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### **Genomic and expression profiling of glioblastoma stem cell-like spheroid cultures identifies novel tumor-relevant genes associated with survival.**

Ernst A, Hofmann S, Ahmadi R, Becker N, Korshunov A, Engel F, Hartmann C, Felsberg J, Sabel M, Peterziel H, Durchdewald M, Hess J, Barbus S, Campos B, Starzinski-Powitz A, Unterberg A, Reifenberger G, Lichter P, Herold-Mende C, Radlwimmer B.

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**PURPOSE:** Glioblastoma spheroid cultures are enriched in tumor stem-like cells and therefore may be more representative of the respective primary tumors than conventional monolayer cultures. We exploited the glioma spheroid culture model to find novel tumor-relevant genes. **EXPERIMENTAL DESIGN:** We carried out array-based comparative genomic hybridization of spheroid cultures derived from 20 glioblastomas. Microarray-based gene expression analysis was applied to determine genes with differential expression compared with normal brain tissue and to nonneoplastic brain spheroids in glioma spheroid cultures. The protein expression levels of three candidates were determined by immunohistochemistry on tissue microarrays and correlated with clinical outcome. Functional analysis of PDPN was done. **RESULTS:** Genomic changes in spheroid cultures closely resembled those detected in primary tumors of the corresponding patients. In contrast, genomic changes in serum-grown monolayer cultures established from the same patients did not match well with the respective primary tumors. Microarray-based gene expression analysis of glioblastoma spheroid cultures identified a set of novel candidate genes being upregulated or downregulated relative to normal brain. Quantitative real-time PCR analyses of 8 selected candidate genes in 20 clinical glioblastoma samples validated the microarray findings. Immunohistochemistry on tissue microarrays revealed that expression of AJAP1, EMP3, and PDPN was significantly associated with overall survival of astrocytic glioma patients. Invasive capacity and RhoA activity were decreased in PDPN-silenced spheroids. **CONCLUSION:** We identified a set of novel candidate genes that likely play a role in glioblastoma pathogenesis and implicate AJAP1, EMP3, and PDPN as molecular markers associated with the clinical outcome of glioma patients.

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