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Why Is PTEN an Important Tumor Suppressor?

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Abstract Phosphatase and tensin homologue deleted on chromosome 10 (PTEN) was originally cloned as a tumor suppressor for brain tumors. Now it is known as a tumor suppressor for many tumor types. In this review, we ask the simple question: why is PTEN such a common and important tumor suppressor? The most obvious answer is that there are no other family members that can replace PTEN. As a result, several pathways critical for cell transformation are misregulated. The most important of these is the phosphoinositide 3-kinase (P13K) PI3K-Akt pathway, which has downstream effects on transcription, proliferation, cell survival, invasiveness, and angiogenesis. In addition, PTEN is linked via several mechanisms to the p53 tumor suppressor. Through p53 and additional mechanisms, loss of PTEN leads to genomic instability. Hence, PTEN is important because its loss misregulates multiple Akt-dependent and -independent pathways critical for the development of cancer. J. Cell. Biochem. 102: 1368–1374, 2007.

Key words: phosphatase; phosphatidylinositol; tumor suppressor; p53; chromosomal aberrations

Phosphatase and tensin homologue deleted on chromosome 10 (PTEN) was originally cloned as a tumor suppressor for gliomas [Li et al., 1997; Steck et al., 1997]. We now know that PTEN is deleted or inactivated in many tumor types, including renal, melanoma, endometrial, breast, prostate, lung, bladder, and thyroid, identifying PTEN as an important tumor suppressor [Simpson and Parsons, 2001]. In addition, the studies of PTEN mutation and deletion may underestimate the role of PTEN in carcinogenesis because in some tumors, PTEN expression is reduced by promoter methylation [Sansal and Sellers, 2004]. In addition, PTEN germline mutations can result in Cowden disease, Bannayan–Zonana syndrome, and Lhermitte–Duclos disease, in which disorganized hamartomas appear in multiple organs [Liaw et al., 1997]. Some of these patients also show defects in neural development, including macrocephaly, mental retardation, cerebellar hypertrophy, ataxia, and seizures [Butler et al., 2005]. Some patients with PTEN mutations and macrocephaly are also autistic. Because of its clinical relevance, PTEN is under study in many laboratories.

The PTEN protein is a phosphatidylinositol phosphate (PIP) phosphatase specific for the 3-position of the inositol ring [Maehama and Dixon, 1998]. Although PTEN can dephosphorylate PI(3)P, PI(3,4)P_2, or PI(3,4,5)P_3, it is likely that PI(3,4,5)P_3 is the most important substrate in vivo (Fig. 1). The balance between PTEN and phosphoinositide 3-kinase (PI3K) determines PI(3,4,5)P_3 levels at the plasma membrane [Iijima and Devreotes, 2002], which in turn, regulates the Akt kinase. In *Drosophila*, the phenotype due to PTEN loss can be reversed by an Akt mutation [Stocker et al., 2002]. In addition, an Akt deficiency reduces tumor promotion for PTEN +/− mice [Chen et al., 2006]. These experiments demonstrate that Akt is critical for the effects of PTEN loss.

In this review, we address the question why is PTEN such an important tumor suppressor? The first and most obvious answer is that PTEN is not a family of enzymes. When a cell loses PTEN, there is no other phosphatase that can fully substitute for PTEN function. Second, the PI3K/PTEN-Akt pathway is a highly influential pathway for tumorigenesis [Vivanco and

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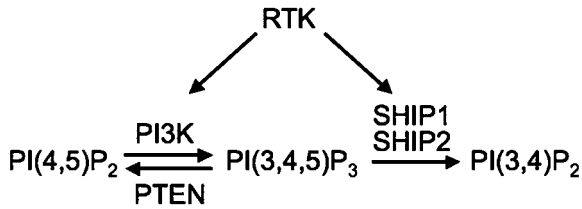

Fig. 1. PTEN and PI3K oppose each other and, thereby, determine levels of $PI(3,4,5)P_3$. RTKs activate PI3K but also activate the SHIP phosphatases to blunt the response. PTEN provides relatively constant degradation of basal $PI(3,4,5)P_3$ levels.

