expert reviews in molecular medicine

Short-term and long-term cellular and molecular events following UV irradiation of skin: implications for molecular medicine

Yasuhiro Matsumura and Honnavara N. Ananthaswamy

Acute ultraviolet (UV) irradiation of normal human skin results in several clinical effects, including sunburn inflammation (erythema) and tanning, histological changes such as thickening of the epidermis, and local or systemic immunosuppression. Chronic UV irradiation leads to photoaging, sustained immunosuppression and photocarcinogenesis. Photocarcinogenesis involves the accumulation of genetic changes, as well as immune system modulation, and ultimately leads to the development of skin cancers. Recent advances in molecular and cellular biology have clarified the mechanisms of photocarcinogenesis, including the formation of DNA photoproducts, DNA repair, the mutation of proto-oncogenes and tumour suppressor genes, and UV-induced immunosuppression. Further investigation and a better understanding of photocarcinogenesis are critical to the development of effective prevention and intervention strategies for human skin cancer.

Ultraviolet (UV) irradiation can be both beneficial and harmful to normal human skin. The beneficial effects comprise killing pathogens on the skin, inducing vitamin D synthesis and treating certain skin diseases such as psoriasis vulgaris. The harmful effects of UV irradiation are immune suppression, photoaging and, above all, skin carcinogenesis. The incidence of skin cancer has been increasing at an astonishing rate over the past several decades, and it is estimated that more than one million new cases of nonmelanoma skin cancer (NMSC) occur each year in the USA (Ref. 1). The relevance of sunlight exposure to the development of NMSC is well known (Ref. 2).

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The skin responds to sun exposure by tanning and thickening, both of which provide some protection from further damage by UV irradiation. The degree of pigmentation in the skin and the ability to tan are important risk factors in skin cancer development, and the risk of NMSC is highest in people who sunburn easily and rarely tan (Ref. 1).

Recent developments in molecular biology and research using laboratory animals have clarified the central role of UV irradiation in the development of NMSC. UV irradiation can damage keratinocytes by forming cyclobutane-type dimers in DNA between adjacent pyrimidine residues, potentially leading to UV 'signature' mutations that can accumulate over time (Ref. 3). The cell can respond to the damage either by repairing DNA to avoid harmful mutations or, if the damage is too serious, by inducing apoptosis to remove potential cancer cells from the population (Ref. 3). Failure of these pathways can result in the loss of control over proliferation and lead to tumour development through the inactivation of tumour suppressor genes or the activation of oncogenes. Immune surveillance in the skin also plays an important role in protecting against skin cancer development. UV exposure suppresses the function of the immune system in the skin, thereby creating a more favourable environment for the development and growth of tumours (Ref. 4).

The purpose of this article is to provide an overview of recent advances in understandings of the short-term and long-term cellular and molecular events following UV irradiation of skin. This will be used as a basis to discuss the search for effective measures to protect against the harmful aspects of UV irradiation and repair pre-existing photodamage.

Short-term effects of UV irradiation on the skin

Acute UV irradiation (a single exposure) induces DNA lesions such as pyrimidine dimers and (6-4) photoproducts that could lead to DNA mutations if they are not repaired. To prevent DNA mutations, cells are equipped with a DNA repair apparatus and p53, a protein that works against DNA mutations. p53 is induced after acute UV irradiation and stops the cell cycle at the G1 phase, thus gaining time for DNA repair. When the DNA damage is too severe, p53 induces apoptosis of the cell in order to inhibit carcinogenesis. These aspects of DNA damage and repair following acute UV irradiation are discussed further in this section.

UV-induced DNA lesions

Sunlight is composed of a continuous spectrum of electromagnetic radiation that is divided into three main regions of wavelengths: UV, visible and infrared (Ref. 3). UV irradiation comprises the wavelengths from 200 to 400 nm, the span of wavelengths just shorter than those of visible light (400–700 nm). UV irradiation is further divided into three sections, each of which has distinct biological effects: UVA (320–400 nm), UVB (280–320 nm) and UVC (200–280 nm).

UVC is effectively blocked from reaching the surface of the earth by the stratospheric ozone layer, although accidental exposure could occur from man-made sources such as germicidal lamps. UVA and UVB irradiation both reach the surface in amounts sufficient to have important biological consequences for the skin and eyes. The importance of UVA contributions to melanogenesis is somewhat controversial. Although UVA is the predominant component of the solar UV irradiation to which we are exposed, it is weakly carcinogenic in mouse experiments on induction of skin cancers and, judging by the UVB-related p53 mutations, this is also likely to hold true for these skin carcinomas in humans. However, some laboratory studies have demonstrated that wavelengths in the UVA region cause not only aging and wrinkling of the skin, but also skin cancer when given in high doses over a long period of time (Ref. 5). By contrast, it is clear that wavelengths in the UVB region of the solar spectrum are absorbed into the skin, producing erythema, burns and eventually skin cancer.

UV irradiation from 245 to 290 nm is absorbed maximally by DNA (Ref. 6). UV irradiation is able to induce mutagenic photoproducts or lesions in DNA between adjacent pyrimidine [thymine (T) or cytosine (C)] residues in the form of dimers: either cyclobutane pyrimidine dimers (CPDs) or (6-4) photoproducts (Fig. 1). CPDs are formed between the C-4 and C-5 carbon atoms of any two adjacent pyrimidines; the double bonds become saturated to produce a four-membered ring (Ref. 7). Similarly, (6-4) photoproducts are formed between the 5′ C-4 position and the 3′ C-6 position of two adjacent pyrimidines, most often between TC and CC residues (Ref. 6). CPDs

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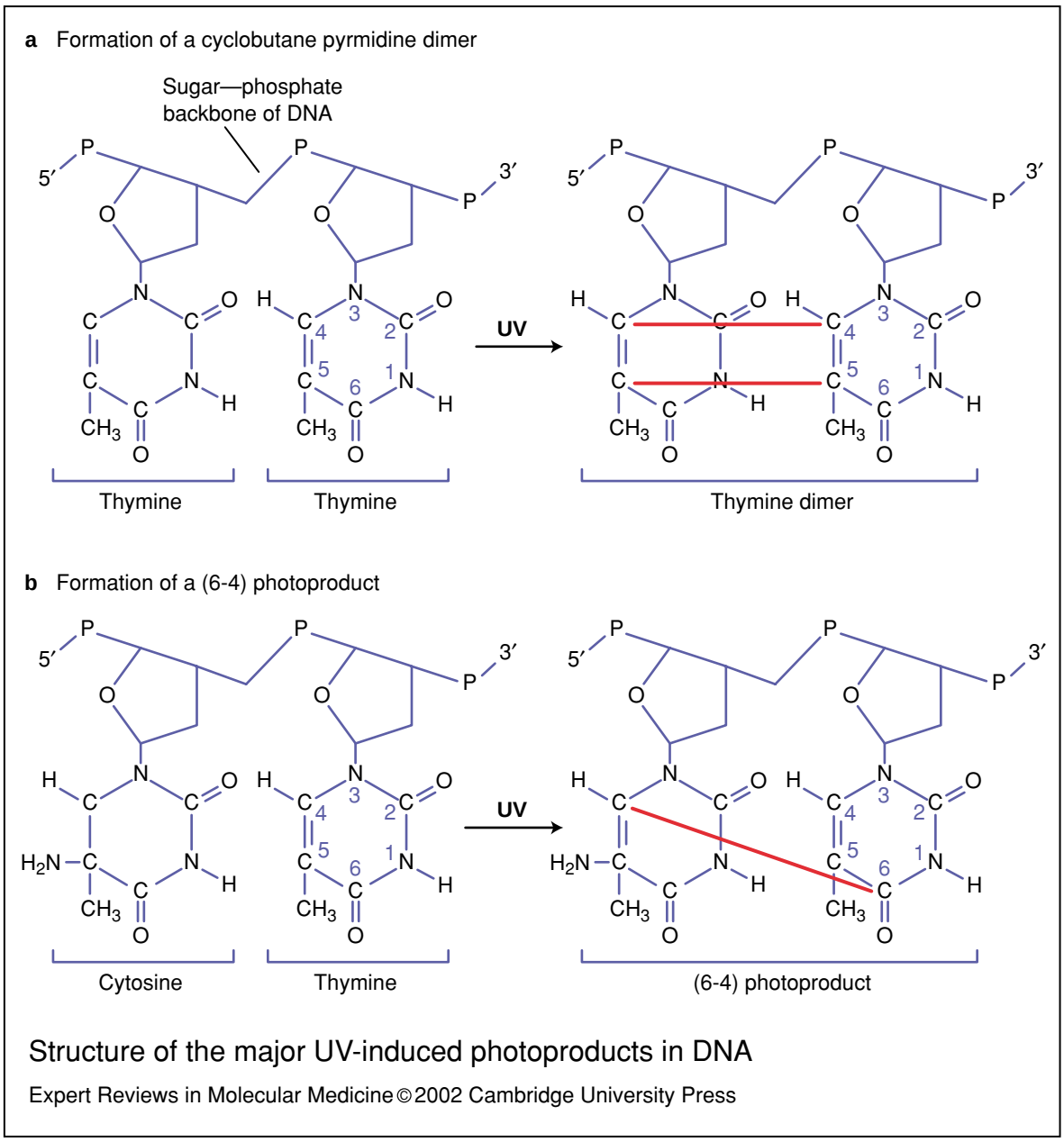

