IJD Review Article

Mini-review: the p53 gene as a bona fide tumor suppressor gene in human skin cancers

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Skin cancer is the out-of-control growth of skin cells that can be divided into keratinocyte carcinoma (non-melanoma) and malignant melanoma. Basal cell carcinoma (BCC) and squamous cell carcinomas (SCC) are the most common forms of keratinocyte carcinoma that may grow to involve other parts of the body. These cancers are caused by exposure to ultraviolet (UV) light, toxic substances, and a family history of skin problems. Different signaling pathways are likely to be involved in skin cancer. The TP53 gene (the gene coding for cellular tumor protein p53) is among the most diverse and complex molecules involved in cellular functions. The p53 pathway can initiate DNA replication, modulate cell cycle events, and interact with tumor suppressor genes (TSGs). Mutations in TP53 can occur in numerous human cancers, leading to cellular immortalization, inappropriate proliferation, and genomic instability. TP53 plays a big role in both melanoma and non-melanoma skin cancers. Despite the intensive investigation to clarify the impact of TP53 mutations in the induction of skin cancer, much remains to be elucidated. In this mini-review, we will discuss the protective role of p53 as a bona fide tumor suppressor gene in human skin cancers.

Keywords: skin cancer, carcinoma, basal cell carcinoma, squamous cell carcinomas

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INTRODUCTION

Skin cancer is an abnormal growth of skin cells that can be classified into keratinocyte carcinoma (KC; non-melanoma) [1-3] and malignant melanoma (MM) [4,5]. Basal cell carcinoma (BCC) and squamous cell carcinomas (SCC) are the most common forms of KC that may grow to involve other parts of the body [6-8]. MM is the least common form of skin cancer (3–5% of total skin cancers) and the most

aggressive type of malignancy that can develop from melanocytes (pigment-producing cells) [9,10]. There are a variety of different skin cancer symptoms, including skin lesions with an irregular border, a firm and red lump or nodule, a bleeding or scabbing sore, a large brownish spot, a painful or dark lesion, and more [11-13]. Most skin cancers are caused by exposure to radiation or toxic substances, excessive sun exposure (ultraviolet [UV] light), a weakened immune system, and a family history of skin cancer [14-17]. Different pathways are likely to be involved in skin cancer [5,18-20]. The TP53 gene (the gene coding for cellular tumor protein p53) is among the most diverse and complex molecules involved in cellular functions [21-23]. As a transcriptional factor, p53 can modulate cell cycle arrest and cell apoptosis and can interact with tumor suppressor genes (TSGs) [24-28]. Genetic alterations within the TP53 gene have a direct correlation with cancer development [29-33]. TP53 mutations play a big role in both melanoma and non-melanoma skin cancers [34,35]. Despite the intensive investigation to clarify the impact of TP53 in the suppression of skin cancer, much remains to be elucidated. In this mini-review, we will discuss the protective role of p53 as a bona fide tumor suppressor gene in human skin cancers.

The biological function of the p53 tumor suppressor gene

The p53 pathway is composed of a network of genes that initiate DNA replication and cell cycle events [36,37]. The p53 protein has several domains such as the amino-terminus domain (the transactivation domain), the proline-rich domain (for an efficient DNA-damage response through apoptosis), the carboxy-terminal basic DNA-binding domain that inhibits p53 binding to sequence-specific DNA (a "hot spot" for mutation), the oligomerization domain, the c-terminal domain (containing three putative nuclear localization signals [NLS]), and the leucine-rich C-terminal nuclear export signals (NES) [38-40]. As a guardian of the genome, p53 prevents cancer through numerous mechanisms and regulates DNA stability, cell apoptosis, cell cycle arrest, hypoxia, oncogenic events, and cellular senescence [41-45]. The p53 protein, by activating or inhibiting key effector genes and a variety of stress-inducing signals, can stimulate a variety of antiproliferative pathways [46,47]. For example, p53 stabilization occurs in response to DNA damage by various kinases such as ATR, ATM, DNA-PK, Chk1, and Chk2 [48]. Post-translational modifications (PTM) of p53 can stimulate the recruitment of p53 binding proteins to specific promoters [49]. The p53 protein interacts with histone acetyltransferase (HAT, CBP/p300) and histone deacetylases (HDAC1 and HDAC2) to modulate transcription [50]. Besides, the MDM2 protein as a ubiquitin ligase and a negative regulator was previously found to mediate the ubiquitination and degradation of p53 [51-53]. Therefore, in response to stress signals, p53-mediated apoptosis can be induced after the inactivation of the MDM2 protein [54]. The mammalian TOR protein (mTOR) signaling pathway (TORC1 and TORC2) positively regulates cell growth and protein synthesis [27,55,56]. Upon oxidative stress or DNA damage, p53 increases the phosphorylation of Sestrin1 (Sesn1), Sestrin2 (Sesn2), and the AMP-responsive protein kinase (AMPK) to inhibit mTOR signaling [57]. The PI3K/Akt signaling pathway, by promoting cell proliferation and differentiation, has a significant role in tumorigenesis [58]. Akt in response to environmental stress increases the nuclear translocation of MDM2 and decreases p53 transcriptional activity [59].

