Review Article

Narrative review: mechanism of ultraviolet radiation-induced basal cell carcinoma

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Background and Objective: Basal cell carcinoma (BCC) is the most widespread malignant skin cancer and also the most common cancer in adults. Although its mortality rate is low, its incidence is increasing, especially in Caucasians. Among many risk factors, ultraviolet radiation (UVR) is the essential factor in forming BCC. However, the molecular mechanisms leading to transformation are not fully understood. This review provides a comprehensive description of the interaction of UVR and genetic features in the pathogenesis of BCC, and specifically, current advances in molecular therapy based on these mechanisms are introduced.

Methods: A literature search was performed in the PubMed database using the search algorithms [(basal cell carcinoma) OR (BCC)] AND [(gene mutation) AND (ultraviolet radiation) AND (carcinogenesis)] to identify relevant publications until April 1, 2020. The database search was not restricted to any language, and relevant references were searched from the identified articles.

Key Content and Findings: This review summarizes the potential mechanisms underlying BCC development due to UVR. UVB can be directly absorbed by DNA and induce skin cancer through intracellular signaling leading to DNA damage and altered gene expression. UVA radiation generates reactive oxygen species (ROS), which causes skin cancer through secondary damage to DNA and usually requires long-term cumulative exposure. Cells can repair damaged DNA, but DNA repair may be faulty due to genetic or environmental factors. As a result, mutations in proto-oncogenes and suppressor genes may occur, leading to tumor formation. Various immune responses of the body are usually reduced after UVR. UVR damages DNA, and its repair system alters the immune system and leads to progressive genetic alterations and tumor formation, genetic alterations, and tumor formation. Based on these advances in molecular mechanisms, targeted therapies such as smoothened (SMO) inhibitors (vismodegib and sonidegib), and immunotherapy such as pembrolizumab [anti-programmed cell death-1 (PD-1)] have been developed. Further future studies on the molecular genetics of UVR in the development of BCC may facilitate new targeted therapies and chemoprevention, thus improving treatment efficacy and prevention.

Conclusions: This review highlights UVR damages DNA and its repair mechanisms, suppression the immune system, causes progressive gene mutations, and ultimately leads to tumor formation. Further studies on the molecular mechanisms associated with BCC will help raising public awareness of UV protection and explore new targeted therapeutic and chemopreventive means.

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Introduction

Non-melanoma skin cancer (NMSC) is the most common type of cancer (1). NMSC mainly includes basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), which account for 70% and 25% of NMSC, respectively (1). Both BCC and squamous carcinoma have a good prognosis, especially in their early stages (2). BCC contributes the least to NMSC mortality (MR), with an estimated MR of 0.02 per 10,000 population (1,2). On the other hand, SCC has a variable metastasis rate of 0.1–9.9% and accounts for approximately 75% of NMSC deaths (1,2). In whites, approximately 50–70% of SCCs and 50–90% of BCCs are caused by ultraviolet (UV) exposure (3).

The most common skin malignancy in Caucasians is BCC, which accounts for approximately 70–80% of all skin cancers (4). Published epidemiological data show that the incidence of BCC is still on the rise (5). Despite the low mortality rate of BCCs, it can lead to substantial morbidity and cosmetic defects that strongly impact health care budgets due to their remarkable high incidence (6). This type of skin tumor usually occurs in chronically sun-exposure sites of the elderly, most commonly on the head and neck (7). Among many etiologies of BCC, the most important is ultraviolet radiation (UVR). It is the leading environmental risk factor for the development of BCC. Some literatures have found that military personnel, engineers, tilers, farmers, lifeguards, mountain guides, and mail carriers more likely to develop skin cancers (mainly basal and SCCs) (8-17). All these individuals have in common the characteristic of being outdoor workers for long periods. Thus, there may be an association between prolonged occupational sun exposure and intense exposure to the sun and inappropriate use of sunscreen during working hours, and the risk of developing NMSC (8,10,18-20). As time goes on, changes in people's dressing style, entertainment, work, lifestyle, and increased life expectancy may lead to increased sun exposure. While most UVR originates from the sun, the incidence of UV-induced skin cancer has risen further due to tanning popularity (21). We receive daily UVR exposure from natural and artificial sources. Long-term exposure can lead to photoaging, such as skin wrinkling, roughness, sagging, freckling, and even benign and malignant tumors. It is recognized that UV exposure is a significant risk factor for BCC. However, the molecular mechanisms leading to transformation are not fully understood. Therefore, this article attempts to summarize the current research progress of UVR in the occurrence and development of BCC. We present the following article in accordance with the Narrative Review reporting checklist (available at https://fomm.amegroups.com/article/view/10.21037/fomm-21-31/rc).

