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AUTHOR'S VIEW

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

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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.

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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

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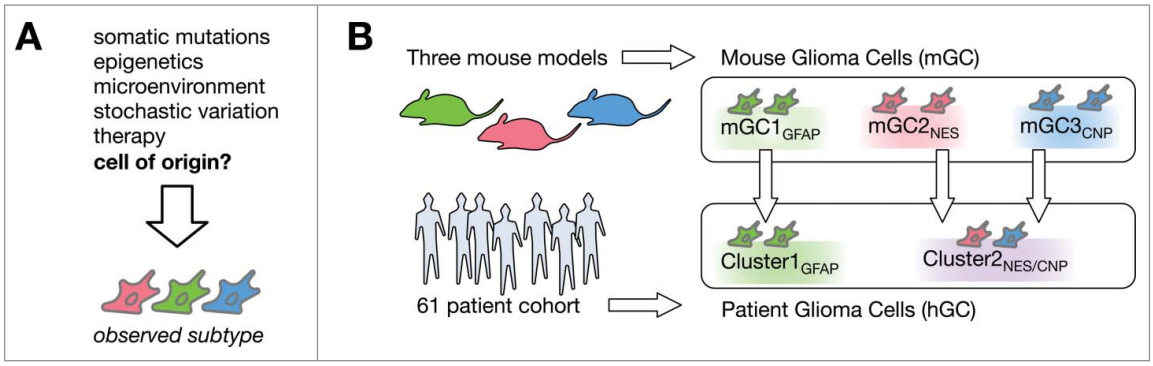

Figure 1. Factoring in cell-of-origin signatures in glioblastoma classification. (A) The assignment of subtypes to glioblastoma samples depends on several factors, ranging from genetic aberrations to choices of algorithm. One factor that has not yet been systematically analyzed is differences in cell 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.

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