The tumor suppressor PTEN interacts with p53 in hereditary cancer (Review)

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Abstract. Numerous hereditary syndromes caused by mutations in multiple tumor suppressor genes can cause cancers. Germline mutations in *PTEN* and *p53* tumor suppressor cause Cowden syndrome and Li-Fraumeni syndrome, respectively. There exists some phenotypic overlap in these syndromes, and they are associated with high risks of breast cancer. The tumor suppressor protein PTEN is a dual-specificity phosphatase which has protein phosphatase activity and lipid phosphatase activity that antagonizes PI3K activity. Cells that lack *PTEN* have constitutively higher levels of PIP3 and activated downstream targets. *PTEN* gene is recognized as one of the most frequently mutated or mutated in many human cancers. Li-Fraumeni syndrome results from germline mutations of the tumor suppressor *p53* gene encoding a transcriptional factor able to regulate cell cycle and apoptosis when DNA damage occurs. The p53 protein cooperates with PTEN and might be an essential blockage in development of mammary tumors. Many findings have demonstrated that PTEN as well as p53 plays a critical role in DNA damage response. This review summarizes the function of PTEN and p53 in carcinogenic cell signaling. In addition, we will discuss the role of PTEN signaling through its interaction with p53 and MDM2 pathways for the potential implications in hereditary cancer prevention and therapeutic intervention.

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Contents

1. Introduction
2. Expression, structure and characteristics of PTEN and p53
3. Protein interaction and functional interplay between PTEN and p53
4. Involvement of PTEN and p53 tumor suppressors in hereditary cancer
5. Perspective

1. Introduction

PTEN (phosphatase and tensin homolog deleted in chromosome 10) is a tumor suppressor gene that is deleted or mutated in a variety of human cancers (1,2). Germ line mutations of *PTEN* are also the cause of *PTEN* hamartoma tumor syndromes (Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, *PTEN*-related Proteus syndrome, Proteus-like syndrome) with increased risk for the development of cancers (3). Cowden syndrome is a rare, autosomal dominant, familial cancer syndrome characterised by hamartomas, acral keratosis, multiple smooth facial papules, and multiple oral papillomas (4). In contrast, Bannayan-Riley-Ruvalcaba syndrome is characterized by lipomatosis, macrocephaly, hemangiomatosis (5). Loss of heterozygosity (LOH) studies suggest that PTEN may play its most important role in advanced cancers of particular tissue (6). Alterations of *PTEN* in tumors are associated with a poor prognosis (7). Germinal mutations of the *p53* gene constitute an etiological genetic base of Li-Fraumeni syndrome, which is a rare genetically and clinically heterogeneous autosomal dominant inherited cancer disorder, characterized by a specific range of tumors observed at an early age, in particular a predominance of bone and soft tissue sarcomas and breast cancer (8). Generally, cells with dysfunctional p53 are predisposed to development of cancer phenotype. Of importance, it is mutated frequently in the common human malignancies of the breast and colon rectum and also in other significant cancers such as glioblastoma with less frequency (9).

The *PTEN* and *p53* tumor suppressors are among the most commonly inactivated or mutated genes in human cancer (10). The PTEN has been shown to be involved in a complex network of interactions with p53 (Fig. 1). Although they are functionally distinct, reciprocal cooperation has been proposed, as PTEN

is thought to regulate p53 stability, and p53 to enhance *PTEN* transcription. Once PTEN is lost, however, the p53 pathway is strongly activated (11,12). Furthermore, an absence of PTEN cooperates with an absence of p53 to promote cancer (13). The inactivation of tumor suppression may be caused by lack of key interaction partners. Recent studies have revealed a functional ubiquitin ligase for tumor suppressors playing a pivotal role in tumor cell survival (14,15). Mutations found in genes such as p53 and PTEN have emerged as high penetrance susceptibility genes and are clinically relevant for determination of cancer risk. In this review, we summarize the current research and our view of how and when PTEN and p53 with their partners transduce signals downstream and the implications for cancer-associated biology.