Methods

In this study, we developed a comprehensive search in the PubMed database until April 1, 2020 by using the following algorithms [(basal cell carcinoma) OR (BCC)] AND [(gene mutation) AND (ultraviolet radiation) AND (carcinogenesis)]. The database search was not restricted to any language, and relevant references were searched from the identified articles (*Table 1*).

Discussion

UVR and BCC

Sunlight consists of a continuous ionization spectrum that includes UVR (100–400 nm), visible light (400–760 nm), and infrared radiation (IR; 760 nm–1 mm). This spectrogram is shown in *Figure 1*. UVR is further divided into three ranges according to the wavelength: UVA (315–400 nm), UVB (280–315 nm), and UVC (100–280 nm). Most UVB and all UVC (wavelengths below 280 nm) are removed by the ozone layer, and these shorter wavelengths do not occur in incident sunlight (22). UVA radiation (90–95%) is the most extensive UVR to reach the Earth's surface, and it extends deep into the cutaneous dermis. Only 5–10% of UVB radiation reaches the Earth's surface and is mostly absorbed by the epidermis. However, the efficiency of UVA-induced biological effects (expressed as the minimum amount of

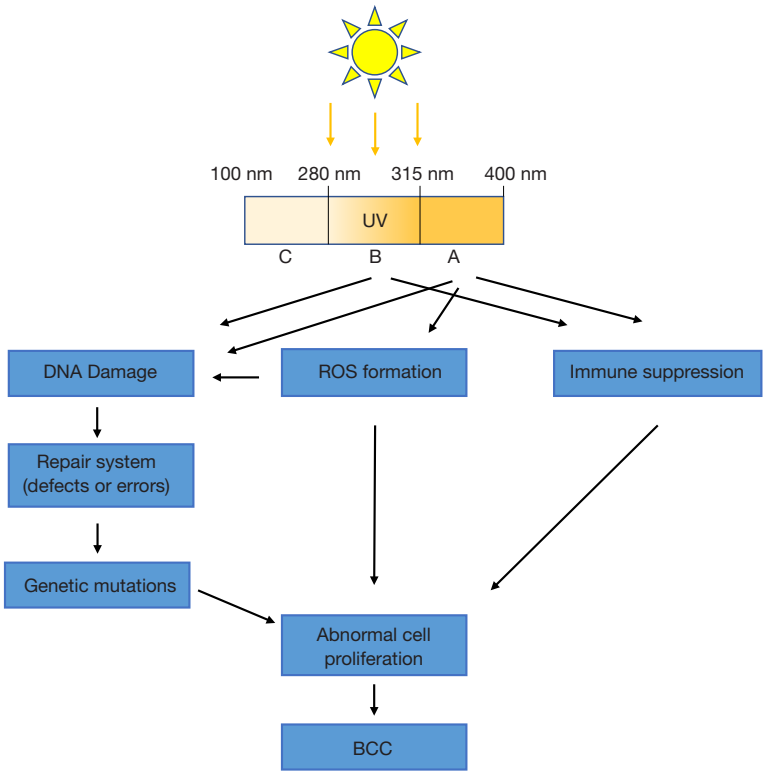

Figure 1 Overview of UV radiation and basal cell carcinoma: Solar UV radiation is mainly of UVA, UVB and UBC types, the first two types of UV radiation cause immunosuppression and DNA damage to human skin. UVA causes DNA damage through ROS, while UVB directly causes DNA damage and immunosuppression, which eventually leads to the formation of basal cell carcinoma. BCC, basal cell carcinoma; ROS, reactive oxygen species; UV, ultraviolet.

erythema) is 1,000 times lower than that of UVB (23,24). The effects of UVB are mainly mediated by chromophores (24-27). At the same time, moderate doses of UVB have significant positive effects on all organisms on Earth, including humans. UVB can induce the production of vitamin D in the skin. In fact, active forms of vitamin D can play important role in photoprotection (28) and skin cancer (29). Vitamin D deficiency (20 ng/mL) is associated with increased incidence and worse prognosis in various types of cancer, including melanoma (30). In contrast, the phenotypic effects of UVA, although weakly absorbed by DNA and a limited number of cellular chromophores (including NADH, reduced NADP, riboflavin, and porphyrins), are mainly caused by cellular oxidative changes induced by reactive oxygen species (ROS) (24,26,27). Several studies have found that the ozone layer has decreased with the increased use of chlorofluorocarbon (CFC)-containing products (31). Depletion of the ozone layer and increased cumulative UV exposure may be responsible for the increased risk of skin cancer in humans with increased longevity (32). The skin is a protective barrier organ with self-regulating sensory and computational capabilities to counteract environmental stresses and maintain and restore balance to damaged skin (25). These complex functions are coordinated by the cutaneous neuroendocrine system, which also communicates in both directions with the central nervous, endocrine, and immune systems, all of which are consistent with controlling the body's dynamic balance (25,33). Although UV is a crucial determinant of the origin and evolution of life on Earth (34), UV absorption by the skin not only stimulates mechanisms that protect skin integrity and maintain global dynamic homeostasis, but it also induces the development of skin pathologies such as cancer, aging, and autoimmunity (35). After absorbing electromagnetic energy and converting it into chemical, hormonal and neural signals in a wavelength-dependent manner, UV regulates global dynamic homeostasis, depending on its tissue penetration and the

