The dark side of the light: mechanisms of photocarcinogenesis

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Abstract Ultraviolet radiation (UVR) can have a beneficial biologic impact on skin, but it is also the most significant environmental risk factor for skin cancer development. Photocarcinogenesis comprises a complex interplay between the carcinogenic UVR, skin, and the immune system. UVB is absorbed by the superficial skin layers and is mainly responsible for direct DNA damage, which, if unrepaired, can lead to mutations in key cancer genes. UVA is less carcinogenic, penetrates deeper in the dermis, and mainly causes indirect oxidative damage to cellular DNA, proteins, and lipids, via photosensitized reactions. UVR not only induces mutagenesis, altering proliferation and differentiation of skin cells, but also has several immunosuppressive effects that compromise tumor immunosurveillance by impairing antigen presentation, inducing suppressive cells, and modulating the cytokine environment. This review focuses upon molecular and cellular effects of UVR, regarding its role in skin cancer development.
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Introduction

Exposure to ultraviolet (UV) light is essential to life and beneficial for human health. Phototherapy uses the properties of ultraviolet radiation (UVR) to treat several human diseases; however, UVR can also have acute and chronic harmful effects on skin, from sunburn and photoaging to photocarcinogenesis. There is strong epidemiologic and biologic evidence that exposure of skin to solar UVR is the most significant environmental risk factor for development of skin cancer (nonmelanoma as well as melanoma), accounting for approximately 93% of all cases.[1] Intermittent UV exposure early in life is associated with basal cell carcinoma (BCC), the most common form of non-melanoma skin cancer (NMSC), comprising 80% of skin cancers (Figure 1).[2] Squamous cell carcinoma (SCC), the second most frequent NMSC, is more strongly linked to cumulative UV exposure (Figure 1). Intermittent UV overexposure and living in lower latitudes are risk factors for malignant melanoma, the deadliest form of skin cancer (Figure 1).[3]

UV light interaction with skin

Solar radiation contains UVR, visible light, and infrared radiation; the energy and wavelength of solar radiation are

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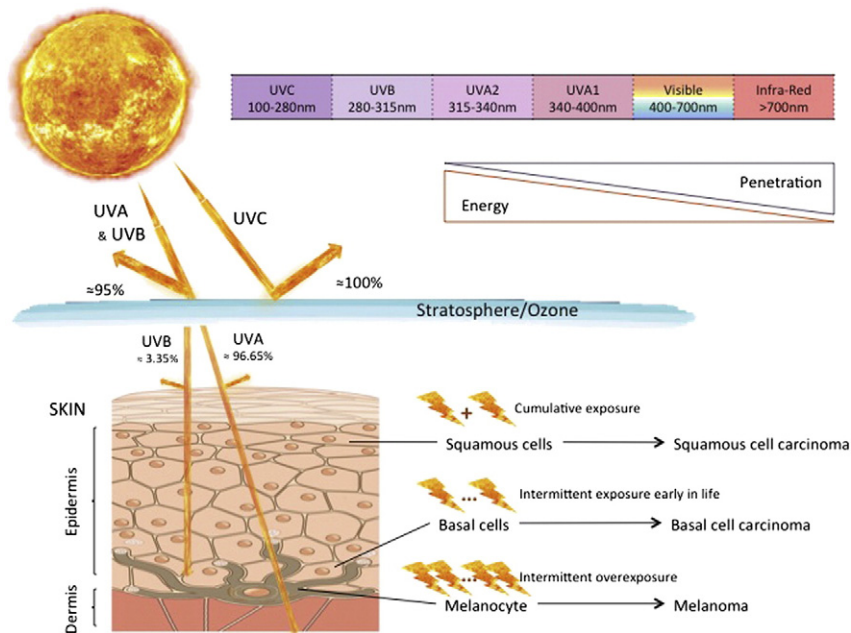(M. M. Valejo Coelho).

