



Commentary

Therapeutic Injury and Tumor Regrowth: Tumor Resection and Radiation Establish the Recurrent Glioblastoma Microenvironment

Daniel J. Silver^{a,b,*}, Justin D. Lathia^{a,b}^a Cleveland Clinic Foundation, Lerner Research Institute, Cleveland, OH 44195, United States^b Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH 44106, United States

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Glioblastoma (GBM) is a disease derived from multiple interconnected layers of complexity with underlying heterogeneity at the tissue, cellular, and genetic levels. Tumor cells extensively infiltrate brain tissue and insinuate themselves into numerous structures throughout the brain, where they subjugate resident neural cell populations into various pro-tumorigenic interactions [1,2]. GBM tumors also harbor multiple unique and hyper-aggressive cancer stem cell (CSC) subpopulations[3] along with an unknown number of poorly defined non-stem tumor cell (NSTC) populations. The clinical standard of care, introduced over a decade ago, combines maximal safe neurosurgical resection with adjuvant chemoradiation [4]. This essentially palliative strategy effectively removes the primary tumor mass and targets a limited population of highly proliferative tumor cells. However, because this strategy does not sufficiently account for the complexities of GBM, treatment-refractory CSCs are either left behind or emerge into the environment generated after clinical intervention. These CSCs then serve as seeds of disease recurrence and ultimately contribute to patient mortality. Understanding the conditions that drive the emergence and/or retention of CSCs will be critical for next-generation therapies.

For reasons that are still poorly understood, nearly 80% of GBM patients experience disease recurrence around the site of primary clinical intervention. There is something special about the environment generated by the therapeutic injuries of tumor resection and radiation therapy that fosters tumor regrowth. In a recent issue of EBioMedicine,

Hide and collaborators investigated the problem of GBM recurrence as it pertains to this special microenvironment and the induction of the CSC state [5]. By highlighting this unique region, the authors effectively separated the interventional growth zone from the more commonly discussed invasive niche [1,2]. While both the interventional and invasive growth zones are defined by established myelinated fiber tracts, the interventional growth zone specifically refers to the white matter immediately adjacent to the site of surgical resection and within the margin of focused radiation.

Hide and colleagues collected three anatomically defined biopsy specimens from 12 GBM patients to define the cellular composition of the interventional growth zone. Material collected from the leading edge of the primary tumor mass approximated this special microenvironment and was compared to the tumor core and a site distal to the edge of the tumor mass. They revealed significant enrichments in oligodendroglial-lineage cells (OLCs) and microglia specifically within the interventional growth zone. Hypothesizing that these cell types secrete some set of factors that drives the stem cell program and the emergence of CSCs, these authors collected conditioned media from cultured OLCs or microglia and applied it to GBM tumor cells. At the mRNA level, the authors reported increased expression of critical pluripotency-regulating genes from tumor cells cultured under these conditions. Additionally, exposure to OLC- or microglia-derived conditioned media enhanced self-renewal in GBM tumor cells as assessed by *in vitro* sphere formation. The authors then applied microarray analysis to mRNA derived from cultured OLCs or microglia to ascertain the set of factors secreted by these cell types. They reported robust expression of acidic fibroblast growth factor (FGF1) and epidermal growth factor (EGF) from OLCs and heparin-binding EGF-like growth factor (HB-EGF) and interleukin-1 β (IL-1 β) from microglia. When applied to cultured GBM tumor cells in sphere-forming conditions, these individual factors enhanced self-renewal at similar or increased levels compared to those achieved by OLC- or microglia-derived conditioned media. Thus, Hide et al. asserted that resident neural cell types present within the interventional growth zone establish a microenvironment that powerfully drives the CSC program and helps to explain the frequency of recurrent tumors emanating from this site.

Beyond their central conclusions, the importance of generating and comparing these 36 specimens cannot be overstated. At minimum,

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* Corresponding author at: Department of Cellular & Molecular Medicine, Cleveland Clinic Lerner Research Institute, 9500 Euclid Avenue (NC10), Cleveland, OH 44195, United States.

E-mail address: silverd2@ccf.org (D.J. Silver).

these specimens, which complement similar efforts to examine tumor cells [6] and CSCs [7] residing in specific anatomical compartments, represent an invaluable resource for the brain tumor research community. For our clinical interventions to account for the complexities of this disease, we must clarify how GBM tumor cells are instructed and protected by the anatomical spaces in which they reside. Hide and colleagues draw welcome attention to the importance of attending to anatomy when studying the cellular and molecular mechanisms that contribute to GBM progression and recurrence.

There are multiple questions that naturally extend from this characterization of the recurrent GBM microenvironment. To assess the degree to which each of the candidate molecules identified from their screening is critical for disease recurrence, their concentrations must be measured in human GBM specimens. Additionally, repeating the gene expression profiling using OLCs and microglia treated with chemotherapy or exposed to radiation may help to refine and focus our efforts on the most critical of these molecules. From a therapeutic perspective, it will be critical to consider the consequences of developing treatment strategies to interfere with the interventional niche. For example, might successful ablation of the interventional niche result in more distal recurrence of disease? Clearly, careful examination of this and other CSC-enriching niches presents an opportunity to deepen our understanding of this disease and develop new, more durable treatment strategies.

Conflict of Interest Statement

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