Glioblastoma Mesenchymal to Proneural Reprogramming by targeting a Pro-Invasive Network of Genes (PING) as novel strategy in personalized care

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Introduction

Mesenchymal Glioblastoma (M-GBM) is known to be the most aggressive and invasive form of Glioblastoma (GBM). Identification of molecular mechanisms driving the invasive phenotype is of considerable interest for a targeted molecular therapy in GBM patients. By utilizing a radiogenomic approach we have previously described a gene network responsible for GBM invasion. The purpose of this study was to uncover and validate this gene network's role in driving GBM in vivo oncogenic properties and its use toward personalized care in GBM.

Methods

PING was identified using radiogenomic FLAIR, MR perfusion/diffusion mapping and validated in two independent national genomic databases (Rembrandt/TCGA). A panel of GBM Stem Cells (GSC) and GBM cell lines (Proneural, Classical and Mesenchymal subgroups) were analyzed for PING status by RT-PCR and Western blotting. Gain (lentiviral expression vectors) and loss (SMARTchoice Inducible shRNA) of function for PING status genetic master regulators (POSTN/CEBPB) was assessed. Self-renewal (limiting dilution assay), Proneural shift (Tuj1+ve, O4+ve, GFAP+ve cells), invasion (Boyden chamber assay), and proliferation (BrdU labeling) were analyzed. Total GSC RNA was used for expression profiling by microarray. Orthotopic xenograft models characterized PING alteration in vivo.

Results

Altering PING in GSC results in significant impact on various cellular properties including invasion in vitro and in vivo. Additionally, quantitative RNA and protein analyses shows that PING expression is associated with in vitro and in vivo mesenchymal to proneural class switching. Cmap derived FDA approved drugs significantly inhibit GSC invasion.

Conclusions

We have uncovered the gene network PING as key mediator of GBM invasion. Additionally, PING alteration can be a novel personalized treatment strategy leveraging GBM therapeutic cellular reprogramming.

Learning Objectives

By the conclusion of this session, participants should be able to: 1) Describe the importance of the described network on the outcome in Glioblastoma, 2) Discuss, in small groups, how these findings will influenced personalized Glioblastoma care 3) Identify an effective treatment, respecting the role of the introduced gene network.