Reviewer’s report

Title: Sequential decitabine and carboplatin treatment increases the DNA repair protein XPC, increases apoptosis and decreases proliferation in melanoma.

Version: 0 Date: 14 Aug 2017

Reviewer: Aaron G. Smith

Reviewer's report:

Overall the data is solid, however a few minor points outlined below should be addressed by the authors.

Figure 1. I think it is important that these experiments are accompanied by XPC protein analysis by western blotting.

Figure 1. Have the authors analysed XPC levels and associated methylation of the CpG island using primary melanocytes, and moreover the response to decitabine. This is particularly important if the central tenet of the paper is that methylation at the CpG island or additional site is responsible for low levels of XPC and hence impaired GG-NER in melanoma.

Figure 4. I assume these data are lacking statistical analysis as at least Me4405 and Mel-RM would appear to be significant. The poor/lack of response of the Sk-Mel-28 line would suggest it is a good candidate for exogenous over-expression studies to further support a role for XPC in the observed sensitisation to Carboplatin (see comment below).

Figure 5. I would suggest that all lines should be independently shown in panel A rather than pooled.

Figure 5 (B). Why has only the dual treatment been shown in this figure. The vehicle and single agent controls also need to be reported here and quantification of senescence performed.

Figure 6B. As for Fig 5B it is important to show all controls (vehicle and single agent).

Figure 6. Given the effect of XPC knockdown on apoptosis and cell viability is modest, despite robust attenuation of XPC induction, the effect of exogenous expression of XPC expression would be useful to clarify if the effects that are being observed are indeed related to XPC expression. Given the Sk-mel-28 line was the only line in which decitabine did not induce XPC and was refractory to increased apoptosis in response to decitabine/carboplatin treatment, it would seem like a good line to chose for such an experiment.
General comment: As GG-NER is also pivotal to the repair of UV induced DNA lesions have the authors tested the effect of decitabine treatment of the response and resolution of UV induced CPD's and/or 6-4-photoproducts? The inclusion of such data would strengthen the argument that the increased sensitivity of the cells to DNA damage was directly related to restored NER capacity.

General comment: MITF is central to melanoma proliferation and viability and even the DNA damage response. Was the expression of MITF examined to preclude it from being responsible for the carboplatin sensitisation observed in figure 4, given that XPC siRNA knockdown in Figure 6 only had a minor effect on the apoptotic response?

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

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