Figure 1. Structure of the major UV-induced photoproducts in DNA. Absorbtion of UV light by DNA induces mutagenic photoproducts or lesions in DNA between adjacent pyrimidines [thymine (T), cytosine (C)] in the form of two main types of dimers. (a) Two adjacent T molecules (shown here), or an adjacent T and C residue, can be converted to a T–T or C–C cyclobutane pyrmidine dimer (CPD), respectively. The double bonds between C-4 and C-5 carbon atoms of any two adjacent pyrimidines become saturated to produce a four-membered ring. (b) In the other type of dimer, (6-4) photoproducts are formed between the 5′ C-4 position and the 3′ C-6 position of two adjacent pyrimidines, either between TC (shown here) or CC residues. For further information, see Ref. 133 **(fig001hah)**.

are produced three times as often overall as (6-4) photoproducts (Ref. 6). Both lesions occur most frequently in areas of tandem pyrimidine residues, which are known as 'hot spots' of UV-induced mutations (Ref. 7). Although both lesions are potentially mutagenic, CPDs are supposed to be the major contributor to mutations in mammals (Ref. 6) as (6-4) photoproducts are repaired much more quickly than CPDs in mammalian cells (Ref. 8).

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If not repaired, UV-induced DNA lesions can lead to mutations in the DNA sequences. These mutations are in the form of C to T and CC to TT transitions, known as UV 'signature' mutations. The 'A rule' has been proposed to explain how UV signature mutations arise from DNA lesions (Ref. 9). According to the A rule, DNA polymerase ε inserts adenine (A) residues by default opposite lesions that it cannot interpret. Subsequently, a mutation is created upon DNA replication of the strands containing base-pair changes. The TT cyclobutane dimers do not result in mutations because A normally is paired with T, and no mutation would result from insertion of A residues by default opposite the dimer. However, with CC CPDs, a CC to TT transition occurs, because two A residues are placed opposite the dimer by default in the place of two guanine (G) residues. In (6-4) photoproducts between a pyrimidine and a C residue, the 5′ residue base-pairs correctly, but the 3′ C residue resembles a non-instructional site (Ref. 7). Thus, a C to T mutation occurs because an A residue is placed opposite the C residue by default.

Repair mechanism of UV-induced DNA lesions

Mammalian cells are equipped with several DNA repair systems that are able to protect the cell from the effects of DNA-damaging compounds by removing DNA lesions (Ref. 10). Depending on the primary DNA lesion, one or more repair pathways become active; these pathways include photoreactivation, base excision repair, mismatch repair, double-stranded break repair and nucleotide excision repair (NER). CPDs and (6-4) photoproducts generated by UV irradiation are primarily repaired by NER, which removes bulky DNA damage in two distinct subpathways (Refs 11, 12): damaged areas of actively transcribed genes are removed by a rapid mechanism called transcription-coupled repair (TCR) and damage to other parts of the genome is removed by a slower pathway called global genome repair (GGR) (Fig. 2). The two subpathways differ only in the first step of NER: DNA damage recognition. In GGR, the protein complex XPC/HHR23B is involved in damage recognition; in TCR, a stalled RNA polymerase II is the damage recognition signal. The Cockayne syndrome (CS) A and B proteins (CSA and CSB) are believed to facilitate this process. The following subsequent stages occur both in GGR and TCR: unwinding of the DNA helix surrounding the DNA lesion, dual incision of the damaged DNA strand, and excision of the damaged section and de novo DNA synthesis.

Defects in both subpathways of NER can lead to three distinct human diseases: xeroderma pigmentosum (XP), CS and trichothiodystrophy (TTD); among these three diseases, only XP patients exhibit a predisposition to skin cancer as well as photosensitivity (Ref. 13). The mean age at which the cutaneous symptoms of XP such as parchment and freckles appear is two years, and patients have a more than 1000-fold increased risk of skin cancer. Basal cell carcinomas (BCCs), squamous cell carcinomas (SCCs) and, less frequently, melanomas appear almost exclusively to sun-exposed areas. Moreover, XP patients have a 10–20-fold increased risk of developing several types of internal cancers by the age of 20 years (Ref. 14). Considering the involvement of NER in the repair of chemically induced DNA lesions, as well as in the repair of lesions induced by cellular metabolites, either category of lesions might play a role in internal neoplasms.

Mehanisms to prevent transmission of damaged DNA

Despite the ability of mammalian cells to repair UV-induced DNA damage, some damage will remain. The cells of the skin contain mechanisms to prevent such DNA damage from leading to skin carcinogenesis. One of these mechanisms is growth arrest followed by DNA repair, and the other is cell death by apoptosis. Both of these mechanisms prevent the transmission of mutations to daughter cells that could otherwise lead to transformation and carcinogenesis. The phosphoprotein p53 is important in both of these mechanisms and is known as a tumour suppressor because it is frequently inactivated or mutated in tumours and transformed cells.

Cell-cycle arrest and DNA repair

Upon DNA damage by UV irradiation, the cell cycle can be arrested by at least two checkpoints: the G1/S phase before DNA replication, and the G2/M phase before chromosome segregation (Ref. 15). UV irradiation is known to influence the activities of various genes involved in cell-cycle control and growth arrest (Refs 16, 17). Among them, the *p53* gene plays a crucial role in regulating the cell cycle upon DNA damage by UV irradiation (Fig. 3). The accumulation of p53

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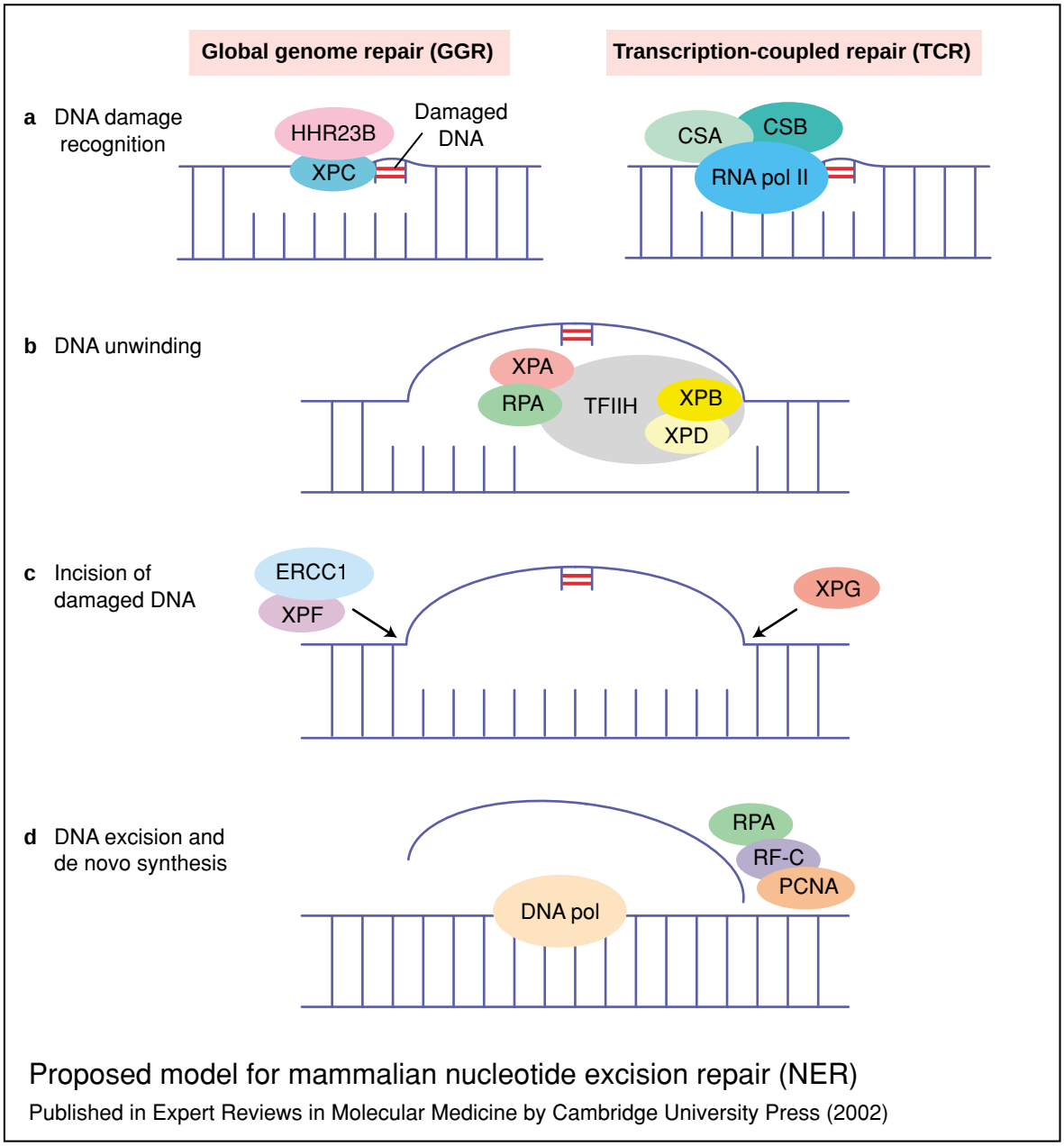

