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Opinion: Bridging gaps and doubts in glioblastoma cell-of-origin

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Introduction

Glioblastoma (GBM) remains one of the deadliest forms of brain cancer to date, with current patient survival stagnating at 12–15 months with treatment (1, 2). Extensive cellular heterogeneity within these neoplasms results from malignant cells in multiple cellular states that dynamically react to their microenvironment (3–6). The described heterogeneity within and between these tumors is believed to dictate the high treatment resistance and fatality rates of these central nervous system (CNS) malignancies (7–9). Drug screening has revealed significant differences in the response of genetically heterogeneous GSC cultures to cancer therapeutics, marking a significant barrier for establishing a standard of care that universally improves clinical outcomes (10, 11).

Intra-tumoral heterogeneity of GBM has been attributed to clonal evolution—in which accumulation of mutations in the cell of origin leads to the development of multiple, cancerous clones with differing therapeutic sensitivities and ability to survive—as well dynamic interactions between GSCs and their tumor microenvironment that can lead to niches with adaptive changes in their epigenetic landscapes (4, 12–15). While these processes can also contribute to inter-tumoral heterogeneity, the ability of different cells of origin to contribute to this heterogeneity has also been discussed (16–18). Various models of GBM have shown there to be multiple distinct neural/glia populations with oncogenic potential. Furthermore, genetic profiling of these distinct models has shown that transcriptionally active oncogenic programs, and thus, tumor drug sensitivity, is cell of origin dependent (16, 18, 19). Being able to understand and identify these cells of

origin, as well as their effects on the clinical course of GBM patients, could be crucial in developing more effective therapeutics for this patient population. This article aims to review evidence supporting various cell types as cells of origin for GBM, as well as the niche that likely gives rise to these GSCs: the subventricular zone (SVZ).

Evaluation of the candidacy of different stem cell populations as glioblastoma cell of origin

Neural stem cells

Historically, it has been suggested that stem cells are the most likely candidate for a GBM cell of origin given their proliferative capacity (20–23). A recent study, in which *Nf1*, *Trp53*, and *PTEN* mutations were targeted to cells at various stages in the neural stem cell (NSC) lineage, was done to test the tumorigenic capacity of stem cells versus more differentiated cells (24). Targeting mutations of these genes to adult neurons (Cam2ka) and immature neurons (Neurod1) did not show any evidence of oncogenic potential, with immunohistochemistry staining (IHC) showing no tumorigenesis or histological abnormalities. When these mutations were induced in late-stage neural progenitors (iDix), abnormal cell proliferation was noted in the subventricular zone and rostral migratory stream, although no intracranial tumors resulted. This was believed to signify a pre-tumorigenic state. Targeting of these mutations to neural stem cells and oligodendrocyte-precursor cells (Syn-1) alone showed oncogenic potential, with intracranial tumors being observed and histological analysis showing a staining pattern consistent with GBM: positive for GFAP, Olig2, Sox2, PDGFR- α . Visualization of the tumors revealed anatomic similarities to Type II GBM (24). These data suggest that stem cells are most susceptible to oncogenic mutations, making them more likely candidates for a GBM cell of origin than more differentiated cells resistant to tumorigenesis. Various other models have confirmed the ability of mutated NSCs to initiate gliomagenesis (16, 25–27).

The presence of an NSC-like population driving gliomagenesis in GBM has been confirmed *via* time-series analyses of GBM models. Integration of whole-exome sequencing and bulk- and single-cell RNA-seq have identified a population of cycling NSCs in these models that persist throughout the entirety of gliomagenesis, unlike non-cycling and adult NSCs that drop in percentage over time. These cycling NSCs were enriched in mesenchymal-like and OPC-like markers often seen in end-stage GBM, validating their potential role in human gliomagenesis (28).

Oligodendrocyte progenitor cells

The presence of an oligodendrocyte-like signature in end-stage GBM has led to the investigation of OPCs as a possible cell of origin (16, 28, 29). In 2011, Liu et al. initiated p53 and Nf1 concurrently into NSCs. The formation of GFP+ tumors occurred around 5 months of age. In order to determine the cell of origin for these tumors, a ratio of green (mutant) to red (WT) cells was determined for each cell type. OPCs were found to have the largest growth advantage ($G/R > 130$), corroborating the enriched expression of OPC markers (Olig2+, CD9, NG2, and PDGFR α) in this GBM tumors (30). Subsequent analyses have confirmed the presence of a population of OPC-intermediates in GBM patients that are reprogrammed to a stem cell-like state, leading to rapid proliferation and increased oncogenic susceptibility (31).

