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PTEN in DNA damage repair

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Abstract

The ability of DNA repair in a cell is vital to its genomic integrity and thus to the normal functioning of an organism. Phosphatase and tensin homolog (PTEN) is a well-established tumor suppressor gene that induces apoptosis and controls cell growth by inhibiting the PI3K/AKT pathway. In various human cancers, PTEN is frequently found to be mutated, deleted, or epigenetically silenced. Recent new findings have demonstrated that PTEN also plays a critical role in DNA damage repair and DNA damage response. This review summarizes the recent progress in the function of PTEN in DNA damage repair, especially in double strand break repair and nucleotide excision repair. In addition, we will discuss the role of PTEN in DNA damage response through its interaction with the Chk1 and p53 pathways. We will focus on the newly discovered mechanisms and the potential implications in cancer prevention and therapeutic intervention.

1. Introduction

Cellular DNA is constantly challenged by either endogenous (reactive oxygen species (ROS) resulting from metabolic processes) or exogenous (ionizing radiation, UV) agents. To effectively repair these DNA lesions, cells are equipped with delicate DNA repair mechanisms to maintain their genomic stability. The main repair mechanisms include nucleotide excision repair (NER), base excision repair (BER), mismatch repair (MMR), DNA double strand break repair (DSBR) and post replication repair (PRR) [1–4]. Specific repair pathways are activated in response to a particular type of lesion generated. The BER and NER pathways are typically activated in response to damage to individual DNA bases, while breaks in one (SSBs) or both (DSBs) require repair by mechanisms such as homologous recombination (HR), single strand annealing (SSA) or non-homologous end joining (NHEJ) [1–5].

Among these DNA repair mechanisms, NER is one of the most versatile and flexible repair systems found in most organisms [6–11]. It is highly conserved in eukaryotes and is critically important in the repair of UV-induced DNA lesions, mainly cyclobutane pyrimidine dimers (CPD) and pyrimidine(6–4)pyrimidone dimers (6–4PP) [12; 13]. The NER pathway involves a number of proteins that detect, unwind and remove damaged DNA. The NER process takes two forms, depending on whether damage detection is linked to

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Conflict of Interest

The authors state no conflict of interest.

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transcription (transcription-coupled repair, TCR) or to the genome more generally (global genome NER, GG-NER). During GG-NER, the cells activate a specific DNA repair mechanism, which involves well-coordinated action of DNA damage-binding proteins 1 and 2 (DDB1 and DDB2) and the xeroderma pigmentosum (XP) proteins (XPA-G) [6–11].

In addition to the direct DNA repair machinery, the cell's DNA repair ability is also regulated by DNA damage response (DDR) pathways [14; 15]. The DDR signal-transduction pathway is activated to coordinate cell-cycle transitions, DNA replication, DNA repair, and apoptosis. The major regulators of the DNA damage response are the phosphoinositide 3-kinase (PI3K)-related protein kinases (PIKKs). These PIKKs include ataxia-telangiectasia mutated (ATM) and ATM and RAD3-related (ATR). ATM and ATR respond to different types of DNA damage: ATM responds to double strand breaks (DSB, typical DNA damage caused by ionizing radiation), and ATR responds to replication stress and UV-induced pyrimidine dimers [14; 15]. The list of ATR substrates is rapidly expanding; however, the best studied is the Ser/Thr kinase checkpoint kinase-1 (Chk1) [16; 17]. ATM activates another checkpoint protein, checkpoint kinase-2 (Chk2) [18–21]. These pathways activate p53 [22–25], phosphorylate H2AX at serine 139 to form γ -H2AX, and regulate other downstream pathways to control DNA repair, checkpoints and apoptosis [14; 26–32]. Defects in the ATR/Chk1 and ATM/Chk2 pathways are known to increase cancer risk [33–38]. Activated by DSB damage, the ATM pathway is essential for DSB repair and acts by phosphorylating downstream targets [14; 15; 39]. Both the ATR and ATM pathways are required for NER to efficiently remove UV-induced DNA lesions [37; 40].

