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## PTEN-A REVIEW

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**ABSTRACT:** PTEN (phosphatase and tension homolog deleted on chromosome 10) is an important key factor in regulating intracellular for cell growth and proliferation by blocking the phosphatidylinositol -3kinase/ AKT protein kinase B (PI3K/Akt) pathway alteration in PTEN is concomitant with many diseases. PTEN is recurrently mutated in several pathological diseases which indicate its significance in general physiological activity. Various cellular proteins are initiated by phosphorylation; in contrast, PTEN is deactivated based on phosphorylation by specific kinases. Therefore, the development of therapeutic agents includes selectively targeting quickness and kinase-domain containing proteins affecting PTEN associated diseases. The present review focuses on the role of PTEN in pathological conditions and a comprehensive list of currently identified modulators of PTEN and explains potential new molecular targets which could be help in the development of drugs for the management of PTEN associated diseases like cardiovascular diseases, diabetes, obesity, cancer, autism, and Alzheimer's diseases.

**INTRODUCTION:** PTEN (Phosphatase and tension homolog deleted on chromosome 10) was initially recognized as a tumor suppressor, discovered in 1997 and it is most frequently mutated gene discovered so far in several neoplastic diseases such as glioblastoma, endometrial cancer, prostate cancer and some other diseases like diabetes and Alzheimer's. Apart from its genetic alterations, PTEN expression is also affected by DNA methylation, mRNA degradation, post-translational modifications, transcription and translational regulation in the cell represents that PTEN is a highly targeted protein in many human diseases<sup>1</sup>.

PTEN is a regularly expressed protein, function as a dual function like specific protein phospholipid phosphatase. It maintains several processes and signals transduction pathway mediated through PtdIns (3,4,5) P3 has been widely considered and it shows a specific function in controlling various physiological and pathological important processes like cell proliferation, motility, cell growth, and survival. This because of increased lipid concentration upon exposure to various stimuli includes growth factors<sup>2</sup>.

**Structure of PTEN:** PTEN **Fig. 1** protein belongs to the PTP (protein tyrosine phosphatase) family, contains 403 amino acids. PTEN crystal structure determination revealed the N-terminal phosphate region and it strongly associated with the C-terminal (C2) domain. These two regions are combining together to form a small catalytic unit and constitute almost the complete protein<sup>3</sup>. N-terminal chain consists of a polybasic substance where continued towards the phosphatase region.

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In opposite, the long C-terminal region has a group of serine and threonine residues that undergoes phosphorylation in several cells.

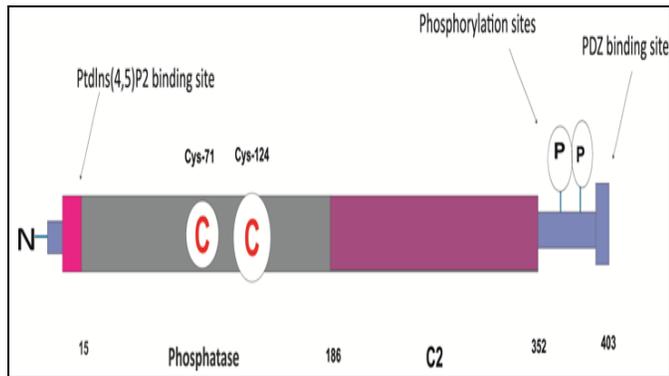


FIG. 1: STRUCTURE OF PTEN

### Regulation of PTEN Function in Normal Cells:

Evidence of PTEN functions was being taken time to develop and show the nature of these regulatory mechanisms. Present various circumstances have been recognized, where PTEN expression is transcriptionally regulated<sup>4</sup>. PTEN in human Cowden disease patients shows various developmental abnormalities and voluminous benign polyps due to the decreased expression of the PTEN protein.

It was helpful for the identification of agonist rosiglitazone as a site for the PPAR $\gamma$  (Peroxisome proliferator-activated receptor  $\gamma$ ), widely used as an antidiabetic agent for the management of elevated sugar levels. In the promoter region of PTEN, where two PPAR $\gamma$  binding sites were recognized and PTEN expression is up-regulated in many cells in response to rosiglitazone<sup>5</sup>. The evidence revealed that the phosphorylation of PTEN in its C-terminal domain is quite constant and dephosphorylation of these residues causes efficient stimulation of protein<sup>6,7</sup>.

