Oxidative-Stress-Sensitive microRNAs in UV-Promoted Development of Melanoma

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Contributor: Alessandra Pecorelli, Giuseppe Valacchi

Exposure to ultraviolet (UV) rays from the sun is one of the most important modifiable risk factors for skin cancer. Melanoma is the most life-threatening type of skin cancer. UV-induced DNA damage and oxidative stress represent two main mechanisms that, directly and indirectly, contribute to melanomagenesis.

Keywords: skin cancer ; sunlight ; redox imbalance ; miRNome ; mutations

1. Introduction

Melanoma and nonmelanoma skin cancers represent the most common malignancies in white populations [1]. Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the prevalent forms of malignant skin cancers that develop from keratinocytes. Melanoma, which originates from melanocytes, is less common than keratinocyte skin cancers, accounting for only about 1–2% of all skin tumors, but it is the most aggressive and lethal type [1][2].

Over the past few decades, the overall rate of skin cancers has been growing worldwide, especially in fair-skinned populations [1][2]. The increased incidence can be related to more efficient and sensitivity diagnostic tools leading to an early detection combined with other factors including changes in individual and social behaviors—e.g., an increase in outdoor activities and different clothing style preferences—and a longer life expectancy accompanied by larger elderly populations [1][2]. In this context, the interaction between unprotected exposure to ultraviolet (UV) rays and genetic susceptibility represents the most important risk factor for skin cancers, as indicated by many epidemiological studies [3][4].

Melanoma results from malignant transformation of melanocytes, which are cells derived from the neural crest that are characterized by the ability to produce the pigment melanin. Melanoma incidence has been steadily increasing over the past few decades, and today it represents the fifth most commonly diagnosed malignancy in the United States. White individuals have a higher probability of developing melanoma than other racial/ethnic groups. In addition, the incidence rises with age, being frequently diagnosed among people aged 65–74, especially in men [5][6].

Melanoma can develop de novo or arise from pre-existing lesions such as congenital or acquired nevi. In addition, melanoma most often occurs on habitually sun-exposed sites of our skin, but it is also found in sun-protected areas including the palm and sole. It is more prone to appear on the trunk (chest and back) in males and on the lower legs in females. Moreover, less common melanoma subtypes can emerge from melanocytes residing in meninges, uvea, and mucosal membranes. Based on clinical and histological features, melanomas are classified into four main subtypes: superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, and acral lentiginous melanoma [7]. Two growth phases commonly characterize the development and progression of melanoma. During the initial radial growth phase, neoplastic melanocytes slowly grow horizontally within the epidermis and sometimes within the papillary dermis. In the vertical growth phase, transformed melanocytes proliferate vertically, invading the dermis and subcutaneous tissue and acquiring a metastatic phenotype [7].

Several signaling pathways have been associated with abnormal proliferation, growth, survival, migratory, and invasive properties of neoplastic melanocytes. In particular, among the underlying molecular aberrations characterizing melanoma and its etiology, the most frequent molecular changes involve genetic mutations of *CDKN2A*, *CCND1*, *CDK4*, *MITF*, *c-KIT* and *MC1R* genes; dysregulation of mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)-Akt pathways; aberrant p53, STAT3, NRF2, NFκB, cadherin, and Wnt signaling pathways; and epigenetic alterations [8][9][10][11][12]. Ultimately, a complex and intricate connection between these aberrant signaling pathways and genetic abnormalities leads to a cascade of molecular events promoting uncontrolled melanocyte growth, proliferation, differentiation, migration and greater cell survival, resistance to apoptosis, invasion, and metastasis, which collectively promote tumorigenesis [8][9][10][11][12].

Important risk factors for the development of melanoma could fall under the concept of the exposome, representing the totality of exogenous exposures that individuals experience over the course of their lives, including geographic residence and pollutome [13][14][15]. In addition, host risk factors such as skin phototype or ethnicity, number of nevi (both congenital or acquired), genetic susceptibility, family history of melanoma, and immunosuppression can interact with environmental components to promote melanomagenesis [13][14][15]. Among the exposome components, certainly the exposure to UV radiation, particularly a history of intense intermittent sun exposure, represents the most important exogenous factor for the development of skin cancers, including melanoma [13][14][15].

2. Ultraviolet Radiation

UV rays are a form of electromagnetic radiation emitted from sunlight and a variety of artificial sources including tanning devices, some lasers, and several types of lamps (i.e., fluorescent, halogen, and incandescent lights). UV rays are categorized according to their wavelengths into UVA (320–400 nm), UVB (280–320 nm), and UVC (100–280 nm).

