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Review

Photocarcinogenesis – Molecular Mechanisms

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A B S T R A C T

The carcinogenicity (photocarcinogenicity) of sunlight to human skin has been recognized more than a century ago. Last decades numerous experimental studies show that UV rays damage DNA, cause gene mutations leading to the development of malignant tumors such basal cell carcinomas, squamous cell carcinomas and melanomas. The tumors occur most frequently in fair skinned people, and the mutations typically are found at dipyrimidine sites with C-T or / and CC-TT tandem double mutations. The authors briefly summarize their investigation of the p53 suppressor gene, and expose their hypothesis of hTERT involvement in cancerogenesis. Also their underline the importance of UV induced immunosuppression in photocarcinogenesis. Psoriatic patients are exposed to numerous cancerogens in their treatment. A better understanding of the mechanisms of photocarcinogenesis could provide new ways in the treatment of skin tumors.

***Key words**: UV radiation, mutation, telomerase, immunosuppression, psoriasis*

Introduction

Malignant skin tumors are the most common tumors in humans and their incidence is steadily increasing in our country and worldwide in the last decades[1–4]. Although a lot of factors may contribute to the development of skin tumors such as ionizing radiations, viruses, arsenic, tar derivates, soot, exposure to products of the distillation of coal, inflammation, genetic factors, immunologic status and others, the most important environmental factor is the ultraviolet radiation (UVR) from the sunlight or from artificial sources[4–8]. In recent years several studies have been performed to investigate the role of UVR in tumorogenesis which demonstrated they can cause irreversible changes in cell genetic material, initiation, promotion and progression of tumors[9–11]. So, exposure to UVR induces photocarcinogenesis i.e. the skin cells acquire genomic alterations that play a key role in the development of the three most common types of skin cancer: basal cell carcinomas, squamous cell carcinomas, which arise from keratinocytes and are collectively named non-melanoma skin cancer (NMSC), and melanomas that derive from melanocytes. They share certain common traits like the rise of incidence with increased exposure to sunlight, increase with age and different susceptibility related to pigmentation i.e. mostly develop in fair skinned people with phototypes I-II after Fitzpatrick according our and other experience[12,13]. On the basis of our investigations and supported by numerous other in skin malignant tumors as well in others cancers the initiating and leading event is the alteration of the cell genetic material: mutation, amplification or deletion of some of its genes, like the suppressor gene p53, with alteration of their protein products and finally alteration of signal pathways [14,15].

Immunosuppression induced by UVR has also a role, and we believe that telomerase has, too. The purpose of this review is to summarize the current knowledge of the cellular and molecular events in photocarcinogenesis even if the heterogeneity of these tumors inevitably have different pathway.

Effects of UV Radiation on DNA

Although the role of sunlight in the development of skin cancer was recognized at the end of the XIX century[16], and the role of UVR in inducing skin cancer was

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demonstrated by Findlay experimentally in albino mice with a quartz-mercury vapor lamp in 1928[17], only the introduction of powerful tools for studying the DNA mutations and advances in genetics, molecular biology and immunology in the last three decades have improved our understanding the process of carcinogenesis and particularly photocarcinogenesis.

UVR represents the portion of the electromagnetic spectrum between visible light and X-rays. According to international convention UVR is divided into three wavelength ranges: long-wave UVA (320–400 nm), medium wave UVB(290–320 nm), and short wave UVC (200–290 nm)[18]. The energy of each part of the radiation is inversely related to the wavelength. UVC, the most energetic, is completely filtered by the ozone layer in the stratosphere, so that the most active part of UVR which reaches the earth surface are UVB rays and make approximately 5% of the UVR reaching the soil. UVB radiations are known to have pleotropic biological effects on the skin, acute or chronic, causing inflammation, apoptosis, local and systemic immunosuppression, and absorbed by DNA, it damages and act directly as a mutagenic[18–21].

