PERSPECTIVE

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DNA damage initiates photobiologic reactions in the skin†

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Ultraviolet (UV) radiation can induce acute and chronic photobiologic reactions in the absence of exogenous chromophores. Nuclear DNA is a major chromophore to initiate UV-induced physiologic reactions. The XPA-gene deficient mouse, an animal model of xeroderma pigmentosum, develops increased photobiologic reactions including acute inflammation, immunosuppression and skin cancers, because of the defect in the excision repair of UV-induced DNA lesions.

Introduction

The skin, which is situated on the outer body, is the first barrier to chemical, biological and physical invaders, including solar ultraviolet (UV) radiation. There are a variety of defense and repair mechanisms in the skin against injurious effects of sunlight. Nevertheless, the skin may develop various damages including inflammation, immunosuppression, aging and cancers after excessive exposure to UV radiation. All photobiologic changes are preceded by photochemical reactions. The first law of photochemistry (Grotthus Draper's law) states that only light absorbed by a molecule (chromophore) can initiate photochemical change. Consequently, any photobiological reaction can occur only when a chromophore absorbs light energy. Until now, nuclear DNA, the *trans*-isomer of urocanic acid, cell membranes and cytoplasmic targets have been proposed as chromophores to initiate photobiologic changes in the skin.

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DNA as a chromophore

When the skin is exposed to sunlight, most of UV energy is absorbed by the DNA of cutaneous cells, and induces DNA damages including cyclobutane pyrimidine dimmers (CPD) and ⟨6–4⟩ photoproducts. It has been long accepted that UV-induced DNA damage appears to be an important molecular trigger for non-melanoma skin cancers (NMSC). Nuclear DNA absorbs the UVB range (280–320 nm) more efficiently than UVA (320–400 nm). This is consistent with the fact that wavelengths in the UVB region are mainly responsible for the induction of skin cancer.[1–3] Although the damages can be rapidly repaired almost completely, the process of damage and repair may lead to mutations in tumor suppressor genes or oncogenes resulting in cancer development after repeated exposures to sunlight.[4]

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More recently, it has become apparent that UVB radiation has immunosuppressive effects, which may also contribute to the etiology of sunlight induced skin cancer.[5,6] Tumors induced by chronic UVB exposures appeared to be highly antigenic since they were rejected immunologically when transplanted onto syngeneic recipients.[7] However, the rejection did not occur when recipients were previously exposed to rather low doses of UVB, which can exert immunosuppressive properties.[8] Most of subsequent studies on UV-induced immunosuppression were performed using the model of cell-mediated immune responses, such as delayed-type hypersensitivity (DTH) and contact hypersensitivity (CHS) to simple chemical substances. Kripke and coworkers demonstrated that DNA served as an important photoreceptor for UVB-induced immunosuppression. First investigations were performed using the marsupial *Monodelphis domestica*, whose cells contain a photolyase DNA repair enzyme that is activated to repair CPD by exposure to photoreactivating visible light. Photorepair of CPD induced by UVB irradiation of the skin prevented suppression of CHS response in the animals.[9] Furthermore, UVB-induced immunosuppression was prevented nearly completely by topical treatment of UVB-irradiated mice skin with functionally active T4 endonuclease V.[10]

Photobiology of xeroderma pigmentosum

Xeroderma pigmentosum (XP), an autosomal recessive disorder, is clinically characterized by extremely high sensitivity to sunlight and a more than 1000-fold increased risk of developing cancers on the sun-exposed skin.[11] The initial symptom usually appears between one and two years of age, showing markedly exaggerated sunburning ever after sunlight exposure for a short time (Fig. 1). In healthy persons, sunburn reaction reaches maximal intensity by 24 h and fades within three days. In contrast, erythema or blisters take several days or weeks to resolve in some patients with XP. In severe cases, enhanced signs of photoaging, such as dry skin (xeroderma), pigmented macules (pigmentosum), teleangiectasia and atrophy, appear at 10 years of age. A comprehensive survey by Kraemer *et al.* of 830 published cases showed that the median age of first NMSC among patients with XP was 8 years, approximately 50 years earlier than that of the normal US population and that half of XP patients in the 10–14 age group had skin cancers[12] (Fig. 2). Cultured cells from XP patients exhibit greatly increased sensitivity to the lethal effects of UV radiation and have a defect in an early step of the excision repair of UV-induced DNA lesions.[13] Cell fusion studies have revealed eight complementation groups in XP (A–G, and variant form). XP genes of all groups have been cloned, and the encoded proteins biochemically characterized. Recently, the roles of the proteins in nucleotide excision repair have been clearly characterized.[14] There is considerable variability in clinical severity or cancer development among complementation groups, correlating roughly with the magnitude of the DNA repair defect. The distribution of the complementation groups is uneven in regions of the world. Groups A, C, D and variant are the most common is Europe and the USA, while in Japan groups A and variant are the most common.[15]

Fig. 1 Acute sunburn erythema in a 6-month-old child with xeroderma pigmentosum.

