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Phosphatase and Tensin Homologue deleted on Chromosome 10: Extending its PTENtacles

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Abstract

Since its discovery in 1997, phosphatase and tensin homologue deleted on chromosome 10 (PTEN) has become one of the most important molecules in tumor biology. Mutations, deletions or dysregulation of PTEN is found in many human tumors. Recent studies have extended the reach of PTEN to include diabetes and neurological diseases such as Parkinson's and Autism. In this review, we summarize the traditionally characterized function of PTEN as the lipid phosphatase that dephosphorylates PI-3,4,5-P₃, and several other newly discovered functions. The inhibition of the phosphatidylinositol-3-kinase (PI3K)/AKT signaling pathway may account for most of PTEN's tumor suppressing function. However, other growth inhibiting functions of PTEN may not involve this pathway. PTEN can also inhibit growth through its protein phosphatase activity and in ways not related to its enzymatic activity at all. We survey the many functions and biochemical interactions of PTEN in cytoplasm, the nucleus and throughout the cell in this paper.

Keywords

PTEN; AKT; PI3K; Tumor; Nucleus

Signaling Network Facts

- PTEN possess both lipid and protein phosphatase activities
- The lipid phosphatase activity of PTEN negatively regulate PI3K/AKT signaling
- Nuclear PTEN may have effect independent of its enzymatic activities
- PTEN is modified posttranslationally by phosphorylation and ubiquitination. Phosphorylation and ubiquitination affects its stability and cellular localization.
- PTEN is the most deleted/mutated phosphatase found in human cancer.
- Further insight into PTEN signaling can be found at <http://ghr.nlm.nih.gov/gene=pten>

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Introduction

In 1997, three laboratories independently reported a tumor suppressor located on human chromosome 10q23. Sequence analysis demonstrated that this gene encodes a phosphatase with homology to tensin and auxilin. This gene was named PTEN for phosphatase and tensin homologue deleted on chromosome 10 (or MMAC1/TEP1) (B. Stiles, Groszer, Wang, Jiao, & Wu, 2004). Later studies demonstrated that PTEN is a negative regulator of a major cell growth and survival signaling pathway, namely the phosphatidylinositol-3-kinase (PI3K)/AKT signaling pathway (Downes et al., 2007; B. Stiles, Groszer et al., 2004). PTEN antagonizes the function of PI3K by dephosphorylating phosphatidylinositol-3,4,5-triphosphate (PI-3,4,5-P₃) (Fig 1), a key product of PI3K responsible for the activation of downstream target molecules including AKT, an oncogenic protein (Downes et al., 2007). This function of PTEN has been the focus of many studies and is the foundation for the molecular mechanisms of PTEN as a tumor suppressor. Loss of *PTEN* has become an important marker for ensuring the sensitivity of chemotherapies targeted at PI3K/AKT signaling pathway (Neshat et al., 2001). Additionally, a role for PTEN that is independent of PI3K/AKT is currently being proposed and explored (Planchon, Waite, & Eng, 2008). Mouse models carrying deletion of *Pten* revealed that PTEN is indispensable for development (B. Stiles, Groszer et al., 2004; Suzuki, Nakano, Mak, & Sasaki, 2008). Studies performed with heterozygous *Pten* deletion mice and using the conditional deletion Cre-LoxP system have revealed much of the physiological function of PTEN (B. Stiles, Groszer et al., 2004; Suzuki et al., 2008). In this review, we will summarize the PTEN-controlled signaling pathways and the biological events involved in PTEN regulation.

Structure and Functions of PTEN

The human PTEN gene encodes a 403 amino acid protein with two main domain structures: the catalytic phosphatase domain and the C2 domain (Das, Dixon, & Cho, 2003). The C2 domain and the short N-terminal sequence (also called PBD domain, phosphatidylinositol 2-phosphate binding domain) are crucial for the binding of PTEN to membrane lipids where its best characterized substrate PI-3,4,5-P₃ is located. The c-terminal tail contains a PDZ binding motif and is thought to play a role in protein-protein interaction between PTEN and scaffolding proteins such as membrane associated guanylate kinase (MAGI) (Vazquez et al., 2001; Wu et al., 2000). The catalytic domain of PTEN is structurally similar to protein tyrosine phosphatases with few reported potential protein substrates including FAK and PTEN itself (Raftopoulou, Etienne-Manneville, Self, Nicholls, & Hall, 2004; Tamura et al., 1998). The discovery that PTEN dephosphorylates PI-3,4,5-P₃, demonstrated for the first time that a lipid phosphatase may play an important role in cell growth and survival. Many studies using either primary tumors or cell lines have established PTEN to be the most deleted phosphatase and second most deleted gene next to P53 in human cancer.

