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Review Article

Sunlight damage to cellular DNA: Focus on oxidatively generated lesions☆

André Passaglia Schuch[a], Natália Cestari Moreno[b], Natielen Jacques Schuch[c], Carlos Frederico Martins Menck[b,*], Camila Carrião Machado Garcia[d]

[a] Departamento de Bioquímica e Biologia Molecular, Centro de Ciências Naturais e Exatas, Universidade Federal de Santa Maria, 97110-970 Santa Maria, RS, Brazil
[b] Departamento de Microbiologia, Instituto de Ciências Biomédicas, Universidade de São Paulo, 05508-000 São Paulo, SP, Brazil
[c] Departamento de Nutriçao, Centro Universitário Franciscano, 97010-032 Santa Maria, RS, Brazil
[d] Núcleo de Pesquisa em Ciências Biológicas & Departamento de Ciências Biológicas, Instituto de Ciências Exatas e Biológicas, Universidade Federal de Ouro Preto, 35400-000 Ouro Preto, MG, Brazil

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ABSTRACT

The routine and often unavoidable exposure to solar ultraviolet (UV) radiation makes it one of the most significant environmental DNA-damaging agents to which humans are exposed. Sunlight, specifically UVB and UVA, triggers various types of DNA damage. Although sunlight, mainly UVB, is necessary for the production of vitamin D, which is necessary for human health, DNA damage may have several deleterious consequences, such as cell death, mutagenesis, photoaging and cancer. UVA and UVB photons can be directly absorbed not only by DNA, which results in lesions, but also by the chromophores that are present in skin cells. This process leads to the formation of reactive oxygen species, which may indirectly cause DNA damage. Despite many decades of investigation, the discrimination among the consequences of these different types of lesions is not clear. However, human cells have complex systems to avoid the deleterious effects of the reactive species produced by sunlight. These systems include antioxidants, that protect DNA, and mechanisms of DNA damage repair and tolerance. Genetic defects in these mechanisms that have clear harmful effects in the exposed skin are found in several human syndromes. The best known of these is xeroderma pigmentosum (XP), whose patients are defective in the nucleotide excision repair (NER) and translesion synthesis (TLS) pathways. These patients are mainly affected due to UV-induced pyrimidine dimers, but there is growing evidence that XP cells are also defective in the protection against other types of lesions, including oxidized DNA bases. This raises a question regarding the relative roles of the various forms of sunlight-induced DNA damage on skin carcinogenesis and photoaging. Therefore, knowledge of what occurs in XP patients may still bring important contributions to the understanding of the biological impact of sunlight-induced deleterious effects on the skin cells.

1. Introduction

Ultraviolet (UV) radiation is part of the spectrum of electromagnetic radiation emitted by the sun and includes the wavelength range from 100 to 400 nm: UVC (100–280 nm), UVB (280–315 nm), and UVA (315–400 nm). The oxygen and ozone in the atmosphere completely absorb the UVC radiation (< 280 nm) and absorb the majority (approximately 90%) of UVB. Thus, the solar UV radiation of relevance to human health and ecosystems consists of UVA and UVB wavelengths [1].

Exposure to UV radiation has both beneficial and adverse effects on human health. UVB irradiation of the skin is the main source of vitamin D, which plays a critical role in the maintenance of calcium homeostasis in the body and in other important processes [2]. In contrast, excessive UVB exposure causes skin cancer, including cutaneous malignant melanoma and the non-melanoma skin cancers, basal cell carcinoma and squamous cell carcinoma [3]. Once thought to be relatively innocuous, UVA is now known to damage DNA, proteins, and lipids, which can result in harmful consequences, such as carcinogenesis and skin aging. Growing evidence has demonstrated that UVA radiation can induce various types of DNA lesions through direct and indirect mechanisms as well as causing mutations in human skin cells. Thus,

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* Corresponding author.
E-mail addresses: schuchap@gmail.com (A.P. Schuch), nacestari@hotmail.com (N.C. Moreno), natielen@yahoo.com.br (N.J. Schuch), cfmmenck@usp.br (C.F.M. Menck), carriao.camila@gmail.com (C.C.M. Garcia).

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the participation of UVA in the process of skin cancer induction, including the cutaneous malignant melanoma, and skin photoaging is now accepted, although the specific mechanisms remain unclear [1,3].

In this review, we present an overview of the incidence of solar UV radiation at the Earth's surface and its absorption by DNA and non-DNA chromophores present inside the cells. The direct and indirect mechanisms of DNA damage by UVB and UVA wavelengths are presented, with emphasis in the photosensitized formation of oxidized DNA bases. Complex cellular systems to avoid the deleterious consequences of sunlight exposure and oxidative stress are also discussed. However, the relative consequences of the DNA lesions directly or indirectly induced by sunlight, especially those induced by UVA radiation, on skin carcinogenesis and skin aging are not clear. It should be added that skin photoaging may also be due to photo damaging of other macromolecules, including protein oxidation and extracellular degradation [4], although we will focus this review on the UV-mediated DNA damage. These deleterious effects of sunlight on skin are highly pronounced in the DNA repair-deficient patients with the syndrome xeroderma pigmentosum (XP). Most XP patients have mutations in one of seven genes (XPA through XPG), whose products are involved in the nucleotide excision repair (NER), a mechanism that removes DNA damage induced by UV radiation, as well as many other lesions that cause distortion of the DNA. Additionally, there are also the so-called XP variants, who have normal NER but are defective in translesion synthesis (TLS) after UV-induced DNA damage, as a consequence of mutations in the *POLH* gene that encodes DNA polymerase eta (Pol eta) [5].

Thus, the NER and TLS defects of oxidatively generated DNA lesions receive special attention in this review. In fact, the participation of NER proteins in the removal of oxidized DNA bases suggests a crosstalk between NER and other DNA repair pathways, and Pol eta may also protect cells from the consequences of DNA damage induced by oxidative stress. Thus, although it has been accepted that DNA pyrimidine dimers are the main lesions responsible for the deleterious effects of sunlight, the participation of the cellular oxidative processes that are induced by UVB and mainly UVA radiation in promoting human skin tumors and aging is still an open question that the cells derived from XP patients may help answer.

2. Solar UV radiation incidence on Earth

The intensity of solar UV radiation can be influenced by several environmental factors. For instance, the height of the sun above the horizon (solar zenith angle) influences the incidence angle of UV radiation according to the latitude, time of day and season. At lower elevations, the pathway through the atmospheric is longer, which results in higher absorption and thus a lower UV intensity. UV radiation is more intense in the tropics, near noon and in the summer [6]. Additionally, higher altitudes also have a thinner atmosphere, which results in less attenuation of the sunlight and an increased UV intensity.

As UV radiation penetrates the atmosphere, ozone, clouds and aerosols can modify its intensity. Cloud cover is by far the most important factor that controls UV radiation for any given latitude and altitude. Furthermore, in polluted urban areas, although aerosols and trace gases may provide protection from UV radiation, these constituents can also scatter light, which increases the total exposure to UV radiation in places shaded from direct sunlight [7]. However, in cloud-free and low-aerosol conditions, ozone is the most important factor in controlling the levels of solar UVB incidence and blocking the photochemical reactions of organic molecules [8]. Therefore, the release of ozone-depleting substances catalyzes the breakdown of ozone to molecular oxygen, which does not absorb UVB radiation. Thus, these substances lead to more UVB radiation passing through the stratosphere, which enhances the photochemical reactions and increases the corresponding biological effects [9].

The discovery of the ozone "hole" in the 1980s has led to critical concern worldwide. Fortunately, the Montreal Protocol continues to be successful in reducing emissions of ozone-depleting substances, and it has been hailed as the most effective environmental treaty ever made [3]. However, ozone-depletion events still continue to occur during the winter and spring over the high latitudes (63–90°) of both hemispheres. Compared to the average total ozone level measured before 1980, the 2010–2013 mean value was lower by ~27% in the southern hemisphere in October and by ~10% in the northern hemisphere in March [10]. Additionally, although the Antarctic ozone hole is located over the polar region, it can also influence the ozone content over southern South America during the spring season, when it increases the UVB incidence at mid-latitudes [11–13]. It has already been demonstrated that polar air masses with a low ozone content can disturb the stratospheric ozone concentration in the South of Brazil [14], where a 1% depletion in ozone content results in an average increase of 1.2% in the UVB intensity [15]. A similar atmospheric phenomenon has already been observed over other mid-latitude regions, such as New Zealand [16] and South Africa [17]. Recently, a dataset containing 35 years of ozone concentration measurements over southern Brazil was analyzed and 72 ozone-depletion events were identified. The average decrease in the ozone content was 9% (± 3.3), and there has been a slight tendency towards a higher frequency of ozone depletion events with time. This is much more apparent from 1997 onwards because the yearly average of events observed from 1979 to 1996 and from 1997 to 2013 increased from 1.1 event per year to 3.1, respectively [18]. Nevertheless, the small ozone values observed in the Arctic can also propagate to mid-latitudes and decrease the ozone content over Western Europe, especially between late March and late April [19].

Regardless of the occurrence of ozone-depletion events in both the Southern and Northern hemispheres, it is important to emphasize that the daily UVA incidence is naturally much higher than the UVB in any given latitude. Latitudinal gradients are stronger for the UVB than for the UVA wavelengths, partly because photons travel a longer path through the atmosphere for the lower solar elevations that prevail at the higher latitudes, which results in a greater absorption of the UVB radiation by the ozone layer [8]. An example of this gradient can be observed in a comparison of the daily UVB and UVA measurements performed at various latitudes in South America [20]. This work demonstrated that the UVB intensity at 5°5'S is approximately 12-fold higher than at 53°1'S, whereas the UVA intensity is only approximately 2-fold higher than at the lower latitude. These gradients reflect the different DNA damage profiles induced at different latitudes [20]. A representative example of an environmental measurement of the solar UVB and UVA incidence on a clear sky summer day (2015) at the latitude of 29°4'S is presented in Fig. 1. These data were obtained using continuous UVB/UVA broadband radiometers (such as the UVB and UVA Radiometers from EKO Instruments Trading, Tokyo, Tokyo-to,

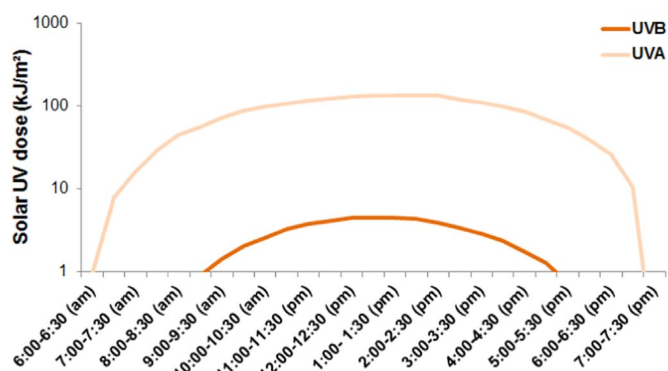

Fig. 1. Illustrative example of an environmental measurement of solar UVB (280–315 nm) and UVA (315–400 nm) incidence in a clear sky summer day (2015) at the latitude of 29°4'S (Southern Brazil) using continuous UVB/UVA broadband radiometers (EKO Instruments Trading, Tokyo, Tokyo-to, Japan).

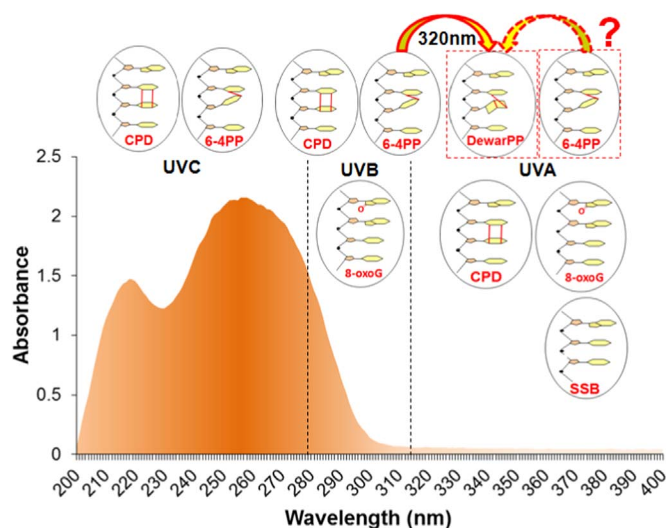

Fig. 2. DNA absorption spectrum and the main types of DNA lesion induced by each UV band. CPD – cyclobutane pyrimidine dimmers; 6-4PP – pyrimidine (6-4) pyrimidone photoproducts; DewarPP – Dewar valence isomer; 8-oxoG – 8-oxo-7,8-dihydroguanine; SSB – single-strand breaks.

Japan) that take measurements at 280–315 nm and 315–400 nm, respectively. As expected, Fig. 1 shows that although it is very low early in the morning and late in the afternoon, the intensity of solar UV radiation reached a maximum at midday. The daily UVA dose measured on this day was approximately 39-fold higher than the daily UVB dose, and the percentage of both UVB and UVA wavelengths corresponded to 2.5% and 97.5% of the total UV incidence, respectively.

3. DNA as the main target of UV radiation in living cells

Although nearly all of the UV incidence on the Earth's surface is in the UVA wavelengths, it is well known that UVA radiation is indeed less harmful than UVB. However, UVA is not completely innocuous because it can be absorbed by different cellular chromophores as well as by DNA (Fig. 2).

At the first glance, Fig. 2 indicates that UVC wavelengths are the most effectively absorbed by DNA, followed by UVB, whereas UVA is poorly (almost not) absorbed. But, interestingly, the total absorption of UVA wavelengths by DNA is only 4.2-fold lower than that of UVB wavelengths, while total incidence on Earth's surface is 20-fold higher for UVA. This information indicates that DNA can absorb UVA radiation and suggests that the direct impact of solar UVA radiation on DNA could be even more drastic than previously assumed. In fact, the absorption of UVA wavelengths by DNA was shown long ago. DNA from different sources was shown to differ in its capacity to absorb light for wavelengths over 300 nm, depending on the G:C content [21]. The authors concluded that probably G absorbs these wavelengths more than A and that this may explain at least part of the biological effects of UVA radiation [21].

In addition, several studies have indicated that UVA radiation can directly induce cyclobutane pyrimidine dimers (CPDs) in DNA [22–30], and a few have shown the formation of pyrimidine (6-4) pyrimidone photoproducts (6-4PPs), albeit in much lower quantities than CPD. In fact, although 6-4PPs were not detected by mass spectrometry in UVA-irradiated DNA molecules, these lesions were detected in both purified DNA and DNA repair-deficient human cells by highly sensitive endonucleases, alkaline sensitivity and immunological assays [27]. Moreover, cells that expressed specific photolyases demonstrated that 6-4PPs are responsible, at least partially, for the cell death that is induced by UVA radiation [30]. Importantly, as these DNA photolesions are slowly induced in cellular DNA by UVA, damage removal by repair is continuously occurring, which protects the cells from the consequences of the lesions [27,30].

4. Direct formation of DNA damage by UV radiation

Several efforts have been made to determine the molecular mechanisms by which sunlight induces carcinogenesis and aging. Certainly, the sunlight absorption directly triggers DNA damage, and it is clear from the literature that UVB and UVA wavelengths are responsible for the vast majority of these lesions. Recently, an important review discussed the role of photoexcited states of DNA bases on the direct mechanism of damage formation and demonstrated the existence of “collective” excited states (i.e., excited states delocalized over at least two bases) and the importance of the DNA configuration at the moment of exposure and the dynamics of the functional changes that occur during the excitation that initiates this process [31].

CPDs are formed by two covalent bonds between the C5 and C6 carbon atoms of adjacent nitrogen bases through Frenkel excitons that result in a diasteromeric ring composed of four elements. In the double helix, the *cis-syn* isomer is more abundant than *trans-syn* isomer whereas in single-stranded DNA, the *trans-syn* isomer predominates. 6-4PPs are formed by one covalent bond between the 5’-end C6 and the 3’-end C4 carbon atoms of adjacent pyrimidines via charge-transfer states, and oxetane and azetidine rearrangements (unstable intermediates) occur when the 3’-end is T or C, respectively [31,32]. CPD is a cyclic and rigid 4-carbon ring and less distortive than the non-cyclic 6-4PP [33–35]. The DNA condensation state also affects the formation of these pyrimidine dimers: specifically, CPDs can be formed in both hetero and euchromatin regions, whereas 6-4PPs are uniquely formed in euchromatin [36]. In addition, regions containing telomeres, G-Quadruplex loops, and 5-methylcytosine are prone to CPD formation [37–40].

The conversion of 6-4PPs to Dewar valence isomers results from the intramolecular 4π electrocyclization of the pyrimidone ring after the photon absorption [24,41]. The mechanism that is theoretically predicted involves a photochemical process with an excited state singlet $\pi\pi^*$. In fact, the formation of Dewar isomers requires two photons: the first induces the formation of the 6-4PP and the second is required for the isomerization of this DNA lesion. In this case, the second photon is more likely to come from the UVA range, which is poorly absorbed by normal DNA bases, but it is efficiently absorbed by 6-4PPs; this is essential for its isomerization into the Dewar form. The pyrimidone moiety of 6-4PPs exhibits a specific absorption at approximately 320 nm: more precisely 315 nm for TC 6-4PP and 325 nm for TT 6-4PP. Dewar valence isomers induce an intermediate distortion in DNA structure (21 degrees) compared to CPDs (10 degrees) and 6-4PPs (44 degrees) [35].

