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Invited Review

The Mechanisms of UV Mutagenesis

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UV-induced mutation/UV damage/UVB/UVA/TLS.

Ultraviolet (UV) light induces specific mutations in the cellular and skin genome such as UV-signature and triplet mutations, the mechanism of which has been thought to involve translesion DNA synthesis (TLS) over UV-induced DNA base damage. Two models have been proposed: "error-free" bypass of deaminated cytosine-containing cyclobutane pyrimidine dimers (CPDs) by DNA polymerase η, and error-prone bypass of CPDs and other UV-induced photolesions by combinations of TLS and replicative DNA polymerases—the latter model has also been known as the two-step model, in which the cooperation of two (or more) DNA polymerases as misinserters and (mis)extenders is assumed. Daylight UV induces a characteristic UV-specific mutation, a UV-signature mutation occurring preferentially at methyl-CpG sites, which is also observed frequently after exposure to either UVB or UVA, but not to UVC. The wavelengths relevant to the mutation are so consistent with the composition of daylight UV that the mutation is called solar-UV signature, highlighting the importance of this type of mutation for creatures with the cytosine-methylated genome that are exposed to the sun in the natural environment. UVA has also been suggested to induce oxidative types of mutation, which would be caused by oxidative DNA damage produced through the oxidative stress after the irradiation. Indeed, UVA produces oxidative DNA damage not only in cells but also in skin, which, however, does not seem sufficient to induce mutations in the normal skin genome. In contrast, it has been demonstrated that UVA exclusively induces the solar-UV signature mutations *in vivo* through CPD formation.

INTRODUCTION

Ultraviolet (UV) light has strong genotoxic effects to produce DNA damage, induce mutations, and, in the worst case, cause the development of tumors. The major natural source of UV is the sun, and solar UV is known to be one of the main causes of human skin cancers.[1,2] UV has been classified into three bands by the wavelength: UVA (320–400 nm), UVB (290–320 nm) and UVC (< 290 nm). UVA is also subclassified into UVA1 (340–400 nm) and UVA2 (320–340 nm). The UV component of the sunlight reaching the earth surface (daylight UV) consists of UVA and UVB (290–400 nm), the UVB portion of which shows a strong carcinogenic effect on the skin,[1,3] whereas some involvement of the UVA portion in carcinogenesis of the skin has also been suggested.[4–6] In this review, we characterize UV-induced mutations in terms of the causative DNA damage and UV wavelengths, and show the latest overview of the mechanism of UV mutagenesis based on recent progress in the molecular knowledge of DNA damage bypassing.

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UV-INDUCED DNA LESIONS

UV produces specific DNA damage such as cyclobutane pyrimidine dimers (CPDs) and pyrimidine(6-4)pyrimidone photoproducts (64PPs) at dipyrimidine sites, where two pyrimidine (Py) bases are juxtaposed in tandem in the nucleotide sequence of DNA. These UV lesions are formed through a photochemical reaction, whose efficiency depends on the wavelength, following direct UV energy absorption by DNA bases.[7] The yields of CPD and 64PP are highest at around 260 nm, and the action spectra of their formation are in parallel to the absorption spectrum of DNA. It is also known that 64PP can change into an isomeric secondary product, Dewar valence isomer, after subsequent absorption of UVA wavelengths around 325 nm.[8–10] These photolesions, CPD, 64PP and Dewar, are assumed to cause UV-specific mutations.

UV also induces oxidative stress in irradiated cells through the production of reactive oxygen species (ROS) by activating some small molecules such as riboflavin, tryptophan and porphyrin,[11–14] which can then activate cellular

oxygen.[15,16] ROS attack DNA and can produce oxidative base damage such as 8-hydroxyguanine (8OH-G) and thymine glycol in DNA or can make strand breaks.[17–19] ROS also attack cellular nucleotide pools, producing oxidized nucleotides such as 8-hydroxydeoxygunanosine-triphosphate (8OH-dGTP), which can still be used as nucleotide precursors for DNA synthesis.[20] Some of these types of oxidative DNA and nucleotide damage are known to be mutagenic.[19,21] Thus, UV can induce oxidative stress-mediated mutations in the cellular genome through an indirect mechanism.

