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Forum Review

Role of Reactive Oxygen Species in Skin Carcinogenesis

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ABSTRACT

Reactive oxygen species (ROS) are associated not only with initiation, but also with promotion and progression in the multistage carcinogenesis model. In the present review, we will focus on the involvement of ROS in skin carcinogenesis, especially that induced by ultraviolet (UV) radiation. UV-specific DNA damage has been well studied thus far. However, recent reports have revealed the previously unknown participation of oxidative stress in UV-induced skin carcinogenesis. Indeed, in addition to transition-type mutations at dipyrimidine sites, G:C to T:A transversions, which may be induced by the presence of 8-oxoguanine during DNA replication, are frequently observed in the *ras* oncogene and *p53* tumor suppressor gene in human skin cancers of sun-exposed areas and in UV-induced mouse skin cancers. Recent studies have shown that not only UV-B, but also UV-A is involved in UV-induced carcinogenesis. A wide variety of biological phenomena other than direct influence by UV, such as inflammatory and immunological responses and oxidative modifications of DNA and proteins, appear to play roles in UV-induced skin carcinogenesis. Furthermore, it has become clear that genetic diseases such as xeroderma pigmentosum show deficient repair of oxidatively modified DNA lesions. The involvement of ROS in skin carcinogeneisis caused by arsenic and chemical carcinogens will also be discussed.
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INTRODUCTION

THERE is considerable evidence suggesting the critical involvement of oxidative stress in carcinogenesis (35, 87). Regular intake of radical scavengers has been shown to protect against cancer development in experimental animal models, as well as in epidemiological studies in humans (1, 17, 99). Chronic inflammatory states, where oxidative stress increases with the migrating inflammatory cells, are closely associated with cancer development (97). In fact, significant benefits have been reported with the intake of nonsteroidal antiinflammatory drugs against colon carcinogenesis (34, 75).

Oxidative stress has been shown to be associated with initiation, promotion or progression processes during multistage carcinogenesis (29, 37). A permanent genetic alteration that is passed on to the progeny of the initiated cells should occur during the initiation of carcinogenesis. It has been reported that reactive oxygen species (ROS) such as hydroxyl radicals and singlet oxygen induce various types of oxidative DNA lesions that are thought to be important for the initiation stage in the carcinogenic process (18, 23). Bacterial mutants defective in the repair of ROS-induced DNA damage exhibit an elevated mutation frequency after exposure to free radical-generating agents (60). The ability of catalase, mannitol, and superoxide dismutase to decrease mutagenesis indicates the involvement of ROS in generating mutations (57). The hydroxyl radical is known to produce thymine glycol, 5-hydroxymethyluracil, and 8-hydroxy-2′-deoxyguanosine (8-OHdG) when it reacts with DNA (18). Of note is the fact that biological sources such as activated polymorphonuclear leukocytes cause DNA base modifications such as 8-OHdG, 2,6-diamino-4-hydroxy-5-formamidopyrimidine, and 4,6-diamino-5-formamidopyrimidine *in vivo*, modifications that are typically induced by hydroxyl radicals (19). ROS are associated with the promotion and progression stages as well. It is recognized that a low level of oxidants can modify cell signaling

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via redox regulation and that these signal modifications have functional consequences (61, 84, 88).

Among many oxidative DNA base modifications, 8-OHdG (42) is now widely accepted as a sensitive marker for oxidative stress, and is either generated under physiological conditions or actively produced via a variety of agents. These include chemicals, *x-radiation*, ultraviolet (UV) light, singlet oxygen mediated by photosensitizers (16, 24), and direct electron transfer that does not involve the participation of ROS (43). The importance of 8-OHdG is that it has an ability to pair with adenine instead of cytosine during DNA replication, thereby causing G:C to T:A transversions (80). High levels of 8-OHdG are observed in various kinds of human and animal cancers (89). 8-OHdG is also detected in the target organs of animal carcinogenesis models induced by ROS (41). Indeed, not a few carcinogens have been indicated to work as radical metabolites (90).

ROLES OF ROS IN UV CARCINOGENESIS

There is ample evidence to demonstrate that solar UV light induces human skin cancers. The fact that "the nearer people live to the equator, the higher the frequencies of skin cancers" is true even among people of the same race (85). Skin cancers can be induced by irradiating mice with UV-B (14, 62). It has been established that cancers are the products resulting from an accumulation of DNA lesions in crucial genes such as oncogenes and/or tumor suppressor genes. UV irradiation causes DNA modifications, and thus is thought to be responsible for sunlight-induced skin cancers (2).

Thus far, studies on UV-induced carcinogenesis have focused on UV-B-induced DNA mutations. However, recent reports indicate the involvement of many other factors (see Fig. 1). Firstly, UV-B induces not only pyrimidine photoproducts, but also DNA lesions modified by ROS. Secondly, UV-A also plays a role in UV-induced carcinogenesis based on animal experiments, although only UV-B has been considered to be responsible. Thirdly, biological responses other than direct influence by UV also appear to be responsible for carcinogenesis. These include immunological and inflammatory responses, modifications of proteins, and redox regulation (100).

The maximum action spectrum of UV-induced carcinogenesis in animal experiments falls into the UV-B (293 nm) range (15). Direct absorption of UV-C (100–290 nm) or UV-B (290–320 nm) by DNA leads to formation of pyrimidine photoproducts, cyclobutane-type pyrimidine dimers, and pyrim-

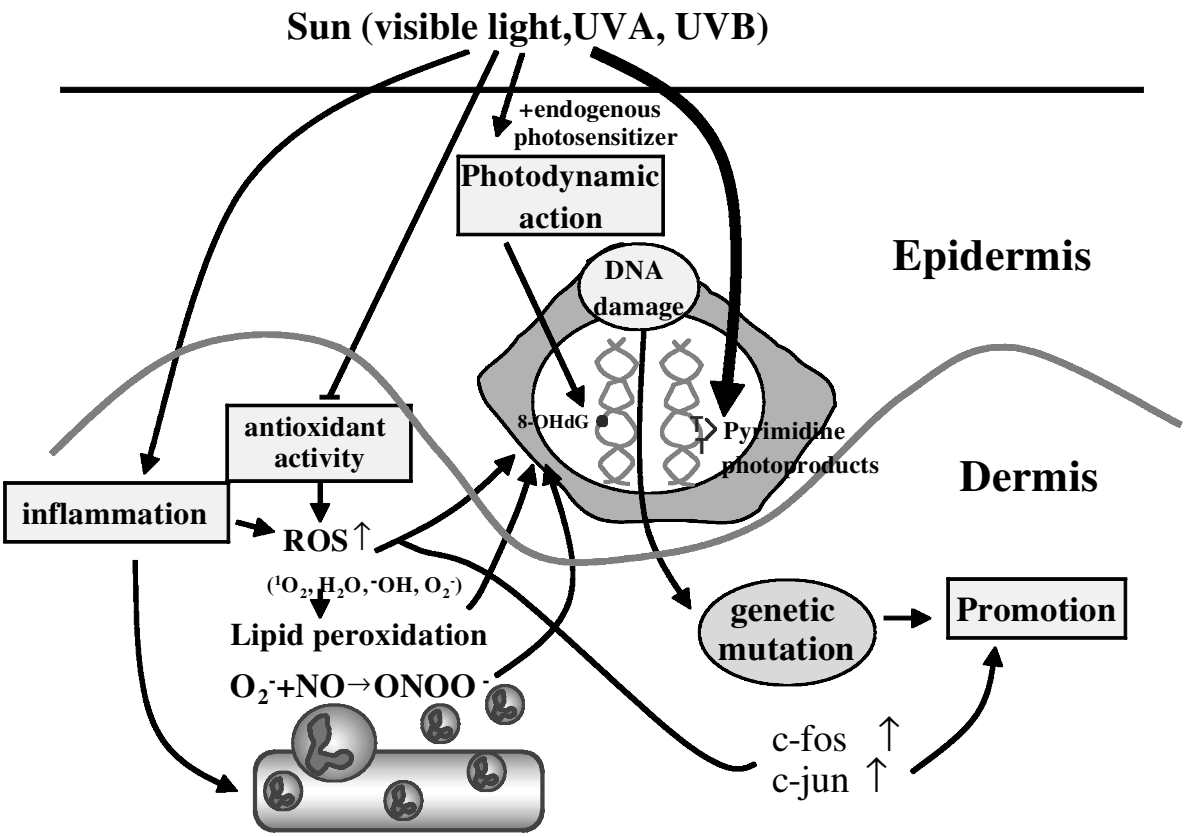

FIG. 1. Mechanisms of UV-induced skin carcinogenesis. UV radiation, mainly UV-B, directly induces pyrimidine photoproducts. UV-B, UV-A, and visible light indirectly induce DNA lesions modified by ROS, especially in the presence of the endogenous photosensitizers *in vivo*. Although the amounts of generated DNA lesions modified by ROS are smaller than those of pyrimidine photoproducts, removal and repair of these products in the skin are slower than those for pyrimidine photoproducts, thus leading to persistent oxidative stress in the skin, which enhances the promotion activity. Furtheremore, inflammation by UV light or sunburn causes oxidative stress in the dermis, which also causes ROS formation. All these mechanisms play a role in UV-induced carcinogenesis. $^1O_2$, singlet oxygen; H_2O_2, hydrogen peroxide; $^{\cdot}OH$, hydroxyl radical; $O_2^{\cdot-}$, superoxide anion; NO, nitric oxide; $ONOO^-$, peroxynitrite.

idine pyrimidone (6-4) photoproducts at adjacent pyrimidines. Previous studies suggested that pyrimidine photoproducts are the major classes of UV-induced DNA lesions involved in cytotoxicity and mutagenesis (20, 44). Pyrimidine photoproducts preferentially induce transition-type base changes (especially G:C to A:T) at dipyrimidine sites, as demonstrated in bacteria (58) and in mammalian shuttle vectors (54). Brash *et al.* reported that the most frequent mutagenic change in nonmelanoma skin cancers is a C to T transition commonly found at CC dinucleotides (10), so this type of mutation is sometimes called a "UV-signature mutation." At the same time, several reports have pointed out that types of mutations that are not theoretically considered to be caused by pyrimidine photoproducts are frequently observed in the human skin cancers of sun-exposed areas (70, 93) and UV-B-induced murine skin cancer (64).

