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The dark side of the light: mechanisms of photocarcinogenesis

Margarida Moura Valejo Coelho, MD, MSc[a,*], Tiago R. Matos, MD, MSc[b,c], Margarida Apetato, MD[a]

[a]*Department of Dermatology and Venereology, Centro Hospitalar de Lisboa Central, Lisbon, Portugal*
[b]*Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA*
[c]*Department of Dermatology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands*

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.

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

Institutional address: Department of Dermatology and Venereology, Centro Hospitalar de Lisboa Central, Alameda de Santo António dos Capuchos, 1169-050 Lisbon, Portugal.
* Corresponding author. Tel.: +351-917-737-546.
E-mail address: margarida.m.v.coelho@chlc.min-saude.pt (M. M. Valejo Coelho).

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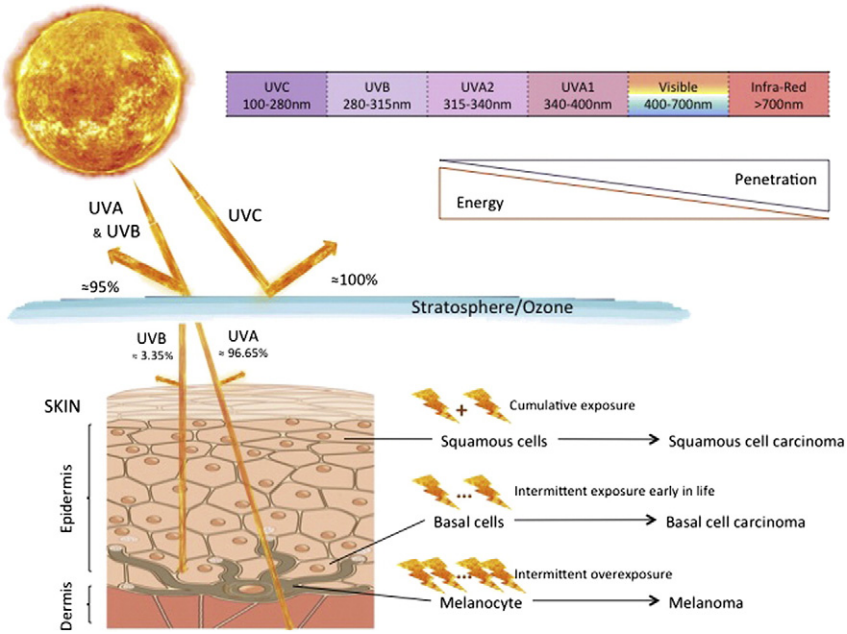

Fig. 1 Ultraviolet (UV) light and the skin. Solar radiation contains ultraviolet radiation (UVR), visible light, and infrared radiation, with energy and wavelength being inversely related. UVR is usually subdivided into three categories-UVA (315-400 nm), UVB (280-315 nm), and UVC (100-280 nm); UVA is 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