Archives of Clinical & Experimental Dermatology

Review | Vol 7 Iss 2
ISSN: 2583-6374
https://dx.doi.org/10.46527/2583-6374.185

Ultraviolet Radiation-Induced Mutagenesis and Oxidative Stress that Drives Melanoma

David John Mackay Smith*

Clinician, SunDoctors Skin Cancer Clinics Noosaville, Queensland, Australia

***Corresponding author:** David John Mackay Smith, Clinician, SunDoctors Skin Cancer Clinics Noosaville, Queensland, Australia, Tel: +61 7 3365 1111; E-mail: davidjmsmith8@gmail.com

Received: September 14, 2025; **Accepted:** October 01, 2025; **Published:** October 12, 2025

Abstract

Skin carcinogenesis has a multistage model where reactive oxygen species, induced by solar radiation, are associated with initiation, promotion and progression. It is appreciated that ultraviolet light directly induces DNA damage in the form of photoproducts, but this sort of mutation is not commonly seen in the driver genes involved in melanoma, such as BRAF. Also, melanoma can occur in non-sun exposed sites. These paradoxes are better explained if it is seen that melanoma is a tumour of oxidative stress as well as direct UV-induced DNA damage. Melanocytes endure exposure to UVR over a lifetime and intermediaries in melanin production can be cytotoxic, so the melanocyte is well served by protective cellular mechanisms. Bulky DNA mutations caused by UV-induced mutations are repaired by nucleotide excision repair. This needs to be immediate and serviced by multiple pathways to maintain genomic stability.

As well as the direct influence of UVR causing transition type mutations at dipyrimidine sites, inflammation, immunological responses and oxidative modification of DNA and proteins play a role, such as G:C to T:A transversions, induced by the presence of 8-oxoguanine during DNA replication.

Oxidative stress induces genomic instability through activation of proto-oncogenes, such as c-fos, c-Jun and c-myc, and modification of transcriptional and repair processes.

1. Introduction

Ultraviolet radiation (UVR)-induced mutagenesis has been extensively studied but many of the driver mutations in melanoma do not fit the canonical UV signature mutational picture**.** This has been interpreted by some investigators to cast doubt on the involvement of UVR in the melanomagenesis process. However, it has been shown that UVR induces a broader spectrum of

Citation: Smith DJM. Ultraviolet Radiation-Induced Mutagenesis and Oxidative Stress that Drives Melanoma. Arc Clin Exp Dermatol. 2025;7(2):185.

mutations, non-canonical UVR-induced mutations, caused by atypical photoproducts and potentially leading to driver mutations, a major contributing factor in melanomagenesis [1].

UVR exposure in skin cells can result in somatic mutations leading to skin cancer. This is typically C to T (C>T) and less commonly CC-> TT substitutions in cytosine containing dipyrimidine sequences within the DNA strands. These are called UV signature mutations [2]. These arise from mutagenic bypass of UV-induced DNA lesions, primarily cyclobutene pyrimidine dimers (CPDs) and 6-4 photoproducts (6-4PPs) [3,4], that form exclusively at dipyrimidine sequences [5]. However, the driver mutations in melanoma, most prominently *BRAF* V600E and *NRAS* Q61R substitutions do not fit this UV-signature pattern.

- *BRAF* V600E is caused by T>A mutation in a non-dipyrimidine context [6-8].
- *NRAS* Q61R is caused by T>C mutation
- *BRAF* V600K is caused by AC>TT substitution, the most common tandem mutation in a melanoma gene.

This tandem mutation involves a non-dipyrimidine sequence (AC), which also does not fit the UV signature [9-11].

In fact, <50% of driver mutations in melanoma are UV signature which is surprising considering the association between acute UV exposure, causing blister sunburn, and melanomagenesis [12]. It appears, however, that UVR also induces abundant non-canonical mutations, including T>C, T>A and AC>TT substitutions. These mutations display the same transcriptional asymmetry as the canonical mutations and are modulated by nucleotide excision repair (NER), indicating that they are caused by UVR photoproducts and this includes these relevant BRAF driver mutational substitutions.

