Reviewer's report

Title: The Critical Role of ERK in Death Resistance and Invasiveness of Hypoxia-selected Glioblastoma Cells

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Reviewer: Candece L. L Gladson

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In this manuscript the authors selected for malignant glioma cells that survive hypoxia and show they are more invasive and have increased levels of phospho Erk. They also show that inhibitors of Erk block the increased invasive phenotype in the hypoxia selected cells and a promoter of Erk activation promotes the invasive phenotype in the parent cells. Supporting their results the authors show that in the hypoxia selected cells there are increased levels of pro-survival proteins and decreased levels of pro-apoptotic protein. Overall the manuscript is interesting; however, there are several questions regarding the data and the presentation of the data that need to be addressed. These concerns are listed below.

Major Compulsory Revisions:

1. In figure 1 and all blotting/gel data the authors need to show molecular weight markers and the relative size of the indicated band. In addition in Panel B of Fig 1 the authors need to indicate if this is cleaved PARP or total PARP.

2. The authors need to show the blots for figure 2. It is helpful to summarize the data in a bar graph and these could be left in.

3. In figure 3 the authors need to specify either in the results section or methods what is the IC50 for each of the Erk inhibitors used and then detail in the figure legend the concentration of the inhibitor relative to the IC50 (i.e. 2-fold the IC50). Also in figure 3 is PMA activating PKC and resulting in increased Erk activity?

4. The authors need to specific for the invasion assay how many replicas they used for each condition and how many times the experiment was repeated.

5. It looks like the immunohistochemical stain in Fig 5 is nuclear. If this is correct the authors need to shown a serial section for each tumor that is stained with hemotoxin and eocin to help the reviewer.

6. The authors need to define each abbreviation in the manuscript someplace.

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.