Table 1 The search strategy summary

Items	Specification
Date of search	April 1, 2020
Databases and other sources searched	PubMed database
Search terms used	[(basal cell carcinoma) OR (BCC)] AND [(gene mutation) AND (ultraviolet radiation) AND (carcinogenesis)]
Timeframe	Until April 1, 2020
Inclusion and exclusion criteria	No searching restrictions
Selection process	Wanlin Fan conducted the selection

Table 2 Clinical subtypes of basal cell carcinoma

Subtypes of BCC	Clinical characteristics
Nodular	Glossy pearly papules or nodules with smooth surface and curled edges, dendritic capillaries, occurring on the head and neck (46-48)
Superficial	Well-defined and erythematous thin patches or plaques with scales, clear in the center and thinning at the edges. Common in the trunk area (48)
Micronodular	Erythema or thin papules/plaques
Infiltrative	Poorly defined, sclerotic, flat or depressed plaques that are white, yellow or pale pink and may be covered with crusts, erosions, ulcers or papules
Morpheaform	Infiltrative plaques with faint borders and shiny surfaces, commonly on the head and neck
Infundibulocystic	Well-defined pearly papules on the head and neck are common in the elderly
Fibroepithelial	Sessile patches of skin color or erythema or pedunculated papules with a predilection for the trunk (49)
Basosquamous	Most found on the head and neck (50)

BCC, basal cell carcinoma.

nature of the chromophores with which UV interacts. This balancing activity is achieved by activating the central nervous system and/or endocrine glands through neurotransmission or chemical messengers in the skin (35). And this type of regulation follows precise neuroendocrine regulatory mechanisms such as hypothalamic-pituitary-adrenal (HPA) (36), corticotrophin-releasing hormone-proopiomelanocortin (CRH-POMC) (37,38), opioids (39), serotonin/melatonergic (27,40,41), secosteroid/steroidogenic (42-44), or NO systems (45,46).

Several clinical subtypes of BCC include nodular, superficial, micronodular, infiltrative, morphologic, infudibulocystic, etc. (47-52) (*Table 2*). Among them, nodular, superficial, and morphologic BCCs are the most common clinical subtypes (47,53). Different clinical subtypes vary in terms of clinical presentation, histopathology, and aggressive behavior. Based on various prognostic factors, BCC can be classified as low, and high risk (54) (*Table 3*).

According to several epidemiological investigations, BCC incidence was found to be less correlated with lifetime cumulative sun exposure and more likely to be associated with intermittent (recreational) sun exposure and childhood exposure (55). Recreational activities, such as sunbathing or water sports on the beach, are associated with an increased incidence of BCC. However, spectators of outdoor sports activities are often unaware of sun exposure dangers (56). In addition to occupational and recreational UV exposure, UV phototherapy has been associated with BCC development.

UV impact on BCC

UV-induced skin carcinogenesis is a complex and sequential

Table 3 Low- and high-risk features of basal cell carcinomas

Grading criteria	Features[1]	Low risk BCC	High risk BCC
Clinical	Forms	Primary	Recurrent, metastatic
	Immune status	Immunocompetent	Immunosuppressed
	Anatomic location	Area L and M	Area H
	Radiotherapy	No	Yes
	Tumor boundaries	Well-defined	Poorly defined
	Tumor dimensions	Surface area[2]: area L, <20 mm; area M, <10 mm	Surface area[2]: area L, >20 mm; area M, >10 mm
		Size/diameter: <5 cm	Size/diameter: >5 cm
	Involvement of specified nerves	Absent	Present
Pathologic	Histologic type/growth pattern	Superficial, nodular, keratotic infundibulocystic, fibroepithelioma of Pinkus	Micronodular, infiltrative, sclerosing morpheaform, basosquamous, metatypical/sarcomatoid
	Perineural invasion	Absent	Present, diameter of involved nerve ≥0.1 mm, multifocality, involvement of named nerves