Fig. 1 Ultraviolet (UV) light and the skin. Solar radiation contains ultraviolet radiation (UVR), visible light, and infrared radiation, with energy and wavelength being inversely related. UVR is usually subdivided into three categories-UVA (315-400 nm), UVB (280-315 nm), and UVC (100-280 nm); UVA is further subdivided into UVA1 (340-400 nm) and UVA2 (315-340 nm). Nevertheless, UVA and UVB should be regarded as a continuum of wavelengths, with gradually changing photobiological properties. Only 5% of the radiation reaches Earth's surface in the UV range. UVR reaching the skin can be partially reflected and scattered, and when it penetrates it can be absorbed by biomolecules (chromophores). UVA reaches the deeper portion of the dermis (around1000 μm), whereas most UVB is absorbed in the epidermis or the upper part of the dermis (160-180 μm). There is strong evidence that exposure of skin to solar UVR is the most significant environmental risk factor for development of skin cancers.

inversely related (Figure 1).[4] The UV portion of the electromagnetic spectrum (100-400 nm) is usually subdivided into three categories−UVA (315-400 nm), UVB (280-315 nm), and UVC (100-280 nm)−based on their respective biologic effects; UVA is further subdivided into UVA1 (340-400 nm) and UVA2 (315-340 nm), with the latter closely resembling UVB.[5,6] UVA and UVB are regarded as a continuum of wavelengths and have gradually changing photobiologic properties.[6]

Although the sun emits large amounts of UVR, only 5% of the radiation reaches Earth's surface in the UV range (96.65% UVA, 3.35% UVB, UVC virtually undetectable) (Figure 1). The atmospheric oxygen and ozone are remarkably efficient at absorbing and attenuating the more biologically harmful bands (UVC, UVB) (Figure 1).[5,6] Despite its nonionizing nature, UVR is significantly injurious to DNA.

Skin, the largest organ of the body, is our privileged interface with the surrounding environment. It functions as an effective metabolically active defense barrier that hinders UVR from penetrating into deeper tissues, thereby protecting the rest of the organism from the deleterious effects of radiation. UVR can be partially reflected from the outer surface of the skin and scattered in various directions. When it penetrates the tissue, it can be absorbed by biomolecules. Within the skin, the depth of penetration of UVR is wavelength-dependent; thus, UVA readily

reaches the deeper portion of the dermis (around 1000 μm), whereas most UVB is absorbed in the epidermis or the upper part of the dermis (160-180 μm) (Figure 1). UVR can have biologic effects even in layers that it does not directly reach.[6] UV-absorbing molecules, the so-called chromophores, absorb photons, eliciting photochemical and photobiologic reactions, which may either change the excited chromophore directly or alter other molecules indirectly through energy transfers (by photosensitized reactions).[6] Chromophores, like melanin and DNA, are extremely well-adapted photoprotective agents, because they can transform the vast majority of UV photons into small amounts of heat that dissipates harmlessly.[5] A small percentage of photons might get through this internal conversion defense and be completely absorbed by DNA, structurally modifying it. Alternatively, a UV photon can hit a chromophore that is unable to quickly reduce it to heat and stays in an excited state for a long time, enabling reactions that indirectly damage DNA and other cell components.[5]

Mechanisms of photocarcinogenesis

The development of skin cancer is a complex phenomenon that involves the stepwise accumulation of molecular and

cellular changes over years or decades. It is typically described in three stages:

1. Initiation, which is an essentially irreversible step wherein genetic alterations occur that ultimately lead to DNA mutation;
2. Promotion, which is the clonal expansion of initiated cells;
3. Progression, which is the malignant transformation.[6,7]

Photocarcinogenesis entails the development of skin cancer as a result of the intricate interplay between UVR, skin, and the immune system. UVR is not merely a complete carcinogen[8] that acts as a tumor initiator and a tumor promoter; it is also immunosuppressive. These two remarkable properties are key to understanding the role of UVR in skin carcinogenesis.

Mutagenesis

The carcinogenic properties of short-wavelength UV light (UVB) are well established.[6] UVB is 1000-10,000 times more carcinogenic than UVA, even though less penetrating.[9] UVA is less erythemogenic and was previously believed to be harmless; however, it too has been shown to be capable of causing skin cancers.[6,10]

DNA is the main molecular target for UVB- and UVA-induced skin carcinogenesis (Figure 2).[11] The overall detrimental effect of UVR on DNA is the sum of direct and indirect mechanisms that produce multiple types of DNA damage and ultimately lead to mutation in key cancer genes participating in cell survival, proliferation, and differentiation.

