Biointerface Research in Applied Chemistry
Platinum Open Access Journal (ISSN: 2069-5837)

Review
Volume 11, Issue 2, 2021, 9587 - 9603
https://doi.org/10.33263/BRIAC112.95879603

Essence of *PTEN*: a Broad-Spectrum Therapeutic Target in Cancer

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Scopus Author ID 55693618000
Received: 18.08.2020; Revised: 11.09.2020; Accepted: 12.09.2020; Published: 15.09.2020

Abstract: The levels of protein tyrosine phosphorylation within a cell is regulated by protein tyrosine kinases and protein tyrosine phosphatases. These protein tyrosine phosphatases (PTP) can act both as positive and negative regulators during cell cycle progression and signal transduction. Phosphatase activity is shown by Phosphatase and Tensin homolog (*PTEN*) protein encoded by *PTEN* gene localized on human chromosome 10. Earlier findings established the role of *PTEN* as a tumor suppressor in Cowden's disease, where *PTEN* mutations resulted in disease outcomes. Subsequent studies found the role of *PTEN* mutations in various human cancers, making it one of the vastly studied tumor suppressor genes. The current review has been planned to get a deeper insight into the potential role of *PTEN* in a variety of physiological processes involved in normal development like cell growth, migration, and differentiation along with the factors, regulation, and underlying mechanism.

Keywords: PTEN; Cancer; cell proliferation; Cell Cycle regulation; intracellular; cytotoxic; tumor suppression; Phosphorylation.

1. Introduction

Protein tyrosine kinase and protein tyrosine phosphatase regulate the level of protein tyrosine phosphorylation within a cell. These protein tyrosine phosphatases (PTP) can act both as a positive and negative regulator during cell cycle progression and signal transduction [1]. A large number of proteins are included in the PTP superfamily, which also comprises of dual specific phosphatases. Phosphatase activity similar to such dual phosphatases is shown by Phosphatase and Tensin homolog (*PTEN*) protein encoded by *PTEN* gene, which is localized on human chromosome 10. The role of *PTEN* as a tumor suppressor was initially found in Cowden's disease, where *PTEN* mutations resulted in disease outcomes [2]. Subsequent studies had found the role of *PTEN* mutations in various human cancers, making it one of the vastly studied tumor suppressor genes [3].

PTEN plays a major role in processes involved in normal development like cell growth, migration, and differentiation by inhibiting signals transduced by phosphotidylinositol-3-kinase (PI3K) [4]. PI3Ks comprises of lipid kinases that activate various signaling pathways through phosphorylation. These are grouped in 3 classes on the basis of substrate preference and sequence homology [5]. Class I PI3Ks can either be activated by receptor tyrosine kinases (RTKs) or by G-Protein coupled receptors (GPCRs), which can further activate

serine/threonine kinase AKT and other downstream pathways. It had been found that genetic alteration in several proteins in PI3K pathway culminates into cancer. Some evidence suggested that constituents of PI3K pathway are highly suitable for pharmacologic intervention and one of the most alluring targets for therapeutic intervention in cancer. Further, the functioning of *PTEN* as PIP_3 3'-phosphatase turns off PI3K pathway, thus renders its tumor suppressor activity (Fig.1). Therefore, the loss of *PTEN* activity could result in uncontrolled signaling through PIK3 pathway leading to cancer [6]. In addition to *PTEN*, *SHIP-2* functions as PIP_3 5'-phosphatase to negatively regulate PI3K and protein kinase B (PKB) pathway, as seen in glioblastoma multiform brain tumors [7,8]. Recently, many functions of *PTEN* independent of PI3K/AKT signaling pathway are also explored [9]. This review, therefore, covers the role of *PTEN* both as a tumor suppressor and metabolic regulator, including its downstream targets. Additionally, epigenetic regulation of *PTEN* is also discussed.

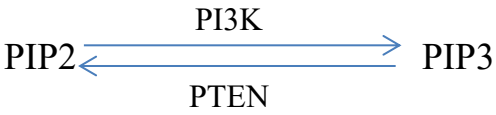

Figure 1. The antagonistic function of PI3K and *PTEN*.

