Genes & Cancer
1(12) 1170–1177

DOI: 10.1177/1947601911407325
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# PTEN Tumor Suppressor Network in PI3K-Akt Pathway Control

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**Abstract**

The PI3K-Akt pathway is a major survival pathway activated in cancer. Efforts to develop targeted therapies have not been fully successful, mainly because of extensive internal intrapathway or external interpathway negative feedback loops or because of networking between pathway suppressors. The PTEN tumor suppressor is the major brake of the pathway and a common target for inactivation in somatic cancers. This review will highlight the networking of PTEN with other inhibitors of the pathway, relevant to cancer progression. PTEN constitutes the main node of the inhibitory network, and a series of convergences at different levels in the PI3K-Akt pathway, starting from those with growth factor receptors, will be described. As PTEN exerts enzymatic activity as a phosphatidylinositol-3,4,5-trisphosphate ($PIP_3$) phosphatase, thus opposing the activity of PI3K, the concerted actions to increase the availability of $PIP_3$ in cancer cells, relying either on other phosphoinositide enzymes or on the intrinsic regulation of PTEN activity by other molecules, will be discussed. In particular, the synergy between PTEN and the circle of its direct interacting proteins will be brought forth in an attempt to understand both the activation of the PI3K-Akt pathway and the connections with other parallel oncogenic pathways. The understanding of the interplay between the modulators of the PI3K-Akt pathway in cancer should eventually lead to the design of therapeutic approaches with increased efficacy in the clinic.

**Keywords:** PTEN, PI3K, Akt, synergy, protein interactions

## The PI3K-Akt Pathway

Phosphoinositides are negatively charged constituents of lipid membranes formed by phosphorylation of hydroxyl groups on positions 3′, 4′, or 5′ of the inositol ring of phosphatidyl inositol (PI) by specific kinases. The PI 3′-OH kinase (PI3K) family comprises 3 classes of proteins that phosphorylate PI, PI-4-phosphate (PI-4-P), or PI-4,5-bisphosphate (PI-4,5-P2 or $PIP_2$) on position 3′.[1] Class I PI3Ks primarily generate PI-3,4,5-trisphosphate ($PIP_3$) from $PIP_2$. $PIP_3$ acts as a second messenger by binding to and activating pleckstrin homology (PH) domain–containing proteins, including the Ser/Thr kinase Akt/PKB. Conversely, $PIP_3$ is hydrolyzed to $PIP_2$ by PTEN that opposes PI3K and specifically dephosphorylates phosphoinositides in position 3′.[2,3]

The signal for $PIP_3$ production stems from the activation of class IA PI3Ks by growth factor receptor tyrosine kinases (RTKs) and of class IB PI3Ks by G protein–coupled receptors (GPCRs).[1] Class IA PI3Ks are the only PI3Ks that have been implicated in cancer thus far.[4] They are heterodimers of a regulatory subunit (p85α, p55α, p50α, p85β, p55γ) and a catalytic subunit (p110α, p110β, p110δ).

The activation of Akt by $PIP_3$ production triggers signaling through a multitude of Akt phosphorylation targets that control cell survival, growth, proliferation, and other cellular processes.[5] Thus, binding of the Akt PH domain to $PIP_3$ unmasks the kinase domain[6] and allows the phosphorylation of Akt on Thr308 in the activation loop by phosphoinositide-dependent kinase 1 (PDK1) and on Ser473 in the carboxyl (C)–terminal hydrophobic motif by the mammalian target of rapamycin complex-2 (mTORC2).[7,8] Conversely, 2 classes of phosphatases, protein phosphatase 2A (PP2A) and PH domain leucine-rich repeat protein phosphatases (PHLPP) 1 and 2, have been described to dephosphorylate and inactivate Akt.[9,10]