The phosphatase and tensin homolog (PTEN) gene encodes a major plasma membrane lipid phosphatase. PTEN functions as a highly effective tumor suppressor in a wide variety of tissues [41; 42]. Considerable biochemical and genetic studies have demonstrated that PTEN is the central negative regulator of PI3K/AKT-mediated signaling; loss of PTEN function in many human cancers leads to increased AKT activation, causing cell proliferation, survival, migration and spreading, all important factors in tumor development and progression [42–47]. Germline PTEN mutations have been found in hereditary cancer syndromes such as Cowden disease (CD), and Bannayan-Zonana syndrome, Lhermitte-Duclos disease, Proteus syndrome and Proteus-like syndrome [48–52]. These syndromes share overlapping clinical features and are characterized by the presence of developmental defects, benign hamartomas and an increased risk of cancer. Mice with PTEN deletion are highly susceptible to tumor induction in multiple organs such as the mammary gland, skin, and prostate [53–59], demonstrating the key role of PTEN in suppressing cancer development. This review will focus on recent advances in identification of novel functions of PTEN in several cellular processes, including PTEN in DNA repair and DNA damage response.

2. The function of PTEN in DNA damage repair

2.1 PTEN in DSB repair

PTEN deletion in mouse embryonic fibroblasts (MEF) causes spontaneous DNA double-strand breaks (DSBs) [60]. Consistent with the genomic instability phenotype in PTEN-deleted cells, Shen and coworkers demonstrated that cells deficient in PTEN have defective DNA DSB repair, possibly due to lack of or downregulation of Rad51 and lack of PTEN at centromeres [60]. PTEN acts on chromatin and regulates expression of Rad51, which reduces the incidence of spontaneous DSBs [60]. Several reports have indicated that reduced levels of PTEN are associated with radioresistance, which can be suppressed by ectopic PTEN expression [61]. This recovery of radiation sensitivity was attributed to the ability of PTEN to suppress the formation of the γ -H2AX foci, a marker for DNA damage, which alternatively suggests that PTEN decreases DSB levels [62].

However, using MEF cells and other types of cells, Gupta and colleagues argue against a role for PTEN in DNA DSB repair [63]. They found that the initial steps of DNA damage sensing and chromatin modification associated with DNA DSBs are similar in cells with and without PTEN, suggesting that defective repair is not the cause of the higher genomic instability observed in PTEN deficient cells [63]. The discrepancy is likely due to the different cell lines and assays used, suggesting that the role of PTEN in DSB repair is cell-type and endpoints dependent. In addition, the checkpoint defect in PTEN null cells may also contribute to the formation of DSBs [64]. Thus the precise role of PTEN in DSB repair needs to be further characterized in great detail in different cancer cell lines *in vitro* and *in vivo*.

2.2 PTEN promotes NER through XPC

Our recent studies have demonstrated that PTEN is essential for efficient NER activity [53]. Using low suberythemal UV radiation, mice with a targeted PTEN downregulation in their epidermis are predisposed to skin tumorigenesis [53; 58]. In human skin malignancies, PTEN is significantly downregulated in both premalignant and malignant skin lesions. Our findings clearly indicate that PTEN positively regulates GG-NER by promoting XPC transcription in keratinocytes. Inhibition of PTEN impairs GG-NER capacity through suppressing the expression of XPC. The PTEN/AKT/p38 axis seems to be critical for regulating XPC levels and thus for affecting GG-NER capacity. Suppression of p38 by AKT signaling reduces XPC levels and thus impairs GG-NER in PTEN-downregulated keratinocytes. In addition, when PTEN is inhibited through increased acetylation by the inhibition of the deacetylase SIRT1, AKT activation is also increased, and thus XPC expression is suppressed through increased nuclear translocation of the transcription repressor p130 [65]. Taken together, our results imply that PTEN positively regulates GG-NER by promoting XPC transcription in keratinocytes through AKT, suggesting PTEN as an essential genomic gatekeeper in the skin through its ability to positively regulate XPC-dependent GG-NER following DNA damage [53].