The isomerization of 6-4PPs into Dewar isomers has been demonstrated and quantified using mass spectrometry and immunological detection in various studies using bacteria, plants, cultured cells, skin samples and animals [42–45]. Recently, a large-scale study using microorganisms exposed to natural sunlight showed that 20% of the 6-4PPs were converted into Dewar isomers [46]. Concerning the mutagenic properties of pyrimidine dimers, 6-4PPs and Dewar isomers are believed to be more mutagenic than CPDs. 6-4PPs preferentially induce TT to TC transition, whereas Dewar isomers convert TC to TT, and CPDs induce C to T transitions [47].

In fact, the DNA damage that results from UVB and UVA exposure preferentially induces C-T transitions in both *in vitro* and *in vivo* models [48–50]. Furthermore, despite the fact that UVB induces more CPDs than UVA at equimutagenic doses, the DNA photoproducts that are induced by UVA are potentially more mutagenic than those induced by UVB [51]. This could be explained by the less effective cell cycle arrest, weak p53 and p95 activation, and consequently, an ineffective cell cycle checkpoint after UVA irradiation, which can lead to the progression of the replication of the damaged DNA and accumulation of mutations [51]. Deamination of cytosine to uracil, or of methylcytosine

to thymine ,within a pyrimidine dimer explains some of these mutations. Replication of a deaminated CPD, for example, by Pol eta, will insert an adenine opposite to uracil or thymine, which gives rise to C to T transitions. This model presupposes, however, that the dimer still has some coding capacity during replication. Eventually, mutations arise due to bypass of the DNA damage by an error-prone TLS polymerase. In fact, it has been shown in yeast that Rad30 (a Pol eta homolog) performs the non-mutagenic bypass of 6-4PPs containing cytosine, Dewar isomers and 8-oxoG. In the absence of Pol eta, another TLS polymerase (Pol zeta) is responsible for performing the bypass, although in this case, the bypass is mutagenic [52]. Recently, it was shown that although Pol eta is responsible for CPD bypass, Pol zeta may act preferentially in the gap filling formed during 6-4PP replication in human cells [53].

Finally, DNA single- and double-strand breaks and DNA cross-links can be formed directly or as the result of cellular metabolism after UVA exposure [54–57]. These lesions are very cytotoxic and, if persistent, can cause chromosomal aberrations and tumorigenic transformation of keratinocytes [58]. However, the capacity of UVA radiation to directly induce double-strand breaks has recently been refuted [59], and the presence of this type of lesion may be an indirect result of DNA damage replication [58,60], or, occasionally, due to UVA-induced clusters of single-strand breaks or the repair of close oxidized bases in the DNA [61].

5. Photosensitized formation of oxidatively generated DNA damage

There are extensive literature reports on investigations of the mechanisms by which reactive oxygen species (ROS) are formed after sunlight exposure. A recent review by Cadet and collaborators (2015) details the mechanisms for ROS generation and their reactions with DNA molecules [62]. In fact, both UVA and UVB radiation can induce intracellular redox processes. Both types of radiation reach the basal layer of epidermis, although UVA radiation penetrates the skin more deeply than UVB, which may be relevant for photocarcinogenesis [63].

The ROS generation by UVB radiation has been known for a long time. This reaction can be demonstrated by the use of various techniques that detect the formation of superoxide anion radical ($O_2^{\bullet -}$) and hydrogen peroxide (H_2O_2), among others [64–71]. The delayed generation of ROS and reactive nitrogen species (RNS) by UVB is attributed to the activation of enzymes, such as cyclooxygenase and the NADPH oxidase pathway, or to the activation of inducible $NO^{\bullet}$ synthase in response to inflammatory mechanisms [69,72–76]. As a result of these processes, UVB irradiation can also induce bystander effects in non-irradiated neighbor cells [77–80].

Non-DNA chromophores that are present in human skin cells also absorb UVA photons, which lead to the formation of photoexcited states with subsequent generation of ROS and RNS, organic free radicals and other toxic photoproducts [81]. In fact, human skin is an abundant source of numerous chromophores with strong absorption in the UVA and blue visible region. Some examples include porphyrins, heme and bilirubin, melanin and melanin precursors, pterins, flavins and NADPH oxidase, trans-urocanic acid and tryptophan. The mechanisms of photosensitization of these endogenous chromophores have been thoroughly discussed previously [81] and will also be discussed in this issue. The photoexcited state intermediate, most often the triplet state of the sensitizer, can directly interact with substrate molecules to produce large amounts of endogenous ROS via type I and II mechanisms [62,81–83]. The type I reaction involves a complex chain of events that begins with energy transfer from a triplet state energy photosensitizer that give rise to ROS such as the $O_2^{\bullet -}$, H_2O_2 and hydroxyl radical ($^{\bullet}OH$). In contrast, the type II reaction involves a direct energy transfer from the triplet state energy photosensitizer to an oxygen molecule, which results in the formation of singlet oxygen ($^1O_2$) and the subsequent oxidation of biomolecules [82,84,85]. Most frequently, the UVA radiation promotes selective guanine oxidation by $^1O_2$, which produces primarily 8-oxo-7,8-dihydroguanine (8-oxoG) [62]. In addition, UVA can also induce ROS through bystander effects and enzymatic activities as described above for UVB [62,76]. Furthermore, a growing body of evidence has suggested that mitochondria, ferritin and NADPH oxidase (Nox-1) participate in the UVA-induced DNA damage [86,87].

Interestingly, recent data have accumulated that show ROS formation after exposure to non-UV wavelengths [88,89]. Specifically, visible light can damage melanocytes through melanin photosensitization and $^1O_2$ generation [90].

Although many ROS participate in cell signaling mechanisms, the generation of these species at high levels can damage biomolecules that are susceptible to oxidation, thus resulting in several consequences for the cell integrity and function. For instance, lipid peroxidation can destabilize the membrane, which can lead to mutagenesis and cell death. The end-products of such reactions, the unsaturated aldehydes, have the ability to form mutagenic adducts of DNA through base alkylation [91,92]. Moreover, oxidized proteins can lose or gain functions inside the cell or form cross-links with the DNA that block DNA replication and transcription [93–97]. In fact, in model studies, more than one hundred oxidation products of nitrogenous bases and 2-deoxyribose have been demonstrated to be induced in DNA [98]. Many of these DNA lesions that were induced by oxidative processes may be associated with carcinogenesis and aging and are thus relevant for the identification of the consequences of the exposure of human skin to sunlight.

Recently, it was demonstrated that CPDs could also continue to be generated in the skin for more than 3 h after exposure to UVA [99]. The formation of this type of DNA lesion occurs because UVA radiation induces the generation of $O_2^{\bullet -}$ and nitric oxide ($NO^{\bullet}$). These species cause a sharp increase in the concentration of peroxynitrite, which degrades melanin. In the nucleus, peroxynitrite excites melanin derivatives to a triplet state that has the high energy of a UV photon. These evanescent electronically excited products transfer their triplet energy to DNA, which creates CPDs in the dark [99]. Therefore, this work is a strong indication that the consequences of UVA exposure for the development of melanoma have been underestimated.

The most studied DNA oxidation product is 8-oxoG, which is considered to be the main oxidized DNA base that is detected after UVA exposure, followed by single-strand breaks (SSB) and pyrimidine oxidation products [25,81]. 8-oxoG can be detected unequivocally by HPLC combined with electrochemical detection and mass spectrometry [100,101] or by less quantitative methodologies such as immunochemical detection and the modified comet assay using a specific glycosylase [101–103]. However, immunoassays that are suitable for the detection of bulky adducts such as CPDs are not appropriate for the measurement of oxidized bases due to a lack of antigenicity that leads to cross-reactivity with canonical bases [104]. This oxidized base can be generated by the attack of $^1O_2$ and $^{\bullet}OH$ as the result of both types II and I photosensitization reactions [101]. 8-oxoG has been detected both immediately after sunlight or UVA and UVB exposure [98] and shortly after UVA irradiation [30,102]. The relative importance of the oxidized DNA bases compared to the pyrimidine dimers in the cellular effects promoted by sunlight exposure is still a matter of debate. According to a recent review, the amount of oxidized DNA lesions is just 1% of total DNA damage induced by UVB [62]. However, the biological role of the redox process induced by UVB is supported by OGG1 knockout mice, which demonstrate an increased susceptibility to skin cancer [103]. In addition, mitochondrial DNA oxidation is also observed during sunlight exposure, and its association with skin aging process is emerging [105].

Although 8-oxoG does not completely block DNA or RNA polymerases and is thus not directly cytotoxic (see below) [106–110], it is known to be highly mutagenic. The oxidation of guanine occurs predominantly by the introduction of an oxo group in the carbon at position 8 in response to $^1O_2$ attack (type II mechanism), and/or in smaller amounts by one-electron (or hydrogen atom) abstraction (type I

mechanism) [101]. These changes combined with a base twist from the anti to a syn position result in an erroneous pairing with adenine, which leads to a potential G-T transversion [111].

Since 2009, UVA radiation has been recognized as a class I carcinogen [112]. However, the mutagenesis induced by UVA and its contribution to skin cancer development is still unclear, probably due to the uncertainty regarding the relative importance of pyrimidine dimers and oxidized bases in this process [113,114]. According to Ikehata and collaborators (2008), only 6% of the total UVA mutation spectrum in mouse skin is the result of the formation of 8-oxoG [50]. This result can be explained by the high efficiency of Base Excision Repair (BER), which quickly eliminates the oxidized bases up to 6 h after exposure. This contributes to the argument that other DNA lesions play major roles in the mutagenesis induced by sunlight [115–118]. In fact, the low levels of G to T transversions are also consistent with a minor role of 8-oxoG lesions in inducing skin tumors. However, in yeast cells that were defective for 8-oxoG repair, UVA was shown to be highly mutagenic [119]. Thus, new studies on the UVA-induced DNA lesions that are generated in response to redox imbalance (reactive aldehydes, ROS and RNS) need to be carried out to understand the relative role of this environmental agent in human skin carcinogenesis. Evidence for DNA damage as a consequence of redox process after UV exposure is increasing [120–123]. The alpha, beta unsaturated aldehydes (malondialdehyde, hydroxynonenal, crotonaldehyde and trans-trans-2,4-decadienal) are able to penetrate into the nucleus and promote the formation of etheno, propano and open adducts in DNA by Michael additions, the consequences of which must be explored [91,92].

6. Consequences of UV exposure to human health

Many of the deleterious human health effects that result from sunlight exposure are associated with a chain of events that begins with the formation of DNA damage. These lesions can lead to inflammatory and immunosuppressive processes in the epithelial tissue as well as accelerated aging and tumor development. However, UVB absorption by skin cells also triggers the synthesis of pre-vitamin D that is subsequently converted to vitamin D, which has many beneficial consequences. A summary for these effects is illustrated in Fig. 3.

Although DNA lesions are substrates for DNA repair, the accumulation of unrepaired DNA damage increases the frequency of mutations,

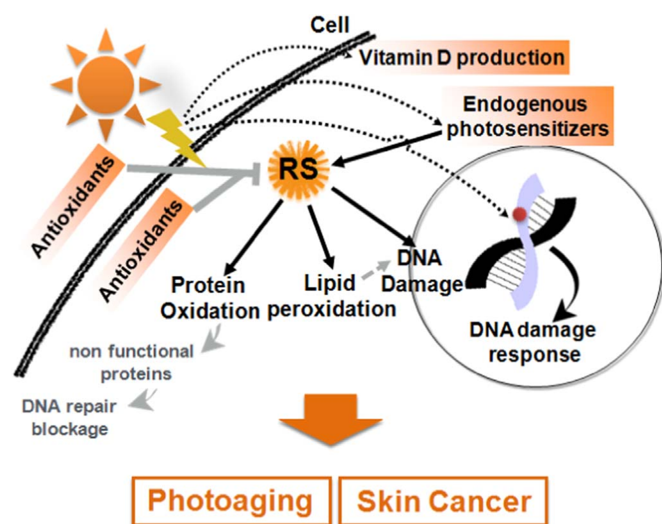

Fig. 3. The solar UV photons are directly absorbed by DNA or by other endogenous sensitizers, which leads to DNA damage and redox process (biomolecule oxidation), respectively. This stimulates numerous cellular consequences, culminating in protoaging and skin cancer. To protect cellular homeostasis, enzymatic and non-enzymatic antioxidants work to suppress the formation and reactions of the reactive oxygen species. The UVB photons are also important for the production of vitamin D.

contributing to the development of the carcinogenic process. It is well known that mutations induced in the genes that are involved in the maintenance of genomic integrity and in the control of the cell cycle result in a high predisposition to skin cancers [5]. In human cells, DNA damage is initially identified by sensor proteins that transmit the signal and initiate the repair mechanisms. However, unrepaired DNA lesions, such as CPDs and 6-4PPs and some oxidized bases (such as 5',8-cyclo-2'-deoxyribonucleoside), can block the polymerases during the replication and transcription processes [110]. In fact, in human cells, DNA damage initiates many cellular responses (DNA damage responses, DDR), which include the cell cycle arrest (G1/S and S/G2), DNA repair and cell death by apoptosis [30,110,124,125]. In addition to apoptosis, UV exposure can also induce necrosis [30,126] and cellular senescence, a marker of aging process [127–130]. The skin aging that results from the accumulation of UV-induced cellular damage is called photoaging. This damage occurs not only in the genomes of keratinocytes, fibroblasts and melanocytes but also in the genomes of epidermal and mesenchymal stem cells [131]. In addition, UV-generated ROS can damage other important structural components, such as actin and collagen [132], which contributes to the loss of integrity of the dermis and epidermis [128]. Furthermore, UV promotes the up-regulation of Mitogen-Activated Protein Kinase (MAPK), which inhibits the cytokine Transforming Growth Factor (TGF-b), thus resulting in collagen degradation and in its impaired replacement [133,134].

MAPK and TGF-b play important roles in other cellular mechanisms that are involved in the response to sunlight. MAPKs are also activated in response to pro-inflammatory mechanisms via human beta defensin 2 (hBD2) and ROS and RNS generation [135–137]. hBD2 is mainly induced by UVB [138,139], and its transcription is regulated by activator protein 1 (AP-1), which is an inhibitor of collagen synthesis and a participant in the inflammatory and immune responses [140]. AP-1 plays an important role in the inflammatory and immune responses by controlling the expression of c-Jun-N-terminal-kinase (JNK) and p38 proteins. The formation of $^1O_2$ by UVA activates the JNK and p38 proteins, which contribute to the stabilization and increased levels of COX-2. This protein is responsible for the production of prostaglandins by oxidizing the arachidonic acid in phospholipids and is involved in tumor promotion by inducing increases in interleukin-8 (IL-8) and vascular endothelial growth factor (VEGF) [141]. In fact, the promotion of angiogenesis by the activation of VEGF in normal keratinocytes has been shown after both UVB and UVA irradiation [142,143]. Pro-inflammatory cytokines (Interleukin-1 (IL-1), IL-6, IL-10, IL-12 and TNF-alpha) are also produced following the production of ROS and DNA damage by UV exposure. These molecules, especially IL-10 and the prostaglandins, have important roles in the immunosuppression induced by UV [144–147]. As a consequence of the redox process, the transcription factor NF-kB pathway is also activated through cytoplasmic I-kB kinase, and this contributes to the formation of cytokines and prostaglandins [148].

Conversely, UVB exposure also promotes vitamin D synthesis through the conversion of 7-dehydrocholesterol, which is present in the plasma membranes of skin cells, to pre-vitamin D_3, which is further isomerized to vitamin D_3 [149]. Vitamin D_3 undergoes two enzymatic oxidation processes, the first in the liver and the second in the kidney, to generate the active form of vitamin D, 1,25-dihydroxyvitamin D [$1,25(OH)_2D_3$], also known as calcitriol [3,149]. It is important to emphasize that 80–90% of vitamin D in the human body is acquired by the cutaneous synthesis, while the remainder is obtained by the ingestion of food that contains this vitamin [2,150,151]. Therefore, factors such as latitude and season affect the dermal production of vitamin D. During the summer and in low-latitude regions, the skin 7-dehydrocholesterol is more efficiently converted into pre-vitamin D_3, mainly due to higher UVB exposure of the population [152]. However, reduced levels of plasma vitamin D are observed even in sunny countries. Thus, the use of sunscreen, the amount of melanin in the skin, the types of clothing, and high levels of pollution can reduce skin

exposure to UVB and consequently decrease the synthesis of vitamin D [151,153,154].

Vitamin D is a major factor that is required for the development and maintenance of bone tissue and for the calcium and phosphorus homeostasis. In addition, the evidence suggests that this vitamin is involved in many other biological processes, including cell differentiation and proliferation, hormonal secretion, immune system and several chronic diseases [155–158]. For instance, analysis of the data from the Third National Health and Nutrition Examination Survey (NHANES III) revealed an inverse relationship between the serum concentrations of vitamin D and the main cardiovascular risk factors, including hypertension, diabetes mellitus, hypertriglyceridemia and obesity in 15,088 individuals in the United States. The authors observed an odds ratio of 1.24 for cardiovascular events, 2.1 for heart failure, and 1.82 for peripheral arterial diseases in adults in whom the levels of 25-hydroxyvitamin D (25(OH)D) were less than 20 ng/ml [159]. Moreover, recent assessments of the 25(OH)D status concluded that approximately 40% of children and adults in the United States, Canada, Europe, Asia, India, South America and Australia are vitamin D-deficient [2,150]. In addition to musculo-skeletal consequences that include rickets in children and osteomalacia, fractures, muscle weakness and falls in older adults, a growing number of other acute and chronic illnesses have now been indicated by epidemiological, observational and experimental studies to be associated with vitamin D deficiency. These include many types of cancer (breast, colon, etc.), autoimmune diseases (e.g., type 1 diabetes, multiple sclerosis and rheumatoid arthritis), infectious diseases, neurocognitive dysfunction including Alzheimer's disease, type 2 diabetes and cardiovascular disease [2,150]. On the basis that oxidative stress is a common cellular condition shared by many of these disorders, it has recently been demonstrated that vitamin D could have a protective effect against ROS. Although an antioxidant role for vitamin D has not yet been clearly demonstrated, vitamin D supplementation has a protective effect against the oxidative stress-induced damage in vascular endothelial cells, which suggests that it could have a potential application to lower the risk of cardiovascular disease [160].

