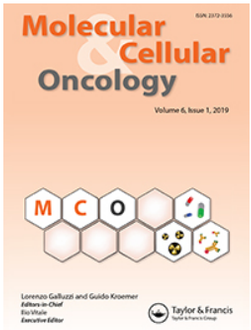

Molecular & Cellular Oncology

ISSN: (Print) 2372-3556 (Online) Journal homepage: https://tandfonline.com/loi/kmco20

Increasing the accuracy of glioblastoma subtypes: Factoring in the tumor's cell of origin

Sven Nelander

To cite this article: Sven Nelander (2019) Increasing the accuracy of glioblastoma subtypes: Factoring in the tumor's cell of origin, Molecular & Cellular Oncology, 6:1, 1302907, DOI: 10.1080/23723556.2017.1302907

To link to this article: https://doi.org/10.1080/23723556.2017.1302907

Accepted author version posted online: 05 Apr 2017.
Published online: 27 Nov 2018.

MOLECULAR & CELLULAR ONCOLOGY
2019, VOL. 6, NO. 1, e1302907 (2 pages)
http://dx.doi.org/10.1080/23723556.2017.1302907

Taylor & Francis
Taylor & Francis Group

AUTHOR'S VIEW

OPEN ACCESS

Increasing the accuracy of glioblastoma subtypes: Factoring in the tumor's cell of origin

Sven Nelander

Rudbeck Laboratory, Department of Immunology, Genetics, and Pathology, Uppsala University, Uppsala, SE, Sweden

ABSTRACT

The transcriptional classification of glioblastoma has proven to be a complex issue. In the absence of strong correlations between underlying genomic lesions and transcriptional subtype, there is a need to systematically understand the origins of the glioblastoma subtypes. A recent integrated analysis of data from both mouse models and patient-derived cells supports that the glioblastoma's cell **of origin** is important in shaping transcriptional diversity and tumor cell malignancy.

ARTICLE HISTORY
Received 1 March 2017
Revised 2 March 2017
Accepted 2 March 2017

KEYWORDS
Cell of origin; data integration; glioblastoma classification; plasticity; systems biology

One of the key challenges for cancer researchers is to translate findings obtained in preclinical models into the clinical domain. As a part of this translation, it is important to develop molecular classification systems that work consistently across many levels of observation, including cells, animal models and patients. Traditionally, the exploration of cancer molecular subtypes has primarily focused on transcript profiles of tumor surgical samples. Applied to cancers of the brain, this approach has produced variable results, depending on the diagnosis. For instance, whereas analyses of medulloblastomas have resulted in signatures that are reproducible, biologically interpretable and clinically relevant,[1] the classification of glioblastomas appears less robust and harder to interpret. Analyses of large glioblastoma cohorts has identified partially overlapping classification systems, in particular the mesenchymal /proneural/ classical/ neural system by Verhaak et al.[2] and the mesenchymal / proliferative / proneural system by Phillips et al.[3] While the reported glioblastoma transcriptional subtypes tend to correlate with underlying genomic lesions, the degree of correlation is only moderate.[2,4] This suggests that, in addition to key driver mutations, one or several additional non-genetic factors are important in shaping the observed expression pattern that we refer to as subtype (Fig. 1A). Such factors likely include variations in stromal content,[4] and plastic variations in gene expression between individual cells,[6] tumor clones[7,8] or regional variation.[4] In addition to these biologic sources of variation, the statistical methodology used to call subtypes is far from standardized, meaning that even if two different teams agree on which subtyping system to use, they might still get different results simply due to variations in their choice of algorithms.

