

PI(3)K/Akt/AICAR Separates PTEN's Role in Cancer

Siyuan Zhang and Dihua Yu

Abstract

The tumor suppressor phosphatase and tensin homolog (PTEN) is a nonredundant phosphatase, counteracting one of the most critical cancer-promoting pathways: the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway. In addition to the canonical function of dephosphorylation of phosphatidylinositol-3,4,5-trisphosphate (PIP3), recent studies showed the intriguing roles of PTEN in regulating genomic instability, DNA repair, stem cell self-renewal, cellular senescence, and cell migration and/or metastasis. Clinically, PTEN mutations and deficiencies are prevalent in many types of human cancers. Severe PTEN deficiency is also associated with advanced tumor stage and therapeutic resistance, such as the resistance to trastuzumab, an anti-HER2 therapy. Currently, targeting the deregulated PI3K/PTEN-Akt signaling axis has emerged as one of the major tenets in anticancer drug development. In this review, we highlight our current knowledge of PTEN function and the recent discoveries in dissecting the PTEN signaling pathway. The deregulations of PTEN in cancers, clinical lessons, and new prospects of rationally designed PI3K/Akt-targeted therapy for effective cancer treatment are also discussed. *Clin Cancer Res*; 16(17); 4325–30. ©2010 AACR.

Background

The tumor suppressor phosphatase and tensin homolog (PTEN), also known as mutated in multiple advanced cancer 1 (MMAC1), was discovered independently by two groups in 1997 (1, 2). The *PTEN* gene is located at chromosome 10q23.31. Loss of heterozygosity at 10q23 occurs frequently in many advanced-stage sporadic tumors; for example, approximately 70% in glioblastomas and 60% in advanced prostate cancers (2). Somatic mutations of *PTEN* have been identified as a prevalent event in many types of tumors, particularly those of the endometrium, brain, skin, and prostate (3). Moreover, Cowden disease patients harboring germline *PTEN* gene mutations have a propensity to develop breast, thyroid, and skin tumors (4). As its name suggests, the PTEN protein sequence is largely homologous to protein phosphatases and a chicken cytoskeletal protein tensin. Human PTEN protein contains 403 amino acids (Fig. 1A). The crystal structure of PTEN revealed two major functional domains (a phosphatase domain and a C2 domain) and three structural regions [a short N-terminal phosphatidylinositol-4,5-bisphosphate (PIP2) binding domain, C-terminal tail containing PEST sequences, followed with a PDZ interaction

motif; ref. 5]. The tumor suppressor function of PTEN is disrupted by two naturally occurring mutations on its phosphatase domain: a C124S mutation that abrogates both lipid and protein phosphatase activity and a G129E mutation that abrogates only lipid phosphatase, but maintains protein phosphatase activity (4). Although the N-terminal phosphatase domain is principally responsible for PTEN's physiological activity, approximately 40% of *PTEN* tumorigenic mutations occur on the C-terminal C2 domain and the tail sequence, suggesting an important role of the C terminal in maintaining PTEN function (6). A number of studies have shown that the C-terminal sequence is critical for maintaining PTEN protein stability (7).

Early studies indicated that PTEN is a dual-specificity protein phosphatase with activity toward highly acidic substrates. PTEN dephosphorylates phosphorylated serine, threonine, and tyrosine residues in peptide substrates *in vitro* (8), protein substrate such as FAK (9), and the eukaryotic translation initiation factor 2 (10). Additionally, PTEN also auto-dephosphorylates itself by its protein phosphatase activity (11). Soon after PTEN was discovered, it was shown that PTEN possesses a potent phosphatase activity for the lipid-signaling second messenger phosphatidylinositol-3,4,5-trisphosphate (PIP3), a lipid product of phosphatidylinositol-3-kinase (PI3K; ref. 12). PTEN hydrolyzes the 3'-phosphate on PIP3 to generate PIP2, thereby directly antagonizing the PI3K function via abrogation of PIP3-mediated activation of downstream signaling events, including PDK1 and Akt/mammalian target of rapamycin (mTOR). The lipid phosphatase activity of PTEN is the best-characterized physiological function contributing to the tumor suppressor function of PTEN. As no other redundant and/or compensatory family members have been found, PTEN is the only known lipid phosphatase counteracting the PI3K pathway. It is not

