Reviewer’s report

Title: Valproic acid-induced amphiregulin secretion confers resistance to temozolomide treatment in human glioma cells

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Reviewer: Wenli Cui

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Major concerns to be addressed

1. As commented above, all the in vitro experiment results got from U87 cell line had better be recapitulated in another different glioma cell line to cement. please make full explanation if unable to do it;
2. In figure 1A, the present histogram actually can't reflect the times of experiment as stated by the authors. if possible, it would be suggested that the current figure 1A whose data should be re-plotted using Graphpad Prism 8.0 version which provided the different histogram choice that can fix my concerns;
3. In figure 1C and 1D, the MWs of cleaved PARP and caspase-3 needs to be labeled; by the same token, the figure 4B, 4D and 4F whose MWs also need to be given;
4. Still in figure 1C and 1D, the concentration of VPA and TMZ when treating was as high as 500um, which far beyond the normal physiological concentration that normal or tumor cell can bear. Please make explanations for why did you select such high working concentration in the study?
5. In figure 2A histograms, where did the error bars go?
6. In figure 2B, the variation of blot of AR needs to be quantified; the same holds true for figure 3A, figure 4B, 4D and 4F;
7. Still in figure 2A, among the four differential proteins that were dramatically up-regulated upon the treatment with VPA in U87 cells, why did you cull the AR instead of the other three cytokines whose increasing folds were almost same as that of AR?
8. all the main findings from in vitro cell line had better be borne out using xenograft mouse model;
9. moreover, the correlation between AR level on clinical tissues and chemoresistance were supposed to be performed; otherwise, the study was at most suggestive rather than conclusive.

Minors to take heed of

1. at the start of abstract, please have in mind that GBM was abbreviation for glioblastoma multiforme instead of glioblastoma;
2. the introduction was a little longer than it should be;
3. in the case of sensitivity, CCK-8 was far more higher than both MTT and XTT, which needs to be heeded of;
4. in statistical analysis, the authors sometimes used SD, then used SEM, please make consistent;
5. The limitations of the study from the outset, such as number of cell lines, shortage of animal model, etc should be noted at the tail of discussion.
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.
No

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