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Source / Izvornik: **Collegium antropologicum, 2007, 31 - Supplement 1, 83 - 85**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:184:784640>

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Download date / Datum preuzimanja: **2024-07-26**



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Epidermal Malignant Tumors: Pathogenesis, Influence of UV Light and Apoptosis

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ABSTRACT

Basal cell carcinoma and squamous cell carcinoma, collectively termed non-melanoma skin cancers are the most common malignant tumors in humans. Basal cell carcinoma grows slowly and metastatic spread is very rare. Squamous cell carcinoma is characterized by infiltrative, destructive growth and metastasis. Long-term exposure of skin to UV light has a great impact on development of these epidermal malignancies. UV light induces cascade of events like well known DNA damage of keratinocytes as well as still completely undetermined influence on apoptotic process through expression of proapoptotic and antiapoptotic molecules. The major role in development of skin cancer is given to proapoptotic p53 molecule or tumor suppressor gene which mutation due to UV exposure leads to resistance of DNA-damaged cell to apoptosis. Other proapoptotic molecules such as Fas ligand (FasL) and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) are strongly expressed in basal cell carcinoma and squamous cell carcinoma that could be explained by the ability of tumor to escape the attack of immune system.

Key words: basal cell carcinoma, squamous cell carcinoma, ultraviolet light, apoptosis, p53, FasL

Introduction

Epidermal malignant tumors are a group of skin cancer arising from epidermal cells. It includes mainly basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), namely together non-melanoma skin cancer (NMSC)^{1,2}. NMSC are the most frequent malignant tumors in whites and its incidence is increasing worldwide^{1,2}.

Basal cell carcinoma accounts for approximately 75% of all the skin tumors³. Although in the past men were more prone to this type of skin cancer, the sexual difference became less pronounced recently. It could be explained by a novel changes in women lifestyle, especially in their endeavor to achieve a »beautiful year-around tan« due to a sun exposure as well as frequent visiting of skin tanning studios^{3,4}. The raised incidence of skin tumors in both sex is also due to a depletion of the ozone layer and its inability to filter out the carcinogenic rays of ultraviolet light (UVB)^{3,4}. BCC grows slowly and metastatic spread is very rare (around 0.05%)^{4,5}.

Squamous cell carcinoma accounts for 10–20% of all skin malignancies and is the second most common skin cancer after BCC^{4,6}. It affects most commonly elderly white men after the age of 40^{4,6}. As well as BCC it is most

consistently related to ultraviolet radiation^{4,6}. Therefore, outdoors occupation, less protective clothing and ozone layer depletion contributes mainly to this raising incidence^{4,6}. Contrary to BCC, which very rarely metastasize, lymphogenic spread of SCC is very often and this malignancy is a major cause of death among non-melanoma skin cancers (NMSC)^{4,6}.

Etiopathogenesis of Epidermal Malignant Tumors

The etiology of non-melanoma skin tumors can be explained as sincarcinogenic effect of different factors such as irradiation, chemical carcinogens, genetic factors, oncogenic viruses and immunosuppression⁶.

The most common factor involved in the pathogenesis of these types of skin tumors is ultraviolet light, due to a sun exposure or use of other UV light sources such as skin tanning studios or PUVA therapy⁸. Fair-skinned individuals (skin type I) who burn easily and do not tan well are more prone to development of skin tumors in

comparison to darkly pigmented persons⁸. Cumulative lifetime UV exposure and intermittent intense sun exposure early in life leading to sunburn both contribute to development of skin cancer⁸. However, 20% of BCCs occurred on non sun exposed skin and therefore the influence of other etiology factors could be of great importance as well⁸.

Ionizing radiation as well as heat could also be a cause of skin cancer development^{4,7}. Chronic ingestion of arsen (in groundwater or as a therapy) as well as industrial exposure are also important risk factors. Other carcinogens include petroleum products, hydrocarbons such as soot, pitch, tar, shale and mineral oil and tobacco^{4,7}.

