UV Radiation in DNA Damage and Repair

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Prolonged exposure to ultraviolet radiation on human skin can lead to mutations in DNA, photoaging, suppression of the immune system, and other damage up to skin cancer (melanoma, basal cell, and squamous cell carcinoma).

DNA repair cancer ultraviolet ROS

1. Introduction

The constant destructive impact of various adverse environmental factors (pollution with toxic substances, various types of natural and artificial radiation, etc.) causes the disturbance of the normal functioning of living cells [1][2][3]. This leads to the development of various diseases, which can eventually result in chronic ones. In turn, the immune and endocrine systems cease to cope with their protective and regulatory functions due to an increase in constant load, and, ultimately, all this can lead to more serious disorders, including cancer. A necessary condition for the occurrence and development of the process of carcinogenesis is DNA mutations. DNA mutations can occur due to mutagenic environmental factors (in particular, UV) when the effective repair does not function [4][5][6]. A person is exposed to intense UV light both in connection with professional activities that require a long stay out of doors and as a result of following fashion trends, sunbathing on the beach, or using special lamps in tanning salons. Prolonged exposure to UV on the skin leads to hyperpigmentation, photoaging due to collagen fiber damage [7], and the accumulation of mutations in the cell's DNA. About 90% of non-melanoma skin cancers and 86% of melanomas are associated with chronic UV irradiation of the skin [8]. UV inhibits the synthesis of ATP and disrupts the immune response, which also contributes to carcinogenesis [8][9]. It was found that chronic exposure to solar radiation is the most important environmental factor involved in the pathogenesis of actinic keratosis and squamous cell carcinoma [9]. It has also been shown that chronic UV radiation in farmers is associated with a high risk of the earlier development of basal cell carcinoma and its aggressive subtypes [10].

2. Possible Mechanisms of DNA Damage by UV Radiation

2.1. Target Molecules for UV Exposure

Targets of UV radiation in living organisms can be various photoactive molecules, for example, pterins, folates, flavins, porphyrins, aromatic amino acids, etc. (**Figure 1**), as well as biopolymers: proteins and nucleic acids [11][12]. Such photoactive molecules transfer into an excited state after the light absorption, and the excess energy can be utilized in several ways, among which three main options are of biological significance.

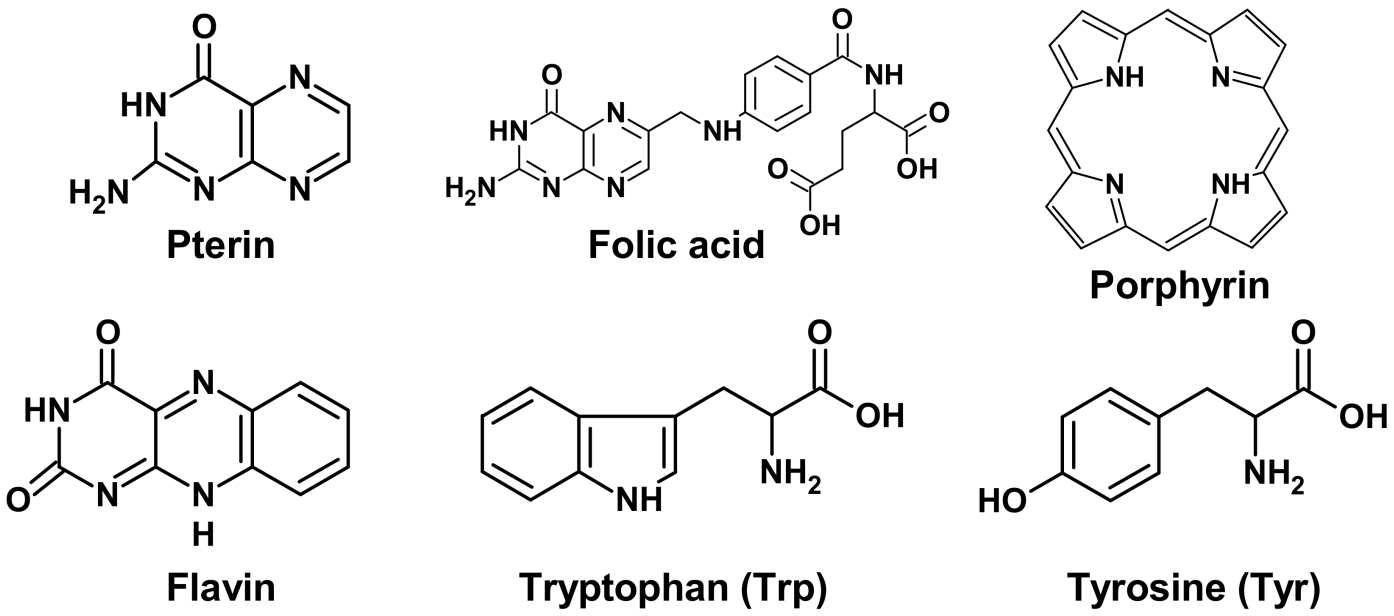

Figure 1. Chemical formulas of low molecular weight biological chromophores.

