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PTEN modulators: a patent review

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Abstract

Introduction—PTEN (phosphatase and tensin homolog deleted on chromosome 10) plays a pivotal role in controlling intracellular signaling for cell survival and proliferation by inhibiting the PI3K/Akt pathway, and its dysfunction is associated with several neoplastic diseases. PTEN is frequently found mutated in many pathological conditions highlighting its importance in normal physiological function. Unlike several cellular proteins which are activated by phosphorylation, PTEN is inactivated upon phosphorylation by specific kinases which phosphorylate serine and threonine residues in its C-terminal region. Therefore, development of therapeutic agents that specifically target kinases and kinase-domain-containing proteins affecting PTEN would lead to the treatment of PTEN-related diseases.

Areas covered—With increasing evidence on the role of PTEN in many human diseases, the present review focuses on the clinical relevance of PTEN with a comprehensive list of currently identified modulators of PTEN, and proposes potentially novel molecular targets which could aid in the development of drug candidates for the treatment of PTEN-related diseases such as cardiovascular diseases, diabetes, obesity, cancer, autism, Parkinson's and Alzheimer's diseases.

Expert opinion—This review describes several target sites that could help in the development of novel drug candidates to regulate or restore the normal physiological functions of PTEN and are essential in the treatment of human diseases where PTEN plays a pivotal role.

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Declaration of interest

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Keywords

cancer; cardiovascular diseases; kinases; modulators; obesity; phosphatase; PTEN; transcription factors

1. Introduction

PTEN (phosphatase and tensin homolog deleted on chromosome 10), first identified as a tumor suppressor, is among the most mutated genes discovered thus far and was found frequently mutated or deleted in several neoplastic diseases, including glioblastoma, endometrial cancer, prostate cancer, and small-cell lung cancer. Specific mutations in the PTEN gene were attributed to hereditary diseases, such as Cowden syndrome, Bannayan-Zonana syndrome (Bannayan–Riley–Ruvalcaba syndrome), Lhermitte-Duclos syndrome, Proteus syndrome, and Proteus-like syndrome, which are clinically referred to as Hamartoma-Tumor Syndromes. Besides its genetic alterations, PTEN expression is also affected by DNA methylation, mRNA degradation, post-translational modifications, transcriptional and translational regulation inside the cell indicating that PTEN is a highly targeted protein in many human diseases [1,2]. Numerous mutations ranging from point mutations to allelic loss have been detected at high frequency in PTEN gene in different malignancies, and cancer genome sequencing further confirms that PTEN is one of the most commonly mutated genes identified [3,4].

PTEN expression has been observed in most tissue types from embryonic to adulthood, hence it is presumed to be expressing constitutively in the cells. However, its stability is regulated by its interaction with other cellular proteins. PTEN gene (NCBI Acc # NM_000314.4, also known as BZS; DEC; GLM2; MHAM; TEP1; MMAC1; PTEN1; 10q23del) contains nine exons with a variable exon 5b; in addition, the 3' end of exon 8 was reported to generate splice variants. This 5.572 kb gene that was mapped onto human chromosome 10q23 region encodes for a 403 aa, 47.17 kDa protein with distinct N-terminal and C-terminal regions. The first six exons encode for a 185 aa N-terminal domain with phosphatase activity, which catalyzes dephosphorylation of phospholipids, and the rest three exons code for the 218 aa C-terminal domain which has C2 subdomain, two PEST sequences and PDZ binding domain [5]. Molecular structure of PTEN shows characteristic regions of a phosphatase protein having P-loop, WPD-loop and the TI-loop regions (Figure 1A). The N-terminal domain is reported to exert phosphatase activity while the C-terminal tail region contains several phosphorylation sites (S362, T366, S370, S380, T382, T383, and S385) which, upon phosphorylation, modulate PTEN functions that are vital to normal cellular activities. Phosphorylation of these amino acid residues by specific kinases along with a predicted structure for the C-terminal tail region is shown in Figure 1B. The functional activity of PTEN is regulated by phosphorylation, oxidation, acetylation and protein–protein interactions, and cellular functions that are regulated by PTEN include cell proliferation, cell cycle progression, chemotaxis, angiogenesis, apoptosis, aging, muscle contractility and DNA damage response. Membrane binding and activation of PTEN which leads to inhibition of the cellular pathways associated with PTEN-related diseases is illustrated in Figure 1C. Also, three of the common cellular signaling pathways that are associated with PTEN are shown in Figure 2.