UV-INDUCED MUTATIONS (UVC-UVB-UVA2)

UV signature

UV induces specific types of mutation: base substitutions of cytosine (C) → thymine (T) at dipyrimidine sites and CC → TT tandem base substitutions, although the latter rarely occur. These two types of mutation are also called UV signature,[2] and their detection suggests past exposure to UV (Table 1). In one of the mechanisms of formation of these UV-specific mutations, deamination of cytosine bases in a CPD is thought to be involved.[22,23]

"Error-free" bypass of deaminated CPD

The cytosine base in a CPD is unstable and easily deaminates resulting in a uracil base (half life 2–100 hrs),[24–27] whereas an intact cytosine base is quite stable (half life 30,000 yrs).[28] Thus, CPDs including cytosine residues are prone to change to uracil (U)-containing CPDs by deamination. Especially, CC dipyrimidines are thought to deaminate synergistically at both cytosines once they have changed to a CPD form, resulting in UU-CPDs at a high frequency.[25,27] These uracil-containing CPDs are presumed to represent the causative DNA damage for UV-specific mutations.

CPDs, 64PPs and Dewar isomers block DNA synthesis by preventing the replicative DNA polymerases from passing through them when they reside on a template strand during DNA replication.[29–31] Although cells try to excise these photolesions by a DNA repair mechanism called nucleotide excision repair (NER), failure in the repair before replication fork passing would lead to a stall and collapse of the fork at the damaged site, which could cause a DNA double strand break and result in cell death. To avoid such an unfavorable outcome, cells have several mechanisms to tolerate, one of which is translesion DNA synthesis (TLS), in which specialized DNA polymerases called TLS polymerases work to overcome the replication blocks by restarting the DNA synthesis stalled at obstructive, damaged bases on a template strand. It is generally supposed that TLS polymerases could perform TLS by relaxing or ignoring the conventional Watson-Crick base-pairing rule between an incoming dNTP and the template base of DNA. In other words, DNA synthesis with TLS should be error-prone and introduce mutations to the cellular genome at a high frequency. However, DNA polymerase (pol) η, which shows a function highly specific to CPD,[32–35] suppresses efficiently the induction of mutations after UV irradiation by performing an error-free TLS opposite CPDs[36] using the base-pairing ability still remaining for CPDs.[37] Actually, patients of a variant form of xeroderma pigmentosum (XP-V), which has deficiencies in the gene *POLH* encoding polη, show high photocarcinogenic sensitivities in skin regions exposed to sunlight. Cells from such patients are also sensitive to UV-induced mutations. Thus, polη seems to suppress CPD-mediated mutations through its "error-free" TLS activity for CPD. With this very activity, however, it could induce C → T and CC → TT mutations unintentionally at the sites of U-containing CPDs produced by deamination (Fig. 1a, b; Table 1, the mechanism A). The induction of CPD-mediated UV-specific mutations depends on a balance between cytosine deamination and polη-mediated TLS as well as that between DNA replication and NER.

Solar-UV signature

It has been known that UVB and daylight UV induce CPDs preferentially at 5-methylcytosine (mC)-containing

Table 1. Types and characteristics of UV-induced mutations

Type	Mutation pattern	Causative damage	Mechanism	Relevant wavelength
UV signature	C → T at Py-Py CC → TT	CPD	A, B	UVC–UVA
		64PP?, Dewar?	B	
Solar-UV signature	C → T at Py-mCpG	CPD	A	UVB–UVA (solar UV)
Non-UV-signature	Triplet mutation	64PP, Dewar, CPD?	B	UVC–UVA?
Oxidative type	G → T	8OH-G	Mispair with dATP	UVA?
UVA fingerprint	T → G	8OH-dGTP?	Mispair with template adenine?	UVA?

A: "error-free" TLS opposite deaminated C in CPD by polη (deamination model, see Fig. 3).
B: error-prone TLS by TLS and replicative polymerases (two-step model, see Fig. 3).
Py: pyrimidine, CPD: cyclobutane pyrimidine dimer, 64PP: pyrimidine(6-4)pyrimidone photoproduct, 8OH-G: 8-hydroxyguanine.