Direct DNA damage

DNA photoproducts are dimers formed by the covalent bonding of two adjacent pyrimidine bases (thymine [T] or cytosine [C]) in the same polynucleotide chain due to direct absorption of UV photons.[6] The 300-nm wavelength of UVB is the most effective for inducing DNA photoproducts in the basal layer of the epidermis.[6] The three major types of bipyrimidine photoproducts are cyclobutane pyrimidine dimers (CPDs), pyrimidine-pyrimidone 6-4 photoproducts (6-4 PPs), and Dewar valence isomers (DEWs) (Figure 2).[11]

CPDs are the dimers most frequently induced by UVB (as well as by UVA, although through an indirect mechanism−see "Indirect DNA damage"); these four-membered cyclobutyl rings are observed at all possible bipyrimidine sites−the T-T dimer is the most common, followed by C-T, T-C, and finally C-C.[6,11] 6-4 PPs are induced only by UVB and are formed three- to fivefold less frequently than CPDs but are considered to be more mutagenic; they result from a covalent bond between two carbons on two neighboring pyrimidines.[6] The T-C 6-4 dimer is the most common of this type. 6-4 PPs are convertible by UVA to their related DEWs via the process of photoisomerization.[11,12]

These bulky DNA lesions can be repaired by the nucleotide excision repair (NER) system.[3,6] If not properly corrected, they are premutagenic by three conceivable models[6,11,13−16]: (1) incorporation of T opposite the altered bases by DNA polymerases that treat them as if they were an adenine (A); (2) direct lesion bypass by an error-prone DNA polymerase that incorporates an A opposite a C within the pyrimidine dimer; and (3) deamination of C within the dimer, giving rise to T or the related uracil, followed by "correct" bypass during DNA replication. These errors may precede or occur during DNA replication, and cause C→T transitions (about 70%) or CC→TT tandem mutations (about 10%) that are termed "signature mutations" for UV(B) mutagenesis, namely they are specific to this mutagen.[3,6,10,15]

Several genes involved in skin carcinogenesis carry a UV signature (Figure 2). Mutations in the tumor suppressor gene *p53* are the most common genetic abnormalities found in SCCs and in their precursors actinic keratoses[6,16,17]; the majority are C→T single-base-transition mutations at dipyrimidine sites, but CC→TT tandems have also been reported.[6,16] Chronically sun-exposed skin also harbors clonal proliferations of epidermal *p53* clones, indicating that these mutations are early events in the pathogenesis of UV-induced SCC.[6] Genes that encode proteins of the Hedgehog signaling pathway (mostly the tumor suppressor gene *Patched* [*PTCH*]), that upregulates antiapoptotic genes when activated, are the most frequently altered in BCCs,[17] and many mutations in this pathway are C→T and CC→TT transitions.[4,10] Somatic (mostly missense) *p53* mutations result in a UV-mutator phenotype and are the second most common genetic alterations found in BCCs.[15,17] Unlike that seen in SCCs, *p53* C→T mutations are generally later events in the carcinogenesis of BCCs and cutaneous melanomas, pointing to UV exposure as an initiator of skin cancers and also as a contributor to their progression.[6] Loss of p53 function impairs cell cycle arrest after UV exposure, which makes cells resistant to apoptosis, increases the likelihood that DNA will be replicated despite unrepaired UV-induced damage, and further increases the mutation frequency and susceptibility to malignant transformation.[6,17] In cutaneous melanoma, several critical genes, including *PTEN* and *CDKN2A*,[6] also carry C→T transitions, thus providing molecular evidence for the significant role of UV exposure in the development of melanoma.

Melanomas in intermittently sun-exposed sites also show a high frequency of T:A→A:T mutations of *BRAF* at one particular site (amino acid substitution V600E), suggesting the occurrence of another type of UV-induced mutation that is not yet fully understood.[6]