Akt phosphorylates a plethora of targets[6,11,12] on RxRxxS/T consensus motifs.[13] Interestingly, many of its effects reside in phosphorylating and inactivating inhibitors of cell cycle progression, survival, glycolysis, angiogenesis, and protein synthesis, thus unlocking most if not all the processes involved in oncogenesis[14] (Fig. 1). For example, Akt phosphorylates and inhibits 2 upstream inhibitors of the small GTPase Ras homolog enriched in the brain (Rheb), tuberous sclerosis complex protein 2 (TSC2)[15-17] and proline-rich Akt substrate of 40 kDa (PRAS40).[18-20] In its turn, Rheb activates mTORC1 by inhibiting FKBP38, a negative regulator of mTORC1.[21] The net effect of Akt activation is activation of mTORC1, which is responsible for the up-regulation of protein synthesis in cells.[22] Another negatively regulated target of Akt is glycogen synthase kinase 3 (GSK3),[23] whose phosphorylation induces Myc and cyclin D1 increased activity with subsequent

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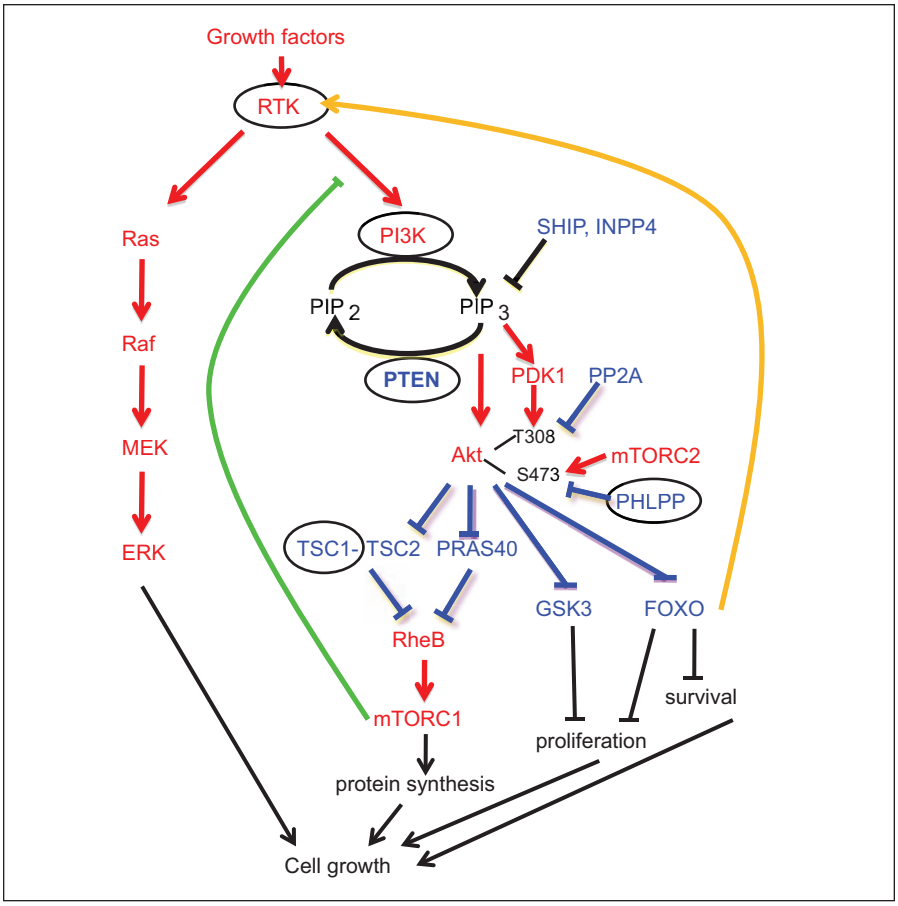


