Chapter 21
The Role of DNA Repair in Photoprotection

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21.1 DNA Damage Induced by Light

21.1.1 Light Sources

Life on earth evolved utilizing solar electromagnetic energy, but at the same time, this energy has adverse biological effects. The extent of the effects on the skin depends greatly on the wavelength of light absorbed by its biomolecules. The most damaging are the shorter wavelengths in the ultraviolet (UV) region because they are most readily absorbed by the skin.

By convention, UV wavelengths are designated as UVA (320–400 nm), UVB (290–320 nm), and UVC (200–290 nm). The shorter the wavelength, the greater absorption of the UV energy by earth's atmosphere. UVC, the shortest wavelength band, is effectively absorbed by atmosphere stratospheric gases and therefore fails to reach the surface of the earth. The ozone molecules and atmosphere efficiently filter UVB, so that only a small fraction actually reaches the earth surface (around 5 %). Its local intensity may vary with the solar zenith angle, which differs by the time of day, the year, the latitude, and the local cloud density. For the long UV wavelengths, 95 % of UVA energy reaches the earth with its steady presence during the day, making it the most abundant [35].

Artificial light from incandescent light bulbs and compact fluorescent lamps present an additional source of UV exposure, mostly UVA. The International Commission on Illumination recommends maximal UV radiation of 30 J/m^2 within 8 h. While the average daily exposure from outdoors is much lower, the cumulative effects might be significant due to prolonged and continual daily exposures [41].

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S.Q. Wang, H.W. Lim (eds.), *Principles and Practice of Photoprotection*,
DOI 10.1007/978-3-319-29382-0_21

21.1.2 Direct DNA Damage

DNA directly absorbs the energy of UVC and UVB irradiation. The adsorbed energy causes intranucleotide cross-linking by dimerization of pyrimidines and formation of *cis-syn* cyclobutane pyrimidine dimers (CPDs) and pyrimidine (6–4) pyrimidone photoproducts (6-4PP) [30, 49]. To a much lesser extent, purine dimers and pyrimidine photohydrates are formed as well. The cyclobutane rings of CPDs are formed between the 5,6 bonds of two adjacent pyrimidine bases (thymine, cytosine, or 5-methylcytosine). CPD formation is influenced by sequence context [42] and formed exclusively at dipyrimidines and preferentially at TT sites. The efficiency of CPD formation at different dipyrimidine sequences is estimated at a ratio of 55:33:11:1 for TT > TC > CT > CC [10]. In addition to the nucleotide sequences, the chromatin structure and its environment have a significant impact on the distribution of CPDs and the rate of their repair. Efficient repair in regions of DNA damage requires nucleosomal rearrangements to allow DNA repair complex initiation.

The formation of (6–4)PPs arise through a complex electron rearrangement resulting in generation of a single covalent bond between position 6 and position 4 of two adjacent pyrimidine bases [27]. The frequency of (6–4)PPs formation by UVB is at the same level as the formation of CPDs but is repaired at much faster rate [49].

For a while it was assumed that UVA could not induce CPDs due to the inability of DNA to efficiently absorb in the UVA range. However, CPDs were readily detected upon UVA exposures [2, 33]. After exposure of cultured cells and the skin to large doses of UVA, higher ratios of oxidized purines to CPDs are found than in naked DNA [4]. Analysis of the CPDs produced by UVA revealed that the predominant site for CPD formation is at TT compared to TC and CT sites and that (6–4)PPs are almost undetectable.

The exact mechanism of CPD formation upon UVA irradiation is still subject of debate. Some data suggests involvement of yet undetermined UVA chromophore that is capable of transferring energy to DNA by photosensitization – a triplet energy transfer mechanism [13]. Other evidence supports direct DNA absorption, with much lower efficiency than that of UVB. This absorption has a very distinctive signature – exclusive TT dimer formation [15].

Recently, a new pathway for formation of CPDs has been described wherein fragments of melanin are excited by UV-induced reactive oxygen and nitrogen species and then transfer the energy to DNA to form CPDs [32] This process is remarkable in that CPDs continue to form even in the dark. The relative importance of this photochemical reaction in the overall yield of DNA damage in intact human skin is an exciting new area of research.