Figure 2. Proposed model for mammalian nucleotide excision repair (NER). NER consists of two subpathways: global genome repair (GGR) and transcription-coupled repair (TCR). (a) The two subpathways differ only in the first step, DNA damage recognition. In GGR, the protein complex XPC/HHR23B binds to the damaged DNA site, recruiting the entire repair protein apparatus to the injury. By contrast, in TCR, a stalled RNA polymerase II fulfils this function at the site of the DNA lesion, facilitated by the Cockayne syndrome proteins CSA and CSB. (b) In the second step, DNA unwinding, the lesions are opened by the concerted action of XPA, replication protein A (RPA), and the bi-directional XPB/XPD helicase subunits of the transcription factor IIH (TFIIH) complex. (c) During incision of the damaged DNA, the exchange repair cross complementing (ERCC1)/XPF complex cuts at the single-strand to double-strand transition on the 5′ side of the damage, and XPG cuts at the 3′ side of the open complex. (d) Finally, DNA excision and de novo synthesis is accomplished by mammalian DNA replication factors such as the heterotrimeric replication protein A (RPA), replication factor C (RF-C), proliferating cell nuclear antigen (PCNA), and DNA polymerase δ and ε. The reaction is completed by ligation of the newly synthesised DNA. Modified figure reproduced with permission from Ref. 12 **(fig002hah)**.

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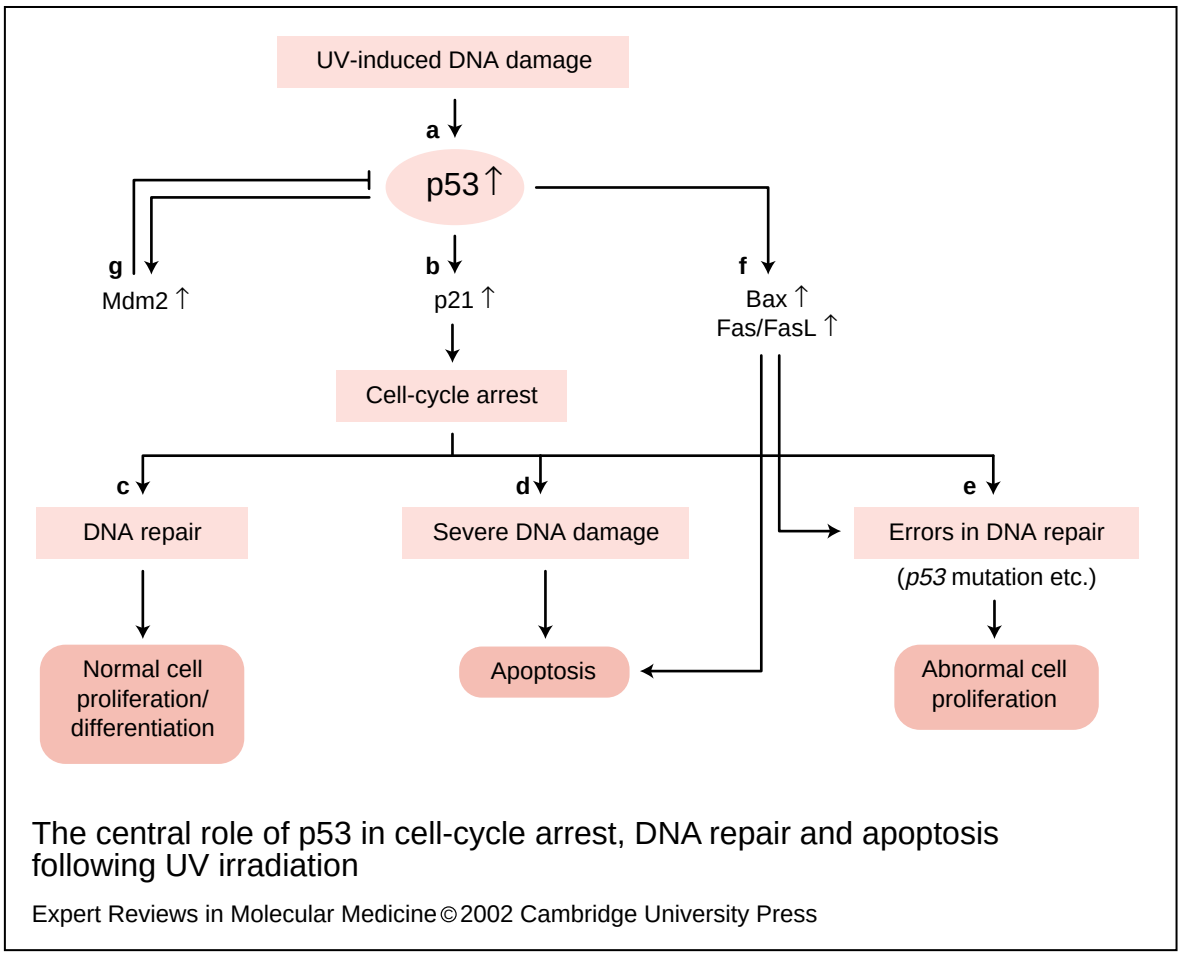

Figure 3. The central role of p53 in cell-cycle arrest, DNA repair and apoptosis following UV irradiation. Despite the ability of mammalian cells to repair UV-induced DNA damage, some damage will remain. Skin cells contain mechanisms to prevent such DNA damage from leading to skin carcinogenesis. (a) The accumulation of p53 protein after exposure to UV irradiation plays a central role in these mechanisms. (b) p53 induces p21, which inhibits formation of complexes required for the cell cycle and thereby leads to cell-cycle arrest. (c) Cell-cycle arrest can provide the cell with time to achieve successful DNA repair and the cell proliferates as normal. (d) If the DNA damage caused by UV irradiation is too severe and cannot be repaired, apoptotic pathways are activated to eliminate damaged cells. (e) If normal DNA repair is not achieved, for instance because of mutations in *p53*, the cell proliferates abnormally, which can lead to carcinogenesis. (f) As a transactivator of transcription, p53 can induce apoptosis by upregulating the expression of apoptosis-promoting (pro-apoptotic) genes such as *Bax*, *Fas*/*Apo-1*, death receptor 5 (*DR5*) or insulin-like growth factor-binding protein 3 (*IGF-BP3*), or by downregulating the expression of apoptosis-suppressing (anti-apoptotic) genes such as *Bcl-2*, cellular inhibitor of apoptosis protein 2 (*c-IAP2*) and neuronal apoptosis inhibitory protein 1 (*NAIP1*) (Ref. 22). If apoptosis is not achieved, for instance because of mutations in *p53* or dysregulation of the *Fas–FasL* interactions, then this might also result in the development of skin cancer. (g) The tumour suppressor activity of p53 is in turn inhibited by the Mdm2 protein, which targets p53 for rapid degradation. The gene encoding Mdm2 is itself activated by p53, thereby providing a negative autoregulatory loop **(fig003hah)**.

protein after exposure to UV irradiation induces a cell-cycle arrest at the G1 phase, which allows the repair of DNA damage before its replication in the S phase (Refs 18, 19). The $p21^{WAF1/CIP1}$ gene was discovered to encode an inhibitor of cyclin-dependent kinase (CDK), whose induction was associated with the expression of wild-type p53 (Refs 20, 21). p21 inactivates the CDK–cyclin complex by forming a complex of CDK2, cyclin-A (or cyclin-E), proliferating cell nuclear antigen (PCNA) and p21, thus leading the cell into G1 arrest. Formation of these complexes leads