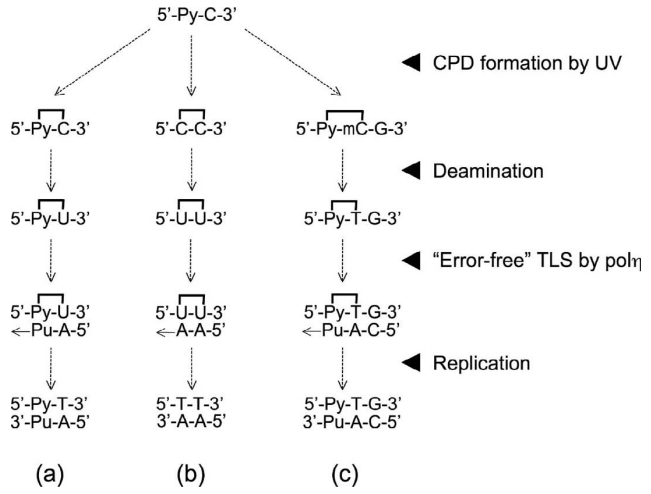

Fig. 1. Mechanistic model of UV-signature mutation formation through deamination-mediated "error-free" TLS of CPDs by polη. (a) The general pathway for PyC → PyT mutations by the deamination-mediated "error-free" TLS. (b) A specific pathway inducing a tandem base substitution of CC → TT. (c) The pathway for the induction of solar-UV signature mutations. Pyrimidine base pairs connected by a bracket indicate CPD dimers. Py, pyrimidine; Pu, purine; mC, methylcytosine.

dipyrimidine sites.[38,39] This site preference of CPD formation requires the methylation of cytosines[39] and is not observed for UVC.[40,41] In the mammalian genome, cytosines are methylated at a high ratio in 5'-CG-3' (CpG) sequences,[42] providing plenty of mC-containing dipyrimidine sites. The abundance in mC suggests a high sensitivity of the mammalian genome at CpG sites to longer wavelength UV such as UVB and UVA. Actually, mutations in the *p53* gene found in human skin cancers, which are most likely to have been induced by solar UV, show the UV signature and occur frequently at the dipyrimidine sites associated with methylated CpG (mCpG).[2,43–45] In mutagenic and carcinogenic studies using mouse skin exposed to UVB, UVA2 or solar UV, similar mutation patterns with frequent recovery of C → T transitions at mCpG-associated dipyrimidine sites have been reported.[46–50] Thus, the UV wavelength range between UVB and UVA2, which coincides with the carcinogenic daylight UV wavelengths, seems to preferentially induce UV-signature mutations at mCpG-associated dipyrimidine (Py-mCpG) sites. Based on these observations, we have proposed calling such UV-specific mutations "solar-UV signature" (Table 1).[45]

In the mechanism by which solar-UV-signature mutations are formed, the "error-free" bypass of deaminated CPDs mentioned above appears to be involved (Fig. 1c). The 3'-mC of CPDs formed at Py-mCpG sequences deaminates more rapidly than the cytosines of CPDs formed in the methylation-free same sequence contexts, resulting in a high frequency of PyT-CPDs,[51] which could be bypassed "error-free" by Polη, finally leading to the solar-UV signature, a C → T transition at the Py-mCpG site.[52]