2. Kinases and kinase-domain-containing proteins that modulate PTEN

Unlike many cellular proteins, PTEN becomes functionally inactive upon phosphorylation at different serine and threonine residues, especially in the C-terminal region. This phosphorylation of PTEN is mediated by specific kinases, which affect PTEN function to

dephosphorylate PIP3 [6]. CK2 is a major protein kinase that phosphorylates PTEN at Thr366, Ser370, Ser380, Thr382, Thr383 and Ser385, and inhibits its stability and activity [7,8]. The kinase LKB1 was also reported to phosphorylate PTEN at residue S385. Although this phosphorylation at S385 residue renders PTEN inactive, subsequent phosphorylation by LKB1 at S380, T382 or T383 residues on PTEN was observed, suggesting a cooperative dependence of S385 phosphorylation with S380, T382 or T383 residues which was confirmed using site-directed mutagenesis. In addition, Src kinase has been specifically found to phosphorylate tyrosine residues in the C-terminal region of PTEN [9]. GSK3 β phosphorylates PTEN at Ser362 and Thr366, which greatly reduces its phosphatase activity [10]. The kinases JNK and JNKK were also reported to inhibit PTEN activity. Besides kinases PICT1 and FRK, the kinase-domain-containing proteins, MAGI and MAST, were also reported to stabilize or activate PTEN [11–15]. RhoA-associated kinase (ROCK) activates PTEN by phosphorylating it at Ser229, Thr232, Thr319 and Thr321 residues [16]. Figure 3 shows some of the kinases and proteins containing kinase domains which either inhibit or enhance PTEN activity, thus modulating its cellular functions.

JNK and PTEN signaling pathways crosstalk and regulate progression of prostate neoplasia to invasive adenocarcinoma with increased activity of JNK signaling in the absence of PTEN. Notably, PTEN and JNK deficiency caused reduced luminal cell–cell interactions and increased luminal cell apoptosis compared to PTEN-deleted mice [17]. Although apparent crosstalk between JNK and PTEN signaling is evident, the exact molecular interactions that connect the two signaling pathways are still unclear. Erythropoietin receptor-mediated activation of Jak2 upregulates Src, which in turn activates CK2a and inhibits PTEN [18]. The specific kinases and kinase-domain-containing proteins that have direct or indirect effects on PTEN are shown in Table 1.

3. Pathological significance of PTEN

3.1 Role of PTEN in the treatment of type 2 diabetes and obesity

Some of the kinases expressed upstream in the pathway can inhibit PTEN. Thus, indirect methods for restoring PTEN function would be to strategically block the upstream kinases using specific inhibitors or antibodies. An effective strategy to address the inhibition of PTEN in type 2 diabetes is to regulate the downstream pathway that converts blood glucose to muscle glycogen. Akt is a key enzyme in insulin signaling that regulates glucose uptake. Since PTEN inhibits formation of PIP3, which is a substrate for Akt, inhibition of PTEN is being considered as a possible drug target to treat type 2 diabetes. In this regard, bisperoxovanadium compounds (bpV), even in the nanomolar range, are reported to be effective as PTEN inhibitors [19]. In hepatocyte-specific conditional PTEN null mice, PTEN is an important regulator of lipogenesis, glucose metabolism, hepatocyte homeostasis, and tumorigenesis in liver [20]. Leptin promotes phosphorylation of PTEN at multiple sites in the C-terminal region and thus inhibiting the phosphatase activity of PTEN. Specific inhibitors of CK2 and GSK3 block this leptin-mediated phosphorylation of PTEN. Interestingly, GSK3 activity is inhibited by insulin which phosphorylates its N-terminal region [21]. These reports, though still are in the preliminary stage, elucidate a clear role for PTEN in diabetes and obesity. The role of PTEN in type 2 diabetes is summarized in Figure 4.

3.2 PTEN inhibition to prevent heart failure

Inhibition of PTEN signaling in the heart may present a novel approach to slow the progression of heart failure in response to pathologically induced biomechanical stress. In PTEN knockout mice that were subjected to aortic banding, a mild reduction in systolic function with minimal ventricular dilation and loss of heart function was observed,

indicating that loss of PTEN prevents the development of heart failure. Thus, inhibition of PTEN expression could be clinically significant in the prevention of heart failure [22].