MURINE UV-INDUCED SKIN CANCER MODELS

We previously produced UV-induced skin cancers on hairless mice and analyzed whether there is any UV-specific mutation in the functionally activated *ras* oncogene alterations (64). Tumor cell lines were established from the UV-induced skin cancers. By transfecting tumor cell DNA, focus-forming transformants were selected, and transformants with activated *ras* oncogene were detected by Southern blot analysis. Among 15 transformed cell lines studied, 10 showed mouse-derived sequences, and all the transformants had extra *ras* genes of mouse origin. As these transformed cells were supposed to have activated *ras,* DNA sequencing was performed. Unexpectedly, transversions were predominant among the mutations (Table 1). Van der Lubbe *et al.* found that introduction of an *in vitro* UV-irradiated N-*ras* gene to Rat2 cells produced transformed cells with mutations resembling those found in our tumors, with eight of 14 (57%) mutations being transversions (92). There are two possibilities for this. One possibility is that the *ras* oncogene needs a transversion-type mutation under the condition that the focus was selected. The other possibility is the involvement of 8-OHdG formation by the indirect action of UV-B. G:C to T:A transversions have also been identified in the *ras* and *p53* genes in the human skin cancers of sun-exposed areas, in addition to transitions at dipyrimidine sites (8, 70). These studies suggested the possibility of 8-OHdG participation in UV-induced skin carcinogenesis. Thereafter, many studies reporting the involvement of 8-OHdG appeared, as will be described below.

Ito *et al.* reported that the photodynamic action of riboflavin caused the formation of 8-OHdG in double-stranded DNA, and that no enhancing effect by D_2O was observed (38). The estimated ratio of 8-OHdG yield to total guanine loss indicated that the photoexcited riboflavin induced 8-OHdG formation specifically at the guanine residues located 5′ to another guanine through electron transfer. The guanine base in genomic DNA is highly susceptible to oxidative stress due to its having the lowest oxidation potential of all the bases. Therefore, G:C to T:A and G:C to C:G transversions frequently occur under oxidative conditions (38). Kino and Sugiyama speculated that in photooxidized responses, 8-oxoguanine (8-oxoGua) initially increased and then decreased with the formation of 2-amino-5-[(2-deoxy-β-D-erythro-pentofuranosyl)amino]-4H-imidazol-4-one, suggesting that nascent 8-oxoGua was further oxidized to 2,5-diamino-4*H*-imidazol-4-one in duplex DNA (45). These facts explain many of our results and others reported about UV-induced mutations. Previously, Reid and Loeb reported that tandem double CC to TT mutations, so-called "UV-signature mutations," were also produced by treatments with ROS, as shown using a sensitive reversion assay (74).

DETECTION OF 8-OHDG IN MOUSE SKIN IRRADIATED WITH UV-B

To examine the involvement of 8-OHdG in UV-induced skin carcinogenesis, 8-OHdG in mouse skin was measured

TABLE 1. TRANSFORMING ACTIVITY OF DNA FROM UV-INDUCED MOUSE SKIN TUMOR CELLS AND THE MUTATIONS IN *RAS* ONCOGENES

	Focus-forming efficiency (no. of foci per 100 μg of DNA)			ras *mutation*			
Tumor cell line	*Primary*	*Secondary*	*Activated* ras	*Position*	*Mutation*		
HL1	2.4	3.3	Ha-*ras*	13	GGC(Gly)	→	GTC(Val)
HL5	1.0	8.0	N-*ras*	61	CAA(Gln)	→	AAA(Lys)
HL6	1.2	5.0	N-*ras*	61	CAA(Gln)	→	CAT(His)
HL9	5.5	23	Ki-*ras*	61	CAA(Gln)	→	GAA(Glu)
HL10	1.8	2.5	N-*ras*	61	CAA(Gln)	→	AAA(Lys)
HL13	0.87	25.5	Ha-*ras*	13	GGC(Gly)	→	AGG(Ser)
HL19	1.0	5.6	N-*ras*	61	CAA(Gln)	→	CAT(His)
HL31	4.5	114	Ha-*ras*	13	GGC(Gly)	→	GTC(Val)
HL41	0.38	1.6	Ki-*ras*	61	CAA (Gln)	→	GAA(Glu)

Modified from Nishigori *et al.* (64).

with HPLC after exposure to UV-B at a dose similar to that used in our protocol for murine UV-induced skin carcinogenesis. UV-B irradiation induced 8-OHdG formation in a dose-dependent manner between 33.5 and 168 kJ/m^2. The yield of 8-OHdG was 2.6/10^{10} dG/J/m^2 (32). This is consistent with the yield of UV-induced 8-OHdG in cultured cells [~ 3/10^9 dG/J/m^2 (65)] considering the transmission of UV-B as ~10%.

Next, we studied the relation between the method of UV exposure and the induced oxidative stress by irradiating mice with UV-B using different protocols: mice were irradiated with a single dose of UV-B at 2 minimal erythema doses (MED)/time or 10 MED/time, three times per week for 1–4 weeks (Table 2) (32, 65). Repeated UV-B exposure at a physiologically relevant dose (2 or 10 MED) generated 8-OHdG in the mouse skin tissue. The amounts of 8-OHdG produced were not completely dose-dependent. Of note was the fact that continuous inflammatory reactions observed at 2 MED of UV exposure were closely associated with 8-OHdG formation. Repeated exposure to 2 MED (total dose 20.4 kJ/m^2) induced much more 8-OHdG than a single exposure to 168 kJ/m^2 (Table 2). The highest amount of 8-OHdG in this study was obtained after 10 MED exposure three times per week for 2 weeks. At the same time, the levels of 4-hydroxy-2-nonenal-modified proteins and 3-nitro-L-tyrosine in the proteins of skin were examined by western blot analysis using monoclonal and polyclonal antibodies against those modified proteins. Signals for 3-nitro-L-tyrosine modifications were significantly increased for the 10 MED-irradiated groups. This implies that not only UV-B itself, but also a chronic inflammatory state is closely associated with 8-OHdG formation because 3-nitro-L-tyrosine is considered to be evidence of nitric oxide-mediated oxidative damage in chronic inflammation (31). Peroxynitrite is generated through the reaction of nitric oxide with superoxide, which is released by infiltrating neutrophils and macrophages (9). Immunohistochemical studies of chronically sun-exposed skin specimens revealed that 8-OHdG was produced not only in the nuclei of epidermal keratinocytes, but also in the inflammatory cells. These results indicate that not only the direct UV energy is involved in skin carcinogenesis, but also an inflammatory condition leading to oxidative stress. Giri *et al.* showed that ROS generation is followed by the development of cutaneous inflammation that is maximal 6 hours after photosensitization (25).

Moore *et al.* reported that proinflammatory cytokine, tumor necrosis factor-α (TNF-α)-deficient mice are resistant to skin carcinogenesis (59). This may be one of the mechanisms by which chronic inflammation increases susceptibility to cancer. This is consistent with the epidemiological fact that intense intermittent sun exposure is a risk factor for skin cancer. Noonan *et al.* reported that a single dose of burning UV radiation to neonates, but not to adults, in hepatocyte growth factor/scatter factor-transgenic mice is necessary and sufficient to induce melanoma with a high incidence (67). This also provides experimental support for the epidemiological evidence that childhood sunburn is a major risk factor for the development of melanomas (7, 98).

Another point is the rate of removal of generated lesions. UV-induced 8-OHdG in mouse skin is removed slowly and still remains at a high level in the epidermis 7 days after exposure, whereas pyrimidine photoproducts are completely repaired within 5 days (32, 71). Persistent oxidative stress in cancer (89) may also cause activation of transcription factors and protooncogenes such as *c-fos* and *c-jun* (13), as well as genetic instability. Such stress may also contribute to maintain the malignant characteristics of neoplasms.

UV-A AND SKIN CANCERS

The role of UV-A in photocarcinogenesis has been controversial. However, recently UV-A has come to be considered as partly responsible for photocarcinogenesis (15). UV-A and visible light in the presence of photosensitizer (53, 76) participate in ROS generation. 8-OHdG is generated in fibroblasts derived from human skin in response to exposure to sunlamp or monochromatic radiation ranging from a UV-B wavelength (312 nm) up to near visible (434 nm). Kvam and Tyrrell demonstrated that the spectrum for the yield of oxidative damage in confluent, non-growing, primary skin fibroblasts implied that it is UV-A and near visible radiation that cause almost all of this guanine oxidation (53). Phillip-

TABLE 2. LEVELS OF 8-OHDG IN MOUSE SKIN AFTER UV-B IRRADIATION

Duration of the exposure	*Dose at one exposure (kJ/m^2)*	*Total dose (kJ/m^2)*	*8-OHdG/10^5 dG**	*Ratio of irradiated/ unirradiated*
0	0	0	2.45 ± 0.54	1
1 day	101	101	3.43	1.4
1 day	168	168	5.15	2.1
1 week	3.4	10.2	3.92 ± 0.17	1.6
2 weeks	3.4	20.4	6.04 ± 0.45	2.4
4 weeks	3.4	40.8	6.08 ± 0.47	2.5
1 week	16.8	50.4	5.12 ± 0.58	2.0
2 weeks	16.8	100.8	14.91 ± 2.38	6.1

Modified from Hattori *et al.* (31) and Hattori-Nakakuki *et al.* (32). UV dose and protocols of UV exposure were added.

*Means ± SEM.

son *et al.* suggested that UV-A radiation is a risk factor in skin carcinogenesis, and demonstrated the significance of ROS in skin carcinogenesis by showing that UV-A radiation, which reduced the plating efficiency, increased the "spontaneous" mutant fraction of a keratinocyte cell line, and that this effect was prevented by catalase (69). This may indicate a role for hydrogen peroxide in UV-A mutagenesis (69). Drobetsky *et al.* found that T to G transversions, a generally rare class of mutation, are induced at high frequency (up to 50%) in UV-A-exposed cells in a mutation detection system involving adenine phosphoribosyltransferase genes (21). Van Kranen *et al.* reported that UV-A-induced murine skin cancers are less frequent than UV-B-induced murine skin cancers, and that the incidence of *p53* alterations in UV-A-induced tumors is low compared with that in UV-B-induced tumors (94). These facts imply that UV-B is more mutagenic and carcinogenic than UV-A. Much of the mutagenic and carcinogenic ability of UV-A may be attributed to ROS. The strong association of the risk for non-melanoma skin cancer and polymorphisms in glutathione *S*-transferases also suggests that oxidative stress plays a role in non-melanoma skin cancer (72, 83). Both epidemiological and experimental models using animals suggest the importance of UV-A irradiation in the development of melanoma (79).