Fig. 2 Multiple skin cancers in an 8-year-old child with xeroderma pigmentosum of group A.

Animal model of XP

A number of investigations have been undertaken to clarify the cellular and molecular abnormalities in XP. However, it has not been completely elucidated how the defect in nucleotide excision repair causes the clinical features of XP. *In vivo* studies using animal models is often helpful to understand the link between clinical and molecular abnormalities. In recent years, mouse genes corresponding to each complementation group of XP have been identified and the encoded proteins characterized biochemically and functionally. Tanaka *et al.* have cloned the XPA gene and its mouse homologue, which may play important roles in damage recognition and coordination of nuclear excision repair processes by interacting with other proteins.[16,17] By means of targeting, murine models of XP have been generated. In our model of group A-XP, the XPA allele was disrupted by insertion of neomycin cassette sequenced into exon 4 of the XPA gene by embryonic stem cell techniques.[18] The XPA gene-deficient mice with CBA, C57BL/6 and CD-1 chimeric genetic background were backcrossed with hairless albino mice of the inbred strains Hos/HR-1, and the resultant hairless XPA (−/−), (±) and (+/+) mice were used in our following experiments. The XPA (−/−) fibroblasts derived from XPA-knockout mice were hypersensitive to killing by UV irradiation, and UV-induced unscheduled DNA synthesis was absent. Removal of CPD and ⟨6–4⟩ photoproduct was not detected after UV-irradiation in the

XPA (−/−) fibroblasts. The mice rapidly and easily developed NMSC after the irradiation with low dose of UVB (Fig. 3).

Fig. 3 UVB-induced squamous cell carcinoma in XPA gene-deficient mouse.

Sunburn reaction in XPA gene-deficient mouse

Patients with group A-XP develop an exaggerated sunburn reactions that take longer than usual to resolve. Then, acute inflammatory reactions to UVB radiation were examined in XPA(−/−) mice.[18,19] The UVB source was a bank of seven fluorescent sunlamps (FL20SE.30; Toshiba Medical Supply, Tokyo, Japan) with an emission spectrum of 275–375 nm peaking at 305 nm. The irradiance of UVB was measured by a radiometer (UVR-305/ 365D (II); Toshiba Medical Supply). Acute inflammation was evaluated by ear swelling response to UVB radiation. Ear thickness was measured with a dial thickness gauge (Peacock, Tokyo, Japan) before and after irradiation at various time points. A single exposure to 100 or 250 mJ cm^{-2} of UVB radiation resulted in significant ear swelling in the XPA (−/−) mice 24 h after irradiation, and the edema was still increasing at day 5 (Fig. 4). In contrast, the wild type and heterozygous (±) mice did not develop significant ear swelling. A higher dose of UVB radiation induced ear swelling in not only (−/−) mice but also (+/+) or (±) mice. However, ear swelling in (−/−) mice was significantly greater than in (+/+) or (±) throughout the study. Histologic changes were more prominent in UVB-irradiated skin of XPA (−/−) mice.[19] At 24 h after 500 mJ cm^{-2}-UVB irradiation, skin samples from XPA (−/−) mice showed intracellular edema and necrosis in the epidermis and subepidermal bullae while only little changes were observed in the epidermis of (+/+) or (±) mice. Moreover (−/−) mice revealed marked inflammatory infiltrates of lymphocytes, pronounced edema, vasodilatation, and prominent extravasation of erythrocytes in the dermis. The XPA(−/−) mice developed enhanced sunburn cell formation after UVB radiation (Fig. 5).[19,20] At 24 h after 50 mJ cm^{-2} of UVB irradiation significantly enhanced sunburn cell formation was induced in the epidermis of (−/−) mice (59.6 ± 32.2/cm, mean ± SD) compared to that in (+/+) and (±) mice (20.6 ± 23.8 and 17 ± 22.8/cm, respectively). Similarly, sunburn cells induced by UVB irradiation at a higher dose (100 mJ cm^{-2}) in (−/−) mice were almost three times as numerous as those in (+/+) or (±) mice.