2. Expression, structure and characteristics of PTEN and p53

The human genomic *PTEN* locus consists of 9 exons on chromosome 10q23.3 encoding a 5.5 kb mRNA that specifies a 403 amino acid open reading frame (16,17). The translation product is a 53 kDa protein with homology to tensin and protein tyrosine phosphatases. *PTEN* is ubiquitously expressed throughout early embryogenesis in mammals (18). *PTEN* gene can be upregulated by early growth regulated transcription factor 1, peroxisome proliferator activated receptor γ (PPARγ), p53, and activating transcription factor 2 (ATF2) (19-22), while transforming growth factor (TGF)-β, nuclear factor κB (NF-κB), and Jun negatively regulate *PTEN* expression (23-25). Of note, rosemary extract represses *PTEN* expression in K562 leukemic culture cells (26). PTEN activity can be regulated by posttranslational regulation including phosphorylation, acetylation, and oxidation. Methylation of the *PTEN* promoter can result in transcriptional silencing of the *PTEN* gene (27). Schematic structure of the predicted PTEN protein is shown in Fig. 2. PTEN negatively regulates the activity of PI3K/AKT signaling through converting phosphatidylinositol 3,4,5-triphosphate (PIP3) into phosphatidylinositol 4,5- bisphosphate (PIP2). The PIP3 is the principal second messenger of the PI3K pathway that mediates receptor tyrosine kinase (RTK) signaling to the survival kinase AKT. Activated AKT transfers a phosphate group to target proteins involved in cell survival, cell cycling, proliferation, and migration, which also are all critical for tumor development (28,29).

PTEN acts as regulator of maintaining basal levels of PIP3 below a threshold for the signaling activation. PTEN protein consists of N-terminal phosphatase, and C-terminal C2, and PDZ (PSD-95, DLG1, and ZO-1) binding domains. The PTEN CX5R(S/T) motif resides within an active site that surrounds the catalytic signature with three basic residues, which are critical for PTEN lipid phosphatase activity. The structure endows PTEN with its preference for acidic phospholipid substrates such as PIP3. Overexpression of PTEN induces growth suppression by promoting cell cycle arrest, which requires lipid phosphatase activity (30,31). Overexpression of PTEN also correlates with decreased levels and nuclear localization of cyclin D1 (32), a key cell cycle molecule regulated by AKT. One mechanism by which PTEN induces cell cycle arrest is the regulation of AKT activity such that levels of the cell cycle inhibitor p27kip1 are increased (33). However,

despite the main role of PTEN as a negative regulator of the PI3K pathway, studies report various tumor suppressive activities for PTEN that are exerted from within the nucleus, where catalysis of PIP3 does not seem to represent a dominant function of this enzyme (34). The nuclear PTEN activities may include the regulation of genomic stability, cell cycle progression, and gene expression.

The *p53* gene, located on chromosome 17p 13.1 and encoding a nuclear 393-amino acid protein, acts to control cell growth and apoptosis (Fig. 2). The p53 protein is a transcription factor which is able to induce G1 arrest of the cell cycle by transactivating several downstream genes. Inactivation of *p53* gene is a common event in the development of most types of cancer. The importance of p53 as an inherited cancer susceptibility gene has been demonstrated in Li-Fraumeni syndrome (35). However, there are still a significant number of Li-Fraumeni families for which no underlying genetic determinant has been identified. It would be beneficial to understand the alterations of genes or additional components involved in DNA damage recognition, DNA repair, and/or cell cycle checkpoint pathways responsible for the specific phenotype.

3. Protein interaction and functional interplay between PTEN and p53

PTEN and p53 is known to interact and regulate each other at the transcription as well as protein level, which could be at the important control machinery for switching between survival and death. This cross talk is frequently a combination of reciprocally antagonistic pathways, which often involves another tumor suppressor gene MDM2, and may serve as an added regulatory effect on the expression of key genes involved in cancer. It has also been revealed that PTEN regulates p53 stability and in turn regulates its own transcriptional activity.