Sawyers, 2002]. Third, PTEN has a network of interactions with the p53 tumor suppressor. Because of p53's pervasive role in cancer, these interactions may be critical. Fourth, PTEN loss results in genomic instability via p53-dependent and -independent mechanisms. We cannot calculate the contribution of each of these mechanisms, and it is likely that their relative importance varies in different tumor types. Nonetheless, we hope that our discussion will convince the reader that PTEN is a potent tumor suppressor because PTEN is a master regulator of multiple Akt-dependent and independent pathways relevant for carcinogenesis.

PTEN IS A UNIQUE PHOSPHATASE

PTEN is a unique protein and not a member of a family of enzymes. PTEN loss is catastrophic because there are no other family members to substitute for it. There is a related PTEN-like phosphatase (PLIP), but it is strongly expressed only in testis and is specific for the 5-position of the inositol ring [Pagliarini et al., 2004]. At first glance, the lack of a PTEN family is surprising. There are multiple genes for each PI3K subunit as well as alternative splicing forms [Hawkins et al., 2006]. A simple interpretation is that multiple PI3Ks allow a diverse set of receptors and signaling pathways to drive PI3K activity. Even though PTEN is broadly expressed, it always does the same job. PTEN efficiently hydrolyzes $PI(3,4,5)P_3$. Following inhibition of PI3K, PTEN reduces $PI(3,4,5)P_3$ levels to negligible levels in less than 5 min [Sharrard and Maitland, 2007]. In addition, the pathways that regulate PTEN phosphatase activity are likely universal [Gericke et al., 2006; Wang et al., 2007]. Since PTEN has similar functions in all tissues, there is no compelling need for other family members.

Two other phosphatases, SHIP1 and SHIP2, are also major regulators of $PI(3,4,5)P_3$ levels [Krystal, 2000]. Like PTEN, SHIP2 is broadly distributed, but SHIP1 is confined to hematopoietic cells. These phosphatases have SH2 domains and are activated by receptor tyrosine kinases. SHIP1 and SHIP2 act on the 5-position of $PI(3,4,5)P_3$, yielding $PI(3,4)P_2$, which can activate some of the same signaling pathways as $PI(3,4,5)P_3$ [Krystal, 2000]. The picture that emerges from many studies is that the SHIP phosphatases blunt the receptor tyrosine kinase-induced increases in $PI(3,4,5)P_3$ levels, but only PTEN effectively decreases basal $PI(3,4,5)P_3$ levels. This is particularly clear for regulation of insulin signaling. SHIP2 has no effect on basal levels of $PI(3,4,5)P_3$, but SHIP2−/− mice are severely hypoglycemic [Lazar and Saltiel, 2006]. In contrast, PTEN, but not SHIP1 or SHIP2, causes growth inhibition and apoptosis when overexpressed in myeloma cells [Lazar and Saltiel, 2006]. PTEN+/− mice develop multiple tumors, but SHIP1−/− mice show only a lymphoproliferative disorder. Hence, SHIP phosphatases have strong effects on signaling with substantial metabolic consequences, but PTEN has a unique effect on basal $PI(3,4,5)P_3$ levels and cancer development.

MULTIPLE CANCER-RELEVANT PATHWAYS DOWNSTREAM FROM AKT

In many tumors, PTEN mutations lead to a hyperactive Akt kinase. The most common point mutations are in the active site of the PTEN phosphatase domain (Cosmic Database, Sanger Center, http://www.sanger.ac.uk/genetics/CGP/cosmic/). Mutations that produce premature termination are also common for PTEN. The domains of PTEN are functionally linked and to our knowledge, PTEN phosphatase domain lacking the C2 lipid binding domain is not active. In addition, mutations in the C-terminus can result in unstable PTEN proteins [Georgescu et al., 1999]. For brain and breast tumors, PI3K and PTEN mutations do not appear to occur in the same tumors [Broderick et al., 2004; Saal et al., 2005]. However, PI3K and PTEN mutations frequently occur in the same endometrial carcinomas [Oda et al., 2005]. These authors suggested that the double mutation offers an advantage because of PTEN's other functions, such as modulation of the p53

tumor suppressor. We will discuss this possibility in the next section.