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doi: 10.1158/1078-0432.CCR-09-2990

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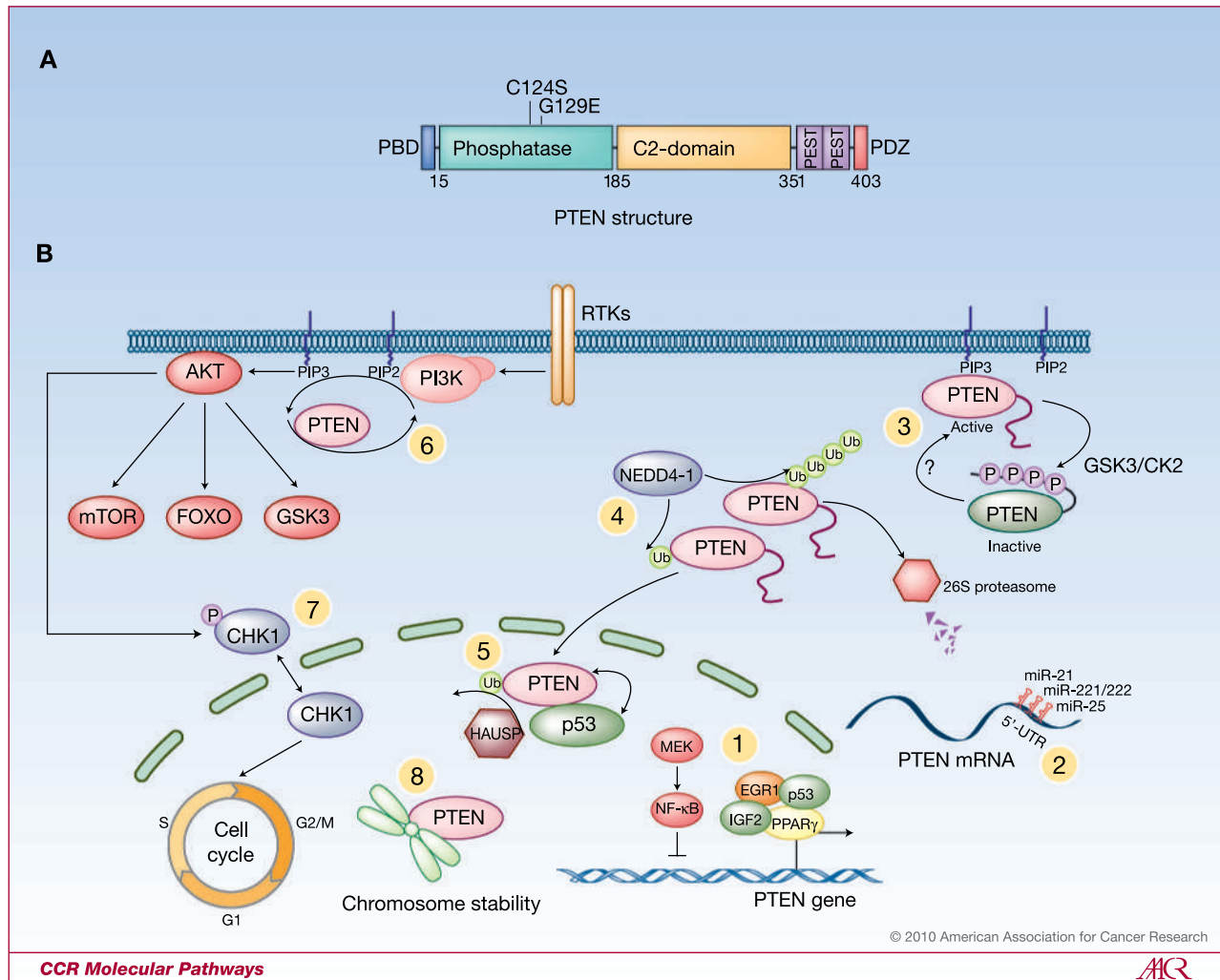