At transcription level. The PTEN and p53 complex enhances p53 DNA binding and transcriptional activity (36). An important p53 function is to act as a transcription factor by binding to the specific DNA consensus sequence in responsive genes, which may increase the synthesis of p21waf1 that is an important protein involved in cell cycle arrest (37). In addition, one of transcriptional targets of p53 is PTEN. One way by which p53 inhibits production of PIP3 indirectly is by inducing the expression of PTEN (38). Under hypoxic conditions PTEN and p53 form a complex in the nucleus and induce strong expression of the tumor suppressor Maspin (39). Loss of PTEN attenuates the induction of Maspin even in the presence of wild-type p53. The integration of PTEN and p53 into a common pathway for the induction of Maspin may constitute a tumor suppressor network (40).

MDM2 is an oncoprotein that controls tumorigenesis, its mRNA level is transcriptionally regulated by p53 in response to DNA damage such as oxidative stress (41). The MDM2 protein and subcellular localization are post-translationally modulated by AKT (42). PTEN inhibits PI3K/AKT signaling that promotes translocation of MDM2 into the nucleus. In addition, PTEN modulates *MDM2* transcription and isoform selection by negatively regulating its promoter (43). In *PTEN*-null cells, *MDM2* promoter activity is upregulated, resulting in increased *MDM2* expression. Furthermore, PTEN controls *MDM2* promoter activity through its lipid phosphatase activity, independent
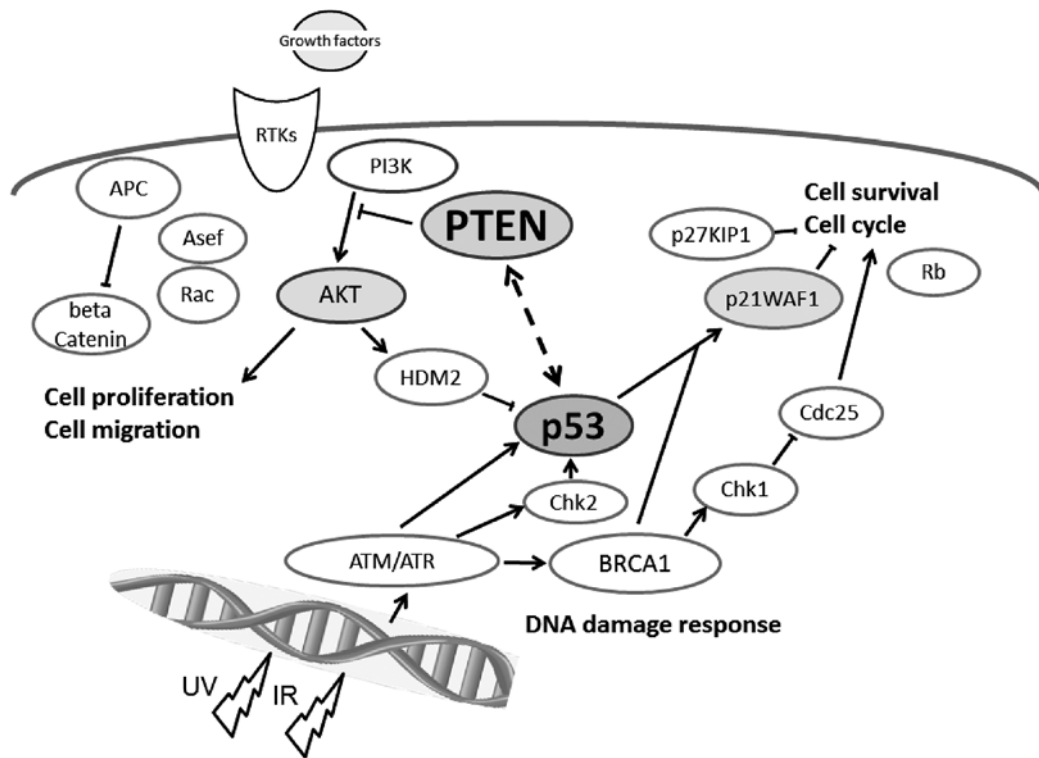
Figure 1. The proposed integrative model of tumor suppressor signaling including PTEN and p53. Examples of molecules known to act on DNA damage response, cell proliferation, and cell cycle via the regulatory pathways are shown. Note that some critical pathways have been omitted for clarity.
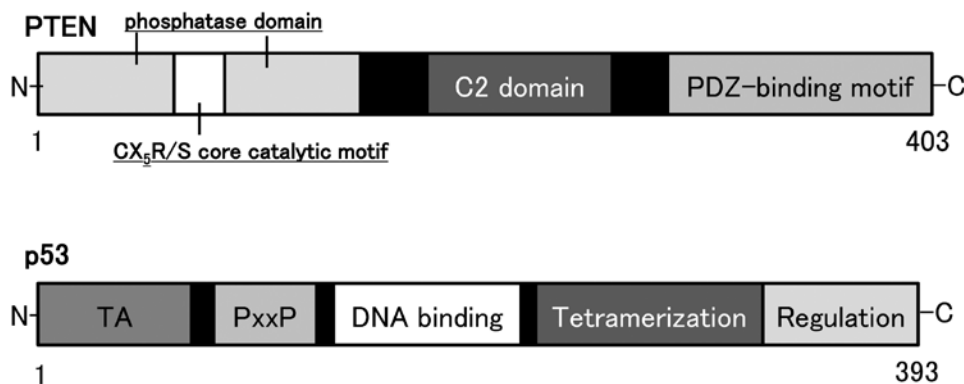

