Redox regulation of tumor suppressor *PTEN* in cancer and aging (Review)

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Abstract. Phosphatase and tensin homologue deleted on chromosome 10 (*PTEN*) has been shown to act as a tumor suppressor whose function includes important roles in regulating oxidative stress, indicating a potential role in oxidative damage-associated cancer. Accumulating evidence has revealed that *PTEN* also acts as a pivotal determinant of cell fate, regarding senescence and apoptosis, which is mediated by intracellular reactive oxygen species (ROS) generation. Cells are continuously exposed to ROS, which represent mutagens and are thought to be a major contributor to cancer and the aging process. Therefore, cellular ROS sensing and metabolism are firmly regulated by a variety of proteins involved in the redox mechanism. In this review, *PTEN* and the roles of oxidative stress in phosphoinositide-3 kinase/AKT signaling are summarized with a focus on the links between the pathways and ROS in cancer and aging.

Contents

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1. Introduction

Reactive oxygen species (ROS) are generated during mitochondrial oxidative metabolism as well as in the cellular response to pathogens, and act as signaling molecules and regulate various physiological processes including proliferation, differentiation, apoptosis and migration (1-3). In addition, protein and lipid oxidation by ROS is proposed as a crucial determinant of health. Many experiments have shown that ROS also have a role in determining cellular senescence in mammalian cells (4). Increased levels of oxidative stress results in macromolecular damage and is implicated in various disease states such as atherosclerosis, diabetes, obesity and cancer (5).

One major source of endogenous ROS comes from mitochondria during the process of oxidative phosphorylation to produce energy in the form of ATP (6). In addition, ROS are produced by intracellular membrane oxidases. Inflammation is a major source of ROS at the sites of tissue. It is important for cells to neutralize ROS before they can damage cellular macromolecules including DNA. A major DNA lesion generated by excessive ROS is 8-oxo-2'-deoxyguanosine, which leads to a single- or double-strand break when left unrepaired (7,8). Persistent breaks can in turn lead to genomic instability. It is widely believed that the accumulation of mutations is a main cause of several aging processes. In addition, oxidative stress is known to shorten telomeres a process likely leading to replicative senescence and aging (9,10). Thus, an abnormal response to increased levels of endogenous ROS would likely affect health and aging. ROS modify the activity of several key enzymes, resulting in the reorganization of the actin cytoskeleton, adhesion and stimulation of cell migration. One mechanism by which ROS are thought to exert effects is through the reversible regulation of target molecules such as PKC; MAPK; phosphoinositide-3 kinase (PI3K); tyrosine phosphatase; and phosphatase and tensin homologue deleted on chromosome 10 (PTEN) (11). However, less is known in regards to the initial regulation of signaling molecules by ROS. Cellular ROS metabolism is tightly regulated by a variety of proteins involved in the redox mechanism.

The proper functioning of several signaling pathways relies on the action of several growth factors and cytokines,

which induce the generation of ROS (12). A number of studies have demonstrated an antioxidant role for tumor-suppressor proteins, activating the expression of antioxidant genes in response to oxidative stress. Tumor-suppressor genes regulate diverse cellular activities including DNA damage repair, cell cycle arrest, cell proliferation, cell differentiation, migration and apoptosis (13). *PTEN* is a tumor-suppressor gene that is frequently deleted or mutated in a variety of human cancers. It has been demonstrated that upregulation of PTEN causes modulation of PI3K/AKT signaling to reduce ROS generation in cells (14). In this review, the tumor suppressor PTEN and its roles in oxidative stress are summarized with a focus on the molecular links and interplay between ROS and the signaling pathways.

2. Expression, structure and characteristics of PTEN

Human genomic *PTEN* locus consists of nine exons on chromosome 10q23.3, encoding a 5.5-kb mRNA that specifies a 403-amino acid open reading frame (15,16). The translation product is a 53-kDa protein with homology to tensin and protein tyrosine phosphatases (PTPs). *PTEN* is ubiquitously expressed throughout early embryogenesis (17). In addition, peroxisome proliferator activated receptor γ (PPARγ) and tumor suppressor p53 can transcriptionally upregulate *PTEN* expression (18,19). Interestingly, rosemary extract represses *PTEN* expression in K562 leukemic culture cells (20). Methylation of the *PTEN* promoter can result in transcriptional silencing of the *PTEN* gene (21). Enzymatic PTEN activity can be regulated by posttranslational regulation including phosphorylation, acetylation and oxidation (22). The *PTEN* gene is the frequently mutated and deleted tumor suppressor in human cancer. Loss of heterozygosity studies have suggested that *PTEN* plays an important role in advanced cancers (23). In addition, alteration of *PTEN* in tumors is associated with a poor prognosis (24). *PTEN* heterozygous mice also develop a number of cancers. In contrast, overexpression of *PTEN* induces growth suppression by promoting G1 arrest (25).

