[Frontiers in Bioscience S2, 11-17, January 1, 2010]

The shady side of sunlight: current understanding of the mechanisms underlying UV-induction of skin cancers

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1. ABSTRACT

The incidence of skin cancer has been rising at an astonishing rate, particularly that of the deadliest skin cancer, melanoma. While the molecular mechanisms of sunlight ultraviolet radiation (UV)-induced non-melanoma skin cancer (NMSC) have been well documented, there is a major gap in our current knowledge of how UV initiates melanoma. However, the components of the retinoblastoma (Rb) pathway, the p53 and the p16 pathways are considered the major targets of UV-induced NMSC and melanoma, respectively. Our recent study has revealed that these two pathways coordinate the early responses to UV radiation in the skin. Here, we review the value of studies targeting these early events of skin carcinogenesis, with specific focus on the critical role of the components of the Rb pathway.

2. INTRODUCTION

Skin cancer is the most common human malignancy in United states. There are over 1 million cases of non melanoma skin cancer (NMSC) occurring each year, and the incidence of cutaneous malignant melanoma (CMM) is rising more rapidly than any other malignancy (1). The relevance of sunlight exposure to the skin cancer epidemic is well known. One of the major contributory factors in this epidemic is increased recreational sun exposure (2, 3). Some protection against sun exposure occurs when the skin tans and thickens, and those who sunburn easily and tan poorly have the least degree of protection, increasing their risk of developing skin cancer. Increased awareness of the dangers of sun exposure has spurred an interest into how ultraviolet (UV) radiation in sunlight causes skin cancer. These concerns are amplified

by increasing discussions on the depleting ozone layer. The world health organization (WHO) estimates that a 10% decrease of ozone level will result in an additional 300,000 NMSC and 4,500 CMM per year (4). The incidence of NMSC increases in proportion to sunlight exposure, as seen in the elderly and outdoor workers (5). Although epidemiological studies supported by laboratory models indicate a relationship between UV light and melanoma (1), our knowledge of the underlying mechanisms is poor (6). This review will discuss the recent findings on the relationship between UV and the molecular mechanisms of NMSC and CMM, with specific interest into the early responses to UV insult, involving the coordination of p16 and the p53 pathways.

2.1. Sunlight ultraviolet radiation

Sunlight is composed of a continuous spectrum of electromagnetic radiation, divided into 3 main wavelengths, including ultraviolet, visible, and infra red. Visible light has a wavelength of 400-700 nm, and UV light compromises the wavelengths just short of visible light, those from 200-400nm. UV light can be divided into UVA (320-400), UVB (280-320), and UVC (280-320). The ozone layer of earth's atmosphere effectively blocks UVC from being absorbed, but both UVA and UVB reach earth's surface in amounts sufficient to damage skin and eyes. Humans are predominantly exposed to UVA, which has been shown to cause skin cancer in animals when given over a long period of time (7-10). Despite its low carcinogenic effect, it plays an important role in skin aging and wrinkling (11). In contrast, UVB causes a plethora of adverse effects ranging from erythema, burns, immune suppression, increased photo aging, and eventually skin cancers (11).

2.2. DNA Damage in the skin

In properly functioning human epidermis, cells turn over about once a month. Stem cells in the basal layer undergo cell division, and the keratinocytes differentiate into squamous cells, producing keratin and other proteins. Eventually, the cells desquamate (12). In UV-induced skin carcinogenesis, cells lose the ability to control proliferation (11). When the DNA of epidermal cells absorbs photons, electron rearrangement leads to the formation of photoproducts at adjacent pyramidine sites (13). In normal cells, these photoproducts can be removed by the nucleotide excision repair mechanism mediated by p53 (14). Photo damage elevates p53 expression in the skin, thus blocking the cell cycle at G1-S phase. This allows repair of damage or apoptosis to eliminate cells with severely damaged DNA (15, 16). In a chronic UV scenario, DNA photoproducts can become carcinogenic and be passed on during replication as C to T or CC to TT mutations. These mutations are known as genetic fingerprints (17). Unfortunately, the p53 gene can itself be mutated by UV radiation resulting in uncontrolled cell proliferation and loss of apoptosis by DNA damaged cells (18). Xeroderma pigmentosum individuals, which have defective DNA repair machinery, extreme sun sensitivity and high incidence of skin cancer, provide evidence of the importance of DNA repair mechanisms (2). UV-induced DNA damage also effects immune surveillance in the skin. Normally, immune surveillance protects against the development of skin cancer. But, UV exposure depresses the function of the immune system leading to an environment that is more favorable to development and growth of tumors (3).

