Reviewer's report

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

Version: 1 Date: 26 August 2008

Reviewer: Harun Said

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Major Compulsory Revision

The authors showed there results using on the cell type namely T98G. Although their results are interesting and also represent an important contribution to the development of cancer treatment approaches, we feel that performing comparative experiments with another glioblastoma cell line that bear other characteristics like GaMG (Akslen LA, Andersen KJ, Bjerkvig R, Anticancer Res. 1988) can give clear conclusive evidence for their finding. If necessary we are ready to provide the research group with that cell line.

Minor Essential Revisions

Within the classification in Table 1 of the manuscript, where a comparison of p-ERK expression in different tumour grade in astrocytic glial tumors was shown, here they should divide analysed samples when plotting it against WHO grade in all four stages of human glioma, since oligodendrome (stage I) has completely different characteristics than stage II and can not be “pooled” together. The same is true for stage three and stage four.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

Kim YJ and his co-workers submitted their research data in this manuscript entitled “The Critical Role of ERK in Death Resistance and Invasiveness of Hypoxia-selected Glioblastoma Cells” to be published in BMC cancer.

It is well known that tumour parenchyma rapid growth leads to chronic hypoxia resulting in the cancer cells selection bearing more aggressive survival and
proliferation behaviour and death-resistant.

Also, identification of key molecules and molecular mechanisms that are responsible for the phenotypic changes associated with chronic hypoxia has valuable implications for the development of a therapeutic modality.

Kim and his co-workers aimed from their study to identify the molecular basis of the phenotypic changes triggered by chronic repeated hypoxia.

In order to accomplish that, they selected hypoxia-resistant T98G cells by repeated exposure to hypoxia and reoxigenation. They determined cell death rate that was by the trypan blue exclusion method and protein expression levels were examined by western blot analysis. Invasive tumour cells phenotype determination was accomplished by the Matrigel invasion assay. Immunohistochemistry analysis was performed to analyze the expression of proteins in the brain tumour samples.

The research group could show that repeated episodes of exposure to hypoxia and normoxia change T98G cells to HRT98G cells that have a more death-resistant and invasive phenotype. As compared with parent cells, HRT98G cells express higher levels of anti-apoptotic proteins such as bcl-2, Bcl-XL, and p-ERK.

Also, the activation or suppression of ERK pathways with a specific activator or alternatively an inhibitor demonstrated that ERK is a key molecule responsible for the death resistance associated with hypoxia and a more invasive phenotype.

Also they were able to show that ERK activation is more common in high grade astrocytic glial tumours exposed to hypoxia than in low grade tumours.

Although their results are helpful for the development of appropriate cancer treatment modalities that act effectively, following minor concerns should be addressed:

1. They showed their results using on the cell type namely T98G. Although their results are interesting and also represent an important contribution to the development of cancer treatment approaches, we feel that performing comparative experiments with another glioblastoma cell line that bear other characteristics like GaMG (Akslen LA, Andersen KJ, Bjerkvig R, Anticancer Res. 1988) can give clear conclusive evidence for their finding. If necessary we are ready to provide the research group with that cell line.

2. Within the classification in Table 1 of the manuscript, where a comparison of p-ERK expression in different tumour grade in astrocytic glial tumors was shown, here they should divide analysed samples when plotting it against WHO grade in all four stages of human glioma, since oligodendrome (stage I) has completely different characteristics than stage II and can not be “pooled” together. The same is true for stage three and stage four.

Therefore, I recommend publishing this manuscript submitted by Kim et al, in
BMC Cancer after fulfilling these minor changes. Since the findings are considered as a genuine contribution therefore I advise the editorial board of BMC cancer not to reject this manuscript.

Also I would like to wish this study group a lot of success in completing the experiments needed for the revision process and also in their future studies.

Dr. Harun Said

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