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Review

Mutations induced by ultraviolet light

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Abstract

The different ultraviolet (UV) wavelength components, UVA (320–400 nm), UVB (280–320 nm), and UVC (200–280 nm), have distinct mutagenic properties. A hallmark of UVC and UVB mutagenesis is the high frequency of transition mutations at dipyrimidine sequences containing cytosine. In human skin cancers, about 35% of all mutations in the *p53* gene are transitions at dipyrimidines within the sequence 5′-TCG and 5′-CCG, and these are localized at several mutational hotspots. Since 5′-CG sequences are methylated along the p53 coding sequence in human cells, these mutations may be derived from sunlight-induced pyrimidine dimers forming at sequences that contain 5-methylcytosine. Cyclobutane pyrimidine dimers (CPDs) form preferentially at dipyrimidines containing 5-methylcytosine when cells are irradiated with UVB or sunlight. In order to define the contribution of 5-methylcytosine to sunlight-induced mutations, the *lacI* and *cII* transgenes in mouse fibroblasts were used as mutational targets. After 254 nm UVC irradiation, only 6–9% of the base substitutions were at dipyrimidines containing 5-methylcytosine. However, 24–32% of the solar light-induced mutations were at dipyrimidines that contain 5-methylcytosine and most of these mutations were transitions. Thus, CPDs forming preferentially at dipyrimidines with 5-methylcytosine are responsible for a considerable fraction of the mutations induced by sunlight in mammalian cells. Using mouse cell lines harboring photoproduct-specific photolyases and mutational reporter genes, we showed that CPDs (rather than 6-4 photoproducts or other lesions) are responsible for the great majority of UVB-induced mutations. An important component of UVB mutagenesis is the deamination of cytosine and 5-methylcytosine within CPDs. The mutational specificity of long-wave UVA (340–400 nm) is distinct from that of the shorter wavelength UV and is characterized mainly by G to T transversions presumably arising through mechanisms involving oxidized DNA bases. We also discuss the role of DNA damage-tolerant DNA polymerases in UV lesion bypass and mutagenesis.

Keywords: UVB; UVA; Mutations; Cyclobutane pyrimidine dimer; Skin cancer; 5-Methylcytosine

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Contents

1. UV-induced DNA photoproducts

Irradiation of DNA or cells with ultraviolet light (UV) induces the formation of several types of mutagenic DNA lesions. The most frequent lesions induced by UVB or UVC radiation are the *cis-syn* cyclobutane pyrimidine dimers (CPDs) and the pyrimidine (6-4) pyrimidone photoproducts [(6-4) photoproducts; (6-4)PPs]. Several minor photoproducts such as purine dimers and pyrimidine mono-adducts are also formed [1]. CPDs are formed between the 5,6 bonds of any two adjacent pyrimidine bases. (6-4)PPs are characterized by a stable bond between positions 6 and 4 of two neighboring pyrimidines and appear to form preferentially at 5′-TC and 5′-CC sequences. They are formed at levels considerably lower than those of CPDs [2,3]. UVA irradiation may induce CPDs in DNA [4,5] and also, through an indirect mechanism, can promote the formation of oxidized DNA bases [6–10].

2. UV and skin cancer mutations

Skin cancer is the most common tumor diagnosed in the United States and the numbers of both non-melanoma and melanoma skin cancers have increased dramatically over the last few decades [11,12]. The available epidemiological evidence indicates clearly that solar UV irradiation is associated with skin cancer [13].

Mutations in cancer-relevant genes are produced by those UV photoproducts that are not repaired before DNA replication. Thus, DNA excision repair systems play an important role in preventing UV mutagenesis. Several human genetic disorders including xeroderma pigmentosum (XP) and Cockayne syndrome (CS) are characterized by a defect in DNA repair. Cells from patients suffering from XP or CS are hypersensitive to UV light. XP is a genetically heterogeneous disease characterized by eight different complementation