[1], features as defined by the National Comprehensive Cancer Network; [2], human skin is divided into three zones according to the risk of invasive keratinocyte carcinoma: area H is a high-risk zone (frontal hairline, central face, nose, eyelids, chin, ears, genitalia, hands, feet, and bald scalp); area M is a medium-risk zone (cheeks, forehead, scalp, neck, and jawline); and area L is a low-risk zone (trunk and extremities, excluding areas H and M). BCC, basal cell carcinoma.

biological process caused by different wavelengths of UV light. UVB can be absorbed directly by DNA, leading to DNA damage and altered gene expression through intracellular signal transduction, which can induce skin cancer. UVA radiation generates ROS, which cause skin cancer through secondary damage to DNA and generally requires chronic cumulative exposure. Cells could repair damaged DNA, but DNA repair may go wrong due to genetic or environmental factors. Therefore, the mutation of proto-oncogenes and suppressor genes may occur, leading to the formation of tumors. Various immune responses of the organism are usually decreased after UV irradiation, which we call immunosuppression. UVR causes damage to DNA and its repair system and changes the immune system, leading to progressive genetic changes and tumor formation (57).

UVR-induced DNA damage

UVB can penetrate several layers of cells into the dermis and perhaps basal cells. The forms of UVB-induced DNA photodamage include pyrimidine dimers, purine and pyrimidine dimers, purine photoproducts, protein-DNA crosslinks single-strand breaks. The most important one is pyrimidine dimers (58).

The direct absorption of UVB photons by DNA bases leads to photoproducts between two adjacent pyrimidine sites [thymine-thymine (TT), cytosine-thymidine (CT), thymidine-cytosine (TC), cytosine-cytosine (CC)] on the same DNA strand. Products include cyclobutane pyrimidine dimer (CPD) and 6-pyrimidine-4-pyrimidinone photoproduct (6-4 PP). Both are essential prerequisites for the increased frequency of mutations and underlie skin cancer induction by UV exposure. Cells can repair 6-4 PP more efficiently. The TC and CC dimers of CPD are the most mutagenic because, in UV-induced skin cancer, the *p53* gene often shows C→T and CC→TT mutations, hence the term UV signature mutation (59). The major photoproduct TT dimer is rarely mutated due to DNA polymerase's repair effect. UVB induces dimer formation through adenine residues and thymine residues on the DNA strand. Although limited in number, such dimers have been shown to cause mutations (59). UVB can also induce guanine oxidation to produce the purine photoproduct 8-hydroxy-2'-deoxyguanosine (8-OHdG). 8-OHdG is a general marker of oxidative stress. Although it accounts for only a small fraction of medium-wave UVB damage, it

can induce G→T translocation, leading to gene mutations. Besides the above three DNA damages, UVB radiation causes other DNA damage types, such as protein-DNA cross-linking and single-stranded DNA breaks (60).

UVR-induced DNA repair

Normal human keratinocytes harbor an effective DNA damage repair system that prevents multiple genetic mutations induced by UV damage. Signaling pathways for DNA damage repair include DNA double-strand break repair (DSB), nucleotide excision repair (NER), base excision repair (BER), mismatch repair (MMR), and post-replication repair (PRR) (61-64). Two major DNA repair systems play a crucial role in UV-induced damage: the NER and BER systems. The NER plays a crucial role in repairing CPDs and 6-4 PPs (65-68).

The BER system can repair single base lesions such as 8-OHdG. This pathway involves depurine/depyrimidine site nucleic acid endonucleases (APEX1/REF-1), proliferating cell nuclear antigen (PCNA), replication protein A (RPA), and enzymatic glycosylation (69). Commonly, glycosylases recognize the lesion, severing the base's glycosyl bond and the leading DNA strand. The lesion presents as a basic site (AP site), identified by the APEX1/REF-1 protein. The APEX1/REF-1 protein produces a single-strand break (a nick site), then repaired by DNA polymerase I and DNA ligase III (69). The BER system activity is controlled by the HOGG1 and inhibited by nitric oxide (NO) (70). Therefore, UVR-induced NO not only leads to DNA damage but also suppresses the BER system's activity, contributing to an increase in gene mutations and the risk of skin cancer (69).

UVR-induced DNA mutation

Basal cell carcinogenesis is the result of the interaction of multiple genetic and environmental factors. Significantly, most of the genes involved in the pathogenesis of BCC exhibit mutational features consistent with UV-induced DNA damage. After UV irradiation, cells normally repair CPD and 6-4 PP lesions through the repair system. However, if the repair system is defective or occasionally repair errors occur, DNA damage will result in genetic mutations. Mutations may affect cell cycle regulation, leading to clonal proliferation and immortalized growth, eventually causing BCC.