UVA rays represent the predominant component of solar UVR and make up about 95% of UV rays that reach the earth's surface. Their energy is relatively small; however, they penetrate deeper into the skin. They cause quick browning, skin aging, and generating a variety of reactive oxygen species (ROS) such as hydrogen peroxyde, superoxyde, peroxy nitrite, which indirectly damage DNA forming purine oxidative (mainly guanin) photoproducts such as 8-oxo7,8dihydro-2'deoxy-guanosine, and strand breaks. UVA inducing matrix metalloproteinases, via AP-1 and NF- B, increase the agressivity of skin cancer. So, even if the UVB and UVA differ in their biological effects and depth of penetration, both radiations can induce DNA damage causing delayed genomic instability and induce ROS which can be involved in all the stages of carcinogenesis, and have also immunosuppressive properties (see recent reviews)[22–25]. Intense acute, intermittent or chronic exposure to UVR of solar origin or from artificial sources, in spite of the cutaneous defense and repair mechanisms (melanin synthesized by melanocytes, stratum corneum, trans-urocanic acid, DNA repair, antioxidant enzymes such as catalase and superoxide dismutase, apoptosis) can lead to the development of precancerous lesions (actinic keratosis) and different skin tumors NMSC and melanoma[7,26].

Epidemiologic studies have assessed the relevance of UVR exposure in the development of non-melanoma cancers: basal cell carcinoma is related to cumulative sun exposure, sunburn in childhood and also to intermittent exposure (on the trunk), while squamous cell carcinoma is more related to lifelong cumulative exposure. In the case of melanoma it seems to be associated with intense intermittent UVR exposure, and is located frequently on the back in males and on the lower legs in females[13,26–29].

UVR Induced Mutation in Tumor Suppressor Genes and in Protooncogenes

Photocarcinogenesis is a complex multistage process involving mutation of more genes and the transformed cells escape from immunosurveillance and undergo clonal expansion.

UVB photons are directly absorbed by nuclear DNA of keratinocytes with transfer energy into biochemical, causing its damage i.e. mutagenic photoproducts which, if not repaired before DNA replication, lead to mutation in cancer relevant genes, partly tumor specific. These genes are: suppressor genes (whose protein products regulate DNA damage, apoptosis, cell cycle control), protooncogenes (whose physiological function is organ growth and tissue repair) when activated become oncogenes, and genes envolved in the regulation of cell cycle[30–32]. Other genes regulating the skin pigmentation are also important in the development of skin tumors and so the investigation of photocarcinogenesis represents a good model of how genetics and environment interact in its pathogenesis.

The DNA damage can be responded with DNA repair, cell cycle checkpoint control, apoptosis and only partly with tolerance (post replication repair or template switching).

UVB induces damage of DNA particularly on neighboring pyrimidine bases thymine (T) and or cytosine (C) on the same strand forming a four-membered cyclobutane ring or 6,4 photoproducts. There are C to T transition or CC to TT double base mutation[33–35]. These changes are exclusive on adjacent dypirimidine sites, so they represent a specific marker of UVR involvement in photocancerogenesis (fingerprints or signature mutations). Such fingerprints can be found also in normal sun exposed areas[36]. Although these are the most common UVR induced DNA damages, there are also some others: protein DNA cross-links, single strand breaks, oxidation damage but they are not specific and can be caused by various carcinogens. Most of UVR induced DNA damage is quickly enzymatically corrected by the nucleotide excision repair (NER) and consist of recognition of the lesion, unwinding of the DNA helix, demarcation of the lesion, dual incision and excision of the damaged region and resynthesis of the gap, and ligation by DNA polymerase and ligase[37–39]. In this repair process among others the XP proteins have an important role. There are also other types of repair mechanisms: base excision repair, mismatch repair, double strand break repair[38]. Goukassian and al. have recently demonstrated on human dermal fibroblasts that after UVR exposure the NER of photoproducts significantly decreases with age from newborns to young persons, and to older people. They also found an age–associated decrease of mRNA level of NER proteins. This decreased DNA repair mechanism related to age is likely to increase the incidence of skin cancer in the elderly[40]. In NER deficient syndromes such as the xeroderma pigmentosum, which comprises 8 varieties from XP-A through XP-G and XP-V, characterized by high

sensitivity to UV rays, with sunburns, freckling and sometimes abnormalities of the central nervous system, the UVR induced damage is not recognized or incorrectly repaired. In the patients the bases remain permanently mutated which lead to an early high incidence of precancerous lesions and skin tumors (squamous cell carcinoma, basal cell carcinoma, melanoma, and other)[41,42]. The XPA is the most severe and XPC the most common variant. Moreover, transgenic mice without these genes have increased photosensitivity and are prone to develop skin tumors[42].