Indirect DNA damage

Unlike UVB, the less energetic UVA radiation is very weakly absorbed by DNA; rather, UVA may be absorbed by other endogenous chromophores such as cytochromes, flavin, heme, NAD(P)H, porphyrins, and collagen crosslinks.[18,19] Its genotoxic and cytotoxic actions are the result of photodynamic effects that are strongly oxygen-dependent (Figure 2).[6,12−14,18] Once UVR is absorbed, mutagenic oxidative reactions
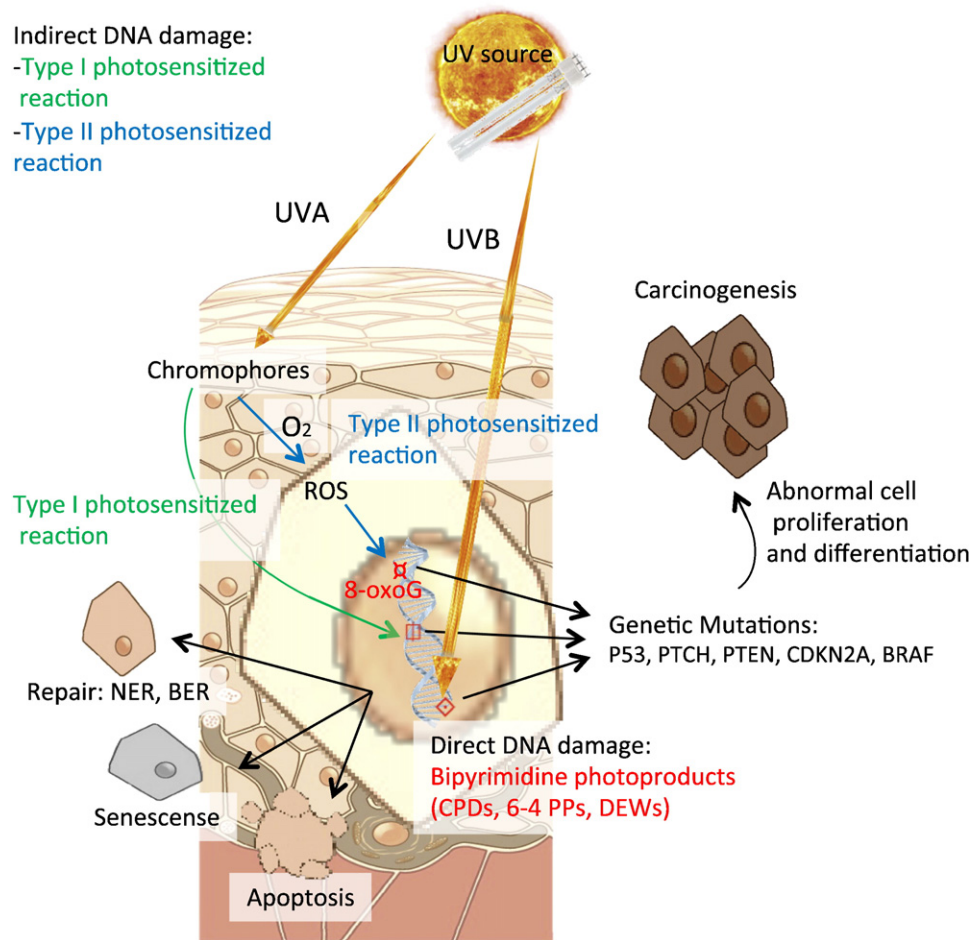
Fig. 2 Ultraviolet (UV) light-induced mutagenesis as a mechanism of photocarcinogenesis. DNA is the main target for UVB- and UVA-induced skin carcinogenesis. Direct DNA damage: DNA acts as a chromophore. UVB is the most effective wavelength for inducing DNA photoproducts. The three major types of photoproducts are cyclobutane pyrimidine dimers (CPDs), pyrimidine-pyrimidone 6-4 photoproducts (6-4 PPs), and Dewar valence isomers (DEWs). These DNA lesions can be repaired by the nucleotide excision repair (NER) system; if not repaired, they are pre-mutagenic. Significant genes in skin carcinogenesis include the tumor suppressor gene p53 (the most commonly mutated in squamous cell carcinomas); genes encoding proteins of the Hedgehog signaling pathway, mostly the tumor suppressor gene Patched (PTCH) (the most commonly mutated in BCCs); and PTEN, CDKN2A, and BRAF (commonly mutated in cutaneous melanoma). Indirect DNA damage: UVA is mainly absorbed by other chromophores that trigger mutagenic oxidative reactions. In type I reactions, the energy is directly transferred to DNA, whereas in type II the energy is transferred to molecular oxygen and then the reactive oxygen species (ROS) are able to damage DNA. The mutagenic 7,8-dihydro-8-oxoguanosine (8-oxoG) is a typical oxidative DNA lesion that emerges from type II reactions, which can be repaired by the base excision repair (BER) mechanism; if unrepaired, it is also mutagenic. Mutated genes can lead to abnormal cell proliferation and differentiation as part of the carcinogenesis process.

between the excited chromophores and cellular DNA may be triggered via two main mechanisms[6,12−14,18]: In type I photosensitized reactions the energy is directly transferred to DNA, whereas in type II photosensitized reactions the energy is transferred to molecular oxygen, with DNA damage occurring via ensuing reactive oxygen species (ROS).