Figure 2. The structures of PTEN and p53 protein. The predicted consensual domain structures for each protein are depicted. The functionally important sites are also shown. TA, transactivation domain; PxxP, proline rich region; C2 domain, a protein structural domain involved in targeting proteins to cell membranes; PDZ, a common structural domain in signaling proteins (PSD95, Dlg and ZO-1).

of p53 (36). Although another transcription factors such as AP-1 are able to modulate *MDM2* transcription, they have been characterized to work through the p53 responsible promoter (44). MDM2 is a key regulator of p53. It regulates the activity of p53 protein by blocking its transcriptional activity, exporting nuclear p53 protein into the cytoplasm, and/or by promoting the degradation of the p53 protein. PTEN upregulates the p53 level as well as its activity by downregulating *MDM2* transcription and p53 binding activity (45). However, in the absence of p53, PTEN may have a role inhibiting MDM2-mediated carcinogenesis through regulation of *MDM2* transcription as well as the isoform selection. MDM2 is degraded, when restricted to the cytoplasm. The ability of PTEN to inhibit the nuclear entry of MDM2 increases the

cellular content and transactivation of the p53 to promote the induction of responsive genes such as *p21* (46).

Protein modification and interaction. p53 and AKT influence the process of apoptosis in opposite ways. The AKT promotes cell survival by suppressing pro-apoptotic proteins such as Bad through phosphorylation (47). There is cross talk between p53 and AKT involving gene transcription as well as posttranslational protein modifications. p53 inhibits PIP3 production indirectly by repressing the catalytic subunit of PI3K. A subsequent p53-induced expression of PTEN causes the p53-PTEN interaction, which then suppresses the cell survival machinery of AKT pathway. AKT phosphorylates MDM2 to translocate into the nucleus (48). In addition, PTEN physically associates with endogenous p53 and regulates
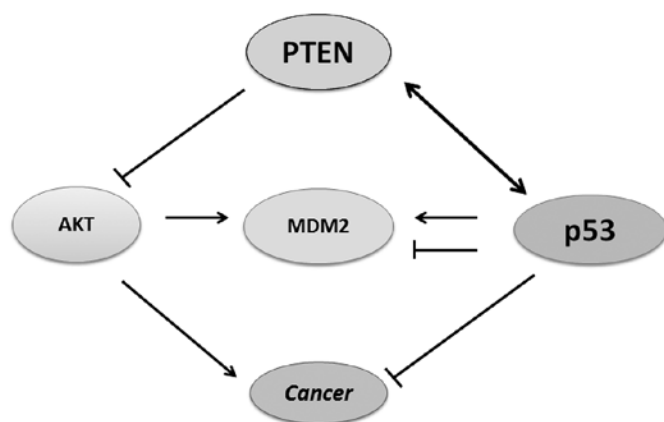
Figure 3. Implication of various feedback loops involving the PTEN-AKT-p53-MDM2 regulatory network. Interactions are shown as arrows indicating activation, while hammerheads indicate inhibition. Note that some critical pathways have been omitted for clarity.

the transcriptional activity of p53 by modulating its DNA binding (36). PTEN is required for the maintenance of p53 acetylation, which is also required for target gene transcription (49).

