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Review

The Role of UV Radiation in the Development of Basal Cell Carcinoma

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A B S T R A C T

Basal cell carcinoma (basalioma, BCC) is undoubtedly the most common malignant skin cancer and the most common human malignancy in general, with the continuous increase in its incidence. BCC is generally a disorder of white individuals, especially those with fair skin. UV radiation is the most important risk factor in the development of BCC. Short-wavelength UVB radiation (290–320 nm, sunburn rays) is believed to play a greater role in BCC formation than long-wavelength UVA radiation (320–400 nm, tanning rays). A latency period of 20–50 years is typical between the time of UV damage and the clinical onset of BCC. Therefore, in most cases BCC develops on chronically sun-exposed skin in elderly people, most commonly in the area of head and neck. UVB radiation damages DNA and its repair system and alters the immune system resulting in a progressive genetic alterations and formation of neoplasm. UV-induced mutations in the TP53 tumor-suppressor gene have been found in about 50% of BCC cases. The mutations that activate the Hedgehog intercellular signaling pathway genes, including PTCH, Sonic hedgehog (Shh) and Smoothened (Smo) play a significant role in cutaneous carcinogenesis. Epidemiologic studies demonstrate the higher incidence of the BCC in more equatorial latitudes than in polar latitudes. Other risk factors for the development of BCC include sun bed use, family history of skin cancers, skin type 1 and 2, immunosuppression, previous radiotherapy, and chronic exposure to toxic substances such as inorganic arsenic. Although rarely metastatic, its malignant nature is sometimes emphasized by the local tissue destruction, disfigurement, and even death if left untreated. Due to extremely high incidence of BCC medical professionals should be aware of the importance of the public education on the etiology of this tumor and the importance of the UV protection.

Key words: *basal cell carcinoma, basalioma, UV radiation, photoimmunology, carcinogenesis*

Introduction

Basal cell carcinoma (BCC) is a malignant epidermal neoplasm which usually develops on chronically photo--exposed areas of the skin in elderly people, most frequently on the head and neck. BCC is the most common of all cancers and it accounts for approximately 80% of all skin cancers[1]. This type of skin tumor is more common in male than in female patients and it is rarely observed in darkly pigmented patients. Published epidemiological data has shown worldwide increasing incidence of BCC at a rate of 3–10% per year. With respect to increased incidence of this rarely life-threatening tumor, BCC has become a significant public health issue[2]. The incidence rates of BCC have increased in Europe, USA and Australia over the past several decades[3,4]. The similar trend has been observed in Croatia. The exact incidence and mortality rates of BCC in Croatia are unknown since they are not routinely reported into the National Cancer Register. Various etiological factors are involved in the occurrence of the disease, predominantly associated with UV radiation, particularly solar UVB radiation. It represents the most significant environmental risk factor for the development of non-melanoma skin cancer (NMSC) in humans[5,6]. During the past century, changes in clothing styles, recreational activities, chronic occupational solar exposure, longevity, and other aspects of lifestyle have resulted in increased exposure to sunlight[7]. Although most ultraviolet radiation comes from the sun, the use of sun beds as artificial sunlight has resulted in a rising incidence of ultraviolet-induced skin cancers. A history of previous irradiation or trauma to skin areas, immuno-

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suppression, or exposure to inorganic arsenicals is also well-known predisposing factor for this form of skin cancer[8]. Multiple BCCs can rarely be hereditary. Inherited conditions with multiple BCCs include: Nevoid Basal Cell Carcinoma Syndrome (Gorlin-Goltz syndrome with multiple BCCs, palmar and plantar pits, odontogenic keratocysts of the jaw, skeletal abnormalities, and calcification of the falx cerebri), Bazex syndrome (follicular atrophoderma, hypotrichosis, localized hypohidrosis, milia, epidermoid cysts, and the early onset of multiple primarily facial, BCCs), Rombo syndrome (atrophoderma vermiculatum, hypotrichosis, blepharitis, milia, peripheral vasodilation with cyanosis, and BCCs), and unilateral basal cell nevus syndrome[7,9]. Despite the low mortality rate, BCCs can cause substantial morbidity and cosmetic disfigurement, with strong impact on health care budgets due to their extraordinary high incidence[10].