Hedgehog (HH) pathway genes

The HH pathway is a highly conserved developmental pathway involved in organogenesis, stem cell maintenance, tissue repair, and regeneration. In the skin, it maintains stem cell populations and controls the development of hair follicles and sebaceous glands (71). The HH pathway is mainly inactive in adults, except for its functions in tissue repair and maintenance (72). The major components of the HH pathway include three secreted ligands [sonic HH (SHH), Indian HH, and desert HH], a negatively regulated receptor [Patched (PTCH)], a positively regulated receptor [smoothened (SMO)], and glioma-associated oncogene (GLI) transcription factors (GLI1, GLI2, and GLI3) (72,73). HH signaling relies on primary ciliary structures, which are highly specialized microtubule-based organelles that protrude from its plasma membrane in nearly all types of cells and act as sensors of extracellular signals (74,75). Usually, extracellular HH ligands bind to PTCH1 receptors, thereby relieving the inhibitory effect of PTCH1 on SMO. Active SMO migrates to primary cilia, a highly specialized microtubule organelle that acts as a sensor of extracellular signals. SMO activates a signaling cascade of interacting proteins, including a repressor of fusion (SUFU), which leads to activation of the GLI family of transcription factors. In the lack of HH ligand, PTCH localizes to cilia and inhibits SMO activity by blocking SMO transport and localization to cilia (76). GLI transcription factors are sequestered in the cytoplasm through various protein mediators such as protein kinase A (PKA) and SUFU. GLI undergoes protease cleavage and the resulting blockers form GLI translocations to the nucleus, thereby repressing translation of HH target genes (*Figure 2A*) (76).

Aberrant HH signaling activation is a hallmark of basal cell carcinogenesis (77). A recent study indicated that over 85% of BCCs have defects in the HH signaling pathway (78,79). Somatic mutations in PTCH were found in 90% of sporadic BCC (80), and gain-of-function mutations in SMO were detected in BCC (81). In particular, recurrent mutations and functional studies in SMO have shown that these mutations lead to abnormal activation of HH signaling and promote tumor development (*Figure 2B*) (81). The frequency of PTCH mutations in BCC patients has been reported to be 11–75% (73,78,80,82-89). About half of these mutations carry the UV signature (i.e., C→T and CC→TT transitions at the pyrimidine locus) (78,83-85,88-90), and these mutations are associated with radiation dose. However, the mutation was not present in SCC, suggesting that PTCH mutations are critical in BCC but not in SCC.

In addition to the canonical HH pathway, which relies on HH-PTCH1 binding and SMO activation, transcriptional