(1) If the molecule is a chromophore of a photoreceptor protein, then the absorbed energy is converted into a signal to trigger various processes. For example, flavin is a chromophore of cryptochromes (CRYs), which are involved in the photoregulation of circadian rhythms.

(2) Important biologically active molecules can undergo partial chemical modification or be completely destroyed, which can lead to a deficiency of these molecules in the body. This is especially true for those substances that cannot be synthesized in the human body. For example, folic acid derivatives are destroyed by UV radiation. This may be the reason for the deficiency of this vitamin in people with fair skin, exposed to increased impact to solar radiation [13].

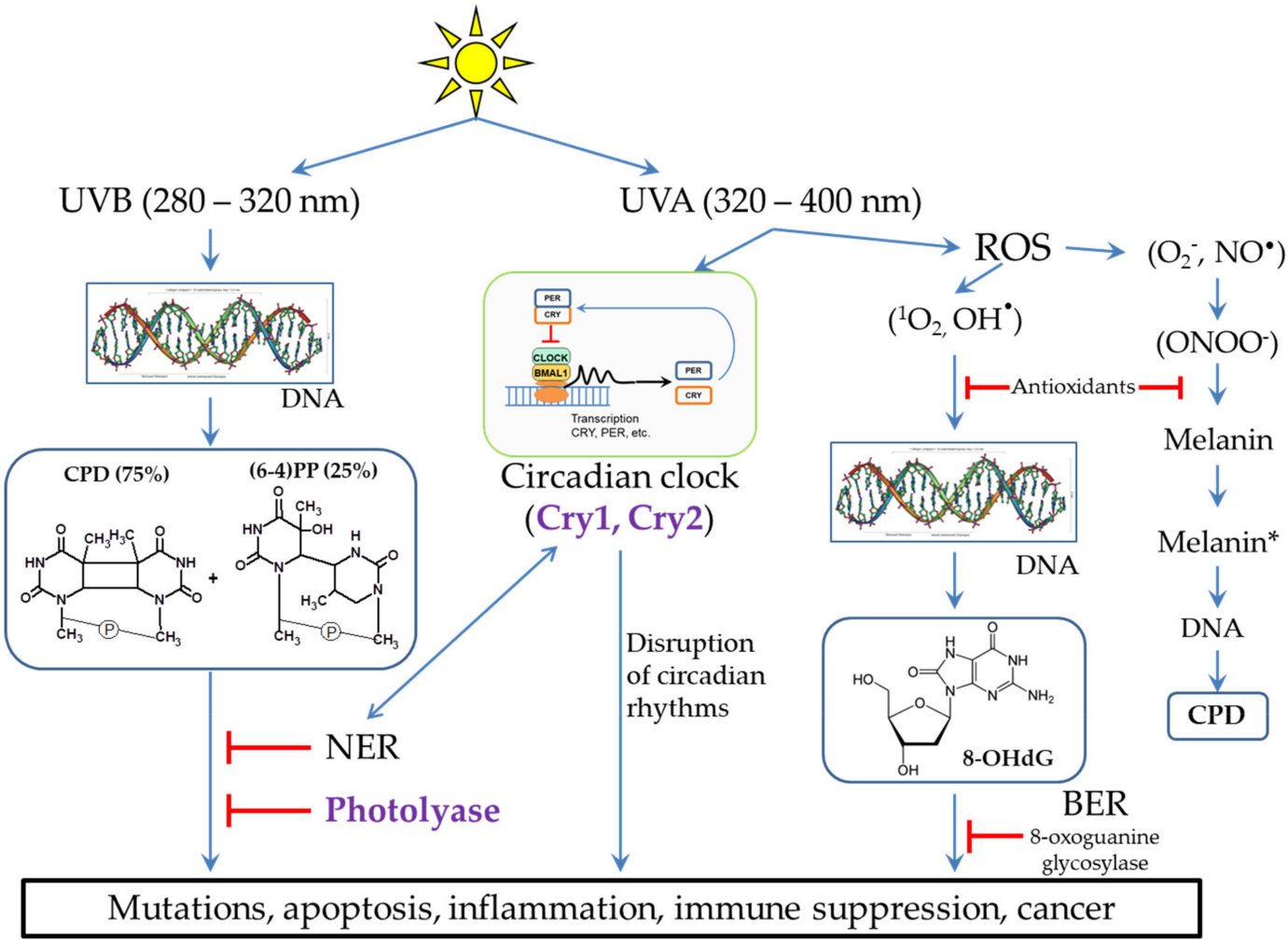

Figure 2. Different UV radiation of DNA leads to different lesions and subsequent occurrence of pathological situations. Methods of lesion prevention and repair are presented. * - The excited state of melanin.

(3) Light-excited molecules can become sensitizers for the destruction of other molecules or lead to the formation of reactive oxygen species (ROS). ROS, in turn, can lead to damage to other molecules, including DNA (**Figure 2**) and lipids [14]. Porphyrins (**Figure 1**) are well-known photosensitizers in medicine, and their ability to generate ROS underlies the photodynamic cancer therapy [15].

2.2. Damaging Effect of UVB Light on DNA

The most dangerous impact of UVB (280–320 nm) radiation is the DNA damage in skin cells. The main products of UVB-irradiated DNA are cyclobutane pyrimidine dimers (CPD, 75%) and pyrimidine-pyrimidone (6-4) photoproducts ((6-4)PP, 25%), in which two neighboring pyrimidines are covalently bound (**Figure 2**). In addition, irradiation can lead to breaks in one or both of DNA chains at once. The formation and accumulation of CPD and (6-4) PP block the DNA replication and transcription, which disrupts the normal functioning of cells. If these lesions are not removed in a timely manner, this can lead to cell death and the occurrence of inflammatory processes at

the tissue level. In some cases, errors in the repair process can lead to the appearance and accumulation of mutations (see Section 3), which can subsequently cause various diseases and skin cancer [16][17][18][19][20].

