Direct and sensitized damage induced by solar radiation to cellular DNA: formation and repair

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Photo-induced damage to DNA is involved in the etiology of most skin cancers as the result of overexposure to solar radiation and/or UVA photons provided by lamps in tan booths. The UVB component of solar light is mostly responsible for the induction of bipyrimidine photoproducts within cellular DNA, the CC to TT tandem mutation being considered as a molecular signature in targeted genes such as p53 of the deleterious action of UV photons. Three main classes of photoproducts including *cis-syn* cyclobutadipyrimidines (P<>P), pyrimidine (6-4) pyrimidone (64-PP) and related Dewar valence isomers (DewPP) are expected to be generated at each of the four main bipyrimidine sites (TT,TC,CT and CC sequences) leading to a total of 12 tandem lesions. Thus, most of the latter photoproducts can be singled out as modified dinucleoside monophosphates after DNA extraction from UVB-irradiated cells and subsequent suitable enzymic digestion. The resulting mixture of photoproducts and overwhelming normal bases is then subjected to a sensitive HPLC-tandem mass spectrometry analysis, allowing the unambiguous and accurate measurement of several bipyrimidine photoproducts at a dose of UVB radiation as low as 0.2 $kJ.m^{-2}$. Thus, cyclobutadithymine (T<>T) and a lesser extent 6-4-TC and T<>C are detected as the main UVB photoproducts in the DNA of fibroblast and keratinocytes human cells. It may be noted that DewPP are barely detectable, in fact only at CC sites, indicating that UVB-induced photoisomerization of 64-PP precursors is at the best a very low process. This is not the case when cells are exposed to solar radiation, since UVA photons are now able to convert partly UVB-generated 64-TC and 64-TT into related Dewar valence isomers. It may be added that T<>T and to a lesser extent T<>C are formed at the exclusion of 64-TT upon exposure of cellular DNA to UVA radiation. This is likely to be rationalized in term of triplet energy transfer mechanism. It was also found that UVA is able to photo-oxidize cellular DNA. This was inferred from the results of a modified comet assay that allows the detection of strand breaks, oxidized pyrimidine bases and modified purine residues respectively. Interestingly, singlet oxygen that is generated by a type II photosensitization mechanism appears to be the main contributor of UVA-mediated oxidatively generated DNA damage. Information on cellular DNA repair of bipyrimidine photoproducts has been also gained from HPLC-MS/MS measurements, showing that 64-PP and DewPP are much better substrates for nucleotide repair enzymes than P<>P.

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