The protein encoded by *PTEN* comprises of 403 amino acid residues with a structurally significant catalytic phosphatase domain and C2 domain. Both N and C-terminus of *PTEN* have crucial sequences as the N-terminus sequence is responsible for the binding of the protein to membrane lipids, and C-terminus contains a binding motif involved in protein-protein interaction [10]. *PTEN* possesses both lipid and protein phosphatase activity *in-vitro* [11], whereas, under *in-vivo* conditions, mostly lipid phosphatase activity is observed [12,13].

2. Diverse roles of *PTEN* in relation to cancer

2.1. Role of PTEN in cell cycle regulation.

A cell cycle is a coordinated event consisting of four distinct phases (G1, S, G2, and M). *PTEN* plays a significant role in normal cell cycle regulation as it controls the re-entry of cells in cell cycle phases resting in G_0 stage. Moreover, it also acts as a regulatory switch from G1/S and G2/M transition. Various studies marked *PTEN* as an important component of multiple checkpoints to prevent uncontrolled proliferation (Fig. 2). Abnormal development of the cephalic region was found in *PTEN* mutant embryos [14-16]. In addition to this, *PTEN* mutants also showed decreased sensitivity to apoptosis.

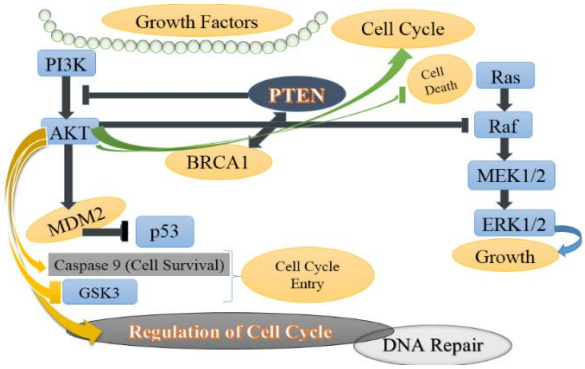

Figure 2. Schematic representation of PTEN involved in cell signaling through the participation of other tumor suppressors such as TP53, MDM2, and BRCA1 performing a variety of physiological functions such as cell proliferation, DNA repair, and regulation of cell cycle, etc.

2.1.1. Role in G1-S transition.

Entry and progression through G1 depend upon cell type and context where each cell undergoes different signals and developmental programs with differential risk of transformation [17]. Progression of the cell through different stages of the cell cycle is mediated by cyclin-CDK complex. Cyclin dependant kinase (CDK) requires cyclin for catalytic competence and different cyclin-CDK complex works during different stages of the cell cycle. In addition to the role of small inhibitory proteins like Inhibitors of CDK4 (INK4), CDK interacting protein/Kinase inhibitory protein (CIP/KIP) [18], and ubiquitin-mediated proteolysis mechanism[19], *PTEN* also regulates G1 progression and G1/S transition. Progression of the cell cycle with accelerated G1/S transition was seen due to the loss of *PTEN* in embryonic stem cells[20]. Expression of p27 ^{Kip1} induced by *PTEN* showed a reduction in CDK2 activity inhibiting G1/S transition[21]. This was further proved that *PTEN* induced G1 arrest requires p27 ^{Kip1}. Collateral deletion of *PTEN* and *p27^{Kip1}* led to the development of prostate cancer, highlighting their importance in tumor suppression [22,23]. Besides *PTEN*-p27 ^{Kip1} pathway, certain other regulators are also involved in *PTEN* mediated control of G1 phase[24]. The role of *PTEN* in cell cycle regulation has been elucidated in Figure 3.

