

Virchow 2011 or How to ID(H) Human Glioblastoma

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In 1865, Virchow was the first to describe gliomas pathologically, segregating them into two groups that we now recognize as low- and high-grade gliomas. In 1926, Bailey and Cushing¹ gave the first modern pathologic description of the most malignant brain tumor, the glioblastoma, calling it spongioblastoma multiforme. They differentiated spongioblastoma multiforme from astrocytoma on the basis of their presumption of a different cell of origin, given the different histologic appearance of the two. By 1940, the term glioblastoma multiforme (GBM) was in widespread use, and Scherer^{2,3} was the first to differentiate between primary and secondary GBM, distinguishing those tumors that arose de novo from those that transformed from a preexisting, lower-grade lesion. The term multiforme referred to the extraordinarily diverse histologic features of these neoplasms. Their variegated appearance could range from small, intense blue cells to huge, multinucleated giant cells, and these wide variations could coexist within the same tumor. The extraordinary histologic heterogeneity may prove challenging for the neuropathologist, but these varying histologic subtypes did not affect prognosis or response to known therapies, although Scherer recognized that secondary glioblastoma was associated with longer survival. The advent of modern molecular profiling, however, is changing our understanding of glioblastoma, and the term multiforme may have a new meaning.

The first attempts to segregate molecular subtypes of glioblastoma began with the study of primary and secondary glioblastoma, which also have two discrete clinical presentations.⁴ Primary GBM represents approximately 95% of all glioblastomas and tends to occur in older patients, whereas secondary GBM arises in younger individuals who have had a previously diagnosed low-grade glioma for many years or even decades before malignant transformation heralds a sudden change in the status of their disease. Primary GBM is characterized by the high frequency of epidermal growth factor receptor (*EGFR*) gene amplification, whereas *p53* mutations characterize secondary GBM. This initial work established that dysfunction of different pathways could lead to histologically identical GBM.

The most recent integrated genomic profiling of GBM has revealed four molecular-genetic subtypes that are defined by their most prominent gene expression alterations and are associated with specific mutations and gene copy number alterations. These disease subtypes are referred to as classical (*EGFR* amplification/overexpression or mutation, phosphatase and tensin homolog [*PTEN*] loss or mutation, *CDKN2A* loss, nuclear export sequence [*NES*] overexpression, activation of Notch and sonic hedgehog pathways); mesenchymal (*NF1* loss, *p53* mutation, *PTEN* loss/mutation,

activation of tumor necrosis factor and nuclear factor- κ B pathways); proneural (platelet-derived growth factor receptor-A amplification, isocitrate dehydrogenase 1 [*IDH1*] mutation, high expression of proneural, eg, Sry-box [*SOX*], and oligodendroglial, eg, *OLIG2*, genes); and neural (*EGFR* amplification/overexpression, expression of neural markers, eg, neurofilament light polypeptide [*NEFL*]).⁵ The subtypes have prognostic significance and defined activity of signaling pathways that characterizes gliomagenesis. Earlier studies identified three subtypes: mesenchymal, proneural, and proliferative.^{6,7} Patients with proneural glioblastomas (as defined by either classification schema) lived longer, particularly compared with those patients with the mesenchymal subtype, in which angiogenesis features prominently. In the article that accompanies this editorial, Lai et al⁸ provide additional clarity with respect to GBM subclassification.

Mutations in the *IDH* genes, particularly the *IDH1*^{R132MUT}, have been shown by several groups to represent some of the earliest mutations in glioma formation and are particularly characteristic of low-grade gliomas; they are seen in more than 70% of grade 2 gliomas and in 50% of grade 3 lesions.⁹⁻¹¹ These data suggest that *IDH* mutations occur early and may initiate glioma formation. Secondary glioblastomas also have a high propensity to harbor *IDH* mutations, which confirms their origin from the prior lower-grade tumor.

Lai et al⁸ explored the presence of *IDH* mutations in what seem clinically to be primary glioblastomas. They examined 618 primary GBMs for the presence of the most common *IDH* mutation in glioma, *IDH1*^{R132MUT}, and 49 such tumors were identified, suggesting that approximately 8% of apparent primary GBMs seem to arise from clinically silent lower-grade tumors. Moreover, these 49 tumors had clinical and pathologic features that identified them as a discrete subgroup. Histologically, they had less necrosis, more oligodendroglial features, and a significantly greater proportion of tumors with promotor methylation of O⁶-methylguanine DNA methyltransferase (*MGMT*), which was a facet of a larger pattern of CpG island hypermethylation. Clinically, *IDH1*^{R132MUT} GBMs had more radiographic features that were reminiscent of low-grade glioma, including nonenhancing disease, less edema, larger size, increased prevalence of cystic and diffuse components, and frontal lobe predominance. Most significantly, patients whose GBM contained an *IDH1* mutation had a significantly longer survival than those with wild-type *IDH1*.

The authors⁸ then examined the transcriptional signatures of both groups of glioblastomas and found that the majority of *IDH1*^{R132MUT} tumors expressed the proneural signature, originally described in 2006, which is substantially similar to the proneural signature that was

described in the initial GBM analysis performed by The Cancer Genome Atlas.^{6,7} In both series, the proneural signature was associated with a better outcome, which is consonant with the improved survival observed with the *IDH1*^{R132MUT} genotype. Some *IDH1*^{R132MUT} glioblastomas were found to possess the proliferative signature, but none had the mesenchymal signature, which carries the worst prognosis. All three signatures could be identified within the population of *IDH1*^{R132WT} tumors, but the preponderance of the mesenchymal subtype likely explained the poor survival that was observed in that cohort. Furthermore, at least one study suggested that although aggressive therapy (concurrent chemoradiotherapy and/or more than three cycles of chemotherapy *v* nonconcurrent chemoradiotherapy or less than four cycles of chemotherapy) increases survival in patients with mesenchymal, neural, and classical tumors, it does not increase survival for patients with proneural tumors, and these tumors may not offer a distinct survival advantage compared with other subtypes.⁵ Because of the unique phenotypic, spatial, and age-related profile of *IDH1*^{R132MUT} tumors, Lai et al proposed that they arise from a non-stem-cell neural precursor that differs from the cell of origin for other GBM subtypes. Like the conjecture of Bailey and Cushing¹ regarding the cell of origin for the spongioblastoma multiforme, and Scherer's insistence that the initiating cell could not be deduced on the basis of histologic features,² this hypothesis requires additional study and proof.

Glioblastoma is among the most deadly of solid tumors, despite recent advances using temozolomide with radiotherapy and, more recently, bevacizumab at recurrence.^{12,13} Patients are beginning to live longer and better, but they all relapse and eventually succumb to their disease, typically within 2 years of diagnosis. Clearly, new approaches are needed, and the future lies in dissecting the underpinnings of this malignancy. In other equally intransigent solid tumors, such as metastatic melanoma, enhanced understanding of molecular drivers has led to novel therapeutics, the promise of which is beginning to be realized, and these tumors are now categorized by their driver mutations (eg, *BRAF* or *KIT* mutant melanoma).^{14,15} It is now possible to imagine that glioblastoma may prove tractable with the same knowledge. We should abandon our clinically based GBM subcategories (eg, primary or secondary GBM) and instead move to a molecularly based classification scheme (eg, *IDH1* mutant glioma), which should guide clinical trial design with agents that target driver mutations. Bailey and Cushing¹ proved prescient in their description of glioblastoma 85 years ago. Now we are beginning to understand exactly how multiforme glioblastoma truly is.

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