**Physiological Role of PTEN:** The below paragraphs indicates the present studies explaining the conventional and potential new cellular functions for PTEN.

**Cell Metabolism:** It clearly stated the cellular macromolecules production required being associated with metabolic processes for cell development. The PTEN-PI3K-AKT-mTOR pathway plays a main part in controlling glucose absorption due to its downstream of the insulin receptor (INSR) and its adaptor molecule.

This signaling enhances insulin-mediated glucose absorption and membrane translocation of glucose transporter GLUT4 by the retardation of RAB-GTPase-activating protein (GAP) AS160 (also called as TBC1D4)<sup>8</sup>. Furthermore, the PI3K-AKT pathway stimulates the fundamental lipogenic transcription factor sterol-regulatory element-binding protein 1C (SREBP1C). The loss of PTEN appears to produce adipogenic-like transformation in liver cells, and gene transcription occurs in lipogenesis and  $\beta$ -oxidation by PPAR $\gamma$  and SREBP1C<sup>1</sup>.

**Cell Motility and Polarity:** It was illustrated that the PTEN and PtdIns (3, 4, 5) P3 have a protective role in the establishment of cell polarity in different cell types as well as neutrophils and neuron. PTEN blocks glioma cell migration and increases the effects of PI3K-independent action of PTEN on migration<sup>9</sup>. Where, PI3K also improves membrane disarrangement, cell motility and cell spreading via downstream effectors like RHO, RAC1 and CDC42<sup>10</sup>. During epithelial morphogenesis, PTEN restricted to the apical plasma membrane and induces the exchanging of PtdIns (3, 4, 5) P3 to PtdIns (4,5) P2 and PtdIns (4,5) P2 causes the binding of CDC42 to the partitioning defective 6 (PAR6)-atypical PKC (aPKC) complex by initiating the annexing 2 (ANXA2) in which it promotes determination of polarity. Therefore, the loss of PTEN may slow down the development of the apical surface and lumen<sup>11</sup>.

**PTEN and Cellular Senescence:** Present evidence states the important physiological functions of cellular senescence in contrast to tumor development and progression. Cellular aging is a programmed process which irreversibly inhibits the cell development and restricts the reflective lifetime of primary cells through the stimulation of oncogenes (a type of senescence that called as oncogene-induced senescence) or the loss of tumor inhibitor genes like PTEN, retinoblastoma-1 (RB1) and neurofibromin-1 (NF1). But, blockade of S phase kinase-related proteins-2 (SKP2) in association with further oncogenic events like RAS activation or loss of PTEN promotes cellular senescence in p19ARF and p53 independent approach<sup>15</sup>. The decreased concentration of PTEN enhances cell development and proliferation. And the complete PTEN loss in the acute phase may

lead to cell aging. Loss of PTEN promotes cellular aging (PICS) is a new approach of cellular aging, in contrast OIS and not initiate hyperproliferation or a DNA damage response<sup>12</sup>.

### **Pathological Role of PTEN:**

**Role of PTEN in the Treatment of Type 2 Diabetes and Obesity:** PTEN controls glucose uptake, where it blocks the formation of PIP3, a substrate for Akt and blockade of PTEN is identified as a potential drug target for type -II diabetes. For example, bisperoxovanadium agent (bpV), even though in nanomolar range it is reported to be efficient as PTEN inhibitors.

In hepatocyte-specific conditional PTEN null mice, PTEN is a main regulator of lipogenesis, glucose metabolism, hepatocytes homeostasis, and liver tumorigenesis. Leptin initiates phosphorylation of PTEN at C-terminal leads to the inhibition of phosphatase activity of PTEN. Specific inhibitors of CK2 and GSK3 hinder this leptin mediated phosphorylation of PTEN. This evidence shows the functions of PTEN in diabetes and obesity still is in the preliminary stage<sup>1</sup>.

### **PTEN Inhibition to Prevent Heart Failure:**

Retardation of PTEN functioning in the heart might provide a new therapeutic approach to decline the development of heart failure in response to pathologically induce biochemical stress. When the PTEN knockout mice were subjected to aortic banding, showed a mild decrease in systolic function with reduced ventricular dilation and heart dysfunction was observed and explaining that PTEN loss suppresses the progression of heart failure. Thus, inhibition of PTEN expression would be clinically important in the prevention of heart failure<sup>13</sup>.