Genetic factors are also involved in development of BCC^{9,10}. Two well known tumor suppressor genes, p53 gene and the patched gene (*ptch*) are the major targets of UV light for BCC induction^{10,11}. The p53 is a tumor suppressor gene involved in cell cycle regulation^{10,11}. Mutation in p53 gene, due mainly to a UV light, arrests a cell growth at G1 phase of the cell cycle, thus preventing a death of UV damaged cells and subsequently allowing a cell proliferation and formation of skin cancer^{10,11}. Mutations in the single gene p53 are present in 40–60% of all skin cancers^{10,11}. The patch gene (*ptch*) is mainly related to nevoid basal cell carcinoma syndrome or Gorlin-Goltz syndrome, an autosomal dominant disorder characterized by the development of multiple BCCs at an early age, medulloblastomas, meningiomas and skeletal abnormalities^{11,12}. The patch gene is located on chromosome 9q22.3^{11,12}. Its allelic loss or inactivation, which occurs in patients with Gorlin-Goltz syndrome, is associated with an abnormal transcription of patch protein^{11,12}. This protein is a cell membrane receptor for the Hedgehog protein family, responsible for transcriptions of other proteins important for cell proliferation and function^{11,12}. Some studies show that this gene also play a role in the pathogenesis of sporadic BCC^{11,12}.

Some oncogenic viruses especially human papilloma-virus (HPV) types 6, 11, 16 and 18 has been identified in a variety of genital, anal and oral SCCs, so their impact in development of this particular skin malignancy is of a great importance⁴. It is believed that genetic parts of HPV viruses E6 and E7 may inhibit p53 gene function and therefore allow replication of malignant clone¹³.

Immunosuppressed patients have a greater risk for development of skin cancers especially SCC^{6,7}. Solid organ transplant recipients are especially susceptible for non-melanoma skin tumors and half of them have multiple tumors on presentation^{6,7}. Risk for SCC in these patients is connected to duration and intensity of immunosuppression^{6,7}.

Within UV spectrum, absorption of UVB by deoxyribonucleic acid (DNA) within epidermal keratinocytes induces a DNA mutation of pyrimidine dimers, especially of tumor suppressor gene or oncogenes^{6,7}. This error is than replicated and transcribed^{6,7}. Although UVB is more potent in producing genetic mutation than UVA and is considered as tumor initiator, molecular studies show that UVA act as tumor promoter to help expand ini-

tiated tumor cells through modulation of protein kinase C, a signal transduction molecule^{6,7}. UVA also causes immunosuppression through secretion of interleukin-10 and subsequent activation of suppressor T-cells^{6,7}.

Chronic skin wound, caused by trauma, ionizing radiation, thermal exposure or chronic skin diseases such as hidradenitis suppurativa and dystrophic epidermolysis bullosa may predispose to squamous cell carcinoma development that is even more aggressive than other SCCs, causing a metastasis rate of 38%^{6,7}. The cause of development of this type of SCC is not yet completely understood^{6,7}.

The Role of Apoptosis in Development of Epidermal Malignant Tumors

Apoptosis is a physiological process of programmed cell death responsible for the homeostasis of a variety of physiological systems in the body, including skin¹⁴. Apoptosis is morphologically characterized by cell shrinkage, nuclear condensation, cellular fragmentation and finally phagocytosis by neighboring cells¹⁵. In skin, cell death by apoptosis is an unique way of regulating keratinocyte proliferation, differentiation and epidermal growth as well^{16,17}. Balance between cell death and cell proliferation maintains homeostasis of epidermal compartment¹⁸.

