

# Molecular and environmental aspects of skin cancers

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## Abstract

Skin cancers are one of the most common cancers in the Caucasian population. A constantly increasing number of non-melanoma skin cancers and malignant melanomas is observed. The incidence of skin cancers is associated mainly with exposure to sunlight. Therefore, agricultural workers who work in open spaces are a particularly vulnerable group. Currently, studies on the pathogenesis of skin cancer focus on the molecular basis associated with ultraviolet radiation. This study is an attempt to summarize the current state of knowledge on this issue. There have been demonstrated mutations in different classes of genes associated with carcinogenesis, including protooncogenes, tumour suppressor genes, genes that control apoptosis, genes encoding transcription factors and DNA repair genes in patients with skin cancers. Mutations in the latter result in reducing the effectiveness of DNA repair and fixation of mutations. All changes at the gene level lead to structural changes, quantitative and dysfunction of proteins encoded by these genes. All these factors contribute to the process of carcinogenesis. Due to increasing number of skin cancers, it seems important to increase knowledge of the molecular basis of skin cancers. This knowledge could be crucial for predicting the course of the disease, and for the development of new therapeutic strategies.

## Key words

skin cancer, malignant melanoma (MM), Basal Cell Carcinoma (BCC), Squamous Cell Carcinoma (SCC), ultraviolet radiation (UVR), carcinogenesis, molecular basis

## INTRODUCTION

The skin is a chemical, physical and immunological barrier separating the interior of the human organism from the environment. It is therefore the perfect organ to protect the integrity of the body. It becomes the first line of defence against biological, physical and chemical agents which can affect and alter the structure and function of the skin [1]. One of these agents is solar energy reaching the earth in the form of radiation, and the skin is the most exposed organ. Increased risk of developing skin cancer has been demonstrated after UV radiation (a part of solar radiation) [2]. Skin cancer is the most common type of cancer in humans. There are three main types of malignant neoplasms: basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and malignant melanoma (MM). BCC and SCC are non-melanoma skin cancers (NMSCs), and they are both derived from keratinocytes; MM has its origin in melanocytes [3].

Epidemiological studies indicate a higher incidence of skin neoplasms in fair-skinned, blond-haired and blue-eyed populations, and its dependence on the cumulative dose of UV radiation during a whole lifetime [4, 5]. However, cumulative UV damage is pivotal for SCCs, whereas one or more heavy sunburns may be significant for BCCs development [6]. There

is no doubt that UV light is a significant factor for both MM and NMSCs development. UV radiation can function as a complete carcinogen or as an initiator of carcinogenesis, which has been shown in mice in which skin cancer was induced without any other agents [3, 7].

BCCs are slow growing, rarely metastasizing tumours (metastasis rate < 0.1%), which are locally invasive and destructive [6]. BCC is very common and is estimated to cause about 80% of all skin cancers. It usually develops on the face and other sun-exposed areas, but one-third of cases are situated on sun-protected parts [8]. Another type of NMSCs – SCC, is more aggressive with metastasis rate reaching 1%, but for some locations, e.g. lips, the rate is even higher [6, 8]. MM is a less common malignancy of the skin, but if not detected at an early stage it is usually lethal. It is estimated that MM is responsible for approximately 75% of deaths from all skin tumours [9]. According to the World Health Organization (WHO), 2 – 3 million of NMSCs and about 130.000 of MM are diagnosed every year. Skin cancers cause 66,000 deaths annually, which makes it a serious public health problem.

## UV RADIATION AND CHANGES IN THE SKIN

UV radiation (100–400 nm) represents 45% of the total sunlight spectrum. According to the International Commission On Lamination it is divided into three parts: UVA (315 – 400 nm), UVB (280 – 315 nm) and UVC (100 – 280 nm) (Fig. 1).