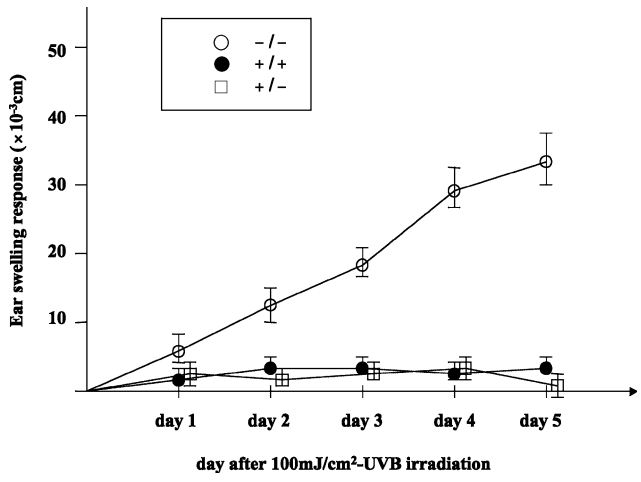

Fig. 4 Enhancement of UVB-induced inflammation in XPA gene-deficient mice.

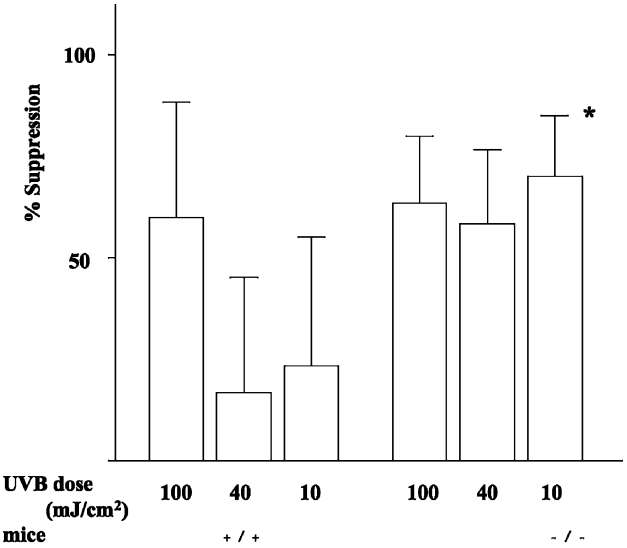

Fig. 5 Enhancement of sunburn cell formation in XPA gene-deficient mice.

DNA has been suspected of being a chromophore for sunburn erythema.[21,22] Freeman *et al.* found that individuals of high UVB sensitivity showed higher pyrimidine dimmer yields than less sensitive persons.[23] The present study using XPA (−/−) mice indicated that the defect in excision repair of pyrimidine dimers is one of the molecular mechanisms involved in the acute photosensitivity in XP. Formation of sunburn cells is regarded as an apoptotic process of keratinocytes that removes the DNA-damaged or mutated cells.[24] Enhanced sunburn cell formation in the XPA (−/−) mice after UVB irradiation may reflect the increase in unrepaired pyrimidine dimmers due to the deficiency in DNA repair. This is supported by the observation that sunburn cell formation was prevented by the topical treatment of skin of UVB-exposed mice with liposomal T4 endonuclease V, an enzyme preferentially involved in the excision repair of pyrimidine dimmers.[25]

The effect of UVB on Langerhans cell in XPA gene deficient mouse

Because epidermal keratinocytes of XPA (−/−) mice were severely damaged by UVB radiation the alteration of Langerhans cells (LC) was also examined. In non-treated skin, approximately the same numbers of LC were found in the XPA (−/−), (+/+) and (±) mice. Single expose to 25 mJ cm^{-2} of UVB reduced the number of LC by 59% of the pre-irradiated level in XPA (−/−) mice 24 h after irradiation. On the other hand, the percentage reductions in the XPA (+/+) and (±) mice were 33 and 38%, respectively. After UVB irradiation at 100 mJ cm^{-2}, the number of LC decreased by almost 100% in the XPA (−/−) mice, but by only 62% in (+/+) mice.

