Progression types after antiangiogenic therapy are related to outcome in recurrent glioblastoma

Bevacizumab’s effects on contrast enhancement in high-grade glioma have created new challenges in determining tumor progression, eventuating in the adoption of the new RANO criteria. Moreover, animal models demonstrate that bevacizumab predisposes to development of a more invasive tumor phenotype characterized by T2/FLAIR signal abnormality distant from the original site of tumor. The frequency of this occurrence in human glioblastoma and its relationship to antiangiogenic treatment have been debated.

The retrospective study of Nowosielski et al characterized patterns of progression in 83 glioblastoma patients receiving bevacizumab for recurrent disease. The patient population was fairly typical. Tumor progression was separated into four categories based upon MRI patterns. Patients who had an initial favorable response to bevacizumab but later progressed with more contrast enhancement were characterized as “cT1 flare-ups”. A 2nd group, “primary non-responders”, were defined as patients who failed to demonstrate reduced contrast enhancement on initial post-bevacizumab imaging. The final two groups showed post-bevacizumab reduction in contrast enhancement but had T2 progression. The “T2-diffuse” group manifested progressively expanding T2 signal abnormality exceeding anatomic boundaries of T1 hypointensity with associated mass effect, while the “T2-circumscribed” patients had bulky T2 progression with sharp borders corresponding to the T1-hypointense signal.

Overall, 32/83 patientts (39%) had T2-only radiographic progression, and T2-only progressors were fairly evenly split into the T2-diffuse and T2-circumscribed groups. Time to tumor progression was longer in T2-diffuse and cT1 flare-up patients than T2-circumscribed progressors (median 4.5 and 5.1 mo versus 1.8 mo). T2-diffuse progressors had a significantly longer overall survival after starting bevacizumab than cT1 flare-ups, primary non-responders, and T2-circumscribed patients (17.7 vs 10.2 vs 4.9 vs 5.0 mo, p < 0.001). The T2-diffuse and cT1 flare-up patients also survived longer after progression on bevacizumab was diagnosed. Interestingly, the time from initial diagnosis to starting bevacizumab was significantly longer in the T2-diffuse group (20 months versus about one year in the other groups).

The authors suggest these four patterns are related to clinical course and also potentially to the mode of bevacizumab resistance. Their observation that 18% of patients fall in the T2-diffuse group supports other studies suggesting distant or diffuse recurrence at the time of progression is not more common with anti-VEGF than non-anti-VEGF regimens. They hypothesize that patients in the T2-diffuse group may have a different biology from the start, as they have a longer interval from diagnosis to bevacizumab initiation. They emphasize the importance of recognizing T2-circumscribed progression since it tends to develop shortly after bevacizumab initiation and has poor overall survival.

While these findings, observed retrospectively on a fairly small patient population, require validation, the percentage of patients with T2-only progression fuels the argument to include T2/FLAIR measures with the more traditional contrast enhancement in determination of glioblastoma response to therapy.

Highlights from the Literature

Contributed by: David Schiff, E. Antonio Chiocca, Krishna Bhat, and Eric Sulman

Edited by: Kenneth Aldape

Reference

Reprogramming glioblastoma cells to a stem-like state – mechanistic insights & therapeutic opportunities

While research efforts in recent years have improved our understanding of GBM pathogenesis, the genetic heterogeneity inherent to GBM lesions continues to complicate the picture and is a major obstacle for targeted therapy. This genetic diversity exists both between tumor types and also between cells in the same tumor, only a fraction of which are capable of tumor propagation. This raises the question of whether these phenotypically distinct cell populations arise de novo simply as a result of the genetic instability within GBM tumors, or whether they represent distinct developmental stages that begin with a population of progenitor tumor cells.