Error-prone bypass of CPD—two-step model

However, the mutagenesis mechanism of polη-mediated "error-free" TLS opposite deaminated CPDs cannot provide a full explanation for all of the UV-specific mutations. First, the UV-signature mutations were detected in organisms such as *Escherichia coli* that lack polη or its homologues.[53,54] Secondly, polη-defective cells such as XP-V cells, in which UV induces mutations at much higher frequencies than in wild-type cells, still show the UV signature as the main types of UV-induced mutations.[55–58] It should therefore be supposed that the UV-signature mutations, at least a part of them, also result from polη-independent pathways (Table 1, the mechanism B). It is known that *E. coli* pol V ($UmuD'_2C$) and eukaryotic polζ, whose deficiency remarkably suppresses UV-induced mutagenesis,[59,60] work in error-prone TLS. Pol V is believed to most frequently insert an adenine opposite damaged sites on a template strand,[61,62] giving mechanical support for the "A-rule" model of bypassing non-instructional DNA lesions.[63,64] Polζ has been shown to specifically extend newly synthesized DNA strands most efficiently from a 3'-terminal adenine residue inserted opposite a damaged site.[65] Consequently, these error-prone TLS polymerases could results in producing the UV-signature mutation of C → T for the UV damage of dipyrimidines. In addition to these polymerases, polι, polκ and REV1 are also thought to be the error-prone TLS polymerases which could be involved in UV mutagenesis. Polι was reported to have a structural similarity to[66] and a physical interaction with[67] polη, which suggested some relevance of this polymerase to UV mutagenesis. Deficiencies of polι activity, however, cause little change in the UV-induced mutation frequency and spectrum in cells,[36,58,68] or in the phenotypes and UV carcinogenicity in mice,[69,70] though sensitize slightly but significantly polη-knockout mice to UV-induced skin cancer.[57,70] Actually, polι is inefficient in inserting nucleotides opposite the 3'-bases of CPDs.[71,72] On the other hand, defects in REV1 suppress UV-induced mutagenesis in both yeast and mammal.[60,73,74] Repression of polκ activities also diminishes the survival and mutagenic response of cells to UV.[36,75,76] REV1 is known to have a deoxycytidyl transferase activity, incorporating cytosines opposite damaged and undamaged sites,[77] which, however, seems inconsistent with its expected role in the induction of UV-specific C → T mutations. Actually, this activity is not indispensable for TLS and tolerance to the DNA damage induced by UV.[78,79] It has been demonstrated that REV1 can interact with various TLS and replicative polymerases and their accessory factors through its C-terminus and N-terminal BRCT domain,[79–86] which suggests that REV1 plays a regulatory and/or structural role in TLS such as switching between replicative and TLS polymerases, and/or between different TLS polymerases.[65,86–89]

Polκ has been suggested to function in the extension step of TLS like polζ.[90] Both polκ and polζ show poor abilities to bypass CPDs and 64PPs by themselves, and rarely or poorly insert nucleotides opposite the 3'-base position of these lesions.[71,91–93] Instead, these polymerases can extend newly synthesized strands efficiently from mismatched terminal nucleotides inserted opposite the 3' base (and 5' base, of course) of CPDs.[71,90] The role as an extender of mispaired primer termini assigned to these polymerases represents a part of the substantial molecular basis for the classical two-step model of UV mutagenesis,[94–96] in which TLS bypass is assumed to proceed through the two steps of insertion and extension of mismatched nucleotides opposite UV lesions. The DNA polymerases responsible for the first misinsertion step, however, have still not been identified clearly, although the involvement of some replicative and/or TLS polymerases such as polδ, polη, polι and REV1 has been suggested for UV mutagenesis.[36,76,71,97]

In conclusion, bypass of CPD seems to be performed through two different TLS pathways: an error-free pathway dependent exclusively on a single DNA polymerase polη, and an error-prone two-step pathway involving several members of inserter and extender DNA polymerases (the mechanisms A and B in Table 1, respectively).

Mutagenicity of 64PP

The mutagenicity of 64PP still remains to be clarified. Although genetic studies have established the significant involvement of 64PP in UV mutagenesis,[98–100] its contribution to the UV-signature mutation has not been determined yet. It is known that, in mammalian cells proficient in DNA repair, the vast majority of UVB-induced mutations are caused by CPD, not by 64PP,[101] which would have precluded the identification of 64PP-mediated mutations. The minor contribution of 64PP to UV mutagenesis would be partly because 64PPs are excised from the mammalian genome much more efficiently than CPDs, resulting in much lower amounts of 64PP than CPD that could induce mutations.