The biological effects of PTEN are dominated by its ability to dephosphorylate the lipid substrate PI-3,4,5-P₃ (Downes et al., 2007). PI-3,4,5-P₃ is formed when PI3K is stimulated as a result of growth factors binding to their receptors coupled to PI3K. PI-3,4,5-P₃ serves as a major signaling molecule for growth factor stimulation. The lipid phosphatase motif of PTEN leads to dephosphorylation of PI-3,4,5-P₃ at the 3' position (Downes et al., 2007). Through this action, PTEN inhibits the activation of downstream effector molecules including the serine/threonine kinase AKT and the protein kinase C (PKC). The activities of these effector molecules depend on the binding of PI-3,4,5-P₃ to their pleckstrin homology domain for activation.

Because of its biological function as a lipid phosphatase, PTEN's function has been traditionally characterized in the cytoplasm and at the plasma membrane. The best

characterized biological function of PTEN is through its ability to negatively regulate the proto-oncogenic protein AKT (Fig 1). Activation of AKT leads to a number of cellular functions including cell growth, survival, cell migration and differentiation, cell and organ size control, metabolism and others (for detailed review, see (Manning & Cantley, 2007)). Direct phosphorylation of downstream targets by AKT mediates these cellular processes regulated by PTEN-PI3K-AKT signaling cascade. Proapoptotic factor BAD, caspases 3 & 9 are among the direct substrates of AKT that play significant roles in cell survival. Phosphorylation of these molecules by AKT renders them inactive and thus leads to cell survival phenotypes. Through phosphorylating forkhead transcriptional factors and inducing their binding to 14-3-3 proteins, AKT blocks their translocation to the nucleus where they can induce gene transcription regulating cell proliferation, survival and metabolic changes. Some cell cycle modulators such as p21, p27 and MDM2 are also directly regulated by AKT.

The PTEN regulated signalings cross talk with several other signaling pathways (Fig 2). Two substrates of AKT play key roles in this cross talk. GSK3 α/β is phosphorylated by AKT on Serine 21/9 which inhibits their activity (Manning & Cantley, 2007). GSK3 β , a key regulator in Wnt signaling, phosphorylates and targets β -catenin for ubiquitin-mediated degradation. The crosstalk between PTEN and Wnt signaling may underscore some of the effects of PTEN in the regulation of stem cell maintenance and G₀-G₁ cell cycle regulation (Backman et al., 2001; Groszer et al., 2001; Kwon et al., 2001; Yilmaz et al., 2006; Zhang et al., 2006). Another substrate of AKT, tuberous sclerosis complex 2 (TSC2) plays a key role in incorporating controls of metabolism, cell size with growth and proliferation (Leung & Robson, 2007). TSC 2, encoding tuberin is responsible for a rare multi-symptom genetic disease, tuberous sclerosis. The heterodimer of TSC1/2 is critical for suppressing mTOR function (Fig 1). TSC is inhibited by PI3K/AKT and upregulated by LKB-AMPK, a signaling cascade responding to energy levels (Y. Li, Corradetti, Inoki, & Guan, 2004). The placement of TSC2 in the PI3K signaling pathway explained some of the clinical similarities between tuberous sclerosis and *Pten* mutation predisposition syndromes such as Cowden's disease. It also highlighted a possible involvement of metabolism in cell proliferation and survival.