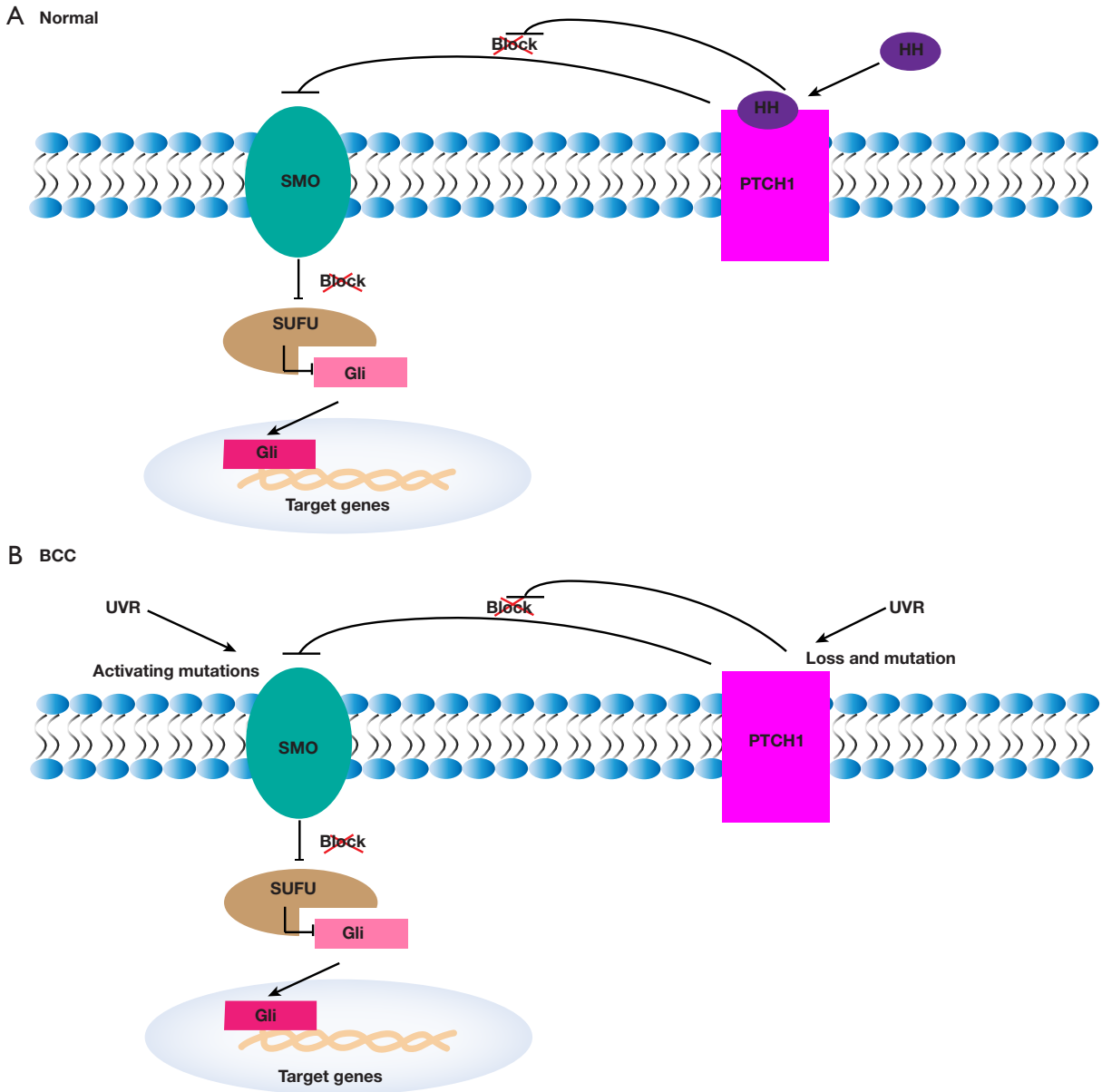

Figure 2 HH pathway in embryonic development (A) and basal cell carcinoma (B). HH, Hedgehog; BCC, basal cell carcinoma; SMO, smoothened; Gli, glioma-associated oncogene; UVR, ultraviolet radiation.

or post-translational modification of GLI can be executed by interacting with various other different oncogenic signaling networks [epidermal growth factor receptor (EGFR), insulin-like growth factor (IGF), transforming growth factor (TGF) β, protein kinase C, (phosphoinositide 3-kinase (PI3K), and nuclear factor κB (NF-κB)]. Non-canonical HH signaling pathways (e.g., EGFR, IGF, TGF pathways) may synergistically promote BCC development through transcriptional or post-translational modifications of GLI bypassing HH-mediated SMO activation (77,91,92). RAS, TGF, PI3K/AKT, NF-κB, and atypical protein kinase C ι/λ (aPKCι/λ) can positively regulate GLI activity, and p53 and PKA negatively regulate GLI activity. The non-canonical regulation of GLI may partly explain the failure of some SMO antagonists in clinical trials. For example, high levels of PKCι/λ were found in basal cells resistant to Vismodegib (93). Therefore, the use of SMO or GLI antagonists in combination with therapeutic strategies

capable of inhibiting atypical HH signaling may reduce the incidence of resistance. Interestingly, topical treatment with imiquimod enhances PKA activity, which leads to GLI phosphorylation and cleavage into its blocker form (94).

P53 gene

Basal cell carcinogenesis is associated with the inactivation of the *P53* gene. The oncogene *P53* is involved in the regulation of the cell cycle and the activation of programmed cell death (95,96). As a gatekeeper of the genome, P53 monitors the integrity of the genome. Once a cell undergoes DNA damage, P53 activates cell cycle checkpoints to repair the damaged DNA. If the repair fails, P53 can cause programmed cell death, thereby preventing mutant cells' production. When various carcinogens inactivate P53, it cannot repair DNA damage and fails to initiate programmed cell death when repair fails, ultimately leading to cell transformation (58). About 50% of BCCs have detectable *P53* mutations. Most of the mutations are C-T, CC-TT alterations, which indicate the importance of UV in BCC with *P53* gene mutations (90, 97-99). One study found that lower levels of *P53* mutations were indeed found in BCC patients who used sunscreen compared to those who did not use sunscreen (100).