A photosensitized triplet energy transfer from an UVA-excited chromophore to DNA bases−type I reaction−is likely the major process of CPD formation subsequent to UVA irradiation.[6,12,18] Unlike the direct excitation of DNA by UVB, the UVA-mediated oxidative mechanism generates CPDs (predominantly T-T dimers) but not 6-4 PPs.[12,18,20] Notably, a recent report about a chemiexcitation mechanism, which

points to melanin as the culprit that links the UV-induced generation of ROS and reactive nitrogen species to DNA damage, suggests that melanin (in particular, pheomelanin) may be carcinogenic despite also being protective against UV-induced skin cancer.[21]

The combination of UV-induced superoxide and excess nitric oxide generates the powerful oxidant peroxynitrite, which degrades melanin to dioxetane-containing lipophilic fragments that can move to the nucleus; dioxetane decomposition then generates a moiety in an electronically excited triplet state, which is capable of transferring its high energy to pyrimidine DNA bases in a radiation-independent manner, and can give rise to the so-called "dark CPDs" for at least 3 hours after

UVA exposure. Because the induction of dark CPDs is crucially dependent on melanin content rather than synthesis,[21] these can contribute to UVR genotoxicity in both melanocytes and keratinocytes, thereby contributing to the risk of melanoma and NMSC.

Type II photosensitized reactions are also detrimental, although to a much lesser extent than type I reactions.[12,20] The mutagenic 7,8-dihydro-8-oxoguanosine (8-oxoG) is a typical oxidative DNA lesion that emerges from the singlet oxygen-mediated oxidation of guanine (G), because this is the base with the lowest oxidation potential and hence the preferential target of photooxidation reactions (Figure 2).[6,22] In contrast to bulky pyrimidine dimers that can only be repaired by NER, this non-bulky oxidative DNA base modification can be processed by a very efficient base excision repair (BER) mechanism, initiated by the enzyme 8-oxoguanine DNA glycosylase-1 (OGG1).[6,23] When unrepaired, 8-oxoG is expected to cause GC→TA or AT→CG transversions in DNA.[12,20,23]

Accounting for an estimated 92% of melanomas,[24] the role of indirect DNA damage in photocarcinogenesis, mostly by UVA and to a far lesser extent by UVB, cannot be overlooked.

Beyond DNA mutagenesis: damage of other molecular targets

Oxidative stress not only affects DNA, but also alters the biologic properties of membrane and cytoplasmic lipids and proteins, which then may contribute to tumor initiation, promotion, and progression.[6,15,18] UVR-induced oxidative stress causes amino acid oxidation, leading to protein carbonylation, an extreme form of irreversible protein damage and dysfunction.[23,25] For example, because loss of function of key DNA repair proteins can have serious consequences for the genomic stability of UV-damaged skin cells, protein carbonylation may be an innovative biomarker of photodamage.[23,25]

Finally, recent studies indicate that the cellular response elicited by UVR exposure is also controlled at the post-transcriptional level on an intermediate time scale that is between fast protein modifications and the much slower transcriptional reprogramming, as various miRNA expression changes are triggered differentially by UVA and UVB damage.[26–28]

Immunosuppression

Photoimmunology is the field of photodermatology that explores the complex relationship between UVR and the immune system.[29] Direct evidence that UVR acts as an immunosuppressant derives from a classic series of experiments in mice showing that UVR prevents the immunologic rejection and eradication of highly immunogenic transplanted UV-induced skin tumors.[30,31]

The immunosuppressive effects of UVR are mostly due to the medium wavelengths (UVB), but the long wavelengths (UVA) also influence immune reactions.[32,33] UVB mainly affects epidermal keratinocytes and Langerhans cells (LCs), but the ability of UVA to penetrate deeper into the dermis allows it to also impact dermal fibroblasts, dermal dendritic cells, endothelial cells, and skin-infiltrating inflammatory cells such as T lymphocytes, mast cells, and granulocytes.[34]

