A connectivity signature for glioblastoma [Abstract]

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Hypoxia upregulates SLC25A39, the putative mitochondrial glutathione transporter, to support glioblastoma growth and metabolism

Katherine Eales[1], Jennie Roberts[1], Cristina Escribano-Gonzalez[1], Colin Watts[2], Daniel Tennant[1]

[1]Department of Metabolism and Systems Research, University of Birmingham, United Kingdom
[2]Department of Cancer and Genomic Sciences, University of Birmingham, United Kingdom

Advancements in prevention, detection and treatment of gliomas over the last 40 years have consistently lagged behind those seen in many other tumour types. The hypoxic nature of glioma adds further complications to therapeutic efficacy, as hypoxia limits efficient drug delivery as well as increasing treatment resistance. Furthermore, it is known that hypoxia induces a metabolic shift in tumours which further contributes to this resistance. Therapies that therefore target both the hypoxic tumour microenvironment and metabolic pathways that sustain growth have significant potential to improve patient prognosis. Of the 53 mammalian SLC25A family members, which transport metabolites across the mitochondrial inner membrane, around 23 lack a defined substrate selectivity. Recent reports have suggested that the previously uncharacterised SLC25A39 member of the family is a putative glutathione transporter. It is therefore of significant importance in the regulation of the mitochondrial anti-oxidant response, and could play an important role in hypoxia. We have shown that SLC25A39 is functionally required to maintain cell proliferation of glioma cell lines and patient tumour cells. Metabolic analysis of these knockout/knockdown models suggest that SLC25A39 activity is required for appropriate function of the mitochondrial metabolic network, and its loss results in significant, wide-ranging metabolic dysfunction that spreads beyond the mitochondria. We have also shown that SLC25A39 expression is rapidly upregulated in response to hypoxia- through a HIF- and oxidative stress-mediated response. Excitingly, loss of SLC25A39 expression led to a sensitisation of hypoxic cells to cisplatin, suggesting that targeting this transporter may be a means of improving therapy efficacy for glioma. These data highlight the importance of identifying unknown metabolic transporters that are important for hypoxic tumour metabolism, thereby exposing a potential way to exploit hypoxic areas in these tumours, subsequently making them more vulnerable to treatment.
Keywords: glioblastoma; hypoxia; metabolism; mitochondria; transporter

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A connectivity signature for glioblastoma

Tobias Kessler[1,3], Ling Hai[2,3], Dirk C Hoffmann[3], Henriette Mandelbaum[3], Ruifan Xie[3], Jakob Ito[3], Erik Jung[1,3], Sophie Weil[1,3], Philipp Sievers[4], Varun Venkataramani[1,3], Daniel Dominguez Azorin[3], Kathi Ernst[5], Denise Reibold[3], Rainer Will[6], Mario L Suva[7], Christel Herold-Mende[8], Felix Sahm[4], Frank Winkler[1,3], Matthias Schlesner[2,9], Wolfgang Wick[1,3]

[1]Department of Neurology and Neurooncology Program, Heidelberg University Hospital, Germany
[2]Department of Bioinformatics and Omics Data Analytics, German Cancer Research Center, Heidelberg, Germany
[3]Department of Clinical Cooperation Unit Neurooncology, German Cancer Research Center, Heidelberg, Germany
[4]Department of Neuropathology, Heidelberg University Hospital, Germany
[5]Department of Pediatric Neurooncology, German Cancer Research Center, Heidelberg, Germany
[6]Department of Genomics and Proteomics Core Facility, German Cancer Research Center, Heidelberg, Germany
[7]Department of Pathology, Massachusetts General Hospital and Harvard Medical School, United States
[8]Department of Neurosurgery, Heidelberg University Hospital, Germany
[9]Department of Faculty of Applied Computer Science and Medical Faculty, University of Augsburg, Germany

Tumor cell extensions called tumor microtubes (TMs) in glioma resemble neurites during neurodevelopment and connect glioma cells to a network that has considerable relevance for tumor progression and therapy resistance. The determination of interconnectivity in individual tumors has been challenging and the impact of tumor cell connectivity on patient survival remained unresolved so far. Here, a connectivity signature from single-cell RNA-sequenced (scRNA-Seq) xenografted primary glioblastoma (GB) cells was established and clinically validated. Thirty-four of 40 connectivity genes were related to neurogenesis, neural tube development or glioma progression, including the TM-network-relevant GAP43 gene. Astrocytic-like and mesenchymal-like GB cells had the highest connectivity signature scores in scRNA-Seq data of patient-derived xenografts and patient samples. In 230 human GBs, high connectivity correlated with the mesenchymal expression subtype, TP53 wildtype, and with dismal patient survival. CHI3L1 was identified as a robust molecular marker of connectivity. Thus, the connectivity signature allows novel insights into brain tumor biology, provides a proof-of-principle that tumor cell connectivity is relevant for patients' prognosis, and serves as a robust biomarker that can be used for future clinical trials.
Keywords: glioblastoma; tumor microtubes; single-cell RNA-sequencing; connectivity; gene expression signature