Table 1 summarizes the most important effects of UV radiation on human health and its biomarkers.

7. Systems that protect cells from sunlight-induced DNA damage

To protect skin cells from the deleterious consequences of sunlight UV, evolution has provided them with numerous systems that either prevent the formation of such damage or remove, repair, or tolerate the DNA lesions. Cells contain a complex system to avoid reactive substances that are formed by sunlight, by either sequestering or removing them from the cell. For example, an antioxidant is a molecule that inhibits or reduces an oxidation process. From the biological point of view, an antioxidant protects biomolecules and cellular structures against the harmful effects of substances that promote oxidation. The endogenous defense system comprises a series of substances that act in different ways to minimize the generation of ROS and their subsequent reactions. Cellular antioxidants include enzymes, non-enzyme substances (glutathione, ascorbate, tocopherols, carotenoids, albumin and bilirubin), proteins, chelating agents, and phenolic and aromatic molecules.

In contrast, several DNA repair mechanisms constantly survey the genome to remove DNA damage. Eventually, if DNA lesions are not removed, cells may still be able to cope with them, by replicating the damaged DNA because many translesion polymerases allow cells to tolerate DNA damage. The main pathway that is involved in the removal of base damage such as that induced by oxidative stress is BER, but certainly other DNA repair pathways contribute to the cell protection. Among these DNA repair processes, NER proteins can act directly or via interaction with other pathways, and these proteins will be the main focus of this section. Importantly, NER defective human syndromes, including XP, dramatically reveal the importance of this repair pathway on human beings. The increased photoaging and extremely high frequency of skin tumorigenesis of XP patients indicate how sunlight-induced DNA lesions can cause serious damage to the human skin.

8. Antioxidants and mechanisms avoiding DNA damage formation

Antioxidant enzymes, such as catalase (CAT), glutathione peroxidase (GPx), superoxide dismutase (SOD), and peroxyredoxins help control the intracellular concentrations of $O_2^{\bullet-}$, H_2O_2 and organic peroxide. CAT is a hemeprotein associated with the peroxisomes, which has high activity in the liver [161]. CAT reduces H_2O_2 to H_2O and O_2, while GPx catalyzes the reduction of hydroperoxides via the oxidation of gamma-L-glutamyl-L-cysteinyl-L-glycine (reduced glutathione - GSH) to form GSSG and H_2O. The product is recycled by glutathione reductase, which converts GSSG into GSH at the expense of NADPH that is derived from the pentose phosphate pathway [162,163]. In addition, several types of SOD are present in the cytosol and in the mitochondria of human cells, where they convert $O_2^{\bullet-}$ into H_2O_2 and molecular oxygen (O_2) [164]. Peroxiredoxins (PRDXs), a ubiquitous family of redox-regulating proteins, are important endogenous antioxidants that protect cells from oxidatively generated damage by reducing H_2O_2 and peroxynitrite and by scavenging thiyl radicals [165].

Other classes of *in vivo* antioxidants are proteins and chelators (such as transferrin and ceruloplasmin) that bind to iron and copper; these can prevent Fenton reactions by blocking the formation of $^{\bullet}OH$, the most reactive ROS [166]. Another important antioxidant is GSH that reacts directly with several ROS, including oxyl radicals ($RO^{\bullet}$), peroxyl radicals ($RO_2^{\bullet}$), $^{\bullet}OH$ and $^1O_2$. GSH also plays an important role as a cofactor of enzymes (GPx, glyoxylase, and prostaglandin endoperoxide isomerase, as well as serving in ascorbate metabolism) and in communication between cells (gap junctions) [167,168]. Moreover, it participates in the detoxification of many substances including peroxides and xenobiotics through the actions of glutathione-S-transferase and glutathione peroxidase. GSH can also oxidize nonenzymatically in the presence of copper and iron to form the thiol radicals ($GS^{\bullet}$ and $GSS^{\bullet}G$), which are intermediates in the generation of oxidized glutathione and ROS (H_2O_2, $O_2^{\bullet-}$, $^{\bullet}OH$) [169].

Heme oxygenase 1 (HO-1) also has important roles in the protection

Table 1
Effects of UV radiation on human health and its biomarkers.

Consequences of UVA and UVB exposure	Biomarkers	References
DNA damage	CPD, 6,4PP, oxidized bases, single strand breaks	22, 25–28, 30–35, 41
Redox process	Biomolecule oxidation	25, 62, 63, 81–85, 91–96
Inflammation	Cytokines (IL-1, IL-6, IL-10, IL-12 and TNF-alpha) COX-2	135–137, 141
Immunosuppression	IL-10, prostaglandins	144–147
Vitamin D synthesis	25-hydroxyvitamin D (25(OH)D) in serum	149, 152
Microenvironment modification	Collagen breakdown	132, 140
Cell death	Apoptosis and necrosis	30, 110, 124, 125
Transcription factor induction	AP-1, NF-kB, Nrf−2	140, 148, 172, 173

against UVA-induced ROS [170,171]. This enzyme is responsible for the heme metabolism to carbon monoxide (CO), ferrous iron and biliverdin. Biliverdin is further reduced to bilirubin by biliverdin reductase. Heme metabolites are also implicated in the anti-inflammatory response through cytokine suppression. The overexpression of HO-1 after UV exposure is controlled by Nrf2 [172], a transcription factor that is involved in the expression of the vast majority of the genes associated with ROS defense, and by the repressor protein Bach1 [173]. Additional effort is needed to completely elucidate the activation and modulation of Nrf2 expression in response to sunlight and to exposure to UVA and UVB separately. Interestingly, although there is evidence that suggests that UVB radiation probably does not activate Nrf2 expression in skin cells, UVA can activate this transcription factor in both fibroblasts and keratinocytes [63,172]. Nrf2 is also modulated by various compounds such as quercetin, ellagic acid, and resveratrol [172], which belong to a class of non-enzymatic antioxidant molecules. Carotenoids are pigments found in the photosynthetic plant tissues and are acquired through the dietary intake of fruits and vegetables. Their antioxidant properties have been studied over the last decades, including their roles in protection from sunlight-induced skin damage [174,175]. In addition, *in vitro* and *in vivo* studies have demonstrated that carotenoids can suppress ROS formation, thus preventing lipid peroxidation, photoinactivation of antioxidant enzymes, and induction of oxidatively generated DNA damage after UVA and UVB exposure [176–180]. Furthermore, studies conducted in humans supplemented with beta-carotene or with a mix of carotenoids showed that the induction of erythema was less pronounced after UV exposure [181–183].

Ascorbic acid (Vitamin C) and alpha-tocopherol (Vitamin E) are the most abundant antioxidants present in the epidermis and dermis followed by various carotenoids (lycopene, beta-carotene and phytoene) [184]. The protective effect of these dietary compounds has been tested in cultured keratinocytes, animal models and humans. Vitamin C, E and polyphenols are able to scavenge ROS, including H_2O_2, $^{\bullet}OH$ and $O_2^{\bullet-}$, decreasing lipid peroxidation and interleukins levels after UVA and UVB exposure [184–190].

9. DNA repair deficiency and human diseases

Several DNA repair pathways are involved in the removal and/or tolerance of DNA lesions in living cells. These pathways are highly conserved throughout evolution, and for human cells they are involved in the maintenance of genome stability to prevent carcinogenesis and aging. This is dramatically demonstrated by DNA repair hereditary defects that give rise to certain rare genetic syndromes, including ataxia telangiectasia, Nijmegen breakage syndrome, Werner syndrome, Bloom syndrome, Fanconi anemia, xeroderma pigmentosum (XP), Cockayne syndrome (CS), trichothiodystrophy (TTD), UV-sensitive syndrome, and XPF/ERCC1 syndrome (XFE). Although the symptoms differ among these conditions, these human disorders share many clinical features that may include photosensitivity, growth retardation, neurological problems, premature ageing, skin alterations including abnormal pigmentation, telangiectasia, xerosis cutis, and pathological wound healing as well as an increased risk of developing various types of cancer [191]. Deficiencies related to the repair of endogenous DNA lesions, including those generated during oxidative stress, are proposed as the main causes for the symptoms that involve developmental and neurological problems as well as premature aging [5,192].

Although BER is an indispensable mechanism for the repair of oxidized DNA bases, none of the human syndromes cited above is associated with mutations in genes of this DNA repair pathway. It is likely that this could be partially explained on the basis that several distinct paralogues of the BER proteins with overlapping functions are encoded by the genome, and the enzymes have relatively low substrate specificities. For example, the DNA glycosylases have a relatively wide specificity to remove damaged bases from the DNA backbone by hydrolyzing the N-glycosidic bond between the sugar C1' and the base [193]. However, persistent oxidatively generated DNA damage and BER activity have been implicated in several other human diseases, in particular cancer and inherited and acquired neurological disorders including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis as well as in aging [194–197]. Another example is *MUTYH*-associated polyposis (MAP) syndrome, in which the patients demonstrate a recessively heritable colorectal polyposis that is linked to an increased risk of colorectal cancer, due to the occurrence of biallelic germline mutations in the MUTYH gene [198]. MUTYH is a mismatch-repairing glycosylase that scans the newly synthesized daughter strand to locate and remove adenine that is mispaired with 8-oxoG [199], but the absence of this protein is sufficient for the phenotype observed in MAP patients.

BER preferentially repairs non-bulky, non-helix-distorting lesions by removing and repairing damage sustained by deamination, alkylation or oxidation processes, including those induced by sunlight. Briefly, the BER mechanism comprises four minimal steps: (i) base lesion recognition and excision by a DNA glycosylase and cleavage of the resulting apurinic/apyrimidinic (AP) site in a concerted reaction by the AP lyase function associated with the DNA glycosylase (bifunctional glycosylases) or by an AP-endonuclease (APE1, for monofunctional glycosylases); (ii) cleaning of 3' blocked termini at the strand break by APE1 and/or polynucleotide kinase 3' phosphatase (PNKP) and 5' blocking phosphodeoxyribose by DNA polymerase β (Polβ); (iii) gap filling by a DNA polymerase; and (iv) nick sealing by DNA ligases to complete repair [200]. There are two major BER sub-pathways in mammalian cells: the long- and short-patch BER (LP-BER, SP-BER, respectively). Short-patch BER replaces excised damage with a single nucleotide using the core proteins: APE1, Polβ, DNA ligase III (LIG3) and X-ray repair cross-complementing protein 1 (XRCC1). In contrast, LP-BER uses APE1 to make a 5' incision at the AP-site and a combination of DNA polymerases β/δ/ε, proliferating cell nuclear antigen (PCNA) and flap endonuclease (FEN1) displaces the strand 3' to the nick producing a flap of 2–10 nucleotides, and then FEN1 endonuclease is responsible for cutting the junction of the single-to-double-strand transition. Pol δ/ε in conjunction with PCNA synthesizes the oligonucleotide to fill the gap, and ligation is performed by Ligase I (LIG1) [195].

In fact, several of the human syndromes listed above are associated with mutations in the genes of NER pathway. NER is a highly versatile and sophisticated DNA repair pathway that counteracts the deleterious effects of numerous structurally unrelated DNA lesions, including lesions that distort the DNA double helix, interfere in base pairing and block DNA duplication and transcription [34]. The first syndrome for which the DNA metabolism defect was described was *xeroderma pigmentosum* (XP; from the Greek, *xero*, dry and *derma*, skin, and the Latin, *pigmentosum*, paint, pigmented) [201,202]. These patients present mainly exacerbated symptoms associated with skin cancer and skin aging. Defective damage removal or tolerance are most likely responsible for the symptoms, and the participation of oxidatively generated DNA damage in these dermal XP symptoms is not completely clear, but they can be related, as illustrated in Fig. 4.

Most XP patients have a defect in NER, which is responsible for the removal of CPD and 6-4PP from the genome, although some XP patients also have defects in the replication of UV-damaged DNA. The main clinical symptom of XP patients is the high frequency of tumors in the sunlight-exposed areas of the skin. Specifically, XP patients under the age of 20 years show a 10,000-fold increase in skin cancer, which demonstrates the substantial importance of DNA repair in cancer prevention in the general population [203–205]. XP patients are also known to have many skin lesions in areas exposed to sunlight, which has a clear parallel with skin photoaging [5]. Twenty to thirty percent of the XP patients also have neurological and or developmental problems that are most likely associated with unrepaired DNA damage [5].

A recently published study analyzed the largest reported cohort of XP patients (89 people; this represents approximately 90% of the XP

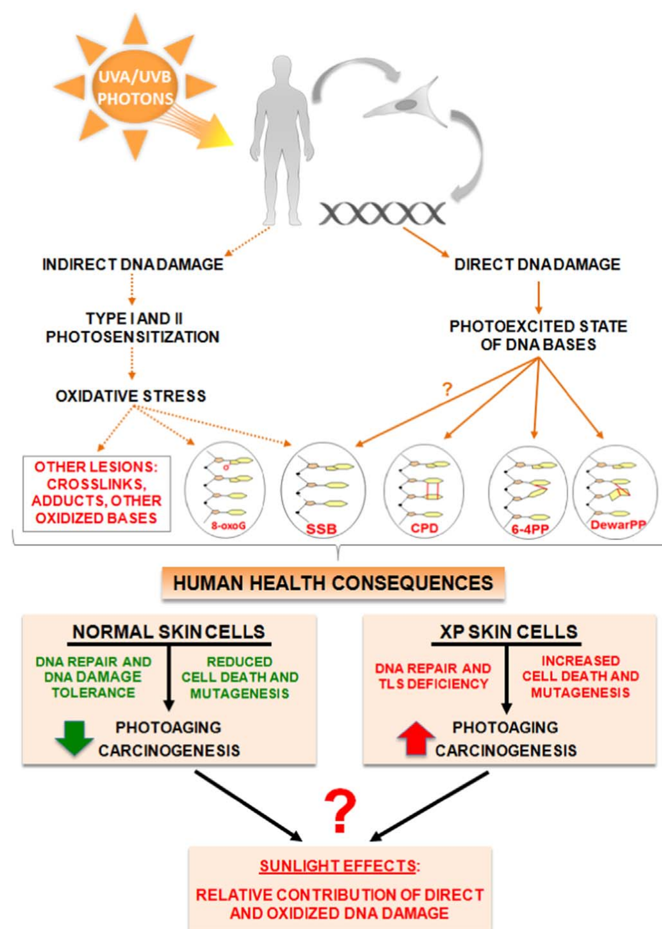

Fig. 4. The DNA damage induced by sunlight has deleterious consequences on human health, such as skin photoaging and carcinogenesis. These consequences are clearly increased in XP patients when compared to the general population. Because these clinical outcomes are increased in XP patients, studies with XP cells may help to better understand the relative contribution of direct and oxidatively generated DNA lesions on these consequences, in both normal individuals and XP patients.

patients in UK) [206]. All participants were examined by the same clinicians using 60 different phenotypical end-points, and in all cases, the observations were correlated with the pathological mutations. The deep phenotyping approach has revealed the heterogeneity of the clinical features between and within complementation groups. The results indicate that skin cancer is most common in XP-C, XP-E, and XP-V patients, which were previously considered to be the milder groups based on cellular analyses. XP-C patients are specifically hypersensitive to ocular damage, and XP-F and XP-G appear to be much less susceptible to skin cancer than other XP groups [206]. However, patients in groups XP-A, XP-D, and XP-G are considered to have the most severe forms of the disease, with early-onset neurological degeneration and abnormally severe sunburn reactions. However, depending on the type and location of the mutation, patients can present milder phenotypes than expected for the gene affected [206].

Curiously, although patients with CS and TTD also have mutations in NER genes, they are cancer-free [207] but generally present developmental defects, neurodegeneration, and accelerated aging [208]. Evidence has shown that NER proteins are involved in repairing oxidatively generated damage [201,209–213]. Recent work using an NER-deficient mouse model provided evidence demonstrating the participation of metabolically induced DNA damage, which, in the absence of repair, blocks gene transcription and results in accelerated aging [214]. In both XP and CS syndromes the severity of the symptoms can be quite variable depending on the complementation group and on the nature of the mutation. Although the participation of NER in the repair of oxidized DNA damage is well accepted, the effects of these types of lesions induced by sunlight, and especially UVA, on the skin of such patients is usually neglected. Thus, it is possible that several types of UVA-induced DNA damage, not only pyrimidine dimers, could be associated with at least a part of the XP patients' dermal symptoms (including tumors and skin photoaging).

10. Relevance of oxidatively generated DNA damage in NER-deficient cells

NER can be summarized as having four sequential steps to remove DNA damage, including (i) lesion recognition, (ii) unwinding the damaged double helix, (iii) cleavage and excision of the damaged strand and (iv) filling the gap in the molecule by DNA synthesis and final ligation. In all those steps more than 30 proteins act in a sequential and concerted manner to effect repair [5,215].

In summary, NER operates by two distinct pathways: global genome repair (GGR), which removes lesions from the entire genome, and transcription-coupled repair (TCR), which repairs transcriptionally active regions. The GGR sub-pathway involves the recognition of DNA lesions throughout the genome and depends on the XPC/HR23B protein complex as the primary DNA-damage detector. For some types of lesions such as CPDs, the damaged DNA-binding (DDB) complex (composed of two proteins, including XPE) is required to improve the efficiency of the damage recognition and removal. In TCR, the RNA polymerase II (RNAPII) is stalled at the sites of the lesions on the transcribed strand, which plays a role in the recognition step. Transcription arrest, damage recognition and the subsequent repair involve CSA and CSB proteins that are required for ubiquitination of the carboxy-terminal domain of RNAPII [5,215,216].