Mutation or dysregulation of other proteins in this pathway can also hyperactivate Akt. In some cases, PI3K is activated by oncogenic point mutations, which occur often in the kinase domain, the adjoining helical domain of the p110α subunit [Samuels et al., 2004] and the PH domain [Carpten et al., 2007]. In a few tumors, Akt activity is elevated due to Akt amplification and overexpression [Vivanco and Sawyers, 2002]. PI3K mutations are common in tumors of the breast, endometrium and colon but are rare in lung and brain tumors [Vogt et al., 2007].

Activation of Akt activates a series of cancer-relevant signaling pathways. Because there are already excellent reviews on the pathways downstream of Akt, we just summarize these pathways in Figure 2 [Vivanco and Sawyers, 2002; Sansal and Sellers, 2004; Cully et al., 2006].

Signaling pathways usually have negative feedback loops to prevent excessive signaling. The PI3K pathway has a feedback loop through the S6 kinase and insulin receptor substrate (IRS) proteins [Gual et al., 2005]. There is also a negative feedback loop through the JNK pathway [Lee et al., 2003]. PTEN loss may inactivate these feedback loops, allowing hyper-activation of the PI3K pathway [Vivanco et al., 2007]. PTEN loss may lead to tyrosine phosphorylation of IRS proteins, thereby, blocking phosphorylation of IRS proteins by S6 kinase [Vivanco et al., 2007]. In addition, PTEN loss may disrupt the JNK loop by downregulation of the JNK phosphatases. PTEN loss also enhances activation of the JNK pathway; the Akt and JNK pathways may cooperatively induce cell transformation [Vivanco et al., 2007].

In contrast to PI3K or PTEN mutations that activate all of the pathways downstream of Akt, mutations of the tuberous sclerosis complex (TSC) only activate the mTOR pathway (Fig. 2). The Akt kinase inhibits the activity of the complex of TSC1 (also known as hamartin) and TSC2 (tuberin) [Bjornsti and Houghton, 2004]. The TSC1–TSC2 complex inhibits the activity of mTOR kinase, which drives protein translation and cell growth (Fig. 2). Hyper-activaton of this pathway feeds back to attenuate PI3K activity via phosphorylation of IRS proteins by the S6 kinase [Manning et al., 2005]. Mutations in TSC1 or TSC2 lead to a disease known as TSC. These patients develop tubers, which are benign tumors in their brain. They also develop macrocephaly, hamartomas of the skin, heart (rhabdomyoma), kidneys (angiomyolipomas), and eyes (phakomas) [Bolton and Griffiths, 1997]. Some of these patients also show autistic behavior [Curatolo et al., 2004]. It is intriguing that activation of one of the Akt pathways leads to a restricted set of benign tumors, but activation of Akt and all of the downstream pathways (Fig. 2) is associated with a broad spectrum of cancers [Cully et al., 2006].

PTEN INTERACTIONS WITH P53

The interaction between PTEN and p53 is important for the development of cancer [Cully et al., 2006]. However, there are two competing

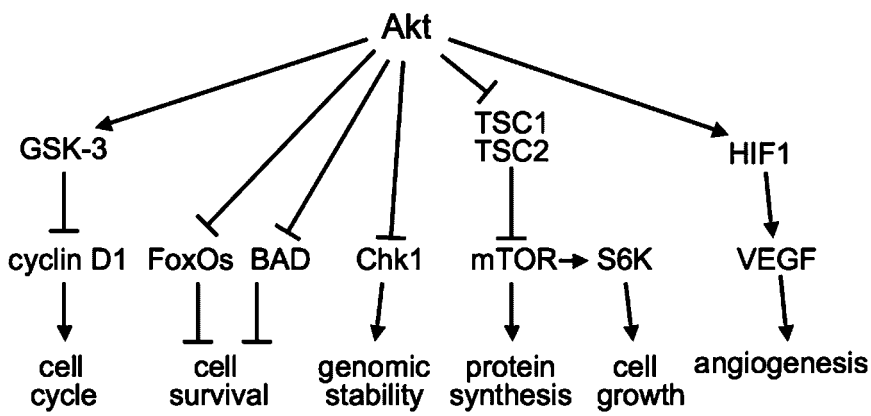

Fig. 2. Akt activates multiple pathway relevant to cancer. Akt enhances cell growth, proliferation, and survival. Akt can inhibit Chk1 and, thereby, reduce genomic stability. Finally through HIF-1 and VEGF, Akt can induce angiogenesis.