The schematic structure of the PTEN protein is shown in Fig. 1. The PTEN protein consists of N-terminal phosphatase, and C-terminal C2 and PDZ (PSD-95, DLG1 and ZO-1) binding domains. The PTEN $CX_5R(S/T)$ motif resides within an active site that surrounds the catalytic signature with three basic residues, which are critical for PTEN phosphatase activity. The structure provides PTEN with its preference for acidic phospholipid substrates such as phosphatidylinositol 3,4,5-triphosphate (PIP3). The PTEN lipid phosphatase activity regulates the AKT kinase pathway through modulation of PIP3 levels, regulating cell proliferation, apoptosis and migration. In addition, AKT activation leads to hypoxia-inducible factor-1 (HIF-1) stabilization, whereas PTEN attenuates hypoxia-mediated HIF-1 stabilization (26). HIF-1 is a critical element for the transcriptional regulation of genes important for adaptation to low oxygen conditions. The instability of mutant PTEN and the reduction of HIF1 degradation have been shown to involve protein interactions (27).

PIP3 is the major second messenger of the PI3K pathway that mediates receptor tyrosine kinase signaling to the survival kinase AKT. PTEN negatively regulates the activity of PI3K/AKT signaling through converting PIP3 to phosphatidylino-

sitol 4,5-bisphosphate (PIP2). Increased levels of PIP3 at the membrane cause PH domain-containing proteins such as AKT to co-localize, resulting in kinase-mediated phosphorylation and activation (28). Activated AKT phosphorylates target proteins involved in cell survival, cell cycling, angiogenesis and metabolism (Fig. 2). PTEN acts as a regulator for maintaining basal levels of PIP3 contrary to those signaling activation. Increased proliferation, survival and motility are the main cellular effects associated with increased PIP3 levels and also contribute to its tumorigenic effects. Dysregulation of the PI3K/AKT pathway has been identified in many malignant cancers (29). PTEN exerts its tumor-suppressive effect by dephosphorylating PIP3, thereby negatively regulating AKT activation and the survival pathway. As elevated levels of PIP3 confer an advantage to cancer cells, inactivating mutations in the *PTEN* gene may be common in tumors.

3. Molecular relationship between PPAR, SIRT and PTEN/AKT through ROS production and DNA damage

Peroxisome proliferator-activated receptors (PPARs) are transcription factors that belong to the nuclear hormone receptor superfamily. The responsive elements in genome DNA are found in various genes that are involved in lipid metabolism and energy homeostasis including lipid transport (30). The expression is modulated by aging. Three subtypes PPARα, PPARδ (also known as PPARβ) and PPARγ, have been identified. Distinct activation of PPARs may account for the specific biological activity of the three PPAR subtypes. Fatty acid can interact with PPARs, which induces upregulation of the expression of enzymes necessary for their removal through mitochondrial oxidation (31). Then, lipid overload results in an increased production of ROS (32). Since PPARs play an essential role in mitochondrial biogenesis and respiration, and detoxification of ROS, defects in this pathway are likely in turn to contribute to mitochondrial impairment. For example, the PPARγ signaling pathway improves many of the mitochondrial insufficiencies (33). PPARγ activation reduces the proliferation of endometrial cells via regulation of PTEN. In addition, knockdown of PTEN with siRNA abrogated the effects of PPARδ on cellular senescence and on generation of ROS (34). Furthermore, ligand-activated PPARδ upregulates the expression of PTEN then suppresses the PI3K/AKT pathway. Activated PPARδ also confers resistance to induced senescence by the upregulation of PTEN, which reduces ROS generation in vascular cells. It has been reported that manganese superoxide dismutase is induced by resveratrol, which may activate PPARα, β and γ, via nuclear translocation and activation of SIRT1 (35). Mammalian SIRT1 (known as yeast homolog Sir2) is a deacetylase implicated in longevity and diverse metabolic processes (36). The enzymatic activity may be regulated by cellular energy, and SIRT1 may serve as a key regulator for obesity related to antioxidant status. PTEN is acetylated on Lys-402, which is in the COOH-terminal PDZ domain-binding motif, indicating a potential role of acetylation in regulating PTEN function (37). The SIRT1 deacetylase is mainly responsible for PTEN deacetylation. Thus, SIRT1 deficiency enhances the acetylation level of target molecules such as PTEN. SIRT1 may be a useful therapeutic targets for age-related diseases including metabolic
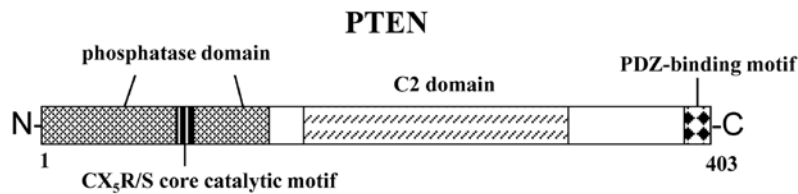
PTEN