Depending on their energy level and the ability to remove or excite electrons in atoms or molecules, causing damage to living tissues, UV rays are divided into ionizing and nonionizing radiation. In this regard, higher-energy UVC rays, which have the shortest wavelengths, are extremely harmful to the skin and eyes. However, they are almost completely absorbed by the ozone layer in the stratosphere; therefore, the only potential detrimental health effect of UVC can arise from the exposure to some UVC lamps and lasers. Stratospheric ozone also protects us from most of the short wavelengths in the UVB band, while less energetic UVA radiation almost completely reaches the Earth's surface without being absorbed by the atmosphere. Accordingly, solar UV rays reaching the ground level comprise approximately 95% UVA and 5% UVB. In this context, it is worth mentioning that depletion of the stratospheric ozone layer due to global environmental changes is likely to have serious impacts on human health in terms of UV exposure within the near future [16]. Furthermore, the growing popularity of artificial tanning, especially among young women, represents another dangerous practice that can increase the risk of skin cancer, in particular when the first exposure is before the age of 35 years.

Concerning the biological effects on exposed human tissues, UVA and UVB rays exhibit both similar and specific attributes. In addition, another important difference is related to the acute (short-term) or chronic (long-term) health outcomes of the UV exposure [17]. All these aspects will be discussed in more detail in the next section. Lastly, although unprotected exposure to UV radiation can cause damage not only to the cutaneous tissue but also to the eyes and even modulate the activity of central nervous, endocrine, and immune systems [18], researchers will focus on describing its harmful effects on the skin, particularly related to the increased chance of developing melanoma.

3. Beneficial and Adverse Health Effects of Sunlight

Sunlight is an essential prerequisite for life on Earth, providing necessary light and energy. However, the shortwave component of sunlight, namely the UV radiation, can have both beneficial and deleterious effects on humans and other living organisms, depending on a combination of different aspects including wavelength (UVA, UVB, or UVC), irradiation dose (intensity x duration), and size of the exposure [19][20].

Among the positive benefits associated with sunlight, especially UV light, the best known is the cutaneous synthesis of vitamin D that begins with the conversion of its precursor 7-dehydrocholesterol to previtamin D3 through a photochemical reaction triggered by UVB rays [21][22]. By regulating the expression of more than 1000 target genes, this essential nutrient and hormone is involved in multiple physiological functions, including support of bones, muscles, and the immune system. Moreover, vitamin D also may be implicated in reducing inflammation and infection rates and in preventing diseases such as some cancers, cardiovascular disease, diabetes, and mood disorders, as well as dermatological conditions [22][23][24][25].

In most cases, the positive effects of sunlight on human health are ascribed to vitamin D's properties; however, it has become increasingly evident that regular solar exposure may be beneficial to human conditions through the action of additional mechanisms. They are related to the UV-stimulated production and release of mediators such as serotonin, endorphins, and melatonin, as well as antimicrobial peptides (AMPs), nitric oxide released from the cutaneous stores, and carbon monoxide from hemoglobin [22][25][26][27]. In this context, phototherapy approaches have been developed to mimic the benefits of sunlight exposure by using a controlled administration of UV radiation to treat skin conditions characterized by localized inflammation due to an overreaction of the immune system including psoriasis, vitiligo, severe eczema, atopic dermatitis, and mycosis fungoides [28].

While humans can benefit from regular exposure to physiological doses of UV light, on the other hand, intermittent intense (short-term) exposures together with chronic (long-term) exposures to UV radiation are usually associated with important adverse health effects. Short-term overexposure to UV is mainly linked to erythema, photodermatoses, tanning, photokeratitis, and photoconjunctivitis, as well as a local and systemic immunosuppressive effect with increased incidence and severity of infectious diseases [29][30][31][32][33][34]. Instead, chronic exposure to UV radiation promotes premature skin aging; increases the risk of skin cancer (melanoma and nonmelanoma); is responsible for cataracts, pterygium, and ocular melanoma; and finally, potentiates various autoimmune diseases and activates some viral diseases [17][20][32][34][35].

Interestingly, both the physiological and pathological changes induced by sunlight, and specifically by UV light, may be related to similar underlying molecular and cellular mechanisms, which will be detailed in the next section. What determines the switch from the appearance of physiological responses to the development of pathological manifestations is the extent of induction of these processes.

4. Molecular Mechanisms of UV Damage to Skin Tissue

As mentioned above, among the three different types of UV, the shorter-wavelength UVC rays could be the most harmful to living organisms. However, as they are blocked by the Earth's ozone layer, their damaging effects on human health are only related to artificially created UVC used in specific applications such as, for example, in germicidal irradiation, or produced by artificial sources such as lasers and mercury lamps. Unlike UVC, natural UVB and UVA bands are not completely absorbed in the atmosphere and reach the Earth's surface in a proportion of approximately 5% UVB and 95% UVA of the total UV energy. Moreover, another important source of UVA and UVB able to impact skin is represented by the growing trend in indoor tanning habits in combination with poor knowledge or awareness of the associated skin health risks.