**Figure 1.** Nonlinear signaling through the PI3K-Akt pathway. Growth factors activate receptor tyrosine kinases (RTKs) that further activate parallel growth pathways. The MAPK pathway, which signals via Ras and downstream effectors, is an example of a linear growth-promoting pathway. The PI3K-Akt pathway is an example of a nonlinear pathway that signals through protein and lipid effectors and through layers of oncoproteins (red) and growth suppressors (blue). Negative feedback loops of the PI3K-Akt pathway are shown in green (repressing) or orange (activating). The effectors of the pathway whose alterations show combinatorial additive effects with PTEN inactivation in cancers are encircled.

increased proliferation.[24,25] Akt also phosphorylates and inhibits the activity of the FOXO transcription factors[26] that induce cell cycle arrest by coordinating the expression of multiple cell cycle regulators[27,28] and apoptosis through the up-regulation of proapoptotic Bcl-2 family members.[29,30]

Interestingly, 2 important negative feedback loops are triggered downstream of mTORC1 and FOXO transcription factors, blunting the effects of the pharmacological inhibition of the pathway (Fig. 1). mTORC1 activation results in transcriptional repression and inhibitory phosphorylation of the adaptor protein insulin receptor substrate 1 (IRS-1) with subsequent decreased PI3K-Akt signaling.[31,32] The inhibition of mTORC1 by rapamycin would therefore trigger activation of PI3K-Akt through inhibition of this negative feedback loop. The FOXO-induced negative feedback loop works by increasing the expression of the insulin receptor with downstream activation of the PI3K-Akt pathway and has been initially identified in *Drosophila*.[33,34] Importantly, this feedback is activated upon pharmacological inhibition of Akt and represents another mechanism to resistance to PI3K-Akt pathway inhibitors.[35]

From the integrated analysis of the PI3K-Akt pathway, one observes immediately that this is not a linear growth pathway, as is the case for the mitogen-activated protein kinase (MAPK) pathway (Fig. 1). Instead, the signals are transmitted through protein-protein or lipid-protein activation, and the pathway is sandwiched with pathway activators between pathway inhibitors. As described below, cancer cells take advantage of the complexity of this pathway to deregulate it at multiple levels in a combinatorial fashion.

## PTEN Tumor Suppressor

*PTEN/MMAC1* (phosphatase and tensin homolog, deleted on chromosome ten) has been identified by positional cloning as a candidate tumor suppressor gene located on chromosome 10q23.[36,37] *PTEN* is frequently inactivated by mutation with loss of heterozygosity (LOH) in a number of cancers including brain, prostate, and uterine cancer (http://www.sanger.ac.uk/genetics/CGP/cosmic). PTEN can also be inactivated by other mechanisms in somatic cancers, including promoter methylation,[38] micro-RNA interference[39] with or without pseudogene loss,[40] phosphorylation,[41] and delocalization from the plasma membrane.[42] *PTEN* transcriptional regulation is also a possibility in tumors, and c-Jun, NF-κB, and HES-1 have been shown to repress *PTEN* transcription downstream of Ras, MKK4, and Notch activation, respectively,[43-47] whereas EGR1, which activates *PTEN* transcription,[48] has been shown to be excluded from the nucleus in tumors with reduced PTEN expression.[49,50] Because of its high frequency of inactivation in somatic cancer, *PTEN* is ranked the second most mutated tumor suppressor gene after *p53*. Similarly to *p53* and other *bona fide* tumor suppressors, germline mutations in *PTEN* gene cause Cowden and Bannayan-Riley-Ruvalcaba cancer predisposition syndromes.[51,52] Cowden syndrome (incidence of 1 in 200,000 births) is

characterized by intestinal hamartomas, mucocutaneous lesions, macrocephaly, fibrocystic disease, and increased risk for developing breast, thyroid, and endometrial cancer.

