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URL:

PTEN

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&md=Retrieve&dopt=full_report&list_uids=5728

EGFR

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&md=Retrieve&dopt=full_report&list_uids=1956

DLL3

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&md=Retrieve&dopt=full_report&list_uids=10683

Developing patterns

Gliomas are currently diagnosed using histopathological criteria; the main prognostic factors are tumour grade and age of the patient. There is now some evidence that gliomas might arise from neural-stem-like cells, so Heidi Phillips and colleagues set out to define the pattern of disease progression in gliomas in relation to stages of neurogenesis, and to establish molecular signature prognostic models.

First, the authors profiled 76 samples from newly diagnosed cases of anaplastic astrocytoma and glioblastoma using microarrays. Three clusters of tumour samples were identified with differential expression of 108 survival related genes — 35 of which were robust markers of the three tumour subtypes. One subtype was found to express genes associated with the normal brain and the process of neurogenesis (known as the proneural subtype), another expressed proliferation associated genes (the proliferative subtype) and a third subtype expressed genes associated with angiogenesis and mesenchymal origin (the mesenchymal subtype). Patients with the proneural subtype had better prognosis (median survival 174.5 weeks) than those with either the proliferation (60.5 weeks) or mesenchymal subtypes (65 weeks). Profiling of an independent set of 31 glioblastoma cases confirmed the prognostic value of this classification. The authors then compared the signatures of 26 pairs of matched specimens — primary and recurrent astrocytoma from the same patient — and found that on recurrence tumours tend to shift towards the mesenchymal phenotype.

So, what are the main features of each subtype, and how do they relate to neurogenesis? The poor prognosis

subtypes showed features of tumour cell proliferation or angiogenesis that were almost absent from the better prognosis proneural subtype. In addition, although poor prognosis subtypes expressed markers of undifferentiated neural stem cells and/or transit amplifying cells (progenitor cells), the proneural subtype expressed markers of neuroblasts or neurons. At the genomic level, most of the proliferative and mesenchymal tumours had losses on chromosome 10, which includes the *PTEN* (phosphatase and tensin homologue) locus, and gains on chromosome 7, which contains the *EGFR* (epidermal growth factor receptor) locus, whereas proneural tumours did not have these alterations. Notch pathway elements, including *DLL3*, were over-expressed in proneural tumours. The authors then investigated whether the phenotypes associated with changes in the Notch pathway and the Akt pathway (which is activated by changes in *PTEN* and *EGFR*) were directly associated with patient survival, and found that levels of

PTEN and *DLL3* mRNA formed a highly significant predictive model of survival in high-grade astrocytoma. These findings are intriguing, as both the Notch and Akt pathways have been implicated as key regulators in neurogenesis.

The authors propose a model for human gliomas in which all molecularly defined subtypes arise from cell types of similar origin, but that differential activation of signalling pathways leads some tumours to maintain more undifferentiated neural-stem-cell-like or transit-amplifying-cell-like phenotypes, whereas others adopt a phenotype closer to that of neuroblasts or immature neurons. Further confirmation of the correlation between stem cell biology and glioma aggressiveness should produce a useful molecular signature prognostic model.

Ezzie Hutchinson, Chief Editor,
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ORIGINAL RESEARCH PAPER Phillips, H. et al. Molecular subclasses of high-grade gliomas predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis. *Cancer Cell* 9, 157–173 (2006)