UV Radiation and BCC

Solar, non-ionizing, ultraviolet electromagnetic waves are well-known, potent, environmental carcinogenic agent closely associated with the development of skin cancer in fair-skinned adults[11]. The concept of the UV radiation as the major etiologic agent in the pathogenesis of NMSC originates from the beginning of the twentieth century followed by astute observations of physicians who noted that skin cancers frequently appeared on the sun-damaged skin of persons who pursued outdoor occupations. Thus sunlight was one of the first agents recognized to be carcinogenic for humans[12]. Since then numerous epidemiological studies have supported the notion that UV radiation causes skin cancer. The most convincing fact is the predominant appearance of these cancers on chronically photo-exposed areas including the face, head, and neck. Within the ultraviolet radiation spectrum, the ultraviolet A (wavelengths between 320 and 400 nm) and particularly ultraviolet B wavebands (wavelengths between 290 and 320 nm) are the most significant, as ultraviolet C (wavelengths between 200 and 290 nm), is mainly filtered out by the ozone layer in the upper atmosphere. Only one per cent of UVB does reach the surface of the earth. Published experimental studies have suggested that stratospheric ozone layer has been decreasing since 1980 due to higher concentration of chlorofluorocarbon agents from everyday use products[7]. The ozone layer depletion and increased cumulative UV radiation exposure due to prolonged lifespan may account for the enhanced risk of skin cancer[11]. Geographically, there is a direct association between the amount of environmental solar radiation and the incidence of skin cancer in fair-skinned population. However, it is important to mention that the incidence of squamous cell carcinoma is more dependent on sunlight exposure than BCC indicating that other factors, in addition to sunlight may be responsible for the development of BCC. According to several epidemiologic studies, the incidence of BCC poorly correlates with cumulative lifetime sun exposure and may be more related to intermittent (recreational) exposure and exposure during the childhood[13]. Additionally, a more recent cohort study with 966 individuals (Kennedy et al.) investigated environmental and genetic risk factors for skin cancer. Their results showed the association of painful sunburns before the age of 20 with all three types of NMSC as well as actinic keratosis. Therefore, cumulative lifetime sun exposure was associated with an increased risk of squamous cell carcinoma (SCC) and actinic keratosis and to a lesser degree with BCC[14].

Large epidemiological studies have shown that recreational activities such as sun exposure on the beach or during water sports are associated with an increased risk of BCC, whereas skiing has shown association with at increased risk of SCC. Yet, spectators at outdoor sporting events are often unaware of sun exposure risk[15]. Besides occupational and recreational UV exposure, UV phototherapy has also been associated with carcinogenic potential. A study conducted by Lim and Stern investigated UVB versus PUVA risk. Although UVB exposure appears to increase the risk of non-melanoma skin cancer, the attributable risk ratio per treatment of PUVA is seven times higher than for UVB for both SCC and BCC, suggesting that the carcinogenic risk of a single PUVA treatment is about seven times higher than for a single UVB treatment. Their results demonstrated that large number of UVB treatments (more than 300) confers modest but significantly increased risk of NMSC in adults. Thus, the modest risk associated with UVB therapy must be considered in the context of a patient's underlying skin cancer risk and against the benefits of therapy[16].

Carcinogenesis in BCC

UV radiation damages DNA and its repair system and alters the immune system resulting in a progressive genetic alterations and formation of neoplasms. Carcinogenesis in BCC involves multiple events in the cell cycle[17]. UVB radiation is absorbed by the nuclear DNA, the most important endogenous chromophore. Absorption of UVB by nucleotides causes the formation of pyrimidine dimers leading to mutations in the tumor suppressor genes p53 and Patched-1 (PTCH1). UV radiation is involved in the mutations of the Hedgehog (HH)/Patched (PTCH)/Gli intercellular signaling pathway genes, including PTCH, sonic hedgehog (SHH) and smoothened (Smo). The HH family of intercellular signaling proteins have crucial role in the signal transduction pathways in embryonic development. However, HH pathway can also play an important role in cutaneous carcinogenesis and, it has been recognized that the SHH pathway is implicated in the etiology of BCC. Mutations in the receptor of SHH, PTCH gene, have been characterized in both, sporadic BCCs and in BCC of patients with rare genetic syndromes such as Gorlin-Goltz syndrome and Xeroderma pigmentosum. Delineation of the biochemical pathway in which PTCH functions may lead to medical therapy for skin cancers, and possibly other malignancies. The SHH signaling is activated by the binding of the SHH protein to the PTCH membrane receptor, which is a tumor sup-