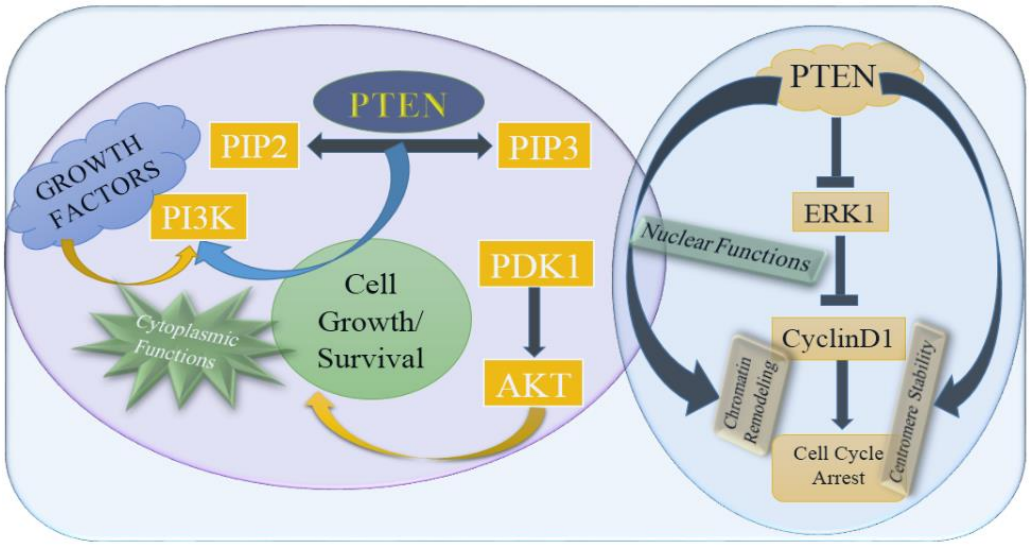

Figure 3. Role of *PTEN* in cell cycle regulation. *PTEN* signaling at the nuclear and cytoplasmic levels has been shown with a coordinating role in the facilitation of diverse mechanisms in cell cycle regulation. The *PTEN* localization at the subcellular levels is a determinant of its functional aspects. At the cytoplasmic level, there is a downregulation of AKT, along with an increase in the levels of other associated components leading to apoptosis. While at the nuclear level, *PTEN* downregulates *ERK*, increasing the cyclin D1 levels leading to cell cycle arrest, overall genomic stability, and increased apoptosis.

Along with cytoplasmic localization, *PTEN* is also found in the nucleus to induce G1 arrest independently [25]. Oxidative stress causes *PTEN* phosphorylation resulting in nuclear accumulation by inhibiting nuclear export[26]. Regulation of G1 phase by *PTEN* is mediated by the upregulation of p27 ^{Kip1} by cytoplasmic *PTEN* and downregulation of cyclin D1 by nuclear PTEN [27]. Nuclear *PTEN* can further cause acetylation of p53 in response to DNA damage resulting in G1 arrest[28]. G1 arrest can also be mediated by nuclear *PTEN* in combination with SPRY2 (Sprouty RTK Signaling Antagonist 2)[29]. Thus, *PTEN* inhibits premature progression to S phase and also regulates DNA fork progression during S phase. *PTEN* recruits damage response proteins in case of replication stress [30]and further interacts with single-strand DNA binding protein and DNA helicase for stabilization of the replication

fork [31]. The loss of *PTEN*, therefore, results in replication errors enhancing genomic toxicity [32].

2.1.2. Role in G2-M transition.

The involvement of *PTEN* in G2-M transition was found in *PTEN* deficient cells, which showed the accelerated transition from G2/M to G1 in response to radiation-induced DNA damage [33]. This was further validated as *PTEN* null embryonic stem cells showed premature exit from G2 on radiation treatment [34]. Phosphorylation of *PTEN* by CHK1 (Checkpoint kinase 1) can cause cells with hindered DNA replication to enter G2/M[35]. Inhibition of Notch signaling and dephosphorylation of *PTEN* can result in prometaphase arrest preventing the progression of the cell cycle [36]. *PTEN* can also be dephosphorylated by TOPK (lymphokine-activated killer T cell-originated protein kinase) to control mitotic entry [37]. *PTEN* further interacts with TOP2A (DNA topoisomerase IIα) at the decatenation checkpoint in G2 phase for removal of entangled DNA before mitotic entry [38]. During mitosis, loss of *PTEN* affects the integrity of centrosomes and mitotic spindle, resulting in misalignment of chromosomes, variable ploidy, and tumorigenesis [39]. These mitotic defects can be mediated by increased expression and phosphorylation of PLK1 (polo-like kinase) having oncogenic potential. *PTEN* controls the expression and phosphorylation level of PLK1, thereby protecting cell division and polyploidy [40,41]. Mutual interaction is set between *PTEN* and PLK1, where they control each other's phosphorylation to mediate their function during mitotic exit. Similarly, reciprocal regulation between *PTEN* and APC/C^{CDH1} (Anaphase promoting complex) promotes the transition from mitotic exit to the next cell cycle. CDH1 causes APC/C induced ubiquitination of *PTEN*, resulting in *PTEN* degradation and mitotic exit [42].