Genomic sequencing of mutations arising in mammalian cells induced by experimental UV exposure confirms that UVB primary induces UV signature mutations. However, these studies have not provided the origin of atypical substitution patterns that may cause many of the driver mutations in melanoma. Mutations arising from UV photoproducts have two distinctive characteristics

- These mutations appear in cells deficient in nucleotide excision repair (NER) pathways, which deal with helix-distorting DNA lesions, such as bulky UV photoproducts [13].
- UV signature mutations are depleted from the transcribed strand of expressed genes. This transcriptional asymmetry, which appears in melanoma, is due to more efficient repair of these mutations along the transcribed strand by transcription-coupled NER (TC-NER), initiated when RNA polymerase stalls at these bulky lesions [14,15]. This asymmetry is elevated in tumours with germline deficiency of the XPC gene required for global genomic-NER (GG-NER), which repairs photoproducts in intergenic DNA and the non-transcribed strand [16].

2. Non-Canonical Mutations Induced by UV Photoproducts

Laughery et al exposed diploid yeast cells to artificial UV light and sequenced the genomes of individual isolates to identify UV-induced mutations. They found X10 mutation rate in irradiated as compared to non-irradiated controls, concluding that most mutations were UV-induced. They then analysed the trinucleotide context of single nucleotide substitutions in these irradiated cells, finding 32% C>T mutations at either 3’ or 5’ position of dipyrimidine sequences, the typical UV signature. They also identified high levels of T>C substitutions (42%) and T>A mutations (18%), each enriched at specific trinucleotide contexts. T>C substitutions associated with TTA, TTC, TTG and TTT i.e. (TTn) sequences as well as CTn trinucleotides. Most occurred at the 3' position of a dipyrimidine, likely from UV photoproducts. This contrasted with the T>A mutations at ATA and TTA trinucleotides within a non-dipyrimidine sequence suggesting non-canonical photoproducts [1].

They went on to analyse UV-induced mutations in yeast strains prepared with deficiencies in either the GG-NER or the TC-NER sub pathways. They found X2 increase of mutations in the strains deficient in GG-NER but not in the strains matched to the TC-NER deficiency. The greatest increase was in the C>T mutations in a pyrimidine sequence as expected but there was also an increase in T>A mutations (in 3' dipyrimidine and non-dipyrimidine contexts) and T>C mutations (5' and 3' dipyrimidine context). This suggested that these non-canonical UV-induced mutations also originate from UV-photoproducts repaired by the NER pathway [1].

Examining the transcriptional asymmetry of these mutations in wild and NER deficient strains, they found that wild cells had lower mutational density on the transcribed (TS) relative to the non-transcribed (NTS) strand constant with faster repair of the TS by the TC-NER pathway. Strains deficient in GG-NER showed increased mutational density on the NTS, elevating transcriptional asymmetry compared to the TC-NER deficient strains, which nearly eliminated transcriptional asymmetry of these UV-induced mutations [17]. Wild cells with C>T dipyrimidine sequence mutations (canonical UV-signature) showed transcriptional asymmetry with 2-3 X mutational density on the NTS, bulky photoproducts repaired by both NER sub-pathways. Some C>A mutations (TCn trinucleotide sequences) and non-canonical T>C mutations were elevated in GG-NER deficient strains indicating that they also arise from bulky photoproducts.

Previous studies indicated that UV light can induce rare, atypical photoproducts at TA dinucleotides [18,19]. FIG 1. However, T>A mutations (TTn sequences) showed transcriptional asymmetry associated with the NTS as well as TTA sequences showing elevated mutations on the TS relative to the NTS. This indicates that nTA mutations originate from a lesion on the opposite DNA strand, at a corresponding TAn sequence and the central adenine in this context is mutated to thymine, A>T mutation. T>A substitutions in a nTA sequence context comprised 66% of T>A mutations and 12% of all mutations in their wild cell database and are therefore a frequent UV-induced mutation.

3. Tandem Mutations Associated with Atypical UV Photoproducts

UV irradiation of yeast cells also induced many tandem double substitutions. The most frequent was an AC>TT substitution, double the rate of the canonical CC>TT, UV-induced tandem mutation, amongst a range of other double substitutions. AC>CT tandem mutations were also common. The frequency of these tandem mutations was elevated in GG-NER deficient strains, with transcriptional asymmetry favouring the NTS, indicating that these AC and CT sequences originate from UV lesions repaired by NER. CT>nn tandem mutations likely arise through mutagenic bypass of CPDs and 6-4 PPs in dipyrimidine sequence.