pression protein. PTHC inhibits the expression of HH target genes – glioma transcription factor-1 (Gli-1) and PTCH-1 which are involved in cell proliferation. The third component of the SHH pathway is the transmembrane protein Smoothened (Smo). In the absence of Shh, PTCH inhibits Smo which results in the blocking of target genes. On the other hand, binding of HH to PTCH suspends the inhibitory effect of PTCH on its signaling partner Smo[18]. It is clear that the disruption of the intercellular HH signaling pathway is closely linked to the development of BCC. However, specific UV induced mutations can be found only in approximately 50% of sporadic BCCs. Thus, cumulative UVB radiation cannot be considered to be single etiologic risk factor for BCC development[19]. In addition, about 50% of BCC cases carry mutations in the p53 tumor suppressor gene. Tumor suppressor genes, p53 and PTCH1, are cell cycle regulators, regulating G1/S phase cell cycle progression, and also in charge of DNA damage monitoring[20]. Both large and small deletions in p53 and PTCH1 genes can be found in BCCs, which allow uncontrolled cell cycle progression, resistance to apoptosis, stimulated angiogenesis, replication of damaged DNA, therefore leading to further carcinogenic mutations or gene amplification. Clonal expansion of the initial mutated cell may also be driven by sunlight[21].

Furthermore, UV radiation induces the release of prostaglandins and cytokines by the keratinocytes. Among the proinflammatory mediators released by keratinocytes, there are interleukin 1 and 6, while IL 10 and TGF-β represent cytokines with immunosuppressive properties. Production of the fibroblast growth factor and vascular endothelial growth factors results in angiogenesis, while inactivation of cellular adhesion molecules, such as E-cadherin, facilitates local tissue destruction.

There is also increasing evidence that UV radiation can affect extra-nuclear molecular targets located in the cytoplasm and the cell membrane, including cell surface receptors, kinases, phosphatases and transcription factors. UVB also alters antigen-presenting function of Langerhans cells that leads to immunosuppression[9]. Immunosuppressive drugs inhibit a physiologic function of the immune system in recognition and destruction of clonal expansion of precancerous lesions. In the absence of exogenous influences, mutant clones and pre-cancers tend to regress. Chemotherapeutic agent 5-fluorouracil (5--FU) causes regression of dysplasia by elimination of initiated cells, perhaps through enhanced apoptosis. Conversely, retinoic acid temporarily suppresses clonal expansion[21]. The most important defense mechanisms in the protection of human skin against UV radiation involve melanin synthesis and active repair mechanisms. Low pigmentation capacity in Caucasians and rare congenital defects in DNA repair are mainly responsible for protection failures. The important function of nucleotide excision DNA repair gene (NER) in protection against skin cancer becomes obvious in rare genodermatosis Xeroderma pigmentosum, where mutations in various NER genes lead to multiple skin cancers[19]. When a mutation confer apoptosis resistance, as p53 mutations do, subsequent UV exposure will be more likely to kill normal cell than the mutated ones. The latter can expand into a clone, where only a single cell requires additional mutation.

Clinical Features of BCC

Clinically, BCC usually presents as a slowly expanding, translucent, well-demarcated, pearly papule or nodule with telangiectasias. It is usually located on the upper two-thirds of face, above the line connecting the angle of the mouth and earlobe. However, several different subtypes have been described[8]. Clinical variants of BCC include nodular, ulcerated, pigmented, superficial, sclerosing, cystic, fibroepithelioma, and Gorlin-Goltz syndrome[22,17]. Each varies in terms of clinical presentation, histopathology and aggressive behavior. Dermatoscopy as a relatively new, non-invasive diagnostic technique may be helpful in diagnosis of BCC, since there are many clinical presentations of BCC. Major dermatoscopic features of BCC are: arborizing scattered vascular pattern, teleangiectactic or atypical vessels, milky-pink background and yellow or brown dots/globules[23]. However, a biopsy is essential for the diagnosis and management of the skin cancer. Histologically, the BCC is composed of basaloid keratinocytes with characteristic peripheral palisading of the large, relatively uniform, hyperchromatic nuclei and retraction of the stroma around the tumor islands, creating the pseudovascular spaces around the tumor nests. Immunohistochemical studies are needed to exclude melanoma[24,25].