2.2. PTEN as a tumor suppressor.

PTEN is one of the most frequently mutated genes in human cancers, and germ-line mutations in *PTEN* can result in rare autosomal dominant inherited cancer syndromes [43]. Somatic mutations occur throughout *PTEN* gene along with specific hotspots [44]. These mutations can result in increased cell proliferation, reduced cell death, and tumor development. Mutations also lead to loss of *PTEN* function or reduced levels of *PTEN* in most of the cases. Genetic inactivation of *PTEN* is frequently found in glioblastoma, melanoma, endometrial, prostate, colon, and bladder cancer, whereas reduced expression is observed in lung and breast cancer[45-47]. Analysis of $PTEN^{hy/+}$ mouse model revealed that even subtle reduction in *PTEN* expression could promote cancer susceptibility in mice, highlighting the importance of *PTEN*-controlled pathways for tumor development [48]. In addition to genetic mutations in *PTEN*, epigenetic silencing, transcriptional repression, and post-translational modifications can result in loss of *PTEN* function.

3. Metabolic activities

Though *PTEN* is globally accepted as a potent tumor suppressor gene its role in metabolic regulation has recently been highlighted by genetic studies. The phosphatase activity of *PTEN* reduces the level of PIP_3 that functions as a critical secondary messenger[49]. Studies on *C. elegans* and *Drosophila* showed the involvement of *PTEN* in growth control and metabolism.

3.1. Regulation of glucose metabolism.

Binding of Insulin and Insulin-like growth factors (IGF-1 and IGF-2) to insulin and IGF receptors can either result in direct activation of PI3K or can phosphorylate insulin receptor substrate (IRS) for PI3K activation [50]. Activation of PI3K/AKT results in elevated insulin levels that are sensed by adipocytes and myocytes to initiate glucose uptake. Insulin/PI3K signaling induces membrane trafficking of GLUT4 through phosphorylation of AS160 at Thr642 by serine/threonine kinase AKT in adipocytes [51]. AKT further phosphorylates other targets that are indulged in regulating glucose metabolism. Phosphorylation and inhibition of GSK3 activate glycogen synthase in addition to the regulation of β-catenin and cell cycle. Liver-specific *PTEN* null mutation in mice caused phosphorylation of GSK3 and accumulation of glycogen in hepatocytes [52]. Additionally, AKT mediated phosphorylation of FOXO in hepatocytes blocked transcription of glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK) involved in gluconeogenesis [53]. These two enzymes are also transcriptionally repressed through phosphorylation of peroxisome proliferator-activated receptor-gamma co-activator (PGC-1α) by AKT [54]. Regulation by AKT and blockage by *PTEN* mediates the response of metabolic organs like liver, muscle, and adipose tissue to elevated insulin levels [55]. A similar response was seen in mice where *PTEN* deletion in the liver caused strong down-regulation of PEPCK and moderate down-regulation of G6Pase. Similarly, the deletion of *PTEN* in mice adipose tissues showed increased insulin sensitivity, increased membrane localization of GLUT4, and resistance to streptozotocin-induced diabetes [55,56].

3.2. Regulation of lipid metabolism.

Lipid metabolism is also controlled through *PTEN*-regulated PI3K signaling. *PTEN*/PI3K/AKT signaling controls the expression of sterol receptor element-binding protein (SREBP) at multiple levels. SREBP functions as a critical master regulator involved in lipogenesis by binding to the promoter of lipogenic enzyme genes. The transcription of *SREBP* is repressed by the forkhead transcriptional factor, FoxO1 that is a downstream target of AKT [57]. A study demonstrated that induction of SREBP1 transcription is also dependant on TORC1 activity by using rapamycin and siRNA to inhibit mTORC1 [58,59]. But contradictory results were seen in *TSC1*-deficient mice having a defect in mTORC1 signaling [60,61]. SREBP cleavage-activating protein (SCAP) and insulin-induced gene (Insig) controls the processing of SREBP. SCAP mediates cleavage and movement of mature SREBP to the nucleus in response to sterol demand. This action is inhibited by the binding of Insig to SCAP. Interaction of Insig and SCAP is blocked either by inhibition of PI3K/AKT activity or by oxysterols that suppress the expression of Insig-1 [62]. This results in the processing of SREBP that is both mTORC1-dependent and mTORC1-independent [63]. Both TORC1 and FoxO1 are downstream targets of *PTEN*/PI3K/AKT signaling control SREBP expression and lipogenesis. Additionally, the expression of *Fasn* by SREBP is inhibited by the binding of Maf-1 to the promoter of *Fasn*. The expression of *MAF-1* is itself regulated by *PTEN* through AKT2 and mTOR [64,65]. These signaling responses were validated in *PTEN* deficient mice. Loss of *PTEN* in mice liver resulted in heightened *de novo* lipogenesis through *SREBP* induction and *Fasn* expression. Activation of AKT2 caused elevated lipogenesis, which is both mTOR dependant and independent, and this effect was reversed by the deletion of *Akt2* [66]. Additionally, the gain of function of FOXO1 induced lipid synthesis [67].