Both non-melanoma skin cancers and melanomas are induced by solar light, but there are some differences. Melanocytes show resistance to UV-B-induced apotosis. Increased pheomelanin photosensitizes DNA and thus induces DNA damage. Eumelanin predominates in mouse melanocytes, whereas various compositions of eumelanin and pheomelanin are observed in human melanocytes depending on the skin type. Therefore, careful consideration is necessary when comparing the results in mice with those in humans (33).

SKIN CANCER DEVELOPMENT IN GENETIC DISORDERS

In mammalian cells, DNA lesions are fixed by several kinds of repair systems, such as nucleotide excision repair (NER), base excision repair, and mismatch repair (95). If the DNA lesions remain at the replication fork, homologous recombination or translesional DNA synthesis systems may work on them there. Bulky DNA lesions causing DNA conformational changes, such as UV-induced pyrimidine photoproducts, are removed by NER. DNA lesions existing in actively transcribed genes are removed by transcription-coupled repair (TCR). This enables the prompt and selective repair of the transcriptionally active strand, and consequently maintains cellular function and survival, whereas lesions prevailing in other parts of the genome are removed in a slow and nonselective manner, designated global genome repair. Deficiency in NER may lead to three kinds of human genetic diseases: xeroderma pigmentosum (XP), Cockayne syndrome (CS), and trichothiodystrophy. Among patients with these three syndromes, only patients with XP (subdivided into XP-A through XP-G according to the responsible genes) are predisposed to skin cancers. XP-A, the severest type among the types of XP, reveals severe photosensitivity that is noticed at an age of <1 year and early onset of both non-melanoma skin cancers and melanomas as early as an age of <10 years (63, 95). The majority of *p53* mutations in skin cancers from XP patients are CC to TT base substitutions, "UV-signature mutations" (22, 77, 81). XP patients have a 10–20-fold increased risk of developing internal malignancies as well (49). One possible explanation for this is that patients with XP have a deficiency in the repair of chemically induced DNA lesions in the internal organs. Some investigators have suggested a repair insufficiency for oxidative modifications in XP cells (73, 78). Moreover, recent studies have shown that the NER pathway is involved in the removal of 8,5′-purine cyclodeoxynucleoside lesions, which are induced by ROS, and this is considered to be a possible causative type of DNA damage responsible for neurological manifestations in XP patients (11, 52). Patients with CS are deficient in TCR. They show physical and mental retardation and photosensitivity, although they are not predisposed to develop skin cancers. Le Page *et al.* found that CS cells, including CS-B, XP-B/CS, XP-D/CS, and XP-G/CS, not only lack TCR, but cannot remove 8-oxoGua in the transcribed strand, whereas XP cells and normal cells show strand-specific removal of 8-oxoGua and thymine glycol. They also found that defective TCR leads to a mutation frequency at 8-oxoGua of 30–40% compared with the normal 1–4% (55). Mutation of MSH2, one of the mismatch repair genes, is reported to result in Muir–Torre syndrome, an autosomal dominant genetic disorder predisposing to both sebaceous skin tumors and internal neoplasms (51).

Nevoid basal cell carcinoma syndrome (NBCCS) is an autosomal dominant disease characterized by the development of tumors such as multiple basal cell carcinomas (BCCs) and odontogenic keratocysts, and by developmental abnormalities (28). Germline mutations in the *PTCH* gene have been identified in patients with NBCCS (12, 30, 40, 91).

The role of UV in the development of BCCs in NBCCS was indicated by the site-specific distribution of the BCCs in NBCCS patients (26). In the general population, ~10% of BCCs occur on the trunk, versus 35% in NBCCS cases. The site-specific distribution of BCCs in Japanese patients with NBCCS also shows the same tendency (66). This suggests that NBCCS patients might be sensitive to low-dose sun exposure or intermittent intense sun exposure because these anatomical sites are where people receive occasional intermittent intense sun exposure. Skin fibroblasts from patients with NBCCS are hypersensitive to UV-B, but not to UV-C radiation in comparison with skin fibroblasts from normal individuals, and they are not impaired in the removal of thymine dimers (3, 66). One report indicated that removal of 8-OHdG in fibroblasts after UV-B exposure is slightly impaired in NBCCS cells in comparison with normal cells, implying that oxidative stress may play a role in the development of BCCs and other tumors in NBCCS (66). Aszterbaum *et al.* reported that UV-A and ionizing radiation enhance the growth of BCCs and trichoblastomas in *patched* heterozygous knockout mice (5), in accordance with our data (66).

ROS AND PROMOTION

It is recognized that low levels of oxidants can modify cell-signaling proteins and that these modifications have functional consequences (61). Gopalakrishna and Jaken

pointed out that various antioxidant preventive agents also inhibit protein kinase C (PKC)-dependent cellular responses and speculated that PKC is a logical candidate for redox modification by oxidants and antioxidants, and that PKC modification may determine their cancer-promoting and anticancer activities, respectively (27). TNF-α-deficient mice are resistant to skin carcinogenesis induced by 7,12-dimethylbenz (12)anthracene (DMBA) and 12-*O*-tetradecanoylphorbol 13-acetate (59). Proinflammatory cytokine TNF-α is a critical mediator of tumor promotion, acting via a PKC-α and AP-1-deficient pathway (4). Arnott *et al.* also reported that the frequency of DNA adduct formation and c-Ha-*ras* mutations was the same in wild-type and TNF-α (−/−) epidermis after DMBA treatment. This implies that the pathway of TNF-α is independent of carcinogenic initiation. ROS has been reported to enhance the expression of *c-fos, c-jun, c-myc*. By the use of cDNA arrays, Jean *et al.* showed that UV-A induces genes encoding transcription factors (EGR-1, ETR-101, c-JUN, ATF4) (39).

CHEMICALLY INDUCED SKIN CARCINOGENESIS

Arsenic is widely found in nature in the form of either metalloids or chemical compounds (36), and is a well established carcinogen. Although experimental animal models of arsenic-induced cancer have not been successfully developed (36), several findings suggest a relationship between ROS and arsenic. Dimethylarsenic acid (DMAA), one of the major metabolites of inorganic arsenics, induces DNA damage via formation of superoxide and dimethylarsenic-peroxyl radical (101, 102). Recently, a significant increase in the formation of 8-OHdG in the livers of rats after administration of DMAA was reported (96). Increased levels of 8-OHdG were reported in 78% of 28 cases of arsenic-related skin neoplasms and arsenic keratosis in comparison with only one of 11 cases (9%) of arsenic-unrelated Bowen's disease ($p < 0.001$ by κ^2 test) (56). This suggests the involvement of ROS in the carcinogenesis of arsenic-induced human skin cancers.

DMAA has the potential to promote rat liver carcinogenesis, possibly via a mechanism involving stimulation of cell proliferation and DNA damage caused by ROS. ROS induced by arsenic may work as a promoter for cells in which carcinogenesis has been initiated by other carcinogens (96). Persistent oxidative stress in cancer (89) may also cause activation of transcription factors and protooncogenes such as *c-fos* and *c-jun* (13), as well as genetic instability. Such stress may also contribute toward maintaining the malignant characteristics of arsenic-related neoplasms.

Other chemicals associated with promotion of skin carcinogenesis include a free radical-generating compound, benzoyl peroxide, that enhances malignant conversion of murine skin benign papillomas into carcinomas (6, 50). 4-Nitroquinoline 1-oxide (4-NQO) is a potent carcinogen that causes squamous cell carcinoma of the tongue (46). A possible mechanism of the carcinogenic action of 4-NQO is the formation of quinoline-adenine cyclic adducts (86). Kohda *et al.* found that a considerable amount of 8-OHdG was generated in the DNA of Ehrlich ascites cells exposed to 4-NQO, and in calf thymus DNA treated with 4-hydroxyaminoquinoline 1-oxide and seryl-AMP (47, 48). Nunoshiba and Demple reported that in *E. coli* 4-NQO was a powerful inducer of the *soxS* gene, which is induced by superoxide generators such as paraquat, and that mutant strains that were deficient in either superoxide dismutase or oxidative DNA repair enzymes were hypersensitive to 4-NQO (68). These findings suggest that 4-NQO generates superoxide, which plays a role in carcinogenesis in addition to the formation of cyclic adenine adducts.

CONCLUDING REMARKS

In UV-induced skin carcinogenesis, the mutagenic nature of pyrimidine photoproducts has been well studied. Recently, it has been established that oxidative stress plays an important role in UV-induced skin carcinogenesis. Oxidative stress is important in other skin carcinogenesis models as well. The authors believe that global studies will be necessary to see whether there are any target genes or proteins for ROS in different various types of carcinogenesis in the near future.

ABBREVIATIONS

BCC, basal cell carcinoma; CS, Cockayne syndrome; DMAA, dimethylarsenic acid; DMBA, 7,12-dimethylbenz (12)anthracene; MED, minimal erythema dose; NBCCS, nevoid basal cell carcinoma syndrome; NER, nucleotide excision repair; 4-NQO, 4-nitroquinoline 1-oxide; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; 8-oxoGua, 8-oxoguanine; PKC, protein kinase C; ROS, reactive oxygen species; TCR, transcription-coupled repair; TNF, tumor necrosis factor; UV, ultraviolet; XP, xeroderma pigmentosum.

REFERENCES

1. Ames BN. Dietary carcinogens and anticarcinogens: oxygen radicals and degenerative diseases. *Science* 221: 1256–1264, 1983.
2. Ananthaswamy HN and Pierceall WE. Molecular mechanisms of ultraviolet radiation carcinogenesis. *Photochem Photobiol* 52: 1119–1136, 1990.
3. Applegate L, Goldberg L, Ley R, and Ananthaswamy H. Hypersensitivity of skin fibroblasts from basal cell nevus syndrome patients to killing by ultraviolet B but not by ultraviolet C radiation. *Cancer Res* 50: 637–641, 1990.
4. Arnott C, Scott K, Moore R, Hewer A, Phillips D, Parker P, Balkwill F, and Owens D. Tumour necrosis factor-alpha mediates tumour promotion via a PKC alpha- and AP-1-dependent pathway. *Oncogene* 21: 4728–4738, 2002.
5. Aszterbaum M, Epstein J, Oro A, Douglas V, Le Boit P, Scott M, and Epstein EH Jr. Ultraviolet and ionizing radiation enhance the growth of BCCs and trichoblastomas in patched heterozygous knockout mice. *Nat Med* 5: 1285–1291, 1999.

