Reviewer’s report

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

Version: 2 Date: 25 November 2008

Reviewer: Candece L. L Gladson

Reviewer’s report:

In this revised manuscript the authors have satisfactorily responded to the vast majority of the prior reviewers’ criticisms. They have performed additional experiments and incorporated them into the manuscript. The manuscript shows that hypoxia-selected glioblastoma cells are more resistant to apoptosis and have altered expression of apoptotic regulatory proteins, as well as increased activation of Erk. Furthermore inhibiting Erk activation with a small molecule inhibitor or downregulating it with siRNA causes an increase in cell death, suggesting Erk is necessary for this increased survival. Also, the authors show that the hypoxia-resistant glioblastoma cells are more invasive through Matrigel, and blocking Erk activation or downregulating Erk with siRNA inhibits the increased invasiveness. Lastly the authors demonstrate an increase in the number of glioblastoma cells expressing pErk and a marker of hypoxia, as compared to low grade tumors. This is an interesting manuscript with novel findings. There remain two small essential revisions that the authors should be able to address and they are listed below.

Minor Essential Revisions

1) Include molecular weight markers on the gels and indicate the relative migration of bands; this was requested previously.

2) The authors need to show in figure 7 a serial section stained with H&E to determine if pErk and a hypoxia marker are expressed in tumors cells or stromal cells (blood vessels or reactive astrocytes).

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.