Reviewer's report

Title: Decreased transcription-coupled nucleotide excision repair capacity is associated with increased p53- and MLH1-independent apoptosis in response to cisplatin

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Reviewer: RICKY A SHARMA

Reviewer's report:

The manuscript “Decreased transcription-coupled nucleotide excision repair capacity is associated with increased p53- and MLH1-independent apoptosis in response to cisplatin” presents novel results in clear manner. The results relating to apoptosis are convincing, but of limited relevance on their own. I believe the manuscript would be acceptable for publication with the following revisions, which I have outlined below.

Minor Revisions:
1. Since more than one method was used to assess apoptosis, it would be helpful if the methods used to assess the levels of apoptosis were referred to in the presentation of results, perhaps with the reason for that assay or corroboration by alternative assays. Several of the Westerns are overexposed and may need to be rerun with less protein to reach publication standard.
2. It is not clear why Ku86 was selected as a loading control
3. What is the starred band on the MLH1 blot shown in figure 3?
4. In the Discussion, why do the authors think the p53-null cells have faulty repair of the UV adducts in the HRC assay. How do the data compare to those of previous publications?
5. Does CSB knock-down sensitise the different versions of the HCT116 cell line to a similar extent?
6. The investigators should consider corroborating certain results using an alternative siRNA sequence, e.g. one targeted at a DNA repair pathway not involved in TC-NER. I would suggest one of the backup non-essential BER proteins.

Major Compulsory Revisions-
1. The authors do not discriminate clearly between drug sensitivity and drug resistance. The two concepts are not synonymous. The authors should review the terminology used in the abstract and main text, particularly on page 14 when they refer to “recurrence of resistant disease.”
2. Based on assays of cell death, the authors state D50 values and claim that “targeting TC-NER may represent a means of increasing the responsiveness of tumours to cisplatin.” Acceptance of this manuscript requires at least some
degree of corroboration of the cell death endpoints by either metabolic assay results (e.g. MTT assay) and IC50 values or, preferably, clonogenic assays.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

'I declare that I have no competing interests'