Fig. 1. PTEN pathway and regulation. **A**, PTEN protein structure. PTEN protein contains: an N-terminal PIP2-binding motif, a phosphatase domain, a C2 domain, a C-terminal tail containing PEST sequences, and a PDZ interaction motif at the end (5). Two naturally occurring mutations on the phosphatase domain disrupt PTEN's phosphatase activity: C124S mutation, which abrogates both lipid and protein phosphatase activity, and G129E mutation, which abrogates only lipid phosphatase but not protein phosphatase activity. **B**, PTEN is regulated at different levels. 1, PTEN mRNA transcription is activated by EGR1, IGF2, PPAR γ , p53, etc., and inhibited by MEK-mediated NF- κ B activation. 2, PTEN mRNA is also post-transcriptionally regulated by PTEN targeting miRs, including miR21, miR221/222, and miR25. PTEN protein is extensively regulated by post-translational modifications. 3, Protein stability is primarily regulated by phosphorylation of C-terminal tail domains (Thr366, Ser370, Ser380, Thr382, Thr383, and Ser385). The phosphorylation leads to a "closed" state of PTEN and maintains PTEN stability. Dephosphorylation of the C-terminal tail opens the PTEN phosphatase domain, thereby increasing PTEN activity. 4, NEDD4-1 is an E3 ligase of PTEN, which mediates PTEN poly- and mono-ubiquitination. Polyubiquitin leads to proteasomal degradation of PTEN. Mono-ubiquitination of PTEN promotes its nuclear translocation. 5, Ubiquitin-specific protease HAUSP deubiquitinates PTEN in the nucleus, and leads to PTEN nuclear exclusion. PTEN biological function includes membrane function and nuclear function. 6, On the cell membrane, PTEN dephosphorylates PIP3 and consequently suppresses the PI3K pathway. 7, PTEN also regulates the cell cycle through Akt-mediated cytoplasmic sequestration of cell-cycle regulator CHK1. 8, PTEN physically associates with centromeres in the nucleus and maintains chromosome stability.

surprising that loss of PTEN has a substantial impact on multiple aspects of cancer development.

Besides through genetic mutations, the PTEN expression level can be regulated through multiple mechanisms including transcriptional and/or post-transcriptional regulations, protein-protein interactions and/or post-translational modifications, and alterations of subcellular localization (Fig. 1B). Because of its important physiological functions, PTEN is constitutively expressed in normal tissues.

A number of factors have been shown to transcriptionally regulate PTEN mRNA, including transforming growth factor β (13), early growth regulated transcription factor 1 (EGR1; ref. 14), insulin-like growth factor 2 (IGF-2; ref. 15), peroxisome proliferation-activated receptor γ (PPAR γ ; ref. 16), and p53 (17). More intriguingly, complex cross-talk exists between PTEN and other pathways, including the RAS-mitogen-activated protein kinase (MAPK) pathway. The MAP/ERK kinase (MEK)-c-jun-NH-kinase

(JNK) pathway suppresses PTEN transcription via activation of nuclear factor κ B (NF- κ B), which directly binds to and suppresses the PTEN promoter (18); whereas PTEN opposes JNK signaling independent of Akt inhibition (19). PTEN mRNA is also post-transcriptionally regulated by PTEN-targeting microRNAs (miR). For example, miR-21 regulates PTEN gene expression in human hepatocellular cancer (20), and miR-221 and -222 target PTEN, contributing to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) resistance (21). Recently, intronic miR-106b-25 cluster, has been shown to be another PTEN-targeting miR locus in prostate cancer (22).

