Reviewer's report

Title: Modulation of Ras Signaling Alters the Toxicity of Hydroquinone, a Benzene Metabolite and Component of Cigarette Smoke

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Reviewer: Tiziana Venesio

Reviewer's report:

In the present manuscript, North and collaborators provide findings supporting the role of both NF1 and Ras signalling in the modulation of hydroquinone toxicity involved in myeloid disease development.

Data are novel and can provide interesting insights on hydroquinone-molecular induced toxicity, however some results need to be furtherly investigated.

Major essential revisions:

Results Section:

Paragraph "Modulation of Ras signaling in yeast alters the toxicity of hydroquinone".

1. Based on results reported in figure 1(1B and 1C) the authors support the hypothesis that in yeast deletion of Ras1 results into an increased tolerance to HQ treatment, whereas deletion of Ras2 has no effect. Although in case of ras2 there is no statistically difference between wt and ras2 deleted strains, at the highest HQ concentration there is the same tendency found in the case of ras1 deleted strain. It could be helpful to compare directly ras 1 and ras 2 deleted strains.

2. The presence of ras1 and 2 deletion as well as ras overexpression should be shown.

Paragraph "Increased genotoxicity is seen in murine bone marrow cells lacking Nf1 following HQ treatment.

Murine bone marrow cells lacking Nf1 showed a higher MN formation in PCEs than the controls. This difference is particularly significant at 50 uM HQ. The authors have considered that at higher HQ concentrations there could be a toxic effect?"

Paragraph "Murine bone marrow progenitor cells lacking Nf1 show increased proliferation relative to WT following treatment with HQ"

Nf1-/- progenitors demonstrated increased survival to HQ exposure in comparison to WT (Fig3). The authors suggest that the proliferative effect could be achieved via ERK1/ERK2. It would be necessary to demonstrate the activation of the MAPK pathway in these cells by western blot or, at least, by immunostaining
Minor Essential Revisions.

Results
Paragraph "Increased genotoxicity is seen in murine bone marrow cells lacking Nf1 following HQ treatment.
1. The first three lines should be moved into discussion
2. In line 15 there is a an editing error "control controls".

Figure Legends
1. Figure 1: it would be helpful to explain the meaning of AUC

References
Reference 2: Am J Pathol instead of The American Journal of Pathology
Reference 14: Clin Cancer Res instead of Clinical cancer research etc
Reference 22: the same as above

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
'I declare that I have no competing interests'