One aspect that so far has not been systematically factored into the analysis of glioblastoma subtype is the tumor's cell of origin.[9] In a recent collaboration between two teams specializing in cancer systems biology and glioblastoma mouse genetics, we analyzed data from mouse glioblastoma cells initiated from three distinct cell types along the glial cell differentiation axis.[10] The targeting of each cell type was mediated via the replication-competent leukosis virus splice acceptor / tumor virus A (RCAS/tv-a) mouse glioma model, adapted to target-specifc cell populations expressing the markers Nestin (NES), 2′,3′-Cyclic-nucleotide 3′-phosphodiesterase (CNP) and Glial Fibrillary Acidic Protein (GFAP).[10] Subsequent isolation of glioblastoma cells from the mouse tumors thus enabled both molecular and functional characterization of experimental glioblastomas of different cellular origins. In a cross-species approach, transcript profiling data from these cell-of-origin variant mouse glioblastoma cells were used to establish a 196 gene Mouse Cell-of-Origin (MCO) signature, which was subsequently applied to classify the human samples (Fig. 1B). We found that mouse glioblastomas induced in neural stem-cell-like GFAP-positive cells in the subventricular zone of adult mice showed accelerated tumor development, compared with the more differentiated NES or CNP-positive cells. Human glioblastoma cells classified as matching each of these groups showed a similar difference in phenotype, the GFAP-positive cells being more self-renewing and tumorigenic. The new classification, however, was not predictive of survival.

Taken together, the study underlines cell of- origin as a possible key factor that should be factored into the analysis of glioblastoma molecular subtypes. Importantly, while the results support that variations in tumor's cell of origin are (in the mouse experimental setting) sufficient to induce marked changes in the transcriptional pattern and phenotype, they do not demonstrate that such variations are necessary. The study also highlights the need to develop

CONTACT Sven Nelander sven.nelander@igp.uu.se Rudbeck Laboratory, Department of Immunology, Genetics, and Pathology, Uppsala University, Uppsala, SE, 751 85, Sweden.

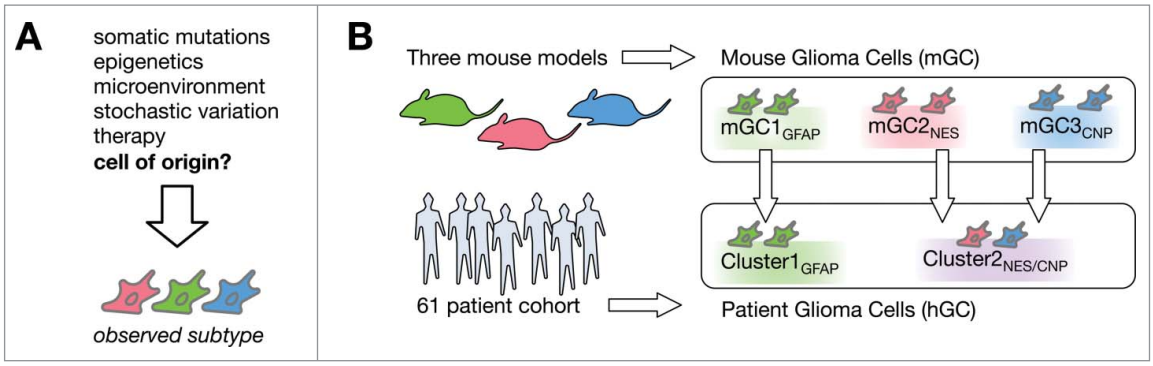

Figure 1. Factoring in cell-of-origin signatures in glioblastoma classification. (A) The assignment of subtypes to glioblastoma samples depends on several factors, ranging from genetic aberrations to choices of algorithm. One factor that has not yet been systematically analyzed is differences in cell of origin. (B) In a recent work by Jiang et al.,[10] glioblastoma cells from three glioblastoma mouse models reflecting different cellular origins were isolated. Following transcript profiling, Mouse Cell-of-Origin (MCO) signatures were used to stratify human glioblastoma cells. Joint stratification of both patient-derived cell lines and model cell lines can help obtain robust signatures for preclinical and clinical investigation.

the computational frameworks to define origins of molecular subtypes that are applicable across multiple layers of data or experimental systems. Recent analytical concepts that are applicable to glioblastoma classification include integrative modeling to reveal epigenetic programs,[4,11] in silico dissection methods to isolate cell-intrinsic variational components,[5] or straightforward PCA-like-based models that downplay the need for a sharp subdivision but rather emphasize a continuum across e.g. the mesenchymal-proneural gradient.[8] Building on these advances, a final classification of glioblastoma will likely be based on multi-layered analysis across cells, mouse models and patient samples.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