Subsequently, the repair process follows the same path through the binding of the TFIIH complex via interaction with either XPC or the arrested transcription machinery. TFIIH includes the XPB and XPD proteins, which are 3'–5' and 5'–3' ATP-dependent DNA helicases, respectively. This complex unwinds ~30 bp at the damaged DNA site, which is covered by a single RPA (Replication Protein A) protein and XPA homodimer. These proteins are probably involved in the correct three-dimensional assembly of the NER machinery prior to the endonucleolytic cleavage step. Then, the DNA around the damaged site is cleaved by the XPF-ERCC1 5' and the XPG 3' endonucleases. Once the damaged oligonucleotide is removed, resynthesis is performed by proliferating cell nuclear antigen (PCNA) and replicative DNA polymerases δ and ε, which use the 3'-hydroxyl extremity generated by the XPF/ERCC1 incision as a primer to synthesize DNA at the 30-nucleotide-gap. The resulting nick at the 5' end of the gap is sealed by DNA ligase I or III, thus restoring the original DNA molecule in an error-free manner [5,215,216].

The clinical heterogeneity of symptoms presented by patients with NER-associated disorders raises the question of whether defects in this pathway are solely due to impaired repair of helix-distorting DNA lesions, such as the photoproducts CPDs and 6-4PPs. The defects in the roles of the NER proteins in the repair of oxidatively generated DNA damage may be the underlying mechanism behind the accelerated aging and neurodegeneration in CS patients, increased risk for internal cancer development in XPC and neurodegeneration in XPA patients, and the complex phenotypes of XPB, XPD, and XPG patients [201,212,217]. In addition, oxidized DNA bases that are mainly generated by UVA radiation and are different from the classical photoproducts may also affect the skin and induce important symptoms, including cancer. However, little is known about the effect of UVA in NER-deficient cells, and this deserves to be investigated.

CS proteins play critical roles in TC-NER. In addition, CSB can interact with chromatin-bound RNAPII, which suggests that these two proteins are combined in high molecular weight protein complexes [218,219]. Thus, it has been suggested that CSB can stimulate

transcriptional elongation by RNAPII to add one nucleotide to the nascent transcript, which implies a functional interaction between these two proteins [219–221]. CSA is a component of a protein complex that contains also the COP9 signalosome (CSN), a known regulator of cullin-based E3 ubiquitin ligases [216]. In a mechanism that is not well understood, CSA translocates to the stalled RNAPII-CSB complex at the DNA damage site in a CSB-dependent manner [218,222]. The CSA-containing ubiquitin ligase complex has been implicated in the ubiquitination and subsequent degradation of CSB as well as in the termination of the TC-NER process and the restoration of transcription [223]. An integrated model would include the ubiquitination of CSB or the RNAPII large subunit by CSA as a signal for CSB to disassemble the initial TCR complex, leaving the NER complex to finish the job [216].

In addition, the CSA and CSB proteins might have an additional function in the removal of oxidatively generated DNA damage in the nuclei and mitochondria. Studies indicate that human cells deficient in CSB or CSA are more sensitive to H_2O_2 treatment [224] and that primary fibroblasts and keratinocytes from CSA patients are hypersensitive to potassium bromate, a specific inducer of oxidative damage [225]. Furthermore, primary fibroblasts derived from CSA and CSB patients also present an altered redox balance with increased steady-state levels of intracellular ROS as well as basal and induced oxidated DNA [226]. Less information is available for CSA than for CSB, but CSA appears to be involved in the response of oxidatively generated DNA damage in humans [212]. For CSB, it is already known that it can interact with several members of BER pathway, including the strand-break response protein poly(ADP-ribose) polymerase-1 (PARP1), endonuclease VIII-like 1 (NEIL1) DNA glycosylase, and APE1 [227]. In addition, CSB has a regulatory effect on OGG1 expression, and a deficiency in CSB leads to the accumulation of 8-oxoG in DNA [102,228]. Emerging evidence also indicates that CS proteins have additional roles in maintaining mitochondrial DNA (mtDNA) stability, probably by anchoring the BER machinery at lesion sites in mtDNA [229,230]. For instance, after oxidative stress, CSA and CSB proteins are present in mitochondria, where they can directly interact with mtDNA, mtOGG1 and mitochondrial single-stranded DNA-binding protein (mtSSBP-1) [230]. In addition, it has been shown that mtDNA damage accumulates in CSB-defective cells [231].

However, it is important to mention that Brooks (2013) has proposed that although defective TC-NER could explain sun sensitivity in CS patients, a combination of transcription abnormalities that affect RNA polymerases I and II provides an alternative explanation for many aspects of CS-associated neurologic disease and other internal features of CS [232]. Thus, although several lines of evidence support the idea that CS symptoms may be partially explained by the involvement of CSA and CSB in the repair of oxidatively generated DNA lesions and that the accelerated aging may be due to the accumulation of DNA damage in the mitochondria, this is still matter of debate and additional studies are required to gain further insights into the molecular mechanisms that involve the CS proteins in the repair of oxidized DNA bases.

Nevertheless, defects in both XP and CS can occur together in the same patient, which gives rise to a XP/CS phenotype [233]. In these patients, the skin manifestations of XP are observed together with the neurological features of CS, such as calcification of the basal ganglia, demyelination, and cerebellar dysfunction. In general, XP/CS cases are associated with mutations in the *XPB*, *XPD*, or *XPG* genes [234], although mutations on these same genes can also be associated with XP (affecting the skin) only.

The participation of XPG in the repair of oxidized pyrimidines such as 5,6-dihydroxy-5,6-dihydrothymine (thymine glycol) may involve the promotion of binding of the DNA glycosylase-AP lyase hNth1 to the damaged site in human cells [235]. In addition, melanocytes derived from a XPG patient appeared to be deficient in the repair of oxidatively generated DNA damage, which suggested that XPG participates in the repair of these DNA lesions [236]. In fact, fibroblasts from a XPG patient who presented the XP/CS clinical phenotype were shown to be sensitive to UV radiation as well as to photoactivated methylene blue, which generates $^1O_2$ and also reacts with guanine through type I photosensitization mechanism [237], while some XPG mutations (from XP patients with no clinical symptoms related to CS) affect sensitivity to UV radiation but not of oxidatively generated DNA damage [238]. Therefore, mutations in the *XPG* gene support the model that suggests that the development of CS in XPG patients may be related to inefficient excision of endogenous oxidatively generated damage. Clearly, variants of the XPG protein may lead to divergent and complex phenotypes. These observations suggest that the XP phenotype may arise from missense mutations in the *XPG* gene that generally result in a stable XPG protein, whereas XP/CS originates from mutations that result in a truncated and/or unstable XPG protein [238–240].

The helicases must unwind DNA at the right place and time to maintain genomic integrity or gene expression. XPB and XPD are helicases that are present in the human TFIIH complex and catalyze the separation of the DNA duplex by moving along this macromolecule powered by ATP binding and hydrolysis during transcription and repair [241]. In addition to photosensitivity, mutations in the *XPB* and *XPD* genes can also induce premature aging with profound neurological defects as well as increased cancer risk [202]. In DNA repair process, after initial damage recognition and binding of other repair proteins, TFIIH is recruited to the damage opening approximately 27 nucleotides of the excision bubble. Then, the XPD bound to the damaged DNA interacts with XPG and promotes DNA incision. Finally, removal of TFIIH is necessary for re-synthesis of the incised damaged strand. Therefore, mutations on XPB or XPD that destabilize TFIIH generally lead to cell death and tissue degeneration whereas mutations that cause defects in the helicase or ATPase activities disrupt repair and lead to cancer [241]. Despite scarce information regarding the role of either the XPB and XPD helicases in the repair of oxidized DNA bases in the nucleus, it was recently demonstrated that XPD localizes in mitochondria where the helicase activity is critical for the protection of the mtDNA by facilitating the repair of oxidatively generated DNA damage [242].

XPC is one of the key DNA damage-recognition proteins in the GGR and mutations in this gene can increase cancer risk, although neurodegeneration is rarely seen on this group of patients [5,243]. The human XPC forms a heterotrimeric complex that includes the HR23B and centrin-2 proteins. HR23B seems to stabilize XPC, whereas centrin-2 is required to enhance the damage-recognition function of XPC [5,216]. This complex binds to various types of helix-distorting lesions, but it does not bind exactly at the damaged site. XPC protein seems to distinguish between damaged DNA and the native double helix by sensing the single-stranded character of the non-hydrogen-bonded bases in the undamaged strand [241]. In addition to the main role of the XPC complex in the recognition of DNA-distorting lesions, it has been demonstrated that it can functionally interact with several BER proteins, including 3-methyladenine DNA glycosylase, thymine DNA glycosylase (TDG), uracil-DNA glycosylases (UDG), apurinic/apyrimidinic endonuclease 1 (APE1), and 8-oxoguanine DNA glycosylase (OGG1) [244–251]. The proposed mechanism suggests that the XPC complex might bend DNA at the damaged site to facilitate the loading and turnover of the BER glycosylases through protein interaction [244]. A strong indication of this additional function of XPC in the repair of oxidized DNA bases is provided by a mutation that weakens the interaction with OGG1 and, consequently, its cleavage activity. In fact, this mutation was found in one of the rare cases of XPC patients who demonstrate neurological problems [252]. Additionally, studies using human keratinocytes and fibroblasts from XPC patients showed that this protein is important to prevent the accumulation of oxidatively generated DNA damage and its killing effects after exposure to oxidants, such as potassium bromate, X-rays, and methylene blue plus visible light [244,245,253]. However, it is important to mention that the rapid recruitment of XPC to sites of oxidized DNA lesions in living cells occurs

without triggering the recruitment of other GG-NER factors [254].

With regard to the role of XPA in the cellular responses to oxidative stress, it has been shown that fibroblasts that lack functional XPA demonstrate increased genotoxicity and a reduced capacity to repair damage when subjected to oxidative stress [255]. It has been proposed that 5',8-cyclo-2'-deoxyribonucleosides may explain the severe cases of neurodegeneration found in XPA patients because these bulky lesions are exclusively repaired by the NER pathway [256,257]. However, the biological relevance of this type of DNA damage is unclear because they are very rare lesions, due to the very low efficiency of •OH-mediated formation [258]. Furthermore, analysis of the autopsied brains of XPA patients revealed increased oxidized DNA and RNA molecules, enhanced lipid peroxidation, and a disturbed expression of Cu/ZnSOD and MnSOD enzymes, which suggested the existence of oxidative stress in the brain cells of these patients [259]. The induction of clusters of oxidized bases might also be the result of oxidative stress with important biological consequences in the cells [260–262]. Interestingly, recent evidence has indicated that oxidatively generated tandem base damage such as two vicinal 8-oxoG modifications, when in the transcribed strand, may increase mutagenesis in cells that lack XPA protein, which indicated that close base damage may depend on NER [217]. This is consistent with the results of a previous study that revealed that the TCR of 8-oxoG is dependent on OGG1, XPA, CSB, UVSSA, and the actively elongating RNA polymerase II, which suggests that there is crosstalk between the DNA repair pathways [213].

Another important, but normally neglected, fact concerning sunlight exposure is that UVA radiation can promote the oxidation of the proteins that are involved in DNA repair, which would impair the removal of the DNA damage. This appears to be particularly relevant with respect to the NER pathway. Recently, it was clearly shown that the oxidative stress generated by UVA promotes oxidation of RPA, which debilitates the ability of the NER to remove photoproducts from human keratinocytes [263]. The susceptibility of the NER proteins to the oxidation generated by UVA or other substances compromises the cell protection against DNA damage, which has clear implications for carcinogenesis [264]. This aspect indicates how protein oxidation can affect the cells' abilities to repair DNA damage, which will be further discussed in another article from this issue.

11. Oxidatively generated DNA damage and translesion synthesis

Some XP patients have a normal capacity to remove DNA lesions from their genome but still demonstrate symptoms associated with sensitivity to sunlight including a high frequency of skin tumors and photoaging. These patients are known as XP variants, and they lack the Pol eta activity [265]. Pol eta is encoded by the *POLH* gene, which has the primary function of properly performing the TLS of damaged DNA, inserting AA in sites that contain TT dimers induced by UV radiation [266,267]. This function contributes to the protection of human cells from the potentially mutagenic effects of UV radiation [268]. In Pol eta-deficient cells, the TT dimers are replicated less efficiently by other DNA polymerases of TLS (usually of Y family), which results in a mutator phenotype that is probably responsible for the high frequency of tumors in these patients [268,269]. As previously noted, UV radiation induces mainly C to T transitions whereas in XP-V cells, the occurrence of T to A transversions, and high levels of G to T and G to C transversions are also observed [265,270]. This raises the question of whether pyrimidine dimers are the only components responsible for this increase in mutagenesis in the XP-V cells or if oxidatively generated DNA damage can also participate in the carcinogenesis process observed in the XP-V patients.

There is evidence that Pol eta performs the bypass of other types of DNA lesions, including O4-methylthymine, O6-methylguanine, and acetylaminofluorene, cisplatin and oxaliplatin adducts. It can also perform the bypass, with moderate efficiency, of 8-oxoG, which has a potentially important role in the suppression of mutations due to this oxidatively generated DNA lesion in human cells [109,271]. Pol eta can insert A or C opposite a site with 8-oxoG, which may result in a G to T transversion. However, in the absence of Pol eta, other TLS polymerases maybe less efficient, which would increase the frequency of this type of mutation. Because UVA radiation may induce oxidized bases, the contribution of these lesions to the process of skin cancer formation in XP-V patients is not known [108,109]. A previously published study in which *Saccharomyces cerevisiae* was exposed to simulated sunlight supports the role of Pol eta in TLS of CPDs and 6-4PPs [52]. Despite growing interest in understanding how mutations contribute to high rates of skin cancer that are due to sunlight exposure, knowledge on the effects of UVA and UVB radiation in human XP-V cells is scarce. Furthermore, these patients have skin lesions that resemble the normal products of photoaging. Thus, studies of the responses of XP-V cells to these wavelengths may help us to understand the origins of the sunlight effects in normal skin.

12. Concluding remarks

Solar UV radiation is a ubiquitous environmental genotoxic agent to which almost everyone is exposed on a daily basis. The effects of UV radiation on human health depend on the amount and type of radiation impinging on the body. Although UVB photons have the highest efficacy to generate the mutagenic and cytotoxic pyrimidine dimers (i.e., CPDs and 6-4PPs), they are also responsible for initiating the synthesis of vitamin D in the skin through the absorption of UVB radiation by 7-dehydrocholesterol. Therefore, exposure to UVB should not be entirely avoided because this would create a huge burden of skeletal disease from vitamin D deficiency. Thus, public health messages regarding safe exposure to the sun are very important to guide people to prefer recurrent shorter periods of exposure to achieve vitamin D production while minimizing the harmful consequences of UV-induced DNA damage due to prolonged exposures.

Sunlight-induced DNA damage is considered to be the main cause for the genetic changes responsible for skin lesions and carcinogenesis including malignant melanoma. However, it is generally accepted that single oxidized DNA bases (i.e., 8-oxoG) are efficiently and quickly (3–6 h) eliminated from the genome by the BER pathway. Nevertheless, oxidizing agents can induce other types of DNA lesions including bulky lesions that block DNA transcription. Thus, these results also raise questions regarding the roles of NER proteins in the repair of DNA damage that is oxidatively generated by sunlight. Similarly, tolerance mechanisms involving the bypass of these lesions may participate in the protection of cells from the deleterious consequences of sunlight. These consequences of sunlight are more evident in XP patients, who are defective in NER or TLS. Thus, what emerges for now is a complex scenario where the mechanisms of additional functions of NER proteins and Pol eta still need to be fully understood, mainly because the range of oxidatively generated DNA lesions induced by sunlight is large. Further studies need to be performed to define the mechanistic basis of the NER and TLS involvement in the cellular consequences of the sunlight-induced oxidation of DNA bases and to address whether this process might be a relevant factor in the development of skin cancer and photoaging.