Treatment of BCC

The therapy of choice for the majority of primary BCCs is surgical excision, which allows validation of surgical margins. The choice of treatment is determined by the size and location of the tumor, clinical subtype of BCC, borders, immunosuppression, the patient's age, and patient's comorbidities. Cryosurgery, electrosurgery, radiotherapy, photodynamic therapy, topical cytotoxic agents (5-fluorouracil) and immunomodulators (Imiquimod cream) have been used to treat superficial BCC and are advantageous for elderly patients, those wishing to avoid invasive procedures and those with comorbidities. These methods have been associated with higher recurrence rates of BCCs in comparison with surgical excision. Microscopically controlled surgery or Mohs surgery is the preferred treatment for sclerosing, recurrent, large BCCs, poorly defined, and for those tumors in anatomical areas which necessitate tissue conservation, such as the eyes, nose, lips and ears[26]. All patients with BCC require follow-up, regardless of the treatment modality used as, as approximately 40% will develop a secondary or recurrent BCC on the treated site within 5 years[27]. The most important factor in prevention of the development of BCC is the avoidance of excessive sun exposure of the skin. Photoprotection is one of the fundamental measures in the prevention of BCC. Dermatologists as

well as other health professionals should educate their patients on the use of sunscreen. The use of a highly effective broad-spectrum UVA and UVB sunscreen can prevent the photo-induced immunosuppression and the DNA damage that leads to the development of BCC. Combination of UVA and UVB filters in the adequate sun care products may offer a powerful protection against UV-induced effects[28,29]. The health care providers should also encourage the parents to apply sunscreen on their children skin since it has been estimated that 75–80% of total lifetime dose of solar radiation is received before the age of twenty[9].

Conclusion

Undoubtedly, skin exposure to the UV radiation is the main cause of skin cancer, with BCC being the most frequently occurring skin cancer as well as the most common malignancy in humans. The role of UV radiation in the development of BCC has been proven and explained trough several previously described mechanisms. Therefore, due to extremely high incidence of BCC medical professionals should be aware of the importance of the public education on the etiology of this tumor and the importance of the UV protection.

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ULOGA UV ZRAČENJA U NASTANKU BAZEOCELULARNOG KARCINOMA

SAŽETAK

Bazeocelularni karcinom (bazaliom, BCC) je neosporno najčešći zloćudni tumor kože i najčešći zloćudni tumor u ljudi, a njegova učestalost u stalnom je porastu. BCC je uglavnom bolest bijelaca, osobito osoba svijetle puti. Izloženost kože UV zrakama je najvažniji i najčešći uzrok nastanka BCC. Vjeruje se da UVB zrake kratke valne duljine (290–300 nm, zrake koje uzrokuju opekline) imaju značajniju ulogu u nastanku BCC, nego UVA zrake duge valne duljine (320–400 nm, zrake koje uzrokuju tamnjenje kože). Razdoblje mirovanja od 20 do 50 godina je karakteristično vrijeme od UV oštećenja do kliničke pojave BCC. Stoga, u većini slučajeva BCC nastaje na kronično osunčanoj koži u odraslih osoba, najčešće u području glave i vrata. UVB zrake oštećuju DNA i mehanizme njezinog popravka, te mijenjaju imunološki odgovor rezultirajući genetičkim promjenama i nastankom tumora. UV zrake potiču mutaciju p53 tumor-supresor gena. Mutacije koje rezultiraju aktivacijom Hedgehog staničnog signalnog puta, uključujući gene PTCH, Sonic hedgehog (Shh) i Smoothened (Smo), imaju značajnu ulogu karcinogenezi tumora kože. Epidemiološke studije ukazuju na veću učestalost BCC u ekvatorijalnim, nego u polarnim krajevima. U ostale rizične čimbenike za nastanak BCC spadaju: uporaba solarija, pozitivna obiteljska anamneza tumora kože, tip kože I i II, sklonost nastanku pjegavosti u djetinjstvu, imunosupresija, prethodna radioterapija i kronična izloženost toksičnim noksama, poput anorganskog arsena. Iako vrlo rijetko metastazira, neliječen BCC može postati invazivan, lokalno agresivan, pa i smrtonosan. S obzirom na izuzetno visoku učestalost BCC, liječnici bi trebali biti svjesni važnosti edukacije pučanstva o etiologiji ovog tumora i važnosti UV zaštite.