6. Athar M, Lloyd J, Bickers D, and Mukhtar H. Malignant conversion of UV radiation and chemically induced mouse skin benign tumors by free-radical-generatingcompounds. *Carcinogenesis* 10: 1841–1845, 1989.
7. Autier P and Dore J. Influence of sun exposures during childhood and during adulthood on melanoma risk. EPIMEL and EORTC Melanoma Cooperative Group. European Organisation for Research and Treatment of Cancer. *Int J Cancer* 77: 533–537, 1998.
8. Basset-Seguin N, Moles J, Mils V, Dereure O, and Guilhou J. TP53 tumor suppressor gene and skin carcinogenesis. *J Invest Dermatol* 103: 102S–106S, 1994.
9. Beckman J and Koppenol W. Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and ugly. *Am J Physiol* 271: C1424–C1437, 1996.
10. Brash D, Rudolph J, Simon J, Lin A, McKenna G, Baden H, Halperin A, and Ponten J. A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. *Proc Natl Acad Sci U S A* 88: 10124–10128, 1991.
11. Brooks P, Wise D, Berry D, Kosmoski J, Smerdon M, Somers R, Mackie H, Spoonde A, Ackerman E, Coleman K, Tarone R, and Robbins J. The oxidative DNA lesion 8,5′-(S)-cyclo-2′-deoxyadenosine is repaired by the nucleotide excision repair pathway and blocks gene expression in mammalian cells. *J Biol Chem* 275: 22355–22362, 2000.
12. Chidambaram A, Goldstein A, Gailani M, Gerrard B, Bale S, Di Giovanna J, Bale A, and Dean M. Mutations in the human homologue of the *Drosophila* patched gene in Caucasian and African–American nevoid basal cell carcinoma syndrome patients. *Cancer Res* 56: 4599–4601, 1996.
13. Crawford D, Zbinden I, Amstad P, and Cerutti P. Oxidant stress induces the proto-oncogenes c-fos and c-myc in mouse epidermal cells. *Oncogene* 3: 27–32, 1988.
14. Das M, Bickers D, Santella R, and Mukhtar H. Altered patterns of cutaneous xenobiotic metabolism in UVB-induced squamous cell carcinoma in SKH-1 hairless mice. *J Invest Dermatol* 84: 532–536, 1985.
15. de Gruijl F. Action spectrum for photocarcinogenesis. *Recent Results Cancer Res* 139: 21–30, 1995.
16. Devasagayam TP, Steenken S, Obendorf MS, Schulz WA, and Sies H. Formation of 8-hydroxy(deoxy)guanosine and generation of strand breaks at guanine residues in DNA by singlet oxygen. *Biochemistry* 30: 6283–6289, 1991.
17. Diplock A, Charleux J, Crozier-Willi G, Kok F, Rice-Evans C, Roberfroid M, Stahl W, and Vina-Ribes J. Functional food science and defence against reactive oxidative species. *Br J Nutr* 80 (Suppl 1): S77–S112, 1998.
18. Dizdaroglu M. Oxidative damage to DNA in mammalian chromatin. *Mutat Res* 275: 331–342, 1992.
19. Dizdaroglu M, Olinski R, Doroshow JH, and Akman SA. Modification of DNA bases in chromatin of intact target human cells by activated human polymorphonuclear leukocytes. *Cancer Res* 53: 1269–1272, 1993.
20. Drobetsky E, Grosovsky A, and Glickman B. The specificity of UV-induced mutations at an endogenous locus in mammalian cells. *Proc Natl Acad Sci U S A* 84: 9103–9107, 1987.
21. Drobetsky E, Turcotte J, and Chateauneuf A. A role for ultraviolet A in solar mutagenesis. *Proc Natl Acad Sci U S A* 92: 2350–2354, 1995.
22. Dumaz N, Drougard C, Sarasin A, and Daya-Grosjean L. Specific UV-induced mutation spectrum in the p53 gene of skin tumors from DNA-repair-deficient xeroderma pigmentosum patients. *Proc Natl Acad Sci U S A* 90: 10529–10533, 1993.
23. Floyd RA. Role of oxygen free radicals in carcinogenesis and brain ischemia. *FASEB J* 4: 2587–2597, 1990.
24. Floyd RA, West MS, Eneff KL, and Schneider JE. Methylene blue plus light mediates 8-hydroxyguanine formation in DNA. *Arch Biochem Biophys* 273: 106–111, 1989.
25. Giri U, Sharma S, Abdulla M, and Athar M. Evidence that in situ generated reactive oxygen species act as a potent stage I tumor promoter in mouse skin. *Biochem Biophys Res Commun* 209: 698–705, 1995.
26. Goldstein A, Bale S, Peck G, and Di Giovanna J. Sun exposure and basal cell carcinomas in the nevoid basal cell carcinoma syndrome. *J Am Acad Dermatol* 29: 34–41, 1993.
27. Gopalakrishna R and Jaken S. Protein kinase C signaling and oxidative stress. *Free Radic Biol Med* 28: 1349–1361, 2000.
28. Gorlin R. Nevoid basal-cell carcinoma syndrome. *Medicine (Baltimore)* 66: 98–113, 1987.
29. Guyton K and Kensler T. Oxidative mechanisms in carcinogenesis. *Br Med Bull* 49: 523–544, 1993.
30. Hahn H, Wicking C, Zaphiropoulous P, Gailani M, Shanley S, Chidambaram A, Vorechovsky I, Holmberg E, Unden A, Gillies S, Negus K, Smyth I, Pressman C, Leffell D, Gerrard B, Goldstein A, Dean M, Toftgard R, Chenevix-Trench G, Wainwright B, and Bale A. Mutations of the human homolog of *Drosophila* patched in the nevoid basal cell carcinoma syndrome. *Cell* 85: 841–851, 1996.
31. Hattori Y, Nishigori C, Tanaka T, Uchida K, Nikaido O, Osawa T, Hiai H, Imamura S, and Toyokuni S. 8-Hydroxy-2′-deoxyguanosine is increased in epidermal cells of hairless mice after chronic UVB exposure. *J Invest Dermatol* 107: 733–737, 1996.
32. Hattori-Nakakuki Y, Nishigori C, Okamoto K, Imamura S, Hiai H, and Toyokuni S. Formation of 8-hydroxy-2′-deoxyguanosine in epidermis of hairless mice exposed to near-UV. *Biochem Biophys Res Commun* 201: 1132–1139, 1994.
33. Hill H and Hill G. UVA, pheomelanin and the carcinogenesis of melanoma. *Pigment Cell Res* 13 (Suppl 8): 140–144, 2000.
34. Huls G, Koornstra J, and Kleibeuker J. Non-steroidal anti-inflammatory drugs and molecular carcinogenesis of colorectal carcinomas. *Lancet* 362: 230–232, 2003.
35. Hussain S, Hofseth L, and Harris C. Radical causes of cancer. *Nat Rev Cancer* 3: 276–285, 2003.
36. IARC. Arsenic and arsenic compounds. In: IARC *Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol 23: Some Metals and Metallic Compounds*. Lyon, France: IARC Press, 1980, pp. 39–141.
37. Irani K, Xia Y, Zweier JL, Sollott SJ, Der CJ, Fearon ER, Sundaresan M, Finkel T, and Goldschmidt-Clermont PJ.

