Reviewer’s report

Title: Resveratrol abrogates the Temozolomide-induced G2 arrest leading to mitotic catastrophe and senescence in glioma cells

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Reviewer: Renata Cozzi

Reviewer’s report:

The manuscript is certainly interesting and presents a large amount of data that deserve a reorganization to make them more readable. Many results present in the supplementary figures should be retrieved in the canonical figures since they are essential for the overall work.

MAJOR COMPULSORY REVISIONS

1. First of all, how were resveratrol doses chosen? How were treatment times chosen?

2. Results section
   • Page 8 line 3 and Fig1: which TMZ dose reduces cell number? Perhaps 1000 µM but p values are missing both for R and TMZ single treatments
   • Supp Fig 5A and page 8 lines 4-6: TMZ treatment per sè does not show any toxicity in primary glioma cells
   • Fig 2 FigS3 FigS5 and page 8 lines 16: as far as autophagy induction, RT treatment effect seems more likely to be additive with respect to R and TMZ alone

Fig 3a FigS4 and page 8 lines 22-29: The authors state that “resveratrol did not alter cell cycle distribution……… “, but in R treated samples DNA profiles are quite different from control ones!!!. On the other hand from literature data it is well known that in cancer cells R treatment is able to cause cell cycle delay both at G1/S transition and during S progression (eg. Ahmad et al, Clin Cancer Res 2001 ;7:1466–1473. Larrosa et al, J Agric Food Chem 2003;51:4576–4584. Leone et al, Mol Carcinog 2008 ;47:587–598)

   • Fig 3B how was “DNA damage index” on Y axis calculated since the scoring of damage was performed as “arbitrary value range from 0-4”?

   • Fig3C how do the authors explain the slight induction of #H2AX, ATM and Chk2 after R treatment?

   • Fig 4C what on X axis? And on Y axis? Page 9 lines 26-27: how do the authors explain the presence of micronuclei after R treatment?

Page 9 lines 32-34 and Fig 4C: R treatment induces a strong (significant??) increase in large nuclei considered by the authors a feature of senescence. Anyway from Fig 5B R treatment does not seem to induce senescence as
measured by SA-beta-gal assay. How do the authors explain this discrepancy? In this regard, the title of the manuscript should be changed avoiding the statement that Resveratrol leads to senescence.

Perhaps the large nuclei are polyploidy cells that together with micronuclei induction could explain the induction of DDR signalling. In other word R treatment induces DNA double strand breaks and chromosome malsegregation in U87 cells through an inhibitory effect on topoisomerase II (see Leone et al, Cancer Letters 295 (2010) 167–172)

• MINOR ESSENTIAL REVISIONS
  o Correct paragraph numbers in Mat and Met section
  o DCFH assay is not described in Mat and Met
  o Page 8 line 3 change “cell number of gliomas” in “number of glioma cells”
  o Fig 3 legend: page 13 line 23: R is missing
  o Fig 3A and Supp Fig 4: the sum (subG1-G1-S-G2) should be 100

DISCRETIONARY REVISIONS
I would suggest to reorganize the figures since it is hard to find data and results as they are currently organized

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’