Editorial

On the subventricular zone origin of human glioblastoma

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Comment on: Lee JH, Lee JE, Kahng JY, *et al.* Human glioblastoma arises from subventricular zone cells with low-level driver mutations. Nature 2018;560:243-7.

Submitted Nov 09, 2018. Accepted for publication Nov 23, 2018.

doi: 10.21037/tcr.2018.11.31

View this article at: http://dx.doi.org/10.21037/tcr.2018.11.31

Introduction

The cancer stem cell theory posits that a small subset of cancer cells with self-renewing capacity, popularly known as cancer stem cells and experimentally defined as tumor-initiating cells, maintains the tumor with its heterogeneous lineages of cancer cells (1,2). Identification of these cells is critical for effective cancer therapy, because often after conventional radiation and chemotherapies, which predominantly eradicate proliferative tumor cells, the therapy-resistant cancer stem cells reconstitute the tumor, heralding clinical relapse and therapy failure (2,3). Since the discovery of therapy-resistant glioblastoma stem cells that can initiate tumors (4) and cause post-therapy tumor recurrence (5), the glioblastoma cell of origin, which holds the key to improving the meager arsenal of effective glioblastoma therapies and the median 16-month patient survival (6,7), has remained elusive. The recent work by Lee and colleagues (8) provides a direct evidence supporting the long-standing hypothesis that cells resident in the subventricular zone (SVZ), a neural stem cell niche which lies in the lateral walls of the lateral ventricles in the brain, are the cells of origin for glioblastoma in humans (9). Their work supports that the cancer stem cell model holds true in the case of glioblastoma and has important implications for exploring novel therapeutic approaches in its treatment.

Summary of novel findings

Lee and colleagues demonstrated that cells in the SVZ contained driver mutations of IDH wild-type glioblastoma (6). In 28 patients with various intracranial tumors (specifically, 16 IDH wild-type glioblastomas without SVZ invasion), they systematically sequenced triple-matched samples of the tumor, pathologically and radiologically tumor-free SVZ, and blood (or tumor-free cortical tissue). The tumor-free SVZ in 9 of the 16 (56.3%) patients with IDH wild-type glioblastoma already had at least one somatic, low-level (as low as 1% of the mutational burden) driver mutation that was present at high levels in the tumor. All the 9 tumor-free SVZ samples had a mutation in the *TERT* coding or promoter region. Other mutations were also found in *EGFR*, *PTEN* and *TP53*. Single-cell targeted sequencing of an IDH wild-type glioblastoma and its single-cell-derived clonal cell populations demonstrated that all clones had mutations shared with the respective tumor-free SVZ, in addition to the tumor-private mutations. On the other hand, tumor-free SVZ (in another patient) had few clones with the shared mutations of the respective tumor but lacked the tumor-private mutations. Through laser microdissection of the SVZ microarchitecture in two patients and targeted deep sequencing, *TERT* promoter mutation was found to be enriched only in *GFAP*-positive, astrocyte-like stem cells of the astrocytic ribbon of the SVZ (10). When some of the discovered driver mutations (*p53*, *Pten*, and *Egfr*) were engineered specifically in the neural stem cells of the SVZ in mice, the mutated neural stem cells developed tumors, two-thirds of which were distant from the SVZ, especially in the dorsolateral-caudal cortex. Immunostaining of these migrating neural stem cells confirmed oligodendrocyte-precursor cell to be the major cell type contributing to tumor formation. Thereby, Lee and colleagues provide a direct evidence that SVZ cells containing driver mutations migrate to distant regions and clonally evolve into glioblastoma.

There were at least two noteworthy aspects of the study that facilitated the generation of these results. One was the systematic sequencing of triple-matched samples of the tumor, tumor-free SVZ, and blood (or cortex) which led to discovery of low-level driver mutations in the tumor-free SVZ. Second was the willingness of the neurosurgeons to perform supra-total resections. Availability of normal brain tissue samples to study was important to the discovery of the cellular origins of glioblastoma.

Clinical implications

The work by Lee and colleagues provides an important insight into why glioblastoma occasionally can be multifocal or multicentric (i.e., multiple radiologically distinct lesions) and inevitably recurs in virtually all patients, despite a radiologically complete resection followed by optimal chemotherapy and radiation therapy. It implies that in addition to any residual and therapy-resistant tumor cells, cells resident in the SVZ, distant from the tumor and the site of surgical and radiation therapies, can incite tumor recurrence as they emigrate. In addition to local tumor therapy, therapy targeted at these cells may be necessary for effective treatment of glioblastoma.

Currently, the SVZ as a whole is under investigation as a potential therapeutic target due to several prior observations. For example, human xenografted glioblastoma cells can specifically invade the SVZ in mice (11,12), and SVZ invasion by glioblastoma is associated with drastically increased recurrence and decreased patient survival (13,14). Therefore, several clinical studies have assessed the impact of SVZ radiation in addition to the standard of care treatment for glioblastoma (15), and a clinical trial is currently underway (ClinicalTrials.gov Identifier: NCT02177578) to determine the effectiveness of SVZ radiation in a randomized setting.

Future directions

The work by Lee and colleagues sprouts several potential explorations. These include deeper confirmations of their findings given the limited number of samples used and the possibility for a presence of tissue sampling bias in their results. For example, what are the cellular origins of IDH mutant glioblastomas (3 studied) and 7 of the 16 IDH wild-type glioblastomas without a discovered mutation in their respective tumor-free SVZ samples? Deeper understanding of the tumor-inciting events is also necessary to inform therapeutic explorations. For example, what are the mechanisms or environmental events that cause the mutated neural stem cells to explode into tumors? Specifically, how might mutations in the *TERT* coding or promoter region in the neural stem cells, found in all the tumor-free SVZ samples studied by Lee and colleagues that had a genetic aberration, result in gliomagenesis is intriguing. Lastly, understanding the environmental factors that govern neural stem cells with cancer driver mutations to differentiate to mature neurons when migrating to the olfactory bulb may broaden our approaches of therapy development. Overall, the work by Lee and colleagues is foundational and places a foot in the long-elusive doorway of the cellular origins of diffuse gliomas.

Acknowledgments

I thank Pamela Lane for language editing assistance.
Funding: This work was supported by the National Cancer Institute at the National Institutes of Health (F32 CA224962 to AM Mistry).

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Xian-Xin Qiu (ShanghaProton and Heavy Ion Center (SPHIC), a.k.a. the Proton and Heavy Ion Center of Fudan University Shanghai Cancer Center (FUSCC), Shanghai, China).

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2018.11.31). The author has no conflicts of interest to declare.

Ethical statement: The author is 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.

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Cite this article as: Mistry AM. On the subventricular zone origin of human glioblastoma. Transl Cancer Res 2019;8(1):11-13. doi: 10.21037/tcr.2018.11.31