Initial studies have shown that the expression of PTEN induces a marked decrease of proliferation because of cell cycle arrest in G1 phase[53,54] attributed to an increase of p27Kip1[54] and decreased level and nuclear localization of cyclin D1.[55] PTEN also inhibits the migration of cells,[56] likely by involvement of Rac and cdc42, but not of RhoA.[57] All these effects are most likely mediated via the hydrolysis of $PIP_3$ by PTEN[2,58] and the repression of downstream pathways activated by protein interactions with $PIP_3$. Recently, a structural role has been proposed for PTEN, in the maintenance of apical-basal polarity in polarized epithelial cells, by maintaining a segregated apical pool of $PIP_2$ that would compartmentalize $PIP_2$-binding proteins to the apical membrane.[59-61] It is possible that loss of this function contributes to the epithelial-mesenchymal transition (EMT) observed in the progression of epithelial cancers.

## PTEN Loss and Intrapathway Additive Activation

Fourteen years after its discovery as a tumor suppressor,[36,37] PTEN reveals itself as a highly regulated tumor suppressor that behaves differently in different types of tumors. In some tumors, such as glioblastoma in which 10q chromosome deletion is present in 70% of cases,[62,63] mutation with LOH of *PTEN* eliminates both alleles and therefore completely eliminates its expression. This situation conforms to Knudson's 2-hit hypothesis for a tumor suppressor in which the complete gene elimination is required for tumor growth.[64] In other types of tumors, PTEN shutdown is not complete. Mutations of one allele, transcriptional repression, epigenetic or posttranslational mechanisms, all of which would achieve partial inactivation of PTEN, and a combination of these mechanisms are also possible, leading to a continuum of lower than normal levels of functional PTEN in tumors. These mechanisms of reduced expression would exemplify a haploinsufficient tumor suppressor model for PTEN, and examples for such a behavior are found in both Cowden syndrome, in which not all tumors show LOH, and in most somatic cancers. In mice heterozygous for *PTEN*, both principles apply in that some tumors lose the *PTEN* second allele and some tumors do not.[65,66] The fact that the levels of PTEN inversely correlate with tumorigenesis and Akt activation has been experimentally proven in mice with hypomorphic and hypermorphic PTEN alleles.[67] It appears that even a small reduction of PTEN levels confers growth advantage to tumor cells, but the higher the reduction is, the more rapidly the tumor develops. This result explains why cancer cells target one or more of the plethora of mechanisms regulating PTEN levels and activity.

An interesting twist on the understanding of the PI3K-Akt pathway activation in tumors came from the discovery of apparently redundant coexisting PTEN inactivating mutations and PI3K activating mutations in endometrial cancer.[68] In a linear pathway, such as MAPK or Wnt-APC-β-catenin, mutations in proteins activating the pathway in the same way are mutually exclusive in tumors because either a second mutation does not confer growth advantage to cells or perhaps this second mutation is even detrimental to cells in the context of a "just right" level of pathway activation.[69] In the PI3K-Akt pathway, coexisting PI3K and PTEN mutations are present (Fig. 1), and at least, in endometrial, breast, and colorectal cancer, they seem to occur with a cumulative frequency equal to the product of the 2 frequencies, as if the 2 alterations are independently selected for.[4] Although the cumulative frequency does not indicate synergism between mutations in PI3K and PTEN, it also excludes redundancy or mutual exclusivity, as in linear pathways. As these mutations are likely to occur sequentially, they might represent an alternative mechanism of eliminating both alleles of PTEN. In addition, the 2 proteins might have different functions other than $PIP_3$ accumulation and might also respond to different genetic configurations of the cells at the time when the mutations occur.

PTEN is not the only phosphatase that contains the levels of $PIP_3$. The ubiquitously expressed phosphoinositide 5′ phosphatase SHIP-2 that hydrolyzes $PIP_3$ to PI-3,4-P2 has been previously shown to attenuate the activation of Akt in PTEN-negative glioblastoma cells.[70] Recently, INPP4B, a 4′ phosphoinositide phosphatase that specifically dephosphorylates PI-3,4-P2, and by this further inhibits Akt, has been described as a tumor suppressor in breast and prostate cancers.[71-73] It would be worth investigating whether SHIP-2 or INPP4B inactivation coexists with PTEN loss in a subset of these tumors, leading to higher Akt activation and thus to another convergent mechanism of PI3K-Akt activation.