3.3 Regulation of mitochondrial metabolism.

The involvement of PI3K/AKT signaling in mitochondrial function has been discovered while elucidating molecular signals underlying "Warburg effects" [50]. The involvement of AKT is found in the inner and outer mitochondrial membrane along with the mitochondrial matrix. Binding of hexokinase II to mitochondrial voltage-dependent anion channel (VDAC) is promoted by AKT that causes phosphorylation of glucose molecules and conversion to ATP at the mitochondrial outer membrane [68,69]. Localization of AKT in the inner mitochondrial membrane [70] whereas within the mitochondrial matrix, AKT causes phosphorylation of GSK3β and pyruvate dehydrogenase (PDH) to regulate mitochondrial respiration [71]. Mitochondrial localized AKT further regulates transcription of mitochondrial DNA as a promoter of HMG-CoA contains FOXO-3 response element [72]. Members of PGC-1 family function as transcriptional co-activator by binding to estrogen-related receptors (ERRs) for mitochondrial function. ERRα is the best-characterized isoform of ERRs that is abundantly expressed in high oxidative organs [73]. The activity and expression of ERRα are increased by the binding of PGC-1α [49]. Activation of AKT causes phosphorylation and activation of CREB transcription factor, which in turn induces transcription of PGC-1 upon activation. PGC-1 as a co-activator increases transcription of ERRα to initiate transcription of mitochondrial genes [74].

Additionally, *NRF1*, which is also involved in the transcription of mitochondrial genes, contains a substrate consensus sequence of AKT where phosphorylation of NRF1 by AKT induced Tfam expression in hepatoma cells [75]. Thus, AKT controls mitochondrial gene transcriptional networks either by direct phosphorylation of FOXO and NRF1 or indirectly by inducing expression of ERRα. Similarly, overexpression of *NRF1* and *AKT* imitated the effect of TFAM to overrule ion-induced mitochondrial damage confirming the involvement of PI3K/AKT/FOXO signaling pathway in the regulation of mitochondrial gene transcription [76,77].

4. Regulation of *PTEN* at the post-translational level

The activity of *PTEN* can be regulated at genetic, epigenetic, and post-translational levels [78]. *PTEN* function can be lost partially or completely by genetic alterations occurring due to allelic loss, point, or truncation mutations [79]. Epigenetic alteration includes gene silencing due to promoter hypermethylation [80]. Post-translational modification of *PTEN* includes phosphorylation, ubiquitination, sumoylation, acetylation, and oxidation (Fig. 4).

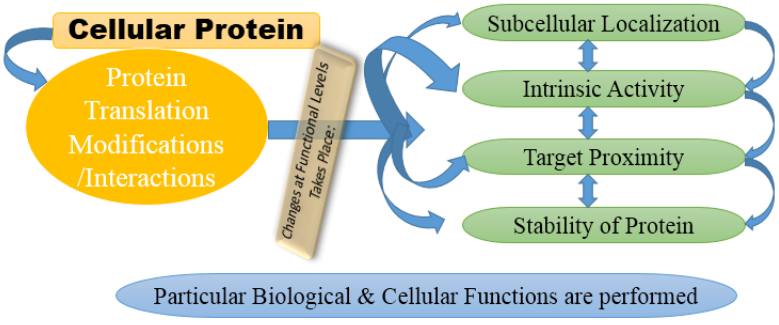

Figure 4. Post-translational regulation of *PTEN*. Post-translational regulation of *PTEN* commands its detailed cellular and biological functions; at cellular levels, specific PTM's/interactions generate biochemically distinctive subpopulations of *PTEN*, which is having certain biochemical and cellular properties for diverse and dedicated cellular and biological functions.

