Published in final edited form as:

J Invest Dermatol. 2009 September ; 129(9): 2109–2112. doi:10.1038/jid.2009.79.

PTEN: New Insights into Its Regulation and Function in Skin Cancer

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Abstract

Skin cancer is the most common cancer in the United States. UV radiation in sunlight is the major environmental factor causing skin cancer development. PTEN (phosphatase and tensin homolog deleted on chromosome 10), a recently discovered tumor suppressor gene, is frequently mutated, deleted, or epigenetically silenced in various human cancers. PTEN negatively regulates the oncogenic phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathways. PTEN is clearly a critical tumor suppressor for skin cancer in humans and in mice. This review summarizes the recent progress in the function of PTEN in the development of skin cancer, including basal-cell carcinoma, squamous-cell carcinoma, and melanoma. The regulation of PTEN by UV radiation is also discussed in association with skin carcinogenesis. Understanding the fundamental mechanisms that lead to the reduction of PTEN function in skin carcinogenesis and the essential association with UV radiation opens up new opportunities for molecular chemoprevention and therapy of skin cancer by targeting PTEN pathways.

INTRODUCTION

Skin cancer is the most common type of cancer in the United States. Each year more than one million new cases are diagnosed, accounting for more than 40% of all cancers diagnosed. Skin cancers include basal-cell carcinoma (BCC), squamous-cell carcinoma (SCC), known as non-melanoma skin cancer, and melanoma. BCCs and SCCs account for ~80 and 16% of all skin cancers, respectively, whereas malignant melanomas account for only 4% of all skin cancers (Bowden, 2004). BCCs and SCCs are both derived from the basal layer of the epidermis of the skin. BCCs are slow growing and rarely metastasize, whereas SCCs can be highly invasive and may metastasize (Bowden, 2004). In contrast, melanoma is derived from melanocytes and the mortality associated with melanoma is high. UV irradiation in sunlight (Ramos *et al.*, 2004; Erb *et al.*, 2008) is the major environmental factor causing skin cancer. The rising incidence rates of BCC, SCC, and melanoma are highly associated with increased exposure to UV radiation because of increased sun exposure caused by sunbed tanning for cosmetic purposes, increased outdoor activities, changes in clothing style, increased longevity, and/or ozone depletion (Rigel, 2008).

PTEN (phosphatase and tensin homolog deleted on chromosome 10) functions as a highly effective tumor suppressor in a wide variety of tumor tissues (Suzuki *et al.*, 2008) by negatively regulating the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway

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CONFLICT OF INTEREST

The authors state no conflict of interest.

(Maehama and Dixon, 1998). Loss of PTEN function through deletion, mutation, and/or decreased expression, has been found both in human sporadic cancers (Steck *et al.*, 1997; Kohno *et al.*, 1998; Birck *et al.*, 2000; Harima *et al.*, 2001; Byun *et al.*, 2003) and in hereditary cancer syndromes (Liaw *et al.*, 1997; Marsh *et al.*, 1997; Harima *et al.*, 2001). This ubiquitous and evolutionarily conserved signaling cascade influences many functions, including cell growth, survival, proliferation, migration, and metabolism (Endersby and Baker, 2008). Although largely unknown, similar or distinct PTEN involvement may exist in skin carcinogenesis.

The review here is to provide a new perspective of PTEN regulation and function in skin carcinogenesis, its interaction with other critical signaling pathways involved in skin cancer, and its regulation by environmental UV radiation. Furthermore, the possibility of selectively targeting PTEN chemoprevention and therapy of skin cancer is also discussed.

PTEN IN SKIN CANCER

Functional studies supported the hypothesis that PTEN is a critical tumor suppressor in skin cancer. Loss of PTEN activity through mutation, deletion, or reduced expression has been shown to play an important role in skin tumor development. Germline mutations in PTEN, detected in patients with Cowden's disease and Bannayan–Riley–Ruvalcaba syndrome (Bonneau and Longy, 2000), lead to the loss of PTEN function, which increases the risk of tumorigenesis in skin as well as in other organs (Liaw *et al.*, 1997; Trojan *et al.*, 2001).

