Reviewer's report

Title: Different Biological Effects of Two Major Types of UV-induced DNA Damage: CPD Causes Mutation and 6-4PP Induces Apoptosis.

Version: 1 Date: 14 June 2005

Reviewer: Peter Daniel

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General

In their manuscript “Different Biological Effects of Two Major Types of UV-induced DNA Damage: CPD causes Mutation and 6-4PP Induces Apoptosis” Lo et al. investigate the capacity of two different types of UVB-induced DNA damage, that is the formation of cyclobutane pyrimidine dimers (CPD) and pyrimidine (6-4) pyrimidone photoproducts (6-4PP), to induce apoptosis. To this end, the authors employed a cell line derived from a patient with Xeroderma pigmentosum (XP) which is deficient for nucleotide excision repair (NER). They show that the major type of UVB-induced DNA-damage is the formation of CPD whereas 6-4PP lesions are less abundant. Functional reconstitution of XPA cells with either CPD- or 6-4PP photolyase (PL) and photoreactivation by UVA results in a specific decrease in the number of the corresponding DNA-lesions. In turn, expression of CPD-PL and 6-4PP-PL rescues UVB-irradiated XPA cells from undergoing apoptotic cell death with 6-4PP-PL reconstitution being more efficient as compared to cells re-expressing CPD-PL. However, exposure to pTpT dinucleotides, a mimick of CPD-lesions, does not induce apoptosis. Instead, treatment with pTpT arrested cells in G1 phase of the cell cycle. This effects of pTpT was confirmed in vivo by demonstrating that cutaneos pTpT treatment does not induce apoptosis in keratinocytes.

In this thoroughly done work the authors show the differential effect of CPD and 6-4PP lesions in terms of inducing either cell cycle arrest or apoptosis upon UVB-irradiation. This will help to extend our knowledge on understanding the differential impact of DNA-damaging UV irradiation that ultimately forces the damaged cell to decide between an attempt to repair the damage or to die. Therefore the manuscript should be considered for publication in BMC Cancer. However, a revised version of the manuscript should address the following points:

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. To illustrate the increased rate of either CPD or 6-4PP lesions upon UVB-irradiation a dose-response curve should be provided in Fig. 1 rather than showing the relative number of lesions for a single dose of 300 J/m2.
2. In Fig. 2A a control for equal loading, i.e. re-probing with an antibody against actin, should be added.
3. In Fig. 4 the relative number of cells in each phase of the cell cycle (G0/G1, S and G2/M) should be given (i.e. within the histograms or as a separate table) to quantify the induction of cell cycle arrest upon pTpT. Also the number of sub-G1 cells should be indicated. A positive control for induction of apoptosis, i.e. treatment with FasL, should be included.
4. A hallmark of apoptosis is the exposure of phosphatidyl-serine on the outer leaflet of the cell membrane. Furthermore, apoptosis involves the cleavage and activation of caspases. The authors should consider to provide such data to confirm the induction of apoptosis upon UV-irradiation and rescue from apoptotic cell death upon reconstitution with 6-4PL (and CPD-PL).

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
1. Within the text (page 10, last line) the table showing apoptosis rates upon UVB irradiation in control, 6-4PL, CPD-PL or 64-PL/CPD-reconstituted cells is designated Table 1. In the Figure legends (page 18) it is termed “Table 3.1”. This should be corrected.
2. The authors should re-check page numbers; page 19 is missing in the present version of the manuscript.

Discretionary Revisions (which the author can choose to ignore)

What next?: Accept after minor essential revisions

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

I declare that I have no competing interests