3.3 Genetic role of PTEN in autism

Three genetic mutations in the PTEN gene (H93R in exon 4 and D252G and F241S in exon 7) have been identified which leads to macrocephaly/autism syndrome [23]. Targeted inactivation of PTEN in the differentiated neurons of the cerebral cortex in mice resulted in increased response to sensory stimuli with neuronal hypertrophy, including hypertrophic and ectopic dendrites and axon tracts with increased synapses. This suggests that defects in PTEN cause macrocephaly and autistic syndrome in mice [24].

3.4 Other diseases in which PTEN could be a therapeutic target

Besides the obvious role of PTEN in preventing neoplastic diseases, recent evidence also suggests its role in several other diseases, such as Parkinson's, Alzheimer's and allergy/inflammation.

In adipose tissue, binding of insulin to insulin receptors activates PI3K signaling. Since PTEN inhibits PI3K pathway, it acts as a negative regulator of insulin signaling and insulin sensitivity. Interestingly in neuronal tissues, PTEN regulates neuronal insulin signaling and resistance through its phosphatase activity that inhibits FAK/ERK signaling which is critical for negative regulation of neuronal insulin. With increasing evidence that impaired insulin signaling in the brain acts as a mediator for chronic neurodegenerative disorder, Alzheimer's disease, it is clear that regulating PTEN could be a therapeutic approach in treating the disease [25].

Mutation in the PTEN-induced putative kinase 1 (PINK1) gene has been identified to cause early onset of autosomal recessive Parkinson's disease which was linked to PARK6 locus on chromosome 1p [26,27]. This study supports that haploinsufficiency of PINK1 may indicate a susceptibility factor toward Parkinson's disease and therefore modulation of PTEN activity could be an effective treatment strategy.

Intratracheal administration of adenovirus-expressing PTEN reduces eosinophilic inflammation and airway hyperresponsiveness in allergen-challenged mice, indicating that PTEN inhibits allergic inflammation and that PTEN gene therapy could be beneficial in treating allergic/inflammatory disorders in the airways [28].

4. Therapeutic inhibitors used in PTEN-associated pathologies

Receptor tyrosine kinases are predominantly growth factor receptors that mediate outside-in signaling through cell survival pathways, mostly through PI3K/Akt or Ras/MEK axis, and regulate cell proliferation, migration and intracellular metabolism. Targeting these kinases is a logical approach to achieve anticipated therapeutic benefits of PTEN expression or inhibition in the treatment of specific diseases. Since PTEN plays a prominent role in inhibiting PI3K/Akt-mediated cell survival pathway, use of its agonists or mimetics to inhibit cell growth, cell division, cell proliferation and/or cell migration could prove to be an effective approach in the treatment of neoplastic diseases. Overexpression of PTEN with subsequent activation of IGF-1 affects cell cycle progression in saphenous vein smooth muscle cells. Also, overexpression of PTEN in smooth muscle cells inhibits IGF-1-induced cellular proliferation mediated by PI3K–Akt axis, and PTEN inactivation leads to sustained levels of increased temporal expression of pAkt in smooth muscle cells [29,30]. The inhibitors and other therapeutic drugs that are currently used To Whom It May Concern: treat various PTEN-associated diseases are listed in Table 2.

5. Possible therapeutic targets that affect PTEN expression

5.1 Transcription factors

Aside from post-translational modifications, PTEN expression can be regulated at both the transcriptional and translational levels under various pathological conditions. Thus, targeting transcription factors that regulate PTEN is a promising strategy for developing therapeutic drugs.

