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Unmasking the multiforme in glioblastoma

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Abstract

Classification of glioblastomas into various molecular entities is required for the successful application of targeted therapeutics and personalized cancer therapy. Analyses of gene expression, genomic mutations and DNA copy number identified four molecular subtypes among histopathologically indistinguishable glioblastomas. This classification suggests the existence of distinct paths of tumor cell origin and variation in therapeutic sensitivity.

Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor in adults. Patients with this type of tumor who are treated aggressively with surgery, radiation and chemotherapy face a median survival of only 15 months, and 2 year and 3 year survival rates of only 28% and 10%, respectively.[1] This dismal prognosis has driven the search for molecular determinants of glioma malignancy and therapeutic resistance, with the ultimate goal of developing targeted therapeutics that are more effective than currently available treatments. One component of this quest is to develop a molecular characterization of glioblastoma that can be used to predict natural history and treatment response. Identification of distinct molecular tumor subtypes is also expected to augment the application of personalized targeted therapeutic strategies. The Cancer Genome Atlas (TCGA) Research Network was established to generate a catalog of genomic abnormalities that alter and potentially drive tumorigenesis in specific cancers.[2] TCGA chose GBM to be the first cancer studied and, in 2008, conducted an interim integrative analysis of DNA copy number, gene expression and DNA methylation patterns found in glioblastoma tumor samples. The research network identified three critical pathways that are altered at high frequencies in glioblastoma, namely receptor tyrosine kinase signaling, p53 signaling, and retinoblastoma signaling. By building on the initial multidimensional TCGA genomic database, Verhaak *et al.* now propose a new molecular glioblastoma classification.[3]

Verhaak and colleagues conducted multidimensional genomic and hierarchical cluster analyses on 200 glioblastomas and 2 normal brain samples, validating their findings using an independent set of GBM expression profiles as well as glioblastoma xenograft models. On the basis of these results, the researchers propose a molecular stratification of glioblastoma consisting of four clinically relevant tumor subtypes—classical, mesenchymal, proneural and neural.[3] This stratification system has potentially important implications for our understanding of the origins of glioblastoma cells, the heterogeneity in glioblastoma cell

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Competing interests
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behavior, and tumor natural history. The system could also aid the identification of new therapeutic targets and the development of personalized therapy.

Previous genomic, transcriptomic and proteomic studies elucidated the molecular complexity and heterogeneity of glioblastoma and identified molecular fingerprints linked to variations in prognosis and/or therapeutic responses.[4,5] The four classifications proposed by Verhaak *et al.* place this molecular heterogeneity within a developmental biological context. In a somewhat similar fashion to the earlier molecular classification system proposed by Phillips *et al.*,[6] Verhaak and colleagues' scheme is based on the intriguing finding that the various glioblastoma subtypes can be related to specific normal neuronal lineages.[3] Indeed, the researchers found that the proneural, classical and neural subtypes were enriched for genes differentially expressed by oligodendrocytes, astrocytes and neurons, respectively.[3] Obvious questions regarding the origins of glioblastomas resurface from these associations. Notably, do the various subtypes develop from a common susceptible multipotent stem-like cell precursor but along different pathways, or are these subtypes derived from distinct, more-differentiated cells of origin? Direct evidence for tumor initiation at the level of a stem cell precursor is lacking, although the gene expression patterns identified by Verhaak *et al.*, taken together with their evidence suggesting that tumors do not transition between subtypes, seem to favor distinct developmental pathways from a common multipotent precursor.[3] A definitive answer to the question posed above might lurk within existing molecular databases but is more likely to come from studies that combine multidimensional bioinformatics with hypothesis-based science. Regardless of the method of investigation, future research that is stimulated by the multidimensional genomic analyses of Verhaak *et al.* and others will push the boundaries of the rapidly expanding interfaces between molecular oncogenesis, developmental neuroscience and neural stem cell biology.

One expected utility of a disease classification scheme, whether histopathological or molecular in nature, is the ability to describe discrete entities that predict distinct clinical behaviors. The WHO classification of infiltrative astrocytomas into various grades—grade II (low grade), grade III (anaplastic) and grade IV (glioblastoma)—has served this practical purpose reasonably well. No molecular classification scheme for glioblastoma is yet ready for routine clinical practice; however, some success has been experienced in using molecular characteristics of glioblastoma to predict prognosis and/or treatment response, with more success on the horizon. Heterogeneity in O^6-methylguanine-DNA methyltransferase (*MGMT*) gene silencing provides an excellent example. *MGMT* silencing, through methylation of the gene's promoter, sensitizes cells to alkylating agents. One study has shown that *MGMT* promoter methylation is a reliable outcome predictor in patients with newly diagnosed glioblastoma who are treated with temozolomide and radiation, with methylation being associated with increases in the rates of progression-free and overall survival.[1] Another example comes from the work of Colman and colleagues who, using a PCR-based methodology, identified a nine-gene expression profile that seemed to distinguish between favorable and poor outcomes in patients with glioblastoma independently of *MGMT* promoter methylation status.[5] A third example stems from the discovery that mutations in *IDH1* and *IDH2* (genes encoding $NADP^+$-dependent isocytrate dehydrogenases) are commonly found in grade II and grade III glioma and secondary but not primary glioblastoma. Yan *et al.* showed that *IDH1* and *IDH2* mutations are markers of a favorable prognosis in cases of grade III glioma and glioblastoma.[7] Verhaak *et al.* found that *IDH1* mutations segregate almost exclusively to the proneural glioblastoma classification—the tumor subtype associated with the most favorable survival rate.[3] Moreover, in a retrospective analysis of treatment responses, the researchers found that the proneural subtype benefitted least from combination therapies that were more intensive and potentially more toxic than standard regimens.[3] These associations between molecular tumor subtypes, patient prognosis and treatment response raise the prospect that molecular

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stratifications might be used to optimally balance prognosis and the intensity of treatment regimens for individual patients.

Current standard therapies are not designed to take into account the complex genetic backgrounds of tumors or to take advantage of increasingly accessible information regarding specific tumor-promoting molecular pathways. Molecular classification schemes provide a framework for the development of personalized therapeutic strategies that go beyond current traditional treatments. For example, the proneural subtype described by Verhaak *et al.* might be most sensitive to platelet-derived growth factor receptor (PDGFR) inhibition and cell differentiation strategies, as these tumors have a high frequency of *PDGFRA* mutations and overexpress genes (such as members of the *SOX* gene family) that are associated with arrested neural development. By contrast, classic subtypes might be selectively sensitive to epidermal growth factor receptor (EGFR) inhibition, as such tumors exhibit a high rate of *EGFR* amplification, as well as activating mutations or deletions in this gene. The potential benefits of a molecular stratification for glioblastoma are not yet realized. Nevertheless, excitement and expectation exist that such schemes will eventually allow neuro-oncologists to selectively direct the expanding armamentarium of expensive designer drugs to patients who will benefit most, thereby limiting treatment costs, reducing the risk of adverse events and optimizing efficacy.

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