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References

[1] A.P. Schuch, C.C. Garcia, K. Makita, C.F. Menck, DNA damage as a biological sensor for environmental sunlight, Photochem. Photobiol. Sci. 12 (2013) 1259–1272.
[2] M.F. Holick, Vitamin D deficiency, N. Engl. J. Med. 357 (2007) 266–281.
[3] R.M. Lucas, M. Norval, R.E. Neale, A.R. Young, F.R. de Gruijl, Y. Takizawa, J.C. van der Leun, The consequences for human health of stratospheric ozone depletion in association with other environmental factors, Photochem. Photobiol. Sci. 14 (2015) 53–87.
[4] A. Kammeyer, R.M. Luiten, Oxidation events and skin aging, Ageing Res. Rev. 21 (2015) 16–29.
[5] C.F. Menck, V. Munford, DNA repair diseases: what do they tell us about cancer and aging?, Genet. Mol. Biol. 37 (2014) 220–233.
[6] R.L. McKenzie, P.J. Aucamp, A.F. Bais, L.O. Bjorn, M. Ilyas, S. Madronich, Ozone depletion and climate change: impacts on UV radiation, Photochem. Photobiol. Sci. 10 (2011) 182–198.
[7] R.L. McKenzie, P.J. Aucamp, A.F. Bais, L.O. Bjorn, M. Ilyas, Changes in biologically-active ultraviolet radiation reaching the Earth's surface, Photochem. Photobiol. Sci. 6 (2007) 218–231.
[8] A.F. Bais, R.L. McKenzie, G. Bernhard, P.J. Aucamp, M. Ilyas, S. Madronich, K. Tourpali, Ozone depletion and climate change: impacts on UV radiation, Photochem. Photobiol. Sci. 14 (2015) 19–52.
[9] F.R. de Gruijl, J.C. van der Leun, Environment and health: 3. Ozone depletion and ultraviolet radiation, CMAJ 163 (2000) 851–855.
[10] WMO, Scientific Assessment of Ozone Depletion: 2014. Global Ozone Research and Monitoring Project. Geneva, Switzerland: WMO (World Meteorological Organization), 2015.
[11] A.T.J. de Laat, R.J. van der, A.A.F. Allaart, M. van Weele, G.C. Benitez, C. Casiccia, N.M.P. Leme, E. Quel, J. Salvador, E. Wolfram, Extreme sunbathing: Three weeks of small total O3 columns and high UV radiation over the southern tip of South America during the 2009 Antarctic O3 hole season, Geophys. Res. Lett. 37 (2010).
[12] A.F. Pazmiño, S. Godin-Beekmann, M. Ginzburg, S. Bekki, A. Hauchecorne, R.D. Piacentini, E.J. Quel, Impact of Antarctic polar vortex occurrences on total ozone and UVB radiation at southern Argentinean and Antarctic stations during 1997–2003 period, J. Geophys. Res. Atmos. 110 (2005) 1–13.
[13] V.W.J.H. Kirchhoff, Y. Sahai, C.A.R. Casiccia, F. Zamorano, V. Valderrama, Observations of the 1995 ozone hole over Punta Arenas, Chile, J. Geophys. Res. Atmos. 102 (1997) 16109–16120.
[14] V.W.J.H. Kirchhoff, N.J. Schuch, D.K. Pinheiro, J.M. Harris, Evidence for an ozone hole perturbation at 30° south, Atmos. Environ. 33 (1996) 1481–1488.
[15] R.A. Guarnieri, L.F. Padilha, F.L. Guarnieri, E. Echerc, K. Makita, D.K. Pinheiro, A.M.P. Schuch, L.S. Boeira, N.J. Schuch, A study of the anticorrelations between ozone and UV-B radiation using linear and exponential fits in southern Brazil, Adv. Space Res. 34 (2004) 764–768.
[16] E.J. Brinksma, Y.J. Meijer, B.J. Connor, G.L. Manney, J.B. Bergwerff, G.E. Bodeker, I.S. Boyd, J.B. Liley, W. Hogervorst, J.W. Hovenier, N.J. Livesey, D.P.J. Swart, Analysis of record-low ozone values During the 1997 winter over Lauder, N.Z. Geophys. Res. Lett. 25 (1998) 2785–2788.
[17] N. Semane, H. Bencherif, B. Morel, A. Hauchecorne, R.D. Diab, An unusual stratospheric ozone decrease in the Southern hemisphere subtropics linked to isentropic air-mass transport as observed over Irene (25.5°S, 28.1°E) in mid-may 2002, Atmos. Chem. Phys. 6 (2006) 1927–1936.
[18] A.P. Schuch, M.B. Dos Santos, V.M. Lipinski, L.V. Peres, C.P. Dos Santos, S.Z. Cechin, N.J. Schuch, D.K. Pinheiro, E.L.S. Loreto, Identification of influential events concerning the Antarctic ozone hole over southern Brazil and the biological effects induced by UVB and UVA radiation in an endemic treefrog species, Ecotoxicol. Environ. Saf. 118 (2015) 190–198.
[19] B.H. Petkov, V. Vitale, C. Tomasi, A.M. Siani, G. Seckmeyer, A.R. Webb, A.R.D. Smedley, G.R. Casale, R. Werner, C. Lanconelli, M. Mazzola, A. Lupi, M. Busetto, H. Diemoz, F. Goutail, U. Kohler, B.D. Mendeva, W. Josefsson, D. Moore, M.L. Bartolome, J.R.M. Gonzalez, O. Misaga, A. Dahlback, Z. Toth, S. Varghese, H. De Backer, R. Stubi, K. Vanicek, Response of the ozone column over Europe to the 2011 Arctic ozone depletion event according to ground-based observations and assessment of the consequent variations in surface UV irradiance, Atmos. Environ. 85 (2014) 169–178.
[20] A.P. Schuch, T. Yagura, K. Makita, H. Yamamoto, N.J. Schuch, L.F. Agnez-Lima, R.M. MacMahon, C.F. Menck, DNA damage profiles induced by sunlight at different latitudes, Environ. Mol. Mutagen. 53 (2012) 198–206.
[21] J.C. Sutherland, K.P. Griffin, Absorption spectrum of DNA for wavelengths greater than 300 nm, Radiat. Res. 86 (1981) 399–409.
[22] R.M. Tyrrell, Induction of pyrimidine dimers in bacterial DNA by 365 nm radiation, Photochem. Photobiol. 17 (1973) 69–73.
[23] Z. Kuluncsics, D. Perdiz, E. Brulay, B. Muel, E. Sage, Wavelength dependence of ultraviolet-induced DNA damage distribution: involvement of direct or indirect mechanisms and possible artefacts, J. Photochem. Photobiol. B. 49 (1999) 71–80.
[24] D. Perdiz, P. Grof, M. Mezzina, O. Nikaido, E. Moustacchi, E. Sage, Distribution and repair of bipyrimidine photoproducts in solar UV-irradiated mammalian cells. Possible role of Dewar photoproducts in solar mutagenesis, J. Biol. Chem. 275 (2000) 26732–26742.
[25] T. Douki, A. Reynaud-Angelin, J. Cadet, E. Sage, Bipyrimidine photoproducts rather than oxidative lesions are the main type of DNA damage involved in the genotoxic effect of solar UVA radiation, Biochemistry 42 (2003) 9221–9226.
[26] S. Mouret, C. Baudouin, M. Charveron, A. Favier, J. Cadet, T. Douki, Cyclobutane pyrimidine dimers are predominant DNA lesions in whole human skin exposed to UVA radiation, Proc. Natl. Acad. Sci. USA 103 (2006) 13765–13770.
[27] A.P. Schuch, R. da Silva, Galhardo, K.M. de Lima-Bessa, N.J. Schuch, C.F. Menck, Development of a DNA-dosimeter system for monitoring the effects of solar-ultraviolet radiation, Photochem. Photobiol. Sci. 8 (2009) 111–120.
[28] Y. Jiang, M. Rabbi, M. Kim, C. Ke, W. Lee, R.L. Clark, P.A. Mieczkowski, P.E. Marszalek, UVA generates pyrimidine dimers in DNA directly, Biophys. J. 96 (2009) 1151–1158.
[29] S. Mouret, C. Philippe, J. Gracia-Chantegrel, A. Banyasz, S. Karpati, D. Markovitsi, T. Douki, UVA-induced cyclobutane pyrimidine dimers in DNA: a direct photochemical mechanism?, Org. Biomol. Chem. 8 (2010) 1706–1711.
[30] B. Cortat, C.C. Garcia, A. Quinet, A.P. Schuch, K.M. de Lima-Bessa, C.F. Menck, The relative roles of DNA damage induced by UVA irradiation in human cells, Photochem. Photobiol. Sci. 12 (2013) 1483–1495.
[31] D. Markovitsi, UV-induced DNA damage: the role of electronic excited States, Photochem. Photobiol. 92 (2016) 45–51.
[32] J. Cadet, S. Mouret, J.L. Ravanat, T. Douki, Photoinduced damage to cellular DNA: direct and photosensitized reactions, Photochem. Photobiol. 88 (2012) 1048–1065.
[33] J.S. Taylor, H.F. Lu, J.J. Kotyk, Quantitative conversion of the (6-4) photoproduct of TpdC to its Dewar valence isomer upon exposure to simulated sunlight, Photochem. Photobiol. 51 (1990) 161–167.
[34] R.P. Rastogi, Richa, A. Kumar, M.B. Tyagi, R.P. Sinha, Molecular mechanisms of ultraviolet radiation-induced DNA damage and repair, J. Nucleic Acids 2010 (2010) 592980.
[35] J.H. Lee, G.S. Hwang, J.K. Kim, B.S. Choi, The solution structure of DNA decamer duplex containing the Dewar product of thymidylyl(3-5')thymidine by NMR and full relaxation matrix refinement, FEBS Lett. 428 (1998) 269–274.
[36] C. Han, A.K. Srivastava, T. Cui, Q.E. Wang, A.A. Wani, Differential DNA lesion formation and repair in heterochromatin and euchromatin, Carcinogenesis 37 (2016) 129–138.
[37] P.J. Rochette, D.E. Brash, Human telomeres are hypersensitive to UV-induced DNA Damage and refractory to repair, PLoS Genet. 6 (2010) e1000926.
[38] D.G. Su, H. Fang, M.L. Gross, J.S. Taylor, Photocrosslinking of human telomeric G-quadruplex loops by anti cyclobutane thymine dimer formation, Proc. Natl. Acad. Sci. USA 106 (2009) 12861–12866.
[39] S. Tommasi, M.F. Denissenko, G.P. Pfeifer, Sunlight induces pyrimidine dimers preferentially at 5-methylcytosine bases, Cancer Res. 57 (1997) 4727–4730.
[40] D.H. Lee, G.P. Pfeifer, Deamination of 5-methylcytosines within cyclobutane pyrimidine dimers is an important component of UVB mutagenesis, J. Biol. Chem. 278 (2003) 10314–10321.
[41] T. Douki, Relative Contributions of UVB and UVA to the Photoconversion of (6-4) Photoproducts into their Dewar Valence Isomers, Photochem. Photobiol. 92 (2016) 587–594.
[42] Y. Takeuchi, M. Murakami, N. Nakajima, N. Kondo, O. Nikaido, The Photorepair and Photoisomerization of DNA lesions in Etiolated cucumber cotyledons after irradiation by UV-B depends on wavelength, Plant Cell Physiol. 39 (1998) 745–750.
[43] U. Pogoda, de la Vega, P. Rettberg, T. Douki, J. Cadet, G. Horneck, Sensitivity to polychromatic UV-radiation of strains of Deinococcus radiodurans differing in their DNA repair capacity, Int. J. Radiat. Biol. 81 (2005) 601–611.
[44] R. Moeller, E. Stackebrandt, T. Douki, J. Cadet, P. Rettberg, H.J. Mollenkopf, G. Reitz, G. Horneck, DNA bipyrimidine photoproduct repair and transcriptional response of UV-C irradiated Bacillus subtilis, Arch. Microbiol. 188 (2007) 421–431.
[45] R. Moeller, T. Douki, P. Rettberg, G. Reitz, J. Cadet, W.L. Nicholson, G. Horneck, Genomic bipyrimidine nucleotide frequency and microbial reactions to germicidal UV radiation, Arch. Microbiol 192 (2010) 521–529.
[46] J.A. Meador, A.J. Baldwin, J.D. Pakulski, W.H. Jeffrey, D.L. Mitchell, T. Douki, The significance of the Dewar valence photoisomer as a UV radiation-induced DNA photoproduct in marine microbial communities, Environ. Microbiol. 16 (2014) 1808–1820.
[47] T. Douki, E. Sage, Dewar valence isomers, the third type of environmentally relevant DNA photoproducts induced by solar radiation, Photochem. Photobiol. Sci. 15 (2016) 24–30.
[48] G.P. Pfeifer, Y.H. You, A. Besaratinia, Mutations induced by ultraviolet light, Mutat. Res. 571 (2005) 19–31.
[49] U.P. Kappes, D. Luo, M. Potter, K. Schulmeister, T.M. Runger, Short- and long-wave UV light (UVB and UVA) induce similar mutations in human skin cells, J. Invest. Dermatol. 126 (2006) 667–675.
[50] H. Ikehata, K. Kawai, J. Komura, K. Sakatsume, L. Wang, M. Imai, S. Higashi, O. Nikaido, K. Yamamoto, K. Hieda, M. Watanabe, H. Kasai, T. Ono, UVA1 genotoxicity is mediated not by oxidative damage but by cyclobutane pyrimidine dimers in normal mouse skin, J. Invest. Dermatol. 128 (2008) 2289–2296.
[51] T.M. Runger, B. Farahvash, Z. Hatvani, A. Rees, Comparison of DNA damage responses following equimutagenic doses of UVA and UVB: a less effective cell cycle arrest with UVA may render UVA-induced pyrimidine dimers more mutagenic than UVB-induced ones, Photochem. Photobiol. Sci. 11 (2012) 207–215.
[52] S.G. Kozmin, Y.I. Pavlov, T.A. Kunkel, E. Sage, Roles of Saccharomyces cerevisiae DNA polymerases Poleta and Polzeta in response to irradiation by simulated sunlight, Nucleic Acids Res. 31 (2003) 4541–4552.
[53] A. Quinet, D.J. Martins, A.T. Vessoni, D. Biard, A. Sarasin, A. Stary, C.F. Menck, Translesion synthesis mechanisms depend on the nature of DNA damage in UV-irradiated human cells, Nucleic Acids Res. 44 (2016) 5717–5731.
[54] J. Dunn, M. Potter, A. Rees, T.M. Runger, Activation of the Fanconi anemia/BRCA pathway and recombination repair in the cellular response to solar ultraviolet