Photocarcinogenesis implicates the mutation i.e. inactivation of one or more tumor suppressor genes (antioncogenes) with altered aminoacid sequences in their coded protein product, deletion or overactivation of some protooncogenes which become oncogene and the encoded protein releases the cell from growth restraints. The suppressor gene products in normal cell are inactivated by binding to other proteins or by phosphorilation, in neoplastic cell they are mutated or deleted. Tumor suppressor genes usually are recessive i.e. require the inactivation or deletion of both alleles[15,43,44]. Interestingly enough, such recessive genes can seem dominant, if one allele is heredited and the other inactivated by some environmental agent (UVR), in agreement with the Knudson s' »two hits model» theory[44,45]. Point alterations of the suppressor gene p53, » the guardian of the genome»(firstly presumed to be an oncogene) are the most frequent mutations in human cancers. It can be activated by numerous form of cell stress: irradiation, hypoxia, chemicals etc[43]. UVR induces mutation of p53 gene typically on pyrimidine sites. Its protein product, a transcriptional factor and key of cell regulation, is expressed at very low levels in normal cells, and this – »wild type», cannot be demonstrated by immunohistochemistry, while the mutant is easily observed. P53 is regulated by human double minute2 (Hdm2) protein, that bind it inhibiting its transcriptional activity and is then degraded in the proteosome. p53 is able, after DNA damage, to induce transcription of p21 a cyclin kinase inhibitor which prolong or arrest the cell cycle in the G1 phase allowing the repair of DNA, enhance apoptosis (programmed cell death) of mutated cells upregulating the expression of proapoptoptic genes (Bax, Fas), inhibit angiogenesis, and also take part in the DNA repair[46–48]. Experiments in UV irradiated transgenic mice P53-/- have shown a reduction in apoptosis. So, the deletion or mutation of p53 gene or inactivation of the protein product by Hmd2 can lead to the development of tumors. Jiang and al. have demonstrated in knock out mice that UV irradiation induces sooner and more skin tumors in p53 -/- and P53 +/-animals, and even ocular melanoma than in controls[49]. Mutation of p53 genes have been detected in approximately 50% of all human tumors; in basal cell carcinoma it is mutated in about 30–50% of the cases, and in a greater percentage in squamous cell cancer. Our investigation also demonstrated an increase of p53 in some proliferative dermatoses and skin tumors[15]. Recent studies have shown that in basal cell carcinoma the codon 177 have been mutated, whilst in squamous cell carcinoma the same occurred on codon 278[48]. In skin carcinomas p53 is an early mutation, whilst in melanoma it is uncommon and occur later. Experiments in UV irradiated knock out Gadd 45a mice demonstrated the importance of this protein and p53 in inducing apoptosis[50].

The patched gene PTCH., firstly discovered in the fruit fly (Drosophyla melanogaster) where it is involved in embryonic development, later in humans (9q22.3 chromosome), which germline mutation underlies the nevoid basal cell carcinoma syndrome (Gorlin syndrome), characterized by early development of numerous basal cell carcinomas, skeletal abnormalities, meningiomas, pamoplantar pits[51]. This gene is also mutaded in 30–40% of sporadic cases of basal cell carcinoma[52,53]. It also presents C-T and CC-TT transitions characteristic for UV induced damage. PTCH is also a suppressor gene and if the mutation is not corrected, the product, a transmembranous protein, cannot inhibit the activation of another transmembranous protein, the smoothened (SMO), and consequently the hedgehog signaling pathway with activation of the gli2 trancription factors in the nucleus which upregulates antiapoptotigc genes (bax). In transgenic mouse strains, it has been demonstrated that mutated or inactivated PTCH cannot control the cell cycle and lead to apoptosis. Naturally, mutations of PTCH and /or SMO favour the cells' growth, proliferation and cell survival, and the development of basal cell carcinoma[54–56]. In the development of squamous cell cancer the sonic-hedgehog signal pathway plays no role, but p53, which is present even in actinic keratoses.