The majority of PTEN studies focus on the enzymatic function of PTEN and its role in antagonizing the PI3K/AKT signaling pathway. Recent evidence indicates that it may have effects beyond its ability to dephosphorylate PIP3. The ability of PTEN to directly dephosphorylate protein substrates is still being explored even though the identities of the substrates remain illusive. In earlier studies, PTEN was reported to be a protein exclusively located in the cytoplasm while more recent evidence shows that PTEN can be both cytoplasmic and nuclear (Planchon et al., 2008; B. Stiles, Wang et al., 2004; B. L. Stiles et al., 2006). Analysis of tumor cells vs. control cells also indicated that the nuclear PTEN plays an important role in inhibiting tumorigenesis (Planchon et al., 2008). A lysine mutation K289E in Cowden's syndrome later led to the discovery of ubiquitination as a mechanism controlling the shuttling between the cytoplasm and the nucleus (Chi et al., 1998). Upon mono ubiquitination by its E3 ligase, PTEN is imported to the nucleus (Trotman et al., 2007). Deubiquitination in the nucleus keeps it from reentering the cytoplasm where it is degraded. The nuclear PTEN is thought to play a role independent of its lipid phosphatase activity although existence of PI-3,4,5-P₃ in the nucleus has been documented. In the nucleus, PTEN may promote p53 stability and transcriptional activity by directly associating with p53 (Tang & Eng, 2006). This is independent of the effect of PTEN on MDM2 through AKT activity (Freeman et al., 2003). On the other hand, recent studies also indicated that p53 may be induced to compensate for the loss of *Pten* in some situations (Chen et al., 2005). Nuclear PTEN is also capable of dephosphorylating MAPK and directly regulating cyclin D1 in addition to its effect through AKT (Y. H. Shen et al., 2006). Further evidence shows that PTEN physically interacts with the centromere specific binding protein C (CENP-C) to increase centromere stability as well as regulating DNA break repair through upregulation of Rad 51 transcription (W. H. Shen et

al., 2007). Nuclear PTEN also regulates histone acetylation through interaction with acetylase PCAF and p300/CBP and may impose another level of regulation on p53 (A. G. Li et al., 2006; Okumura et al., 2006).

Regulation of PTEN

PTEN is regulated on several levels. PTEN RNA expression is regulated by several transcriptional factors (For detailed description and references, see (Tamguney & Stokoe, 2007). PTEN was first found to be a TGF β -regulated gene (D. M. Li & Sun, 1997). In TGF β sensitive cells, PTEN is readily down-regulated by TGF β treatment. Other negative regulators of PTEN transcription include NF κ B and c-JUN. The tumor suppressor p53 interacts with PTEN on several levels including transcription. p53 directly binds to the promoter of PTEN to regulate its transcription. In response to UV irradiation, PTEN is also induced to promote cell death under the transcriptional regulation of an early growth response gene EGR-1. When these mechanisms are lost, either p53, PTEN or EGR-1, cells fail to induce cell death in response to UV damage leading to tumor development. Another notable regulator of PTEN transcription is PPAR γ . PPAR γ is the orphan nuclear receptor responsible for the effect of the antidiabetic drugs of the thiazolidinedione class. This class of drugs binds to PPAR γ as its ligand and induces its activation. The activated PPAR γ controls the transcription of a number of genes involved in metabolism, rendering the drugs effective for diabetes. The fact that PPAR γ activation also induces PTEN expression and inhibition of AKT leads to the hypothesis that these drugs may be used for cancer therapy as well. Other more recent discoveries includes Sprouty homologue (SPRY2), active transcriptional factor 2 (ATF2) and microRNAs such as miR 19 and miR 21 (Meng et al., 2007).

PTEN protein has a relatively long half life and is speculated to be regulated by posttranslational modifications. Indeed, PTEN is modified by phosphorylation, acetylation, ubiquitination and oxidation (For detailed description and references, see (Gericke, Munson, & Ross, 2006)). These modifications contribute to PTEN's stability, activity, subcellular localization and protein interactions. Two kinase candidates are reported to phosphorylate PTEN, casein kinase 2 (CK2) and GSK3 β , both on the C-terminal tail. Phosphorylation of PTEN by CK2 on S370 and S385 leads to the stabilization of PTEN. The resultant effect on its catalytic activity is unclear. GSK3 β phosphorylation on S362 and T366 may represent a negative feedback loop for PTEN/PI3K signaling pathway. The C2 domain of PTEN has multiple potential phosphorylation sites for modification. One of them, S380 is a candidate site associated with Gliomas in which PTEN mutation is high. RhoA associated kinase and PI3K p110 δ subunits are thought to play roles in regulating PTEN through various phosphorylation sites including those residing at the C2 domain. Acetylation of PTEN occurs on two lysine residues 125 and 128 by the action of PCAF. These acetylations affect the substrate specificity of PTEN towards PI-3,4,5-P $_3$. In the presence of hydrogen peroxide, PTEN inactivation is thought to be a result of the formation of a disulphide bond between Cys124 and Cys71. This inactivation is reversible and may account for the regulation of PTEN by environmental changes.