Growth factor-activated AKT signaling promotes progression of cell cycles by acting on downstream factors involved in controlling the G1/S and/or G2/M transitions. Several studies have also implicated AKT in modulating DNA damage responses and genome stability (50). AKT therefore modifies downstream signaling in complex ways. In addition, PTEN also plays a critical role in DNA damage repair and DNA damage response through its interaction with p53 pathways in an AKT-independent manner (51). Furthermore, nuclear PTEN is sufficient to reduce tumor progression in a p53-dependent manner. It has also been suggested that nuclear PTEN plays a unique role to protect cells upon oxidative damage and to regulate carcinogenesis (52), thus, the PTEN-p53-MDM2-AKT loop becomes dominant (Fig. 3).

Protein degradation. One aspect of the PTEN tumor suppressor signaling is achieved through stabilization of the p53 protein. PTEN has been shown to physically interact with p53 and prevent its degradation by excluding a portion of p53 protein from the p53 and MDM2 complex. Evidence indicates the existence of a link between PTEN and p53 functions through the control of the phosphorylation state of MDM2. AKT mediates MDM2 nuclear translocation by its phosphorylation. In the nucleus, MDM2 negatively regulates p53 by binding and signaling for destabilization (53). Therefore, attenuation of the AKT pathway by PTEN protects p53 from MDM2 mediated degradation and inactivation. The p53 and MDM2 complex is transported from the nucleus into the cytoplasm where MDM2 serves as an E3 ubiquitin ligase (54). Consequently, p53 and MDM2 form a regulatory feedback loop in which p53 positively regulates MDM2 expression, whereas MDM2 negatively regulates the level of p53 protein. Thus, PTEN may protect p53 from MDM2-mediated degradation, whereas p53 can enhance the transcription of PTEN (Fig. 3). Therefore, inactivation of either gene result in lower protein levels of the other gene.

The instability of PTEN correlated with its missense mutations has been shown to involve protein interactions. PTEN may be regulated by ubiquitin-mediated proteasomal degradation, a common mechanism to control protein levels. In cells, a ubiquitin ligase NEDD4-1 negatively regulates PTEN stability by catalyzing PTEN ubiquitination (55). As truncation or mutation of the C2 domain of PTEN makes the protein unstable and accelerates protein degradation, the C2 domain seems to regulate the phosphatase domain through maintaining the protein stability (56). In addition to the C2 domain, the C-terminus of PTEN contains two PEST (proline, glutamic acid, serine and threonine) sequences involved in ubiquitin protein degradation pathway. Treatment of cells with proteasome inhibitors can cause an increase of PTEN protein level (57,58). Several NEDD4-like E3 also regulate p53. Interestingly, multiple NEDD4-like E3 show ligase independent function. Furthermore, most of NEDD4-like E3 are frequently regulated by phosphorylation, ubiquitination, translocation, and transcription in cancer cells. NEDD4-like ubiquitin protein ligase-1 (NEDL1) is a type E3 ubiquitin protein ligase. Functional interaction of NEDL1 with p53 might contribute to the induction of apoptosis in cancer cells bearing wild-type p53 (59,60).