Since no efficient error-free TLS polymerase working specifically on 64PP, such as polη on CPD, has been found, some error-prone TLS polymerases should be involved in the TLS of such lesions. Polζ is known to be essential to the tolerance for 64PP[102] and necessary for efficient TLS opposite 64PPs.[88,103,104] However, as mentioned above, polζ itself has little ability to insert nucleotides opposite the 3'-base of 64PPs, though it can extend efficiently from the inserted terminal nucleotide opposite the 3'-base of the lesion. Thus, the TLS of 64PP by polζ should require some inserter polymerases, for which several replicative and TLS polymerases such as polδ, polη and polι have been suggested as candidates,[33,34,71,72,97,103–105] while these inserters are poor at extending from the mismatched termini opposite 64PPs. On the other hand, another extender polymerase for TLS, polκ, shows the inability to extend from the terminal nucleotides inserted opposite the 3'-base of 64PPs[90] suggesting that polκ makes little contribution to the TLS of 64PP, which was confirmed by a genetic study.[104]

The contribution of another TLS polymerase REV1 is unique. REV1 plays a significant role in bypassing 64PPs,[89,97,103] whereas its polymerase activity seems dispensable for the TLS reaction.[78,79] It was reported that REV1 deficiency induced frameshift mutations with insertion or deletion of a nucleotide or two at 64PP sites, suggesting a role of REV1 in maintaining the frame fidelity of the TLS reaction on UV-damaged templates.[103] REV1 is known to interact with a variety of DNA replication and TLS factors through its several specific domains such as the N-terminal BRCT domain,[84] polymerase-associated domain (PAD),[83,85,86] ubiquitin-binding motif (UBM),[106,107] and conserved C-terminal domain (CTD),[81,108] and each domain has been shown to be involved in DNA damage tolerance and mutagenesis after UV exposure.[78,79,109,110] It was also shown that REV1 works for TLS in two different steps of replication of damaged DNA: one is in the replication fork stalling at damaged template DNA (replicative TLS) and the other is in single-strand gaps left at damaged sites behind the replication fork progression (gap-filling or postreplicative TLS).[89] The N-terminal BRCT domain of REV1 seems to be more involved in the replicative TLS,[89] and has been shown to interact physically with PCNA irrespective of UV irradiation,[84] whereas the CTD has been suggested to be necessary to the postreplicative or both the modes of TLS.[109] Polζ is known to interact with REV1 through this CTD,[81,109] and has been shown to work preferentially in the postreplicative TLS.[111] 64PPs seem to be bypassed mainly through the polζ-dependent postreplicative TLS with the help of REV1,[88,89,111] whereas most of CPDs are bypassed through the replicative TLS, which should be performed by polη alone or by combinations of replicative and TLS polymerases, probably, with the help of REV1,[88,89] as already mentioned above. These same polymerase combinations could work more effectively in the postreplicative TLS of CPDs that remain to be bypassed after DNA replication, because Rev1 protein is expressed at levels 50-fold higher in G2 and M phases than in G1 and most S phases of cell cycle in yeast.[112] Actually, the yeast *RAD6*-dependent DNA damage tolerance pathway, which includes polζ/Rev1-mediated error-prone TLS, has been shown to operate effectively in the G2/M phase uncoupled from replication forks.[113,114]

Mutagenicity of Dewar isomer

Daylight UV has a broad wavelength range from UVB to UVA (290–400 nm). The shorter wavelength portion could produce 64PPs in the cellular genome, most of which, however, should be transformed subsequently into Dewar isomers by longer wavelength components (~325 nm) of the same daylight UV resulting in a large amount of Dewar isomers and residual 64PPs after solar UV irradiation.[115,116]

Thus, the Dewar isomer is likely to be one of the important types of DNA damage involved in the solar UV genotoxicity. However, the genotoxic properties of Dewar isomers have been less explored compared with CPD and 64PP. Dewar isomers destabilize DNA duplexes as much as 64PPs, which distort DNA more severely than CPDs.[117] Accordingly, repair of Dewar isomers is as rapid as 64PP and in contrast to the slow removal of CPD from the cellular genome, as evidenced in a study with human keratinocytes using HPLC together with tandem mass spectrometry.[118]