21.1.3 Indirect DNA Damage

Indirect DNA damage is a result of UV energy absorption by either proteins or DNA-bound chromophores through photosensitization. As a result of photooxidation, the generated superoxide radicals or singlet oxygens react with nucleotides and

form several kinds of base lesions. The *8-oxo-7,8-dihydro-2′-deoxyguanosine* (8-oxo-dGua) is the most frequent and therefore most studied UVA-induced oxidative base lesion. If not repaired prior to the DNA replication, 8-Oxo-dGua mispairs with 2′-deoxyadenosine (dA) and induces G → T transversion mutations which are considered the fingerprint mutations of UVA-induced oxidized guanines in human skin carcinogenesis [4]. UVA induces DNA strand breaks and oxidized pyrimidines at a much lower frequency.

Melanocytes that secrete UV-absorbing melanin provide localized protection from the sun's electromagnetic energy. Just in the recent decade, the accumulated evidence reveals that the melanin, an optical absorber, free radical scavenger, and antioxidant, can also form melanin radicals in the presence of metal ions. In such a way, the melanin becomes a strong oxidant and might be involved in a UV-mediated DNA damaging events [38] and as noted above perhaps even CPD formation. Partially polymerized melanin is particularly effective in photooxidation in that it promotes 8-oxo-dGua formation in presence of singlet oxygen [29]. In an animal model, the incidence of UVA-induced melanoma was associated with oxidative DNA damage, and the increase in production of 8-oxo-dGua required both UVA and melanin [28].

21.2 DNA Repair

The knowledge of DNA repair pathways has gone from an arcane corner of nucleic acid biochemistry to the subject of a college textbook [11]. The molecular details of the reactions that lead to reversal, or removal and resynthesis, of damaged DNA can be found there. Here we discuss the particular aspects of DNA repair that can prevent photodamage and their sequelae.

DNA damage induced either directly or indirectly by sunlight is roughly randomly distributed among the target nucleotides in the genome. However, because the information content of the nucleotides is not randomly distributed within the genome, the biological consequences of DNA lesions are not of equal importance. As a result, repair of a minority of lesions, such as in the exons or on the transcribed strand, has much greater biological importance than repair of others in the introns or non-transcribed strands. DNA repair systems, both endogenous and therapeutic, have indeed focused on repairing some regions, such as transcribed strands, faster than others, in order to relieve phototoxic effects.

Here we will focus only on the main DNA repair pathways for photodamage.

21.2.1 Nucleotide Excision

Nucleotide excision employs a complex of enzymes to recognize gross distortions in the double helix and cut out a strip of approximately 30 nucleotides surrounding the lesion causing the distortion. The bulkier the lesion, the more readily nucleotide

excision repair recognizes it, and conversely, the more subtle the nucleotide modification, the longer it takes to find and remove them. The great advantage of this system is that it is not lesion specific, so that nucleotide excision repair can remove damage that the organism has never experienced before, including modern chemical carcinogen adducts that were invented in the last 100 years.

This pathway has many substrates, but it is not fast. It may take only 10 min to incise UV-induced lesions [18], but following a sunburn it may take 12 h to remove half the cyclobutane pyrimidine dimers in exposed skin [43].

21.2.2 Base Excision

Base excision repair uses one lead glycosylase enzyme that recognizes a small class of modified bases and releases them from the phosphodiester backbone to create vacant (abasic) sites in DNA. These sites are then repaired by a common set of enzymes that remove the damaged regions on one strand and replace only about 4 nucleotides. The lead enzymes have narrow substrate specificity, but fortunately, several are custom fit for DNA damage induced by sunlight. Important oxidation photoproducts, particularly 8-oxo-dGua, are quickly and efficiently repaired by base excision repair in about 6 h.

One strategy for enhancing DNA repair is to introduce into skin cells glycosylases specific for cyclobutane pyrimidine dimers. This shifts the repair pathway from nucleotide to base excision repair. Not only does it speed up repair but it also reduces the frequency of mutagenic mistakes [46].

