UKE Paper of the Month Mai 2024

A prognostic neural epigenetic signature in high-grade glioma

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ABSTRACT:

Neural–tumor interactions drive glioma growth as evidenced in preclinical models, but clinical validation is limited. We present an epigenetically defined neural signature of glioblastoma that independently predicts patients' survival. We use reference signatures of neural cells to deconvolve tumor DNA and classify samples into low- or high-neural tumors. High-neural glioblastomas exhibit hypomethylated CpG sites and upregulation of genes associated with synaptic integration. Single-cell transcriptomic analysis reveals a high abundance of malignant stemcell-like cells in high-neural glioblastoma, primarily of the neural lineage. These cells are further classified as neural-progenitor-cell-like, astrocyte-like and oligodendrocyte-progenitor-like, alongside oligodendrocytes and excitatory neurons. In line with these findings, high-neural glioblastoma cells engender neuron-to-glioma synapse formation in vitro and in vivo and show an unfavorable survival after xenografting. In patients, a high-neural signature is associated with decreased overall and progression-free survival. High-neural tumors also exhibit increased functional connectivity in magnetencephalography and resting-state magnet resonance imaging and can be detected via DNA analytes and brain-derived neurotrophic factor in patients' plasma. The prognostic importance of the neural signature was further validated in patients diagnosed with diffuse midline glioma. Our study presents an epigenetically defined malignant neural signature in high-grade gliomas that is prognostically relevant. High-neural gliomas likely require a maximized surgical resection approach for improved outcomes.

STATEMENT:

This is the first time that a neural epigenetic signature has been identified as a prognostic marker in high-grade glioma. Our work opens a completely new view of the molecular mechanisms underlying tumor progression and highlights the potential for targeted therapeutic strategies. It showcases how an interdisciplinary team of physicians and data scientists can close the gap of transitioning machine learning to the bedside.

BACKGROUND:

The work was carried out in multiple UKE departments, including the Klinik und Poliklinik für Neurochirurgie, the Institut für Neuropathologie, the III. Medizinische Klinik und Poliklinik (Nephrology, Rheumatology, and Endocrinology), and the Institute of Medical Systems Biology, in collaboration with four other university medical centers in Germany. The study was led by Franz Ricklefs (PI), Sonja Hänzelmann (Co-PI), Dieter H. Heiland (Co-PI), Richard Drexler, and Robin Khatri. Their scientific interest includes bridging the gap between biomedical data modeling and clinical applications to improve glioblastoma treatment. The study was funded by the German Research Foundation (DFG) and the Federal Ministry of Education and Research (BMBF).