2.3 PTEN in the nucleus

PTEN, once considered a strictly cytoplasmic protein, is now known to be present in the nucleus [66]. Nuclear PTEN affects a variety of biological functions and plays a role in chromosome stability, DNA repair, cell cycle arrest and cellular stability. It was suggested that a unique role of nuclear PTEN is to arrest and protect cells upon oxidative damage and to regulate tumorigenesis [67]. Nuclear PTEN has been proposed to regulate the cell cycle through suppression of cyclin D1 activity [68], and also to act as a proapoptotic factor, as apoptotic stimuli promote the nuclear accumulation of PTEN [69]. Liu et al. have proposed that nuclear localization of PTEN can mediate these tumor suppressive activities independent of the AKT pathway by inhibiting anchorage-independent growth and inducing accumulation of the cells in G1 [70]. In addition, Shen and colleagues demonstrated a novel nuclear function of PTEN in maintaining chromosomal integrity independent of its ability to regulate the PI3K/AKT pathway through two novel mechanisms: (1) physical interaction with CENP-C to maintain centromere stability and (2) transcriptional regulation of Rad51 to control DSB repair and to suppress chromosomal instability arising due to DSBs [60].

The reasons for the change of the cellular localization of PTEN are still under investigation. Despite the absence of a classic nuclear localization signal, PTEN enters the nucleus by several mechanisms, including simple diffusion, active shuttling, cytoplasmic-localization-signal-dependent export and monoubiquitylation-dependent import [71]. Chung and coworkers associated PTEN with MVP (Major Vault Protein), a putative nuclear-cytoplasmic transport protein that mediates PTEN nuclear importation. This is dependent on two nuclear-localization-signal-like sequences: NLS4 (amino acids 65–269KKDK)

necessarily pairs with NLS2 (amino acids 60–164 RTRDKK) or NLS3 (amino acids 233–237 RREDK) to direct the importation of PTEN to the nucleus as mediated by MVP, but independent of PTEN phosphorylation and of its phosphatase activity [72]. It was recently reported that nuclear importation of PTEN is cell cycle dependent and regulated by the PI3K/AKT/mTOR/S6K signaling cascade [73]. So the mechanisms for nuclear importation of PTEN are unclear. However, nuclear-cytoplasmic partitioning of PTEN is a promising biological marker. The absence of nuclear PTEN is associated with more aggressive disease in patients with esophageal squamous cell carcinoma, cutaneous melanoma [74; 75], colorectal cancer, pancreatic islet cell tumors and cases of large B cell lymphoma [76]. Whether a shift in the cellular localization of PTEN might have a role in the pathogenesis of tumors remains to be elucidated.

2.4 PTEN interaction with Chk1

PTEN is found to be regulated by Chk1, an important signal transducer in the cell cycle checkpoint pathway [77]. Chk1 depletion decreases phosphorylation and total levels of PTEN. Phosphorylation of both Chk1 and PTEN at specific sites is critical for successful recovery of the cell cycle after stalled DNA replication, thus linking the Chk1-PTEN proteins in an important cell cycle regulatory pathway. Phosphorylation of Chk1 by ATR at Ser137 is necessary for CKII-mediated phosphorylation of PTEN at Thr383 and is important for cell cycle recovery, indicating the roles of Chk1 and PTEN in the DNA damage response pathway and in the regulation of cell cycle transitions.

On the other hand, PTEN regulates DNA damage response pathway. Loss of PTEN impairs Chk1-mediated checkpoint activation due to cytoplasmic sequestration of ubiquitinated Chk1 [78]. PTEN null cells display a partially defective checkpoint in response to ionizing radiation. Loss of PTEN and subsequent activation of AKT impair Chk1 through phosphorylation, ubiquitination, and reduced nuclear localization to promote genomic instability in tumor cells [78]. Another consequence of reduced Chk1 function in PTEN deficient cells is the accumulation of double-strand DNA breaks [64]. In PTEN deficient cells, increased DNA damage together with failure to arrest in size upon radiation may lead to radiosensitivity [79].