Casein kinase II-mediated phosphorylation stabilizes the PTEN protein by preventing its proteasomal degradation, while keeping it in an inactive state. Inhibition of the PTEN phosphorylation by the Casein kinase II results in increased PTEN activity and a corresponding reduction in AKT activation (61). Importantly, inhibitors of Casein kinase II also activate p53 function in wild-type, but not in p53 mutant cells. Activation of p53 function is involved in increased DNA-binding ability, transcriptional activation, increased expression of p53 target genes, associated with cell cycle progression and apoptosis. In addition, inhibitors of Casein kinase II increase senescence p53-dependently (62), thus, Casein kinase II may control the PTEN and the p53 balance.

4. Involvement of PTEN and p53 tumor suppressors in hereditary cancer

The *PTEN* gene is found in 80% of Cowden syndrome patients (63,64). Mutations of the *PTEN* gene are thus frequent in hereditary cancer syndromes, and are found in all exons except 1, 4, and 9 in Cowden syndrome (63-65). These mutations target the *PTEN* gene not only at its coding regions, but also at exon-intron boundaries and promoter regions, most of which have a major impact in the *PTEN* protein levels of expression, being causative of PTEN functional deficiency and considered as pathogenic (66,67). It has been suggested that the differential expression of the *PTEN* gene correlates with the different phenotypes. Mutations targeting the *PTEN* coding region include frame-shift and nonsense mutations, which also generate unstable truncated PTEN proteins, as well as missense mutations that result in individual amino acid changes. Functional analyses of these missense mutations have revealed that the amino acid substitutions generate PTEN proteins with impaired intrinsic catalytic activity and/or protein stability (68-70).

Some examples have been described of missense PTEN mutations that do not affect the intrinsic catalysis nor the

stability of the protein, but rather impair essential regulatory PTEN properties, such as binding to membranes or nuclear entry (71). PTEN hamartoma tumor syndrome is the term used to describe Cowden syndrome (65). Mutations in *PTEN* together with p53 make the tumor suppressor genes one of the most frequently affected in human malignancies in solid tumors (72-74). *PTEN* is considered haplo-insufficient to prevent certain malignancies, suggesting that dosage is important for its function, as it is influenced by a given point mutation in the catalytic activity of the enzyme (75). Tumors initiated by a subtle downregulation of a tumor suppressor gene can progress in the absence of LOH of the wild-type allele (76). These regulatory cues are presumed to play a key role in tumorigenesis through the alteration of the appropriate levels, localization, and activity of PTEN. However, it has been shown that *PTEN* germ-line SNPs are unlikely to have an important role in hereditary prostate susceptibility (77). The lifetime risk of breast cancer for Cowden syndrome patients is 81% (78), and bilateral risk-reducing mastectomy with immediate reconstruction is performed to eliminate further risk of breast cancer (79).

5. Perspective

Advances in the field of hereditary cancer genetics have led to an improved understanding of detection and prevention strategies. Germline genetic testing for mutations in PTEN and p53 allows for the identification of individuals at increased risk for breast, ovarian and other cancers. PTEN and p53 may be regulated and interact with each other at multiple levels including transcription, protein modulation, and protein stability (80,81). Understanding the regulation is crucial for the effective design of novel cancer therapeutics. In addition, it is important to investigate the functional linkage between PTEN, p53 and MDM2 isoforms in human cancer samples, and elucidation of interaction-specific functions may provide insight into regulatory aspects of these tumor suppressors as well as opportunities for therapeutic intervention. Further mechanistic studies are needed in order to understand the precise molecular mechanisms for the effective treatment of both cancer and other diseases with their alteration.

Acknowledgements

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