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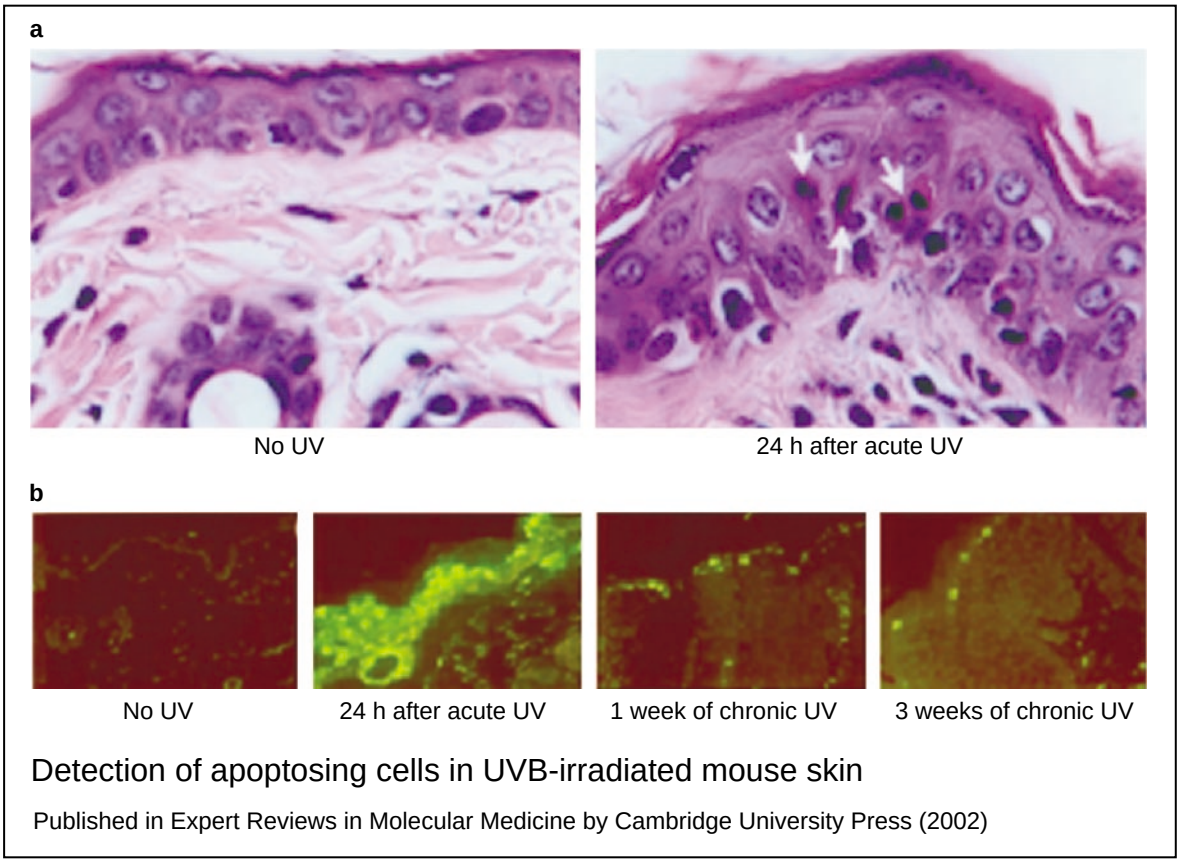

Figure 4. Detection of apoptosing cells in UVB-irradiated mouse skin. (a) Haematoxylin–eosin (HE) staining of specimens from non-irradiated mouse and 24 h after UV exposure. In the irradiated sample, the nuclei are seen to be shrinking, and the cytoplasms are becoming eosinophilic in sunburn cells (white arrows), indicating that apoptosis is occurring. (b) The presence of apoptosing cells (fluorescing green) detected using terminal deoxynucleotidyl transferase nick-end labelling (TUNEL) assay of specimens from non-irradiated mouse, 24 h after exposure, after 1 week of chronic exposure, and after 3 weeks of chronic exposure. The number of TUNEL-positive, apoptosing cells is highest 24 h after acute (single) UV irradiation. The number decreases significantly after 1 week or 3 weeks of chronic UV irradiation. Modified figure reproduced with permission from Ref. 87 **(fig004hah)**.

to the accumulation of hypophosphorylated retinoblastoma protein (pRb), causing the release of the E2F transcription factor, which is necessary for DNA synthesis (Refs 20, 21). The tumour suppressor activity of p53 is in turn inhibited by the Mdm2 protein, which targets p53 for rapid degradation. The gene encoding Mdm2 is itself activated by p53, thus providing a negative autoregulatory loop (Ref. 12). If normal DNA repair is not achieved, for instance because of mutations in *p53*, the cell proliferates abnormally, which can lead to carcinogenesis.

Cell death by apoptosis

If the DNA damage caused by UV irradiation is too severe and cannot be repaired, apoptotic pathways are activated to eliminate damaged cells (Fig. 4), and p53 again plays a leading role (Fig. 3). As a transactivator of transcription, p53 can induce apoptosis either by upregulating the expression of apoptosis-promoting (pro-apoptotic) genes such as *Bax*, *Fas/Apo-1*, death receptor 5 (*DR5*) or insulin-like growth factor-binding protein 3 (*IGF-BP3*), or by downregulating the expression of apoptosis-suppressing (anti-apoptotic) genes such as *Bcl-2*, cellular inhibitor of apoptosis protein 2 (*c-IAP2*) and neuronal apoptosis inhibitory protein 1 (*NAIP1*) (Ref. 22).

p53-induced apoptosis involves several mechanisms that are determined by cell type and apoptotic stimulus, and the *Bcl-2* gene family plays a crucial role in these. The *Bcl-2* gene family is composed of the pro-apoptotic gene group

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(*Bax*, *Bad*, *Bak*, *Bcl-x$_S$*, *Bik*, *Bim* and *Mtd/Bok*) and the anti-apoptotic gene group (*Bcl-2*, *Bcl-w*, *Bcl-x$_L$* and *Mcl-1*) (Refs 23, 24). Bax and Bcl-2 proteins, which are homologous but have opposing effects on apoptosis, can form heterodimers in cells, and their interaction is critical to the ability of *Bcl-2* to block cell death (Ref. 25). p53 induces apoptosis by disrupting the balance between these proteins, upregulating the *Bax* gene and downregulating the *Bcl-2* gene.

Another important p53-induced apoptotic mechanism is through Fas expression. Wild-type p53 can activate the *Fas* gene by binding to its transcriptional activation site and promotor region (Ref. 26). In addition, p53 promotes the redistribution of cytoplasmic Fas to the cell surface through transportation from the Golgi complex (Ref. 27). Recent studies have shown that UV-induced formation and apoptosis of sunburn cells are mediated by the p53 pathway and have implicated Fas interactions as being important (Refs 28, 29). Ziegler et al. (Ref. 28) reported that the inactivation of *p53* in mouse skin reduced the appearance of sunburn cells, implying that the elimination system of precancerous keratinocytes is hampered when the cells harbour *p53* mutations caused by UV irradiation. Hill et al. (Ref. 29) investigated the function of interactions of Fas with Fas ligand (FasL) in UV-induced keratinocyte apoptosis and found that this interaction was essential for the elimination of UV-damaged keratinocytes. In addition, they found that the accumulation of *p53* mutations in the epidermis after chronic UV irradiation was observed at a much higher frequency in *FasL*-deficient mice (14 out of 20 mice, i.e. 70%) than in wild-type mice (1 out of 20 mice, i.e. 5%). They concluded that FasL-mediated apoptosis is important for skin homeostasis and that the dysregulation of Fas–FasL interactions might be central to the development of skin cancer.

Effects on murine skin

The molecular and cellular changes that occur after acute UV irradiation have been analysed using laboratory animals. These include changes in the proteins involved in cell-cycle activity, proliferation and apoptosis. Chronic UV irradiation induces skin cancers by damaging these functions in keratinocytes. In addition, the mechanism of UV-induced immunosuppression has been investigated at the molecular and cellular levels.

Induction of sunburn cells and protein expression after acute UV irradiation

Ouhtit et al. (Ref. 30) reported the effects of UV irradiation on the time course for induction of sunburn (apoptotic) cells and expression of proteins known to be associated with growth arrest and apoptosis in murine skin. Mice were irradiated with a single dose of UV and the skin tissues were analysed at various times after irradiation. p53 protein expression was induced early in the epidermis (maximum levels, 12 h after irradiation), followed by p21 expression, which peaked at 24 h. High levels of Bax expression were observed 24–72 h after irradiation, with a concomitant decrease in Bcl-2 expression. Coinciding with these changes, apoptotic cells began to appear 6 h after irradiation and reached a maximum at 24 h. PCNA expression was initially confined to the basal layer and then became dispersed throughout the basal and suprabasal layers of the skin at 48 h, paralleling the appearance of marked hyperplasia (an abnormal increase in the number of cells). These observations suggest that UV irradiation induces apoptosis mediated by the p53/p21/Bax/Bcl-2 pathway in murine skin and that the dead cells are replaced by hyperproliferative cells, leading to epidermal hyperplasia.

Wild-type p53 can simultaneously induce both G1 growth arrest and apoptosis in the same cell type (Ref. 31). Cotton et al. (Ref. 32) reported that p53 expression in cultured normal keratinocytes is predominantly perinuclear; however, exposure of cells to UVB irradiation induces a major shift of p53 expression to the nucleus. They also found that high doses of UVB irradiation induced cells to undergo apoptosis, whereas low doses did not induce apoptosis but appeared to stimulate repair of the DNA damage caused by the irradiation. Intermediate doses of UVB irradiation induced a heterogeneous population of cells to undergo either DNA repair or apoptosis, and the dose also influenced the cellular localisation of p53. These data imply that p53 plays a role in both the repair of UV-induced DNA damage and the induction of apoptosis, and might function as a central control checkpoint in the response to UV-induced DNA damage.