Figure 1. Schematic structure of the PTEN protein. The predicted consensual domain structures for each protein are depicted. The functionally important sites are also shown. C2 domain, a protein structural domain involved in targeting proteins to cell membranes; PDZ, a common structural domain in signaling proteins (PSD95, Dlg, ZO-1).
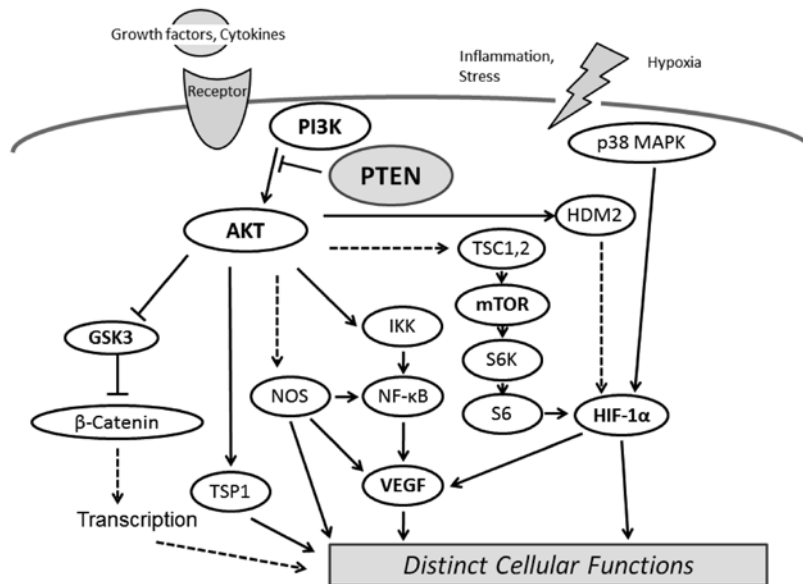

Figure 2. Schematic representation of PI3K/AKT/PTEN signaling. Examples of molecules known to act on the regulatory pathways are shown. Note that some critical pathways have been omitted for clarity.
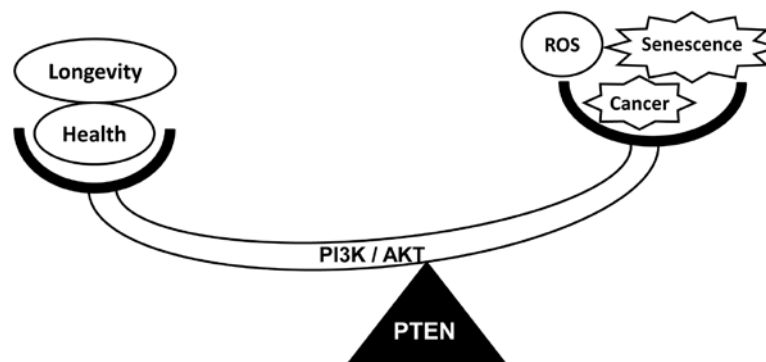

Figure 3. Cancer or apoptosis, longevity or senescence; these are issues for individual health. Determination of either a healthy or unhealthy state may be caused by the balance of PI3K/AKT functions on PTEN in cells.

disorders. Overexpression of SIRT1 in cancer tissue, compared with normal tissue, has been demonstrated, suggesting that SIRT1 may act as a tumor promoter (38). Actually, SIRT1 promotes carcinogenesis of hepatocellular carcinoma through the PI3K/AKT signaling pathway. In addition, SIRT1 decreases PTEN acetylation and inactivates the function of the pathway in a deacetylase-dependent manner (39).