Another example of additive activation of the pathway is the coexistence of RTK mutations or amplifications and PTEN mutations[74] (Fig. 1). These events have been studied mainly in breast cancer, in which PTEN mutations confer resistance to HER2 inhibition,[75-77] and also in glioblastoma, in which EGFR mutations or amplifications coexist with PTEN mutations.[62,78] In this case, the signaling through the RTKs activates multiple parallel pathways involved in growth, including the PI3K-Akt pathway.

Theoretically, PTEN inactivation could cooperate with Akt oncogenic activation to boost the pathway in tumors. However, even if Akt amplifications and activating mutations have been reported in cancers,[1,79] they have a low frequency, as compared to the activating mutations of PI3K.[80] What appears though to be an important cooperation at the level of Akt activation is the coexistence of PTEN loss with PHLPP loss that synergistically activates Akt in glioblastoma (our unpublished observations). Other cooperative effects of PTEN with downstream modulators of the PI3K-Akt pathway are not yet well defined. Of

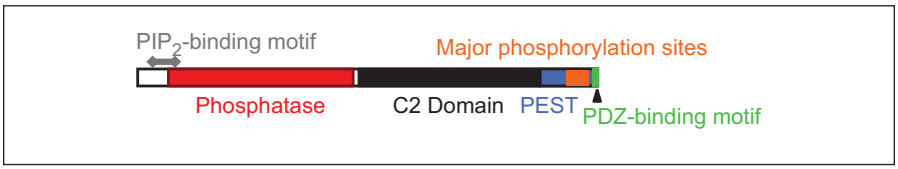


**Figure 2.** Diagram of PTEN domain structure.

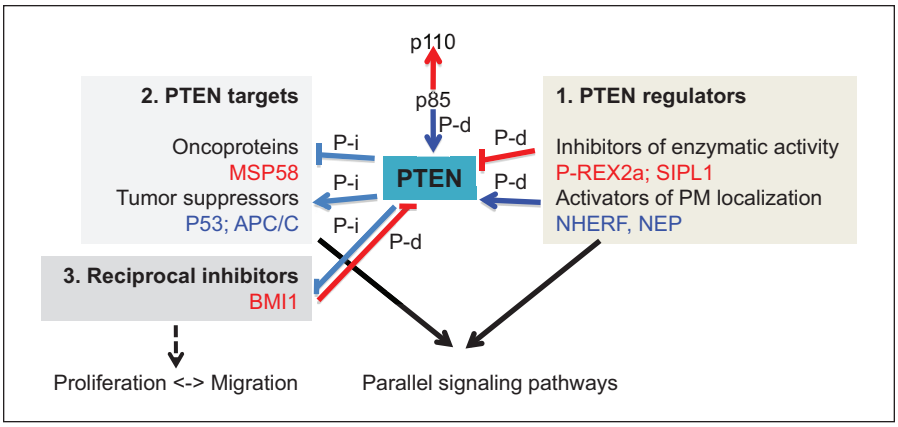


**Figure 3.** Three categories of PTEN-interacting proteins. Examples in each category are shown in red (oncoproteins) or blue (tumor suppressor proteins) and discussed in the text. PTEN phosphatase-dependent (P-d) or phosphatase-independent (P-i) connections resulting in oncogenic and tumor suppressor effects relevant for human cancers are shown with red and blue arrows, respectively.

note is that in bladder cancer, besides the coexistence of PTEN and PI3K double alterations, double PTEN and TSC1, or even triple PTEN, PI3K and TSC1 alterations have been reported, again suggesting nonredundancy by multiple hits in the activation of the PI3K-Akt pathway[81] (Fig. 1).