In a recent Cell publication, Suva et al provide compelling evidence for the latter interpretation, modeling GBM as a unidirectional developmental process. Methodologically, the study is predicated on differentiating two phenotypically distinct cell types each derived from human tumors: stem-like tumor propagating cells (TPCs) generated in serum-free conditions and

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differentiated progeny (DGCs) grown in serum as monolayers. Using a functional genomics approach, the study uncovers four key transcription factors (POU3F2, BRN2, SOX2, SALL2, and OLIG2), which, when introduced into differentiated GBM cells, are sufficient to reprogram them into a TPC-like state. Induction of these four factors reactivates transcription of their endogenous loci and results in histone acetylation of their 325 differentially expressed target genes. Phenotypically, TF-transduced DGCs (so-called iTPCs) are indistinguishable from culture-derived TPCs. They effectively regain the ability to form tumors in vivo and can be differentiated back to DGCs when cultured in the presence of serum. To identify possible therapeutic targets specific to the TPC transcriptional program, the authors investigated differentially expressed downstream targets of the four TFs used in the reprogramming cocktail. In particular, they focused on RCOR2 and LSD1, both components of the histone-demethylase complex, shown to be highly enriched in TPCs. Mechanistically, this complex could mediate many of the epigenetic changes observed following TPC induction. RCOR2 could effectively substitute for OLIG2 in the reprogramming cocktail, underscoring its importance as a key mediator of the TF effect. Moreover, inhibition of LSD1 resulted in cell death exclusively in TPCs, and significantly improved survival in a mouse xenograft model of GBM, highlighting its potential utility as a therapeutic target to selectively eliminate progenitor cells.

Taken together, these results suggest the existence of a cellular hierarchy in GBM, in which tumor cells differentiate from a small population of stem-like progenitors. The two-cell type model of GBM pathogenesis adopted here may suggest a hierarchy in which cells only move from stem-like to differentiated phenotype. However, the possibility of retrograde de-differentiation has not been ruled out. The conversion from DCG to TPC with the introduction of four key TFs suggests greater cellular plasticity between phenotypes, which could occur in specific clinical contexts. Because the cell types used in this analysis were generated in vitro, it is unclear to what extent the tumor microenvironment may influence these genetic programs and the direction of the differentiation process. More importantly, by using only proneural subtypes for the study, the importance of these TF-mediated genetic programs in other categories of GBM requires additional investigation. Despite these methodological limitations, this work provides compelling evidence for a core set of TFs that define a population of tumor progenitor cells in this model of GBM, and identifies a promising new therapeutic target, LSD1, with the potential to selectively kill this population of cells that is likely responsible for much of the resistance to therapy and ultimately the poor prognosis for patients with newly diagnosed GBM.

Reference

In vivo radiation response of proneural glioma characterized by protective p53 transcriptional program and proneural-mesenchymal shift

Radiation-induced p53 response and a parallel proneural to mesenchymal transition in GBM. Patients afflicted with GBM are treated with ionizing radiation (IR) and concurrent chemotherapy following surgery. Despite this aggressive treatment modality, the tumor recurs within a few months and in many cases at the very site of irradiation. Previous work using human GBM specimens have shown that tumors that present with a proneural (PN) transcriptome signature tend to shift to a mesenchymal (MES) pattern upon recurrence. Although subsequent studies have identified master transcriptional regulators that drive this transition, if these signatures are exclusively a feature of tumor cells and the influence of IR on these signatures is not known.

Using a PDGF-B driven transgenic mouse model of PN glioma, Halliday et al, report an in vivo mechanistic evidence of a PN to MES transition (PMT) in GBM in response to radiation. Treating these mice with single dose of 10 Gy IR caused apoptosis almost exclusively in the tumor bulk enriched with Olig2+ cells. Importantly since PDGF contained an HA tag, the authors showed that the HA+ cells and Olig2+ cells co-localized and cell death was primarily restricted to these cell types. To study the global gene expression patterns post-radiation, they induced PDGF driven gliomas in Olig2 knock-out mice in which, both transcripts that are enriched in ribosomes as well as those that are more efficiently translated could be studied simultaneously. In this model, the authors found that the total transcript levels were significantly altered upon exposure to IR rather than their translational efficiency even when PTEN was silenced. Amongst all transcripts examined, the primary gene categories that were upregulated included those involved in apoptosis, cell cycle arrest as well as growth factors and cytokines. Conversely, only a handful of genes that were downregulated were those involved in oligodendrocyte differentiation.