Complete loss of PTEN has been shown to induce activation of p53-dependent cellular senescence, and combined inactivation of PTEN and Trp53 shows unconstrained tumor growth, indicating that mutants with partial PTEN function may have a selective advantage for the treatment of PTEN deficiency in cancer [31]. Active NOTCH1 increases PTEN expression through CBF-1 and MYC transcription factors. In addition, activation of NOTCH1 represses PTEN expression through the HES-1 transcription factor. This is indicative of the many roles played by NOTCH1. Thus, the regulation of PTEN by NOTCH1 could be a therapeutic strategy in the use of NOTCH1 inhibitors in leukemia [32]. RAS-mediated PTEN suppression is mediated by TGF- β -dependent mechanism, and the oncogenic RAS-RAF-MEK-ERK pathway suppresses PTEN levels through the transcriptional factor, c-Jun [33–35]. The stress kinases, including MEKK4 and JNK, promote resistance to apoptosis by suppressing transcription of PTEN mediated by NF- κ B [36]. The aforementioned reports demonstrate a strong transcriptional regulation of PTEN mediated by different cellular factors. Table 3 lists some of the known transcription factors that regulate PTEN expression. Since several synthetic compounds are known to affect these transcription factors, their application in the therapy of PTEN-associated diseases is becoming increasingly significant.

5.2 Cellular proteins that regulate PTEN expression

Several cellular proteins, including phosphatases, either directly or indirectly affect PTEN expression primarily via protein–protein interactions. These proteins interact with PTEN by binding to its N-terminal region, C-terminal region and the PDZ binding domain. Some of these proteins also help in the translocation of PTEN across the cytoplasm.

Another approach is to prevent the degradation of PTEN mediated by ubiquitin proteasomal pathway using proteasome inhibitor “MG132,” which has proven to be effective. NEDD4-1, which is E3 ubiquitin-protein ligase, interacts with PTEN and the overexpression of NEDD4-1 leads to ubiquitination of PTEN. Therefore, inhibition of NEDD4-1 may help in the development of a strategic therapeutic drug that can upregulate PTEN in cancer [37]. WWP2 has recently been identified as an E3 ubiquitin ligase for PTEN, which mediates its ubiquitination-dependent degradation. Although the associated kinase has yet to be identified, it is evident that phosphorylation at Tyr155 in PTEN is essential for WWP2-assisted PTEN ubiquitination [38]. The cellular proteins that interact with PTEN are summarized in Table 4.

6. Conclusions

Under various pathological conditions, PTEN has been a primary target for the derailment of the normal cellular physiology. Thus, the protection of PTEN from the cellular proteins that affect its expression and functions is a promising approach for restoring normal cellular function. Along these lines, several therapeutic drugs have been developed that assist proper functioning of PTEN through indirect mechanisms and several inhibitors of specific kinases that directly modulate PTEN functions have also been developed. From the therapeutic perspective, the present review identifies potential targets for the development of drugs to help in the treatment of diseases in which PTEN expression is affected. In addition to the list

of current drugs used in the treatment of PTEN-associated diseases, this review identifies specific kinases, cellular proteins and transcription factors that act as modulators of PTEN, which should garner them strong consideration as promising candidates to develop patentable therapeutic drugs.

7. Expert opinion

PTEN is a vital protein phosphatase. Strategic approaches to inhibit or activate PTEN could be employed in the treatment of several human diseases. Accordingly, several kinases, transcription factors and cellular proteins have been identified that directly or indirectly act on PTEN. This indicates transcriptional, translational and post-translational regulations as the key mechanisms by which PTEN functions are regulated. It is noteworthy that the absence of the C-terminal tail region of PTEN did not affect its cellular functions or its stability, but phosphorylation of specific residues in its C-terminal tail region would lead to its functional inactivation. However, its catalytic activity toward lipid substrates was found decreased when phosphorylated at other residues. A possible auto-inhibitory mechanism was proposed which suggests that the phosphorylation of PTEN in its C-terminal tail region would lead to conformational changes in its structure, as a result, the C-terminal tail region directly interacts with C2 domain leading to masking of its PDZ binding region. These structural changes could lead to functional inactivation of PTEN.

Functional attributes of PTEN are regulated by its phosphorylation at different serine and threonine residues in the C-terminal region, and this phosphorylation is mediated by specific kinases both upstream and downstream to PTEN. The kinases CK2, GSK3 and Src have a direct effect on PTEN by phosphorylating it and rendering it inactive, and the kinases MKK4, IKK and STK11 impede PTEN activity mediated by other cellular proteins. Interestingly, kinases, including ROCK, PICT1 and RAK, activate PTEN by phosphorylation; and other proteins, including MAGI and MAST, stabilize PTEN through indirect mechanisms.