In contrast, AC>nn tandem mutations showed little sequence conservation and are therefore unlikely to be due to mutagenic bypass of canonical UV photoproducts but like A>T single mutations in nTA sequence, caused by atypical UV photoproducts.

4. Non-Canonical Mutations in Melanoma

Kubab's study of mutagenesis in human cells reported that only UV signature mutations (C>T and CC>TT) were enriched following low dose UV, but other mutations were also identified e.g. T>A and T>C. Low abundance combined with high numbers of background mutations in all cell lines led to them being overlooked [20]. Laughery's investigations reveal that UVR can induce a more diverse spectrum of mutations than previously suspected. Yeast isolates repeatedly irradiated with UVC revealed four novel classes (C>A, C>T, T>A and T>C) comprising nearly 50% of mutations identified in the study, emphasizing their significance in UV-induced mutagenesis. Further analysis suggesting that similar mutations classes maybe present in melanoma, although at a reduced frequency and concealed by the preponderance of UV signature mutations in these tumours. They found that two of the mutation classes were caused by atypical UV photoproducts, a TA photoproduct and an unknown lesion at adenine-cytosine dinucleotides. UV exposure may stimulate oncogenic mutations in *BRAF,* and potentially other melanoma driver genes, by inducing the formation of rare, but highly mutagenic, photoproducts.

Detection and characterization of novel UV mutational signatures was achieved using diploid yeasts. They are much more tolerant of UV light than mammalian cells and can be repeatedly exposed to high UV doses, accumulating mutations arising from rare UV photoproducts. Rapid proliferation ensures that rare or rapidly repaired DNA photoproducts persist to S phase, contributing to mutagenesis. e.g. Many of their detected T>C mutations arise from 6-4PPs [21], yet these are so rapidly repaired that few persist through the longer mammalian cell cycle [22]. Also, yeast have a much lower number of background mutations than mammalian cells grown in cell culture accentuating the mutations arising directly from UV exposure. Measuring UV mutagenesis in repair-deficient yeast strains allowed identification of which class of mutation are caused by bulky UV photoproducts as well as identifying the DNA strand involved.