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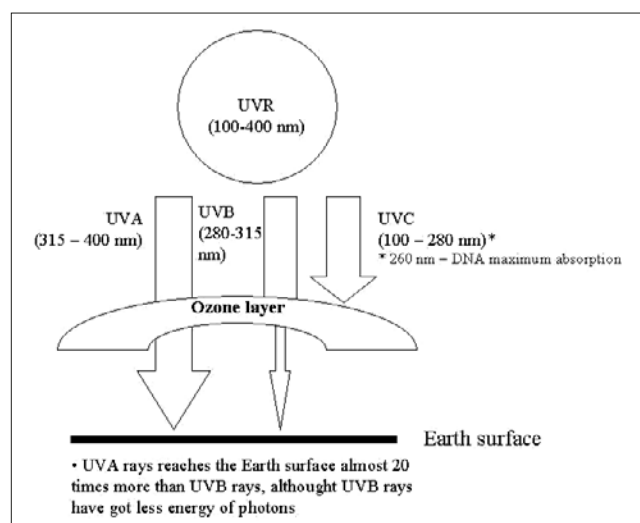


Figure 1. Scope of ultraviolet radiation reaching the Earth's surface [1]

UVC is the most harmful spectrum to genetic integrity because DNA has an absorption maximum at a wavelength of 260 nm but, fortunately, nearly all solar UVC is blocked by the ozone layer [1]. Pollutants like chlorofluorocarbons (CFCs) increase ozone depletion. Literature data show that each 1% of decrease in the ozone layer results in the increase of skin cancer: BCC 1.7% and SCC 3% annually. Moreover, studies show that the geographic variation in incidence of non-melanoma skin cancer is associated with sun irradiance and exposure [5]. UVA radiation, in turn, reaches the earth surface and is about 20 times greater than UVB. Moreover, UVA has a deeper penetration into the skin than UVB. UVA deposits up to 50% of energy in the stratum papillare of the dermis, whereas UVB is almost completely absorbed in the epidermis. UV radiation is responsible for solar keratosis, skin aging, and skin cancer development [1, 4].

DNA is a major cellular chromophore with maximum absorption peak at 260 nm (UVC range), but skin lesions are also produced at longer wavelengths including UVA and UVB ranges [10]. This direct effect of UV radiation (especially UVB, but also a small part of the UVA band, 315–327 nm) causes the formation of covalent bonds in adjacent pyrimidines, leading to the formation of photoproducts, among which cyclobutane pyrimidine dimers (CPDs) and (6–4) pyrimidine-pyrimidone photoproducts [(6–4)PPs] are the most frequent products. Furthermore, the latter can isomerize to Dewar valence isomers (DewPPs) by absorption of UVA irradiation, which are a third type of UV-induced photoproducts [7]. All of these pathological changes appear around 80,000 times per cell in one hour of sunlight exposure, and they also become a physical barrier for replication and transcription, initiate C to T and CC to TT transitions, which are called UV signature mutations [7, 11]. Among these, CPDs are regarded as more mutagenic because of their profusion and slow repair. Incorrect repair of these lesions leads to errors in DNA synthesis and genomic mutations in the epidermal cells, which cause the development of cancer cells in the context of active cell proliferation [1].

However, absorption of UV photons can also occur in an indirect way. In the presence of photosensitizers, the distribution of the electrons is changed, creating an excited singlet state. This excited molecule can interact with DNA molecules, producing free radicals or with molecular oxygen,