**Genetic Role of PTEN in Autism:** In PTEN gene, the three genetic mutations (H93R in exon4 and D252G and F241S in exon 7) have been recognized and it causes macrocephaly or an autistic syndrome. Specific deactivation of PTEN in neurons of cerebral cortex in mice caused an elevated action to sensory stimuli with neuronal hypertrophy, including hypertrophic and ectopic dendrites and axon tracts with increased synapses. This explains that an abnormality in PTEN induces macrocephaly and autistic syndrome in mice<sup>10</sup>.

**Other Diseases in which PTEN could be a Therapeutic Target:** The current study also explains its role in various other diseases such as Parkinson's, Alzheimer's and allergy or inflammation. In neuronal cells, PTEN maintains neuronal insulin pathway and limits its phosphatase activity that blocks FAK/ERK signaling, where it significant for negative regulation of neuronal insulin. The increased support shows that reduce insulin signaling in the brain acts as a mediator for chronic neurodegenerative disease, it is clearly stated that regulation of PTEN could be a new approach to the management of disease<sup>11</sup>.

### **Therapeutic Inhibitors Used in the Treatment of**

**PTEN - Related Diseases:** Tyrosine kinase receptors are the growth factor receptor that mediates signals through cell survival pathways, frequently through PI3K/Akt or Ras/MEK and maintains the cell proliferation, migration, and intracellular metabolism. These kinases are targeted as a therapeutic benefit of PTEN regulation or inhibition in the management of targeted diseases. The inhibitors and Therapeutic agents used in the treatment of various PTEN-related diseases are listed in **Table 1**.<sup>14</sup>

### **Applications of PTEN in Human Disease**

**Therapy:** The effect of PTEN is not only helped in inhibiting cancer cell growth and propagation, but also in controlling numerous cellular processes. Deactivation of PTEN is being explored as a potentially useful beneficial tool.

### **Nerve Regeneration and Neurosurvival-Related**

**Diseases:** Neuronal PTEN downregulates the signaling of PI3K/AKT/GSK-3 $\beta$ /mTORM pathway regulates axon development and nerve revival in both central and peripheral nervous system that take place during embryonic development and after the nerve damage or ischemia. Moreover, PTEN has the main function in decreasing the synaptic action mediated *via* NMDA and AMPA receptors. The blockage of PTEN is a sensible molecular target to revert neurological injury under pathological conditions<sup>15, 16</sup>. In Alzheimer's disease (AD) patients, there is a PTEN association in the regulation of tau protein phosphorylation and neurotoxicity induced by amyloid $\beta$  (A $\beta$ ) peptide in human cell lines cultures and mouse primary neuron cells has been reported<sup>17, 18</sup>.

**TABLE 1: THERAPEUTIC AGENTS IN THE TREATMENT OF PTEN-RELATED DISEASES**

Drug	Target	Effect on PTEN
Ublituximab	NFkB-Snail-RKIP	Induces PTEN and sensitizes
Trastuzumab (Herceptin)	HER2	TRAIL apoptotic pathway
Pertuzumab	HER2 dimerization	Increases PTEN activity through Src inhibition
Rituximab	PI3K-Akt pathway	Activates PTEN, similar to Trastuzumab
Cetuximab	EGFR	Induces PTEN
		PTEN loss is associated with non-responsiveness to Cetuximab
Sunitinib	PDGFR signaling	Induces PTEN expression
Gefitinib (ZD1839, Iressa)	EGFR	Loss of PTEN results in gefitinib resistance
Erlotinib	EGFR	PTEN loss contributes to erlotinib resistance
Resistin (cytokine)	p38MAPK and ATF2	Increases PTEN expression by activating p38MAPK and ATF2, and leads to decreased Akt and Enos
Simvastatin	NFkB	Increases PTEN expression level by inhibiting NFkB
Lovastatin (Mevacor)	PPAR-g	Increases PTEN expression
Rosiglitazone (Avandia, PPAR-g agonist)	PPAR-g	Upregulates PTEN expression

**Ischemia or Reperfusion (I/R) Tissue Injury:**

Ischemic reperfusion related diseases are the most common cause of deaths in humans because of tissue damage by the oxygen demand, which activates ROS-mediated damage and pro-inflammatory response. Where, the signaling mediated through PI3K/AKT/mTOR pathway is an important protective effect against ischemia-reperfusion associated damaged and inhibition of PTEN has been reported as a selective therapeutic involvement in I or R cardiac damage<sup>19, 20</sup>. The treatment of bisperoxovanadium and vanadium derivatives showed protective effects against I/R cardiac damage and enhanced cardiac functions<sup>21</sup>.