Poly-ubiquitination is a common mechanism to tag proteins for targeted proteasome degradation. PTEN is also subjected to such proteasome mediated degradation. An E3 ubiquitin ligase for PTEN has been identified to be NEDD4-1 (neuron precursor cell expressed, developmentally downregulated-4-1) though disagreement is still being debated (Fouladkou et al., 2008; W. H. Shen et al., 2007; Trotman et al., 2007). Interestingly, NEDD4-1 appears to both enhance PTEN function and lead to its degradation. NEDD4-1 can both monoubiquitinate and polyubiquitinate PTEN through regulations that are yet to be determined. Monoubiquitination of PTEN on lysine residues K13 and K289 is essential for its shuttling into the nucleus where additional growth inhibitory functions of PTEN independent of PI3K/AKT may occur. In the cytoplasm, polyubiquitination of PTEN targets it to proteasome degradation

also using NEDD4-1 as the E3 ubiquitin ligase. Thus, it appears, through regulating PTEN stability and nuclear shuttling, NEDD4-1 can have both tumor suppressive and oncogenic functions. How NEDD4-1 balances these two tasks and the mechanisms regulating the switch remains to be determined.

PTEN and human disease

PTEN was first discovered by analyzing a segment of chromosome 10 found to be associated with prostate cancer and gliomas (Eng, 2003). Since then, PTEN has been deemed one of the most important genes in human cancer. Approximately 30% of human cancer carry some kind of mutations/deletions or dysregulated *PTEN* expression, most notably gliomas, prostate and endometrium cancers. This astonishing figure marked *PTEN* as the second most deleted/mutated gene in human cancer next to p53 which is found to be mutated in 50% of human cancer. Germline deletion/mutation of *PTEN* is associated with several autosomal dominant tumor predisposition syndromes including Cowden's disease (CS), Bannayan-Zonana syndrome (BZS) and Lhermitte-Duclos disease (LDD) (Eng, 2003). These patients often suffer from hamartomas in multiple organs with a tendency toward malignant transformation. In addition to hamartomas syndrome, a subset of the patients with CS and BZS also display macrocephaly (Buxbaum et al., 2007; Herman et al., 2007). This discovery led to further identification of *PTEN* as a gene associated with Autism where a high percentage of patients present macrocephaly as part of the symptoms (Butler et al., 2005). These analyses greatly expanded the role of PTEN to include non-neoplastic diseases. Neurological diseases such as Parkinson's are associated with PTEN function through PINK 1 (PTEN induced kinase-1) and DJ-1 and the commonly speculated interaction between PTEN and oxidative damage (Gasser, 2007). Due to its role in regulating PI3K/AKT signaling, PTEN is thought to be a regulator in insulin signaling and thus may play a role in metabolic syndromes such as diabetes. Experimental evidence have demonstrated that when *Pten* is deleted, animals demonstrate insulin sensitivity phenotype (B. Stiles, Wang et al., 2004; B. L. Stiles et al., 2006). Cowden's disease patients who are carriers of *Pten* mutation also presented with improved insulin sensitivity (Iida et al., 2000). Genetic evidence indicates that lack of one of the AKT isoforms, AKT2 may contribute to familial type II diabetes (George et al., 2004).

Taken as a whole, this evidence suggests that in addition to regulating cell growth and survival, PTEN is also a multifunction protein that has a wide spectrum of functions in many cellular processes. It is not clear how these processes may interact with each other and how one may modulate the balance to treat each of the pathological conditions resulted from malfunction of PTEN. Recent studies have reestablished the theory that metabolic changes observed with tumor cells are not side effects but major contributors to the progression of the malignancy. How tumor suppressors like PTEN may regulate this process to control the progression of the tumor growth is an area that needs further study. The mechanisms behind the regulation of oxidative damage and mitochondrial function by PTEN may provide clues to such an understanding.