RAS gene

RAS genes are divided into three proto-oncogenes, H-ras, K-ras, and N-ras, which together encode 21 kDa proteins. These three genes share 70% homologous sequences (101). RAS proteins are located on the inner surface of cells and bind to GTP, thus participating in signal transduction. It was found that RAS mutations occurred mainly at codons 12, 13, and 61 (102). When bound to GTP, the RAS gene is activated. The mutation may lead to activation by decreasing the rate of hydrolysis of GDP by GTP. However, RAS genes do not seem to be common in BCC at present.

UVR-induced immunosuppression

UVR-induced immunosuppression plays a crucial role in skin carcinogenesis (103). UVR production such as CPDs has been reported to cause immunosuppression (104). UVR significantly reduces the antigen-presenting capacity of skin dendritic cells, thereby suppressing the local immune response (Langerhans) and promoting the evasion of tumor immune surveillance by premalignant and early melanoma cells (36,37,103,105). Furthermore, exposure to UVB promotes the migration of UVR-damaged Langerhans cells to regional lymph nodes, which leads to the expansion of regulatory T cells and decreases effector and memory T cells, resulting in suppression of the adaptive immune system (105,106). UVR also stimulates other molecules with immunosuppressive properties such as prostaglandins, platelet-activating, IL-10, and ROS (107).

UVB is a significant skin stressor that, on the one hand, causes several skin lesions, including cancer (108-110), and on the other hand, is necessary for vitamin D production (111,112), activation of local neurohormones (25,38) and stimulation of melanin deposition (4,34,38-40,109,113-116). UVB induces the production of POMC peptides that are immunosuppressive (33,37,38) and glucocorticoids at local and systemic levels (117-119). Cutaneous melanin pigments play a crucial role in protection from the harmful effects of solar radiation. Melanin formation is complexly regulated by multiple factors that interact in a hormonal, automatic, quasi-automatic, or endocrine manner through pathways activated by receptor-dependent and non-dependent mechanisms (115). The above findings fully illustrate the apparent relationship between UVR and immunosuppression in skin cancer formation.

Treatment of BCC

Surgery

The treatment of BCC is usually determined by patient characteristics, such as comorbidities and ages, and tumor characteristics, classified into low- and high-risk tumors (*Table 2*). The majority of treatment options for primary BCC are surgical, including resection with postoperative margin evaluation and Mohs micrographic surgery (MMS) (120,121). Low-risk primary BCC is usually treated using surgical resection. High-risk BCC may then be considered for MMS, especially for sclerosis, recurrence, large BCCs, poorly defined, and tumors in anatomic areas that require tissue preservation, such as the eyes, nose, lips, and ears (122,123).

Non-surgical destructive treatments

Non-surgical destructive treatments include electrodissection and curettage (EDC) and cryosurgery. EDC uses electricity to destroy the remaining cancer cells in the tumor bed when scraping the tumor from the skin and is mainly applied to low-risk BCC in non-hairy areas of the extremities and trunk (122,123). Cryosurgery uses liquid nitrogen to destroy tumor cells through a freeze-thaw cycle and is suitable for low-risk tumors where other effective treatments are limited (122-126).

Light-based therapy

Light-based therapies mainly use discrete wavelengths of light to target BCC and can be divided into photodynamic therapy (PDT) and laser. PDT uses photosensitizers to wake up in rapidly dividing cells selectively, and the ROS produced destroys the rapidly proliferating cancer cells when exposed to the light source. PDT can be used to treat low-risk superficial tumors in non-hairy areas. Laser therapy is used to ablate skin cancers with a carbon dioxide laser (122,127). Alternatively, a pulsed dye laser is employed to selectively convert light into heat energy within the blood vessels, thereby destroying tumor tissue (128,129).

Radiation therapy

In radiation therapy, high-energy rays such as X-rays or particles (photons, electrons, or protons, most commonly electron beams) are traditionally used to destroy BCC (122,130). X-ray brachytherapy can also be administered to the tumor with the aid of a shielded surface. Radiation therapy can be given first when surgery is not feasible for low-risk tumors. Radiotherapy should not be used for skin cancer patients who have genetic disorders (e.g., basal cell nevus syndrome, erythroderma) or connective tissue diseases (e.g., lupus, scleroderma). It is also not recommended for patients younger than 60 years of age (131).

Topical treatment

Topical treatment regimens are usually appropriate for superficial BCC, including 5-fluorouracil (132), imiquimod (132), tazarotene (133), ingenol mebutate (134) and diclofenac (135). Dosing regimens and outcomes vary between drugs and are influenced by tumor location, side effects, and patient compliance. Patients with contraindications to surgery could be treated with intratumoral drug injections (e.g., methotrexate, 5-fluorouracil, bleomycin, or interferon) (136).