2.3. Non-melanoma skin cancer

NMSC, including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are the most common skin cancers. Over one million new cases of NMSC occur each year in the United States (5). Although mortality from NMSC is low, morbidity is high due to disfigurement and medical costs. It is estimated that treatment cost per year is over $500 million dollars (2). Unfortunately, the incidence of skin cancer is expected to increase emphasizing the importance of prevention and treatment efforts (11). Since 1985, BCC rates have increased by 35%. BCCs mostly occur in individuals at an age over 30, and they are most commonly manifest on sun-exposed areas such as the face, the head, and the neck. BCCs do not metastasize, but must be treated as soon as possible to prevent invasive growth. The most frequent treatment is surgery to remove the primary tumor, but chemotherapy, cryotherapy, radiation, or topical treatments may also be used (4, 18). According to the WHO, SCC rates have increased by as much as 133% since 1985. Although less common than BCC, squamous cell carcinoma (SCC) carries a risk for metastasis. Most SCCs develop from precursor lesions such as actinic keratosis (AK) and are diagnosed on sun-exposed areas of the head, neck, and dorsal hands. Generally, SCC can metastasize to regional lymph nodes and are usually detected 1-3 years after the initial diagnosis. Therapy for SCC is similar to that for BCC mentioned above, with surgery again being the most common treatment (4, 18).

2.4. Melanoma

Melanoma, the deadliest skin cancer, is the most common form of cancer for young adults 25-29 years old. More than 116,500 new cases of melanoma will be diagnosed in the United States in 2008. In the United States, the lifetime risk in developing melanoma is 1 in 75, and the five year survival rate for metastatic melanoma is only 14% (18). Although melanoma is much less common than NMSC, it affects younger population and mortality rates are high for thicker lesion (19). CMM affects pigmented cells found in the epidermal layer of skin known as melanocytes (20). Evidence indicates that CMM risk factors are both genetic and environmental. CMM incidence is rapidly increasing and shows resistance to currently available therapies. Understanding the mechanisms involved in CMM development is therefore needed (21).

3. MOLECULAR MECHANISMS OF UV-INDUCED NON-MELANOMA SKIN CANCERS

Our previous studies have extensively contributed to a better understanding of the molecular and cellular mechanisms implicated in the early responses to UV radiation during photocarcinogenesis (11, 12, 15, 22-31). The components of the p53 pathway emerge as the major targets of UV-induced NMSC as described in figure

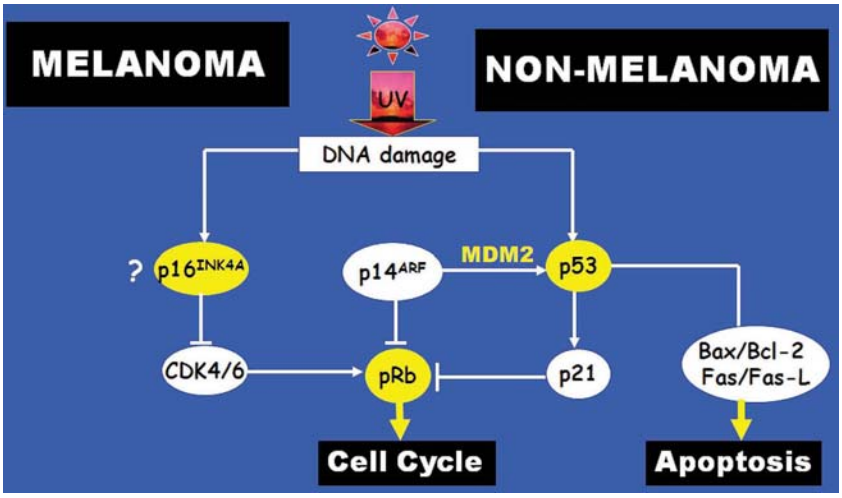

Figure 1. Schematic representation of the components of the Rb pathway, p53 and the p16 subpathways, involved in UV-induction of non-melanoma and melanoma skin cancers.