2.3. The Influence of UVA Light on the Processes Occurring in Skin Cells

It is believed that UVA radiation (320–400 nm) is not as harmful as UVB. In small doses, UVA light is necessary for a human because it is a signal for various photoregulatory proteins, in particular for restarting circadian rhythms, which, in turn, regulate many different processes in the body (**Figure 2**). However, in high doses, UVA radiation can lead to the suppression of the immune system and the formation of ROS through photosensitization reactions [9][14][18][21]. ROS cause oxidative stress and photoaging, and this can also lead to skin cancer [20]. DNA can be damaged by ROS to form 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-OHdG) (**Figure 2**), which, such as CPD, interferes with normal cell functioning [9][14][18][20][21]. ROS activate the expression of matrix metalloproteinases, which cause degradation of collagen fibers, leading to the appearance of wrinkles and skin aging [7][20][22][23].

A special pathway of the destructive effect of UVA radiation on DNA is caused by cell damage in the presence of melanin (**Figure 2**). Back in 2003, it was shown that oxidative damage is not the main type of UVA-induced damage in skin cancer. Thus, oxidized pyrimidines, single-chain breaks, oxidized purines (8-OHdG), and CPD are formed in a ratio of 1:1:3:10. Moreover, it was found that UVA generates CPD with a large predominance of thymine dimers, which indicates their formation through photosensitized triplet energy transfer [24]. In further studies, it was shown that melanin is the photosensitizer of the process. Melanin properties are two-fold: 1) when the melanin synthesis is completed, melanin in a certain geometric configuration in keratinocytes performs a protective function, but 2) it can have pro-oxidant properties during partial polymerization in melanocytes when exposed to UV radiation. The potential role of UVA in skin carcinogenesis is also confirmed by epidemiological studies showing an increased risk of melanoma among the users of tanning lamps producing UVA radiation [25].