Expression of PTEN is also regulated by several transcription factors, notably p53, Egr-1, E2F1, and PPAR- γ , which activate PTEN expression by binding to different sites in its promoter region. Contrary to this, the transcription factors, Evi1, JUN, GATA2, SNAIL, NOTCH1 and NF κ B, prevent expression of PTEN. Several cellular proteins have also been identified which regulate PTEN. Among these, MAG, SHP-1, NEP, RhoA, SPARC, β -arrestin, Semaphorin 4D, NHERF-1, NHERF-2, SPRY2, the p17 matrix protein from HIV-1 and the YSV tripeptide activate or increase PTEN expression levels while Src, CSIG, p110 δ subunit of PI3K, tissue transglutaminase-2, PGE synthase-1, P-REX2a, PCAF, SIPL1, MAN2C1, NEDD4-1 and reactive oxygen species suppress or negatively regulate PTEN expression in the cells.

Additionally, several monoclonal antibodies, protein inhibitors, synthetic and natural compounds have been identified which modulate PTEN. With high significance of PTEN in establishing normal cellular functions, PTEN modulators are specifically explored. In this regard, the present review highlights numerous possibilities for the development of novel therapeutic interventions with promising commercial interests. In addition, this review summarizes several potential targets for the treatment of major human diseases in which PTEN plays a pivotal role, such as cancer, type 2 diabetes, obesity, cardiovascular diseases, Alzheimer's, autism, and Parkinson's disease.

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Article highlights

- PTEN regulates normal physiological functions in the cell by inhibiting biochemical pathways that induce cell proliferation, cell survival, protein synthesis, and other cellular activities.
- Some of the PTEN-related diseases in human include cardiovascular diseases, diabetes, obesity, cancer, autism, Parkinson's and Alzheimer's diseases.
- At the genetic level in several pathological conditions, PTEN gene is deleted, mutated or methylated. At the protein level, PTEN gene is modified due to phosphorylation, acetylation and oxidation, indicating that it is a highly targeted gene/protein whose loss of function leads to many pathological conditions in human.
- Several transcription factors and cellular proteins also affect PTEN expression.
- Specific kinases and kinase-domain-containing proteins phosphorylate PTEN at several amino acid residues in its C-terminal tail region.
- Development of novel PTEN agonists or mimetic compounds could lead to restoration of its normal cellular functions.
- Development and use of monoclonal antibodies, peptide or inhibitors specific to kinases, transcription factors and cellular proteins that affect PTEN could be of high therapeutic value in the treatment of PTEN-related diseases.

This box summarizes key points contained in the article.

Figure 1.

A. Represents the Chain A structure of PTEN with PDB id “1D5R” with P-loop, WPD-loop and TI-loops, as highlighted, which are phosphatase characteristic regions. **B.** Shows specific residues that are phosphorylated by different kinases in the C-terminal tail region of PTEN. The panel B also shows the possible β -sheet structural features of the C-terminal tail region. **C.** Illustrates membrane binding and activation of PTEN which leads to inhibition of cellular pathways that are associated with specific human diseases, as described.

Figure 2. PTEN inhibits different cellular pathways

The inhibitory role of PTEN is highlighted to indicate its molecular targets in cellular signaling pathways that affect cell migration, proliferation, survival and protein synthesis.

Figure 3. PTEN modulation by kinases or kinase-domain-containing proteins

Different intracellular proteins that target PTEN to inhibit or activate its cellular functions are shown. This inhibition or activation of PTEN functions is primarily mediated through phosphorylation of specific residues in its C-terminal region.

Figure 4. Role of PTEN in type 2 diabetes

Figure shows the intracellular insulin regulation pathway and the interference of PTEN through the regulation of glucose metabolism.

Table 1

Specific kinases and kinase-domain-containing proteins as potential targets for the development of therapeutic drugs which can restore normal PTEN functions.