1. Chronic UV radiation mutates the sensor of DNA damage, p53, at specific sites which are essential to p53 function in regulating cell proliferation and apoptosis (12, 15, 23-27).

3.1. The components of the p53 pathway

Human p53 gene is highly conserved, and is localized on chromosome 17p13. It contains 11 exons encoding a 53,000 molecular weight protein containing 393 amino acids (32) with a number of well-characterized functional domains. Activation of p53 by phosphorylation, dephosphorylation, and acetylation yields a potent sequence specific DNA-binding transcription factor important in modulating multiple cellular functions. These functions include gene transcription, DNA synthesis and repair, cell cycle control, senescence, and apoptosis (33-37). As described in figure 1, UV-irradiation activates the sensor of DNA damage, p53, which induces its downstream target genes including the cell cycle inhibitor, p21 which halts cell division via Rb to allow the repair of DNA damage. If the damage is severe, apoptosis is triggered through p53-dependent Bax/Bcl-2 pathway and/or via Fas/Fas-ligand pathway to eliminate keratinocytes carrying Uv-damaged DNA. Dysfunction of these mechanisms occurs when p53 is mutated. These findings indicate the importance of the components of p53 pathway in the onset of UV-induced NMSC. Defining all the players that function as upstream regulators and downstream mediators of the p53 signaling pathway remains a significant challenge.

The p53 gene can be mutated by UV irradiation resulting in uncontrolled cell proliferation and loss of apoptosis of DNA damaged cells. Mutations of p53 are found in about 56% of BCC (11) and >90% of SCC (16). The importance of p53 inactivation in NMSC is further demonstrated by the observation that homozygous and heterozygous p53 knockout mice develop skin tumors much earlier than wild-type mice upon exposure to UV light (38). In SCC, following UV exposure, p53 mutations accumulate with clonal expansion of affected keratinocytes and the formation of premalignant actinic keratosis. These premalignant lesions can regress or progress to invasive SCC depending on environmental factors and the status of the immune system. p53 also plays an important role in BCC formation, but additional mechanisms besides p53 is known.

3.2. Deregulation of Apoptosis by UV

Our previous studies have significantly contributed to our understanding of the mechanisms by which UV radiation induces NMSC. This complex process involves both mutagenic and immunosuppressive pathways that are most likely triggered by UV-induced DNA damage (11). As described above, excessive damage induced by UV-irradiation leads to apoptosis (39). However, following chronic UV exposure, photoproducts can persist and become carcinogenic mutations, particularly the UV-signature mutations in the p53 gene C to T or CC to TT (16). Nine hotspot p53 mutations were identified in human skin tumors at codons 152, 177, 179, 196, 245, 247/248, 273, 277 and 281/282 (17, 40). Several lines of evidence indicate that these mutations play a critical role in the initiation process of skin photocarcinogenesis (17). Certain mutations can confer oncogenic function to p53 leading to deregulation of its p53-dependent apoptosis function. With sustained exposure to UVB, cells with p53 mutations clonally expand to form mutated p53 clones in the epidermis (13, 41). Thus, deregulation of UV-induced apoptosis might be the initiating event in photocarcinogenesis (24, 26).

3.3. Other key genes in NMSC

Although p53 is an essential early event in BCC, some of these tumors originate through UV light mediated mutations of the genes implicated in the hedgehog signaling pathway, including ptch and Smo (18). These genes are essential for the maintainance of cell growth and differentiation via the downstream Gli genes. Mutations inactivating ptch gene and gain of function mutations in

Smo have been described in BCCs associated with solar UV exposure (42). These mutations lead to dysfunction of the hedgehog signaling pathway generating abnormal cell proliferation, and contributing to the onset of BCC tumors.

4. MOLECULAR MECHANISMS OF UV-INDUCED MELANOMA

Accumulating evidence shows that the risks of CMM include both genetic and environmental factors (21). Cytogenetic tudies have identified two genes linked to melanoma, CDKN2A (INK4a/ARF) located at 9p21 locus and CDK4 located at 12q13 locus. In human melanoma, the most common genetic lesion is loss of INK4a/ARF locus along with the activation of the BRAF mutation (43). CDKN2A (INK4a/ARF) locus encodes for two distinct tumor suppressor proteins: p16INKa, the inhibitor of kinase 4A, and p14ARF (44-47). Although the functional relationship between genes and sunlight pathogenesis is not well understood, the development of animal models has, however, linked UV to melanoma development (48, 49). These models have identified the p16/Rb pathway as the major target of UV-induced melanomagenesis.