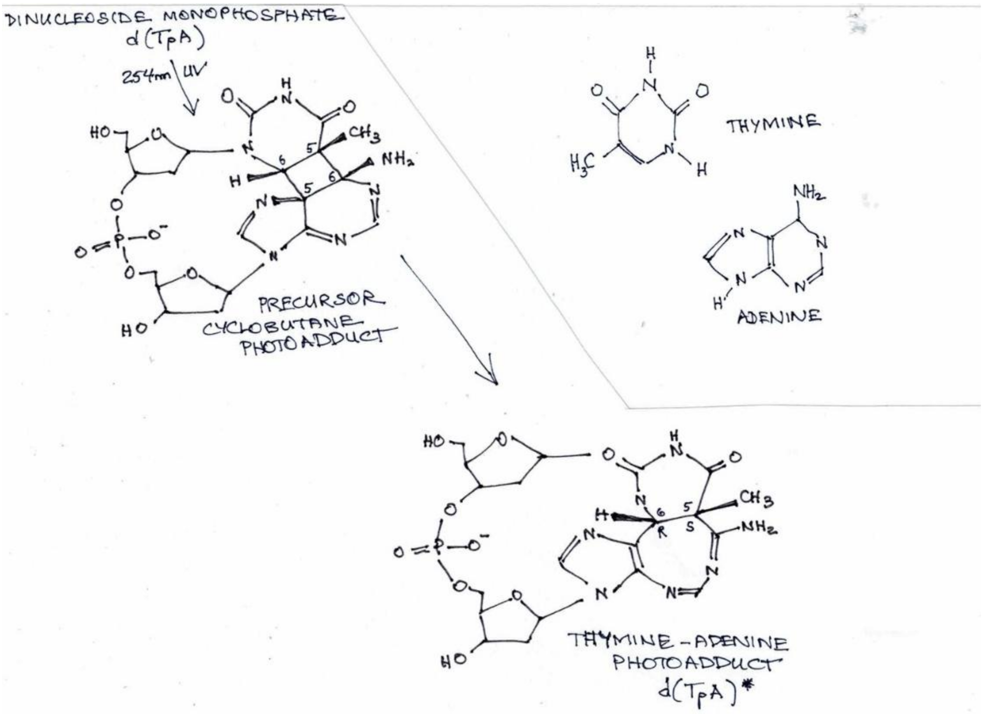

FIG. 1. **Structure of thymine-adenine and precursor cyclobutane photoadducts.**

Produced by direct UV excitation of dinucleoside monophosphate, d(TpA), confirming the presence of a central 1,3-diazacyclooctatriene ring linking the remnants of the T and A bases. It is probable that the primary photoreaction is mechanistically analogous to pyrimidine dimerization despite having a much lower quantum yield.

The mutations induced by UVC light are similar to the spectrum induced by solar UVB light, but it more robustly induces rare and less common UV lesions, such as the 6-4pps [5,23]. Some of these UV-induced non-canonical mutations can be induced in normal sun-exposed human skin [24]. For instance, epidemiological data has shown that the BRAF V600K and R mutations occur almost exclusively in melanoma in chronically sun exposed areas of the head and neck and are more prevalent in geographical regions with higher ambient UV light [25]. They both result from the non-canonical tandem AC>TT mutation.

5. Oxidative Stress

Reactive oxygen species (ROS) directly oxidise biomolecules affecting cellular phenotype and oxidation of guanine in DNA (8-oxodG) induces transversion mutations but beyond that, oxidation of guanine in RNA (O^8G) affects RNA-RNA interactions, altering post-transcriptional regulation and modification of redox controlled gene expression.

ROS are continually generated by aerobic metabolism, i.e. cellular respiration in mitochondria [26]. These ROS are used as intra- and inter-cellular messengers, so production needs to be balanced by antioxidant pathways to maintain cellular redox homeostasis [27]. Ultraviolet radiation (UVR) and other sources of oxidation, such as visible light, can result in a loss of homeostatic regulation resulting in oxidative stress (OS).

Oxidative stress can directly oxidise proteins, lipids and nucleotides, as well as interfering in redox signalling. The production of melanin by melanocytes is an oxidative process with cytotoxic intermediaries making the melanocyte a particular cellular target of OS.

Oxidative modification of guanine of nucleic acids can form 8-oxo-7,8-dihydroguanine (8-oxoG) [28] either as a component of DNA and RNA or as a free nucleotide which can be incorporated through DNA replication [29] or RNA transcription [30]. First identified in DNA of carcinogenic molecules related to OS and now widely used as a ROS biomarker.

Clinically, in DNA the *syn* conformation of 8-oxo-dG base pairs with adenine, whereas the *ante* conformation still pairs with unoxidized guanine [31] FIG. 2. Thus, 8-oxo-dG can cause Guanine to Thymine (G>T) transversions in the melanocyte genome, like the C>T transversions of UVR signature mutation with melanomagenic potential [32].

With exposure to OS, guanine in RNA is more vulnerable to producing 8-oxoguanine than in DNA because it is more temporal and an unstable intermediate [33]. It can serve as an epitranscriptional modification altering RNA-RNA interactions in a redox-dependent manner [34,35].

