Inhibition of FGFR1 downregulates stemness, epithelial-mesenchymal transition associated genes and sensitizes glioblastoma tumor spheres to radiotherapy.

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Purpose: Glioblastoma (GBM) is the most malignant brain tumor with very limited therapeutic options. Standard multimodal treatments, including surgical resection and combined radio-chemotherapy do not target the most aggressive subtype of glioma cells, glioblastoma stem cells (GSC). GSCs are thought to be responsible for tumor initiation, progression, and relapse. Furthermore, GSCs have been associated with the expression of mesenchymal features as a result of epithelial-mesenchymal transition (EMT) thereby inducing tumor dissemination and radio-chemo resistance. We have previously demonstrated that FGF-2 controls cells radioresistance and that expression of FGFR1 in the tumor of patients with GBM was an independent prognostic factor of overall survival and time to progression after radio-chemotherapy.

Experimental Design: The aim of this work was to investigate the specific role of FGFR1 in patient-derived GBM cells (GC1 and GC2) cultured as neurospheres.

Results: Silencing FGFR1 significantly increased in vitro cells sensitivity to ionizing radiation shown by 3D clonogenic assay. Moreover, FGFR1 inhibition enhanced significantly the radiation-induced cell death. In accordance with clonogenicity data, FGFR1 knockdown combined with irradiation resulted in the significant increase in the subG1 cell population compared to the control. Moreover, the expression of an oncogenic transcription factor implicated in GBM stem cell maintenance and radioresistance FoxM1 was determined by qPCR and western-blot, and was significantly reduced in silenced FGFR1 cells. We also tested the influence of FGFR1 or FoxM1 downregulation on the expression of EMT associated genes. We found that FGFR1 or FoxM1 inhibition caused a strong reduction of Zeb1, Twist1, and Gli2 in GC1 and GC2. In the GBM stem-cell like GC1 and GC2, the effect of FGFR1 and FoxM1 inhibition on the expression of neural stem cells markers was assessed by qPCR and shown a decrease in expression of Nestin and Musashi-1. Moreover FGFR1 or FoxM1 inhibition induced a significant decrease in migratory ability of the cells.

Conclusion: Our data establishes the proof-of-concept of FGFR1 inhibition as a new treatment for radiosensitizing these aggressive tumors. Considering that we previously showed that FGFR-1 expression in GBM patients is an independent prognostic factor of survival and time to progression after radio-chemotherapy, our present study highly suggests the interest to associate a FGFR1 inhibitor which affects stemness and invasive properties of GBM with radiotherapy in clinical trials for patients with glioblastoma.