Glioma Stem Cells Driven by Distinct BMI-1 and EZH2 Transcriptional Pathways Targeted Separately or Synergistically

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Introduction

Glioblastomas (GBMs) are lethal cancers characterized radiologically and histologically by enhancing, angiogenic margins, and necrotic centers with pseudopallisading necrosis.

Methods

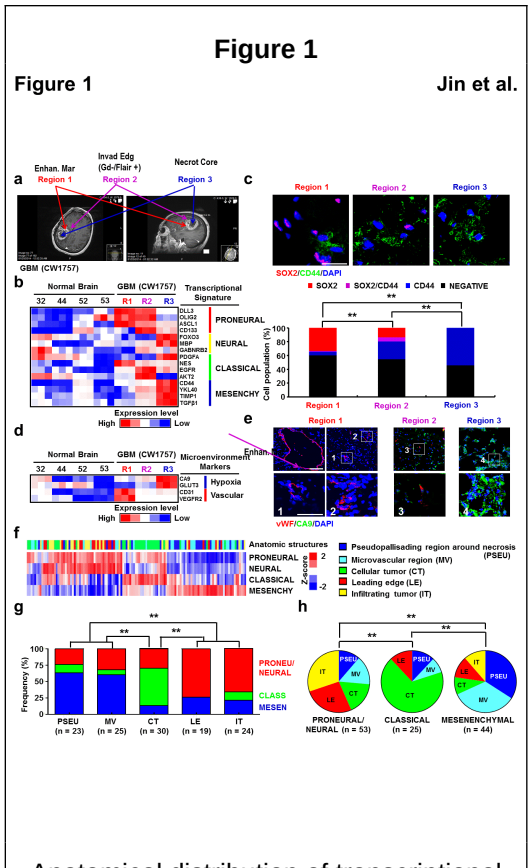
We collected tissue from various anatomically and histologically distinct regions of several human GBMs, annotating the source of each specimen using an IRB-approved protocol. We then characterized these histologically distinct regions according to their distinct histologic, transcriptional, and metabolic profiles in vitro as well as in pre-clinical murine models under an IACUC-approved protocol. We also studied the effect of non-FDA approved agents in our murine model. (This will be disclosed).

Learning Objectives

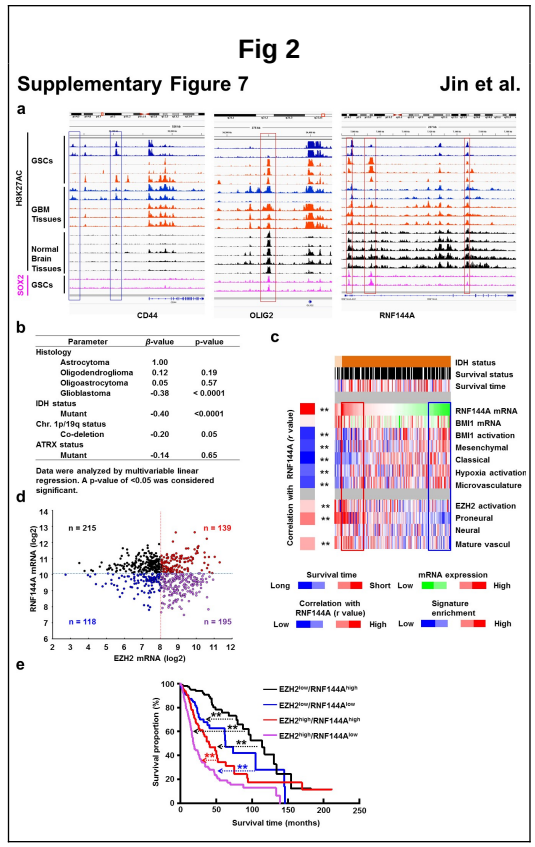
By the conclusion of this session, participants should be able to better describe: 1). the relationship between radiographically distinct tumor regions and various stem cell niche as well as; 2). the molecular and 3). phenotypical characterstics of these niche and 4) how to target them

Results

Both the enhancing margin and the necrotic core harbor distinct populations of glioma stem cells (GSCs). The enhancing regions were characterized by a proneural profile, while the hypoxic regions demonstrated a mesenchymal pattern. We thus investigated the epigenetic regulation of these two niches. Proneural, perivascular GSCs activated Olig 2 via EZH2 ($p < 0.002$). In contrast, mesenchymal GSCs in hypoxic regions expressed high levels of Glut 1, Glut 3, MCT 1, and MCT 4, and HIF1a via BMI1 protein, which promoted cellular survival under stress due to down regulation of the E3 ligase RNF144A ($p < 0.02$). Using both genetic and pharmacologic inhibition, we found that proneural GSCs are preferentially sensitive to EZH2 disruption, whereas mesenchymal GSCs are more sensitive to BMI1 inhibition ($p < 0.01$). Interestingly, since GBMs contain both proneural and mesenchymal GSCs, combined EZH2 and BMI1 targeting proved more effective than either agent alone both in culture ($p < 0.008$) and in vivo ($p < 0.04$).



Anatomical distribution of transcriptional profiles in glioblastoma.



Conclusions: Strategies that simultaneously target multiple epigenetic regulators within the same GBM may be synergistic in overcoming therapy resistance caused by intratumoral heterogeneity and interconversion of cells from one transcriptional subtype to another. This strategy may also be useful in combination with conventional treatment.

Reference: JinX, Kim JLY, Wu A, Wallace LC, Prager BC, Sanvoranart T, Gimple RC, Wang X, Mack SC, Miller TE, Huang P, Valentim CL, Zhou Q, Barnholtz-Sloan JS, Bao S, **Sloan AE***, & Rich JN*: Nature Medicine Published online 09 October, 2017.