4.1. Phosphorylation.

Phosphorylation targets C2 and C-terminal domains of *PTEN* to modulate its activity [81-82]. Phosphorylation leads to a closed conformational state of *PTEN*, resulting in inactivation and increased stability. Increased phosphorylation causes reduced expression of *PTEN*, as seen in the case of gastric cancer [83,84]. *PTEN* in non-phosphorylated open state conformation shows increased association with the membrane [85]. So, dephosphorylation of *PTEN* is necessary before binding to membrane proteins. *PTEN* phosphorylation can be caused by multiple kinases that target specific sites. Abnormal regulation of *PTEN* by multiple cancer-specific kinases is shown in Table 1.

Table 1. Abnormal *PTEN* regulation by multiple cancer-specific kinases.

Specific Kinases	**Sites of *PTEN* targeted through phosphorylation**	**Abnormal Effects**	**Tumor Type**
CK2	Ser 370, Ser 380,Ser 385, Thr 382,	Decrease in phosphatase activity	Lymphoblastic Leukaemia, Endometrial carcinoma
RAK	Tyr 336	Irregularity in function and degradation of *PTEN*	Breast Cancer
PLK1	Thr 366,Ser 370,Ser 380,	Inactivation and degradation of *PTEN*	Prostate Cancer
LKB1	Ser 380,Ser 385, Thr 382, Thr 383	Inactivation of *PTEN*	Lung Squamous cell carcinoma, Ovarian cancer

PTEN is phosphorylated by glycogen synthase kinase-3β (GSK3β) at Ser362 and Thr366. GSK3β mediated phosphorylation of *PTEN* can function as a negative feedback loop of the PI3K signaling pathway [86]. Mutation at one of the phosphorylation sites (Ser385) promoted dephosphorylation events to regulate *PTEN* function. In addition to this, the interaction between COOH-terminal and CBRIII motif of the C2 domain was identified, and the auto-inhibitory role of COOH-terminal on *PTEN* membrane recruitment and phosphatase activity was suggested [87]. Moreover, RhoA-associated protein kinase (ROCK) mediated phosphorylation can lead to membrane translocation of *PTEN* [88]. The catalytic subunit of PI3K, p110 inactivates *PTEN* via RhoA and ROCK pathway through increased tyrosine phosphorylation of *PTEN* [89].

Similarly, Src family tyrosine kinase, FRK (Fyn-related kinase), promotes phosphorylation on Tyr336, causing *PTEN* stability [90]. The activity and stability of *PTEN* depend upon the site of phosphorylation and kinase involved. Phosphorylation of C2 domain of *PTEN* causes increased membrane affinity with decreased degradation. On the other hand, phosphorylation of the C-terminal domain caused a conformational change and increased stability with decreased activity and membrane targeting [79].

4.2. Ubiquitination and Sumoylation of PTEN.

PTEN levels can also be affected by downregulation through the ubiquitin/proteasome pathway. Loss of *PTEN* function due to ubiquitin-mediated degradation is considered to be the cause of non-small cell lung carcinoma [91]. Overexpression of NEDD4-1 induces ubiquitination of *PTEN* at Lys13 and 289 causing ubiquitin-mediated *PTEN* degradation [92]. Some reports indicated NEDD4-1 mediated *PTEN* regulation in the bladder, gastric, and colorectal cancers, but the deletion of *NEDD4-1* in mice and cultured cells does not prevent ubiquitination of *PTEN* [93]. This indicated role of additional E3 ligases like WWP2 (WW domain-containing protein 2) and X-linked inhibitor of apoptosis protein (XIAP) in regulating *PTEN* protein levels [94]. Polyubiquitination of *PTEN* results in degradation and loss of tumor

suppressor activity, whereas monoubiquitination causes nuclear transport and genomic stability. *PTEN* contains two PEST sequences that are a unique mark of ubiquitin-mediated degraded proteins [95]. Recently additional ubiquitination site (Lys66) was found in *PTEN*, which showed a major role in *PTEN* stability [96]. Inhibition of proteasome-mediated *PTEN* degradation is considered as a therapeutic approach for *PTEN* stability [97]. Deubiquitylase HAUSP/USP7 (Herpesvirus associated ubiquitin-specific protease) can reverse the monoubiquitination of *PTEN*, preventing nuclear import [98]. Mislocalization of *PTEN* is considered as a cause of central nervous system tumors and lymphomas [99].