Since induction of large number of genes requires recruitment of transcription factors (TFs) to gene promoters, gene set enrichment analyses (GSEA) was performed to identify TFs whose binding motifs were enriched. The authors found that p53 and E2F family target genes were dominant after exposure to IR especially in gliomas that were Ink4a/Arf-/- . The p53 protein was localized in the nucleus following IR exposure and silencing p53 reduced survival in mice, and importantly canceled the expression of a vast majority of genes that were induced upon radiation implicating p53 as a master TF of the radiation response. The authors subsequently examined the global alteration of PN and MES genes as defined by the TCGA study and found marked reduction of PN and a gain of MES transcripts following radiation. Importantly this shift was seen in Olig2+ tumor bulk and occurred within 2h of IR exposure implying that PMT indeed occurs in the tumor cells and was due to an increase in the MES gene expression pattern rather than enrichment of these sub-populations given the short time within which this transition occurs. Finally the authors examined the contribution of p53 to this transition and found that unlike the other responses to radiation, PMT occurred in a p53-independent fashion in these tumors.

With previous studies demonstrating that MES glioma cells are radio-resistant, the study by Halliday et al further emphasizes the importance of understanding the plasticity of transcriptomic signatures and their contribution to radiation resistance. Furthermore, it has become apparent that both cell intrinsic and extrinsic mechanisms may contribute to PMT and future clinical trials that incorporate radiation must take these findings into consideration.
An observational study with stereotactic radiosurgery for patients with multiple brain metastases

Brain metastases are a frequent consequence of metastatic solid tumors and represent a primary focus of neurosurgical and neuro-radiation oncology efforts. Historically treated with whole brain radiation (WBRT), awareness of the toxicity from WBRT, including neurocognitive decline, has increased as survival times have improved for patients. Initially an adjunct to WBRT in patients with only a few brain metastases, SRS alone has become a standard treatment for some patients. Current American Society for Radiation Oncology (ASTRO) guidelines state that level 1 evidence supports SRS alone for up to four metastases. Nevertheless, there has been increasing interest in extending this treatment to patients with larger numbers of tumors.

In the report by Yamamoto and colleagues, nearly 1,200 patients with up to 10 brain metastases were enrolled in a prospective observational study of SRS alone conducted in 23 centers in Japan using Gamma Knife for treatment delivery. The primary endpoint of this non-inferiority trial was overall survival between patients with 2-4 metastases versus those with 5-10 metastases. In fact, the study demonstrated an essentially equivalent survival between these groups of patients of approximately 11 months. This non-inferiority persisted even after adjusting for covariates such as tumor type, age, performance status, or control of extracranial disease. To compare the neurocognitive function between the groups, the authors compared results of longitudinal mini-mental status exams (MMSE) and found no difference in the rate of MMSE maintenance between the groups.

Direct comparisons of these results to WBRT may be challenging, as the functional impact on neurocognition was assessed using MMSE rather than more sensitive, objective instruments. In addition, WBRT treatment itself is evolving to address neurocognitive impact, for example by sparing the hippocampus or combining with memantine, a neuroprotective agent. Perhaps as important is a comparison of cost effectiveness between the two modalities. Nevertheless, the landmark study by Yamamoto et al suggests that there may be subsets of patients with four or more brain metastases who may benefit from SRS rather than WBRT. It provides compelling evidence to pursue randomized trials in this patient population, several of which are ongoing in the United States (NCT01592968, NCT01644591, NCT01731704).

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