light, Cancer Res. 66 (2006) 11140–11147.
[55] I. Elvers, F. Johansson, P. Groth, K. Erixon, T. Helleday, UV stalled replication forks restart by re-priming in human fibroblasts, Nucleic Acids Res. 39 (2011) 7049–7057.
[56] M.B. Vallerga, S.F. Mansilla, M.B. Federico, A.P. Bertolin, V. Gottifredi, Rad51 recombinase prevents Mre11 nuclease-dependent degradation and excessive PrimPol-mediated elongation of nascent DNA after UV irradiation, Proc. Natl. Acad. Sci. USA 112 (2015) E6624–E6633.
[57] M.B. Federico, M.B. Vallerga, A. Radl, N.S. Paviolo, J.L. Bocco, M. Di Giorgio, G. Soria, V. Gottifredi, Chromosomal Integrity after UV Irradiation Requires FANCD2-Mediated Repair of Double Strand Breaks, PLoS Genet. 12 (2016) e1005792.
[58] K. Wischermann, S. Popp, S. Moshir, K. Scharfetter-Kochanek, M. Wlaschek, F. de Gruijl, W. Hartschuh, R. Greinert, B. Volkmer, A. Faust, A. Rapp, P. Schmezer, P. Boukamp, UVA radiation causes DNA strand breaks, chromosomal aberrations and tumorigenic transformation in HaCaT skin keratinocytes, Oncogene 27 (2008) 4269–4280.
[59] J. Cadet, T. Douki, Oxidatively generated damage to DNA by UVA radiation in cells and human skin, J. Invest. Dermatol 131 (2011) 1005–1007.
[60] J.L. Rizzo, J. Dunn, A. Rees, T.M. Runger, No formation of DNA double-strand breaks and no activation of recombination repair with UVA, J. Invest. Dermatol. 131 (2011) 1139–1148.
[61] R. Greinert, B. Volkmer, S. Henning, E.W. Breitbart, K.O. Greulich, M.C. Cardoso, A. Rapp, UVA-induced, DNA double-strand breaks result from the repair of clustered oxidative DNA damages, Nucleic Acids Res. 40 (2012) 10263–10273.
[62] J. Cadet, T. Douki, J.L. Ravanat, Oxidatively generated damage to cellular DNA by UVB and UVA radiation, Photochem. Photobiol. 91 (2015) 140–155.
[63] E. Sage, P.M. Girard, S. Francesconi, Unravelling UVA-induced mutagenesis, Photochem. Photobiol. Sci. 11 (2012) 74–80.
[64] H. Yasui, T. Hakozaki, A. Date, T. Yoshii, H. Sakurai, Real-time chemiluminescent imaging and detection of reactive oxygen species generated in the UVB-exposed human skin equivalent model, Biochem. Biophys. Res. Commun. 347 (2006) 83–88.
[65] T. Hakozaki, A. Date, T. Yoshii, S. Toyokuni, H. Yasui, H. Sakurai, Visualization and characterization of UVB-induced reactive oxygen species in a human skin equivalent model, Arch. Dermatol. Res. 300 (Suppl 1) (2008) S51–S56.
[66] K.U. Schallreuter, J.M. Wood, Thioredoxin reductase - its role in epidermal redox status, J. Photochem. Photobiol. B. 64 (2001) 179–184.
[67] B. Kalyanaraman, V. Darley-Usmar, K.J. Davies, P.A. Dennery, H.J. Forman, M.B. Grisham, G.E. Mann, K. Moore, L.J. Roberts, 2nd, H. Ischiropoulos, Measuring reactive oxygen and nitrogen species with fluorescent probes: challenges and limitations, Free Radic. Biol. Med. 52 (2012) 1–6.
[68] H. Wang, I.E. Kochevar, Involvement of UVB-induced reactive oxygen species in TGF-beta biosynthesis and activation in keratinocytes, Free Radic. Biol. Med. 38 (2005) 890–897.
[69] G.H. Jin, Y. Liu, S.Z. Jin, X.D. Liu, S.Z. Liu, UVB induced oxidative stress in human keratinocytes and protective effect of antioxidant agents, Radiat. Environ. Biophys. 46 (2007) 61–68.
[70] H.R. Rezvani, F. Mazurier, M. Cario-Andre, C. Pain, C. Ged, A. Taieb, H. de Verneuil, Protective effects of catalase overexpression on UVB-induced apoptosis in normal human keratinocytes, J. Biol. Chem. 281 (2006) 17999–18007.
[71] M. Horikawa-Miura, N. Matsuda, M. Yoshida, Y. Okumura, T. Mori, M. Watanabe, The greater lethality of UVB radiation to cultured human cells is associated with the specific activation of a DNA damage-independent signaling pathway, Radiat. Res. 167 (2007) 655–662.
[72] D.E. Heck, A.M. Vetrano, T.M. Mariano, J.D. Laskin, UVB light stimulates production of reactive oxygen species: unexpected role for catalase, J. Biol. Chem. 278 (2003) 22432–22436.
[73] S.M. Beak, Y.S. Lee, J.A. Kim, NADPH oxidase and cyclooxygenase mediate the ultraviolet B-induced generation of reactive oxygen species and activation of nuclear factor-kappaB in HaCaT human keratinocytes, Biochimie 86 (2004) 425–429.
[74] S.K. Katiyar, S.M. Meeran, Obesity increases the risk of UV radiation-induced oxidative stress and activation of MAPK and NF-kappaB signaling, Free Radic. Biol. Med. 42 (2007) 299–310.
[75] U. Wolfle, P.R. Esser, B. Simon-Haarhaus, S.F. Martin, J. Lademann, C.M. Schempp, UVB-induced DNA damage, generation of reactive oxygen species, and inflammation are effectively attenuated by the flavonoid luteolin in vitro and in vivo, Free Radic. Biol. Med. 50 (2011) 1081–1093.
[76] F. Yogianti, M. Kunisada, E. Nakano, R. Ono, K. Sakumi, S. Oka, Y. Nakabeppu, C. Nishigori, Inhibitory effects of dietary Spirulina platensis on UVB-induced skin inflammatory responses and carcinogenesis, J. Investig. Dermatol. 134 (2014) 2610–2619.
[77] J. Dahle, O. Kaalhus, T. Stokke, E. Kvam, Bystander effects may modulate ultraviolet A and B radiation-induced delayed mutagenesis, Radiat. Res. 163 (2005) 289–295.
[78] J. Dahle, E. Kvam, T. Stokke, Bystander effects in UV-induced genomic instability: antioxidants inhibit delayed mutagenesis induced by ultraviolet A and B radiation, J. Carcinog. 4 (2005) 11.
[79] J.R. Whiteside, T.J. McMillan, A bystander effect is induced in human cells treated with UVA radiation but not UVB radiation, Radiat. Res. 171 (2009) 204–211.
[80] M. Widel, A. Krzywon, K. Gajda, M. Skonieczna, J. Rzeszowska-Wolny, Induction of bystander effects by UVA, UVB, and UVC radiation in human fibroblasts and the implication of reactive oxygen species, Free Radic. Biol. Med. 68 (2014) 278–287.
[81] G.T. Wondrak, M.K. Jacobson, E.L. Jacobson, Endogenous UVA-photosensitizers: mediators of skin photodamage and novel targets for skin photoprotection, Photochem. Photobiol. Sci. 5 (2006) 215–237.
[82] J. Cadet, T. Douki, J.L. Ravanat, P. Di Mascio, Sensitized formation of oxidatively generated damage to cellular DNA by UVA radiation, Photochem. Photobiol. Sci. 8 (2009) 903–911.
[83] H. Swalwell, J. Latimer, R.M. Haywood, M.A. Birch-Machin, Investigating the role of melanin in UVA/UVB- and hydrogen peroxide-induced cellular and mitochondrial ROS production and mitochondrial DNA damage in human melanoma cells, Free Radic. Biol. Med. 52 (2012) 626–634.
[84] C.S. Foote, Mechanisms of photosensitized oxidation. There are several different types of photosensitized oxidation which may be important in biological systems, Science 162 (1968) 963–970.
[85] C.S. Foote, Definition of type I and type II photosensitized oxidation, Photochem. Photobiol. 54 (1991) 659.
[86] A. Valencia, I.E. Kochevar, Nox1-based NADPH oxidase is the major source of UVA-induced reactive oxygen species in human keratinocytes, J. Invest. Dermatol. 128 (2008) 214–222.
[87] M.A. Birch-Machin, H. Swalwell, How mitochondria record the effects of UV exposure and oxidative stress using human skin as a model tissue, Mutagenesis 25 (2010) 101–107.
[88] M.E. Darvin, S.F. Haag, J. Lademann, L. Zastrow, W. Sterry, M.C. Meinke, Formation of free radicals in human skin during irradiation with infrared light, J. Invest. Dermatol. 130 (2010) 629–631.
[89] S. Arndt, S.F. Haag, A. Kleemann, J. Lademann, M.C. Meinke, Radical protection in the visible and infrared by a hyperforin-rich cream–in vivo versus ex vivo methods, Exp. Dermatol 22 (2013) 354–357.
[90] O. Chiarelli-Neto, A.S. Ferreira, W.K. Martins, C. Pavani, D. Severino, F. Faiao-Flores, S.S. Maria-Engler, E. Aliprandini, G.R. Martinez, P. Di Mascio, M.H. Medeiros, M.S. Baptista, Melanin photosensitization and the effect of visible light on epithelial cells, PLoS One 9 (2014) e113266.
[91] I.A. Blair, DNA adducts with lipid peroxidation products, J. Biol. Chem. 283 (2008) 15545–15549.
[92] M.H.G. Medeiros, Exocyclic, DNA adducts as biomarkers of lipid oxidation and predictors of disease. Challenges in developing sensitive and specific methods for clinical studies, Chem. Res. Toxicol. 22 (2009) 419–425.
[93] P.M. Girard, M. Pozzebon, F. Delacote, T. Douki, V. Smirnova, E. Sage, Inhibition of S-phase progression triggered by UVA-induced ROS does not require a functional DNA damage checkpoint response in mammalian cells, DNA Repair 7 (2008) 1500–1516.
[94] J.D. Hoerter, C.S. Ward, K.D. Bale, A.N. Gizachew, R. Graham, J. Reynolds, M.E. Ward, C. Choi, J.L. Kagabo, M. Sauer, T. Kuipers, T. Hotchkiss, N. Banner, R.A. Chellson, T. Ohaeri, L. Gant, L. Vanderhill, Effect of UVA fluence rate on indicators of oxidative stress in human dermal fibroblasts, Int. J. Biol. Sci. 4 (2008) 63–70.
[95] M.J. Davies, Protein oxidation and peroxidation, Biochem. J. 473 (2016) 805–825.
[96] M. Radman, Protein damage, radiation sensitivity and aging, DNA Repair 44 (2016) 186–192.
[97] D. Graindorge, S. Martineau, C. Machon, P. Arnoux, J. Guitton, S. Francesconi, C. Frochot, E. Sage, P.M. Girard, Singlet oxygen-mediated oxidation during UVA radiation alters the dynamic of genomic DNA replication, PLoS One 10 (2015) e0140645.
[98] J. Cadet, J.R. Wagner, Oxidatively generated base damage to cellular DNA by hydroxyl radical and one-electron oxidants: similarities and differences, Arch. Biochem. Biophys. 557 (2014) 47–54.
[99] S. Premi, S. Wallisch, C.M. Mano, A.B. Weiner, A. Bacchiocchi, K. Wakamatsu, E.J. Bechara, R. Halaban, T. Douki, D.E. Brash, Photochemistry. Chemiexcitation of melanin derivatives induces DNA photoproducts long after UV exposure, Science 347 (2015) 842–847.
[100] S. Frelon, T. Douki, J.L. Ravanat, J.P. Pouget, C. Tornabene, J. Cadet, High-performance liquid chromatography–tandem mass spectrometry measurement of radiation-induced base damage to isolated and cellular DNA, Chem. Res. Toxicol. 13 (2000) 1002–1010.
[101] J.P. Pouget, T. Douki, M.J. Richard, J. Cadet, DNA damage induced in cells by gamma and UVA radiation as measured by HPLC/GC-MS and HPLC-EC and Comet assay, Chem. Res. Toxicol. 13 (2000) 541–549.
[102] A. Javeri, J.G. Lyons, X.X. Huang, G.M. Halliday, Downregulation of Cockayne syndrome B protein reduces human 8-oxoguanine DNA glycosylase-1 expression and repair of UV radiation-induced 8-oxo-7,8-dihydro-2'-deoxyguanine, Cancer Sci. 102 (2011) 1651–1658.
[103] M. Kunisada, K. Sakumi, Y. Tominaga, A. Budiyanto, M. Ueda, M. Ichihashi, Y. Nakabeppu, C. Nishigori, 8-Oxoguanine formation induced by chronic UVB exposure makes Ogg1 knockout mice susceptible to skin carcinogenesis, Cancer Res. 65 (2005) 6006–6010.
[104] J. Cadet, T. Douki, J.L. Ravanat, Measurement of oxidatively generated base damage in cellular DNA, Mutat. Res. 711 (2011) 3–12.
[105] M.A. Birch-Machin, E.V. Russell, J.A. Latimer, Mitochondrial, DNA damage as a biomarker for ultraviolet radiation exposure and oxidative stress, Br. J. Dermatol 169 (Suppl 2) (2013) 9–14.
[106] M.I. Martinez-Jimenez, S. Garcia-Gomez, K. Bebenek, G. Sastre-Moreno, P.A. Calvo, A. Diaz-Talavera, T.A. Kunkel, L. Blanco, Alternative solutions and new scenarios for translesion DNA synthesis by human PrimPol, DNA Repair 29 (2015) 127–138.
[107] M.J. Burak, K.E. Guja, E. Hambardjieva, B. Derkunt, M. Garcia-Diaz, A fidelity mechanism in DNA polymerase lambda promotes error-free bypass of 8-oxo-dG, EMBO J. 35 (2016) 2045–2059.
[108] S.D. McCulloch, R.J. Kokoska, P. Garg, P.M. Burgers, T.A. Kunkel, The efficiency and fidelity of 8-oxo-guanine bypass by DNA polymerases delta and eta, Nucleic

Acids Res. 37 (2009) 2830–2840.
[109] H. Kamiya, A. Yamaguchi, T. Suzuki, H. Harashima, Roles of specialized DNA polymerases in mutagenesis by 8-hydroxyguanine in human cells, Mutat. Res. 686 (2010) 90–95.
[110] L.F. Batista, B. Kaina, R. Meneghini, C.F. Menck, How, DNA lesions are turned into powerful killing structures: insights from UV-induced apoptosis, Mutat. Res. 681 (2009) 197–208.
[111] W.L. Neeley, J.M. Essigmann, Mechanisms of formation, genotoxicity, and mutation of guanine oxidation products, Chem. Res. Toxicol. 19 (2006) 491–505.
[112] F. El Ghissassi, R. Baan, K. Straif, Y. Grosse, B. Secretan, V. Bouvard, L. Benbrahim-Tallaa, N. Guha, C. Freeman, L. Galichet, V. Cogliano, WHO IARC Monograph Working Group, A review of human carcinogens–part D: radiation, Lancet Oncol. 10 (2009) 751–752.
[113] D.L. Mitchell, A.A. Fernandez, R.S. Nairn, R. Garcia, L. Paniker, D. Trono, H.D. Thames, I. Gimenez-Conti, Ultraviolet A does not induce melanomas in a Xiphophorus hybrid fish model, Proc. Natl. Acad. Sci. USA 107 (2010) 9329–9334.
[114] A.A. Fernandez, L. Paniker, R. Garcia, D.L. Mitchell, Recent advances in sunlight-induced carcinogenesis using the Xiphophorus melanoma model, Comp. Biochem. Physiol. C Toxicol. Pharmacol. 155 (2012) 64–70.
[115] A. Besaratinia, S.I. Kim, G.P. Pfeifer, Rapid repair of UVA-induced oxidized purines and persistence of UVB-induced dipyrimidine lesions determine the mutagenicity of sunlight in mouse cells, FASEB J. 22 (2008) 2379–2392.
[116] J.P. Spencer, A. Jenner, O.I. Aruoma, C.E. Cross, R. Wu, B. Halliwell, Oxidative DNA damage in human respiratory tract epithelial cells. Time course in relation to DNA strand breakage, Biochem. Biophys. Res. Commun. 224 (1996) 17–22.
[117] V.I. Grishko, W.J. Driggers, S.P. LeDoux, G.L. Wilson, Repair of oxidative damage in nuclear DNA sequences with different transcriptional activities, Mutat. Res. 384 (1997) 73–80.
[118] L. Lan, S. Nakajima, Y. Oohata, M. Takao, S. Okano, M. Masutani, S.H. Wilson, A. Yasui, In situ analysis of repair processes for oxidative DNA damage in mammalian cells, Proc. Natl. Acad. Sci. USA 101 (2004) 13738–13743.
[119] S. Kozmin, G. Slezak, A. Reynaud-Angelin, C. Elie, Y. de Rycke, S. Boiteux, E. Sage, UVA radiation is highly mutagenic in cells that are unable to repair 7,8-dihydro-8-oxoguanine in Saccharomyces cerevisiae, Proc. Natl. Acad. Sci. USA 102 (2005) 13538–13543.
[120] P.K. Vayalil, C.A. Elmets, S.K. Katiyar, Treatment of green tea polyphenols in hydrophilic cream prevents UVB-induced oxidation of lipids and proteins, depletion of antioxidant enzymes and phosphorylation of MAPK proteins in SKH-1 hairless mouse skin, Carcinogenesis 24 (2003) 927–936.
[121] L.A. Schneider, W. Bloch, K. Kopp, A. Hainzl, P. Rettberg, M. Wlaschek, G. Horneck, K. Scharffetter-Kochanek, 8-Isoprostane is a dose-related biomarker for photo-oxidative ultraviolet (UV) B damage in vivo: a pilot study with personal UV dosimetry, Br. J. Dermatol. 154 (2006) 1147–1154.
[122] A.R. Svobodova, A. Galandakova, J. Sianska, D. Dolezal, J. Ulrichova, J. Vostalova, Acute exposure to solar simulated ultraviolet radiation affects oxidative stress-related biomarkers in skin, liver and blood of hairless mice, Biol. Pharm. Bull. 34 (2011) 471–479.
[123] A.T. Ibrahim, Negative impacts of ultraviolet-A radiation on antioxidant and oxidative stress biomarkers of African catfish Clarias gariepinus, Photochem. Photobiol. Sci. 14 (2015) 1337–1345.
[124] W.K. Kaufmann, J.E. Cleaver, Mechanisms of inhibition of DNA replication by ultraviolet light in normal human and xeroderma pigmentosum fibroblasts, J. Mol. Biol. 149 (1981) 171–187.
[125] Y. Shindo, T. Hashimoto, Ultraviolet B-induced cell death in four cutaneous cell lines exhibiting different enzymatic antioxidant defences: involvement of apoptosis, J. Dermatol. Sci. 17 (1998) 140–150.
[126] G. Tringali, B. Sampaolese, M.E. Clementi, Expression of early and late cellular damage markers by ARPE-19 cells following prolonged treatment with UV-A radiation, Mol. Med. Rep. (2016).
[127] E. Strozyk, D. Kulms, The role of AKT/mTOR pathway in stress response to UV-irradiation: implication in skin carcinogenesis by regulation of apoptosis, autophagy and senescence, Int. J. Mol. Sci. 14 (2013) 15260–15285.
[128] F. Poon, S. Kang, A.L. Chien, Mechanisms and treatments of photoaging, Photodermatol. Photoimmunol. Photomed. 31 (2015) 65–74.
[129] F. Debacq-Chainiaux, C. Borlon, T. Pascal, V. Royer, F. Eliaers, N. Ninane, G. Carrard, B. Friguet, F. de Longueville, S. Boffe, J. Remacle, O. Toussaint, Repeated exposure of human skin fibroblasts to UVB at subcytotoxic level triggers premature senescence through the TGF-beta1 signaling pathway, J. Cell Sci. 118 (2005) 743–758.
[130] M. Cavinato, R. Koziel, N. Romani, R. Weinmullner, B. Jenewein, M. Hermann, S. Dubrac, G. Ratzinger, J. Grillari, M. Schmuth, P. Jansen-Durr, UVB-induced senescence of human dermal fibroblasts involves impairment of proteasome and enhanced autophagic activity, J. Gerontol. A Biol. Sci. Med. Sci., (2017) (in press).
[131] U. Panich, G. Sittithumcharee, N. Rathviboon, S. Jirawatnotai, Ultraviolet radiation-induced skin sging: the role of DNA damage and oxidative stress in epidermal stem cell damage mediated skin aging, Stem Cells Int. 2016 (2016) 7370642.
[132] H. Yamaba, M. Haba, M. Kunita, T. Sakaida, H. Tanaka, Y. Yashiro, S. Nakata, Morphological change of skin fibroblasts induced by UV Irradiation is involved in photoaging, Exp. Dermatol. 25 (Suppl 3) (2016) 45–51.
[133] G.J. Fisher, H.S. Talwar, J. Lin, P. Lin, F. McPhillips, Z. Wang, X. Li, Y. Wan, S. Kang, J.J. Voorhees, Retinoic acid inhibits induction of c-Jun protein by ultraviolet radiation that occurs subsequent to activation of mitogen-activated protein kinase pathways in human skin in vivo, J. Clin. Investig. 101 (1998) 1432–1440.
[134] T. Quan, T. He, S. Kang, J.J. Voorhees, G.J. Fisher, Ultraviolet irradiation alters transforming growth factor beta/smad pathway in human skin in vivo, J. Invest. Dermatol. 119 (2002) 499–506.
[135] D.N. Syed, F. Afaq, H. Mukhtar, Differential activation of signaling pathways by UVA and UVB radiation in normal human epidermal keratinocytes, Photochem. Photobiol. 88 (2012) 1184–1190.
[136] Y. Bermudez, S.P. Stratton, C. Curiel-Lewandrowski, J. Warneke, C. Hu, G.T. Bowden, S.E. Dickinson, Z. Dong, A.M. Bode, K. Saboda, C.A. Brooks, E.F. Petricoin, 3rd, C.A. Hurst, D.S. Alberts, J.G. Einspahr, Activation of the PI3K/Akt/mTOR and MAPK signaling pathways in response to acute solar-simulated light exposure of human skin, Cancer Prev. Res. 8 (2015) 720–728.
[137] M.R. Farrukh, U.A. Nissar, P.J. Kaiser, Q. Afnan, P.R. Sharma, S. Bhushan, S.A. Tasduq, Glycyrrhizic acid (GA) inhibits reactive oxygen Species mediated photodamage by blocking ER stress and MAPK pathway in UV-B irradiated human skin fibroblasts, J. Photochem. Photobiol. B 148 (2015) 351–357.
[138] S.J. Seo, S.W. Ahn, C.K. Hong, B.I. Ro, Expressions of beta-defensins in human keratinocyte cell lines, J. Dermatol. Sci. 27 (2001) 183–191.
[139] M. Kim, K.Y. Park, M.K. Lee, T. Jin, S.J. Seo, Adiponectin suppresses UVB-induced premature senescence and hBD2 overexpression in human keratinocytes, PLoS One 11 (2016) e0161247.
[140] J. Mineshiba, F. Myokai, F. Mineshiba, K. Matsuura, F. Nishimura, S. Takashiba, Transcriptional regulation of beta-defensin-2 by lipopolysaccharide in cultured human cervical carcinoma (HeLa) cells, FEMS Immunol. Med. Microbiol. 45 (2005) 37–44.
[141] M.A. Bachelor, G.T. Bowden, UVA-mediated activation of signaling pathways involved in skin tumor promotion and progression, Semin. Cancer Biol. 14 (2004) 131–138.
[142] J.W. Zhu, X.J. Wu, Z.F. Lu, D. Luo, S.Q. Cai, M. Zheng, Role of VEGF receptors in normal and psoriatic human keratinocytes: evidence from irradiation with different UV sources, PLoS One 8 (2013) e55463.
[143] J.H. Chung, H.C. Eun, Angiogenesis in skin aging and photoaging, J. Dermatol. 34 (2007) 593–600.
[144] S.E. Ullrich, Mechanism involved in the systemic suppression of antigen-presenting cell function by UV irradiation. keratinocyte-derived IL-10 modulates antigen-presenting cell function of splenic adherent cells, J. Immunol. 152 (1994) 3410–3416.
[145] C. Nishigori, D.B. Yarosh, S.E. Ullrich, A.A. Vink, C.D. Bucana, L. Roza, M.L. Kripke, Evidence that DNA damage triggers interleukin 10 cytokine production in UV-irradiated murine keratinocytes, Proc. Natl. Acad. Sci. USA 93 (1996) 10354–10359.
[146] A. Boonstra, A. van Oudenaren, B. Barendregt, L. An, P.J. Leenen, H.F. Savelkoul, UVB irradiation modulates systemic immune responses by affecting cytokine production of antigen-presenting cells, Int. Immunol. 12 (2000) 1531–1538.
[147] G.M. Halliday, Inflammation, gene mutation and photoimmunosuppression in response to UVR-induced oxidative damage contributes to photocarcinogenesis, Mutat. Res. 571 (2005) 107–120.
[148] V. Muthusamy, T.J. Piva, The UV response of the skin: a review of the MAPK, NFkappaB and TNFalpha signal transduction pathways, Arch. Dermatol. Res. 302 (2010) 5–17.
[149] M.F. Holick, Evolution, biologic function, and recommended dietary allowances for vitamin D (Vitamin D: Physiology, Molecular Biology, and Clinical Applications), Humana Press, New Jersey, 1999.
[150] M. Wacker, M.F. Holick, Sunlight and Vitamin D: a global perspective for health, Dermatoendocrinology 5 (2013) 51–108.
[151] D. Kockott, B. Herzog, J. Reichrath, K. Keane, M.F. Holick, New approach to develop optimized sunscreens that enable cutaneous Vitamin D formation with minimal erythema risk, PLoS One 11 (2016) e0145509.
[152] A.R. Webb, L. Kline, M.F. Holick, Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin, J. Clin. Endocrinol. Metab. 67 (1988) 373–378.
[153] P. Lips, Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications, Endocr. Rev. 22 (2001) 477–501.
[154] C.A. Baggerly, R.E. Cuomo, C.B. French, C.F. Garland, E.D. Gorham, W.B. Grant, R.P. Heaney, M.F. Holick, B.W. Hollis, S.L. McDonnell, M. Pittaway, P. Seaton, C.L. Wagner, A. Wunsch, Sunlight and vitamin D: necessary for public health, J. Am. Coll. Nutr. 34 (2015) 359–365.
[155] E.S. Ford, U.A. Ajani, L.C. McGuire, S. Liu, Concentrations of serum vitamin D and the metabolic syndrome among U.S. adults, Diabetes Care 28 (2005) 1228–1230.
[156] S. Liu, Y. Song, E.S. Ford, J.E. Manson, J.E. Buring, P.M. Ridker, Dietary calcium, vitamin D, and the prevalence of metabolic syndrome in middle-aged and older U.S. women, Diabetes Care. 28 (2005) 2926–2932.
[157] N.J. Schuch, V.C. Garcia, L.A. Martini, (Vitamin D and endocrine diseases)Arq. Bras. Endocrinol. Metabol. 53 (2009) 625–633.
[158] S.L. McDonnell, L.L. Baggerly, C.B. French, R.P. Heaney, E.D. Gorham, M.F. Holick, R. Scragg, C.F. Garland, Incidence rate of type 2 diabetes is 50% lower in GrassrootsHealth cohort with median serum 25-hydroxyvitamin D of 41 ng/ml than in NHANES cohort with median of 22 ng/ml, J. Steroid Biochem. Mol. Biol. 155 (2016) 239–244.
[159] D. Martins, M. Wolf, D. Pan, A. Zadshir, N. Tareen, R. Thadhani, A. Felsenfeld, B. Levine, R. Mehrotra, K. Norris, Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey, Arch. Intern. Med. 167 (2007) 1159–1165.
[160] M.J. Haas, M. Jafri, K.R. Wehmeier, L.M. Onstead-Haas, A.D. Mooradian, Inhibition of endoplasmic reticulum stress and oxidative stress by vitamin D in endothelial cells, Free Radic. Biol. Med. 99 (2016) 1–10.