producing reactive oxygen species (ROS). These products create direct DNA damage – single-strand breaks or DNA-to-protein cross-links, and they can also decrease the skin immune response [7, 12]. Research data implicate ROS accumulation as a popular phenomenon in many cancer cells. They can cause direct damage to DNA by increasing cell mutation frequency, and by functioning as a secondary messenger in signaling cascades. This is the main way of DNA damage caused by UVA radiation, but UVA between 328 nm – 347 nm can induce direct and indirect effect on DNA [1, 12]. 8-oxo-7,8-dihydroguanine (8-oxoGua) seems to be the most important oxidative product, which can be a reliable biomarker in the cancer development. 8-oxoGua in combination with other pathological changes can indicate the transformation of a benign to a more invasive lesion, and they also can induce abnormal modifications in adjacent DNA bases. In normal cells, 8-oxoGua is removed by the base excision repair (BER) pathway, but repair systems are not efficient in cumulative oxidative stress and changes persist [12]. UV irradiation also causes an increased level of nitric oxide (NO), which results in the inactivation of DNA repair enzymes by nitrosylation, and inhibition of some steps in nucleotide excision repair (NER) [13]. Moreover, an elevated level of NO causes the loss of its advantageous effects, such as the regulation of the inflammation process or relaxation the smooth muscle cells [13, 14]. Furthermore, NO combined with ROS is changed into peroxynitrite, which initiates oxidative and nitrosative damage in DNA and leads to lipid peroxidation. Poly(ADP-ribose)polymerase, activated by peroxynitrite, leads to energy depletion by NAD<sup>+</sup> reduction, ATP formation and drives cells to death [13].

The development of skin cancer is multi-factorial and occurs not instantly after sun exposure, but after a long latency period. These facts confirm the hypothesis of multi-step carcinogenesis. There are three main groups of genes in which occurring mutations can lead to neoplastic transformation: proto-oncogenes (important growth regulators in normal cell division), tumour suppressor genes (negative growth regulators) and DNA repair genes [15].

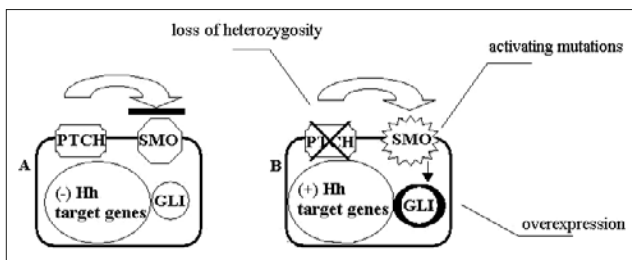
The best example of a tumour suppressor gene is p53. This is a complex molecule involved in numerous pathways, and has the task of guarding genomic stability. Its importance is confirmed by the fact that approximately 100 of known proteins are regulated by p53. There is p53 over-expression in the skin after UV exposure. Depending on the dose of UVB, p53 can arrest the cell cycle, allowing repair to DNA damage (low dose), or it can lead to apoptosis (high dose of UVB), preventing an oncogenic transformation. Disturbance of the p53 function can be caused by direct mutations or indirectly by inactivation of p14ARF (p53 activator), or over-expression of MDM2 (p53 inhibitor). It is noteworthy that these mechanisms are inhibited when skin cells accumulate mutations in the p53 gene [16]. In humans, p53 is mutated in approximately 50% of all cancers, a percentage also confirmed in BCC, but in SCC that frequency reaches over 90% [3, 17]. Ras, in turn, is an example of proto-oncogen. It codes small GTPase, which transmitting signal within cell. Mutations in the *ras* gene can cause production of continuously activated Ras proteins, leading to overactive cell signaling, and finally resulting in the development of skin cancer [18]. In the context of skin cancer development, besides mutations in BER and NER DNA repair systems, the mammalian mismatch repair (MMR) system should be

taken into consideration. Mutations occurring in its genes lead to deficiency in the repair of UV-induced pyrimidine dimers [19].