Molecular therapy

Identifying tumor-specific genetic alterations is currently one of the hottest areas of cancer research, and the resulting new molecular therapeutic approaches include mainly target therapy and immunotherapy.

Target therapy

Targeted therapy is available for patients with metastatic BCC or locally advanced unresectable BCC. This therapy focuses on SMO inhibitors (vismodegib and sonidegib) to inhibit the activation of the SHH signaling pathway that is frequently mutated in BCC (137-141). The FDA approved Vismodegib in 2012 for the treatment of local advanced or metastatic BCCs (142). Follow-up studies found objective efficacy rates of 48% and 33% in patients with locally advanced and metastatic BCC, respectively (143). However, almost all patients experienced at least one of the following adverse reactions: hair loss, muscle cramps, weight loss, postural disturbances, diarrhea, or fatigue. And grade 3 or 4 adverse reactions occurred in 25% of patients (144). Another study showed that vismodegib significantly reduced the incidence of new BCC and the size of existing tumors. However, only 17% of patients were able to tolerate the drug consistently throughout the study period. Hepatotoxicity has also been reported, and the drug should be used with caution in patients with severe liver disease (145).

A second HH pathway inhibitor, sonidegib, is approved by the FDA to treat locally advanced BCC that has recurred after surgery or radiation therapy or that cannot be treated with surgery or radiation therapy. A clinical (BOLT) trial of LDE225 found response rates of 44% to 58% for locally advanced BCC and 8% to 17% for metastatic BCC (146). Notably, Hou *et al.* recently reported that the first successful case of periocular locally advanced BCC with oral sonidegib (141). However, almost all patients experienced at least one adverse reaction, with the most commonly occurring grade 3 or 4 adverse reactions being creatinine kinase and lipase elevations. Unlike vismodegib, sonidegib should be taken on an empty stomach and should not be used concomitantly with potent or moderate CYP3A inhibitors (147).

Immunotherapy

Immunotherapy blocks immune checkpoint proteins by monoclonal antibodies such as anti-programmed cell death-1 (PD-1) and PD-ligand-1 (PD-L1), thereby enhancing the anti-tumor immune response. Several immune-related markers have been found to correlate with the pathogenesis of BCC (148-153), suggesting the potential use of immunotherapy to treat BCC. Recent case reports have found the efficacy of anti-PD-1 therapy for advanced BCC, both on initial treatment and after developing resistance to HH pathway inhibitors (154-156). The effectiveness of pembrolizumab (anti-PD-1) in combination with vismodegib for the treatment of metastatic or unresectable BCCs is being studied (NCT02690948) in a phase 1 clinical trial (157).

Prevention of UVR-induced BCC

As solar UVR is the most important environmental risk factor for the development of BCC (158), protection against UVR is a fundamental approach to preventing BCC. The measures include avoiding direct exposure to the sun at noon (10 a.m. to 2 p.m.), taking care not to get burned, avoiding tanning and avoiding tanning beds; taking special care near water, snow, and sand; taking care to find shade; wearing protective clothing, hats, and sunglasses when necessary; applying sunscreen to protect against UVA and UVB radiation-induced immunosuppression and DNA damage (159) as well as regular whole-body skin cancer screening (160).

Furthermore, new chemoprevention methods have emerged, such as the use of nicotinamide (vitamin B3) (161). Vitamin B3 prevents ATP depletion and glycolytic blockage caused by UVR, thus enhancing cellular DNA repair. It also reduces radiation-induced immunosuppression. A series of studies (161-163) concluded that nicotinamide (500 mg/d twice/d) could be an effective method for preventing BCC, especially for secondary prevention in high-risk patients with existing BCC. Besides, some studies have found that the cyclooxygenase-2 (COX-2) inhibitor celecoxib reduces the risk of BCC (164,165). Due to the lack of relevant evidence and conflicting results, it is currently not recommended for chemoprevention (166). PDT may reduce the incidence of actinic keratoses (AK) cases (167), but its preventive effect on BCC has been rarely reported and needs to be validated in more extensive studies (168).

Long-term monitoring is also essential for patients with BCC. In the National Comprehensive Cancer Network (NCCN) guidelines, it is recommended that patients with BCC undergo a whole-body skin examination every 6 months to 1 year for the first 2 years after diagnosis and then annually after that (169). Patients are also encouraged to self-monitor.

Conclusions

No doubt, UVR is a fundamental cause of BCC. The role and mechanism of UVR in the development of BCC are discussed in detail. Therefore, physicians should educate the public about the importance of UV protection in preventing BCC. Meanwhile, the further study of the molecular genetics of UVR in the development of BCC may promote new targeted therapies and chemoprevention, resulting in improved therapeutic efficacy and prevention.

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