In pigmented melanocytes, CPD occurs both instantly and within a few hours after UV irradiation in the dark. The path of CPD occurrence in the dark is partially similar to bioluminescence and is as follows. UV activates nitric oxide synthases, which generate a nitric oxide radical ($NO^{\bullet}$), and NADPH oxidases, which generate superoxide-anion radical (O_2^{-}). Further, these radicals interact with each other to form strong oxidant peroxynitrite ($ONOO^{-}$) (**Figure 2**). Peroxynitrite oxidizes melanin while exciting the melanin electron to a high-energy level. This is the process of "chemical electron excitation" in melanin: a non-radiative triplet energy transfer to DNA occurs with the formation of CPD [26][27]. UVA and peroxynitrite contribute to the solubilization of melanin and increase the permeability of the nuclear membrane to melanin. This pathway can be considered as a melanin-dependent pathogenesis of melanoma. In the same way, the chemical excitation of melanin can trigger pathogenesis in other tissues, in which nitric oxide and superoxide anion radicals arise in cells containing melanin [28]. It is important to note that photodynamic therapy of skin cancer with red light does not cause CPD formation in the presence of melanin [29].

Exposure to strong UV radiation is the main etiological environmental factor for all forms of skin cancer, including melanoma. The ability to repair DNA determines the risk of skin cancer. The sensitivity of cells to the severe effects of UV radiation depends on the degree of skin pigmentation. In turn, the process of melanogenesis can be

disrupted when exposed to various exogenous etiological environmental factors, including UV [30]. Disruption of melanogenesis occurs in a number of dermatological diseases, including vitiligo [31][32][33]. The study of melanogenesis and the ways of its regulation are important for the development of new photoprotective strategies for the prevention of skin cancer.

3. DNA Repair Systems Involved in the Photodamage Removal

Cells have many different mechanisms for repairing each type of DNA damage that occurs spontaneously and is caused by exogenous factors [6][34]. The main mechanisms of DNA repair include: direct repair, when the enzyme restores the original structure without removing damaged nucleotides; excision repair, through the removal of damaged sites, followed by the synthesis of new nucleotides: base excision repair (BER) and nucleotide excision repair (NER); repair of unpaired bases (mismatch repair); repair of single-strand and double-strand breaks [6][34]. To remove photodamage, both direct repair with the participation of the DNA photolyase [4][35][36] and NER for CPD and (6-4)PP or BER for 8-OHdG [4][20][37] are used (**Figure 3**).

