3K, AKT and mTOR inhibitors have appeared or even entered clinical trials, there are still few studies on drugs related to PTEN. However, whether to develop an activator or an inhibitor of PTEN still needs follow-up experimental studies to provide more evidence.

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Disclosure of conflict of interest

None.

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