The depth of penetration of the different UV rays into the skin depends on the wavelength, with the longest UVA rays able to penetrate much deeper into the skin than UVB and UVC. Indeed, UVC light is barely able to penetrate the skin's outermost layer, while UVB penetrates completely through the epidermis and marginally into the papillary dermis. Conversely, UVA affects the full thickness of the dermis, both the papillary and reticular layers, including the underlying subcutaneous tissue [18][36].

In general, UVA rays are considered less harmful than UVB due to their lower energy levels. Nevertheless, as mentioned above, they are more abundant in natural sunlight and more penetrating than UVB rays; therefore, UVA light is not exactly innocuous. In fact, thanks to their ability to penetrate into the dermis and induce damage to collagen and elastin, UVA rays are the main cause of skin photoaging, wrinkles, and loss of elasticity. On the other hand, UVB light is mainly associated with erythema, edema, immunosuppression, and skin cancer. Furthermore, based on recent observations, UVA rays have also been recognized as carcinogenic due to their immunosuppressive and mutagenic properties [37].

Regarding the molecular mechanisms of UV-induced injury, both UVA and UVB can produce adverse biological effects by targeting, directly and indirectly, cutaneous biomolecules such as DNA, proteins, and lipids. In fact, the damage can result from a direct adsorption of UV photons by different macromolecules, which results in lesions that alter their structure and function [38][39][40][41][42]. In particular, DNA is one of the main UV chromophores in the cutaneous tissue, and its direct UV absorption leads to photochemical reactions with the formation of two major types of DNA lesions such as cyclobutane pyrimidine dimers (CPD) and pyrimidine-pyrimidone (6–4) photoproducts (6–4PP). Moreover, UV light is absorbed by other cutaneous non-DNA chromophores such as urocanic acid, melanin and its precursors, heme and bilirubin, porphyrins, amino acids (i.e., tryptophan, tyrosine, phenylalanine, histidine, and cysteine), and carotenoids. Photon absorption by these non-DNA chromophores changes their molecular structure and induces formation of photoexcited states able to transfer the excitation energy to other interacting molecules with the generation of free radicals, ROS, and other toxic photoproducts that, in a vicious circle, propagate the photochemical damage to DNA and the other macromolecules within the cutaneous tissue [38][39][40].

Moreover, UVB and mainly UVA radiation can also lead to an indirect oxidative-mediated damage of cutaneous macromolecules by stimulating ROS/RNS (reactive nitrogen species) production through enzymatic reactions catalyzed by enzymes such as NADPH oxidase, cyclooxygenase, and xanthine oxidase, or by the involvement of mitochondria [38][39][40]. When UV-stimulated ROS target DNA molecules, various types of oxidative DNA lesions are induced, including DNA single-strand breaks, DNA–protein crosslinks, and altered DNA bases. In particular, the oxidation of the guanine bases, which produces 8-oxo-7,8-dihydroguanine (8-oxoG), is the most abundant form of oxidative DNA damage. Furthermore, UV-induced ROS also attack other major biomolecules, causing protein oxidation and lipoperoxidation that compromise cellular ultrastructure and function [38][39][40]. In this regard, it is worth mentioning that melanocytes are more

vulnerable to UV-mediated oxidative injury than other skin cells, since their specialized function, namely the melanin synthesis, is an energy-consuming process that itself contributes to generating a large amount of ROS.

Through these direct and indirect effects on the cutaneous biomolecules, UVA and UVB are able to induce a cascade of other molecular and cellular signaling interactions that include, among others, activation of transcription factors, altered gene expression, changes in the cell cycle, induction of inflammatory responses, cellular senescence, and apoptosis [17]. Furthermore, through bystander signaling mechanisms involving the release of microvesicles and exosomes, UV radiation can propagate dangerous molecular signals from the irradiated cells to neighboring nonhit cells through the extracellular space, causing further diffusion of harmful mediators able to fuel OxInflammatory phenomena into the cutaneous tissue [43][44][45][46].

Altogether, these UV-triggered molecular and cellular signaling events have a profound impact on the cutaneous tissue, as they are able to produce both physiological and pathological effects. Indeed, as previously stated, the same mechanisms stimulating, for example, the production of vitamin D and AMPs can also promote the development of premature skin aging and carcinogenesis [22][26][27].

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