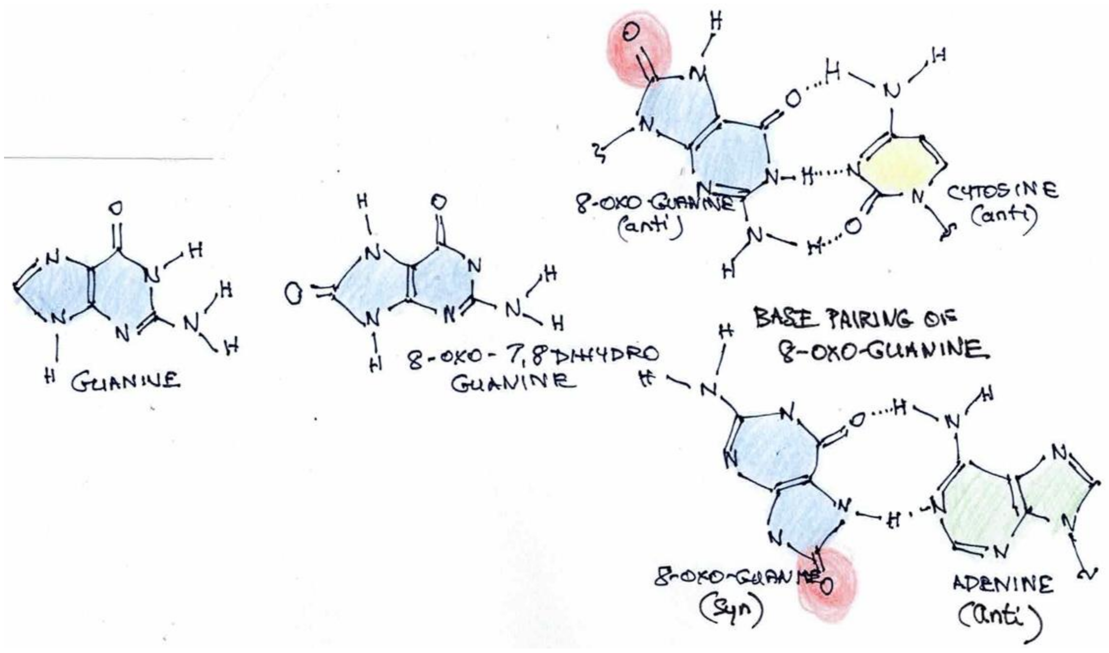

FIG. 2. **Base pairing possibilities of 8-oxoguanine with both adenine and cytosine.**

8-oxoguanine is highly mutagenic because of its propensity to pair with adenine in a *syn* conformation causing G>T mutation. DNA polymerase beta accommodates the 8-oxoguanine template in the *syn* conformation, incorporating adenine in the replicating strand.

6. 8-Oxoguanine in DNA

Cells trigger specific DNA damage response to repair these mutations, cell cycle checkpoint and base excision repair (BER) pathways [36]. DNA oxidation is the most abundant form of damage and relevant to disruption of redox homeostasis inducing inflammation and senescence [35]. Oxidative adducts modify bases and nucleotides as well causing phosphate backbone breakages. Redox potential of guanine oxidation is affected by surrounding sequence composition. Purine rich sequences neighbouring oxidised bases are favoured due to migration of radical cations [37,38]. 8-oxodG is highly mutagenic because of its propensity to pair with adenine in a *syn* conformation causing G>T mutation with adenine incorporated into the replicated strand. 8-oxoG can be formed not only in the DNA molecule but also in free nucleotides which are particularly vulnerable to oxidation. These can then be inserted, in their syn conformation, opposite adenine, avoiding recognition as damaged bases, resulting in an A>C mutation, termed polymerase-indued toxicity.

7. 8-Oxoguanine Repair Pathways

8-oxoguanine DNA glycosylase (OGG1) recognises, removes and repairs 8-oxodG via base excision repair (BER) pathways [39]. Single base lesions are repaired by short patch BER in the absence of helical distortion. Mutations causing bulky distortions in the helical structure are delt with by Nucleotide excision repair (NER). First, the damaged base is removed by DNA glycosylase. The remaining apurinic-apyrimidinic (AP) site is processed by endonuclease activity, and the AP sugar-phosphate backbone is cleaved to form a single-strand break (SSB). The resulting gap is filled and rejoined by either the single nucleotide match (short patch BER) or by synthesising a 2-10 nucleotide sequence (long patch BER) to correct the damage [39].

Monofunctional MutY DNA glycosylase (MUTYH) and bifunctional 8-oxodG DNA glycosylase (OGG1) based on AP lipase activity are responsible for clearing 8-oxodGs and the paired misincorporated adenine from DNA strand. The DNA glycosylases leave an AP site that is handled by other proteins in the BER pathway. Monofunctional DNA glycosylases require separate AP endonucleases (APE1 and 2) whereas bifunctional DNA glycosylates are sufficient to create a SSB by cleavage of the AP sugar-phosphate backbone [40].