Reverse-genetic studies in *E. coli* with reporter DNA constructs possessing a site-specific UV lesion showed that 64PPs and Dewar isomers formed at TT sequences in DNA could frequently induce T → C transitions at the 3' side of TT dipyrimidines,[29,119,120] at which, however, only small numbers of mutations were observed in mammalian genetic studies *in vivo* after UVB irradiation,[46–48] which produces both 64PPs and Dewar isomers in the skin genome. Moreover, most of those *in vivo* mutations induced at TT sites were T → A transversions,[47,48] which would be more likely induced by CPDs formed at TT sites, as shown before.[30] In addition, a duplex DNA containing a TT-Dewar isomer is more stable when the Dewar isomer pairs with AA than with 5'-GA-3' sequences, supporting the low recovery of T → C mutations at TT sites after UV irradiation.[121] Another reverse-genetic study also showed that 64PPs and Dewar isomers formed at 5'-TC-3' sequences in DNA could induce C → T transitions most frequently at the 3' side of the dipyrimidine,[31] which seems consistent not only with the UV signature but also with spectra of the *in vivo* UVB-induced mutation.[46–48] A yeast genetic study using a solar simulator, which should induce more Dewar isomers than 64PPs in DNA, suggested that the mutagenic bypass of Dewar isomers depends not on polη but on polζ.[122]

Non-UV-signature mutation—triplet mutation

We reported that a class of UV-specific mutations, the triplet mutation, which is separate from the UV signature, is induced in mouse skin after UVB irradiation especially remarkably in the genetic backgrounds of NER deficiency.[123–126] Triplet mutations were also detected in a retrospective search among previous reports on studies of the UV-induced mutation spectra in mammalian cells and *p53* mutations in skin cancers.[127] The triplet mutation is defined as a multiple base substitution or frameshift within a three-nucleotide (triplet) sequence which includes a dipyrimidine sequence.[123,127] Most of the triplet mutations detected in those studies occurred at triplet sequences with a dipyrimidine at their 3'-side two bases.[127] Triplet mutations appeared notably in genetic backgrounds and physiological conditions leading to NER deficiency[127] suggesting that UV-induced DNA damage that causes triplet mutations should be repairable by NER. Since CPD is a relatively poor substrate for NER in mammalian cells,[128] it would be excluded, at least, from candidates of major causative damage, although a minor contribution could not be ruled out. On the other hand, it is highly probable that 64PPs and/or Dewar isomers are the main causative DNA damage since these photolesions are removed rapidly from damaged DNA in mammalian cells[118] (Table 1). We have proposed a model for the induction mechanism of the triplet mutation based on error-prone TLS opposite UV photolesions (Fig. 2).[127] This model supposes that misinsertions by the TLS could occur not only opposite the photolesions but also opposite the undamaged template base one-nucleotide downstream from the lesions, and predicts that errors could occur at the extension step as well as at the insertion step in the two-step model of UV mutagenesis mentioned above,[94–96] which is consistent with the error-prone character of TLS polymerases specializing in the extension, polζ and polκ.[71,90] In addition, the pattern of base changes observed in triplet mutations suggests that the error-prone TLS causing those mutations largely follows the A-rule,[63,64,127] which is also consistent with the preference of polζ for a terminal mismatched nucleotide to extend from.[65]

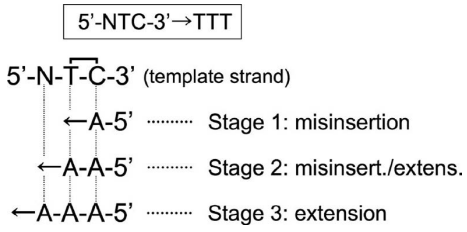

Fig. 2. Error-prone TLS model for triplet mutation formation. A mutation of 5'-NTC-3' to TTT is shown as an example of triplet mutations (N: any nucleotide). The 5'-NTC-3' triplet is on the template strand and a UV photolesion resides at the TC dipyrimidine (bracket). A daughter strand is synthesized opposite the UV lesion by TLS polymerases from the right to the left in the figure, and the lesion is bypassed in the two steps of misinsertion and extension (stage 1 to 3). As shown, errors could happen not only at the insertion steps opposite the lesion (stages 1 and 2) but also at the extension step opposite the undamaged base directly downstream of the lesion (stage 3).