## Structure-Function Analysis of PTEN

*PTEN* encodes a 403–amino acid protein that comprises a phosphatase domain, a C2 domain that binds phospholipid membranes,[82] and a C-terminal tail that contains 2 PEST sequences with Ser/Thr phosphorylation sites and a PDZ (PSD95/Dlg/ZO1) binding motif[83,84] (Fig. 2). The importance of the phosphatase activity in tumor progression is underscored by a number of mutations occurring in the catalytic site that solely disrupt the enzymatic activity of PTEN.[85,86] Other modifications shown to reversibly inhibit PTEN's catalytic site are oxidation of the cysteine (Cys124)[87-89] or acetylation of the lysines (Lys125 and Lys128)[90] in the catalytic pocket. It is possible that these reversible modifications take place dynamically in tumor cells as dictated by the microenvironment conditions. A host of other mutations, especially in the C2 domain, but also in the phosphatase domain, cause misfolding of the protein and significantly reduce both its half-life and enzymatic function.[83,91] Following these studies on PTEN protein stability, 2 mechanisms of PTEN degradation were identified, cleavage by caspase-3[92] and ubiquitination by NEDD4-1.[93]

Tumor-derived mutations that do not affect the enzymatic activity of PTEN *in vitro* were also identified. These were studied and found to affect the compartmentalization of PTEN in the cell, either by sequestering PTEN in the nucleus[94] or importantly by interfering with PTEN's recruitment to the plasma membrane. Besides the C2 domain, PTEN contains 2 other regions with lipid-binding properties, an N-terminal $PIP_2$-binding motif and a positively charged region in the phosphatase domain.[95,96] Mutations found in the C2 domain or the $PIP_2$-binding motif disrupt the binding to phospholipid membranes and affect the tumor suppressor function of PTEN.[82,91,96]

The C-terminal tail of PTEN is also the target of mutations in tumors. As mentioned, this region contains the main phosphorylation sites mapped to residues Ser362, Thr366, Ser370, Ser380, Thr382, Thr383, and Ser385, and the kinases involved are casein kinase 2 (CK2), GSK3β, LKB1, and MAST.[84,97-101] The phosphorylation of the tail has been shown to enhance PTEN stability but at the same time decrease its phosphatase activity.[84] This apparent contradiction has been recently reconciled by the finding that the phosphorylated tail interacts with the rest of the molecule to confer a "closed" stable conformation that would be less interactive with phospholipid membranes and therefore less active.[102] Of the kinases that inactivate PTEN according to this mechanism, CK2 has been shown to be overexpressed in T cell acute lymphoblastic leukemia and to participate in PTEN inactivation.[41] The C-terminal PDZ-binding motif of PTEN is also targeted for deletions or mutations in tumors. Its function has been related to the involvement of PTEN in suppression of cell migration,[103] inhibition of protein synthesis,[104] and stabilization of PTEN at the plasma membrane.[42,105]

## PTEN-Interacting Proteins as Regulators of Cancer

The activity of PTEN is modulated by posttranslational modifications that include oxidation, acetylation, phosphorylation, ubiquitination, and proteolytic cleavage and by protein-protein interactions. All these influences affect the enzymatic activity of PTEN directly or indirectly by modifying the protein conformation, stability, lipid membrane binding, and subcellular distribution. It is therefore straightforward to examine in tumors the deregulations of the enzymes that act on PTEN or of its interacting proteins that alter its activity, stability, and subcellular localization, in an attempt to delineate posttranslational

PTEN-inactivating occurrences. Besides the effects on PTEN physiology, protein-protein interactions may also lead to the modification of the partner by PTEN. The molecules that interact with PTEN can be classified as 1) proteins that regulate PTEN, 2) proteins that are regulated by PTEN, and 3) potentially "2-way" proteins (Fig. 3). Examples for the 3 categories are provided below.