Potential target	Effect on PTEN	Refs.
CK2 (casein kinase 2)	Inactivates PTEN by phosphorylating at S370 and S385	[8]
GSK3 β (glycogen synthase kinase)	Inhibits PTEN activity by phosphorylation at S362 and T366	[10]
ROCK (RhoA-associated Kinase)	Activates PTEN and targets it to the plasma membrane; phosphorylates at S229, T232, T319, T321	[16]
MKK4 (JNKK or SEK1)	Suppresses PTEN transcription via direct binding of NF κ B to PTEN promoter	[36]
Src Kinases	Inhibits PTEN by phosphorylation at tyrosine residues	[39]
IKK	Transient expression of PTEN suppressed IKK activation and TNF-induced NF κ B DNA binding and transactivation	[40]
JNK	Loss of PTEN upregulates JNK indicating, PTEN inhibits JNK	[41]
Jak2	Upregulates Src which activates CK2 and leads to inhibition of PTEN	[18]
PICT1	Upregulates PTEN levels and phosphorylates at S380	[14]
PLK-1	Plk1 phosphorylates PTEN at Thr366 and/or Ser370 and promotes its association with chromatin.	[42]
STK11 (LKB-1)	Binds to the N-terminal end of C2 domain of PTEN and forms a cytoplasmic complex	[9]
RAK (FRK, Fyn-related kinase)	Activates PTEN by phosphorylation at Tyr366 and regulates PTEN stability and function	[15]
MAGI-2 & 3 (membrane-associated guanylate kinase inverted)	Stabilizes PTEN through interactions with vinculin and β -catenin	[11,12,43]
MAST1, MAST3 (microtubule-associated serine-threonine kinase)	Stabilizes PTEN by phosphorylation	[13]
PDK1 (phosphoinositide-dependent protein kinase)	A target of PTEN that induces neoplasia in PTEN null conditions and in elevated levels of Akt and S6K	[44]

Table 2

List of therapeutic drugs that enhance PTEN activity.

Drug	Target	Effect on PTEN	Patentee/provider (Refs.)
Ublituximab	NFκB-Snail-RKIP	Induces PTEN and sensitizes TRAIL apoptotic pathway	LFB Biotechnologies US20120100133; [45,46]
Trastuzumab (Herceptin)	HER2	Increases PTEN activity through Src inhibition	Genentech & UCLA US20110165155A1 [47,48]
Pertuzumab	HER2 dimerization	Activates PTEN, similar to Trastuzumab	Genentech US20110044977A1 [49,50]
Rituximab	PI3K-Akt pathway	Induces PTEN	IDEC Pharmaceuticals EP1974747B1 [51,52]
Cetuximab	EGFR	PTEN loss is associated with nonresponsiveness to cetuximab	Yeda & Sanofi-Aventis EP0667165 [53,54]
Sunitinib (Sutent, SU11248)	PDGFR signaling	Induces PTEN expression	Sugen-Pfizer US6573293 [55,56]
Gefitinib (ZD1839, Iressa)	EGFR	Loss of PTEN results in gefitinib resistance	AstraZeneca EP1509230B1 [57,58]
Erlotinib	EGFR	PTEN loss contributes to erlotinib resistance	OSI Pharmaceuticals US6900221 [59,60]
Resistin (cytokine)	p38MAPK and ATF2	Increases PTEN expression by activating p38MAPK and ATF2, and leads to decreased Akt and eNOS	Identified in University of Pennsylvania [61]
Simvastatin	NFκB	Increases PTEN expression level by inhibiting NFκB	Apotex, Inc. US5393893 [62,63]
Lovastatin (Mevacor)	PPAR-γ	Increases PTEN expression	MERCK US4231938 [64,65]
Rosiglitazone (Avandia, PPAR-γ agonist)	PPAR-γ	Upregulates PTEN expression	GlaxoSmithKline (GSK) US7358366 [64,66]
NVP-AEW541 (IGF-1R inhibitor)	IGF-1R	Induces radiosensitization in a PTEN-dependent manner	Novartis [67]
PP1, Herbimycin (Src inhibitors)	Src	Reduces pervanadate-induced tyrosine phosphorylation of PTEN	EMD Biosciences [39]
γ-Secretase inhibitor (NOTCH1 inhibitors)	NOTCH1	Upregulates PTEN expression	SelleckBio [32]
DMAT (CK2 inhibitor)	CK2-Leptin	Prevents leptin from phosphorylating PTEN at Ser-370 and Ser-385 residues but not at Thr-366 residue	Sigma [21]
CT99021 (GSK3 inhibitor)	GSK3	Prevents leptin from phosphorylating only Thr-366 residue of PTEN	SelleckChem [21]
Salinosporamide A (NPI-0052)	PTEN & RKIP	Induces expression of PTEN and RKIP	Univ of California Oakland & Nereus Pharmaceuticals US20090148445 [68]
Sodium Selenite	Thioredoxin, Akt, CK2	Increases PTEN activity	[69]

Table 3

Transcription factors that regulate PTEN expression.