UV-induced immune suppression

The skin contains Langerhans cells (LCs) that serve as antigen-presenting cells (APCs) and are capable of communicating with T, and

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probably non-T, lymphocyte cells. In addition, keratinocytes produce several cytokines that might also participate in immune recognition in the skin. These cells, together with the regional draining lymph nodes that serve them, have been labelled 'skin-associated lymphoid tissues' (SALT) by Streilein and colleagues (Ref. 33). UV irradiation induces immunosuppression by affecting this system, including suppressing contact hypersensitivity (CHS) (Ref. 34) and delayed-type hypersensitivity (DTH) (Ref. 35), which could possibly permit the growth of emerging skin tumours produced by the effects of UV-induced DNA damage.

Skin cancers induced by UV irradiation in mice are highly antigenic and, when transplanted into genetically identical mice, most are rejected by the immune system of the recipient (Ref. 36). However, these tumours grow and eventually kill the host when they are transplanted into mice exposed to a short course of UV irradiation. This observation suggests that exposing mice to UV irradiation interferes with the ability of the immune system to reject developing skin cancers. This defect can be passively transferred with lymphoid cells, probably because of the presence of suppressor T cells derived from UV-irradiated mice (Ref. 37). These suppressor T cells prevent the rejection of transplanted, UV-induced, murine tumours, but not the rejection of tumours induced by other carcinogens.

Most attention has focused on the epidermal LCs and keratinocytes in order to determine how UV irradiation brings about systemic changes in host immunity. Exposure to UV irradiation alters the morphology of LCs, downregulates the expression of major histocompatibility complex (MHC) class II antigens on their surface (Ref. 38), and alters the cell-surface expression of costimulatory molecules such as CD80, CD86 (Ref. 39) and intercellular cell adhesion molecule 1 (ICAM-1; CD154) (Ref. 40). These changes inhibit the antigen-presenting function of LCs, and thus the immune response is not initiated. Instead, the suppressive pathway of the immune system is activated, resulting in the production of suppressor T cells (Ref. 41). On the other hand, keratinocytes release various cytokines upon UV irradiation, including interleukin 1 (IL-1), IL-4, IL-6, IL-10 and tumour necrosis factor α (TNF-α) (Ref. 42). These cytokines appear to work both locally and systemically to alter the function of APCs. Among them, IL-10 has been shown to directly impair the function of APCs (Ref. 43). Moreover, in UV-irradiated keratinocytes, anti-IL-10 monoclonal antibody (mAb) prevented supernatants from suppressing the induction of DTH in vivo, and the injection of antibodies against IL-10 into UV-irradiated mice partially inhibited in vivo immunosuppression (Ref. 44). These studies suggest that the release of IL-10 by UV-irradiated keratinocytes plays an essential role in the induction of both local and systemic immunosuppression after UV irradiation.

Effects on human skin

The clinical changes in human skin after UV exposure have been described for many years and include sunburn inflammation, suntan and histological changes. Recently, these phenomena have been analysed using molecular techniques, leading to the suggestion that the genetic background of individuals might explain their different reactions to UV exposure.

Sunburn inflammation and protective responses after acute UV irradiation

The major acute clinical effects of UV irradiation on normal human skin are sunburn inflammation (red skin; erythema) and tanning (enhanced melanogenesis). The histological changes following UV irradiation include thickening of the outer layer of the epidermis (stratum corneum), epidermis and dermis, as well as intercellular and perivascular swelling (oedema) in the dermis, and perivascular infiltration. The individual erythemal and tanning responses of human skin are largely genetically determined. Recent studies suggest a possible role for polymorphism in the melanocyte-stimulating hormone (MSH) receptor (Ref. 45), although other genes are also likely to be involved. The following responses to the first seasonal exposure to 30 minutes of midday sunlight have been used to characterise skin type for fair-skinned persons: (1) skin type 1, always burn, never tan; (2) skin type 2, usually burn, rarely tan; (3) skin type 3, rarely burn, usually tan; and (4) skin type 4, never burn, always tan.

Sunburn erythema is the most conspicuous and well-recognised acute cutaneous response to UV irradiation, particularly in fair-skinned individuals. In some individuals, erythema resulting from UV irradiation is biphasic, with a transient flush being seen within seconds and a delayed erythema that peaks minutes to hours

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later (Ref. 46). The immediate reaction is usually seen only in individuals with skin type 1 or 2, but the delayed response is a consistent one, reaching a peak by 6–24 h depending on dose (Ref. 47). The molecules responsible for light absorption (chromophores) that initiate the process of sunburn inflammation have not been precisely identified. However, the action spectrum of erythema is consistent with the hypothesis that UV interactions with DNA are of major importance (Ref. 48), suggesting that the principal event is direct damage to DNA by UVB and short UVA wavelengths. Indirect oxidative damage might also occur secondarily to endogenous photosensitiation reactions at longer wavelengths.

The skin pigmentation response following UV irradiation is also biphasic, comprising immediate pigment darkening (IPD) and the delayed formation of new melanin (Ref. 49) (Fig. 5). IPD is maximal seconds after UV exposure and apparently results from the alteration and redistribution of melanin moieties already present in the skin. IPD is thought to provide protection against damage to epidermal basal cell nuclei by forming 'nuclear caps' (Ref. 49). Delayed tanning (DT) following UV exposure is the result of both UVB and UVA irradiation. DT from UVB exposure is associated with an increase in the activity and number of melanocytes. Single exposures increase only activity, while subsequent doses are required to increase numbers of melanocytes. Melanocyte tyrosinase activity also increases, melanocyte dendrites elongate and branch, and melanosome numbers and size increase (Ref. 50). Accelerated melanin transfer to keratinocytes then results in a large increase in melanin granules in the epidermis. UVA-initiated tanning has distinct effects that are wavelength dependent: UVA irradiation between 340 and 400 nm increases melanin density localised to the basal cell layer; whereas, UVA irradiation between 320 and 340 nm increases the synthesis and transfer of melanised melanosomes to the epidermis (Ref. 51).

The increase in the dose of UV irradiation required to sunburn in chronically irradiated subjects is not only the result of tanning but also of hyperplasia of the stratum corneum, epidermis and dermis. UV-induced hyperplasia results from increased epidermal and dermal mitotic activity about 24–48 h after acute UV exposure and is also associated with increased synthesis of DNA, RNA and proteins (Ref. 52). This occurs after a transient period of cell-cycle arrest regulated by the activity of nuclear p53 protein, which, as mentioned above, plays a crucial role in DNA repair and in protecting the genome from potentially deleterious mutations before mitosis begins (Refs 53, 54).

Dermal changes also occur following both UVB and UVA irradiation exposure. Particularly after UVA irradiation, superficial and some deeper blood vessels show early endothelial swelling, leading to their partial occlusion with perivascular oedema. A mixed perivascular infiltrate that consists mainly of mononuclear cells and T cells, together with neutrophils, also occurs, beginning within hours and peaking 24–48 h after exposure to both UVB and UVA irradiation (Refs 55, 56). All of the histological changes mentioned above are temporary and, in the absence of further UV exposure, the skin cells return to normal within 1–2 weeks.

Immunological response after acute UV irradiation

Exposure to erythemogenic doses of UV irradiation decreases the proportion of peripheral T cells and reduces the blastogenic response of peripheral blood mononuclear cells to T-cell mitogens (Ref. 57). Exposure to 1 h of summer sunlight on 12 occasions resulted in a significant increase in $CD8^+$ (suppressor/cytotoxic) T cells and a decrease in $CD4^+$ (helper/inducer) T cells in peripheral blood (Ref. 58). Furthermore, irradiated subjects demonstrated reduced cutaneous responses to dinitrochlorobenzene (DNCB), increased nonspecific suppressor cell activity, decreased natural killer (NK)-cell activity, and a decrease in the CD4/CD8-cell ratio compared with controls (Ref. 59). One report suggests that humans vary in their susceptibility to the inhibition of CHS by a fixed absolute dose of local UVB irradiation (Ref. 60). In this study, a dose of UVB irradiation that depletes LCs from the skin was followed by application of DNCB; 60% of normal individuals in the protocol became sensitive to DNCB, whereas the remaining 40% did not; 92% of patients with skin cancer did not respond to DNCB, and 45% of them became tolerant to DNCB; no normal subjects became tolerant. These data suggest that a genetic basis for susceptibility to UVB irradiation can effect suppression of CHS by UVB and that this could be a risk factor for skin cancer susceptibility (Ref. 60).