Given that adult, OPCs proliferate much less than their neonatal counterparts, the oncogenic potential of these more quiescent cells has been studied to validate this much more robust population as a possible origin of GBM. Induction of concurrent p53 and NF1 mutations into adult OPCs by Galvao et al. showed a consistent formation of gliomas. Tracking of these mutated adult-OPCs revealed a multi-step reactivation process, in which an increase in proliferative rate was followed by a period of dormancy that led to eventual gliomagenesis. Hematoxylin and eosin (H&E) staining confirmed the high cellularity and invasiveness of these tumors, which are features typical of GBMs, validating the oncogenic potential of these OPCs (32).

Recent miRNA surveillance of GBM tumors also revealed that oligodendrocyte lineage cells (Olig2+, NG2+, O4+) and macrophages (Iba1+, CD163+) were increased at the border of these tumors, with three of the top miRNAs (miR-219-5p, miR-219-2-3p, and miR-338-3p) in this region relating to oligodendrocyte differentiation (33). Co-culturing TMZ-sensitive GBM cells with conditioned medium (CM) from OPCs and macrophages increased chemotherapy resistance in these cells, resulting in a cell viability increase from 70% to 85% ($p < 0.05$) (33). Such data suggest that OPCs may play an imperative role in not only initiating tumorigenesis but also maintaining the proliferative state of GSCs in GBM patients.

Multiple cells of origin

While a stem cell population is widely accepted as the likely cell of origin, the inter- and intra-heterogeneity seen in GBM provides the possibility of there being more than one cell of origin. In 2011, Lai et al. compared the radiographic, anatomic, and genomic/transcriptomic characteristics of human isocitrate

dehydrogenase mutant (IDH^{R132MUT}) GBMs to isocitrate dehydrogenase wild type (IDH^{WT}) GBMs (18). Analysis revealed that IDH^{R132MUT} GBMs were found to have a significant predominance in the frontal lobe ($p < 0.0001$) when compared to their IDH^{WT} counterpart, especially surrounding the rostral extension of the lateral ventricle. Transcriptomic data confirmed differences between the two groups, as well, with IDH^{R132MUT} GBMs predominantly expressing a pro-neural subtype and IDH^{WT} GBMs—although they were found to have a variety of signatures – expressing a predominantly mesenchymal subtype. This data, in combination with distinct age-frequency patterns between the two types of GBMs, suggests that IDH^{R132MUT} GBMs and IDH^{WT} GBMs are spatially and temporally restricted, and thus, most likely arise from different cells of origin (18). A recent study using multi-omics to characterize the heterogeneity of glioma cells was similarly able to distinguish five-spatially distinct lineage states (glial-related, radial glia/inflammatory, NPC, OPC, and “reactive-hypoxia”) within and between GBM patients (4). Analysis of these niches showed that each spatially distinct population played distinct pro-tumorigenic roles within the GBM tumor, with the “reactive-hypoxia” cells supporting resilience through enhancement of genomic instabilities and the “reactive-immune” cells increasing cell-to-cell communication with the immune compartment. The presence of multiple stem cell-like populations (NPC, OPC, radial glia) within and between tumors highlights the challenge of delineating a single cell of origin for GBM. While some transcriptional programs (reactive hypoxia and immune) seemed to arise from interactions of the tumor with its microenvironment, it is unclear whether the different stem cell lineages within these tumors arose from their distinct lineages or by proxy of epigenetic dysregulation in one cell of origin (4).

Subsequent models of GBM created using various tumor-initiating cells (NSCs, OPCs, astrocytes) have further supported the hypothesis of multiple cells of origin for GBM (19, 25, 30, 32). In a study by Wang et al., genetically engineered mouse models (GEMMs) were created by inducing common GBM-driver mutations in NSCs and OPCs (16). Transcriptome analysis revealed that GBMs arising from each cell lineage had distinct phenotypic and molecular differences, with NSC initiated tumors expressing EGFR/SOX9+ (Type I) and OPC initiated tumors expressing ERBB3/Sox10+ (Type II) (Figure 1). These gene expression signatures were analyzed in a human GBM database, with 107 Type I candidates and 68 Type II candidates being found (16). A similar study, in which astrocytes and neural stem/progenitor cells (NSPCs) were targeted with common GBM driver mutations, showed that tumors between the two models with different cells of origin had distinct latency to symptom timelines and protein

expression (19). This indicates that latency and transcriptomic effects of driver mutations are likely cell of origin dependent and may explain the prevalence of GBM inter-tumor heterogeneity, both in terms of phenotype and clinical course.