As mentioned previously, numerous reports have shown that PTEN interaction with other proteins and post-translational modification of PTEN at C-terminal domains are the major mechanisms regulating PTEN protein stability, which has been extensively reviewed elsewhere (see ref. 23). In its inactive state, PTEN is phosphorylated on a cluster of serine and threonine residues located on its C-terminal tail, including Thr366, Ser370, Ser380, Thr382, Thr383, and Ser385 residues. The phosphorylation leads to a "closed" state of PTEN and maintains PTEN stability. As PTEN is being activated, dephosphorylation of its C-terminal tail opens its phosphatase domain, thereby increasing PTEN activity. Meanwhile, the open state of PTEN is more susceptible to ubiquitin-mediated proteasomal degradation (24). NEDD4-1 is a recently identified E3 ligase of PTEN, which mediates PTEN mono- and polyubiquitination (25). A number of PTEN-interacting proteins have been shown to regulate PTEN level and activities. Phosphatidylinositol 3,4,5-trisphosphate RAC exchanger 2a (P-REX2a) is a PTEN-interacting protein identified recently. Through direct binding to PTEN, P-REX2a inhibits PTEN lipid phosphatase activity and activates the PI3K pathway (26). Tyrosine kinase Rak, a putative tumor suppressor, physically interacts with PTEN and phosphorylates PTEN on Tyr336, thereby protecting PTEN from interaction with E3 ligase NEDD4-1 and subsequent degradation (27).

The functionality of PTEN is also regulated by subcellular localization. PTEN interacts with a number of membrane-anchored proteins, for example, MAGI, PAR-3, NHERF, via its C-terminal PDZ domain, and dephosphorylation of PIP3 is facilitated through PTEN membrane recruitment (23). PTEN mono-ubiquitination controls PTEN nuclear entry (25). The promyelocytic leukemia protein-herpes virus-associated ubiquitin-specific protease (HAUSP, also known as USP7) network controls PTEN deubiquitination and PTEN nuclear exclusion (28).

The nonredundant PIP3 lipid phosphatase activity makes PTEN one of the most important tumor suppressors. Upon PTEN loss, excessive accumulation of PIP3 at the plasma membrane recruits and activates Akt family members, potently driving cell proliferation, apoptosis resistance, angiogenesis, and metabolism machinery through phosphorylation and activation of Akt's downstream signaling proteins, namely mTOR, GSK3, FOXO, BAD, p27, etc. (29). PTEN mutations and hetero- or homozygous deletions are common phenomena in many

types of human cancers, and have been reviewed extensively (see refs. 3, 30, 31).

In addition to the readily apparent role of PTEN in regulating PI3K/Akt-driven tumor progression, PTEN also plays other critical roles in multiple aspects of cancer development as follows (Fig. 1B):

1. *Genomic instability*: The recent study on the nuclear function of PTEN revealed an intriguing function of PTEN in maintaining genomic stability. PTEN was found to be physically associated with centromeres. Disruption of PTEN leads to extensive centromere breakage and chromosomal translocations (32). Loss of PTEN triggers Akt-mediated cytoplasmic sequestration of cell-cycle regulator CHK1 via phosphorylation and ubiquitination. Consequently, disrupted G₂-M cell cycle promotes genomic instability and accumulation of DNA double-strand breaks (DSB) in tumor cells (33, 34). Consistently, PTEN-null cells exhibit spontaneous DNA DSBs, and nuclear exclusion of PTEN has been associated with cancer progression (28). Clinically, PTEN loss is a common event in breast cancers bearing DSB repair gene *BRCA1* deficiency (35).
2. *Stem cell self-renewal*: PTEN has essential roles in lineage fate determination of hematopoietic stem cells (HSC). In leukemia, PTEN loss promotes self-renewable leukemia stem cells formation and leukemogenesis, which lead to HSC depletion via a cell-autonomous mechanism (36, 37). mTOR has been shown to be the key mediator of this process, which implies a clinical application of mTOR inhibitor rapamycin in treatment of leukemia-initiating cells (38). Moreover, PTEN negatively regulates neural stem cell self-renewal by modulating G₀-G₁ cell-cycle entry (39). p53 and PTEN cooperate in the regulation of normal and cancer stem and/or progenitor cell differentiation, self-renewal, and tumorigenic potential (40).
3. *Cellular senescence*: A surprising finding from a gene knockout study showed that acute and complete inactivation of PTEN triggers growth arrest through the p53-dependent cellular senescence pathway *in vitro* and *in vivo* (41). p53-dependent cellular senescence provides a favorable selection for cells that maintain PTEN levels. Further studies showed that interactions between PTEN and p53 are context-dependent. PTEN can regulate p53 protein levels and activity through phosphatase-dependent and -independent mechanisms. PTEN loss leads to inactivation of p53 in embryonic stem cells and brain tissues (42). However, others reported that PTEN loss activates p53 in prostate tumor and colorectal cancer cell lines (41, 43).
4. *Cell migration and metastasis*: PTEN negatively regulates intracellular levels of PIP3 in cells, which is critical for chemo-attractant gradient sensing (44). PTEN accumulates at a contralateral subcellular side of the migration leading edge and is required for proper chemotaxis (45). Although PTEN controls