PTEN in BCC

Loss of PTEN function may be critical for BCC formation through activating Sonic Hedgehog (Shh) signaling. BCC, at the molecular level, is characterized by aberrant activation of Shh signaling, usually because of mutations either in the *patched* (*Ptc*) or *smoothened* (*Smo*) genes (Reifenberger, 2007), or because of hyperactivation of this pathway. It is interesting that PTEN may be critical for Shh signaling. Recent studies have shown that PI3K/AKT activation is essential for Shh signaling by controlling PKA-mediated Gli inactivation (Riobo *et al.*, 2006). Although little is known regarding PTEN function in BCC, loss of PTEN function in BCC would upregulate the PI3K/AKT pathway to stimulate even low-level ligand-dependent or ligand-independent Shh signaling caused by mutations in Hedgehog pathway components. Although deletions of 10q23, where PTEN is located, were found to be an infrequent event in BCC (Quinn *et al.*, 1994), the inactivation of PTEN by other mechanisms may play an important role in BCC development.

PTEN in SCC

The critical role of genetic PTEN suppression in SCC has been shown in humans and in mice. The tumor suppressing function of PTEN in SCC has been shown in patients with Cowden's disease, *in vitro* in human keratinocytes, and *in vivo*, using a chemical skin carcinogenesis model. The association of cutaneous SCC with Cowden's disease has also been reported (Nuss *et al.*, 1978; Camisa *et al.*, 1984). The decreasing levels of PTEN expression are correlated with a malignant transformation of the skin induced by UVA (315–400 nm), as shown by the formation of SCC in nude mice (He *et al.*, 2006).

Mice with PTEN deletion and mutation are highly susceptible to tumor induction (Suzuki *et al.*, 1998). Conditional knockout of PTEN in skin leads to neoplasia in skin (Li *et al.*, 2002; Suzuki *et al.*, 2003; Backman *et al.*, 2004), thereby showing the pivotal role of PTEN in skin cancer development. PTEN deficiency in mice causes increases in cell proliferation, apoptotic resistance, stem-cell renewal/maintenance, centromeric instability, and DNA double-strand breaks (Groszer *et al.*, 2001; Kimura *et al.*, 2003; Wang *et al.*, 2006; He *et al.*, 2007; Shen *et*

et al., 2007; Yanagi *et al.*, 2007), which can enhance susceptibility to carcinogens and the occurrence of secondary genetic or epigenetic alterations that can lead to skin cancer development.

Complex mechanisms may mediate the inactivation of PTEN. Somatic mutations, deletion, or promoter hypermethylation of PTEN have not been detected in SCCs of human skin (Quinn *et al.*, 1994; Kubo *et al.*, 1999; Murao *et al.*, 2006). Thus, the inactivation of PTEN by other mechanisms may be involved in SCC pathogenesis, including inactivation of the protein and/or epigenetic silencing, and the mechanism(s) by which its function and activity are regulated remain to be established.

Loss of PTEN function may occur as an early or late event, and PTEN loss has contributed to skin cancer development. Immunohistochemical studies have shown that, in mouse skin tumors, PTEN immunoreactivity was clearly confined to differentiating areas of the papillomas, and to the most differentiating areas in SCC samples, whereas PTEN staining is lost in non-differentiating infiltrative areas of SCCs, suggesting the expression and localization of PTEN in tumor sections that represent the different stages of mouse skin carcinogenesis (Segrelles *et al.*, 2002).

PTEN in melanoma

Loss of PTEN function has been implicated in the development of melanoma (Wu *et al.*, 2003). A high frequency of PTEN mutations has also been detected in malignant melanomas (Bonneau and Longy, 2000). On the basis of melanoma cell lines and mainly metastatic tumors, many studies also showed that PTEN played a significant role in sporadic cutaneous melanomas (Tsao *et al.*, 1998). PTEN inactivation was a late event likely related to melanoma progression rather than to initiation, and the translocation of PTEN expression from nuclear predominance to cytoplasmic predominance occurs from melanocyte to primary melanoma to metastasis melanoma. The potential genetic interaction among *NRAS*, *BRAF*, and *PTEN* may play a critical role in melanoma development (Tsao *et al.*, 2004).

Loss of PTEN function also increases AKT3 activation in melanoma. AKT3 protein, but not AKT1 or AKT2 protein, was found to be increased in melanoma cell lines when compared with normal melanocytes. Mechanisms of AKT3 deregulation occurred through a combination of overexpression of AKT3, accompanying copy number increases of the gene, and decreased PTEN protein function, occurring through loss or haploinsufficiency of the PTEN gene (Stahl *et al.*, 2004; Robertson, 2005).