Subventricular zone as location of cell of origin niche

The subventricular zone (SVZ), which lies along the lateral ventricle, consists of multiple cell populations (astrocytic lineage [type B1 and B2], neuroblasts [type A], and transit-amplifying cells [type C]) that represent the largest reservoir of NSCs in the human brain (34, 35). Astrocytic-like NSCs give rise to transit-amplifying cells (TACs), which in turn produce neuroblasts that migrate throughout the SVZ and along the rostral migratory stream (RMS) to the olfactory bulb where they can differentiate into immature neurons (36). Many molecular characteristics are shared between glioblastoma stem cells (GSCs) and NSCs, making the SVZ the main suspect of GBM tumorigenesis and recurrence (7, 37).

Genetic comparison of subventricular zone neural stem cells to glioma stem cells

Suspicion of the SVZ in GBM gliomagenesis has led to comparative studies between GSCs and NSCs residing in the SVZ. In a study done by Lee et al., deep-sequencing of matched tissues (non-tumor SVZ, glioblastoma tumor, and cortex) from IDH^{WT} GBM patients showed that 56.3% of these patient's SVZs expressed low levels of driver mutations observed in their tumors (38). A paired model where common GBM-driver mutations were induced in cortical cells showed no spread of these cells to the SVZ, confirming that the observed SVZ-cells with low-level driver mutations were the initiating population and not a migratory niche (38). Further analyses using immunofluorescence (IF) and IHC staining have confirmed the presence of GSC-like cells in the SVZ of GBM patients. These GSC-like cell niches stain positive for a combination of CD133; Sox2; CD9+, as well as GBM-related chemokines and receptors: stromal-derived factor-1alpha (SDF-1alpha), C-X-C receptor type 4 (CXCR4), osteopontin, and CD44 (39). Moreover, common SVZ-related markers such as glial fibrillary acidic protein (GFAP) and vimentin have also been found to be highly expressed in GSCs in other models (37).

Subsequent transcriptome analyses of GSCs have identified a cell population in GBM tumors similar to outer radial glia