Furthermore, the recovery of LC density was slower in the XPA (−/−) mice than in the (+/+) or (±) mice.[19]

UV-induced immunosuppression in XPA-gene deficient mouse

It has been suggested that DNA damage is an initial event of UV-induced immunosuppression. Moreover, epidermal LC, an antigen presenting cell, was easily damaged by UVB radiation. Then, the effect of UVB radiation on CHS was examined in XPA (−/−) mice. The mice were sensitized by epicutaneous application of 25 µl of 1% dinitrofluorobenzene (DNFB) solution on abdominal skin. CHS was elicited by application of 20 µl of 0.2% DNFB solution on the surface of each left ear 6d after sensitization. Ear thickness was measured before and 24 h after application of the challenge dose. The XPA (−/−) mice developed CHS to DNFB similarly to the XPA (+/+) and (±) mice. Sensitization with DNFB in the skin that had been exposed to 100 mJ cm^{-2}-UVB resulted a significantly decreased CHS response in both XPA (+/+) and (−/−) mice (59.1 and 54.1% suppression, respectively). In the XPA (−/−) mice, almost the same degree of suppression was induced by lower doses of UVB radiation such as 40 and 10 mJ cm^{-2} (69.4 and 56.3% suppression, respectively), whereas less suppression was induced in the (+/+) mice (18.6 and 21.7% suppression, respectively) and in the (±) mice (30.9 and 18.4% suppression, respectively) (Fig. 6). The results indicate that UVB-induced local immunosuppression was enhanced in the XPA (−/−) mice.

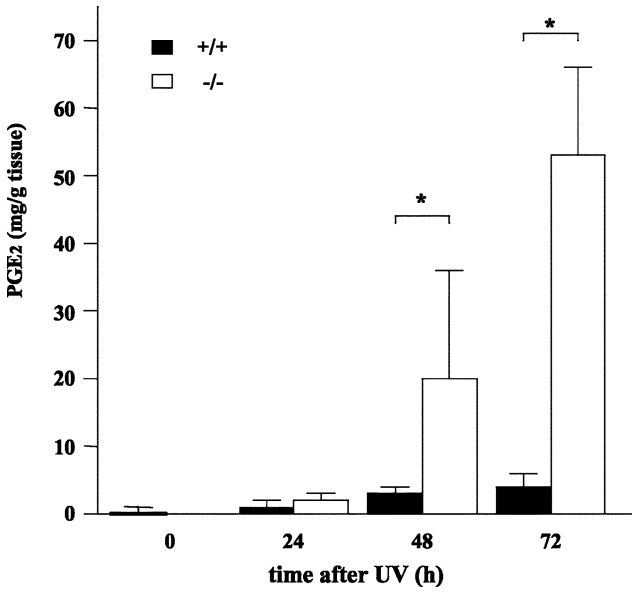

Fig. 6 Enhancement of UVB-induced immunosuppression in XPA gene-deficient mice.

Next, the experiments of systemic immunosuppression were performed. Exposure to UVB at a dose of 500 mJ cm^{-2} 5 days before sensitization with DNFB on non-irradiated skin induced stronger suppression of CHS in the XPA (−/−) mice than in the (+/+) or (±) mice (100 *vs.* 76.5 or 76.7%, respectively). Although UVB radiation at 125 mJ cm^{-2} produced only little suppression in (+/+) or (±) mice (43.1 or 41.9%) suppression, respectively), it produced pronounced suppression in (−/−) mice (92.0% suppression).[19]

There are reports that XP patients have defect in cell-mediated immunity, such as impaired cutaneous responses to recall antigens[26,27] and contact sensitizers.[26,28] Our investigations suggest that these immune deficiencies are not innate, but acquired after exposures to sunlight.

Inhibitory effect of indomethacin on UV-induced ear swelling and immuno-suppression

Prostaglandin E_2 (PGE_2) is well known to be a major mediator in UV inflammation,[29,30] and to have an immunosuppressive effect.[31,32] Then, we examined the effect of indomethacin (IND), a potent inhibitor of PG biosynthesis, on the enhanced ear swelling response and immunosuppression after UVB irradiation in the XPA (−/−) mice. Topical application of 1% IND immediately after UVB irradiation significantly inhibited ear swelling in both XPA (+/+) and (−/−) mice. A nearly similar level of percent suppression was observed in both mice. UVB-induced local immuno-suppression was almost completely abrogated by topical application of 1% IND on exposed skin immediately after irradiation in both mice.[33]

Remarkable increase of PG production and cyclooxygenase 2 expression after UVB irradiation in XPA-gene deficient mouse

Inhibitory effects of IND in the enhancement of acute UV reactions in the XPA (−/−) mice suggested that UVB radiation produced a high amount of PGs in these mice. The amounts of PGD_2, PGE_2 and PGF_2 in mouse ears at 0, 24, 48 and 72 h after irradiation with 250 or 500 mJ cm^{-2} of UVB were determined by enzyme immunoassay.[32] The amounts of PGs in the XPA (−/−) mouse skin significantly increased at 48 and 72 h after irradiation. Among three PGs, PGE_2 most markedly increased to levels 4–10 fold higher than those of PGD_2 and PGF_2. Furthermore, the amount of PGE_2 in (−/−) mice was approximately 8- and 15-fold higher than that in (+/+) mice at 48 and 72 h after irradiation, respectively (Fig. 7). The amount of PGE_2 in the skin of UV-irradiated (−/−) mice was not detected by treatment of 1% IND at 24 and 48 h after irradiation.