UVR induces antigen-specific, long-term immunosuppression.[32,33] It alters local immune responses but also causes systemic immunosuppression via the release of circulating mediators by the UV-stimulated keratinocytes.[32,33] Additionally, despite its known effects being mostly on the acquired immune system, UVR also seems to influence innate immunity.[32]

UVR-induced immunosuppression is largely responsible for the therapeutic effects of phototherapy in many inflammatory dermatoses and lymphoproliferative skin diseases.[34] However, By disturbing the mechanisms of tumor immunosurveillance, it is also involved in photocarcinogenesis.

Molecular targets

Nuclear DNA is a preferential chromophore for UVB, and its UV-induced damage (eg, CPD formation) is considered a major molecular trigger, critically responsible for signaling photoimmunosuppression.[23,29,32,33,35] Topically applied exogenous DNA repair enzymes can prevent the immune system suppression induced by UVR.[36]

UVR also affects cytoplasmic and membrane targets acting as additional photoreceptors for UVR-induced immunosuppression.[33] Trans-urocanic acid (UCA), present in large amounts in the stratum corneum, is an epidermal chromophore that undergoes photoisomerization to its cis-UCA conformation upon UV exposure; cis-UCA, whose receptor is 5-HT_{2A}, is involved in skin photocarcinogenesis by acting as a mediator of UV-induced immunosuppression.[29,32,33,35,37] Membrane phospholipids absorb UVR and lead to lipid peroxidation and transcription factor activation, favoring cytokine release and contributing to immunosuppression.[4,38,39] UVR exposure promotes oxidative stress, which induces not only DNA damage, but also the production of oxidized phospholipids, including platelet-activating factor (PAF).[35] PAF, secreted by keratinocytes almost immediately after UV exposure, is a lipid mediator of inflammation, being involved in photoimmunosuppression and photocarcinogenesis.[35,40]

Mechanisms and effects

UVR mediates its immunosuppressive effects by a myriad of processes, including the disturbance of skin antigen presentation, the induction of cells with suppressive activities, and the modulation of cytokines and other soluble mediators.[29]

Altered antigen presentation. Skin contains several populations of antigen-presenting cells (APCs), including epidermal LCs, different types of dermal dendritic cells, and migrating immunosuppressive macrophages/monocytes recruited into the dermis and epidermis upon UV stress.[15,29] Exposure of skin to UVR results in a profound depletion of LCs, the major APCs within the epidermis, by induction of their

apoptotic death and/or cell migration out of skin.[32] UV-induced DNA damage is the molecular trigger for the migration of LCs.[41]

Viable photodamaged LCs are still capable of reaching the regional draining lymph nodes, but their capacity to present antigens to T cells is altered.[32] UVR impairs the antigen-presenting function of APCs directly by inducing unrepaired DNA damage and cytotoxicity, and indirectly by stimulating the production of immunosuppressive mediators (eg, interleukin-10 [IL-10]) by keratinocytes and macrophages. Inhibition of expression of intercellular adhesion molecule-1 (ICAM-1) by UVR may be responsible for the impaired adherence between LCs and lymphocytes.[32] The deleterious influence of UVR on effector T-cell activation contrasts with the induction of regulatory T cells (T_{reg}) by photodamaged LCs, resulting in antigen-specific immunotolerance rather than sensitization.[32,42,43] It leads to an immunosuppressive positive feedback loop, where T_{reg} negatively influence antigen presentation to effector T cells.[29] UV exposure also affects LCs' capacity to stimulate different subsets of $CD4^+$ T-cell clones; this results in preferential suppression of T_{h1}-mediated immune responses.[32,44]