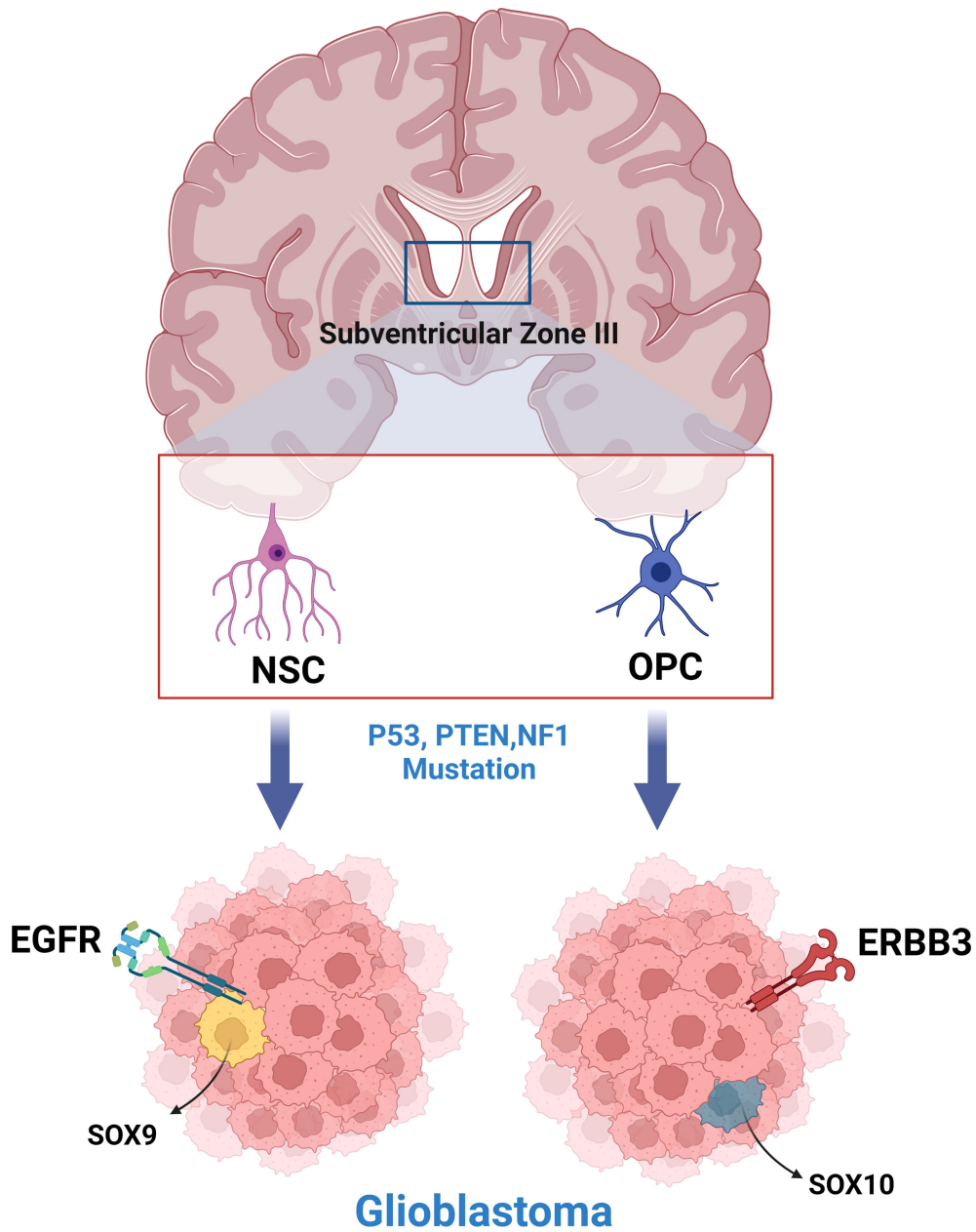


FIGURE 1
Neural stem cells and oligodendrocyte progenitor cells of the subventricular zone produce phenotypically and molecularly distinct glioblastoma tumors when engineered to express common glioblastoma driver mutations.

(oRG): NSCs that are abundant in the SVZ during human cortical development (6, 40, 41). Live time-lapse imaging showed that these oRG-like GSCs underwent mitotic somal translocations typical of neonatal oRGs. Progeny of these GSCs were seen to undergo cell divisions of their own, demonstrating their ability to amplify a cell population and their potential to initiate tumorigenesis (6).

Models of glioblastoma implicating subventricular zone neural stem cells in glioblastoma gliomagenesis

The initiation of tumors *via* genetic modifications of NSCs in the SVZ has been well studied. In one instance, p53 mutations

were induced in mice *via* a Cre-flox system. Almost all of the p53^{flox/flox} and p53^{flox/KO} (85% and 84%, respectively) mice developed neurological symptoms (tremor, ataxia, etc.) that indicated high grade glioma (HGG) formation. Forty percent of these tumors showed characteristics common to GBM, such as necrosis and microvascular proliferation, confirming a GBM phenotype. Stained tumor cells exhibited high levels of Beta-galactosidase, an enzyme commonly expressed by SVZ NSCs and OPCs. To determine if these SVZ cells were the cell of origin, Wang et al. looked at which cell niches primarily accumulated the p53^{delta5-6} protein. Eighty percent of p53^{delta5-6}-positive cells were found to be within the adult SVZ niche and seventy-seven percent of these cells were found to be actively dividing. Although most of these cells were labeled as SVZ-B stem cells, they were shown to be able to differentiate into Olig2+ SVZ-C progenitor cells, confirming their oncogenic potential (42). Other similar models inducing common-GBM driver mutations in SVZ NSCs have confirmed the oncogenic potential of this niche (38, 43, 44). In one of these studies, serial sections showed that over time, genetically engineered NSCs were able to migrate from the SVZ to various regions of the brain, such as the olfactory bulb and dorsolateral caudal cortex. Here, they proliferated and developed into high-grade malignant gliomas (38).