The activation of a protooncogene is dominant: change in one allele has effect and can stimulate growth or proliferation of the cell. In humans oncogenes are genes of the ras family, which encode a membrane protein. Their activation occurs by point mutations in DNA. Studies with amplification by PCR, have found activated ras sometimes in basal cell carcinoma, squamous cell carcinoma and melanoma[57,58].

The development of melanoma commonly is stepwise: nevus, dysplasia, radial growth phase, vertical growth, and metastasis. In familiar melanoma patients carry germ line mutation in the locus cyclin dependent kinase inhibitor 2A gene (CDKN 2A) on the chromosome 9p21. It encodes two supressor proteins p16 (inhibitor kinase 4A-INK4A) and p14 or Arf (alternative reading frame)[59–61]. The p16 function is to inhibit the complexing ciklin-CDK4 and 6 and consequently the phosphorilation of pRB, release of E2F which drives the G1 in S phase of the cell cycle. Sometimes the mutation of this gene has been found also in sporadic cases of melanoma, some with C-T transitions[62]. Experiments in transgenic mice have shown the inactivation of retinoblastoma/p16 pathway, which lead to development of melanoma[63]. The function of p14 is to sequester the Mdm2, increasing so the regulatory p53 activity. A recent international study by Curtin et al. on 126 cases of melanoma has demonstrated that in mucosal and acral melanomas there is commonly a loss of the CDKN2A locus[64]. Another DNA

mutation found in melanoma, but also in naevi is BRAF, which is present in approximately 50% of the cases, and is the most frequently mutated gene in this tumor, especially on the non sun exposed areas (trunk, legs). It is a protooncogene that activates the MEK family[59]. In 25–50% of non familiar melanoma is inactivated by mutation or deletion the suppressor gene phosphatase and tensin (PTEN), which is located on chromosome 10q and encodes a phosphatase. Mutation of BRAF and PTEN occur frequently together[59]. In recent years, there has been much concern for humans regarding solar or artificial UVA in the induction of melanoma[65].

Recent studies suggested that telomerase is highly expressed in more than 85% of cancer cells, including melanoma, but not in the normal somatic cells [66]. Telomerase is a ribonucleoprotein that is responsible for maintaining telomeres length on the end of the chromosomes[66–67]. The role of telomere is to protect chromosomes from degradation and from aberrant recombination during replication prolonging the life span of the cell. This enzyme is mainly repressed in human cells, resulting in progressive loss of telomeres and shortening of the chromosome with successive cell divisions. Finally, chromosomes reach a critical length at which cell division ceases, senescence begins, and the cell ultimately undergoes apoptosis or cell death. It has been suggested that telomerase plays a role in anti-tumor immunity in cancer patients leading to insufficient host reaction to tumor and its progression[68].

Telomerase reverse transcriptase has been shown to induce CTL response direct against hTERT-positive tumor cells resulting in cell death. Since human T cells express hTERT upon activation hTERT- specific CTLs could also mediate killing of activated T cells in an auto-immune manner leading to decrease absolute counts of T lymphocyte subset and altered lymphocyte homeostasis in patients with carcinoma. We hypothesized these mechanisms to overwhelm apoptosis and initiate proliferation of melanoma cells[69].