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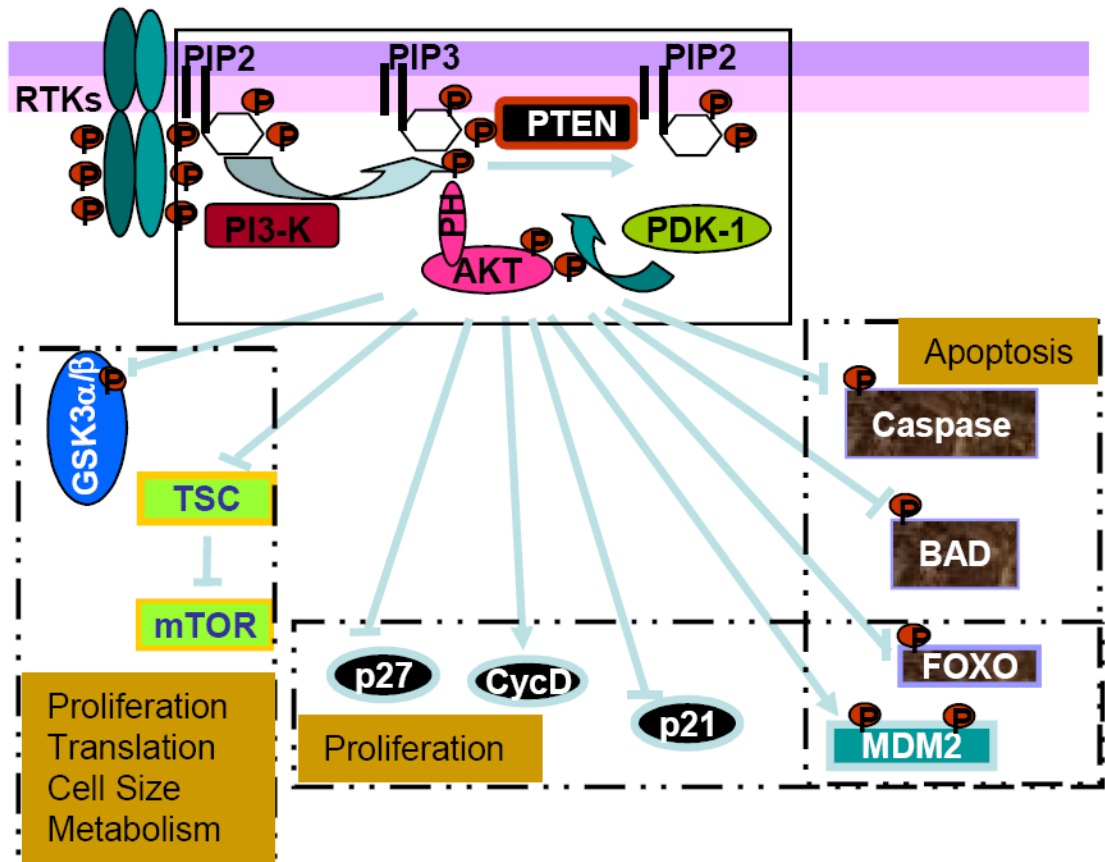


Figure 1. Signaling network regulated by PTEN

PTEN is the lipid phosphatase that negatively regulates the PI3K signaling pathway. PI3K is induced as a result of receptor binding and activation of receptor tyrosine kinase (RTK). PI3K phosphorylates the membrane lipid PIP₂ to form PIP₃. PTEN, the lipid phosphatase removes the phosphate and reduce PIP₃ levels in the cell. By this action, PTEN blocks the receptor binding signal from propagating downstream. These downstream signals include a number of kinases that contain the pleckstrin homology (PH) domain such as PDK1 and AKT as well as others. Binding of PIP₃ to the PH domain allows the exposure of residues on AKT that is critically needed for its activation. Binding of PIP₃ to the PH domain also adds lipid moiety to the molecules and allows their association with membranes. The phosphorylation of AKT by PDK1 leads to its full activation. AKT, a proto-oncoprotein when activated acts as a central control for proliferation, cell survival, translation, cell size, and cell metabolism. AKT, being a serine/threonine kinase directly phosphorylates and regulates the molecules involved in these processes. Phosphorylation of GSK3α/β blocks their inhibitor activity on glycogen synthase and β-catenin. Phosphorylation of TSC2 blocks its ability to inhibit mTOR, thus allowing the downstream translational events to propagate. A prominent function of AKT on cell survival is mediate by its direct phosphorylation and negative regulation on caspases 3 and 9 as well as BAD, a proapoptosis factor. Phosphorylation of the forkhead transcription factor FOXO blocks the ligand dependent cell death as well as having an effect on cell proliferation. Phosphorylation of MDM2 by AKT leads to its cytoplasmic translocation and thus blocks its effects on p53 degradation. This is believed to be one of the mechanisms for PTEN and p53 to interact. AKT also has direct effect on cell cycle regulators like p21, p27 and cyclin D.