Similarly, sumoylation mediated by SUMOs (Small ubiquitin-like modifiers) regulates *PTEN* activity through covalent attachment to the C2 domain of *PTEN* at Lys254 and 266. Sumoylation facilitates the binding of *PTEN* to the plasma membrane and downregulation of PI3K/AKT pathway, suppressing tumor progression [100]. An additional common site (K289) for SUMO mediated modification and monoubiquitination was found on *PTEN*. Monoubiquitination results in nuclear localization, whereas sumoylation results in recruitment to the plasma membrane. The exclusion of sunoylated *PTEN* from the nucleus made cells hypersensitive to DNA damage [101].

4.3. Acetylation of PTEN.

Stimulation by growth factors initiates acetylation of *PTEN* at Lys125 and 128 (K125 and K128) by lysine acetyltransferase 2B (KAT2b)/PCAF (p300-CREB binding protein), reducing catalytic activity of *PTEN* [102]. *PTEN* can also be acetylated at the PDZ binding domain (Lys402) by CREB binding protein, which affects the interaction of *PTEN* with PDZ domain-containing partners. Acetylation of *PTEN* can be reversed by deacetylase sirtuin 1 as *Sirt-1* deficient cells contained hyper-acetylated *PTEN* [103].

4.4. Oxidation of PTEN.

The activity of *PTEN* depends on the presence of highly reactive cysteine residue in the catalytic site that functions as protein tyrosine phosphatase sensitive to oxidation [104]. The catalytic activity of *PTEN* is inactivated by oxidation as a result of environmental stress or cellular strategy. Reactive oxygen species (ROS) in the form of H_2O_2 can oxidize cysteine to inactivate *PTEN*. This is done by the formation of a disulfide bond between Cys124 and Cys71 [105,106]. The role of ROS in *PTEN* inactivation was studied [107], where treatment of murine macrophage cell line with lipopolysaccharide and phorbol acetate increased the percentage of inactive oxidized cellular *PTEN*. Thioredoxin prevents oxidation mediation inactivation of *PTEN* [105]. Interaction between peroxiredoxin 1 (PRDX1) and *PTEN* forms the *PTEN*-PRDX1 complex that prevents oxidation of *PTEN* by inhibition of disulfide bond formation [108]. This was evident as incubation of cells with thioredoxin reductase inhibitor (2,4-dinitro-1-chlorobenzene) delayed the reduction of oxidized *PTEN* and overexpression of thioredoxin reductase promoted resumption of tumor suppressor activity of *PTEN*. Additionally, the activity of *PTEN* can also be affected by the oxidation of *PTEN*-binding partners [109]. Increased ROS levels in tumor cells can initiate *PTEN* inactivation through oxidation and subsequent activation of the PI3K/AKT signaling pathway. The use of ROS scavengers as an approach can enhance *PTEN* activity against lymphoblastic leukemic cells [79].

5. Transcriptional and post-transcriptional regulation of *PTEN*

The regulation of *PTEN* is also undertaken at transcriptional and post-transcriptional levels. Transcription of *PTEN* is regulated by several transcriptional factors that include p53, early growth response protein 1 (EGR-1), peroxisome proliferation-activator receptor γ (PPARγ) [50], and active transcription factor 2 (ATF2) [110]. Transcriptional repression of *PTEN* is promoted by SNAIL and SLUG [111], where these two compete with p53 to bind to the promoter of *PTEN.* Additionally, transcription of *PTEN* is regulated by binding of nuclear kappa B (NFkB), AP-1 transcription factor subunit c-Jun, and Notch signaling co-regulatory CBF-1 (C-promoter binding factor-1) to promoter region [112,113].

6. RNA mediated regulation of *PTEN*

Recently, RNA mediated regulation of *PTEN* is reported through RNA-RNA interaction by microRNAs and long non-coding RNAs. Several miRNAs were found to bind to 3'-UTR of *PTEN* mRNA. This is supported by the fact that the reduction in *PTEN* mRNA levels is observed by a simultaneous increase in levels of various miRNAs [114-116]. A sequence similar to *PTEN* mRNA is shared by long non-coding RNA encoded by *PTEN* pseudogene transcript *PTEN*P1 [117]. This transcript stabilizes *PTEN* mRNA by binding to *PTEN* targeting miRNAs. Negative *PTEN* regulation is promoted by binding of an antisense transcript of this pseudogene to *PTEN* promoter [118,119].