cell migration, the exact role of PTEN in tumor invasion and metastasis is still elusive.

5. *Tumor microenvironment*: A significant role of PTEN in regulating the tumor microenvironment has been recently reported. Genetic knockout of *PTEN* in fibroblasts of mouse mammary gland tumors creates a tumor-permissive stroma, which accelerates the initiation, progression, and malignant transformation of mammary epithelial tumors (46).

Clinical-Translational Advances

Targeting PI3K/Akt to Overcome PTEN Functional Loss

The receptor tyrosine kinase (RTK)/PI3K/Akt pathway is one of the most potent driving forces promoting tumor progression. The major consequences of PTEN mutations and deficiencies are PI3K/Akt pathway hyperactivation. Because of the substantial role the hyperactivated PI3K pathway plays in cancer development, targeting PI3K signaling is one of the most concentrated areas of anticancer drug development. More than 100 lead compounds targeting multiple nodes of PI3K signaling, including PI3K, Akt, mTOR, etc., are in the preclinical drug-development pipeline. A great number of promising agents have entered intensive phase I, II, and III clinical investigations. At the time of writing this review, a total of 195 clinical trials are ongoing for PI3K pathway-targeting agents in various cancer types, including 33 trials for PI3K inhibitors, 68 trials for Akt inhibitors, and 95 trials for mTOR inhibitors (<http://www.ClinicalTrials.gov>). Rapamycin and its analogs, which inhibit the mTOR complex, are the clinically most advanced agents. Temsirolimus (CCI-779, Wyeth Pharmaceuticals) was approved by the U.S. Food and Drug Administration (FDA) in 2007 for treatment of advanced renal-cell carcinoma.

Although PI3K signaling is an obvious target for cancer therapy, given the redundancy and complex feedback regulation existing in the PI3K pathway, the clinical efficacy of many PI3K pathway inhibitors is modest, which largely hinders the clinical usage of PI3K inhibitors as single agents. Huge challenges facing us require more in-depth understanding of the pathway. Firstly, emerging evidence has indicated that different PI3K isoforms, besides generally believed functional redundancy, have their own distinct roles in cancer development. Collectively, recent studies have suggested that PTEN-null tumors are more dependent on PI3K isoform p110 β but not p110 α (47), and are thereby sensitive to p110 β inhibitors (48). On the other hand, PTEN-loss tumors harboring gain-of-function *PIK3CA* mutations (e.g., H1047R and E545K) seem to be more dependent on p110 α . Because of this complexity, isoform-specific inhibitors and personalized treatment are clearly warranted in the clinic. With the recent advances in dual- or multispecific-targeting drug design, novel agents such as NVP-BEZ235, which targets mutation-specific forms of PI3K as well as mTOR, have delivered an exciting and promising preclinical efficacy