Mitogenic signaling mediated by oxidants in Ras-transformed fibroblasts. *Science* 275: 1649–1652, 1997.
38. Ito K, Inoue S, Yamamoto K, and Kawanishi S. 8-Hydroxydeoxyguanosine formation at the 5′ site of 5′-GG-3′ sequences in double-stranded DNA by UV radiation with riboflavin. *J Biol Chem* 268: 13221–13227, 1993.
39. Jean S, Bideau C, Bellon L, Halimi G, De Meo M, Orsiere T, Dumenil G, Berge-Lefranc J, and Botta A. The expression of genes induced in melanocytes by exposure to 365-nm UVA: study by cDNA arrays and real-time quantitative RT-PCR. *Biochim Biophys Acta* 1522: 89–96, 2001.
40. Johnson RL, Rothman AL, Xie J, Goodrich LV, Bare JW, Bonifas JM, Quinn AG, Myers RM, Cox DR, Epstein EH Jr, and Scott MP. Human homolog of patched, a candidate gene for the basal cell nevus syndrome. *Science* 272: 1668–1671, 1996.
41. Kasai H. Analysis of a form of oxidative DNA damage, 8-hydroxy-2′-deoxyguanosine, as a marker of cellular oxidative stress during carcinogenesis. *Mutat Res* 387: 147–163, 1997.
42. Kasai H and Nishimura S. Hydroxylation of deoxyguanosine at the C-8 position by ascorbic acid and other reducing agents. *Nucleic Acids Res* 12: 2137–2145, 1984.
43. Kasai H, Yamaizumi Z, Berger M, and Cadet J. Photosensitized formation of 7,8-dihydro-8-oxo-2′-deoxyguanosine (8-hydroxy-2′-deoxyguanosine) in DNA by riboflavin: a non singlet oxygen mediated reaction. *J Am Chem Soc* 114: 9692–9694, 1992.
44. Keyse S, Amaudruz F, and Tyrrell R. Determination of the spectrum of mutations induced by defined-wavelength solar UVB (313-nm) radiation in mammalian cells by use of a shuttle vector. *Mol Cell Biol* 8: 5425–5431, 1988.
45. Kino K and Sugiyama H. Possible cause of G-C→C-G transversion mutation by guanine oxidation product, imidazolone. *Chem Biol* 8: 369–378, 2001.
46. Kitano M. Host genes controlling the susceptibility and resistance to squamous cell carcinoma of the tongue in a rat model. *Pathol Int* 50: 353–362, 2000.
47. Kohda K, Tada M, Kasai H, Nishimura S, and Kawazoe Y. Formation of 8-hydroxyguanine residues in cellular DNA exposed to the carcinogen 4-nitroquinoline 1-oxide. *Biochem Biophys Res Commun* 139: 626–632, 1986.
48. Kohda K, Tada M, Hakura A, Kasai H, and Kawazoe Y. Formation of 8-hydroxyguanine residues in DNA treated with 4-hydroxyaminoquinoline 1-oxide and its related compounds in the presence of seryl-AMP. *Biochem Biophys Res Commun* 149: 1141–1148, 1987.
49. Kraemer K, Lee M, and Scotto J. DNA repair protects against cutaneous and internal neoplasia: evidence from xeroderma pigmentosum. *Carcinogenesis* 5: 511–514, 1984.
50. Kraus A, Munro I, Orr J, Binder R, Le Boeuf R, and Williams G. Benzoyl peroxide: an integrated human safety assessment for carcinogenicity. *Regul Toxicol Pharmacol* 21: 87–107, 1995.
51. Kruse R, Rutten A, Hosseiny-Malayeri H, Bisceglia M, Friedl W, Propping P, Ruzicka T, and Mangold E. "Second hit" in sebaceous tumors from Muir–Torre patients with germline mutations in MSH2: allele loss is not the preferred mode of inactivation. *J Invest Dermatol* 116: 463–465, 2001.
52. Kuraoka I, Bender C, Romieu A, Cadet J, Wood R, and Lindahl T. Removal of oxygen free-radical-induced 5′, 8-purine cyclodeoxynucleosides from DNA by the nucleotide excision-repair pathway in human cells. *Proc Natl Acad Sci U S A* 97: 3832–3837, 2000.
53. Kvam E and Tyrrell R. Induction of oxidative DNA base damage in human skin cells by UV and near visible radiation. *Carcinogenesis* 18: 2379–2384, 1997.
54. Lebkowski J, Clancy S, Miller J, and Calos M. The lacI shuttle: rapid analysis of the mutagenic specificity of ultraviolet light in human cells. *Proc Natl Acad Sci U S A* 82: 8606–8610, 1985.
55. Lehmann A. Nucleotide excision repair and the link with transcription. *Trends Biochem Sci* 20: 402–405, 1995.
56. Matsui M, Nishigori C, Toyokuni S, Takada J, Akaboshi M, Ishikawa M, Imamura S, and Miyachi Y. The role of oxidative DNA damage in human arsenic carcinogenesis: detection of 8-hydroxy-2′-deoxyguanosine in arsenic-related Bowen's disease. *J Invest Dermatol* 113: 26–31, 1999.
57. McBride TJ, Preston BD, and Loeb LA. Mutagenic spectrum resulting from DNA damage by oxygen radicals. *Biochemistry* 30: 207–213, 1991.
58. Miller J. Mutagenic specificity of ultraviolet light. *J Mol Biol* 182: 45–65, 1985.
59. Moore R, Owens D, Stamp G, Arnott C, Burke F, East N, Holdsworth H, Turner L, Rollins B, Pasparakis M, Kollias G, and Balkwill F. Mice deficient in tumor necrosis factor-alpha are resistant to skin carcinogenesis. *Nat Med* 5: 828–831, 1999.
60. Muller J and Janz S. Assessment of oxidative DNA damage in the oxyR-deficient SOS chromotest strain *Escherichia coli* PQ300. *Environ Mol Mutagen* 20: 297–306, 1992.
61. Nakamura H, Nakamura K, and Yodoi J. Redox regulation of cellular activation. *Annu Rev Immunol* 15: 351–369, 1997.
62. Nishigori C, Tanaka M, Moriwaki S, Imamura S, and Takebe H. Accelerated appearance of skin tumors in hairless mice by repeated UV irradiation with initial intense exposure and characterization of the tumors. *Jpn J Cancer Res* 83: 1172–1178, 1992.
63. Nishigori C, Moriwaki S, Takebe H, Tanaka T, and Imamura S. Gene alterations and clinical characteristics of xeroderma pigmentosum group A patients in Japan. *Arch Dermatol* 130: 191–197, 1994.
64. Nishigori C, Wang S, Miyakoshi J, Sato M, Tsukada T, Yagi T, Imamura S, and Takebe H. Mutations in ras genes in cells cultured from mouse skin tumors induced by ultraviolet irradiation. *Proc Natl Acad Sci U S A* 91: 7189–7193, 1994.
65. Nishigori C, Hattori Y, Arima Y, and Miyachi Y. Photoageing and oxidative stress. *Exp Dermatol* 12 (Suppl 2): 18–21, 2003.
66. Nishigori C, Arima Y, Matsumura Y, Matsui M, and Miyachi Y. Fibroblasts derived from patients with nevoid basal cell carcinoma syndrome are slightly impaired in

removal of UVB induced 8-hydroxyguanosine. *Br J Dermatol* (in press).
67. Noonan F, Recio J, Takayama H, Duray P, Anver M, Rush W, De Fabo E, and Merlino G. Neonatal sunburn and melanoma in mice. *Nature* 413: 271–272, 2001.
68. Nunoshiba T and Demple B. Potent intracellular oxidative stress exerted by the carcinogen 4-nitroquinoline-N-oxide. *Cancer Res* 53: 3250–3252, 1993.
69. Phillipson R, Tobi S, Morris J, and McMillan T. UV-A induces persistent genomic instability in human keratinocytes through an oxidative stress mechanism. *Free Radic Biol Med* 32: 474–480, 2002.
70. Pierceall W, Goldberg L, Tainsky M, Mukhopadhyay T, and Ananthaswamy H. Ras gene mutation and amplification in human nonmelanoma skin cancers. *Mol Carcinog* 4: 196–202, 1991.
71. Qin X, Zhang S, Oda H, Nakatsuru Y, Shimizu S, Yamazaki Y, Nikaido O, and Ishikawa T. Quantitative detection of ultraviolet light-induced photoproducts in mouse skin by immunohistochemistry. *Jpn J Cancer Res* 86: 1041–1048, 1995.
72. Ramsay H, Harden P, Reece S, Smith A, Jones P, Strange R, and Fryer A. Polymorphisms in glutathione *S*-transferases are associated with altered risk of nonmelanoma skin cancer in renal transplant recipients: a preliminary analysis. *J Invest Dermatol* 117: 251–255, 2001.
73. Reardon J, Bessho T, Kung H, Bolton P, and Sancar A. In vitro repair of oxidative DNA damage by human nucleotide excision repair system: possible explanation for neurodegeneration in xeroderma pigmentosum patients. *Proc Natl Acad Sci U S A* 94: 9463–9468, 1997.
74. Reid TM and Loeb LA. Tandem double CC to TT mutations are produced by reactive oxygen species. *Proc Natl Acad Sci U S A* 90: 3904–3907, 1993.
75. Ricchi P, Zarrilli R, Di Palma A, and Acquaviva A. Nonsteroidal anti-inflammatory drugs in colorectal cancer: from prevention to therapy. *Br J Cancer* 88: 803–807, 2003.
76. Rosen J, Prahalad A, Schluter G, Chen D, and Williams G. Quinolone antibiotic photodynamic production of 8-oxo-7,8-dihydro-2′-deoxyguanosine in cultured liver epithelial cells. *Photochem Photobiol* 65: 990–996, 1997.
77. Sato M, Nishigori C, Zghal M, Yagi T, and Takebe H. Ultraviolet-specific mutations in p53 gene in skin tumors in xeroderma pigmentosum patients. *Cancer Res* 53: 2944–2946, 1993.
78. Satoh M, Jones C, Wood R, and Lindahl T. DNA excision-repair defect of xeroderma pigmentosum prevents removal of a class of oxygen free radical-induced base lesions. *Proc Natl Acad Sci U S A* 90: 6335–6339, 1993.
79. Setlow R, Grist E, Thompson K, and Woodhead A. Wavelengths effective in induction of malignant melanoma. *Proc Natl Acad Sci U S A* 90: 6666–6670, 1993.
80. Shibutani S, Takeshita M, and Grollman AP. Insertion of specific bases during DNA synthesis past the oxidation-damaged base 8-oxodG. *Nature* 349: 431–434, 1991.
81. Spatz A, Giglia-Mari G, Benhamou S, and Sarasin A. Association between DNA repair-deficiency and high level of p53 mutations in melanoma of Xeroderma pigmentosum. *Cancer Res* 61: 2480–2486, 2001.
82. Srinivasan C, Liba A, Imlay JA, Valentine JS, and Gralla EB. Yeast lacking superoxide dismutase(s) show elevated levels of "free iron" as measured by whole cell electron paramagnetic resonance. *J Biol Chem* 275: 29187–29192, 2000.
83. Strange R and Fryer A. The glutathione *S*-transferases: influence of polymorphism on cancer susceptibility. *IARC Sci Publ* 148: 231–249, 1999.
84. Sun Y and Oberley LW. Redox regulation of transcriptional activators. *Free Radic Biol Med* 21: 335–348, 1996.
85. Tada M and Miki Y. Malignant skin tumors among dermatology patients in university hospitals of Japan. A statistical survey 1971–1975. *J Dermatol* 11: 313–321, 1984.
86. Tohme N, Demeunynck M, Lhomme M, and Lhomme J. Formation of a cyclic adenine adduct with a 4-nitroquinoline *N*-oxide metabolite model. *IARC Sci Publ* 70: 241–245, 1986.
87. Toyokuni S. Iron-induced carcinogenesis: the role of redox regulation. *Free Radic Biol Med* 20: 553–566, 1996.
88. Toyokuni S. Reactive oxygen species-induced molecular damage and its applicaton in pathology. *Pathol Int* 49: 91–102, 1999.
89. Toyokuni S, Okamoto K, Yodoi J, and Hiai H. Persistent oxidative stress in cancer. *FEBS Lett* 358: 1–3, 1995.
90. Trush MA and Kensler TW. Role of free radicals in carcinogen activation. In: *Oxidative Stress: Oxidants and Antioxidants,* edited by Sies H. London: Academic Press, 1991, pp. 277–318.
91. Unden A, Holmberg E, Lundh-Rozell B, Stahle-Backdahl M, Zaphiropoulos P, Toftgard R, and Vorechovsky I. Mutations in the human homologue of Drosophila patched (PTCH) in basal cell carcinomas and the Gorlin syndrome: different in vivo mechanisms of PTCH inactivation. *Cancer Res* 56: 4562–4565, 1996.
92. Van der Lubbe J, Rosdorff H, Bos J, and Van der Eb A. Activation of N-ras induced by ultraviolet irradiation in vitro. *Oncogene Res* 3: 9–20, 1988.
93. van der Schroeff J, Evers L, Boot A, and Bos J. Ras oncogene mutations in basal cell carcinomas and squamous cell carcinomas of human skin. *J Invest Dermatol* 94: 423–425, 1990.
94. van Kranen H, de Laat A, van de Ven J, Wester P, de Vries A, Berg R, van Kreijl C, and de Gruijl F. Low incidence of p53 mutations in UVA (365-nm)-induced skin tumors in hairless mice. *Cancer Res* 57: 1238–1240, 1997.
95. Vogelstein B and Kinzler KW. *The Genetic Basis of Human Cancer.* New York: McGraw–Hill, 1998.
96. Wanibuchi H, Hori T, Meenakshi V, Ichihara T, Yamamoto S, Yano Y, Otani S, Nakae D, Konishi Y, and Fukushima S. Promotion of rat hepatocarcinogenesis by dimethylarsinic acid: association with elevated ornithine decarboxylase activity and formation of 8-hydroxydeoxyguanosine in the liver. *Jpn J Cancer Res* 88: 1149– 1154, 1997.
97. Weitzman SA and Gordon LI. Inflammation and cancer: role of phagocyte-generated oxidants in carcinogenesis. *Blood* 76: 655–663, 1990.
98. Whiteman D, Whiteman C, and Green A. Childhood sun exposure as a risk factor for melanoma: a systematic re-