[161] S.L. Marklund, N.G. Westman, E. Lundgren, G. Roos, Copper- and zinc-containing superoxide dismutase, manganese-containing superoxide dismutase, catalase, and glutathione peroxidase in normal and neoplastic human cell lines and normal human tissues, Cancer Res. 42 (1982) 1955–1961.
[162] R. Brigelius-Flohe, Tissue-specific functions of individual glutathione peroxidases, Free Radic. Biol. Med. 27 (1999) 951–965.
[163] S. Toppo, L. Flohe, F. Ursini, S. Vanin, M. Maiorino, Catalytic mechanisms and specificities of glutathione peroxidases: variations of a basic scheme, Biochim. Biophys. Acta 1790 (2009) 1486–1500.
[164] H.J. Forman, Redox signaling: an evolution from free radicals to aging, Free Radic. Biol. Med. 97 (2016) 398–407.
[165] C. Ding, X. Fan, G. Wu, Peroxiredoxin 1 - an antioxidant enzyme in cancer, J. Cell Mol. Med. (2016).
[166] M.W. Hentze, M.U. Muckenthaler, N.C. Andrews, Balancing acts: molecular control of mammalian iron metabolism, Cell 117 (2004) 285–297.
[167] R. Barhoumi, J.A. Bowen, L.S. Stein, J. Echols, R.C. Burghardp, Concurrent analysis of intracellular glutathione content and gap junctional intercellular communication, Cytometry 14 (1993) 747–756.
[168] F.Q. Schafer, G.R. Buettner, Redox environment of the cell as viewed through the redox state of the glutathione disulfide/glutathione couple, Free Radic. Biol. Med. 30 (2001) 1191–1212.
[169] G. Wu, Y. Fang, S. Yang, J.R. Lupton, N.D. Turner, Glutathione metabolism and its implications for health, J. Nutr. 134 (2004) 489–492.
[170] R.M. Tyrrell, Solar ultraviolet A radiation: an oxidizing skin carcinogen that activates heme oxygenase-1, Antioxid. Redox Signal. 6 (2004) 835–840.
[171] R.M. Tyrrell, V.E. Reeve, Potential protection of skin by acute UVA irradiation - from cellular to animal models, Prog. Biophys. Mol. Biol. 92 (2006) 86–91.
[172] M. Schäfer, S. Werner, Nrf2-A regulator of keratinocyte redox signaling, Free Radic. Biol. Med. 88 (2015) 243–252.
[173] C.M. Ravala, J.L. Zhongb, S.A. Mitchella, R.M. Tyrrell, The role of Bach1 in ultraviolet A-mediated human heme oxygenase 1 regulation in human skin fibroblasts, Free Radic. Biol. Med. 52 (2012) 227–236.
[174] W. Stahl, H. Sies, Carotenoids and flavonoids contribute to nutritional protection against skin damage from sunlight, Mol. Biotechnol. 37 (2007) 26–30.
[175] H. Sies, W. Stahl, Nutritional protection against skin damage from sunlight, Annu. Rev. Nutr. 24 (2004) 173–200.
[176] K. Someya, Y. Totsuka, M. Murakoshi, H. Kitano, T. Miyazawa, The antioxidant effect of palm fruit carotene on skin lipid peroxidation in guinea pigs as estimated by chemiluminescence-HPLC method, J. Nutr. Sci. Vitaminol. 40 (1994) 315–324.
[177] I. O'Connor, N. O'Brien, Modulation of UVA light-induced oxidative stress by beta-carotene, lutein and astaxanthin in cultured fibroblasts, J. Dermatol. Sci. 16 (1998) 226–230.
[178] N.M. Lyons, N.M. O'Brien, Modulatory effects of an algal extract containing astaxanthin on UVA-irradiated cells in culture, J. Dermatol. Sci. 30 (2002) 73–84.
[179] U.C. Obermuller-Jevic, P.I. Francz, J. Frank, A. Flaccus, H.K. Biesalski, Enhancement of the UVA induction of haem oxygenase-1 expression by beta-carotene in human skin fibroblasts, FEBS Lett. 460 (1999) 212–216.
[180] H. Sies, W. Stahl, Carotenoids and UV protection, Photochem. Photobiol. Sci. 3 (2004) 749–752.
[181] W. Stahl, U. Heinrich, H. Jungmann, H. Sies, H. Tronnier, Carotenoids and carotenoids plus vitamin E protect against ultraviolet light-induced erythema in humans, Am. J. Clin. Nutr. 71 (2000) 795–798.
[182] U. Heinrich, C. Gartner, M. Wiebusch, O. Eichler, H. Sies, H. Tronnier, W. Stahl, Supplementation with beta-carotene or a similar amount of mixed carotenoids protects humans from UV-induced erythema, J. Nutr. 133 (2003) 98–101.
[183] W. Stahl, U. Heinrich, S. Wiseman, O. Eichler, H. Sies, H. Tronnier, Dietary tomato paste protects against ultraviolet light-induced erythema in humans, J. Nutr. 131 (2001) 1449–1451.
[184] E. Fernandez-Garcia, Skin protection against UV light by dietary antioxidants, Food Funct. 5 (2014) 1994–2003.
[185] C. Wolf, A. Steiner, H. Honigsmann, Do oral carotenoids protect human skin against ultraviolet erythema, psoralen phototoxicity, and ultraviolet-induced DNA damage?, J. Investig. Dermatol. 90 (1988) 55–57.
[186] K. Werninghaus, M. Meydani, J. Bhawan, R. Margolis, J.B. Blumberg, B.A. Gilchrest, Evaluation of the photoprotective effect of oral vitamin E supplementation, Arch. Dermatol. 130 (1994) 1257–1261.
[187] J. Fuchs, H. Kern, Modulation of UV-light-induced skin inflammation by D-alpha-tocopherol and L-ascorbic acid: a clinical study using solar simulated radiation, Free Radic. Biol. Med. 25 (1998) 1006–1012.
[188] E.A. Offord, J.C. Gautier, O. Avanti, C. Scaletta, F. Runge, K. Kramer, L.A. Applegate, Photoprotective potential of lycopene, beta-carotene, vitamin E, vitamin C and carnosic acid in UVA-irradiated human skin fibroblasts, Free Radic. Biol. Med. 32 (2002) 1293–1303.
[189] M. Placzek, S. Gaube, U. Kerkmann, K.P. Gilbertz, T. Herzinger, E. Haen, B. Przybilla, Ultraviolet B-induced DNA damage in human epidermis is modified by the antioxidants ascorbic acid and D-alpha-tocopherol, J. Investig. Dermatol. 124 (2005) 304–307.
[190] H.J. Forman, O. Augusto, R. Brigelius-Flohe, P.A. Dennery, B. Kalyanaraman, H. Ischiropoulos, G.E. Mann, R. Radi, L.J. Roberts, 2nd, J. Vina, K.J. Davies, Even free radicals should follow some rules: a Guide to free radical research terminology and methodology, Free Radic. Biol. Med. 78 (2015) 233–235.
[191] J. Knoch, Y. Kamenisch, C. Kubisch, M. Berneburg, Rare hereditary diseases with defects in DNA-repair, Eur. J. Dermatol. 22 (2012) 443–455.
[192] J.A. Marteijn, H. Lans, W. Vermeulen, J.H. Hoeijmakers, Understanding nucleotide excision repair and its roles in cancer and ageing, Nat. Rev. Mol. Cell Biol. 15 (2014) 465–481.
[193] H. Ide, M. Kotera, Human DNA glycosylases involved in the repair of oxidatively damaged DNA, Biol. Pharm. Bull. 27 (2004) 480–485.
[194] M.L. Hegde, A.K. Mantha, T.K. Hazra, K.K. Bhakat, S. Mitra, B. Szczesny, Oxidative genome damage and its repair: implications in aging and neurodegenerative diseases, Mech. Ageing Dev. 133 (2012) 157–168.
[195] G.S. Leandro, P. Sykora, V.A. Bohr, The impact of base excision DNA repair in age-related neurodegenerative diseases, Mutat. Res. 776 (2015) 31–39.
[196] D. Ray, D. Kidane, Gut microbiota imbalance and base excision repair dynamics in colon cancer, J. Cancer 7 (2016) 1421–1430.
[197] S. Narayan, A.S. Jaiswal, B.K. Law, M.A. Kamal, A.K. Sharma, R.A. Hromas, Interaction between APC and Fen1 during breast carcinogenesis, DNA Repair 41 (2016) 54–62.
[198] F. Grasso, S. Di Meo, G. De Luca, L. Pasquini, S. Rossi, M. Boirivant, M. Biffoni, M. Bignami, E. Di Carlo, The MUTYH base excision repair gene protects against inflammation-associated colorectal carcinogenesis, Oncotarget 6 (2015) 19671–19684.
[199] F. Mazzei, A. Viel, M. Bignami, Role of MUTYH in human cancer, Mutat. Res. 743–744 (2013) 33–43.
[200] A. Sancar, L.A. Lindsey-Boltz, K. Unsal-Kacmaz, S. Linn, Molecular mechanisms of mammalian DNA repair and the DNA damage checkpoints, Annu. Rev. Biochem. 73 (2004) 39–85.
[201] M.C. Moraes, J.B. Neto, C.F. Menck, DNA repair mechanisms protect our genome from carcinogenesis, Front. Biosci. 17 (2012) 1362–1388.
[202] J.O. Black, Xeroderma pigmentosum, Head Neck Pathol. 10 (2016) 139–144.
[203] V.M. Maher, L.M. Ouellette, R.D. Curren, J.J. McCormick, Frequency of ultraviolet light-induced mutations is higher in xeroderma pigmentosum variant cells than in normal human cells, Nature 261 (1976) 593–595.
[204] J.E. Cleaver, Cancer in xeroderma pigmentosum and related disorders of DNA repair, Nat. Rev. Cancer 5 (2005) 564–573.
[205] J.J. DiGiovanna, K.H. Kraemer, Shining a light on xeroderma pigmentosum, J. Investig. Dermatol. 132 (2012) 785–796.
[206] H. Fassihi, M. Sethi, H. Fawcett, J. Wing, N. Chandler, S. Mohammed, E. Craythorne, A.M. Morley, R. Lim, S. Turner, T. Henshaw, I. Garrood, P. Giunti, T. Hedderly, A. Abiona, H. Naik, G. Harrop, D. McGibbon, N.G. Jaspers, E. Botta, T. Nardo, M. Stefanini, A.R. Young, R.P. Sarkany, A.R. Lehmann, Deep phenotyping of 89 xeroderma pigmentosum patients reveals unexpected heterogeneity dependent on the precise molecular defect, Proc. Natl. Acad. Sci. USA 113 (2016) E1236–E1245.
[207] W.R. Zhang, G.L. Garrett, J.E. Cleaver, S.T. Arron, Absence of skin cancer in the DNA repair-deficient disease Cockayne Syndrome (CS): a survey study, J. Am. Acad. Dermatol. 74 (2016) 1270–1272.
[208] M. Hayashi, R. Miyata, N. Tanuma, Oxidative stress in developmental brain disorders, Adv. Exp. Med. Biol. 724 (2012) 278–290.
[209] S. Hashimoto, H. Anai, K. Hanada, Mechanisms of interstrand DNA crosslink repair and human disorders, Genes Environ. 38 (2016) 9.
[210] J.T. Reardon, T. Bessho, H.C. Kung, P.H. Bolton, A. Sancar, In vitro repair of oxidative DNA damage by human nucleotide excision repair system: possible explanation for neurodegeneration in xeroderma pigmentosum patients, Proc. Natl. Acad. Sci. USA 94 (1997) 9463–9468.
[211] P.T. Bradford, A.M. Goldstein, D. Tamura, S.G. Khan, T. Ueda, J. Boyle, K.S. Oh, K. Imoto, H. Inui, S. Moriwaki, S. Emmert, K.M. Pike, A. Raziuddin, T.M. Plona, J.J. DiGiovanna, M.A. Tucker, K.H. Kraemer, Cancer and neurologic degeneration in xeroderma pigmentosum: long term follow-up characterises the role of DNA repair, J. Med. Genet. 48 (2011) 168–176.
[212] J.P. Melis, H. van Steeg, M. Luijten, Oxidative DNA damage and nucleotide excision repair, Antioxid. Redox Signal. 18 (2013) 2409–2419.
[213] J. Guo, P.C. Hanawalt, G. Spivak, Comet-FISH with strand-specific probes reveals transcription-coupled repair of 8-oxoGuanine in human cells, Nucleic Acids Res. 41 (2013) 7700–7712.
[214] W.P. Vermeij, M.E. Dolle, E. Reiling, D. Jaarsma, C. Payan-Gomez, C.R. Bombardieri, H. Wu, A.J. Roks, S.M. Botter, B.C. van der Eerden, S.A. Youssef, R.V. Kuiper, B. Nagarajah, C.T. van Oostrom, R.M. Brandt, S. Barnhoorn, S. Imholz, J.L. Pennings, A. de Bruin, A. Gyenis, J. Pothof, J. Vijg, H. van Steeg, J.H. Hoeijmakers, Restricted diet delays accelerated ageing and genomic stress in DNA-repair-deficient mice, Nature 537 (2016) 427–431.
[215] R.M. Costa, V. Chigancas, S. Galhardo Rda, H. Carvalho, C.F. Menck, The eukaryotic nucleotide excision repair pathway, Biochimie 85 (2003) 1083–1099.
[216] B. Pascucci, M. D'Errico, E. Parlanti, S. Giovannini, E. Dogliotti, Role of nucleotide excision repair proteins in oxidative DNA damage repair: an updating, Biochemistry 76 (2011) 4–15.
[217] A. Sassa, N. Kamoshita, Y. Kanemaru, M. Honma, M. Yasui, Xeroderma pigmentosum group A suppresses mutagenesis caused by clustered oxidative DNA adducts in the human genome, PLoS One 10 (2015) e0142218.
[218] M. Fousteri, W. Vermeulen, A.A. van Zeeland, L.H. Mullenders, Cockayne syndrome A and B proteins differentially regulate recruitment of chromatin remodeling and repair factors to stalled RNA polymerase II in vivo, Mol. Cell 23 (2006) 471–482.
[219] A.J. van Gool, E. Citterio, S. Rademakers, R. van Os, W. Vermeulen, A. Constantinou, J.M. Egly, D. Bootsma, J.H. Hoeijmakers, The Cockayne syndrome B protein, involved in transcription-coupled DNA repair, resides in an RNA polymerase II-containing complex, EMBO J. 16 (1997) 5955–5965.
[220] C.P. Selby, A. Sancar, Cockayne syndrome group B protein enhances elongation by RNA polymerase II, Proc. Natl. Acad. Sci. USA 94 (1997) 11205–11209.
[221] L. Proietti-De-Santis, P. Drane, J.M. Egly, Cockayne syndrome B protein regulates the transcriptional program after UV irradiation, EMBO J. 25 (2006) 1915–1923.
[222] S. Kamiuchi, M. Saijo, E. Citterio, M. de Jager, J.H. Hoeijmakers, K. Tanaka,