1) In the first category, there are proteins that interact and inhibit PTEN enzymatic activity or, conversely, ligands that increase PTEN activity through stabilization at the plasma membrane. $PIP_3$-RAC-exchanger-2a (P-REX2a) binds tightly to PTEN and inhibits its enzymatic activity.[106] In breast cancers, P-REX2a is up-regulated preferentially in the PTEN wild-type tumors, and of these, especially in those exhibiting PI3K mutations, demonstrating a 2-tiered selectivity correlated with an incremental Akt activation. The P-REX2a-PTEN protein-protein inhibition thus constitutes an excellent example of both an alternate mechanism to genetic or epigenetic inhibition of PTEN and of the use of this mechanism for additive effects within the PI3K-Akt pathway. Another example of a direct inhibitor of PTEN phosphatase activity is Shank-interacting protein-like 1 (SIPL1), which has been shown to be elevated in PTEN wild-type cervical cancer.[107] My group studies the $Na^+/H^+$-exchanger-3-regulatory-factor (NHERF) PTEN-interacting proteins NHERF1 and NHERF2, which bind to PTEN through PDZ domain interactions, and stabilizes it to the plasma membrane to contain the activation of PI3K.[42,108,109] NHERF1 is either displaced from the membrane or lost in cancers of different origins, such as glioblastoma, breast, colorectal, and hepatocellular cancers.[42,110-114] NHERF1 loss has been shown to contribute to the activation of Akt in tumors[42,115,116] but also to the activation of other oncogenic pathways, such as the Wnt-β-catenin pathway.[113,117,118] Therefore, NHERF1 alterations may simultaneously up-regulate parallel oncogenic pathways, including the PI3K-Akt pathway, conferring an enhanced growth advantage to tumor cells. Another example of a multitasking interactor and activator of PTEN is neutral endopeptidase 24.11 (NEP/CD10).[119] NEP cleaves a host of physiologically active peptides through its extracellular domain, limiting their signaling, and binds to PTEN through its intracellular domain, recruits it to the plasma membrane, and increases $PIP_3$ hydrolysis and Akt suppression.[120] Interestingly, the phosphorylation of NEP by CK2 decreases the binding of PTEN and increases Akt activation.[121] This finding implicates the kinase CK2 as a double-negative regulator of PTEN via diminished recruitment to the plasma membrane by NEP and via maintenance of a PTEN "closed" conformation by direct phosphorylation of PTEN's tail.

2) From the second category of PTEN-interacting proteins, PTEN inhibits the transformation induced by the MSP58 oncogenic protein through interaction via PTEN's tail.[122] In this case, a hit on PTEN would deregulate both PTEN and its ligand, thus involving the PI3K-Akt pathway through PTEN and also a parallel oncogenic pathway through PTEN's ligand. A couple of examples in this category define a role for PTEN in the nucleus by interacting and regulating the stability of p53 tumor suppressor[123,124] or by increasing the activity of the anaphase-promoting complex/cyclosome (APC/C) E3 ubiquitin ligase through interaction with its components, leading to increased degradation of the cell cycle apparatus involved in the M-G1 transition.[125] Importantly, the effect of PTEN on all the interacting proteins in this category is independent of its phosphatase activity and dependent only on an intact interaction region in PTEN, usually situated in the C-terminal half of the molecule.