21.2.3 Photoreactivation

Photoreactivation is a direct reversal of DNA damage mediated by a light-activated enzyme that uses the energy captured from light to reverse aberrant covalent bonds formed in DNA by photon absorption from sunlight. These enzymes are found ubiquitously in plants, reptiles, and marsupials but not mammals including humans. It seems our photolyase gene has been hijacked by evolution to become a blue light sensor for the circadian rhythm!

Photolyases have been found for both CPD and (6–4)PPs, the two most common direct forms of photodamage. Despite being derived from another kingdom, these enzymes perform a quick and efficient repair inside human cells [39].

21.2.4 Lesion Bypass by Polymerase

Human cells harbor a fail-safe mechanism for handling DNA photodamage. They have polymerase η (eta) that, during replication of a photodamaged DNA template, quickly and efficiently inserts the correct nucleotide opposite a pyrimidine lesion.

Although this doesn't remove the damage, it preserves the genome integrity until an excision mechanism can recognize and remove it. A genetic defect in this fail-safe mechanism produces the cancer-prone xeroderma pigmentosum variant phenotype.

21.2.5 Cellular Regulation of DNA Repair

DNA repair enzymes and pathways are closely coordinated with the rest of the cell's functions. Foremost among these coordinators is the p53 protein. Loss of its function is a perquisite for many skin cancers. DNA damage triggers release of p53 protein from its inhibitor, which frees it to form a transcription activator for its target genes. Most of these genes code for cell cycle checkpoints, inhibitors of proliferation and activators of DNA repair. Sustained activation of p53 protein leads to apoptosis and cell death. In this way, p53 gives the cell a greater opportunity to repair its DNA and, failing that, a road to suicide to avoid mutations and oncogenic transformation.

A large number of DNA Damage Response (DDR) proteins, many of them activated by p53, work together to signal that cell cycling should stop [7]. DNA repair activity is further tied to the health status of the cell through AMPK (5'-AMP-activated protein kinase), which senses energy levels in cells and whose activation increases DNA repair [44]. Furthermore, single-stranded breaks in DNA produced during repair can activate poly(ADP-ribose) polymerase to consume NAD, which saps the cell of molecules essential to production of ATP and lower cellular energy.

DNA repair is tied not only to the cell cycle but also to the circadian rhythm. This should not be surprising since the risk of photodamage to skin DNA is directly related to the presence of the sun in the sky. The genes and proteins in human cells that produce a feedback loop to create the circadian clock (BMal1, Clock, Cryptochrome, and Period) also regulate the cell cycle and DNA repair [34]. The peak of DNA repair capacity is late afternoon, just as the accumulation of daytime sun damage to skin DNA is reaching its maximum.

The DDR genes, including p53, work through regulation of transcription. Downstream of transcription, miRNA (micro-RNA) are also modulated following UV, and they further regulate the DDR genes by increasing or decreasing gene silencing complexes [31]. Cell survival after UV is dependent on the proper functioning of the gene silencing apparatus.

Many of the steps of the DDR pathways involve protein modification of the downstream target. These modifications include classical phosphorylation, acetylation, and, as we have discussed, poly(ADP-ribosyl)ation, which serve to activate or inhibit enzyme activity. Another form of modification is ubiquitin and/or SUMO (small ubiquitin-related modifier) additions to protein, which may coordinate assembly of protein complexes or designate them for destruction to make way for a repair response [40].

21.2.6 Therapeutic Intervention with DNA Repair

The simplest way to intervene in DNA repair is to accelerate the first step of DNA repair, the recognition and incision of damaged bases. This has been accomplished by encapsulating various enzymes in liposomes for delivery into skin cells, including T4 endonuclease V [47] and *M. luteus* UV endonuclease [8] for CPDs, OGG1 for 8-oxo-dGua [45], and photolyase for direct reversal of CPDs [39]. These exogenous but small enzymes are indeed able to enter the nucleus and recognize and then repair DNA damage in mammalian skin.

