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: Enrique Castellon

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Manuscript BMC Cancer: Resveratrol abrogates the Temozolomide-induced G2 arrest leading to mitotic catastrophe and senescence in glioma cells. Eduardo C. Filippi-Chiela, et al.

General comment:

This work deal with the potential mechanism by which Resveratrol (Rsv) may potentiate the toxicity of Temozolomide (TMZ) in glioma cells. As authors state, TMZ induces formation of O6-methyl-guanine which impairs DNA replication. On the other hand, O6-methyl-guanine-DNA methyltransferase (MGMT) repairs most of the DNA damage produced by TMZ. Therefore, it is well known that status of expression, activity or promoter methylation of MGMT strongly correlate with TMZ resistance in glioblastoma. In the last years, several drugs and natural compounds (including Rsv) has been studied and proposed as combined therapy in order to potentiate TMZ effects (for updated review see Nakada et al, Front Oncol. 2012;2:98). The strategy for enhancing temozolomide against malignant glioma). It is not clear what is really novel in the present paper. The authors claim that Rsv does not reduce the DNA damage response (DDR), instead, it forces cell to go through the cell cycle inducing mitosis catastrophe. It would be interesting to check the status of MGMT in glioma cells used and evaluate whether Rsv have any effect on it. Even when the author’s hypothesis is interesting, no direct evidence about the actual mechanism of Rsv action is provided. How does Rsv inhibit TMZ-induced cell cycle G2-arrest? This main mechanistic question remains unsolved. Actually, it is not even addressed. Additionally, many flaws should be properly clarified

Specific comments (Compulsory revision):

- In Material and Methods section it is stated that 3 glioma cell lines and a glioma primary culture were used in the study. However, only results from one cell line are showed and discussed. Why those cell lines were chosen? Do they represent different stages of glioblastoma? From which type of glioblastoma was obtained the primary culture?

- In supplementary material, results of other cell lines are provided. This results show differences between cells. This should be properly discussed, indicating other differences between those cells that may explain the distinct responses.

- Supplementary figure 5 is the only one showing primary culture results.
Interestingly, those cells are not responding to TMZ alone (graph A). This should be discussed.

-Figure 1 is difficult to understand. Apparently, there is no statistical difference (at least it is not indicated) between different concentrations of TMZ alone (comparing only white bars). Does it mean that TMZ between 100 and 1000 uM (alone) have no effect on cell number? The same occurs when comparing R30 regarding TMZ different concentrations (comparing all grey bars) and with R100 (comparing all black bars). Multi-group tests should be used.

-A similar situation occurs when analyzing figure 2 B.

-References should be updated and carefully revised. For example reference 28 has nothing to do with resveratrol effects on prostate cancer. Ref. 29 has no relation with Rsv and melanoma.

-Discussion, including the above questions, should be extensively improved.

**Level of interest:** An article of limited interest

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I have no competing interests