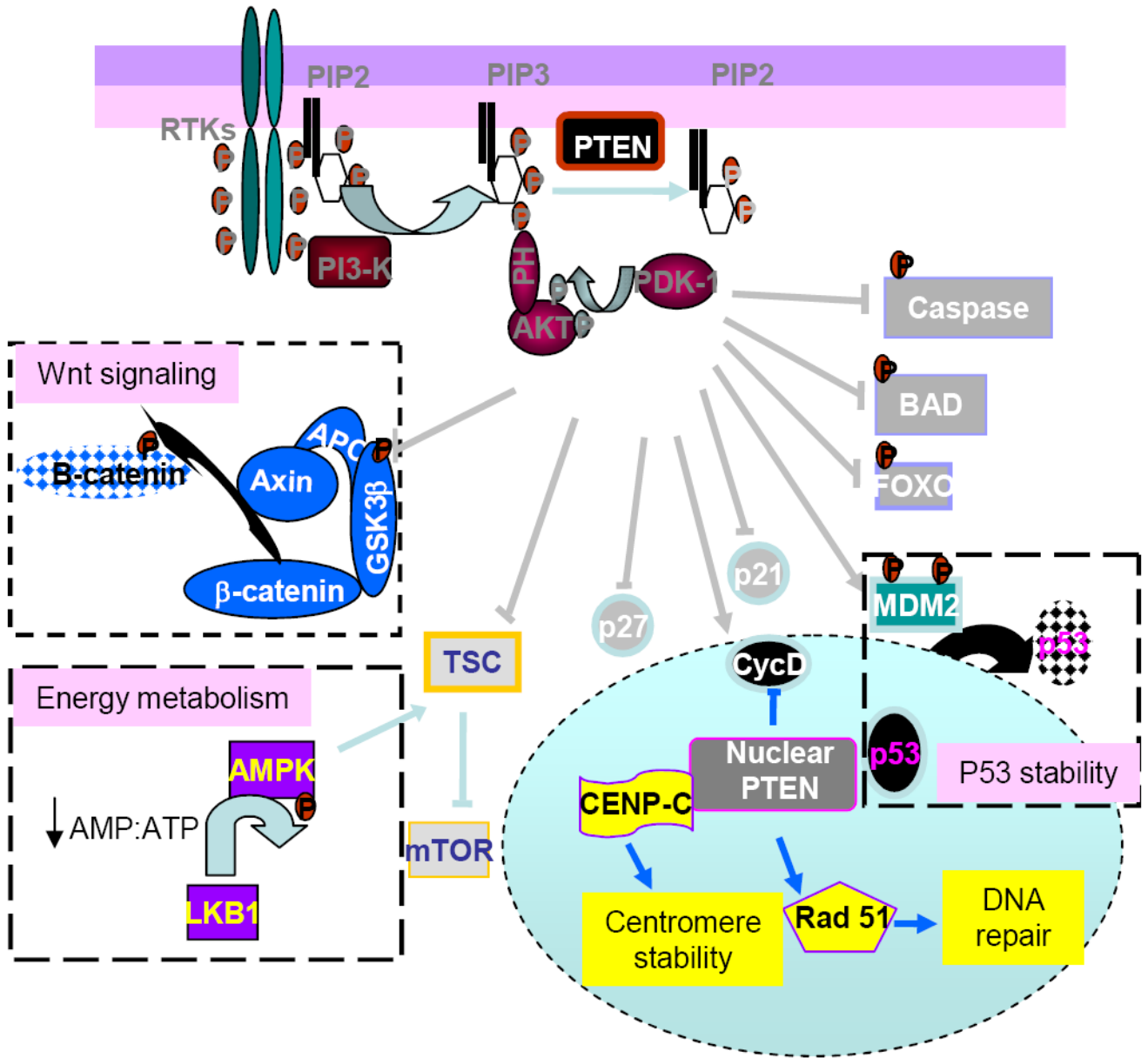


Figure 2. Crosstalks between PTEN and other signaling networks

The PTEN regulated PI3K/AKT signaling cross talks with several other signaling pathways. These pathways include the Wnt signaling pathway, the energy signaling pathway, as well as p53 signaling. Through inhibiting GSK3β, activation of AKT leads to the stabilization of β-catenin, a critical factor in Wnt signaling. PI3K/AKT signal also cross talks with energy signaling pathway at TSC. Whereas AKT phosphorylates and inhibit TSC, AMPK, a kinase activated in response to an increase in AMP:ATP ratio phosphorylates and activates TSC. In addition to its function primarily through AKT in the cytoplasm, nuclear PTEN may have its unique functions. These include direct association with p53, CENP and regulation of rad 51 to control the later stages of the cell cycle and DNA repair mechanisms.