Immunosuppression

Thirty years ago Kripke and al. demonstrated in UV irradiated mice the importance of the immune response in the carcinogenesis[70]. She found that UV induced skin tumors were highly antigenic and rejected when transplanted in syngenic mice. However, the transplanted tumors grow progressively if the recipients were exposed to UVR, and this effect was transferable to other animals with T lymphocytes[71,72]. This observation led to the hypothesis that UVR suppressed the immune system both locally and systemically[73,74]. So, UVR inducing immunosuppression interferes with immunological mechanism of tumor immunosurveillance[73]. UV radiations (UVA and UVB) induce DNA damage, particularly photoproducts which trigger immunosuppression: alter antigen presentation, depletion of Langerhans cells from the epidermis, as they are more sensitive to UVR than keratinocytes, emigration to the regional lymph nodes, and the induction of regulatory T cells[75–78]. The result is down-regulation of the cellular immune response such as induction and elicitation of contact hyper sensitivity, and also an inhibition of NK cell activity. However, the humoral part of the immune response is not alterated. These immunodepressive effects contribute to cancer development as the cellular immune mechanisms can destroy tumor cells, whilst on the other side UVR also induces in keratinocytes expression of perforin and granzymes and may aquire cytotoxicity against other cells[79].

Many molecules have been suggested as potential mediators of immunosuppression. While some authors believe the damage of DNA is the primary cause of immunosuppression, others link it to the presence of the chromophore transuranic acid in the stratum corneum, which upon UVR exposure isomerizes in the cis configuration that has immunosuppressive action[80–82]. This was proved with antibody against cis trans uranic acid[83]. Some also think that exposure to UVR promotes formation of free radicals and membrane lipide peroxydation which can lead to immunosuppression. Finally, there is the possibility that upon UV irradiation of keratinocytes, they release neuropeptids and the alpha melanocyte stimulating hormone (MSH) which present immunomodulatory effects[83,84]. This has been demonstrated in mice to which áMSH was applied topically or intravenously before the sensitization with contact allergens. The animals were not sensibilized, but developed specific tolerance[85]. Most of the studies of UVR induced immunosuppression have been made in vitro or in rodents using UVB; there is data that UVA can also induce immunosuppression in men and mice, and the application of UVA sunscreen abrogates this[86]. Epidemiological data of skin cancer in patients on immunosuppressive therapy supports this hypothesis[87,88], and experiments in rodents as well as the use of sunscreen confirmed this.

Patients with psoriasis may be at high risk to develop precancerous lesions and skin cancer because they use UVR, PUVA, immunosuppressive drugs, tars in the treatment, but it is of great interest that rarely cancer develop on the site of psoriatic lesions. It may be that the presence of TNF , INF in the lesions drive the keratinocytes to senescence and growth arrest.

In conclusion, we can say that epidemiological, experimental and molecular studies strongly suggest that UVR induces skin tumors, and photocarcinogenesis and immunosuppression are linked and induced by UVR damage of the DNA. The field of photobiology is rapidly enlarging and further investigation will clarify and lead to a better understanding of photocarcinogenesis and allowing new treatments of cancer. Today, public information and photoprotection can help in avoiding skin cancer.

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FOTOCARCINOGENEZA – MOLEKULARNI MEHANIZMI

S A Ž E T A K

Uloga sunčanih zraka u nastanku tumora kože (fotokarcinogeza) utvrđena je prije jednog stoljeća. Brojne eksperimentalne studije zadnjih decenija ukazale su na ulogu UV zračenje u oštećenju DNA, pojavi mutacija gena što dovodi do nastanka malignih tumora kože kao što su bazaliomi, spinaliomi i melanomi. Ovi se tumori češće razvijaju u osoba svjetlije puti. Mutacije inducirane UV zrakama nastaju tipično na dipirimidinskim dimerima s C-T i CC-TT s duplim mutacijama. Autori ukratko iznose svoja istraživanja p53 supresorskog gena i pretpostavku o ulozi hTERT u kancerogenezi. Posebice, ukazuju na ulogu UV zraka na pojavu imunosupresije i njenom značenju u nastanku tumora. Psorijatični bolesnici su tijekom života izloženi u svrhu liječenja UV zrakama i drugim kancerogenima. Bolje razumijevanje mehanizama fotokarcinogeneze može koristiti u pronalaženju novih načina liječenja kožnih tumora.