The hormone α-MSH protects the skin not only by inducing protective pigment but also by inducing p53 and subsequent reduction in cell cycling and initiation of DNA repair [14], a property that may be shared with the α-MSH analog afamelanotide, now undergoing clinical testing.

Induction and synchronization of the circadian rhythm by delivery of peptides to skin cells has been reported to amplify DNA repair [25]. Application of such peptides at night may therefore accelerate repair of DNA damage accumulated during the day.

Binding of certain ligands to receptors activates DNA repair even in the absence of a DNA damage inducing signal. IL-12 binding to its receptor increases repair of UV-induced cyclobutane pyrimidine dimers [36]. The toll-like receptors TLR-3 and TLR-4 mediate damage-associated pattern recognition (DAMP). Agonists of these receptors modulate DNA repair after UV [1, 12]. They may act in part by activating p53 [26]. Since extracellular DNA is recognized as DAMP and bound by TLRs, this may explain the observations that dTpT and small oligonucleotides activate DNA repair through a p53-dependent mechanism [22]. TLRs also distinguish pathogenic from benign surface bacteria, and this may also explain the long-standing observation that extracts of probiotic bacteria enhance DNA repair [3].

HMGB1 (high-mobility group protein B1) is a component of histones but also participates in intercellular communication and recruitment of stem cells to the skin from bone marrow. It is able to activate DNA repair and increase survival after UV [21]. This may provide a new use for compounds modulating HMGB1 levels in the skin.

21.2.7 Botanical Induction of DNA Repair

Antioxidants naturally block oxidation of DNA and are discussed in Chap. 20. There are recurrent reports of antioxidants inhibiting the formation of cyclobutane pyrimidine dimers by UV (e.g., [23]). One explanation might be that antioxidant polyphenols, such as from green tea or polypodium leucotomos, induce IL-12, which then activates the DNA repair pathways to remove cyclobutane pyrimidine dimers [17]. Another may be that antioxidants inhibit energy transfer by oxidized melanin fragments [32].

Topically applied ginseng saponin and silymarin reduce UV toxicity in part by increasing nucleotide excision repair [5, 16]. Interestingly, topically applied caffeine may improve skin health after UV by *inhibiting* DNA repair and forcing more skin cells into apoptosis [20].

The depletion of ATP by poly(ADP-ribose) polymerase may be countered by oral niacin intake and thereby prevent the energy crisis and reduction in DNA repair following UV [19].

21.3 Clinical Consequences of Unrepaired Photodamage to DNA

DNA damage contributes to many of the sequelae of UV exposure, as evidenced by animal studies, by DNA repair deficiency diseases, and by enhancing DNA repair in human skin.

Within a few days after sufficient UV exposure, mouse and human skin develop a reduced ability to properly respond to specific sensitizing antigens [50]. DNA damage, especially CPDs, contribute to this immunosuppression by inducing the release of immunosuppressive soluble mediators and impairing antigen-presenting cells. This reduced ability to respond may allow highly antigenic precancerous skin cells to escape immune surveillance and form a tumor. Enhancing DNA repair reduces the immunosuppressive effect of UV in humans [24, 39].

Chronic UV exposure accelerates the appearance of aging. Especially in lightly pigmented people, this appears as an increase in skin wrinkling and uneven pigmentation. DNA damage contributes to destruction of collagen by inducing the expression of the collagenase MMP-1 [9]. DNA damage is also a trigger for skin pigment production, since one of the purposes of the pigment is to absorb UV and block additional DNA damage [6].

Finally, DNA damage is a central element in the development of skin cancers, including squamous and basal cell carcinoma and melanoma. Mutations in tumor suppressor genes are frequently identified in all these cancers that have the changes characteristic of UV-induced DNA damage [37]. In animal models of DNA repair deficiency and the human genodermatosis xeroderma pigmentosum (XP), with defective DNA repair, the rates of UV-induced skin cancer are greatly increased. Enhancing DNA repair in normal or XP patients reduced their development of new actinic keratoses and basal cell carcinomas [8, 48].

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