Interestingly, our recent findings demonstrated that PTEN loss increases UVB-induced Chk1 activation in keratinocytes in an AKT-independent manner [53]. It is likely that the effect of PTEN on checkpoint pathways depends on the type of DNA damage, the repair efficiency, the waveband-specific signaling pathways between UVB and UVC [80; 81], and/or the cell-type-specific response to PTEN inhibition, similar to the difference findings on the regulation of Rad51 expression [60; 63]. In our keratinocyte response to UVB-induced DNA damage, the checkpoint response appears to be passive, associated with the levels of unrepaired DNA damage, and to depend on the PTEN levels but not AKT activation, further underscoring the importance of constitutive PTEN levels in reducing susceptibility to UVB tumorigenesis [53]. Much more investigation is needed to elucidate these important differences at the molecular level.

2.5 PTEN interaction with p53

p53 is a transcription factor that maintains the integrity of the genome in response to DNA damage by inducing genes involved in cell cycle arrest, DNA repair and cell death. The p53 tumor suppressor gene controls cellular responses to DNA damage and forms a critical link to downstream effectors of growth arrest or cell death [82]. The PTEN gene has been shown to be involved in a complex network of interactions with p53 [83]. Nuclear PTEN leads to p53-mediated G1 growth arrest, suggesting that nuclear PTEN plays a unique role in arresting and protecting cells upon oxidative damage and a cooperative role with p53 in

tumor suppression [67]. p53 was found to undergo a two-phase response in irreparably damaged cells. Wip1 and PTEN are induced by p53 during both the early and late phases of the cellular response, thus the ATM-p53-Wip1 loop may cooperate with the p53-Mdm2 loop to elicit p53 pulses in the early phase, whereas the p53-PTEN-AKT-Mdm2 loop may become dominant later and drive p53 to a high level [84]. Freeman and colleagues showed that PTEN regulates p53 protein levels and transcriptional activity through both phosphatase-dependent and phosphatase-independent mechanisms. PTEN regulates the transcriptional activity of p53 by modulating its DNA binding activity, which provides a novel mechanism in which the loss of PTEN can functionally control “two” hits in the course of tumor development by concurrently modulating p53 activity [85]. PTEN was also found to play an essential role in regulating p53 expression and activity through distinct mechanisms [85]. The up-regulation of PTEN inhibits AKT and MDM2, which enhance the level of p53, thereby inducing G2/M arrest and apoptosis [86]. AKT activation via overexpression of a constitutively active form or via the loss of PTEN can overcome a G2/M cell cycle checkpoint that is induced by DNA damage [87].

3. Conclusions and future directions

Emerging new evidence has indicated that PTEN is vital for proper DNA repair, including DSB repair and NER. PTEN also has an indirect role in genomic integrity by regulating DNA damage response pathways such as Chk1 and p53. Based on the roles of PTEN in DNA repair, PTEN acts as a vital tumor suppressor. Loss of PTEN in human cancers may enhance radiosensitivity. On the other hand, loss of PTEN also increases cell survival and reduces DNA repair, which may lead to genomic instability and compromises therapeutic success. Targeting PTEN-related pathway, such as mammalian target of rapamycin (mTOR), has been shown to prevent tumorigenesis. Indeed, rapamycin, an mTOR-specific inhibitor, prevented leukemia development in PTEN-null mouse models [88–91]. However, the effectiveness of rapamycin may require PTEN deletion or genetic loss of function. The presence of wild-type PTEN allele(s) may compromise the efficacy of rapamycin, as recent studies show that mTOR inhibition decreases PTEN transcription and thus increases AKT activation [92; 93]. Further detailed mechanistic understanding of the roles of PTEN in DNA repair and DNA damage response in different tissues and cell types will help us fully understand the precise molecular mechanisms by which PTEN maintains genomic stability and contributes to tumor suppression and therapeutic efficacy, and will ultimately facilitate the development of effective agents and strategies to better prevent and treat cancer.

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