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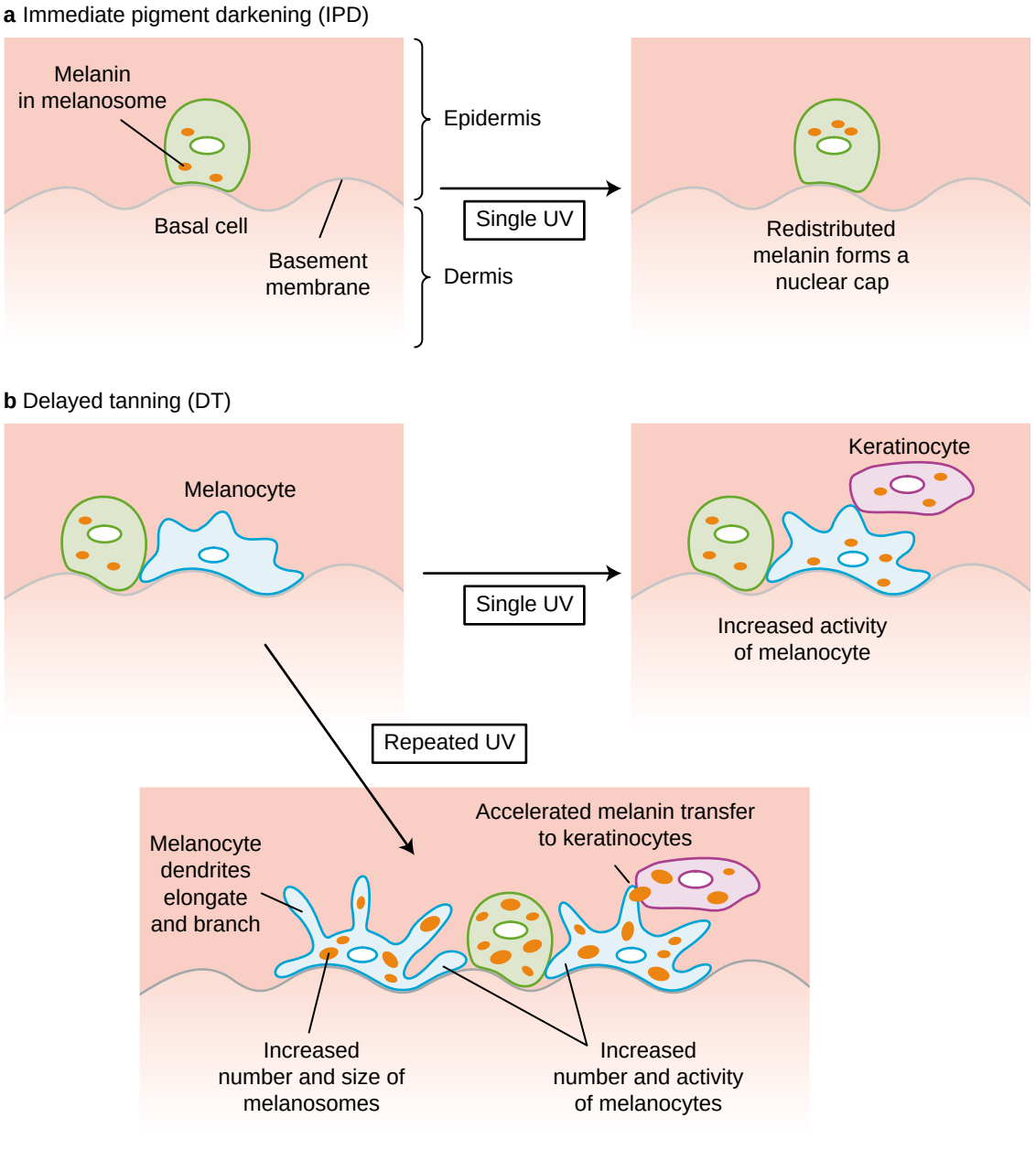

The mechanism of skin pigmentation after UV irradiation

Figure 5. The mechanisms of skin pigmentation after UV irradiation. The skin pigmentation response following UV irradiation comprises immediate pigment darkening (IPD) and delayed tanning (DT). (a) IPD results from the alteration and redistribution of melanin moieties already present in the skin by forming 'nuclear caps' to protect cell nuclei from UV-induced damage. (b) DT is associated with an increase in the activity and number of melanocytes. Single UV exposure increases the activity of melanocytes. In repeated UV exposure, the number of melanocytes increases, the number and size of melanosomes increases, and melanocyte dendrites elongate and branch. Accelerated melanin transfer to keratinocytes then results in a large increase in melanin granules in the epidermis **(fig005hah)**.

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The involvement of the immune system in human skin carcinogenesis is suggested by the increased risk of malignancy in patients undergoing immunosuppressive therapies. The increased risk of skin cancer in renal transplant patients is approximately sevenfold (Ref. 61), and patients treated with immunosuppressive chemotherapeutic agents also appear to be at increased risk for the development of skin cancer (Ref. 62). By analogy, the immunosuppressive state caused by UV irradiation could lead to an increased risk of skin cancers; however, definitive evidence for specific immunological involvement has not been shown.

Long-term effects of UV irradiation on the skin

Chronic UV irradiation (repeated exposure) causes skin aging, mutations in oncogenes and tumour suppressor genes, and skin carcinogenesis. These aspects of DNA damage following repeated exposure to UV irradiation are discussed in this section.

Skin aging

Actinically damaged skin, or photoaging, is the result of chronic sun exposure. The clinical symptoms include dryness (roughness), irregular pigmentation [e.g. freckling, flat patches of increased pigmentation (lentigines), persistant hyperpigmentation], wrinkling, elastosis (fine nodularity and/or coarseness) and telangiectasia (dilation of pre-existing blood vessels creating small focal red lesions). These features are predominantly observed in fair-skinned white individuals with a history of ample past sun exposure and usually involve the face, neck, or extensor surface of the upper extremities.

Although UVB photons are much more energetic than UVA photons and are mostly responsible for sunburn, suntanning and photocarcinogenesis (Ref. 63), UVA is also suspected of playing a substantial role in photoaging. UVA induces the formation of reactive oxygen species that readily react with membrane lipids and amino acids (Ref. 63). Membrane damage results in the release of arachidonic acid and leads to activation of secondary cytosolic and nuclear messengers that activate UV response genes. Human skin exposed daily for one month to suberythemic doses of only UVA demonstrated epidermal hyperplasia, stratum corneum thickening, LC depletion, and dermal inflammatory infiltrates with deposition of lysozymes on the elastic fibres (Refs 64, 65). These changes suggest that frequent casual exposure to sunlight while wearing a UVB-absorbing sunscreen may eventually result in damage to dermal collagen and elastin in ways expected to produce photoaging.

UV-induced mutations and skin carcinogenesis

Carcinogenesis caused by UV irradiation often involves the inactivation of one or more tumour suppressor genes or the activation of growth-stimulatory proto-oncogenes. Tumour suppressor genes are negative growth regulators and are usually recessive in that both copies of the gene must be inactivated before loss of control over cell growth occurs. The accumulation of proteins that bind to and sequester tumour suppressor proteins can also make the cell more susceptible to further mutations. By contrast, the activation of oncogenes is dominant in that a change in only one copy of the gene will have an effect. Proto-oncogenes, the normal versions of oncogenes, act to control cell proliferation and differentiation. Carcinogenesis can result either from the expression of a mutant version or from an altered gene product. Several genes have been extensively studied and shown to have important roles in skin carcinogenesis, including *p53*, *p16*/*p19*, *patched* and *ras*, and these will be discussed further below.

p53 tumour suppressor gene

Several investigators have detected *p53* gene mutations in a large proportion of human SCCs, BCCs and actinic keratoses (skin lesions that are abnormally sensitive to the effects of UV and are considered to be precursors to SCCs) (Refs 28, 66, 67, 68, 69, 70, 71, 72, 73). Ziegler et al. reported that *p53* gene mutations were detected at a higher frequency (50–90%) in NMSCs than in internal malignancies (Ref. 28). The predominant alterations are C to T and CC to TT transitions at dipyrimidine sites. *p53* mutations have also been found at high frequencies in skin cancers from patients with XP (Refs 74, 75, 76). In such cases, the majority of mutations are CC to TT tandem base substitutions, and most occur on the nontranscribed strand of DNA, implying preferential repair of UV-induced lesions on the transcribed strand.

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Mutations in the *p53* gene appear to be an early genetic change in the development of UV-induced skin cancers (Refs 28, 72, 76). *p53* gene mutations have been detected in normal sun-exposed human skin (Refs 72, 77) as well as in UV-irradiated mouse skin (Refs 78, 79). In addition, *p53* gene mutations were detected at a high frequency in human actinic keratoses (Refs 28, 71). More-recent studies have revealed that noncancerous skin adjacent to skin cancers harbours *p53* gene mutations that are distinct from those present in the skin cancers (Ref. 80, 81). Zhang et al. (Ref. 82) studied microscopic clones of keratinocytes mutated in the *p53* gene using epidermal sheets. They found that clonal expansion was continually driven by UVB without any additional proliferative mutation, implying that the initial *p53* gene mutation in combination with UV irradiation are the essential factors in UV-induced skin carcinogenesis.

One report (Ref. 83) compared the frequency and type of *p53* mutations in BCCs found in sun-exposed body areas (face, ear, forearm, etc.) with those found in less-exposed areas (axilla, flank, thigh, etc.). The frequency of *p53* gene mutations in the two groups was not very different (37.5% in sun-exposed BCCs and 43.8% in less-exposed BCCs); however, the types of mutations were significantly different. In sun-exposed BCCs, all of the samples except one (which had two A to T transitions in adjacent locations) were C to T transitions, and most of them (four out of five BCCs) were located at dipyrimidine sites. By contrast, only two out of eight mutations detected in BCCs from less-exposed areas showed C to T transitions at dipyrimidine sites. Considering that the frequency of BCCs is much higher in sun-exposed areas (10–100-fold) than in less-exposed areas (Ref. 83), these data imply that UV irradiation has a significant effect on human skin carcinogenesis.