view of epidemiologic studies. *Cancer Causes Control* 12: 69–82, 2001.
99. Willett W and MacMahon B. Diet and cancer—an overview (second of two parts). *N Engl J Med* 310: 697–703, 1984.
100. Wondrak G, Roberts M, Cervantes-Laurean D, Jacobson M, and Jacobson E. Proteins of the extracellular matrix are sensitizers of photo-oxidative stress in human skin cells. *J Invest Dermatol* 121: 578–586, 2003.
101. Yamanaka K, Hasegawa A, Sawamura R, and Okada S. Dimethylated arsenics induce DNA strand breaks in lung via the production of active oxygen in mice. *Biochem Biophys Res Commun* 165: 43–50, 1989.
102. Yamanaka K, Hoshino M, Okamoto M, Sawamura R, Hasegawa A, and Okada S. Induction of DNA damage by dimethylarsine, a metabolite of inorganic arsenics, is for the major part likely due to its peroxyl radical. *Biochem Biophys Res Commun* 168: 58–64, 1990.

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2. Israr Ahmad, Hugo Jimenez, Nik Soriani Yaacob, Nabiha Yusuf. 2012. Tualang Honey Protects Keratinocytes from Ultraviolet Radiation-Induced Inflammation and DNA Damage†. *Photochemistry and Photobiology* **88**:5, 1198-1204. [CrossRef]
3. F. Yogianti, M. Kunisada, R. Ono, K. Sakumi, Y. Nakabeppu, C. Nishigori. 2012. Skin tumours induced by narrowband UVB have higher frequency of p53 mutations than tumours induced by broadband UVB independent of Ogg1 genotype. *Mutagenesis* . [CrossRef]
4. Thomas G Polefka, Thomas A Meyer, Patricia P Agin, Robert J Bianchini. 2012. Cutaneous oxidative stress. *Journal of Cosmetic Dermatology* **11**:1, 55-64. [CrossRef]
5. Lucy Chen, Judy Y. Hu, Steven Q. Wang. 2012. The role of antioxidants in photoprotection: A critical review. *Journal of the American Academy of Dermatology* . [CrossRef]
6. Bing-rong Zhou, Yang Xu, Di Wu, Felicia Permatasari, Ying-ying Gao, Dan Luo. 2012. Ginsenoside Rg1 protects human fibroblasts against psoralen- and UVA-induced premature senescence through a telomeric mechanism. *Archives of Dermatological Research* . [CrossRef]
7. Gautam Sethi, Muthu K. Shanmugam, Lalitha Ramachandran, Alan Prem Kumar, Vinay Tergaonkar. 2012. Multifaceted link between cancer and inflammation. *Bioscience Reports* **32**:1, 1-15. [CrossRef]
8. LENA GALVEZ RANILLA, EMMANOUIL APOSTOLIDIS, KALIDAS SHETTY. 2012. ULTRAVIOLET PROTECTIVE PROPERTIES OF LATIN AMERICAN HERBS ON SACCHAROMYCES CEREVISIAE AND LIKELY MODE OF ACTION THROUGH THE PROLINE-LINKED PENTOSE PHOSPHATE PATHWAY: FOCUS ON THE YERBA MATE TEA (ILEX PARAGUARIENSIS). *Journal of Food Biochemistry* no-no. [CrossRef]
9. Sebastiano Gangemi, Alessandro Allegra, Mohamed Aguennouz, Andrea Alonci, Antonio Speciale, Antonino Cannavò, Mariateresa Cristani, Sabina Russo, Giovanna Spatari, Angela Alibrandi, Caterina Musolino. 2012. Relationship Between Advanced Oxidation Protein Products, Advanced Glycation End Products, and S -Nitrosylated Proteins With Biological Risk and MDR-1 Polymorphisms in Patients Affected by B-Chronic Lymphocytic Leukemia. *Cancer Investigation* **30**:1, 20-26. [CrossRef]
10. Sabine Fiechter, André Skaria, Helga Nievergelt, Romain Anex, Luca Borradori, Laurent Parmentier. 2012. Facial Basal Cell Carcinomas Recurring after Photodynamic Therapy: A Retrospective Analysis of Histological Subtypes. *Dermatology* **224**:4, 346-351. [CrossRef]
11. O. Arican, P. Ozturk, E.B. Kurutas, V. Unsal. 2011. Status of oxidative stress on lesional skin surface of plantar warts. *Journal of the European Academy of Dermatology and Venereology* no-no. [CrossRef]
12. Ashish Dwivedi, Syed F. Mujtaba, Hari N. Kushwaha, Daoud Ali, Neera Yadav, S. K. Singh, Ratan S. Ray. 2011. Photosensitizing mechanism and identification of levofloxacin photoproducts at ambient UV radiation. *Photochemistry and Photobiology* no-no. [CrossRef]
13. Makoto Kunisada, Flandiana Yogianti, Kunihiko Sakumi, Ryusuke Ono, Yusaku Nakabeppu, Chikako Nishigori. 2011. Increased Expression of Versican in the Inflammatory Response to UVB- and Reactive Oxygen Species-Induced Skin Tumorigenesis. *The American Journal of Pathology* **179**:6, 3056-3065. [CrossRef]
14. Sabry M. Attia. 2011. Influence of resveratrol on oxidative damage in genomic DNA and apoptosis induced by cisplatin. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis* . [CrossRef]
15. Jinran Dai, Haiyin Ma, Jing Fan, Yuzhong Li, Jianguang Wang, Hongmei Ni, Guangmin Xia, Suiyun Chen. 2011. Crude polysaccharide from an anti-UVB cell clone of Bupleurum scorzonerifolium protect HaCaT cells against UVB-induced oxidative stress. *Cytotechnology* . [CrossRef]

16. Farrah Ali, Sarwat Sultana. 2011. Repeated short-term stress synergizes the ROS signalling through up regulation of NFkB and iNOS expression induced due to combined exposure of trichloroethylene and UVB rays. *Molecular and Cellular Biochemistry* . [CrossRef]
17. Anne Pouillot, Luigi L. Polla, Philippe Tacchini, Alice Neequaye, Ada Polla, Barbara PollaNatural Antioxidants and their Effects on the Skin 239-257. [CrossRef]
18. Muthu Shanmugam, Vinay Tergaonkar, Gautam SethiRole of Inflammation in Cancer Development **20115234**, . [CrossRef]
19. James E. Klaunig, Zemin Wang, Xinzhu Pu, Shaoyu Zhou. 2011. Oxidative stress and oxidative damage in chemical carcinogenesis. *Toxicology and Applied Pharmacology* **254**:2, 86-99. [CrossRef]
20. Nam Joo Kang, Seung Ho Shin, Hyong Joo Lee, Ki Won Lee. 2011. Polyphenols as small molecular inhibitors of signaling cascades in carcinogenesis. *Pharmacology & Therapeutics* **130**:3, 310-324. [CrossRef]
21. Meital Portugal-Cohen, Yoram Soroka, Marina Fruši#-Zlotkin, Lilian Verkhovsky, François Menahem Brégégère, Rami Neuman, Ron Kohen, Yoram Milner. 2011. Skin organ culture as a model to study oxidative stress, inflammation and structural alterations associated with UVB-induced photodamage. *Experimental Dermatology* no-no. [CrossRef]
22. Maider Ibarrola-Villava, Maria Peña-Chilet, Lara P. Fernandez, Jose A. Aviles, Matias Mayor, Manuel Martin-Gonzalez, Cristina Gomez-Fernandez, Beatriz Casado, Pablo Lazaro, Ana Lluch, Javier Benitez, Rafael Lozoya, Enrique Boldo, Angel Pizarro, Conrado Martinez-Cadenas, Gloria Ribas. 2011. Genetic polymorphisms in DNA repair and oxidative stress pathways associated with malignant melanoma susceptibility. *European Journal of Cancer* . [CrossRef]
23. Chang Yeob Han, Tran Thi Hien, Sung Chul Lim, Keon Wook Kang. 2011. Role of Pin1 in UVA-induced cell proliferation and malignant transformation in epidermal cells. *Biochemical and Biophysical Research Communications* **410**:1, 68-74. [CrossRef]
24. Anna Nicolaou, Suzanne M. Pilkington, Lesley E. Rhodes. 2011. Ultraviolet-radiation induced skin inflammation: dissecting the role of bioactive lipids. *Chemistry and Physics of Lipids* . [CrossRef]
25. S. Haché, L. Takser, F. LeBellego, H. Weiler, L. Leduc, J. C. Forest, Y. Giguère, A. Masse, B. Barbeau, J. Lafond. 2011. Alteration of calcium homeostasis in primary preeclamptic syncytiotrophoblasts: effect on calcium exchange in placenta. *Journal of Cellular and Molecular Medicine* **15**:3, 654-667. [CrossRef]
26. Kathryn A. Bailey, Susan D. Hester, Geremy W. Knapp, Russell D. Owen, Sheau-Fung Thai. 2010. Gene expression of normal human epidermal keratinocytes modulated by trivalent arsenicals. *Molecular Carcinogenesis* **49**:12, 981-998. [CrossRef]
27. Wei Xie, Kai Wang, Larry W. Robertson, Gabriele Ludewig. 2010. Investigation of mechanism(s) of DNA damage induced by 4-monochlorobiphenyl (PCB3) metabolites. *Environment International* **36**:8, 950-961. [CrossRef]
28. Pooja Sarotra, Gayatri Sharma, Shevali Kansal, Anjana Kumari Negi, Ritu Aggarwal, Rajat Sandhir, Navneet Agnihotri. 2010. Chemopreventive Effect of Different Ratios of Fish Oil and Corn Oil in Experimental Colon Carcinogenesis. *Lipids* **45**:9, 785-798. [CrossRef]
29. James A. Cocores, Noni A. Graham, Mark S. GoldAddictive Disorders in Nutritional Diseases - From an Addictions Viewpoint 287-302. [CrossRef]
30. Yoshiyuki Kimura, Maho Sumiyoshi. 2010. French Maritime Pine Bark (Pinus maritima Lam.) Extract (Flavangenol®) Prevents Chronic UVB Radiation-induced Skin Damage and Carcinogenesis in Melanin-possessing Hairless Mice. *Photochemistry and Photobiology* **86**:4, 955-963. [CrossRef]
31. Arif Tasleem Jan, Majid Rasool Kamli, Imtiyaz Murtaza, Jang Bahadur Singh, Arif Ali, Q.M.R. Haq. 2010. Dietary Flavonoid Quercetin and Associated Health Benefits—An Overview. *Food Reviews International* **26**:3, 302-317. [CrossRef]
32. F. S. Van Osch, M. Piliguian, K. A. Hill. 2010. Spontaneous mutation frequency is elevated in skin of harlequin (hq)/Big Blue(R) mice. *Mutagenesis* **25**:3, 235-242. [CrossRef]