models to describe these interactions. The first model based primarily on cell culture experiments posits a positive feedback loop for PTEN and p53 (Fig. 3A). The PTEN promoter has a p53 binding site, and induction of p53 protein increases PTEN levels [Stambolic et al., 2001]. Furthermore, PTEN is required for p53-induced apoptosis in murine embryonic fibroblasts (MEF), suggesting that this regulatory loop is important for some p53 functions. Conversely, PTEN forms a complex with p53 and protects p53 from mdm2-induced ubiquitinylation and degradation [Mayo et al., 2002; Freeman et al., 2003; Zhou et al., 2003]. PTEN binding to p53 also increases DNA binding of p53 [Freeman et al., 2003]. There is an additional PTEN-regulated pathway that has similar effects. PTEN inactivates the PI3K pathway, leading to decreased phosphorylation of mdm2 by Akt and translocation of mdm2 to the cytoplasm [Mayo and Donner, 2001]. Cytoplasmic mdm2 cannot ubiquitinate nuclear p53, leading to increased levels of p53 protein. These results demonstrate that p53 increases PTEN levels and, conversely, PTEN increases p53 levels. These interactions result in a positive feedback loop (Fig. 3A). The implications for carcinogenesis are important. The prediction is that if a cell loses one of these tumor suppressor genes, there will be decreased levels of the other protein. One genetic hit will lead to decreased activity of two tumor suppressors.

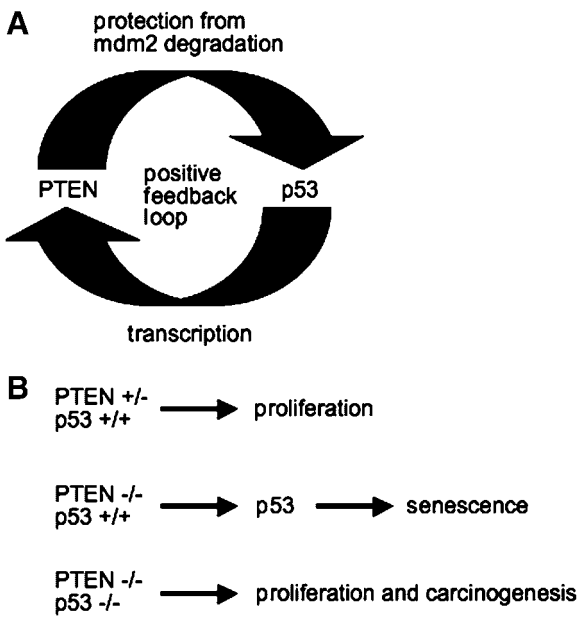

Fig. 3. Proposed models for interactions between PTEN and p53. **A**: Positive feedback loop based on experiments carried out primarily in tumor cell lines. **B**: The alternative model in which loss of one copy of PTEN enhances cell proliferation. Loss of both copies of PTEN activates p53 and induces senescence. If the cells lack p53, then loss of PTEN does not induce senescence and, instead, enhances cell proliferation and carcinogenesis.

The second model posits that PTEN acts through p53 to regulate senescence. Cellular senescence has long been thought to play a role in aging and, more recently, in cancer [Collado et al., 2007]. Normal cells, but not cancer cells, can undergo irreversible growth arrest after many passages in culture. Senescence may contribute to aging by limiting proliferation and regeneration of stem cells. Expression of activated oncogenes in some normal cells (Ras) induces cellular senescence by mechanisms involving the p53 and Rb tumor suppressors. This finding suggests a role for senescence in tumor suppression.