In experiments of photocarcinogenesis using animal models, mutations in the *p53* gene are clearly linked to UVB irradiation, and *p53* alterations seem to be essential for carcinogenesis early in tumour development (Ref. 84). Similar to human skin cancers, most of the *p53* mutations detected in mouse skin cancers were C to T and CC to TT transitions at dipyrimidine sites, and most were located on the nontranscribed strand (Refs 85, 86). Ouhtit et al. (Ref. 87) investigated the timing of *p53* mutations and skin carcinogenesis in mice exposed to continuous UV irradiation. According to their data, *p53* mutations were detected as early as four weeks from the start of exposure, increased progressively, and reached a maximum at around 14 weeks. Skin tumours were first observed at 16 weeks. Half of the irradiated mice had tumours at 25 weeks, and the percentage increased thereafter. Furthermore, the protective role of *p53* in UV-irradiated cells was directly shown using $p53^{-/-}$, $p53^{+/-}$ and wild-type C57BL/6 mice (Ref. 88): $p53^{-/-}$ mice were extremely sensitive to tumour induction via UV irradiation, wild-type mice were resistant, and $p53^{+/-}$ mice showed an intermediate response.

Immunohistochemical detection of p53 protein using anti-p53 mAbs has shown that many *p53* mutations increase the half-life of the protein, allowing the cytosolic accumulation of mutant protein (Ref. 89). Stabilisation and elevation of p53 levels may signify an early event in tumourigenesis. Increased p53 staining is seen in atypical keratinocyte proliferations, actinic keratoses (Ref. 90) and keratoacanthomas (a benign, non-neoplastic, epithelial lesion closely resembling SCCs) (Ref. 91), but it is not seen in benign skin lesions such as seborrheic keratoses (Ref. 92). Overexpression of mutant *p53* was observed at high frequency in human BCCs (Ref. 93). An increase in p53 staining has also been reported during the progression from keratoacanthomas to SCCs (Ref. 94), and primary SCCs to regionally metastatic SCCs (Ref. 95). Immunohistochemistry has the obvious advantage of being a faster and less-expensive screening method for *p53* mutations than DNA analysis, but there does not seem to be a strong correlation between p53 immunostaining and the presence or absence of *p53* mutations (Ref. 96). Some tumours harbouring missense mutations have been negative for p53 expression by immunostaining and, conversely, tumours staining positive for p53 do not always contain mutations (Ref. 97). The lack of correlation between *p53* mutation and immunocytochemical expression could be the result of several factors: certain *p53* mutations could make the protein less stable and more susceptible to degradation; alternatively, some antibodies directed against the mutant p53 protein might also react with wild-type p53.

$p16^{INK4a}$ and $p19^{ARF}$ genes

It has been postulated that the gene(s) responsible for NMSCs is located on chromosome 9p, since

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loss of heterozygosity (LOH) frequently occurs at this locus in SCCs and actinic keratoses (Ref. 98) as well as, less frequently, in a subset of BCCs (Ref. 99). Subsequently, CDK inhibitor 2A (*CDKN2A*) was identified on chromosome 9p21 and was suspected of being involved in the carcinogenesis of SCCs and BCCs. Interestingly, the locus encoding *CDKN2A* gives rise to two distinct transcripts from different promoters: $p16^{INK4a}$ and $p19^{ARF}$ ($p14^{ARF}$ in humans) (Ref. 100).

$p16^{INK4a}$ is composed of exons 1α, 2 and 3, and encodes a CDK inhibitor that specifically inhibits progression through the G1 phase of the cell cycle in cells that express pRb. The CDK inhibitor maintains pRb in its activating state by blocking CDK4 from phosphorylating pRb (Ref. 101). $p16^{INK4a}$ accumulates in HeLa cells after nonlethal UV irradiation and causes cell-cycle arrest, suggesting that an alteration in $p16^{INK4a}$ would constitute an important step in UV-induced carcinogenesis (Ref. 17). $p19^{ARF}$ is composed of exons 1β, 2 and 3, and the protein it encodes stabilises p53 by inhibiting MDM2-dependent p53 degradation, thus specifically activating the p53 pathway (Ref. 102). $p19^{ARF}$ is also thought to be involved in skin carcinogenesis because the targeted disruption of $p19^{ARF}$ renders mice susceptible to SCCs (Ref. 103).

Kubo et al. (Ref. 104) reported that three out of 21 (14%) SCCs in a study of Japanese patients showed hemizygous mutations in the *CDKN2A* gene. All of the mutations were found in exon 2, which is common to $p16^{INK4a}$ and $p19^{ARF}$. Soufir et al. (Ref. 105) examined 20 human SCCs and found four different mutations. All four mutations led to both $p16^{INK4a}$ and $p19^{ARF}$ gene alterations, and three of the four (75%) were UV signature mutations. No SCCs had simultaneous alterations of *p53* and $p16^{INK4a}/p19^{ARF}$, which is in agreement with there being a reciprocal relationship between the genes (Ref. 106).

Compared with their involvement in the development of SCCs, the contribution of $p16^{INK4a}/p19^{ARF}$ disorders to the development of BCCs seems far less. Kubo et al. (Ref. 107) examined 25 sporadic BCCs and found no mutation of $p16^{INK4a}/p19^{ARF}$ genes. Soufir et al. (Ref. 105) found only one mutation (3.5%) out of 18 BCC samples. The mutation was a C to T transition at a dipyrimidine site; however, its pathogenic significance is not clear because the sample also contained a *p53* gene mutation. Saridaki et al. (Ref. 108) investigated 67 sporadic BCCs and found allelic loss of the 9p21-22 locus in 37 of the specimens (55%), but no mutation of the $p16^{INK4a}/p19^{ARF}$ genes. They concluded that these genes do not appear to be implicated by mutational inactivation in the development of BCCs, and other (as-yet unidentified) tumour suppressor genes at this locus could be involved in BCC carcinogenesis.

patched (Ptc) gene

Statistical analysis of the distribution of BCCs in patients with basal cell nevus syndrome (BCNS) suggested that tumours in the syndrome arise through a two-hit mechanism and that the underlying defect might be mutations in a tumour suppressor gene. This hypothesis was strongly supported by the localisation of the *patched* gene (*Ptc* in humans) to chromosome 9q22-31 and the demonstration that the same region was deleted in a high percentage of BCCs and other tumours related to the disorder (Ref. 109). In addition to germline mutations in BCNS patients, *Ptc* mutations and allelic loss containing the *Ptc* locus in sporadic BCCs have been reported. *Ptc* mutations were detected in 12–40% of sporadic BCCs (Ref. 12), and allelic loss was found in 42–69% of the examined specimens (Ref. 12). Azsterbaum et al. reported that three among 26 sporadic BCCs in which *Ptc* mutations were detected were also accompanied with allelic loss of the other *Ptc* locus, suggesting that *Ptc* acts as a classic tumour suppressor gene requiring 'two hits' for tumourigenesis in at least some BCCs (Ref. 110).

The mutational spectrum of *Ptc* in sporadic BCCs is rather diverse and only 41% (11 out of 27 examined samples) exhibited the typical UVB signature (Ref. 12). This result is different from the analyses of *p53* gene mutations in sporadic BCCs, in which most of the mutations were presumably related to UVB irradiation (Ref. 28). The lower incidence of UVB signature mutations in *Ptc* suggests that mutagenic events other than UVB irradiation might also cause *Ptc* inactivation and trigger tumourigenesis. Furthermore, this relatively low fraction of BCC cells that have UVB-induced mutations is consistent with previous clinical studies that have found poor correlation between UVB dose and incidence of BCC, unlike the better correlation between UVB dose and the incidence of SCCs (Refs 111, 112). In contrast to sporadic BCCs, those in XP patients have a high rate of *Ptc* gene mutations (73–88%), as well as a higher frequency of UV-specific mutations

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(75–79%), indicating that the inability of XP patients to repair UV-induced *Ptc* mutations would significantly contribute to the BCC tumourigenesis observed in those patients (Ref. 28).

ras oncogenes

Among the various kinds of oncogenes that have been analysed in rodent and human tumours, *ras* oncogenes are most likely to be involved in carcinogenesis. The family of *ras* oncogenes consists of three members, *H-ras*, *K-ras* and *N-ras*, which encode 21 kDa guanosine triphosphate (GTP)-binding proteins located on the inner surface of the cell membrane (Ref. 113). These proteins participate in signal transduction from the cell surface to the nucleus and in growth control through intrinsic GTPase activities (Ref. 113). Most of the *ras* mutations found in various types of human cancers occur in codons 12, 13 and 61 (Ref. 114), and result in the continuous activation of *ras*-mediated signal transduction. Activated *ras* genes appear to initiate papillomas (benign tumours of the epidermis) (Ref. 115) and, in cooperation with at least one other genetic alteration, can induce malignant conversion (Ref. 116).