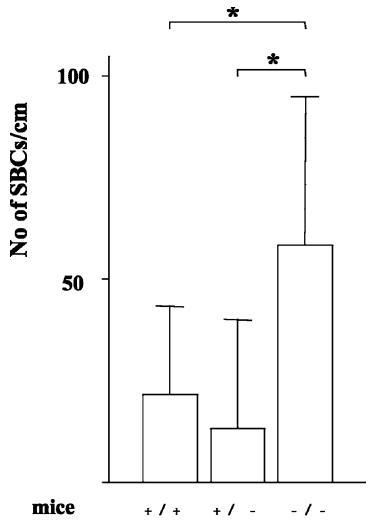

Fig. 7 Increased production of PGE_2 after UVB irradiation in XPA gene-deficient mice.

Increased production of PGs in the skin of irradiated mice suggested that UVB exposure induced synthesis of cyclooxygenase (COX). To analyze the expression of COX-1 and COX-2 genes, mRNA was isolated from the mouse ears after an exposure to 250 mJ cm^{-2}-UVB irradiation, and subjected to RT-PCR analysis. The expression of COX-2 mRNA in (−/−) mice increased from 24 h after UV irradiation on a time-dependent manner. COX-1 mRNA was expressed nearly constantly and was not affected by the UV irradiation in either (+/+) or (−/−) mice.

The molecular mechanisms of the severe inflammation and immuno-suppression found in XPA-deficient mice after UV exposure have not been clarified. This experiment indicated that the mechanisms would be due to increased expression of mRNA for COX-2 and subsequent overproduction of PGE2 after UV exposure.

Enhancement of carcinogen-induced inflammation and immunosuppression in XPA-gene deficient mice

The defect in repair of UV-induced DNA damage enhanced acute inflammation and immunosuppression. Similarly to UVB radiation, a chemical carcinogen, dimethylbenz(*a*)anthracene (DMBA) forms adduct with DNA. XPA protein is required to repair DMBA-DNA adducts. Actually the XPA (−/−) mice easily developed cancers by the topical application of DMBA as well as by UVB radiation.[17] It is known that application of DMBA to the skin depletes LC and suppresses CHS, when a sensitizer is applied to DMBA-treated skin.[34–36] Based on these backgrounds, we investigated if DMBA-induced inflammation and immunosuppression are enhanced in the XPA (−/−) mice.[37] A single application of 0.1 or 0.5% DMBA resulted in significant ear swelling in the XPA (−/−) mice 2 days after application. In contrast, the wild type mice did not develop any significant ear swelling even with a 2.5% DMBA application. There were no differences in ear swelling responses to other primary irritating chemicals, such as croton oil or phenol, between the XPA (−/−) mice and wild type mice.

The number of epidermal LC significantly decreased after application of 0.5% DMBA both in the XPA (−/−) and XPA (+/+) mice. The DMBA application of a lower concentration (0.1%) also greatly reduced LC in the XPA (−/−) mice, but not in the wild-type mice. Sensitization with DNFB on skin that had received a 0.1 or 0.5% DMBA application resulted in almost complete suppression of the CHS response in XPA mice (96 and 94% suppression, respectively). In contrast, less suppression was induced in the wild-type mice with pretreatment using 0.1 or 0.5% DMBA (24 and 36% suppression, respectively). Application of 0.1% DMBA on the back 4 days before sensitization with DNFB on the abdominal skin induced a stronger suppression of CHS in the XPA mice than in wild-type mice (82 *vs.* 45% suppression).

DMBA application induced pronounced production of PGE_2, IL-10, and TNF-α in the skin of the XPA (−/−) mice. Treatment with IND inhibited DMBA-induced inflammation and immunosuppression.

Conclusion

The xeroderma pigmentosum model mouse is an useful experimental animal not only to investigate photosensitivity in the disorder, but also to study photobiology in humans, because photobiologic reactions are greatly intensified in this mouse. It has been well known that high incidence of skin cancers in XP patients is due to the defect in repair of UV-induced DNA damages. Our investigations using XPA gene-deficient mice indicated that acute inflammation and immunosuppression after UVB irradiation are greatly enhanced, when the excess DNA photoproducts remain in the exposed skin. The results strongly suggest that nuclear DNA is an important chromophore to initiate acute as well as chronic photobiologic reactions.

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