PTEN REGULATION BY UV RADIATION

Recent studies show that UV radiation regulates PTEN function in skin cells. UV exposure causes gene alteration of PTEN (Hocker and Tsao, 2007). Inducing Egr-1 by exposing cells to acute UVC (100–280 nm) upregulates the expression of the PTEN messenger RNA and protein, and leads to apoptosis. Loss of Egr-1 expression, which often occurs in human cancers, could deregulate the PTEN gene and contribute to the radiation resistance of some cancer cells (Virolle *et al.*, 2001).

Our recent evidence shows that chronic UVA radiation decreased PTEN expression, and this decrease is required for enhanced cell survival in the transformed human keratinocytes, suggesting that PTEN might be critical for skin carcinogenesis induced by UVA (He *et al.*, 2006). PTEN increases sensitivity to cell death in response to several apoptotic stimuli, including UV irradiation and treatment with tumor necrosis factor α , by negatively regulating the PI3K/AKT pathway (Stambolic *et al.*, 1998), implying that PTEN alterations might be involved in UV-induced skin cancer. UVB (280–315 nm) was also reported to inhibit PTEN

by increasing PTEN phosphorylation in human dermal fibroblasts, as phosphorylation of PTEN downregulates its lipid phosphatase and protein stability (Oh *et al.*, 2006). Thus UV-mediated inhibition of PTEN function may further enhance AKT activation induced by UV radiation.

It is likely that multiple complex interactions at the transcriptional, post-transcriptional, and/or post-translational levels are involved. Systematic characterization of PTEN regulation by UV radiation will not only advance our knowledge of the fundamental mechanisms of PTEN involvement in skin cancer, but also facilitate the development of feasible approaches to prevent PTEN suppression because of chronic UV exposure.

Furthermore, UV-induced production of reactive oxygen species and the resultant oxidative stress exposure plays an important role in photocarcinogenesis caused by UV, and reactive oxygen species are believed to be involved in many inflammatory skin disorders, skin cancer formation, phototoxicity, and skin aging. PTEN activity can be inhibited by reactive oxygen species (Gimm *et al.*, 2000), implying that reduced PTEN activity by UV-induced reactive oxygen species formation might be involved in UV-induced skin tumorigenesis.

CONCLUSIONS AND FUTURE DIRECTIONS

PTEN plays a critical role in skin homeostasis and is a critical tumor suppressor in the prevention of skin carcinogenesis, as shown in humans and in mice. This has positioned PTEN in a central role of tumor suppression by antagonizing PI3K/AKT pathways in skin carcinogenesis. Proper function of PTEN is essential for maintaining the balance in cell proliferation and survival in epidermal cells, including keratinocytes and melanocytes in skin, to prevent transformation.

In addition, UV radiation, the major risk factor causing skin cancer, suppresses PTEN expression, indicating that PTEN may be the critical target for UV-induced skin tumorigenesis. As skin cancer is the most common malignancy in the United States, elucidating the mechanisms of PTEN function, and its regulation and function in the pathogenesis of BCC, SCC, and melanoma will have a broad impact in improving patients' quality of life and reduce the high morbidity associated with these cancers. Targeted PTEN, directly or by interfering with upstream proteins regulating PTEN activity, presents a new and more effective preventive and therapeutic approach in reducing skin cancer burden, as suggested in other cancers. Recently, the protective nature of phytoestrogens has been shown to be partially mediated by increasing PTEN expression, indicating that PTEN may be one of the critical molecular targets for skin cancer prevention and treatment.

Abbreviations

AKT, protein kinase B; BCC, basal-cell carcinoma; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog deleted on chromosome 10; SCC, squamous-cell carcinoma; Shh, sonic Hedgehog.

ACKNOWLEDGMENTS

We apologize to those investigators whose work could not be directly referenced owing to space limitations. Work in the authors' laboratory was supported by the Department of Medicine and the Section of Dermatology at the University of Chicago, the American Skin Association, and the University of Chicago Cancer Research Center (P30 CA014599). The authors are grateful for Dr Ann Motten for her critical reading of this manuscript.

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