The p53 protein can also regulate the G2-M checkpoint regulators cyclin B1/cdc2, which are required for entry into mitosis [60]. After DNA damage, 14-3-3σ protein expression can be activated by p53, blocking the nuclear localization of cyclin B1 [61,62]. In the P16/cyclin D1/retinoblastoma tumor suppressor (Rb) pathway, tumor suppressor protein P14ARF as a cell cycle regulator can interact with MDM2 and activate p53 [63,64]. Notably, p53 can activate the damage-regulated autophagy modulator (DRAM) gene and modulate autophagy in a DRAM-dependent manner that is essential for cell and organismal survival [65]. DRAM, as a lysosomal protein, has also been shown to be critical for p53-mediated programmed cell death [66]. Based on current information, p53 is required for apoptosis and can interact with members of the proapoptotic Bcl-2 family of genes [67,68]. In response to various cell death signals, PUMA, as a unique p53 apoptotic target gene, acts in response to p53 and binds with Bcl-XL protein to activate Bax in the mitochondria [69,70]. As a negative regulator of inflammation, p53 inhibits the secretion of WNT ligands and regulates tumor-associated macrophages and IL-1β and NF-κB activation [71,72]. These insights illustrate the importance of the tumor

suppressor gene p53 in multicellular organisms to limit tumorigenesis and inhibit cancer.

Protective role of p53 in skin cancers

Disruption of p53 function enhances cellular immortalization and gives rise to inappropriate proliferation and genomic instability [68]. Acute p53 activation and genetic alterations within the p53 gene have direct correlations with cancer development [29,73]. Till now, several in vitro and in vivo studies have examined the protective role of p53 in skin cancer [45,74-76]. Analysis of mutations in the p53 gene has revealed a correlation between UV exposure, apoptosis, and skin cancer [77-79].

Exposure to UV radiation can induce repair pathways in the skin [80,81]. The p53 protein has a leading role in the protection of cells in response to DNA damage after exposure to UV [78]. In response to UV radiation in keratinocytes, p53 through the release of paracrine factors triggers cell death, apoptosis, melanocyte proliferation, and melanin synthesis [79,82]. The inactivation of p53 by mutations may play a significant role in the stimulation of skin carcinogenesis by UV radiation [35,83].

