The multiforme of glioblastoma

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See article by Mahlokozera et al, pp. 472–483

Despite the substantial number of academic efforts focused on improving care for patients with glioblastoma (GBM), radiation therapy and chemotherapy with the alkylating agent temozolomide remain the only approved first-line therapies. Although these 2 treatments have been shown to afford survival benefits for patients with GBM, their efficacies are short lived and plagued by the tumors’ development of resistance to therapy. Spatial genetic heterogeneity within tumors is a recognized contributor to treatment failure and driver of development of resistance to therapy in GBM and multiple other cancers. In fact, spatiotemporal genetic heterogeneity is likely responsible for the observed “failures” of previous clinical trials in GBM.

In this issue, Mahlokozera et al evaluated the implications of genomic heterogeneity by performing whole-exome sequencing and targeted telomerase reverse transcriptase promoter sequencing on local but spatially distinct tumor samples in 10 patients with newly diagnosed isocitrate dehydrogenase 1 wild-type GBM. Their results showed that just over half of mutations across 10 tumors were clonal, and that only 3% of the subclonal mutations were shared. Importantly, for the first time, the authors report a hypermutator genotype in one sector of 2 tumors without previous treatment or known genomic deficiencies. In addition to this, the authors found that 80% of cases had potentially druggable mutations that were not shared between sectors, and using an immunogenomics approach they also showed that the distribution of shared to private neoantigens was highly variable across samples.

The results of this study and others beg the question of how this heterogeneity develops in GBM. Traditionally, cancers have been thought to propagate through a Darwinian “survival-of-the-fittest” model whereby cells that accumulate alterations with selective growth advantages will dominate. In such a model, one would expect that the majority of tumors would demonstrate clonal and shared subclonal alterations. In contrast to this, the big-bang model, which has been validated in non-CNS cancers, suggests that tumors grow from a single expansion that produces numerous subclones. In this model, there is an initial highly prevalent alteration burden followed by a period of diversification, and therefore clonal and subclonal alterations arise early in tumor growth, and early subclonal events primarily driven by replication errors are more important determinants of intratumoral heterogeneity than late clonal mutations. Lee et al have shown that multisector profiling of local adjacent regions compared with multicentric distant regions differ dramatically. In GBM, it is likely that the evolution can be conceptualized using both a big-bang model and a multi-universe model whereby distant regions (or focuses) of tumors share very few genomic alterations, resulting in multiple “universes” of genetically distinct tumors.

Although the framework for interpreting evolution and genomic data are largely theoretical, the practicalities for treatment are real. First, it is clear that, even in newly diagnosed untreated GBM, a substantial number of alterations are subclonal and private. Drugs that target ubiquitous truncal as opposed to private genetic alterations are therefore likely to harbor success in treatment. However, it is possible that subclonal and private genomic alterations may contribute to therapy resistance, and therefore we cannot rely on single-agent therapy alone. Mahlokozera and colleagues showed that shared druggable mutations were present in only 40% of tumors. Therefore, a precision oncology approach will be necessary to target the private druggable mutations in individual patients in order to overcome this disease. It is clear that our current standard of single-site biopsy cannot capture the detail of genomic alterations in the entire bulk tumor, and although clonal events, and perhaps shared subclonal events, may be captured in a single biopsy, it is impossible to distinguish these alterations from subclonal private events.

Certainly, single-cell genomic sequencing can, and has, addressed issues of intratumoral heterogeneity and tumor evolution within a single sample. However, the limitations and costs of this approach to sequence all tumor cells combined with informatics resources required to apply this approach preclude its clinical use. What are our alternatives? Morrissy et al found that with as few as 2 biopsies and genomic sequencing, the gestalt extent of heterogeneity (high vs low) can be determined,
with a 50% chance of identifying half of the total number of genetic alterations. Although this does not provide the full repertoire of all actionable mutations, it certainly provides us with more information from our single-biopsy approach and may not be far from application in the clinic.

Although challenging to deal with, the high mutational burden of certain GBMs can be used to our advantage. For example, it is known that increased mutational burden is correlated with response to immunotherapies in solid cancers; therefore, it is possible that immunotherapies may play a larger therapeutic role, particularly in O6-methylguanine-DNA methyltransferase unmethylated GBM. Moreover, the presence of both shared and private neoantigens detected in this study suggests that polyvalent vaccination strategies combined with non-vaccine immunotherapies targeting shared neoantigens may be a viable therapeutic approach that requires further investigation.

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References