Transcription factor	Effect on PTEN expression	Refs.
p53	Activates PTEN by binding in the promoter region	[70]
Egr-1	Activates PTEN and induces apoptosis in irradiation-induced signaling by binding to the 5' UTR of PTEN	[71]
Evi1	Represses PTEN transcription in bone marrow by binding to polycomb group of proteins	[72]
E2F1	Activates PTEN by binding to the 5' UTR and induces p53-independent apoptosis	[73]
PPAR- γ	Activates PTEN by binding to PPRE1 and PPRE2 elements in the promoter	[66]
JUN	Suppresses PTEN expression by binding to AP-1 site in the PTEN promoter	[33]
GATA2	Inhibits PTEN expression and stimulates Akt phosphorylation	[74]
SNAIL	Binds to the PTEN promoter and prevents the association of p53 with the PTEN promoter region	[75]
NOTCH1	Inhibits PTEN through HES-1 transcription factor; increases PTEN transcription by MYC or CBF1	[32]
NF κ B	NF κ B downregulates PTEN expression through IKK β pathway, and this regulation is mediated by the p65 subunit of NF κ B	[76]

Table 4

Cellular proteins that interact with PTEN and regulate its functions.

Target protein	Therapeutic implications	Refs.
p17 (HIV-1 matrix protein)	Activates PTEN by binding to its C-terminal tail region, and suppresses Akt signaling mediated by ROCK	[77]
MAG (myelin-associated glycoprotein)	Activates PTEN and decreases phosphorylated Akt in the neurons	[78]
SHP-1 (SH2 domain containing tyrosine phosphatase)	Selectively binds and dephosphorylates PTEN making it inactive	[39]
NEP	Electrostatically binds to and phosphorylates PTEN in the C-terminal tail region and enhances its stability and phosphatase activity besides recruiting it in the plasma membrane	[79]
RhoA	Activates ROCK which upregulates PTEN	[80,81]
YSV tripeptide	Increased expression of PTEN and other tumor suppressor genes. Activates PTEN and inhibits Akt by dephosphorylating both	[82]
SPARC	Overexpression increases PTEN activity and suppresses Akt both <i>in vitro</i> and <i>in vivo</i>	[83]
Semaphorin 4D	Activates PTEN by dephosphorylation at Ser-380.	[84]
CSIG	Interacts with PTEN mRNA in the 5' UTR and negatively regulates PTEN expression promoting cell proliferation	[85]
β -arrestin	Controls activation of PTEN and also inhibits the antimigratory effects of PTEN	[86]
Tissue transglutaminase-2	Promotes degradation of PTEN by ubiquitin-proteasomal pathway and activates FAK/Akt pathway	[87]
PGE synthase-1	Inhibits expression of PTEN by activating EGFR-PI3K-AKT-mTOR signaling	[88]
p110 δ (catalytic subunit of PI3K)	Inhibits PTEN through RhoA pathway	[89]
P-REX2a	Inhibits PTEN lipid phosphatase activity	[90]
PCAF (p300/CBP-associated factor)	Negative regulator of PTEN, acetylates Lys125 and Lys128	[91]
SIPL1 (Shank interacting protein-like1)	Negative regulator of PTEN inhibits its phosphatase activity	[92]
MAN2C1 (α -Mannosidase 2C1)	A negative regulator of PTEN which inhibits PTEN function by binding to PTEN and prevents its phosphatase activity	[93]
ROS (reactive oxygen species)	Inactivate PTEN by oxidizing Cys124	[94]
NHERF-1, 2 (Na ⁺ /H ⁺ exchanger regulatory factor)	Interacts with PDZ domain of PTEN and restricts PI3K activation effects	[95]
SPRY2	Increases PTEN levels and activity by decreasing PTEN phosphorylation	[96]
NEDD4-1	Polyubiquitylates PTEN and promotes its degradation in the cytoplasm	[37]