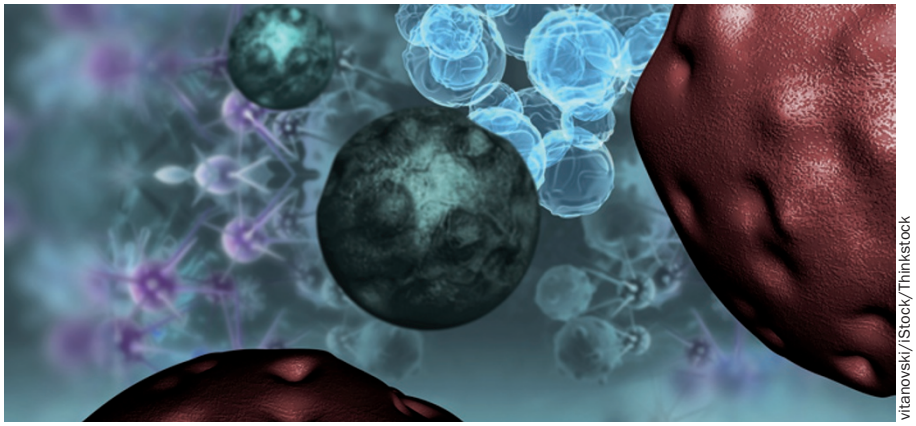
Nature Reviews Neurology **10**, 121 (2014); published online 11 February 2014; doi:10.1038/nrneurol.2014.21

NEURO-ONCOLOGY

Novel biomarkers for high-grade astrocytoma

Signatures based on circulating small noncoding RNAs and gene expression profiles can aid rapid and accurate diagnostic evaluation of high-grade astrocytoma, according to two recent studies. Marta Alonso and colleagues discovered that small noncoding RNAs in microvesicles released by glioblastoma tumours can be used to diagnose glioblastoma from serum samples. In another study, Kumaravel Somasundaram and co-workers demonstrated that a 16-gene signature present in biopsy samples enables anaplastic astrocytoma to be distinguished from glioblastoma.



vitanovski/iStock/Thinkstock

Glioblastoma is the most common malignant primary brain tumour in adults, and with median survival of less than 15 months, it is one of the most deadly cancers. Glioblastomas are fast-growing, invasive tumours, which means that delayed diagnosis can have devastating consequences for the patients: in a short period of time, a tumour that could have been successfully resected can diffusely invade the surrounding brain tissue, leading to poor prognosis and reduced survival.

Solid tumours such as glioblastomas release large quantities of microvesicles into the bloodstream. Previous studies have suggested that these exosomes are packed with tissue-specific proteins and microRNA (miRNA) molecules, which could serve as biomarkers. In a study published in *Neuro-Oncology,* Alonso and her team performed a quantitative assessment of the microRNA contents of serum microvesicles in 25 newly diagnosed, untreated patients with glioblastoma and 25 healthy controls. They found that expression of a splicing-related small noncoding RNA (RNU6–1) and two miRNAs (miR-320 and miR-574-3p) was markedly increased in glioblastoma-associated exosomes. The results were confirmed in an independent validation group of 50 patients.

According to Alonso, RNU6–1 alone or in combination with miR-320 and miR-574-3p could potentially provide a quick, noninvasive way to diagnose glioblastoma in cases where resection or biopsy is contraindicated, or biopsy results are inconclusive. In future, Alonso's team aims to find out whether the exosomal RNA signature could be used as a biomarker for prognosis and treatment response.

In a study published in *PLoS ONE*, Somasundaram and his research group described a method to differentiate anaplastic astrocytoma from glioblastoma. Correct diagnosis is important, because the therapeutic approaches for these two malignant cancers differ. Currently, diagnosis of high-grade astrocytoma is based on histological analysis of biopsy samples, but intratumour variation can lead to inconclusive results.

Somasundaram and colleagues had previously studied transcriptome changes in gliomas and discovered that gene expression profiles could potentially aid tumour grade classification and diagnosis. In their latest study, the investigators assessed gene expression profiles of 50 histologically confirmed anaplastic astrocytoma and 132 glioblastoma samples. The results revealed a 16-gene signature that could differentiate anaplastic astrocytoma from glioblastoma. The results were validated in multiple independent patient cohorts, which confirmed that the 16-gene signature could differentially diagnose anaplastic astrocytoma with 88–99% accuracy. In the few cases in which the 16-gene signature was discordant with the histology-based classification, the tumour-related biomarkers, along with age at diagnosis and patient survival times, suggested that the tumours were expressing both anaplastic astrocytoma-like and glioblastoma-like features. The signature could, thus, aid optimization of treatment for mixed-class astrocytomas.

Somasundaram hopes that other researchers will test the signature in further independent cohorts of patients. Besides differential diagnosis, the 16-gene signature could have prognostic value in high-grade gliomas. The findings also raise the possibility of developing a PCR kit that could be used for diagnosis and classification of gliomas.

According to Alonso, it would be interesting to test whether the 16-gene signature could be found also in circulating exosomes, thereby providing a noninvasive method for differential diagnosis of high-grade astrocytomas.

Hemi Malkki

Original articles Manterola, L. *et al.* A small noncoding RNA signature found in exosomes of GBM patient serum as a diagnostic tool. *Neuro Oncol.* doi:10.1093/neuonc/not218 | Rao, S. A. *et al.* A 16-gene signature distinguishes anaplastic astrocytoma from glioblastoma. *PLoS ONE* **9**, e85200 (2014)