8. Oxo-Guanine And G-Quadraplex Folding in Transcriptional Regulation

There is evidence to support interaction between Guanine oxidation and the G-quadruplex (G4) folding in transcription regulatory regions [33,35,36,41,42].

The G4 is a non-canonical DNA secondary structure which can fold at specific G-rich regions and compete with the canonical double strand form of DNA. A Potential Quadraplex Sequence (PQS) is a G-rich region containing at least four stretches of three Gs which can fold into the 4G. At these regions, a square planar structure, a G triad, can form, held together through Hoogsteen hydrogen bonding and stabilised by an alkali cation. Three G triads can stack together to form the G4 structure. FIG. 3. PQSs and G4s can be found enriched at gene regulatory regions such as promotors, enhancers and at telomers [43,44]. Studies have demonstrated involvement in DNA reproduction, repair, telomere maintenance and genetic/epigenetic instability [47,48].

In addition to changes in genetic information 8-oxodG, particularly produced through physiological metabolism, acts as an epigenetic marker that affects regulatory elements in promoters, methylation of CpG islands, and distribution of histone modifications regulating gene expression [49].

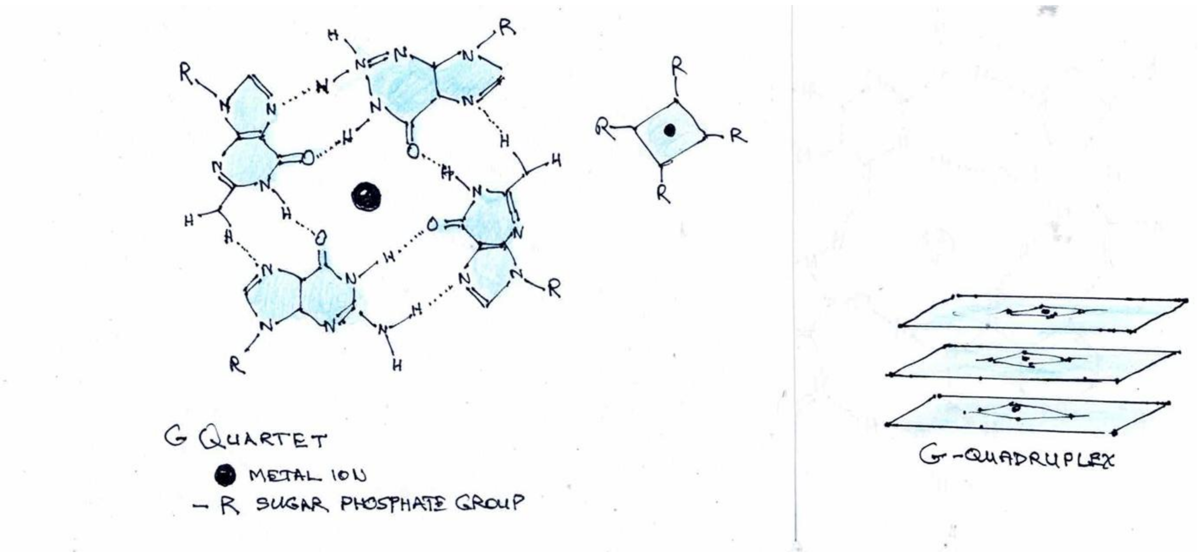

FIG. 3. **Schematic representation of G-quadruplex structures.**

9. Conclusion

It can now be appreciated that the progression to melanomagenesis is much more complex than just UV photons causing mutations in DNA. UV signature mutations are obviously involved, recognised and reproducible but there are a broad range of other mutagenic factors and processes intricately interwoven.

Thousands of oxidation sites within DNA have been identified but the complex relationship between identity and location of DNA adducts and their biological impact are still not fully resolved. However, patterns are emerging related to transcription, repair, chromatin architecture, oxidative potential, and ultimately its impact on tumour suppressors and oncogenes involved in melanoma development.

A balance between damage and repair maintains structural integrity of DNA for transmission of genomic information underlying all processes of life. Of equal importance, however, is control of oxidative processes to maintain cellular redox homeostasis and in this case particularly within the melanocyte due to a long lifespan and its associated accumulation of multiple mutations to fulfill its protective role out at the periphery of the organism where it assesses risk and institutes appropriate adaptive changes.

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