33. Wei Guo, Yu An, Liping Jiang, Chengyan Geng, Laifu Zhong. 2010. The protective effects of hydroxytyrosol against UVB-induced DNA damage in HaCaT cells. *Phytotherapy Research* **24**:3, 352-359. [CrossRef]
34. Isabel F. Almeida, Paulo C. Costa, M. Fernanda Bahia. 2010. Evaluation of Functional Stability and Batch-to-Batch Reproducibility of a Castanea sativa Leaf Extract with Antioxidant Activity. *AAPS PharmSciTech* **11**:1, 120-125. [CrossRef]
35. Xiuzu Song, Nicole Mosby, Jennifer Yang, Aie Xu, Zalfa Abdel-Malek, Ana Luisa Kadekaro. 2009. #-MSH activates immediate defense responses to UV-induced oxidative stress in human melanocytes. *Pigment Cell & Melanoma Research* **22**:6, 809-818. [CrossRef]
36. Edoardo Zattra, Christina Coleman, Simin Arad, Elizabeth Helms, Danielle Levine, Evelyn Bord, Alexandra Guillaume, Mohamad El-Hajahmad, Edwin Zwart, Harry van Steeg, Salvador Gonzalez, Raj Kishore, David A. Goukassian. 2009. Polypodium leucotomos Extract Decreases UV-Induced Cox-2 Expression and Inflammation, Enhances DNA Repair, and Decreases Mutagenesis in Hairless Mice. *The American Journal of Pathology* **175**:5, 1952-1961. [CrossRef]
37. Karen L. Cooper, Ke Jian Liu, Laurie G. Hudson. 2009. Enhanced ROS production and redox signaling with combined arsenite and UVA exposure: Contribution of NADPH oxidase. *Free Radical Biology and Medicine* **47**:4, 381-388. [CrossRef]
38. Mar Larrosa, Cristina Luceri, Elisa Vivoli, Chiara Pagliuca, Maura Lodovici, Gloriano Moneti, Piero Dolara. 2009. Polyphenol metabolites from colonic microbiota exert anti-inflammatory activity on different inflammation models. *Molecular Nutrition & Food Research* **53**:8, 1044-1054. [CrossRef]
39. Ragini Kumari, Kamaleshwar P. Singh, James W. DuMond. 2009. Simulated microgravity decreases DNA repair capacity and induces DNA damage in human lymphocytes. *Journal of Cellular Biochemistry* **107**:4, 723-731. [CrossRef]
40. Y KIM, M SUMIYOSHI, M SAKANAKA, Y KIMURA. 2009. Effects of ginseng saponins isolated from red ginseng on ultraviolet B-induced skin aging in hairless mice. *European Journal of Pharmacology* **602**:1, 148-156. [CrossRef]
41. Maho Sumiyoshi, Yoshiyuki Kimura. 2009. Effects of olive leaf extract and its main component oleuroepin on acute ultraviolet B irradiation-induced skin changes in C57BL/6J mice. *Phytotherapy Research* n/a-n/a. [CrossRef]
42. Anatoly A. Starkov. 2008. The Role of Mitochondria in Reactive Oxygen Species Metabolism and Signaling. *Annals of the New York Academy of Sciences* **1147**:1, 37-52. [CrossRef]
43. Y. Zhong, J. Onuki, T. Yamasaki, O. Ogawa, S. Akatsuka, S. Toyokuni. 2008. Genome-wide analysis identifies a tumor suppressor role for aminoacylase 1 in iron-induced rat renal cell carcinoma. *Carcinogenesis* **30**:1, 158-164. [CrossRef]
44. Yasuhiro Kawachi, Xuezhu Xu, Shiroma Taguchi, Hideko Sakurai, Yasuhiro Nakamura, Yoshiyuki Ishii, Yasuhiro Fujisawa, Junichi Furuta, Takenori Takahashi, Ken Itoh, Masayuki Yamamoto, Fumikazu Yamazaki, Fujio Otsuka. 2008. Attenuation of UVB-Induced Sunburn Reaction and Oxidative DNA Damage with no Alterations in UVB-Induced Skin Carcinogenesis in Nrf2 Gene-Deficient Mice. *Journal of Investigative Dermatology* **128**:7, 1773-1779. [CrossRef]
45. Shinya Toyokuni. 2008. Molecular mechanisms of oxidative stress-induced carcinogenesis: From epidemiology to oxygenomics. *IUBMB Life* **60**:7, 441-447. [CrossRef]
46. T SHEN, Q ZHU, S YANG, C WU, H ZHANG, C ZHOU, X ZHANG. 2008. Trichloroethylene induced cutaneous irritation in BALB/c hairless mice: Histopathological changes and oxidative damage. *Toxicology* **248**:2-3, 113-120. [CrossRef]
47. Wen-Sheng Wu, Jia-Ru Wu, Chi-Tan Hu. 2008. Signal cross talks for sustained MAPK activation and cell migration: the potential role of reactive oxygen species. *Cancer and Metastasis Reviews* **27**:2, 303-314. [CrossRef]
48. R HANS, N AGRAWAL, K VERMA, R MISRA, R RAY, M FAROOQ. 2008. Assessment of the phototoxic potential of cosmetic products. *Food and Chemical Toxicology* **46**:5, 1653-1658. [CrossRef]

49. Brian C. Wulff, Jonathan S. Schick, Jennifer M. Thomas-Ahner, Donna F. Kusewitt, Daniel B. Yarosh, Tatiana M. Oberyszyn. 2008. Topical Treatment with OGG1 Enzyme Affects UVB-induced Skin Carcinogenesis. *Photochemistry and Photobiology* **84**:2, 317-321. [CrossRef]
50. Shannon Reagan-Shaw, Hasan Mukhtar, Nihal Ahmad. 2008. Resveratrol Imparts Photoprotection of Normal Cells and Enhances the Efficacy of Radiation Therapy in Cancer Cells. *Photochemistry and Photobiology* **84**:2, 415-421. [CrossRef]
51. Shinji Oikawa. 2008. Mechanism of Oxidative DNA Damage Induced by Environmental Carcinogens and Antioxidants. *Genes and Environment* **30**:1, 1-9. [CrossRef]
52. Tao LU, Yonghui XU, Elise Saiz MONTTINEN, Norihisa KATO. 2008. Supplementing Vitamin B6 to a Low Vitamin B6 Diet Exaggerates UVB-Induced Skin Tumorigenesis in DMBA-Treated Hairless Mice. *Journal of Nutritional Science and Vitaminology* **54**:3, 262-265. [CrossRef]
53. Yu-Ting Liu, Donghao Shang, Shinya Akatsuka, Hiroki Ohara, Khokon Kumar Dutta, Katsura Mizushima, Yuji Naito, Toshikazu Yoshikawa, Masashi Izumiya, Kouichiro Abe, Hitoshi Nakagama, Noriko Noguchi, Shinya Toyokuni. 2007. Chronic Oxidative Stress Causes Amplification and Overexpression of ptprz1 Protein Tyrosine Phosphatase to Activate #-Catenin Pathway. *The American Journal of Pathology* **171**:6, 1978-1988. [CrossRef]
54. Ronald A Tapp, Jingtao Feng, J Wesley Jones, J Andrew Carlson, Vincent L Wilson. 2007. Single Base Instability Is Promoted in Vulvar Lichen Sclerosus. *Journal of Investigative Dermatology* **127**:11, 2563-2576. [CrossRef]
55. Marcus S. Cooke, Joy E. Osborne, Rajinder Singh, Vilas Mistry, Peter B. Farmer, Mark D. Evans, Peter E. Hutchinson. 2007. Evidence that oxidative stress is a risk factor for the development of squamous cell carcinoma in renal transplant patients. *Free Radical Biology and Medicine* **43**:9, 1328-1334. [CrossRef]
56. S. J. S. Flora, Richa Gupta. 2007. Beneficial effects ofCentella asiatica aqueous extract against arsenic-induced oxidative stress and essential metal status in rats. *Phytotherapy Research* **21**:10, 980-988. [CrossRef]
57. Neeraj Agrawal, Ratan Singh Ray, Mohammad Farooq, Aditya Bhushan Pant, Rajendra Kumar Hans. 2007. Photosensitizing Potential of Ciprofloxacin at Ambient Level of UV Radiation. *Photochemistry and Photobiology* **83**:5, 1226-1236. [CrossRef]
58. Makoto Kunisada, Hiroshi Kumimoto, Kanji Ishizaki, Kunihiko Sakumi, Yusaku Nakabeppu, Chikako Nishigori. 2007. Narrow-Band UVB Induces More Carcinogenic Skin Tumors than Broad-Band UVB through the Formation of Cyclobutane Pyrimidine Dimer. *Journal of Investigative Dermatology* . [CrossRef]
59. Shinya Toyokuni, Shinya Akatsuka. 2007. Pathological investigation of oxidative stress in the post-genomic era. *Pathology International* **57**:8, 461-473. [CrossRef]
60. Meital Portugal, Vivian Barak, Isaac Ginsburg, Ron Kohen. 2007. Interplay among oxidants, antioxidants, and cytokines in skin disorders: Present status and future considerations. *Biomedicine & Pharmacotherapy* **61**:7, 412-422. [CrossRef]
61. Georg T. Wondrak. 2007. NQO1-activated phenothiazinium redox cyclers for the targeted bioreductive induction of cancer cell apoptosis. *Free Radical Biology and Medicine* **43**:2, 178-190. [CrossRef]
62. Neeraj Agrawal, Ratan Singh Ray, Mohammad Farooq, Aditya Bhushan Pant, Rajendra Kumar Hans. 2007. Photosensitizing Potential of Ciprofloxacin at Ambient Level of UV Radiation. *Photochemistry and Photobiology*, ahead of print070710000458009-???. [CrossRef]
63. Jiali Han, Graham A. Colditz, David J. Hunter. 2007. Manganese superoxide dismutase polymorphism and risk of skin cancer (United States). *Cancer Causes & Control* **18**:1, 79-89. [CrossRef]
64. K COOPER, K LIU, L HUDSON. 2007. Contributions of reactive oxygen species and mitogen-activated protein kinase signaling in arsenite-stimulated hemeoxygenase-1 production. *Toxicology and Applied Pharmacology* **218**:2, 119-127. [CrossRef]