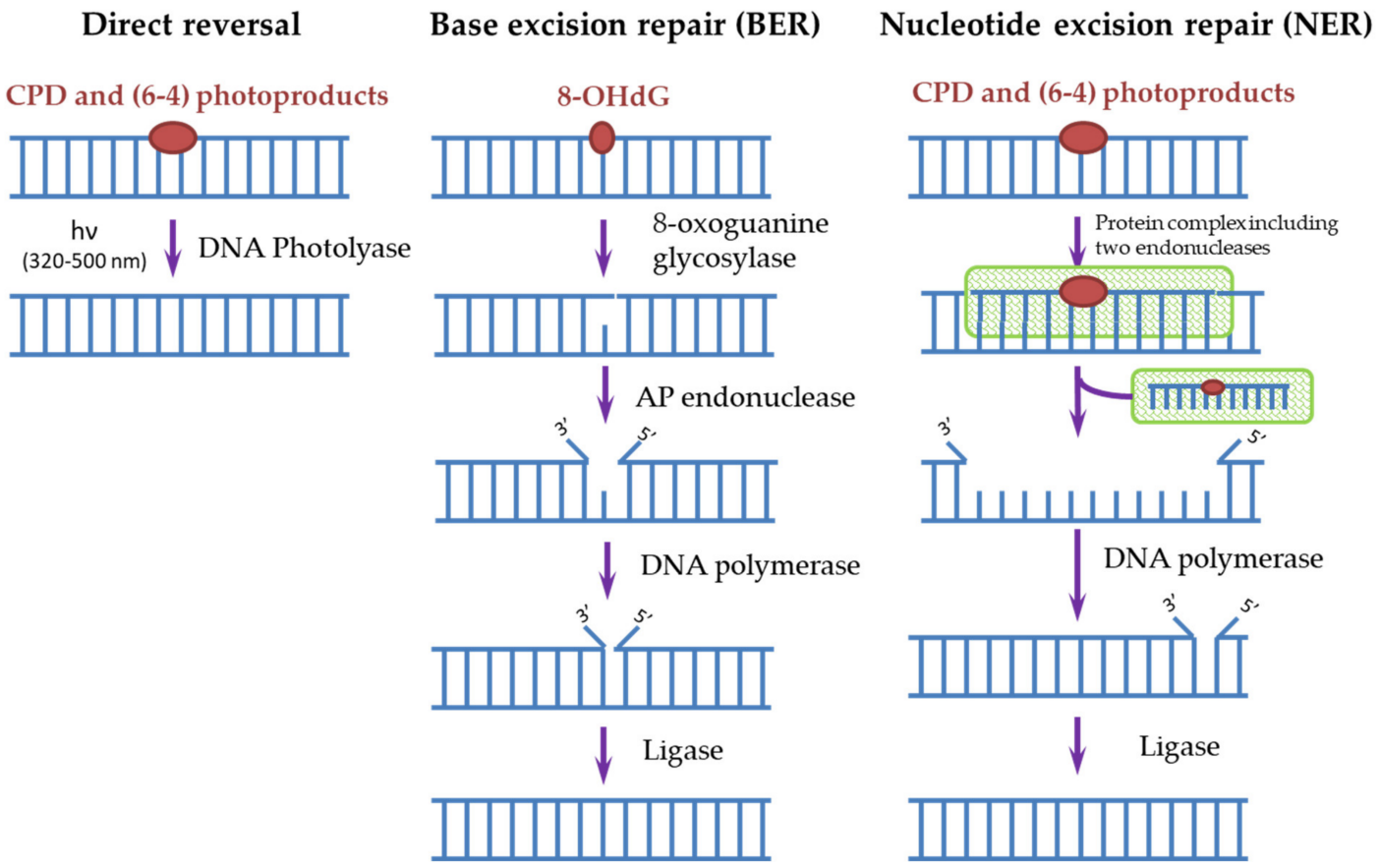

Figure 3. Scheme of direct and excisional repair in photodamaged DNA.

In humans, as in most mammals (except for some marsupials), there are no DNA photolyases and the only system responsible for removing the most dangerous CPDs for DNA is NER. It is known that defects in the NER process

lead to a xeroderma pigmentosum disease (XP). People suffering from this disease are extremely sensitive to sunlight and are susceptible to the development of skin oncological diseases. Genetic analysis of such patients revealed the mutations in seven main genes, called XPA-XPG, responsible for the NER function [35]. In general, more than 20 different proteins take part in the NER process, and it can be triggered in two ways. The first way is global genome NER when the NER enzymes (in humans, these are complexes of RPA, XPA, and XPC proteins) themselves find damaged sites and start the repair process. The second way is transcription-coupled NER, where, during transcription, an RNA polymerase bumps into a damaged site and initiates the repair process. Next, a cascade of reactions involving a protein complex is started, as a result of which endonucleases (XPF and XPG) cut out a DNA oligomer of about 30 nucleotides containing CPD. Then, a polymerase is attached and synthesizes a complementary intact DNA chain. The ligase completes the process by connecting the free ends of DNA chains (**Figure 3**) [4][35][37][38][39]. Both pathways require the involvement of a large number of enzymes, and as a result, the process stretches over time to several hours, thus the processes triggered by CPD dimers, for example, melanogenesis, have time to start in cells. In addition, the repair process itself often occurs with violations and leads to mutations. In such erroneous CPD repair, mutations with cytosine-to-thymine replacement occur most often, which is characteristic for mutations found in cancer cells [9][17][40][41].

The BER system is used to remove 8-OHdG formed as a result of photo-oxidative stress (**Figure 3**). The BER scheme is similar to the NER scheme but includes fewer enzymes. The damaged base is removed by 8-oxoguanine glycosylase, then from 1 to 13 nucleotides near the damaged site are removed by AP endonuclease and synthesized again. Disruption in the BER function leads to fetal mortality or predisposition to cancer and neurological symptoms in animals. NER is able to partially replace BER in case of violations in its operation and also stimulate the enzymatic activity of some BER factors [37].

Furthermore, sometimes the NER system cannot recognize CPD and restore DNA, in this case, a rough “SOS” repair system works: during replication, the affected DNA sections are bypassed and subsequently replaced with nucleotides that are not complementary to the original chain, which can also lead to mutations [42]. Most of the spontaneously occurring mutations that accumulate in cells throughout a person’s life can go unnoticed without any serious consequences, but some of them can change key cellular functions and lead to cancer and aging [9].

Understanding the function of repair systems is important not only because of possible disruptions in their work that lead to the occurrence of oncological diseases but also because of possible mechanisms and places of application in the treatment of these diseases. Many cancer treatment strategies are aimed to destroy the DNA of tumor cells, and in this case, the repair systems existing in these cells will reduce the effectiveness of such treatment [6]. At the same time, during chemotherapy and radiotherapy, not only diseased cells are often affected, but also healthy ones. The ability to speed up the process of restoring these cells after the end of treatment (during the rehabilitation period) will also improve the quality of treatment.

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