By activating RAS and Snail or repressing Rb

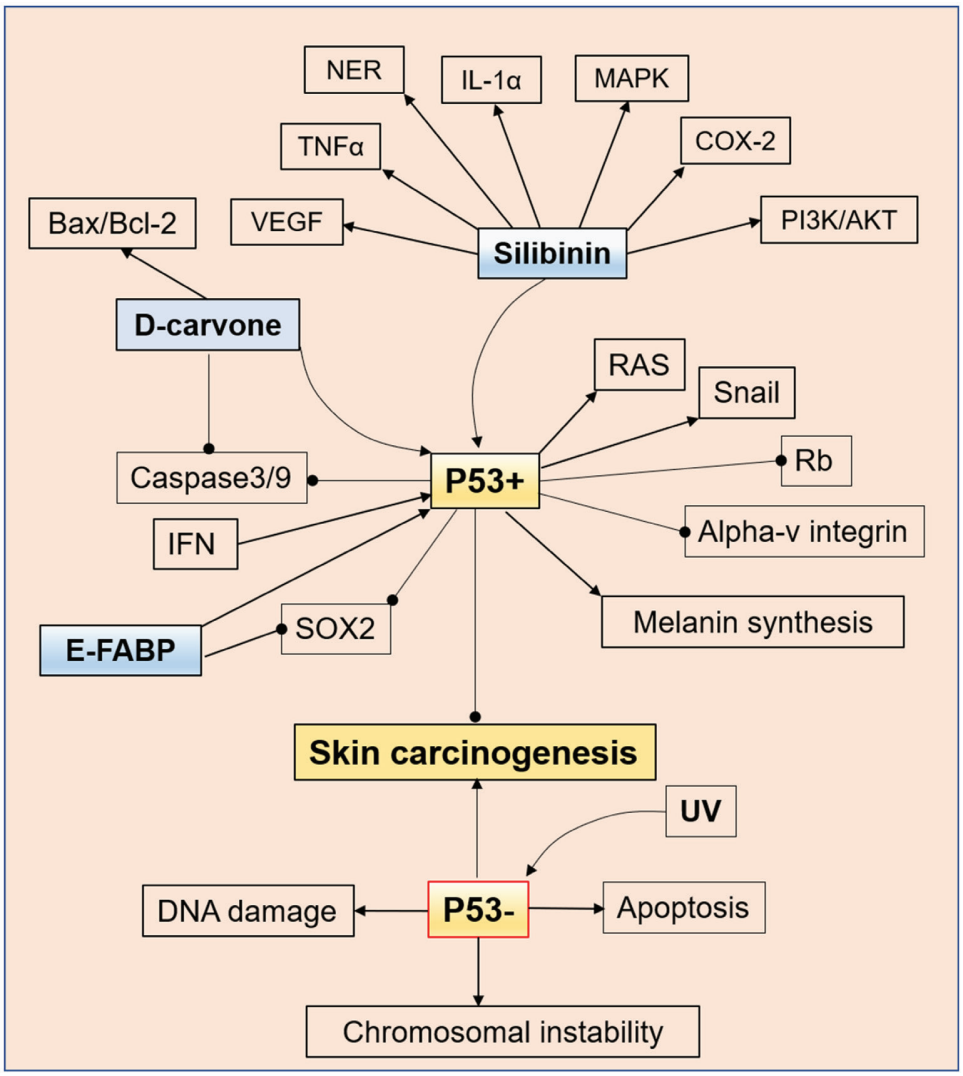

Figure 1. Protective role of p53 against skin cancers
The p53 protein can inhibit skin cancer via the activation of RAS and Snail and the suppression of SOX2, Rb, alpha-v integrin, and the caspase family. Inactivation of p53 by mutations may play a significant role in the stimulation of skin carcinogenesis by UV radiation. Silibinin delivers a therapeutic impact against skin cancer by targeting tumor necrosis factor-α (TNFα), interleukin 1 alpha (IL-1α), cyclooxygenase-2 (COX-2), vascular endothelial growth factor (VEGF), nucleotide excision repair (NER), phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT), p53, and mitogen-activated protein kinase (MAPK). D-carvone can suppress carcinogenesis by regulating the activities of p53, caspase 3/9, and Bax/Bcl-2.

and alpha-v integrin, p53 operates to suppress skin cancer [45]. Therefore, mice lacking p53 can develop spontaneous SCCs after UV light radiation [35]. In the absence of one or two p53 alleles, higher chromosomal instability has been shown in skin and tumors [84,85] (Figure 1). The use of phytochemicals shows their therapeutic impact in treating skin cancer [86,87]. Silibinin is a bioactive flavonolignan that has an anti-cancer effect in the mouse skin tumorigenesis model [34]. In the chronic UVB-exposed skin tumorigenesis study, silibinin was reported to enhance the p53 level, nucleotide excision repair (NER), and repair of DNA damage while minimizing epidermal damages [34,88-90]. Silibinin acts in the chemoprevention of skin cancer by targeting tumor necrosis factor-α (TNFα), interleukin 1 alpha (IL-1α), cyclooxygenase-2 (COX-2), vascular endothelial growth factor (VEGF), phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT), and mitogen-activated protein kinase (MAPK) [91,92]. D-carvone is another chemopreventive agent against skin cancer [93,94]. In 7, 12-dimethylbenz[a]anthracene (DMBA)-induced mouse skin tumorigenesis models, D-carvone can suppress carcinogenesis by regulating the activities of p53, caspase 3/9, and Bax/Bcl-2. In animals treated with DMBA, the levels of Cyt P450, Cyt b5, mutated p53, and Bcl-2 were reduced and the expression of Bax, caspase-3, and caspase-9 was increased1 [95]. SOX2 is a potential cancer stemness marker that controls tumor initiation [96]. The p53 pathway reduces the levels of SOX2 expression [97]. Additionally, type I interferons (IFN) as pleiotropic immunomodulatory cytokines are critical in skin tumor prevention [98,99]. In 12-O-tetradecanolyphorbol-13-acetate (TPA)-induced skin tumorigenesis models, epidermal fatty acid binding protein (E-FABP) plays a role in IFN-induced p53 transcriptional activity and in suppressing SOX2 expression to prevent skin tumorigenesis [100].

These data indicate that p53 works against skin carcinogenesis in cooperation with RAS activation, caspase-3 and caspase-9 inactivation, Snail overexpression, and SOX2, Rb, and alpha-v integrin inactivation.

CONCLUSION

The p53 tumor suppressor gene is involved in cellular functions and cell cycle arrest. As a guardian of the genome, p53 plays a big role in preventing melanoma and non-melanoma skin cancers. Genetic alterations within the p53 gene have a direct correlation with skin carcinogenesis. The p53 protein can inhibit skin cancer via the activation of RAS and Snail and the suppression of SOX2, Rb, alpha-v integrin, and the caspase family. Despite the intensive efforts to clarify the key role of p53 gene mutations in the induction of skin cancer, much remains to be elucidated.

Conflict of interests: None declared.

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