CNS 2018 ANNUAL MEETING
HOUSTON, TEXAS
OCTOBER 6-10, 2018

Identification of Radiation Responsive Genes and Transcriptome Profiling Via Complete RNA Sequencing in a Stable Radioresistant Glioblastoma Model

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Introduction

Current treatment paradigm for glioblastoma (GBM), comprising of surgery, radiotherapy, and chemotherapy is associated with dismal overall survival and high rates of tumor recurrence. The lack of progress in improving treatment efficacy partly stems from limited understanding of the underlying mechanisms behind radiation induced resistance in GBM cells. The present exploratory analysis utilizes RNA sequencing to characterize the impact of irradiation on global mRNA expression.

Methods

To perform the analysis, U87 glioblastoma cell line was irradiated to produce U87-10gy cell line, which was followed by allowing the irradiated cells to grow to confluence for 1 month to generate a stable radioresistant GBM model. Total RNAs from U87 and U87-10gy were then harvested, followed by transcriptome profiling via RNA sequencing. To identify radiation responsive genes, twofold change or greater in mRNA expression levels between U87 and U87-10gy was the selected criteria. Finally, gene ontology analysis was performed to categorize genes based on their functions.

Results

The exploratory analysis revealed upregulation of genes involved with enhancing tumor malignancy and invasion such as BNIP3, MMP3, MMP7, MMP15, TGFBI, NOTCH2, AKT1, AKT3, TNFAIP3, RRM2, CXCL8, FOXM1, HMOX1, PRMT5, KDM2B, CERS6, SPHK1, ZBTB18, and PDK1 (Table 1). In contrast, genes associated with negative regulation of cell survival such as S1PR1, PARP15, HOXA11, and ADGRG1 were downregulated (Table 2).

Learning Objectives

1.Appreciate the role of stable radioresistant glioblastoma cell lines in exploratory analysis to improve current understanding of genetic alterations underpinning treatment resistance in recurrent GBMs.

2.Understand for utility of total RNA sequencing in documenting molecular mechanisms in a radiation resistant GBM model with translational implications.

3.Evaluate changes to global mRNA expression of radiation responsive genes that might be enabling GBM cells to acquire resistance to radiation in recurrent GBMs.

Conclusions

Using an established stable radioresistant GBM model, the present study sheds light on global mRNA expression changes after irradiation. The findings of serve to improve current understanding of the molecular mechanisms associated with radioresistance in GBM and call for further investigations into the role of these differential mRNA expressions in acquiring radioresistance.