## NMSCs DEVELOPMENT

SCC constitutes approximately 20% of NMSCs, 12% of which metastasize, particularly to lymph nodes. Actinic keratosis (AK) and Bowen's disease (Carcinoma *in situ*, CIS) are precursors of SCC. The latter has a higher risk of developing an infiltrating lesion. Patients who suffer from xeroderma pigmentosum (XP, a rare autosomal recessive genetic disorder in which DNA repair after UV radiation is faulty) have a greater predisposition to SCC development. In general, inactivation of p53 gene is the earliest event that can disturb the genome stability. Low expression of angiogenesis inhibitor, TSP-1, loss of p16 (cell cycle inhibitor) and over-expression of cyclin D1, are related to massive inflammatory response leading to tissue destruction [20]. SCC development is also associated with over-expression of Ras (signal transmitter), which is observed in most human SCCs and their precursors. This phenomenon can be caused by Ras point mutation, but studies have demonstrated that it only occurs in 10–30% of cases of human SCC, which indicates that over-expression of Ras is mainly caused by phenocopies oncogenic Ras [21]. Moreover, the disturbance in the activity of glutathione peroxidase (GPX, cytoprotective enzyme, which transforms ROS into a harmless product), elevates the level of peroxide, and increases the risk of cell damage. It has been demonstrated that two of three AKs, and four of five SCCs, had low activity of GPX, but all of them had a raised peroxide level. GPX may be an early indicator of the SCC development [22]. The over-expression of anti-apoptotic proteins belonging to the Bcl-2 family protein, Bcl-xL (a crucial activator for skin carcinogenesis) and Mcl-1 (an essential survival factor for keratinocytes), is observed in SCCs. Their presence proclaims that UVB damaged keratinocytes underwent apoptosis, avoiding the skin cancer development [23, 24].

BCC represents 80% of NMSCs. Its growth is mostly associated with changes in the hedgehog (Hh) signaling pathway (Fig. 2) and damage to p53.



**Figure 2.** Schematic diagram of Hh signaling pathway in normal cell (A) and BCC cell (B) [25]

Excessive activation of the HH pathway is essential for BCC development. It may occur as a result of loss of heterozygosity (LOH) PTCH1, gene function mutation in SMO or over-expression of Gli1 or Gli2 [25]. Interestingly, the majority of mutations in the PTCH gene are C to T transitions and CC-TT double transitions, known as UV signature mutations. This indicates the participation of UV in BCC development

[26]. The cell of origin of BCC remains a contentious issue. There are different subtypes of BCCs because they can arise in different cellular compartment of the skin, depending on induction site. It is also worth noting that BCC development is associated with wounding, which seemed to promote the tumorigenic potential of HH-activated bulge stem cells [24]. Furthermore, genome-wide association studies reported on loci associated only with BCC (PADI6, RHO, KLF14, KRT5, TERT/CLPTM1L), and loci linked with BCC and pigmentation genes (SLC45A2, TYR, MC1R, ASIP). These data confirm the existence of pigmentation dependent and independent pathways in the development of BCC. Moreover, according to reports, genes involved in lipid metabolism may lead to BCC tumorigenesis, whereas genes associated with the extracellular matrix explain the slow-growing properties of BCC [27]. BCC also has an inherited disease predisposing to its development. This is nevoid BCC syndrome (NBCCS), also known as Gorlin-Goltz syndrome, which is an autosomal dominant condition caused by mutation in the PTCH1 gene [25].

## MM DEVELOPMENT

Malignant melanoma (MM) is one of the neoplasms the arising and development of which is closely related to the skin microenvironment. Mutations in gene coding proteins that regulate the proliferation, cell growth, cell cycle and cell death, participate in the growth of this type of tumour. Besides these mutations, the surrounding cells also take part (keratinocytes, fibroblasts, endothelial cells and immune system cells) in tumour expansion. They act at first as anti-cancer factors, but in the later stage they support the fast and aggressive growth of the neoplasm. The state of hypoxia also forms favourable conditions for the development of melanoma [28].