SVZ NSCs have been implicated not only in the initiation of GBM but also in its continued maintenance and recurrence. In a murine model of GBM, SVZ NSCs were shown to re-initiate GBM tumor growth after cell proliferation in the primary tumor was arrested using temozolomide (TMZ) (45). Ablation of these SVZ-niche cells in 8-week-old mutant mice resulted in significantly increased survival and a decrease in overall tumor progression (45). Similarly, in a clinical trial where GBM patients had the SVZ ipsilateral to their tumor treated with radiation, patients who received the treatment had significantly longer progression-free survival (PFS; 12.6 vs. 9.9 months, $p=0.042$) and longer overall survival (OS; 25.8 vs. 19.2 months, $p=0.173$) when compared to patients who received no radiation to their SVZ (46). These data, as well as data from other studies, suggest that GSCs from the SVZ-niche may be able to re-populate primary tumors after treatment and lead to GBM recurrence (47).

Contact of a patient's primary GBM tumor with the SVZ has also been indicated as a prognostic factor of patient survival. In a study by Jafri et al., GBM tumors were classified based off of their contact with both the cortex and the SVZ (type I), just the SVZ (type II), just the cortex (type III), and neither the cortex nor the SVZ (type IV). Patients with tumors involving the SVZ (type I & II) had a poorer two-year OS (23% vs. 48%; $p=0.0002$) and more rapid time to progression ($p=0.003$) than patients with tumors not involving the SVZ (type III & IV) (48). Multiple studies have since linked GBM tumor contact with the SVZ to

shortened time to recurrence and poorer prognosis, possibly due to the findings that SVZ contact with GSCs initiates enrichment of pro-oncogenic programs, such as the epithelial to mesenchymal transition (EMT), NF-kBeta, angiogenesis, and hypoxia gene sets (49–52).

Discussion and final remarks

A definitive cell of origin for GBM has still not been identified. The presence of a large, proliferative niche of NSCs in the SVZ of the adult brain, as well as the accumulating evidence of a stable, cycling NSC population in GBM models, continues to support NSCs as the most likely cell or origin (7, 24, 28, 34, 38). However, multi-omics analyses of genetically engineered models and patient samples suggest that differences in GBM-subtypes may be correlated to transcriptionally active oncogenic pathways that are cell of origin dependent, suggesting that multiple cells of origin may be responsible for the inter-tumoral heterogeneity seen in GBM (16, 19, 32). Better profiling of these cell of origin dependent effects could help with understanding the therapeutic vulnerabilities of genetically distinct tumors between patients, just as other molecular profiling markers have (53, 54).

Recent evidence showing that some GBM patients express low levels of their cancer's driver mutations in their SVZ, as well as the discovery of a population of GSCs that behave similarly to oRG, supports the theory that GBM may develop from NSCs in the SVZ (6, 38). Subsequent models have confirmed the oncogenic potential of this stem cell niche, as well as its possible involvement in the maintenance and recurrence of GBM tumors after treatment (42, 45). Reports on the clinical efficacy of treating GBM patients' SVZs with radiation therapy are conflicting, with some studies showing clear clinical benefits and some showing none (47, 55, 56). The need to initiate further clinical trials studying the effect of RT of the SVZ on GBM patient outcomes is of utmost importance.

Various studies have also elucidated the importance of SVZ to GBM cell-cell interactions in driving gliomagenesis and contributing to poorer outcomes (48, 50, 51, 57, 58). CXCL12/CXCR4 signaling seems to be of particular importance in initiating more extensive migration of GSCs, thus, promoting further malignancy (57). Elucidation of these complex, 3D interactions *via* cerebral organoids would provide a means for identifying molecular patterns and therapeutic vulnerabilities of GSCs in a model that better replicates the complexity of the human brain (59–61).

The cell of origin, as well as the SVZ, play an important role in GBM initiation, maintenance, and recurrence that, to this day, is still not entirely understood. It remains of great interest across

the field of neuro-oncology to focus a significant portion of all future GBM research on uncovering the molecular consequences of the cell of origin differences and SVZ to tumor interactions and how these consequences subsequently affect therapeutic susceptibility and treatment courses of GBM tumors. The ability to sub-type GBMs based off the aforementioned characteristics could greatly improve the accuracy of GBM diagnosis and treatment, and subsequently, improve patient outcomes.

Author contributions

Conception and design: PZ. Interpretation of data: PZ, NJ, and AH. Drafted the manuscript: NJ and AH. Approved the final version to be published: PZ. Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: PZ. All authors contributed to the article and approved the submitted version.

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