Mutations of the *ras* gene were detected in 20–40% of mouse skin cancers initiated by UV irradiation (Refs 117, 118). The mutations occurred at codon 61 of *N-ras*, codon 13 of *H-ras* and codon 61 of *K-ras*. In contrast to the C to T transitions in *p53* gene mutations in mouse skin cancers, transversions were frequently observed in *ras* mutations, suggesting the involvement of DNA damage other than pyrimidine dimers and (6-4) photoproducts [e.g. 8-hydroxydeoxyguanosine (8-OHdG); (Ref. 119)]. In addition to activating point mutations, amplification of the *ras* gene has also been reported in human skin cancers (Refs 120, 121). Since the frequency of *ras* gene mutation or amplification is rather low, it could be coincidental to skin cancer formation or represent only one of several possible pathways by which cells lose growth regulation (Ref. 122).

Research in progress and outstanding research questions

UV irradiation generally causes 'more harm than good' in normal human skin (Fig. 6) and could ultimately result in skin cancer. According to the recommendations to prevent skin cancer development by the International Agency for Research on Cancer (IARC), the most effective way to protect against solar UV irradiation is by staying indoors at midday and wearing adequate clothing (Ref. 123). In addition, the use of sunscreens is also recommended as a means of accomplishing this purpose. The effectiveness of sunscreen has been directly demonstrated using animal models (Refs 78, 79, 124, 125). As mentioned above, *p53* mutations can be detected in UV-irradiated skin a long time before the appearance of skin cancers, both in humans and in experimental mouse models, suggesting that they can serve as a surrogate early biological endpoint in skin cancer prevention studies. Application of sunscreens to mouse skin before each UV irradiation resulted in approximately a 90% reduction in the number of *p53* mutations (Ref. 79). Since *p53* mutations represent an early essential step in photocarcinogenesis, this result implies that inhibition of this event might protect against skin cancer development.

Sunscreens have been shown to protect against UV-induced immune suppression (Ref. 124). Since UVA, as well as UVB, is reported to cause immune suppression in a recent report (Ref. 125), a sunscreen containing both UVA and UVB filters is ideal to block the cancer-promoting effects of solar UV irradiation. However, use of sunscreens alone may not be sufficient to prevent skin cancer because they are limited by cases of noncompliance and, when they are used, must be applied before each exposure to sunlight and reapplied every few hours or after coming into contact with water. Because of these limitations, it could be difficult to completely prevent events such as DNA damage and *p53* mutation. Thus, in addition to the lotions containing sunscreens that are applied before exposure, the use of creams containing agents that enhance the repair of UV-induced DNA damage after sun exposure might abrogate key events in photocarcinogenesis. In fact, recent studies have shown that the treatment of UV-irradiated mouse skin with liposomes containing T4N5 endonuclease or DNA photolyase enhanced the DNA repair of UV-induced pyrimidine dimers and abrogated UV-induced suppression of CHS (Ref. 126) and IL-10 release from keratinocytes (Ref. 127). Recently, Yarosh et al. reported the effectiveness of topically applied T4N5 liposome lotion in preventing skin cancer development in XP patients without significant adverse effects (Ref. 128).

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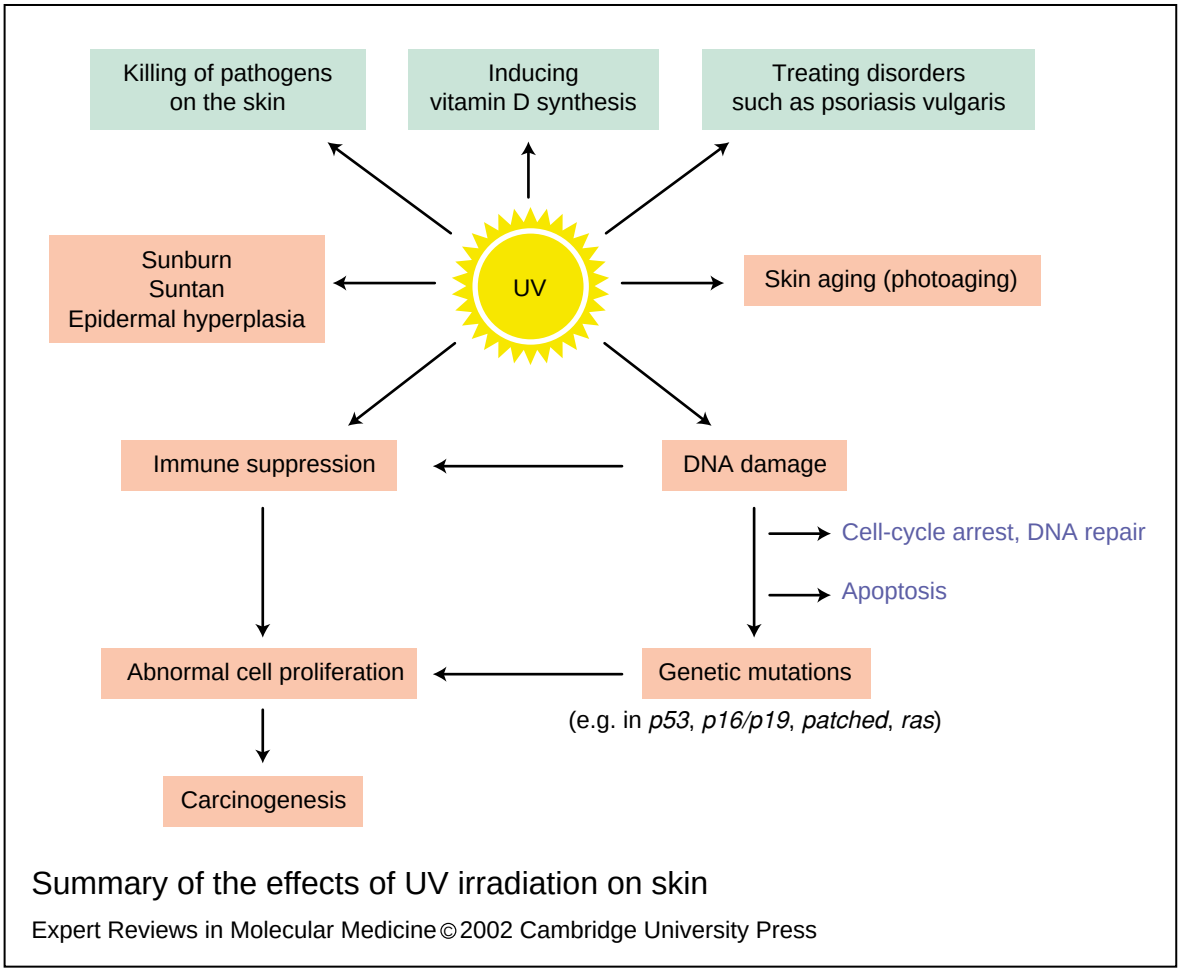

Figure 6. Summary of the effects of UV irradiation on skin. UV irradiation can be both beneficial and harmful to normal human skin. The beneficial effects comprise killing pathogens on the skin, inducing vitamin D synthesis and treating certain skin diseases such as psoriasis vulgaris. The harmful effects include immune suppression and DNA damage, both of which can lead via abnormal cell proliferation and genetic mutation to skin cancer (fig006hah).

In addition, comprehensive skin cancer prevention plans should also include intervention strategies that are directed at later stages of UV-induced carcinogenesis, such as preventing cells containing *p53* mutations from progressing into a tumour or preventing secondary skin tumours. The development and use of new drugs that can scavenge free radicals, or can induce differentiation or apoptosis of premalignant cells, might provide a novel intervention. To date, retinoids (derivatives of vitamin A) (Ref. 129), green tea polyphenols (Ref. 130), silymarin (Ref. 130), butyrated hydroxytoluene (Ref. 131) and carotenoids (Ref. 131) have been reported to be effective in reducing the incidence of UV-induced skin cancers. Among them, retinoids may be the most applicable or effective in reducing the number and severity of new skin cancers in high-risk patients who present with single or multiple primary skin cancers (Ref. 132). Further study should lead to a greater understanding of the genetic and immune suppression pathways in UV-induced carcinogenesis and, as a result, should lead to more-effective protective measures and/or restorative treatment.

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Features associated with this article

Figures

Figure 1. Structure of the major UV-induced photoproducts in DNA (fig001hah).
Figure 2. Proposed model for mammalian nucleotide excision repair (NER) (fig002hah).
Figure 3. The central role of p53 in cell-cycle arrest, DNA repair and apoptosis following UV irradiation (fig003hah).
Figure 4. Detection of apoptosing cells in UVB-irradiated mouse skin (fig004hah).
Figure 5. The mechanisms of skin pigmentation after UV irradiation (fig005hah).
Figure 6. Summary of the effects of UV irradiation on skin (fig006hah).

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