in treatment for tumors bearing gain-of-function *PIK3CA* mutations (49). Secondly, extensive feedback loops and cross-talk have been well noted between the signaling networks driving tumor progression. The mTOR downstream protein p70S6K is a negative regulator of PI3K signaling, through inhibition of insulin receptor substrate 1 signaling. Inhibition of mTOR could release this inhibition and trigger a positive feedback to reactivate PI3K signaling (50). A recent study also suggested additional cross-talk between the PI3K pathway and the RAS-mediated MAPK pathway. Blockade of PI3K signaling may shift the tumor survival signaling to a RAS-MAPK-dependent manner (51). With the above notion in mind, the next generation dual-specific inhibitors or clinical trials of novel combinatorial therapy targeting both PI3K signaling and MAPK signaling are highly expected to counteract the signaling cross-talk and maximize the efficacy of anti-PI3K pathway inhibitors.

Additionally, PI3K signaling inhibitors may be used effectively to overcome the resistance to anti-RTK therapies and chemotherapies. PTEN is the key antagonist of the PI3K/Akt pathway. Loss of PTEN in many types of cancer has been shown to correlate not only with tumor development but also with clinical resistance to many anticancer drugs, especially targeted therapies for the RTK pathway. In breast cancer, the anti-HER2/ErbB2 antibody trastuzumab represents one of the most successful examples of rationally designed targeted therapies in cancer treatment. However, in the clinic, 30% of patients show *de novo* resistance to trastuzumab (52). Our group first showed that PTEN loss in breast tumors confers significant trastuzumab resistance (53). This concept has been further validated in a different patient cohort showing hyperactivation of the PI3K/Akt axis as a result of PTEN loss, and *PIK3CA* gain-of-function mutation (H1047R and E545K) led to worse patient response to trastuzumab (54). Similarly, hyperactivation of PI3K/Akt also has been associated with poor sensitivity to anti-epidermal growth factor receptor (EGFR) therapies (cetuximab and gefitinib) in colon and lung cancer patients (55, 56). Although the efficacy of the dual HER2 and EGFR inhibitor lapatinib seems to be independent of PTEN status (57), the overall lapatinib response is still largely affected by the activity of PI3K pathway (58). In addition, PTEN loss leads to upregulation of anti-apoptotic protein expression, for example, Bcl-2 and FLIPs, which render resistance to traditional chemotherapy and the apoptosis-inducing agent TRAIL (21, 59). To overcome the resistance of anti-RTK therapy, the current theme of rationally designed combinatorial therapy favors the combination of anti-RTK drugs, such as trastuzumab, with inhibitors targeting the compensatory signaling pathway, such as PI3K. For example, our preclinical studies showed that the combination of trastuzumab with either Akt inhibitor or mTOR inhibitor are effective in overcoming PTEN-loss-induced trastuzumab resistance (60). Currently, multiple trials of trastuzumab in combination with either a PI3K inhibitor (e.g., XL147, Exelixis)

or mTOR inhibitor (e.g., RAD001, Novartis) are under clinical evaluation. Similarly, clinical trials combining a PI3K pathway inhibitor with current first-line anti-EGFR therapy are designed for better treatment of EGFR-driven tumors. These trials include XL147 plus erlotinib in the treatment of non-small cell lung cancer (NSCLC) and RAD001 plus cetuximab-gefitinib in the treatment of metastatic pancreatic cancer and prostate cancer, among others (<http://www.ClinicalTrials.gov>).

Clearly, more basic and preclinical mechanistic studies are needed to further elucidate the complexity of the cancer-signaling pathway networks. Evolution of our knowledge of the PI3K/PTEN pathway will guide us to design more powerful weapons to fight cancer.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

The authors would like to thank Mr. Frank J. Lowry and the Yu laboratory members for valuable comments on this manuscript. We apologize for not being able to cite all relevant original research and review articles owing to space limitations.

Grant Support

S. Zhang is a Susan G. Komen Breast Cancer Foundation postdoctoral fellowship awardee (KG091316).

Received 04/30/2010; revised 05/28/2010; accepted 06/01/2010; published OnlineFirst 07/08/2010.

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PI(3)King Apart PTEN's Role in Cancer

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Clin Cancer Res 2010;16:4325-4330. Published OnlineFirst July 8, 2010.

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