Translocation of Cockayne syndrome group A protein to the nuclear matrix: possible relevance to transcription-coupled DNA repair, Proc. Natl. Acad. Sci. USA 99 (2002) 201–206.
[223] R. Groisman, I. Kuraoka, O. Chevallier, N. Gaye, T. Magnaldo, K. Tanaka, A.F. Kisselev, A. Harel-Bellan, Y. Nakatani, CSA-dependent degradation of CSB by the ubiquitin-proteasome pathway establishes a link between complementation factors of the Cockayne syndrome, Genes Dev. 20 (2006) 1429–1434.
[224] G. Spivak, P.C. Hanawalt, Host cell reactivation of plasmids containing oxidative DNA lesions is defective in Cockayne syndrome but normal in UV-sensitive syndrome fibroblasts, DNA Repair 5 (2006) 13–22.
[225] M. D'Errico, E. Parlanti, M. Teson, P. Degan, T. Lemma, A. Calcagnile, I. Iavarone, P. Jaruga, M. Ropolo, A.M. Pedrini, D. Orioli, G. Frosina, G. Zambruno, M. Dizdaroglu, M. Stefanini, E. Dogliotti, The role of CSA in the response to oxidative DNA damage in human cells, Oncogene 26 (2007) 4336–4343.
[226] B. Pascucci, T. Lemma, E. Iorio, S. Giovannini, B. Vaz, I. Iavarone, A. Calcagnile, L. Narciso, P. Degan, F. Podo, V. Roginskya, B.M. Janjic, B. Van Houten, M. Stefanini, E. Dogliotti, M. D'Errico, An altered redox balance mediates the hypersensitivity of Cockayne syndrome primary fibroblasts to oxidative stress, Aging Cell. 11 (2012) 520–529.
[227] T. Iyama, D.M. Wilson, 3rd, DNA repair mechanisms in dividing and non-dividing cells, DNA Repair 12 (2013) 620–636.
[228] G. Dianov, C. Bischoff, M. Sunesen, V.A. Bohr, Repair of 8-oxoguanine in DNA is deficient in Cockayne syndrome group B cells, Nucleic Acids Res. 27 (1999) 1365–1368.
[229] M. Scheibye-Knudsen, M. Ramamoorthy, P. Sykora, S. Maynard, P.C. Lin, R.K. Minor, D.M. Wilson, 3rd, M. Cooper, R. Spencer, R. de Cabo, D.L. Croteau, V.A. Bohr, Cockayne syndrome group B protein prevents the accumulation of damaged mitochondria by promoting mitochondrial autophagy, J. Exp. Med. 209 (2012) 855–869.
[230] Y. Kamenisch, M. Fousteri, J. Knoch, A.K. von Thaler, B. Fehrenbacher, H. Kato, T. Becker, M.E. Dolle, R. Kuiper, M. Majora, M. Schaller, G.T. van der Horst, H. van Steeg, M. Rocken, D. Rapaport, J. Krutmann, L.H. Mullenders, M. Berneburg, Proteins of nucleotide and base excision repair pathways interact in mitochondria to protect from loss of subcutaneous fat, a hallmark of aging, J. Exp. Med. 207 (2010) 379–390.
[231] P.O. Osenbroch, P. Auk-Emblem, R. Halsne, J. Strand, R.J. Forstrom, I. van der Pluijm, L. Eide, Accumulation of mitochondrial DNA damage and bioenergetic dysfunction in CSB defective cells, FEBS J. 276 (2009) 2811–2821.
[232] P.J. Brooks, Blinded by the UV light: how the focus on transcription-coupled NER has distracted from understanding the mechanisms of Cockayne syndrome neurologic disease, DNA Repair 12 (2013) 656–671.
[233] M. Moriel-Carretero, E. Herrera-Moyano, A. Aguilera, A unified model for the molecular basis of xeroderma pigmentosum-Cockayne syndrome, Rare Dis. 3 (2015) e1079362.
[234] B.R. Berquist, V.A. Bohr, Cockayne syndrome, underlying molecular defects and p53, Cell Cycle 10 (2011) 3997–3998.
[235] A. Klungland, M. Hoss, D. Gunz, A. Constantinou, S.G. Clarkson, P.W. Doetsch, P.H. Bolton, R.D. Wood, T. Lindahl, Base excision repair of oxidative DNA damage activated by XPG protein, Mol. Cell. 3 (1999) 33–42.
[236] H.T. Wang, B. Choi, M.S. Tang, Melanocytes are deficient in repair of oxidative DNA damage and UV-induced photoproducts, Proc. Natl. Acad. Sci. USA 107 (2010) 12180–12185.
[237] J. Cadet, C. Decarroz, S.Y. Wang, W.R. Midden, Mechanisms and products of Photosensitized degradation of nucleic acids and related model compounds, Isr. J. Chem. 23 (1983) 420–429.
[238] D.T. Soltys, C.R. Rocha, L.K. Lerner, T.A. de Souza, V. Munford, F. Cabral, T. Nardo, M. Stefanini, A. Sarasin, J.B. Cabral-Neto, C.F. Menck, Novel XPG (ERCC5) mutations affect DNA repair and cell survival after ultraviolet but not oxidative stress, Hum. Mutat. 34 (2013) 481–489.
[239] S. Emmert, H. Slor, D.B. Busch, S. Batko, R.B. Albert, D. Coleman, S.G. Khan, B. Abu-Libdeh, J.J. DiGiovanna, B.B. Cunningham, M.M. Lee, J. Crollick, H. Inui, T. Ueda, M. Hedayati, L. Grossman, T. Shahlavi, J.E. Cleaver, K.H. Kraemer, Relationship of neurologic degeneration to genotype in three xeroderma pigmentosum group G patients, J. Investig. Dermatol. 118 (2002) 972–982.
[240] T. Nouspikel, P. Lalle, S.A. Leadon, P.K. Cooper, S.G. Clarkson, A common mutational pattern in Cockayne syndrome patients from xeroderma pigmentosum group G: implications for a second XPG function, Proc. Natl. Acad. Sci. USA 94 (1997) 3116–3121.
[241] J.O. Fuss, J.A. Tainer, XPB and XPD helicases in TFIIH orchestrate DNA duplex opening and damage verification to coordinate repair with transcription and cell cycle via CAK kinase, DNA Repair 10 (2011) 697–713.
[242] J. Liu, H. Fang, Z. Chi, Z. Wu, D. Wei, D. Mo, K. Niu, A.S. Balajee, T.K. Hei, L. Nie, Y. Zhao, XPD localizes in mitochondria and protects the mitochondrial genome from oxidative DNA damage, Nucleic Acids Res. 43 (2015) 5476–5488.
[243] A. Anttinen, L. Koulu, E. Nikoskelainen, R. Portin, T. Kurki, M. Erkinjuntti, N.G. Jaspers, A. Raams, M.H. Green, A.R. Lehmann, J.F. Wing, C.F. Arlett, R.J. Marttila, Neurological symptoms and natural course of xeroderma pigmentosum, Brain 131 (2008) 1979–1989.
[244] M. D'Errico, E. Parlanti, M. Teson, B.M. de Jesus, P. Degan, A. Calcagnile, P. Jaruga, M. Bjoras, M. Crescenzi, A.M. Pedrini, J.M. Egly, G. Zambruno, M. Stefanini, M. Dizdaroglu, E. Dogliotti, New functions of XPC in the protection of human skin cells from oxidative damage, EMBO J. 25 (2006) 4305–4315.
[245] C.M. Berra, C.S. de Oliveira, C.C. Garcia, C.R. Rocha, L.K. Lerner, L.C. Lima, S. Baptista Mda, C.F. Menck, Nucleotide excision repair activity on DNA damage induced by photoactivated methylene blue, Free Radic. Biol. Med. 61 (2013) 343–356.
[246] J.T. de Melo, A.R. de Souza, Timoteo, T.B. Lajus, J.A. Brandao, N.C. de Souza-Pinto, C.F. Menck, A. Campalans, J.P. Radicella, A.T. Vessoni, A.R. Muotri, L.F. Agnez-Lima, XPC deficiency is related to APE1 and OGG1 expression and function, Mutat. Res. 784–785 (2016) 25–33.
[247] J.H. Min, N.P. Pavletich, Recognition of DNA damage by the Rad4 nucleotide excision repair protein, Nature 449 (2007) 570–575.
[248] U. Camenisch, D. Trautlein, F.C. Clement, J. Fei, A. Leitenstorfer, E. Ferrando-May, H. Naegeli, Two-stage dynamic DNA quality check by xeroderma pigmentosum group C protein, EMBO J. 28 (2009) 2387–2399.
[249] F. Miao, M. Bouziane, R. Dammann, C. Masutani, F. Hanaoka, G. Pfeifer, T.R. O'Connor, 3-Methyladenine-DNA glycosylase (MPG protein) interacts with human RAD23 proteins, J. Biol. Chem. 275 (2000) 28433–28438.
[250] Y. Shimizu, S. Iwai, F. Hanaoka, K. Sugasawa, Xeroderma pigmentosum group C protein interacts physically and functionally with thymine DNA glycosylase, EMBO J. 22 (2003) 164–173.
[251] J.W. Hill, T.K. Hazra, T. Izumi, S. Mitra, Stimulation of human 8-oxoguanine-DNA glycosylase by AP-endonuclease: potential coordination of the initial steps in base excision repair, Nucleic Acids Res. 29 (2001) 430–438.
[252] B.M. Bernardes, de Jesus, M. Bjoras, F. Coin, J.M. Egly, Dissection of the molecular defects caused by pathogenic mutations in the DNA repair factor XPC, Mol. Cell Biol. 28 (2008) 7225–7235.
[253] S.N. Kassam, A.J. Rainbow, Deficient base excision repair of oxidative DNA damage induced by methylene blue plus visible light in xeroderma pigmentosum group C fibroblasts, Biochem. Biophys. Res. Commun. 359 (2007) 1004–1009.
[254] H. Menoni, J.H. Hoeijmakers, W. Vermeulen, Nucleotide excision repair-initiating proteins bind to oxidative DNA lesions in vivo, J. Cell Biol. 199 (2012) 1037–1046.
[255] G.K. Low, E.D. Fok, A.P. Ting, M.P. Hande, Oxidative damage induced genotoxic effects in human fibroblasts from Xeroderma Pigmentosum group A patients, Int. J. Biochem. Cell Biol. 40 (2008) 2583–2595.
[256] P.J. Brooks, The case for 8,5'-cyclopurine-2'-deoxynucleosides as endogenous DNA lesions that cause neurodegeneration in xeroderma pigmentosum, Neuroscience 145 (2007) 1407–1417.
[257] I. Kuraoka, C. Bender, A. Romieu, J. Cadet, R.D. Wood, T. Lindahl, Removal of oxygen free-radical-induced 5',8-purine cyclodeoxynucleosides from DNA by the nucleotide excision-repair pathway in human cells, Proc. Natl. Acad. Sci. USA 97 (2000) 3832–3837.
[258] N. Belmadoui, F. Boussicault, M. Guerra, J.L. Ravanat, C. Chatgilialoglu, J. Cadet, Radiation-induced formation of purine 5',8-cyclonucleosides in isolated and cellular DNA: high stereospecificity and modulating effect of oxygen, Org. Biomol. Chem. 8 (2010) 3211–3219.
[259] M. Hayashi, S. Araki, J. Kohyama, K. Shioda, R. Fukatsu, Oxidative nucleotide damage and superoxide dismutase expression in the brains of xeroderma pigmentosum group A and Cockayne syndrome, Brain Dev. 27 (2005) 34–38.
[260] J. Cadet, J.L. Ravanat, M. TavernaPorro, H. Menoni, D. Angelov, Oxidatively generated complex DNA damage: tandem and clustered lesions, Cancer Lett. 327 (2012) 5–15.
[261] M. Hada, A.G. Georgakilas, Formation of clustered DNA damage after high-LET irradiation: a review, J. Radiat. Res. 49 (2008) 203–210.
[262] J. Cadet, T. Douki, J.L. Ravanat, Oxidatively generated base damage to cellular DNA, Free Radic. Biol. Med. 49 (2010) 9–21.
[263] M. Guven, R. Brem, P. Macpherson, M. Peacock, P. Karran, Oxidative damage to RPA limits the nucleotide excision repair capacity of human cells, J. Investig. Dermatol. 135 (2015) 2834–2841.
[264] E. McAdam, R. Brem, P. Karran, Oxidative stress-induced protein damage inhibits DNA repair and determines mutation risk and therapeutic efficacy, Mol. Cancer Res. 14 (2016) 612–622.
[265] P. Kannouche, A. Stary, Xeroderma pigmentosum variant and error-prone DNA polymerases, Biochimie 85 (2003) 1123–1132.
[266] A. Gratchev, P. Strein, J. Utikal, G. Sergij, Molecular genetics of xeroderma pigmentosum variant, Exp. Dermatol 12 (2003) 529–536.
[267] M. Yuasa, C. Masutani, T. Eki, F. Hanaoka, Genomic structure, chromosomal localization and identification of mutations in the xeroderma pigmentosum variant (XPV) gene, Oncogene 19 (2000) 4721–4728.
[268] Y. Wang, R. Woodgate, T.P. McManus, S. Mead, J.J. McCormick, V.M. Maher, Evidence that in xeroderma pigmentosum variant cells, which lack DNA polymerase eta, DNA polymerase iota causes the very high frequency and unique spectrum of UV-induced mutations, Cancer Res. 67 (2007) 3018–3026.
[269] V. Pages, R.P. Fuchs, How DNA lesions are turned into mutations within cells?, Oncogene 21 (2002) 8957–8966.
[270] Y.C. Wang, V.M. Maher, D.L. Mitchell, J.J. McCormick, Evidence from mutation spectra that the UV hypermutability of xeroderma pigmentosum variant cells reflects abnormal, error-prone replication on a template containing photoproducts, Mol. Cell Biol. 13 (1993) 4276–4283.
[271] Q. Lin, A.B. Clark, S.D. McCulloch, T. Yuan, R.T. Bronson, T.A. Kunkel, R. Kucherlapati, Increased susceptibility to UV-induced skin carcinogenesis in polymerase eta-deficient mice, Cancer Res. 66 (2006) 87–94.
[272] J. Cadet, K.J.A. Davies, Oxidative DNA damage & repair: an introduction, Free Radic. Biol. Med. 107 (2017) 2–12.