UVA-INDUCED MUTATIONS

UVA-induced CPD

It has been believed that the contribution of ROS, which could be produced by UV-induced oxidative stress as already mentioned,[15,16] to UVA-induced mutations should be considerable, because the direct absorption of the photon energy by DNA is extremely low at this wavelength range.[6] However, the assumption has been challenged since CPD formation by UVA, even if it is the longer low-energy component of UVA1, was demonstrated clearly for cellular and skin

DNA in several independent studies.[129–134] UVA1 induces remarkable amounts of CPDs and 8OH-Gs, but no detectable amounts of 64PPs or Dewar isomers.[131–134] UVA1 forms CPDs most preferably at TT dipyrimidine sites and also at TC or CT sites with lower efficiencies, but scarcely at CC sites.[131,133]

UVA-induced mutation in vitro

UVA-induced mutations in mammalian cells have been studied using cultured cells by several groups,[135–138] which, however, reported mutation spectra different from one another, bringing about controversies. Three different types of base substitution characterized the UVA-induced mutation spectrum that each group insisted on. One of those base substitutions is T → G transversion, which was detected most frequently together with the less frequent UV-signature mutation after UVA irradiation and designated as "UVA fingerprint" because it was so unique as to be rarely induced by other mutagenic agents and conditions.[135] Detection of the UVA fingerprint mutations was also reported in a study with human skin tumors.[139] However, T → G transversions were hardly detected in the UVA-induced mutation spectra by other groups, and the mechanism by which they are induced remains unclear, although 8OH-dGTP, one of the oxidative forms of cellular nucleotides, might have induced such mutations (Table 1).[20,21] Another type of the characteristic UVA-induced base substitution was G → T transversion, whose induction was observed at a similar frequency as the UV signature mutations after UVA1 exposure.[136] This result strongly supported a major contribution of ROS to the UVA-mediated mutagenesis because G → T substitution is a representative ROS-specific mutation known to be induced by one of the most mutagenic types of oxidative DNA base damage, 8OH-G.[21] However, the third group of the UVA-induced mutation spectra was characterized exclusively by C → T base substitutions at dipyrimidine sites, namely UV signature mutations,[137,138] supporting the major contribution of CPD, the only known UV-specific DNA photolesion induced remarkably in the UVA range,[131,133] to the UVA-induced mutation.

These discrepancies in the UVA-induced mutation spectrum among the research groups might result from differences in the UVA sources used or in the cell lines used, but more probably could originate from differences in the conditions of the cell cultures such as the ingredients of culture media. Actually, an increase in the concentration of riboflavin, one of the representative endogenous UV photosensitizers, in the media elevated the formation of 8OH-G, the frequency of mutation, and the ratio of G → T transversion in the mutation spectrum in cells after UVA1 irradiation, all of which were counteracted by the addition of a strong antioxidant, vitamin C.[140,141] This observation indicates that the UVA-induced mutation spectrum could be easily changed by variations in the contents of the medium ingredients and suggests that the controversies concerning the UVA-induced mutations will not be resolved as long as cultured cells are used for the study, relying on culture media composed of artificial ingredients.

UVA-induced mutation in vivo

To avoid the improper effects of artificial photosensitizers and antioxidants, *in vivo* evaluations of the UVA-induced mutation spectrum directly in the animal skin were conducted. We studied UVA-induced mutations in mouse skin epidermis using black light lamps at first, and reported a mutation spectrum overwhelmed by the solar-UV signature mutations.[49] However, the black light lamps emit not only UVA but also a small amount of UVB, although we cut off most of the UVB components with a filter. The possibility that a small amount of the residual UVB affected the mutation spectrum could not be excluded. Therefore, we replaced the UVA source with a UVA1 laser, which produces a pure wavelength output of 364 nm without contamination by any other wavelengths, and showed that UVA1 induces the UV-specific mutations, especially the solar-UV signature, but not any ROS-mediated mutations, although the formations of both CPD and 8OH-G were induced in the skin genome after irradiation.[134] This study indicated that UVA indeed induces oxidative stress *in vivo* and makes ROS-mediated DNA damage in the skin, which, however, fails to induce mutations, probably because of the rapid removal of this oxidative base damage from the affected genome by DNA repair, as shown before.[142] On the other hand, CPDs are known to be relatively hard to remove from the genome overall by the mammalian DNA repair system,[143] which probably led to the notable induction of UV-signature mutations in the skin genome after UVA1 irradiation in our study. Thus, UVA, even if it is the longer wavelength UVA1, induces solar-UV signature mutations, but not the oxidative types, *in vivo* in mammalian skin (Table 1), which, however, should be taken with caution because extremely high doses were needed in the case of UVA1 to induce sufficient mutations to evaluate[134] suggesting that UVA1 is a weak environmental mutagen.

