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Differences in molecular profiles of glioblastomas according to location

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See the article by Cho et al, pp. 47–58.

The brain is conceptualized as a single discrete structure, but it may be more helpful to regard it as several organs wired together. The cortex and white matter, midline structures (basal ganglia, thalamus, and midbrain), brainstem, and cerebellum all mature at different rates, and each has its own distinct cellular composition, neurochemistry, and microenvironment. Thus, it follows that certain types of brain tumors preferentially arise in specific regions, at particular stages of development. As humans progress from childhood into adolescence and adulthood, tumor location shifts from the infratentorium and midline to the supratentorium and cerebral hemispheres.[1] While pilocytic astrocytomas and midline infiltrative gliomas are more common in children, adults are far more likely to develop cerebral astrocytomas (including glioblastomas, or GBM) and oligodendrogliomas.[1,2]

Similarly, there are spatial and temporal dimensions to the genetic alterations observed among brain tumors, even among tumors of the same histotype. *BRAF* fusions are most common in pediatric pilocytic astrocytomas arising in the cerebellum, and become less frequent as the patient ages and tumor location shifts to the supratentorium.[3] Among histone H3.3-mutant infiltrative gliomas, those involving K27 tend to arise in the midline of very young patients, whereas mutations in G34 preferentially occur in hemispheric tumors in teenagers and young adults.[4] Diffusely infiltrative gliomas with mutations of isocitrate dehydrogenase 1 (*IDH1*) are characteristic of the frontal and temporal lobes in 20–40 year olds, while the likelihood of a glioma being driven by epidermal growth factor receptor (*EGFR*) increases with advanced age.[5]

In the current issue of *Neuro Oncology*, Cho et al describe the molecular features of a relatively common tumor, GBM, arising in an uncommon location, the cerebellum.[6] Even though the cerebellum is approximately 10% of total brain weight, only 1% of GBMs occur there, making detailed analysis of these tumors rare. The authors analyzed 19 cerebellar GBMs (C-GBMs) from adult patients, showing some interesting similarities to and differences from supratentorial GBM (S-GBM). Although cerebellar tumors as a group are more common in children than adults, C-GBM had the same median patient age as S-GBM, and the 2 entities were similar histologically. Unlike S-GBM, in which mutations of alpha thalassemia/mental retardation syndrome X-linked (*ATRX*) are strongly associated with *IDH1* mutations, and *EGFR* alterations are common, the authors found that C-GBMs sometimes carried mutant *ATRX* without *IDH1* mutation, and did not have mutated or amplified *EGFR*. C-GBMs also showed a higher frequency of alterations of *RAS* and platelet derived growth factor receptor A (*PDGFRA*), and amplification of cyclin-dependent kinase 4 (*CDK4*) and murine double minute 2 (*MDM2*). Despite the relative paucity of *IDH1* mutations in C-GBMs, these tumors disproportionately showed a proneural pattern of mRNA expression. None of their C-GBMs contained any histone mutations, although their cohort was lacking in children and younger adult patients. Telomerase reverse transcriptase (*TERT*) promoter mutations, which are highly characteristic of S-GBMs, were present in only 2 of 19 C-GBMs. The transcriptome and methylome patterns of their C-GBMs were closer to pediatric and adult S-GBMs, and did not resemble other posterior fossa tumors like pilocytic astrocytoma, ependymoma, and medulloblastoma. Even so, they reported the existence of "infratentorial brain region-specific methylation patterns for C-GBM tumors" and specific genes expressed in C-GBM but not S-GBM, most notably *PAX3* and *CSPG4*. In vitro studies suggested greater sensitivity of C-GBM cells to MEK and PDGFRA inhibitors. Together, these results indicate that C-GBMs tend to have a distinct molecular profile from their supratentorial counterparts.

This fits the overall theme of molecular drivers varying greatly according to tumor location and age. A much harder question to answer is why, because that requires sophisticated mouse models in which expression of specific driver mutations can be controlled for location and time, yet still generate tumors. For example, Pathania et al found that H3K27M is lethal in postzygotic cells, and has no effect in postnatal

mice, but can only induce gliomas when it is introduced within a very narrow window during in utero development when pontine neurogenesis is at its peak.[7] Assuming that genomic alterations are more or less stochastic based on frequency of cell division, it would seem that oncogenic "hits" may need to occur not just at the right *time* in development, but also in the right *place*. For reasons that are not yet clear, cells carrying *TERT* and *EGFR* mutations may not enjoy the same growth advantages in the microenvironment of the cerebellum as in the cerebrum.

Since C-GBM is so rare, there is a risk of overinterpreting results in studies like this. For example, the authors report that *IDH1* mutation is less common in C-GBM than S-GBM, because only 1 of 19 C-GBMs had an *IDH1* mutation. But since *IDH1* mutation is found in a mere 10% of S-GBMs,[5] one more *IDH1*-mutant C-GBM would have rendered *IDH1* mutation frequencies identical (the authors excluded secondary GBMs, which are characterized by *IDH1* mutations, without a clearly articulated rationale for doing so). Likewise, they reported that 20% of C-GBM have *ATRX* mutations, compared with 10% of S-GBM. But because the C-GBM denominator was so low, only one fewer case of *ATRX* mutant C-GBM would have completely eliminated any statistical difference. Interpretation of expression and methylation patterns can also be complicated, as such patterns are markedly influenced by the type and extent of admixed nonneoplastic cells, apart from any real differences within tumor cells. Furthermore, although the study is described as "systematic," only 4 and 6 of the 19 C-GBMs actually underwent methylation and expression profiling, respectively. Regarding drug sensitivity, methods for culturing C-GBM cells were not provided, and in any event, neither MEK nor PDGFRA inhibitors have shown activity in GBM clinical trials. Thus, therapeutic options and prognosis in C-GBM remain the same as in S-GBM.

Despite some limitations, the central point of this study—that C-GBM bears a distinct molecular signature apart from S-GBM—is supported by the data and comports with the consensus in brain tumor research. This paper helps us further understand why progress in GBM treatment has been so lacking compared with cancers elsewhere in the body, and further emphasizes the need for large-scale, multi-institutional projects that are powered to study GBMs not just by age, but also by tumor location.

Conflict of interest statement. None declared.

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