The function of melanocytes depends on keratinocytes. When homeostasis of a melanin unit (one melanocyte surrounded by 35 keratinocytes) is disturbed, it leads to the uncontrolled proliferation of melanocytes. This is the first step in melanoma neoplastic transformation [29, 30]. Normally, proliferation of melanocytes takes place during skin growth in childhood. It can also be observed in adults after UV radiation or injury. Melanocytes become independent of keratinocytes, mainly by disruption of their contact. E-cadherin (the crucial protein for cell adhesion) plays a major role in melanocyte-keratinocyte integrity. UV radiation, by activating the ET-1/ET(B) pathway, leads to the reduction of E-cadherin expression, decrease in the sensitivity of melanocytes to apoptosis, increase in their proliferation, and the elevation of the invasive proteins on their surface [28]. Moreover, melanocytes cultured in the absence of keratinocytes had melanoma antigens on their surface, e.g. MCAM (regulate invasive growth of melanoma) [31]. Reduction of E-cadherin expression is accompanied by increased expression of N-cadherin, called cadherin switching, and is additionally regulated by HGF (a factor secreted by fibroblasts). In consequence, melanocytes acquire the ability to interact with fibroblasts and endothelial cells, that together with cadherin switching, promote the melanoma invasive phenotype [32]. Another important molecule is HIF-1 (Hypoxia Induced Factor-1). This is the main response regulator of cells during the hypoxia state and a mediator



of the apoptotic death of keratinocytes after UVB radiation. As a result of UV radiation, positive expression of HIF-1 on melanocytes can be observed. It also occurs during activation of the most important signal pathways in melanoma (MAPK and PI3K pathway). These pathways, in combination with the oncogenic properties of mutated c-Kit protein, lead to the transformation of melanocytes [33]. Furthermore, HIF-1 inhibits proapoptotic activity of the p53 protein and reduces E-cadherin expression [34, 35]. In the context of UV, FAP (a fibroblast activation protein) should be mentioned. This molecule is secreted by the fibroblast after UV radiation. FAP increases the invasiveness of melanoma cells. It is the main protein promoting tumour progression [36]. Bcl-2 family proteins, especially a high level of the Bcl-2 and Mcl-1, are anti-apoptotic proteins that take part in avoiding apoptosis [23]. These data confirm that melanoma aggressiveness is associated with tumour growth promoting environmental factors, in which UV plays a crucial role.

### SKIN CANCER IN FARMERS

Farmers are group of outdoor workers particularly exposed to ultraviolet (UV) radiation. Increased risk of skin cancer being observed among agricultural workers is due to the period of time they spend outdoors. Another factor increasing the risk of skin cancer in farmers is contact with different chemicals, especially pesticides [37]. Pesticides are chemical substances designed for plant protection against pests in agriculture [38]. Exposition to them can cause acute and delayed effects on health, e.g. irritation of the skin and eyes, reduction in fertility, epigenetic modification, and even cancer development [39].

As the skin is the first line of defence exposed to pesticides, farmers during their work, which includes mixing, loading and spraying fields by pesticides, and also cleaning their equipment, are at higher risk of skin irritation, allergy and even development of skin cancer [38]. The first reports of skin cancer due to exposition to pesticides appeared more than half a century ago, and described cases of skin cancer after the use of insecticides in vineyards. They concerned only exposition to arsenic, which was a popular compound of pesticides in the early 20th century [40, 41]. According to the research, chemical substances other than arsenic seem to be an unimportant risk factor for skin cancer development, but they may enhance the carcinogenic effect of sun exposure [42]. The studies showed that development of melanoma was correlated with such pesticides as carbaryl, toxaphene, parathion and manep/mancozeb [43, 44, 45].

Studies demonstrated that cancer risk in farmers was lower than expected, and health effects might be rather related to the mutagenic effect of UV radiation [39]. However, studies on rats confirmed the hypothesis, that UVB radiation, applied together with pesticides, caused the greatest histopathological changes in the skin, than each of them individually [46]. Therefore, farmers should have careful dermatological check-ups [47].

### CONCLUSIONS

Ultraviolet radiation (UV) is an important environmental risk factor in the development of cancer. Skin cancer is one

of the most common cancers in human. Due to the growing rate of skin cancer morbidity, researchers should improve their knowledge of the molecular mechanisms of skin tumour development, and they should try to elaborate treatment techniques as well as prevention methods. Moreover, it should be remembered that farmers have a higher risk of skin cancer development because of their exposition to the sun and chemical agents, especially pesticides, during their work. According to all these facts, they should be taken into special consideration in the context of researches.

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