65. Alfreda Wei, Takayuki Shibamoto. 2007. Antioxidant Activities of Essential Oil Mixtures toward Skin Lipid Squalene Oxidized by UV Irradiation. *Cutaneous and Ocular Toxicology* **26**:3, 227-233. [CrossRef]
66. Sutapa Mukherjee, Madhumita Roy, Subhabrata Dey, Rathindra K. Bhattacharya. 2007. A Mechanistic Approach for Modulation of Arsenic Toxicity in Human Lymphocytes by Curcumin, an Active Constituent of Medicinal Herb Curcuma longa Linn. *Journal of Clinical Biochemistry and Nutrition* **41**:1, 32-42. [CrossRef]
67. Farrukh Afaq, Deeba N Syed, Arshi Malik, Naghma Hadi, Sami Sarfaraz, Mee-Hyang Kweon, Naghma Khan, Mohammad Abu Zaid, Hasan Mukhtar. 2007. Delphinidin, an Anthocyanidin in Pigmented Fruits and Vegetables, Protects Human HaCaT Keratinocytes and Mouse Skin Against UVB-Mediated Oxidative Stress and Apoptosis. *Journal of Investigative Dermatology* **127**:1, 222-232. [CrossRef]
68. David R Bickers, Mohammad Athar. 2006. Oxidative Stress in the Pathogenesis of Skin Disease. *Journal of Investigative Dermatology* **126**:12, 2565-2575. [CrossRef]
69. Shinya Toyokuni, Hiroyuki Yasui, Akira Date, Tomohiro Hakozaki, Shinya Akatsuka, Haruyasu Kohda, Takashi Yoshii, Hiromu Sakurai. 2006. Novel screening method for ultraviolet protection: Combination of a human skin-equivalent model and 8-hydroxy-2'-deoxyguanosine. *Pathology International* **56**:12, 760-762. [CrossRef]
70. A.V. Krylov, H. Adamzig, A.D. Walter, B. Löchel, E. Kurth, O. Pulz, J. Szeponik, F. Wegerich, F. Lisdat. 2006. Parallel generation and detection of superoxide and hydrogen peroxide in a fluidic chip. *Sensors and Actuators B: Chemical* **119**:1, 118-126. [CrossRef]
71. Li Jiang, Yi Zhong, Shinya Akatsuka, Yu-Ting Liu, Khokon Kumar Dutta, Wen-Hua Lee, Janice Onuki, Ken-ichi Masumura, Takehiko Nohmi, Shinya Toyokuni. 2006. Deletion and single nucleotide substitution at G:C in the kidney of gpt delta transgenic mice after ferric nitrilotriacetate treatment. *Cancer Science* **97**:11, 1159-1167. [CrossRef]
72. Hitoshi Nishimura, Hiroyuki Yasui, Hiromu Sakurai. 2006. Generation and distribution of reactive oxygen species in the skin of hairless mice under UVA: studies on in vivo chemiluminescent detection and tape stripping methods. *Experimental Dermatology* **15**:11, 891-899. [CrossRef]
73. Dr. Shinya Toyokuni . 2006. Novel Aspects of Oxidative Stress-Associated Carcinogenesis. *Antioxidants & Redox Signaling* **8**:7-8, 1373-1377. [Abstract] [Full Text PDF] [Full Text PDF with Links]
74. Colin F. Chignell, Barbara M. Kukielczak, Robert H. Sik, Piotr J. Bilski, Yu-Ying He. 2006. Ultraviolet A sensitivity in Smith–Lemli–Opitz syndrome: Possible involvement of cholesta-5,7,9(11)-trien-3#-ol. *Free Radical Biology and Medicine* **41**:2, 339-346. [CrossRef]
75. Mariko Murata, Taro Tezuka, Shiho Ohnishi, Takeji Takamura-Enya, Yoshiharu Hisamatsu, Shosuke Kawanishi. 2006. Carcinogenic 3-nitrobenzanthrone induces oxidative damage to isolated and cellular DNA. *Free Radical Biology and Medicine* **40**:7, 1242-1249. [CrossRef]
76. T Efferth, S M Schwarzl, J Smith, R Osieka. 2006. Role of glucose-6-phosphate dehydrogenase for oxidative stress and apoptosis. *Cell Death and Differentiation* **13**:3, 527-528. [CrossRef]
77. Hiroshi Orimo, Yoshiki Tokura, Ryosuke Hino, Hiroshi Kasai. 2006. Formation of 8-hydroxy-2'-deoxyguanosine in the DNA of cultured human keratinocytes by clinically used doses of narrowband and broadband ultraviolet B and psoralen plus ultraviolet A. *Cancer Science* **97**:2, 99-105. [CrossRef]
78. Shinya Toyokuni, Shinya Akatsuka. 2006. What has been Learned from the Studies of Oxidative Stress-induced Carcinogenesis: Proposal of the Concept of Oxygenomics. *Journal of Clinical Biochemistry and Nutrition* **39**:1, 3-10. [CrossRef]
79. Ki Won Lee, Hyong Joo Lee. 2006. The roles of polyphenols in cancer chemoprevention. *BioFactors* **26**:2, 105-121. [CrossRef]
80. R. S. Ray, N. Agrawal, R. B. Misra, M. Farooq, R. K. Hans. 2006. Radiation-Induced in Vitro Phototoxic Potential of Some Fluoroquinolones. *Drug and Chemical Toxicology* **29**:1, 25-38. [CrossRef]

81. Mahfuzar Rahman, Marie Vahter, Nazmul Sohel, Muhammad Yunus, Mohammad Abdul Wahed, Peter Kim Streatfield, Eva-Charlotte Ekström, Lars Åke Persson. 2006. Arsenic Exposure and Age and Gender-specific Risk for Skin Lesions: A Population Based Case-Referent Study in Bangladesh. *Environmental Health Perspectives* . [CrossRef]
82. Georg T. Wondrak, Myron K. Jacobson, Elaine L. Jacobson. 2006. Endogenous UVA-photosensitizers: mediators of skin photodamage and novel targets for skin photoprotection. *Photochemical & Photobiological Sciences* **5**:2, 215. [CrossRef]
83. J FISCHER, S ROBBINS, M ALZOUGHOOL, S KANNAMKUMARATH, S STRINGER, J LARSON, J CARUSO, G TALASKA, P STAMBROOK, J STRINGER. 2005. Co-mutagenic activity of arsenic and benzo[]pyrene in mouse skin. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis* **588**:1, 35-46. [CrossRef]
84. Jose C. Garcia-Borron, Berta L. Sanchez-Laorden, Celia Jimenez-Cervantes. 2005. Melanocortin-1 receptor structure and functional regulation. *Pigment Cell Research*, ahead of print051103015727002. [CrossRef]
85. Yogeshwer Shukla, Nihal Ahmad, Shannon Reagan-ShawResveratrol as a Radio-Protective Agent **20051449**, 423-438. [CrossRef]
86. L.E. Finlan, N.M. Kernohan, G. Thomson, P.E. Beattie, T.R. Hupp, S.H. Ibbotson. 2005. Differential effects of 5-aminolaevulinic acid photodynamic therapy and psoralen + ultraviolet A therapy on p53 phosphorylation in normal human skin in vivo. *British Journal of Dermatology* **153**:5, 1001-1010. [CrossRef]
87. J. Cebrian, A. Messeguer, R. M. Facino, J. Ma. Garcia Anton. 2005. New anti-RNS and -RCS products for cosmetic treatment. *International Journal of Cosmetic Science* **27**:5, 271-278. [CrossRef]
88. Ki Won Lee, Hyong Joo Lee, Chang Yong LeeVitamin C Blocks Carcinogenic Tumor Formation **20052271**, . [CrossRef]
89. So-Young Kim, Dong-Seok Kim, Sun-Bang Kwon, Eun-Sang Park, Chang-Hun Huh, Sang-Woong Youn, Suk-Wha Kim, Kyoung-Chan Park. 2005. Protective effects of EGCG on UVB-induced damage in living skin equivalents. *Archives of Pharmacal Research* **28**:7, 784-790. [CrossRef]
90. Sudipta Pal, Ajay K. Chatterjee. 2005. Prospective protective role of melatonin against arsenic-induced metabolic toxicity in Wistar rats. *Toxicology* **208**:1, 25-33. [CrossRef]
91. Shinya Toyokuni . 2004. Redox Control of Carcinogenesis and Tumor Biology. *Antioxidants & Redox Signaling* **6**:3, 481-482. [Citation] [Full Text PDF] [Full Text PDF with Links]