4.1. 1. UV and P16/Rb pathway

In a melanoma model driven by H-RAS activation and loss of p19ARF function, UV radiation accelerated melanoma genesis, which was accompanied by amplification of cyclin-dependent kinase (cdk) 6, whereas none of the melanomas arising in the absence of UV treatment possessed cdk6 amplification (50). In addition, UV-induced melanomas showed an inverse relationship between cdk6 amplification and p16INK4a loss, which is consistent with the effects of UV radiation on p16/Rb pathway. In duction of p16INK4a regulates the cell cycle by specifically inhibiting CDK4/6. leading to formation of Rb-E2F complex preventing E2F-responsive genes necessary for entry into S phase of the cell cycle (51). Rb protein is in its non-phosphorylated or active form, EF2 is not activated, and replication is halted. If p16INK4a is inactivated by a missense mutation, deletion, or methylation, the Rb protein is no longer maintained in its active form and cell replication goes unchecked leading to deregulation of the mechanisms controlling cell proliferation (30).

The CDK4 gene, coding for a protein that binds to p16, has also been identified as a melanoma susceptibility gene (52). A CDK4 mutation has been found in melanoma prone families (53, 54) and produces a mutated protein with oncogenec activity; this protein interferes with the binding of the CDK4 protein to p16, preventing inhibition of its enzymatic activity, thereby leading to unchecked cellular division (55) (59 I think this is 49 and I am adding reference 49).

4.2. UV and P53/Rb pathway

The effect of UV radiation on p53 expression in the skin has been well documented (1-3, 5-15, 29). In a mouse model, p53 expression increased 12 hours after UV exposure. Following this, p21 protein increased arresting the cell cycle and permitting repair of UV DNA damage in the skin. Apoptosis is induced in the skin through p53 dependant or independent pathways following severe damage (15). Although the role of the components of the p53 pathway is well established in NMSC development, its relationship with melanomagenesis is unclear. However, our recent study revealed that the components of the p53 pathway might play an essential role in regulating cell proliferation and apoptosis, particularly in response to higher doses of UV radiation (32). Moreover, the cell cycle inhibitor p14ARF regulates HMD2, an E3 ubiquitin ligase controling p53 degradation and stability (56). p14ARF prevents the interaction between p53 and HDM2 resulting in the accumulation of p53 protein, which in turn induces p21 to arrest cell cycle as described above. These events are disrupted when ARF is mutated and loses its tumor suppression function, potentially contributing to melanoma development (30). Thus, the p16/Rb and the components of the p53 pathway play a major role in coordinating the early responses to UV radiation in the skin (32).

5. CONCLUSION

The evil side of sunlight is evidenced by the alarming rise in the incidence of skin cancer over the past few decades. Despite the slow progress in elucidating the mechanisms by which UV induces melanoma, findings from our own work and others have significantly impacted our current knowledge of these mechanisms. Sunlight UV radiation appears to target the two tumor suppressor genes, p53 and p16, the main backbone regulators of the Rb pathway, at the early stages of photocarcinogenesis. UV seems to favor the p16/Rb pathway in melanoma, while it affects the ARF-independent p53 pathway in NMSC. As more pieces of the puzzle continue to fit together to help guide the development of targeted therapies for skin cancers, protecting our skin from sunlight can prevent its evil side.

6. AKNOWLEDGEMENT

This work was supported by the Louisiana Cancer Research Consortium of New Orleans

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Abbreviations: Rb: Retinoblastoma, NMSC: non melanoma skin cancer, CMM: cutaneous malignant melanoma, UV: ultraviolet WHO: world health organization, BCC: basal cell carcinoma, SCC: squamous

cell carcinoma, AK: actinic keratosis, Ptch: Patched gene, Smo: smoothened gene, p16INKa: the inhibitor of kinase 4A, CDK4: cyclin dependenet kinase 4, HMD2: human double minute 2 gene.

Key Words: Sunlight Ultraviolet Radiation, Skin Cancer, p53, p16, Rb, Cell Proliferation, Apoptosis, Review

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