References

1. Taylor MD, Northcott PA, Korshunov A, Remke M, Cho YJ, Clifford SC, Eberhart CG, Parsons DW, Rutkowski S, Gajjar A, et al. Molecular subgroups of medulloblastoma: the current consensus. Acta Neuropathol 2012; 123(4):465-72; PMID:22134537; http://dx.doi.org/10.1007/s00401-011-0922-z
2. Verhaak RG, Hoadley KA, Purdom E, Wang V, Qi Y, Wilkerson MD, Miller CR, Ding L, Golub T, Mesirov JP, et al. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. Cancer Cell 2010; 17(1):98-110; PMID:20129251; http://dx.doi.org/10.1016/j.ccr.2009.12.020
3. Phillips HS, Kharbanda S, Chen R, Forrest WF, Soriano RH, Wu TD, Misra A, Nigro JM, Colman H, Soroceanu L, et al. Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis. Cancer Cell 2006; 9(3):157-73; PMID:16530701; http://dx.doi.org/10.1016/j.ccr.2006.02.019
4. Kling T, Ferrarese R, O hAilin D, Johansson P, Heiland DH, Dai F, Vasilikos I, Weyerbrock A, Jornsten R, Carro MS, et al. Integrative Modeling Reveals Annexin A2-mediated Epigenetic Control of Mesenchymal Glioblastoma. EBioMedicine; 2016; 12:72-85.
5. Wang Qianghu, Hu Xin, Muller Florian, Kim Hoon, Squatrito Massimo, Millelsen Tom, Scarpace Lisa, Barthel Floris, Lin Yu-Hsi, Satani Nikunj, et al. Tumor evolution of glioma intrinsic gene expression subtype associates with immunological changes in the microenvironment. bioRxiv 2016; http://dx.doi.org/10.1101/052076; URL http://biorxiv.org/content/early/2016/05/08/052076
6. Patel AP, Tirosh I, Trombetta JJ, Shalek AK, Gillespie SM, Wakimoto H, Cahill DP, Nahed BV, Curry WT, Martuza RL, et al. Single-cell RNA-seq highlights intratumoral heterogeneity in primary glioblastoma. Science 2014; 344(6190):1396-401; PMID:24925914; http://dx.doi.org/10.1126/science.1254257
7. Sottoriva A, Spiteri I, Piccirillo SG, Touloumis A, Collins VP, Marioni JC, Curtis C, Watts C, Tavare S. Intratumor heterogeneity in human glioblastoma reflects cancer evolutionary dynamics. Proc Natl Acad Sci USA 2013; 110(10):4009-14; PMID:23412337; http://dx.doi.org/10.1073/pnas.1219747110
8. Segerman A, Niklasson M, Haglund C, Bergstrom T, Jarvius M, Xie Y, Westermark A, Sonmez D, Hermansson A, Kastemar M, et al. Clonal Variation in Drug and Radiation Response among Glioma-Initiating Cells Is Linked to Proneural-Mesenchymal Transition. Cell Rep 2016; 17(11):2994-3009; PMID:27974212; http://dx.doi.org/10.1016/j.celrep.2016.11.056
9. Zong H, Verhaak RG, Canoll P. The cellular origin for malignant glioma and prospects for clinical advancements. Expert Rev Mol Diagn 2012; 12(4):383-94; PMID:22616703; http://dx.doi.org/10.1586/erm.12.30
10. Jiang Y, Marinescu VD, Xie Y, Jarvius M, Maturi NP, Haglund C, Olofsson S, Lindberg N, Olofsson T, Leijonmarck C, et al. Glioblastoma Cell Malignancy and Drug Sensitivity Are Affected by the Cell of Origin. Cell Rep 2017; 18(4):977-90; PMID:28122246; http://dx.doi.org/10.1016/j.celrep.2017.01.003
11. Kling T, Johansson P, Sanchez J, Marinescu VD, Jornsten R, Nelander S. Efficient exploration of pan-cancer networks by generalized covariance selection and interactive web content. Nucleic Acids Res 2015; 43(15):e98; PMID:25953855; http://dx.doi.org/10.1093/nar/gkv413