7. Regulation of *PTEN* by protein-protein interactions

PTEN activity can be affected by interacting proteins. Most of these interactions are mediated by *PTEN* C-terminal PDZ-BD and involves interaction with scaffold proteins. These interactions can alter the role of *PTEN* as a tumor suppressor by causing a change in its conformation, location, and stability [78]. Binding of interacting protein, melanocortin-1 (MC1R) prevents ubiquitination and degradation of *PTEN* [120]. Similarly, the ubiquitination of *PTEN* by NEDD4-1 is inhibited by binding of FRK (Fyn-related kinase) to *PTEN*. *PTEN* localization can be regulated by interacting proteins that can influence its function and activity. Increased membrane localization of *PTEN* is influenced by scaffold proteins like β-arrestins and membrane-associated guanylate kinase inverted 2 (MAGI2). This causes the activation of the phosphatase activity of *PTEN* [121,122]. *PTEN* interacts with the adaptor protein NHERF (Na^+/H^+ exchanger regulatory factor) through the PDZ domain to form a ternary complex that prevents activation of the PI3K/AKT pathway [123]. Movement of *PTEN* towards the cellular membrane is regulated by motor protein myosin V which enhances its phosphatase activity [124]. Similarly, tumor suppressor activity and stability of *PTEN* is enhanced after its interaction with mammalian DLG1 (discs large homolog 1) [125]. The lipid phosphatase function of *PTEN* can also be activated after interaction with p85 [126]. Disruption in p85-*PTEN* binding through mutation in the *p85* gene increased PIP3 levels and AKT phosphorylation [127]. Binding of microtubule-associated Ser/The kinase 2 (MAST2) to PDZ motif of *PTEN* increased *PTEN* phosphorylation [128]. The lipid phosphatase activity of *PTEN* is also influenced by other regulators, including PREX2a (PIP3 dependent RAC exchanger factor 2a) [129], SIPL1 (Shank-interacting protein-like 1) [130], and MAN2C1 (α-mannosidase 2C1) [131].

8. Epigenetic alteration of *PTEN*

The role of epigenetics in *PTEN* expression has been proposed where promoter methylation suppressed *PTEN* expression in various types of cancer [132]. Methylation is mostly related to transcriptional repression, but *PTEN* transcription is not downregulated by promoter methylation under all conditions. This condition was discovered in patients with Cowden syndrome (CS) and Cowden like syndrome (CLS) lacking *PTEN* mutations [133]. *PTEN* promoter hyper-methylation showed no detectable effect on *PTEN* expression in such patients. However, the expression of another gene, *KILLIN* sharing *PTEN* promoter and transcribing in the opposite direction, was affected. This *KILLIN* gene is the target of p53 and is responsible for p53 induced apoptosis [134]. In addition to this, an important finding showed predominant methylation of *PTEN* pseudogene (psi*PTEN*) rather than *PTEN* in cell lines and tumors [135]. Their investigation showed 98% identity between both genes, which also covers the subsequent part of *PTEN* promoter. As a result, such an enormous level of homology challenges the methylation study of the *PTEN* gene. So, nucleotide differences between both sequences should be critically considered for performing *PTEN* methylation analysis as results obtained might not reflect the exact methylation status of *PTEN*.

9. Conclusion

The detailed insight into the various regulatory components of the *PTEN* pathway reveals its multifaceted potential in a variety of physiological processes involved in normal development like cellular growth, migration, and differentiation, along with the factors and regulation. Owing to its tumor suppression, *PTEN* is a commonly mutated gene, reported in several types of cancers. This gene plays a significant role in the regulation of cell growth, survival, proliferation, genomic stability, and cell motility as well. Loss of *PTEN* activity is a major troublesome that hinders in identifying the clinical aspects of its activity. Still, a number of studies are going on in developing *PTEN* inhibitors, which look promising and be biologically active. A specific inhibitor or activator can target *PTEN*, resulting in its inhibition/activation at pharmacological levels, which can be helpful in the treatment of Breast Cancer. A thorough insight into the *PTEN* pathway can further help us in the exploration of more developed and updated cancer therapies.

Funding

This research received no external funding.

Acknowledgments

The authors are obliged to Maharishi Markandeshwar (Deemed to be University) Mullana (Ambala) for providing the requisite platform to carry out this work.

Conflicts of Interest

The authors declare no conflict of interest.

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