4. Molecular relationship between WRN and PTEN/AKT through ROS production and DNA damage

Werner syndrome, which is characterized by the early onset of premature age-associated pathologies including elevated cancer incidence, is a rare autosomal disease caused by the lack of a functional nuclear RecQ-like DNA helicase, the WRN protein (40). Diploid fibroblasts have a short lifespan and

extensive genomic instability. The WRN protein is a helicase involved in DNA repair, replication, transcription and telomere maintenance. Repair mechanisms of DNA damage, including oxidative DNA damage at telomeres require the presence of WRN, which plays a critical role in optimizing double-strand break repair mechanisms due to its end-processing helicase and exonuclease activities. It was subsequently found that, in addition to a 3'-5' helicase activity, the WRN protein also possesses a 3'-5' exonuclease activity (41). Withdrawal of the WRN protein by knockdown through RNA interference produces and accelerates cellular senescence phenotype and DNA damage responses (42). The depletion of the WRN protein also leads to increased HIF-1 complex stabilization and activation (43). HIF-1 is also implicated in the molecular mechanisms of ageing. HIF-1 activation in the absence of WRN involves the generation of mitochondrial ROS. Studies indicate that the WRN protein regulates HIF-1 activation by affecting mitochondrial ROS production. As mentioned above, activation of the PI3K/AKT pathway leads to HIF-1 stabilization, whereas PTEN attenuates HIF-1 stabilization. Mutation of PTEN can also destabilize HIF-1. Mice lacking the helicase domain of the WRN homologue exhibit many phenotypic features of Werner syndrome, including a shorter mean lifespan compared to wild-type animals (44). Vitamin C supplementation rescues the shorter mean lifespan of *WRN*-mutant mice and reverses several related abnormalities (45). The deletion of AKT homologues protects against age-dependent defects, raising the possibility that modulation of the PTEN/AKT pathway protects against premature aging syndromes. Downregulation of the PI3K/AKT pathway by PTEN expression may protect against age-dependent DNA damage and cancer (Fig. 3), including the premature disorders observed in Werner syndrome.

5. Catalytic activity of PTEN is modulated by ROS

ROS directly interact with signaling molecules to modulate the signaling in a variety of cellular processes such as proliferation and survival. In fact, the catalytic activity of PTEN is modulated by ROS, and cellular PTEN phosphatase activity is inhibited by oxidative stress (46). PTEN inactivation then causes an increase in cellular PIP3 levels; PIP3 accumulation occurs at the plasma membrane and activation of the downstream PIP3 target including AKT, indicating a functional role for elevated intracellular ROS. In addition, activated PI3K/AKT signaling causes increased expression of several genes related to cell survival. Endogenous oxidant production in macrophages inactivates a fraction of the cellular PTEN, and this is also associated with an oxidant-dependent activation of downstream signaling (47). It has been reported that ROS levels are increased in retinal pigment epithelium cells in association with phosphorylation and inactivation of PTEN (48). PTEN phosphorylated inactivation and the consequent AKT activation in cells are inhibited by antioxidant treatment. ROS mediate PTEN inactivation but do not affect PTEN expression. On the other hand, mitochondrial PTEN protein levels are decreased by N-acetylcysteine and increased by H_2O_2 (49). The increase in mitochondrial PTEN may further promote ROS production in cells. However, exposure of purified PTEN to H_2O_2 results in inactivation of PTEN in a time- and concentration-dependent manner (50). Analysis of various cysteine mutants

has indicated that the essential Cys residue in the active site of PTEN specifically forms a disulfide bond during oxidation (51). The uncontrolled generation of ROS may contribute to cell proliferation by inhibiting PTEN function. In fact, inactivation of PTEN is implicated in the tumorigenesis of prostate cancer. This may have implications for the carcinogenic processes in which PIP3 and oxidants are produced.

6. Perspective

It is accepted that one of the hallmarks of aging is the accumulation of DNA damage caused by ROS, which are produced during normal metabolism and inflammatory reactions. ROS are known to induce genomic alterations such as point mutations and deletions, inhibit tumor-suppressor genes and/or activate oncogenes. It has been shown that another tumor suppressor p53 also promotes ROS production and participates in the induction of apoptosis (52). ROS are known to be critical for senescence, and the p53 target genes that increase ROS may also play an important role in senescence induction. As ROS can regulate PTEN, the role of PTEN in modulating ROS may form part of a feedback loop. The induction of ROS is likely to play a role in cell growth inhibitory responses such as the induction of senescence. Premature senescence has a compensatory role in apoptosis in the absence of the tumor suppressor PTEN through the AKT/ROS/p53 pathway. Furthermore, increasing ROS can enhance insulin signaling to attenuate the development of insulin resistance. Enhanced ROS-dependent insulin signaling is attributable to the oxidation and inhibition of PTEN. Given the importance of PTEN in regulating metabolism, there may be much evidence linking PTEN to diabetes and senescence. A better understanding of the intricate relationships between ROS and aging via the PTEN pathway may provide clues to ROS-mediated aging pathways for new drug discovery. Future experiments may determine which pathways are responsible for the redox imbalance noted in the human PTEN mutant.

Acknowledgements

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