Induction of regulatory cells. Antigens present in the skin, including skin tumor epitopes, are taken up by cutaneous APCs, a necessary precondition for the generation of effector and regulatory T lymphocytes; cell-mediated immune responses reflect the balance between these T cell types with opposite effects.[29] After UV exposure, the generation of T_{reg} upon the encounter of an antigen proceeds unimpeded and their homing-receptor pattern is altered to favor migration into the skin,[45] whereas the number of effector T cells diminishes.[29] The imbalanced increase of T_{reg}, expressing their phenotypic markers $CD4^+$, $CD25^+$, $CTLA4^+$, $FoxP3^+$, and secreting IL-10, leads to a suppressed immune response.[29,46,47] This shift from T-cell-mediated immunity to immunosuppression favors tumor growth.[46] In addition, UV-induced natural killer T cells appear to be involved in the suppression of antitumor immunity,[32] namely by producing the T_{h2} cytokine IL-4.[48] Other UVR-activated immune cells producing IL-10, such as mast cells and regulatory B cells, might also play a part in photoimmunosuppression, but their role is not clearly established.[33]

Favoring of immunosuppressive mediators. UVR stimulates the production of a variety of cytokines by transformed cytotoxic keratinocytes and immune cells.[4,29,32] These anti-inflammatory and/or immunosuppressive products enter the circulation and inhibit immune responses at areas of skin not directly exposed to UVR (systemic immunosuppression).[32]

Among these UV-induced mediators, the major player of immunosuppression appears to be IL-10, a T_{h2} cytokine. Released by UV-irradiated keratinocytes in response to the formation of CPDs or cis-UCA,[49] macrophages migrating into UV-irradiated skin, and UV-induced T_{reg}, this cytokine acts on LCs, abrogating their ability to present antigens and inducing immunologic tolerance.[29,32] IL-10 enhances the proliferation of T_{reg}, while suppressing T-cell-mediated defense mechanisms, facilitating the growth of UV-induced skin tumors.[29] It also inhibits T_{h1} immune reactions, while favoring a T_{h2} shift.[29,32] The resulting cytokine discrepancy may be responsible for the photoimmunosuppression. Interestingly, SCCs and BCCs show a predominance of T_{h2}-type cytokines, such as IL-10 and IL-4.[46]

Transforming growth factor-β, another immunosuppressor increased by UVR exposure, has an important role together with IL-10 in suppressing T-cell cytotoxic activity and favoring T_{reg}.[46]

Prostaglandin E_2(PGE_2), cis-UCA, PAF, serotonin (5-HT), tumor necrosis factor-α, and neuropeptides, such as calcitonin gene-related peptide and α-melanocyte stimulating hormone, are also players in UV-induced immunosuppression.[29,32] Many of these UV-induced agents activate ROS synthesis, producing their immunosuppressive effects by damaging DNA and interfering with its repair, thus establishing a strong mechanistic link between inflammation and carcinogenesis.[29,35] Others upregulate UV-inducible genes, such as cyclo-oxygenase 2, that can also enhance the synthesis of other immunosuppressive mediators such as the prostanoid PGE_2 by keratinocytes and LCs.[29,32–35]

In contrast, UVR exposure lessens the production of immunostimulatory molecules, such as IL-12 and IL-23.[46] IL-12, a cytokine secreted by epidermal LCs and keratinocytes,[41] is regarded as a counterbalance to IL-10.[32] It promotes T-cell-mediated immunity by supporting the production of effector T cells that secrete the proinflammatory interferon-γ, favoring T_{h1} immune responses.[29] The most relevant effect of IL-12, shared by the structurally related IL-23, is probably their capacity to induce the NER system of DNA repair, thereby accelerating the removal of UV-induced DNA lesions (CPDs).[41,50] After UVR exposure, skin dendritic cells, for instance, exhibit a diminished capacity to synthesize IL-12 and, consequently, repair their photodamaged DNA.[29] Considering their protective role against the major molecular triggers of photocarcinogenesis, the downregulation of the interleukins IL-12 and IL-23 by UVR can also contribute toward skin cancer development.[32,41,50]

Conclusions

Skin carcinogenesis is a stepwise, complex process in which UVR is a recognized complete carcinogen. The myriad of molecular changes induced by UVB and UVA ultimately trigger mutagenic events that lead to altered skin cell proliferation and differentiation as well as immunosuppression, two key conditions for the development of cutaneous neoplasms.

The accumulation of irreversible skin cell photodamage, under impaired tumor immunosurveillance, explains the

increased risk of skin cancer associated with natural UV light exposure and justifies the concern about the carcinogenic potential of phototherapy using artificial UVR.

Conflicts of interest

The authors declare no conflict of interest.

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