The process by which keratinocytes undergo apoptosis is a multistep program that includes several mechanisms. Briefly, the »extrinsic« apoptotic pathway is mediated by binding of Fas ligand (FasL) or TNF to specific death receptors thus leading to the activation of different caspases in an ordered sequence^{19,20}. The »intrinsic« pathway involves mitochondrial release of multiple proapoptotic factors that ends in final activation of the caspase-3²¹. Both, apoptosis induced through death receptors and mitochondria, ends in the activation of the effector caspase-3, responsible for the cleavage of a variety of intracellular substrates and for the activation of caspase-activated deoxyribonuclease that initiates DNA cleavage²². Finally, the process ends in the formation of apoptotic bodies and its phagocytosis by neighbouring macrophages and dendritic cells²². The process of apoptosis is controlled by proteins of the Bcl-2 family, i.e. several proapoptotic (Bax, Bak, Bad, p53) and antiapoptotic (Bcl-2, Bcl_{xL}) proteins²¹.

The major feature of non-melanoma skin cancer is their resistance to apoptosis²³. In UV unexposed skin, FasL and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) are mainly expressed at basal keratinocytes and less in the upper layers of epidermis, while TRAIL-R1 and R2 dominate in the upper layer of epidermis²⁴. Upon the UV light exposure FasL, TRAIL and TRAIL-Rs are downregulated transiently. Consequently, apoptotic cells are found throughout the epidermis. When BCC or SCC has developed, the expression of Fas and TRAIL are strongly upregulated in both tumors, as well as the expression of several apoptosis inhibitors like bcl-2 and FLIP²⁴.

Tumor suppressor p53 gene is included in repairment of UV-induced DNA damage, therefore p53 gene is considered as »guardian of the genome«²⁵. If repairment of DNA is not possible, DNA damaged keratinocytes are eliminated by programmed cell death or apoptosis, under the control of p53 gene²⁵.

However, p53 gene could be itself a direct target of UV radiation. Mutation of this gene can lead to uncontrolled keratinocyte proliferation and disability to undergo apoptosis. Mutation in the p53 gene are detected in about 56% of BCC and in >90% of SCC²⁶.

In UV non-exposed skin the expression of FasL prevents the influx of inflammatory cells from dermis into epidermis and also eliminates DNA-damaged cells that have the potential to transform²⁷. Upon UV exposure,

the expression of FasL is downregulated and mutated cells could not be eliminated by apoptosis. However, after a development of skin tumor, upregulation of FasL protects the tumor from immune-mediated damage providing its immune escape and further expansion²⁸. Moreover, upregulation of FasL and TRAIL in BCC and SCC protects the tumor from T cell attack, while at the same time lack of death receptors (TRAIL R1, R2 and Fas) prevent tumor cell death²⁹. So, it seems that apoptosis plays an important role in the development and expansion of NMSC. Therefore, future challenges include the clinical implications of these data directed toward development of new apoptosis-based therapeutics in BCC/SCC treatment.

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EPIDERMALNI MALIGNI TUMORI: PATOGENEZA, UTJECAJ UV ZRAČENJA I APOPTOZA

SAŽETAK

Bazocelularni karcinom i spinocelularni karcinom, skupno nazvani nemelanomski kožni tumori, su najčešći maligni tumori u ljudi. Bazocelularni karcinom sporo raste i metastazira vrlo rijetko. Spinocelularni karcinom je karakteriziran infiltrativnim, destruktivnim rastom i metastazama. Dugotrajno izlaganje kože ultraljubičastom zračenju značajno utječe na nastanak ovih epidermalnih kožnih novotvorina. Ultraljubičasto zračenje potiče slijed događaja, kao što su dobro poznato oštećenje DNA keratinocita, kao i još uvijek nedovoljno rasvijetljen proces programirane stanične smrti, odnosno apoptoze regulacijom ispoljavanja proapoptotičkih i antiapoptotičkih molekula. Glavna ulogu u nastanku kožnih tumora pridaje se proapoptotičkoj p53 molekuli ili tumor supresor genu čija mutacija uzrokovana izlaganjem ultraljubičastom zračenju vodi do otpornosti stanice s oštećenom DNA na apoptozu. Ostale proapoptotičke molekule kao na primjer FasL i TRAIL su također snažno ispoljene u bazocelularnom i spinocelularnom kožnom karcinomu, što može objasniti sposobnost tumorskih stanica da se obrane od napada imunog sustava.