This model for PTEN/p53 interactions is based on an interesting observation in prostate tumors [Chen et al., 2005]. About 70% of primary prostate tumors in the clinic have lost one copy of PTEN but retain one functional copy. They proposed that for these early tumors, loss of both copies of the PTEN gene would lead to activation of p53 and induction of senescence, thereby, blocking tumor progression (Fig. 3B). For advanced tumors that lack functional p53, loss of the second PTEN gene does not induce senescence and, instead, contributes to tumor progression.

These authors use a mouse model for prostate cancer to analyze the role of senescence in carcinogenesis [Chen et al., 2005]. They used a Probasin promoter to drive expression of Cre in the prostate. In this system, loss of PTEN leads to prostate cancer. Loss of p53 does not cause any obvious pathological changes, but p53 loss considerably speeds the cancer induced by PTEN loss. None of the mice with PTEN loss died after 10 months. In contrast, all of the mice with loss of both PTEN and p53 were dead by 7 months, demonstrating a synergistic response to deletion of PTEN and p53. Using MEFs, they demonstrated that loss of both copies of PTEN, but not loss of one copy, increases p53 levels by about 1.5-fold and induces senescence. The increase in p53 levels appears to be due to increased levels of $p19^{Arf}$, which sequesters mdm2 and stabilizes p53. They also examine senescence in vivo in their mouse model. Tumors lacking both copies of PTEN increased

p53 levels by 10-fold. In addition, β-galactosidase, which is a marker for senescence, was detected for many cells in these tumors. Finally, prostates lacking p53 had normal levels of PTEN, contradicting the prediction shown in Figure 3A.

The disagreement between the two models likely reflects the cells used for the studies. Normal cells can enter senescence in response to many stimuli. Tumor cells have evolved to avoid senescence. In addition, cell culture and in vivo models can differ dramatically.

PTEN AND GENOMIC STABILITY

Loss of PTEN can also cause genomic instability, and there are two proposed mechanisms for this phenomenon. The first is that loss of PTEN leads to activation of Akt and phosphorylation of the DNA damage checkpoint kinase Chk1 on serine 280, resulting in Chk1 monoubiquitination [Puc et al., 2005]. As a result, there is an impaired response to DNA damage with reduced phosphorylation Chk1 on serine 345 and translocation of Chk1 to the nucleus. Even without irradiation, loss of PTEN led to increased numbers of double stranded DNA breaks (DSB). They suggested that it was due to malfunctioning Chk1, which may also play a role in the normal cell cycle [Puc and Parsons, 2005]. These authors examined sections of breast carcinomas and found that tumor cells lacking functional PTEN showed little nuclear Chk1. They proposed that this mechanism facilitates genomic instability and tumor progression in vivo.

Recently, a second mechanism was proposed for PTEN's role in genomic stability [Shen et al., 2007]. These investigators found that MEFs lacking PTEN acquired centromeric breaks as well as chromosome translocations. Based on these observations, they tested for an association of PTEN with chromosomes. By immunofluorescence microscopy, they detected PTEN at the centromere, and co-immunoprecipitated PTEN with the CENP-C centromeric protein.

Like Parsons and co-workers [Puc and Parsons, 2005], they observed DSBs in cells lacking PTEN. They proposed that loss of PTEN decreases expression of Rad51, which is a DNA repair protein that reduces the incidence of DSBs. A ChIP assay revealed that PTEN associates with the Rad51 promoter. Given the complexity of DNA repair and its close connection to the cell cycle, it may very well be that PTEN affects the incidence of DSBs by multiple mechanisms.

FUTURE DIRECTIONS

The theme of this review is that PTEN affects a remarkable number of regulatory pathways and cellular processes. This widespread misregulation poses a tremendous challenge for cancer therapy. How does one fix so many defects? One approach is to use PI3K inhibitors [Luo et al., 2003]. However, such inhibitors will not repair the pathways that require PTEN protein. In addition, aneuploidy and chromosomal aberrations are irreversible. Instead, it may be more fruitful to seek changes in signaling and cell cycle that make the cancer cells vulnerable to novel drugs [Chan, 2004; Kawabe, 2004].

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