Nature Reviews Clinical Oncology | Published online 1 Aug 2017; doi:10.1038/nrclinonc.2017.122

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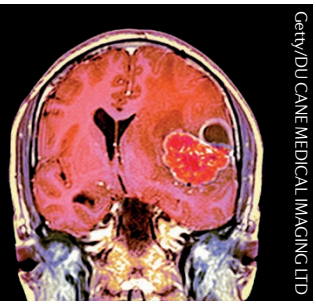
Glioblastoma subtypes revisited



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Glioblastoma (GBM) was previously classified into four subtypes (classical, neural, proneural, and mesenchymal) based on transcriptional features; however, the original classification, to varying degrees, included the transcriptomes of tumour-associated nonmalignant cells in the analysis. Now, the findings of a comprehensive longitudinal analysis of the GBM tumour transcriptome, excluding other cell types, reveal the existence of three (as opposed to four) distinct forms of GBM, and confirm the existence of GBM-subtype plasticity.

First author Qianghu Wang explains, "our interest was motivated by the question of how tumours evolve over time, and whether they maintain their transcriptional subtype at different stages of tumour development. In order to address that question, we needed to make sure the classification was tumour-cell based and not microenvironment/nonmalignant-cell based".

Researchers distinguished GBM-specific mRNAs from those associated with nonmalignant cells using three methods: comparisons of patient samples with their matched cell cultures; sequencing of RNA from single GBM cells; and comparisons of core versus peripheral biopsy samples. The more-stringent separation of the transcriptomes of GBM and non-GBM cells revealed three subtypes that were strongly enriched with mRNAs associated with the classical, proneural, and mesenschymal subtypes; however, none of these subtypes showed any enrichment with mRNAs associated with the neural subtype, suggesting this subtype arose from contamination of the original samples with nontumour cells.

Many GBM tumours have a high level of intratumour heterogeneity, as confirmed in this analysis. However, among patients with tumours with the lowest levels of heterogeneity, differences in median survival duration were observed between subgroups: 11.5, 14.7, and 17.0 months among those with mesenchymal, classical, or proneural tumours, respectively.

Researchers then investigated the phenotypic plasticity of GBM using paired samples taken prior to treatment, and upon recurrence. A total of 91 pairs were analyzed using the renewed gene-signature methods revealing that only 55% of GBM samples retained their original subtype. Changes in the microenvironment were also monitored longitudinally: notable differences in the presence of several immune cell types were observed, including enrichment of hypermutated GBM with $CD8^+$ T cells, suggesting sensitivity to CTLA-4 inhibition.

In conclusion, the findings of this investigation shed new light on the clinical course and subtypes of GBM, which remains notoriously unresponsive to treatment. When asked about future directions, Co-corresponding author Roel Verhaak explains: "we are currently developing a reference dataset of 500 longitudinally profiled GBMs (as well as 500 samples of each of the other two major glioma types) as part of an international consortium". He further adds that "longitudinally collected datasets, as reported in our study, are going to be front and centre in understanding how therapy resistance works in GBM", whilst highlighting that "this work would not have been possible without substantial contributions from the other laboratories involved, led by Erik Sulman and Do-Hyun Nam".

Peter Sidaway

ORIGINAL ARTICLE Wang, Q. *et al.* Tumor evolution of glioma-intrinsic gene expression subtypes associates with immunological changes in the microenvironment. *Cancer Cell* **32**, 42–56 (2017)