**Wound Healing and Tissue Regulation:** The tissue repair process is totally controlled by the PI3K/AKT/mTOR signaling pathway.

Therefore, the activity of PTEN has been related to slow down the healing process in various human cell types and rodent models such as lung epithelial damage, muscle regeneration and gastric mucosal integrity model<sup>20</sup>.

**During Infection:** A negative activity for PTEN in the host protective phagocytic functions like reduced chemotaxis, employment to infected sites and Fcγ-R-mediated responses have been evaluated through *ex-vivo* macrophage cell models and myeloid cells PTEN knockout mice<sup>22, 23, 24</sup>. This supports the possible usage of PTEN inhibitors to increase the phagocytic immune action after bacterial infection, particularly in decreased innate immune response or immune system reduction therapies<sup>24</sup>.

**Infertility:** The study of acute PTEN knockout mice represents, the PTEN is needed to inhibit the stimulation of primordial ovarian follicles, not in developing follicles and failure of this PTEN activity might cause the premature ovarian failure. This proposes the potential usage of PTEN inhibition in *in-vitro* fertility intervention<sup>25</sup>.

**Therapy Based on Stem Cells:** PTEN shows specific action in stem cell maintenance and self-renewal with specific alterations in growth and tumorigenesis<sup>26, 27</sup>. PTEN knockout in mammalian spermatogonial stem cells resulted in enhanced Nanog expression and in human cell reprogramming and mouse fibroblast cells, where the PTEN role has also been documented based upon the increased generation of induced pluripotent stem cells<sup>28, 29</sup>. This provides a possible use for PTEN inactivation in situations where bone formation and regeneration needs to be enhanced.

**Cancer-Associated Diseases:** Although, PTEN acts as a major tumor suppressor in various cancer types. Few shreds of evidence have underlined the feasibility of PTEN pharmacological inhibition, might be an anticancer therapeutic approach under certain condition. It has been explained that PTEN deleted prostate in mice and also in PTEN deleted MEFs or PTEN lack in human glioblastoma cell, a p53- dependent senescence program is enhanced (PTEN loss induced cellular senescence, PICS) that limits tumorigenic process<sup>7, 30</sup>.

**Insulin-Resistance Metabolic Diseases:** PTEN-PIP3 phosphate activity counteracts with insulin signaling causes inhibition of PTEN, which

provides a potential therapeutic approach in the management of type-II diabetes<sup>31, 32</sup>. Likewise, systemic decreasing PTEN levels with antisense oligonucleotides returned insulin resistance are needed to understand the regulation of PTEN expression in insulin-responsive tissues by TNF $\alpha$  and upon PTEN catalysis inhibition<sup>33</sup>.

**Pain Relief or Antinociception:** PTEN plays a role in regulating hyperalgesia and nociception has been reported based on the results observed from rats and mouse models of migraine showed an increased mechanical threshold and minimal spinal trigeminal neuron activation upon PTEN knockout, in related with reduced tyrosine phosphorylation of the NMDA receptor<sup>34, 35</sup>. Moreover, PTEN has been playing a crucial role in the negative regulation in the sensory of the  $\delta$  opioid analgesic receptor ( $\delta$ R) expression<sup>36</sup>.

#### CONCLUSION & FUTURE PERSPECTIVES:

PTEN is one of the most commonly mutated genes are often suppressed. Important efforts have been developing selective and biologically active PTEN inhibitors and to provide them as specific experimental and clinical interventions. It provides a molecule targeting PTEN that is commonly used in the research and also as a proof of concept where PTEN pharmacological inhibition would be useful for human welfare in most of the diseases or conditions. Further research needs to concentrate these studies will help and elucidate the exact actions of PTEN in the pathogenesis of diseases and provide a new path for early diagnosis and for recognizing of novel gene therapy approaches for treatment.

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