3) The interactions in the third category are still to be characterized. BMI1, a polycomb protein that maintains the proliferation potential of hematopoietic and neural stem cells through the repression of cell cycle inhibitors, has been shown to interact with PTEN.[126] Similarly to the interactions with p53 and APC/C, this interaction takes place in the nucleus and reduces BMI1's function independently of PTEN's phosphatase activity. BMI1 has also been shown to reduce PTEN's inhibition of Akt, most likely by sequestration of PTEN in the nucleus. Finally, the colocalization of the 2 proteins appears to be significantly enhanced in prostatic intraepithelial neoplasia and carcinoma as compared to normal prostate epithelial cells.[126] It is not clear what is the net effect on growth due to this type of interaction because PTEN would exert opposing influences either in the cytoplasm or in the nucleus. Similarly to the other nuclear effects of PTEN, the phosphatase-independent functions of PTEN might actually represent inhibitory crosstalks of the PI3K-Akt pathway, necessary to shut down cell proliferation during other cellular processes, such as cell migration that requires PI3K-Akt activation. In fact, we have recently shown that this proliferation-migration switch takes place *in vivo* in invading glioblastoma cells, even in the absence of PTEN.[127] These migratory cells up-regulate Akt activation and stem cell behavior, which would be compatible with the activation of both Akt and BMI1 in the absence of PTEN. In this case, the suppression of MAPK via an inhibitory Akt-mediated phosphorylation most likely accounts for the reduction in proliferation.[128]

An intriguing protein-protein interaction is the one between PTEN and the p85 regulatory subunit of PI3K.[129,130] p85 interacts with the dephosphorylated active form of PTEN in a high molecular weight complex that comprises also p110β but not p110α.[130] The p85-PTEN interaction increases the enzymatic activity of PTEN and is enhanced after stimulation with epidermal growth factor.[129] Hence, p85 regulates both the increase and the decrease of $PIP_3$ levels following growth factor stimulation via association with p110 PI3K and PTEN, respectively. How this interaction regulates PTEN in cancer is still to be determined.

## Conclusions

The discovery of *PTEN* as a tumor suppressor gene and the breakthrough finding

that it functions as a $PIP_3$ phosphatase have put the PI3K-Akt pathway on the map of important cancer pathways.[2,36,37] In the years that followed, the PI3K-Akt signaling has been delineated as a non-linear pathway that contains multiple levels of regulation and feedback loops. This elucidation process is still ongoing, and many regulatory mechanisms are being discovered, as a result of diagnostic studies or of specific therapies for different nodes in this pathway that are being developed and tested in clinical trials. PTEN remains the main negative regulator of the PI3K-Akt pathway and the target of a host of modulating proteins that are also affected in cancer. As discussed, the disruption of PTEN regulators may affect parallel oncogenic pathways besides the PI3K-Akt pathway, interconnecting these influences at the level of PTEN. In turn, PTEN is not only dedicated to inhibit the PI3K-Akt pathway but also, through protein-protein interactions, inhibits other growth pathways, thus becoming a major growth signaling inhibitor. Other emerging functions of PTEN, such as regulator of cell polarity or, as hypothesized here, regulator of a switch between cell proliferation and migration states, could also have key influences on the progression on various types of cancer. In conclusion, the integration of all these functions and connections makes of PTEN a central inhibitory node with a major impact in cancer.

## Acknowledgments

I am very grateful to my postdoctoral mentor, Dr. Hidesaburo Hanafusa, for his honesty, open-mindedness, and unfailing example as a scientist, as well as for encouraging me in studying the regulation of the PTEN tumor suppressor. This review is dedicated to him. I also thank all the alumni of the Hanafusa laboratory for their friendship and scientific exchanges. Warm thanks for encouragement on this project go to Kathrin Kirsch, my bench mate during my postdoctoral years and good friend thereafter, and to Tomo Shishido and Tsuyoshi Akagi, who helped me with advice, reagents, and constant friendship. I also thank all the members of my laboratory who further developed the PTEN project and especially Yoko Takahashi, Fabiana Morales, Jennifer Molina, and Yuho Hayashi. Special thanks for insightful discussions go to my collaborators T.J. Liu, Gilbert Cote, Seth Corey, Xiaomin Chen, and Randy Legerski.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the authorship and/or publication of this article.

## Funding

This work was supported by the National Cancer Institute [grant number CA107201] and corresponding ARRA supplement and by bridge funds from the MD Anderson Cancer Center.

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