Whereas the acute mutagenic effects of UVA have been widely studied, the influence of chronic exposure, which might enhance oxidative stress, should be also evaluated. A mutation spectrum of the *p53* gene in skin cancers induced experimentally by chronic exposure to UVA1 was studied using albino hairless mice, and was found to show exclusively a single hotspot mutation of a solar-UV signature.[144] It was reported previously that UVA induced malignant melanomas in fish skin,[4] in which photosensitized melanin radicals, which would not be produced in albino mice, were produced by the irradiation suggesting a major role of the UVA-induced oxidative stress in the carcinogenesis of melanoma.[145] Another group, however, provided recently persuasive evidence that UVA makes no significant contribution to

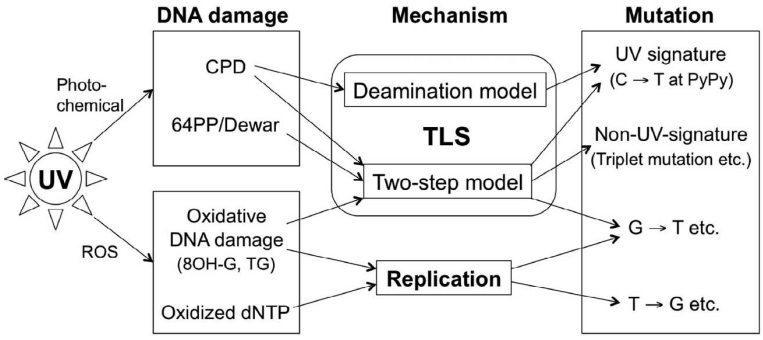

Fig. 3. Schematic overview of the mechanism of UV mutagenesis. DNA lesions UV is thought to produce are linked to the mutations detected after UV exposure in previous studies, mediated by possible intervening molecular mechanisms. The details of the deamination and two-step models are given in Fig. 1 and Fig. 2, respectively. The mutations mediated through replication could occur by incorporating incorrect nucleotides opposite damaged bases or damaged nucleotides opposite intact but mismatched template bases because of an altered base-pairing ability with the damaged molecules. TG, thymine glycol; PyPy, dipyrimidine.

the melanogenesis in pigmented fish skin.[146] These results may suggest again a major contribution of CPD to chronic UVA genotoxicity.

CONCLUSION

It has been known that UV could exert its genotoxicity through direct photochemical and indirect ROS-mediated pathways, which produce mutagenic DNA damage such as CPD and 8OH-G, respectively. However, we have now learned that the former pathway seems to dominate all over the UV wavelengths at least in normal cells and healthy skin. Mutagenesis with such directly produced DNA damage is mainly mediated through mechanisms based on TLS, for which two models have been proposed: the model of "error-free" bypass of a deaminated cytosine-containing CPD by polη, and the model of error-prone two-step bypass, which consists of misinsertion and (mis)extension steps, by multiple TLS/replicative polymerases. Although the former model could explain the UV-signature mutation, the latter two-step model should also contribute because polη is not necessary to induce the mutation. Moreover, the two-step model should be relevant to the mutagenicity of 64PP and Dewar isomer, and could explain the triplet mutation, one of the UV-specific non-UV-signature mutations, although the contributing polymerases and causative DNA damage remain to be clearly identified. Wavelength influences the spectrum of UV-induced mutation as evidenced by the specifically frequent recovery of the solar-UV signature after exposure to UVB and UVA. These wavelengths comprising the solar UV induce CPDs preferentially at methylated cytosine-associated dipyrimidine sites as well as at TT dipyrimidine sites, resulting in the solar signature. However, the mechanism of the wavelength-dependent formation of the site-specific CPDs has not been solved yet. A schematic overview of the mechanism of UV mutagenesis is given in Fig. 3.

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