

ABSTRACT

Brain. 2022 Jul 28:awac222. doi: 10.1093/brain/awac222. Online ahead of print.

Astrocyte immunometabolic regulation of the tumour microenvironment drives glioblastoma pathogenicity.

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Malignant brain tumours are the cause of a disproportionate level of morbidity and mortality among cancer patients, an unfortunate statistic that has remained constant for decades. Despite considerable advances in the molecular characterization of these tumours, targeting the cancer cells has yet to produce significant advances in treatment. An alternative strategy is to target cells in the glioblastoma microenvironment, such as tumour-associated astrocytes. Astrocytes control multiple processes in health and disease, ranging from maintaining the brain's metabolic homeostasis, to modulating neuroinflammation. However, their role in glioblastoma pathogenicity is not well understood. Here we report that depletion of reactive astrocytes regresses glioblastoma and prolongs mouse survival. Analysis of the tumour-associated astrocyte transcriptome revealed astrocytes initiate transcriptional programmes that shape the immune and metabolic compartments in the glioma microenvironment. Specifically, their expression of CCL2 and CSF1 governs the recruitment of tumour-associated macrophages and promotes a pro-tumorigenic macrophage phenotype. Concomitantly, we demonstrate that astrocyte-derived cholesterol is key to glioma cell survival, and that targeting astrocytic cholesterol efflux, via ABCA1, halts tumour progression. In summary, astrocytes control glioblastoma pathogenicity by reprogramming the immunological properties of the tumour microenvironment and supporting the non-oncogenic metabolic dependency of glioblastoma on cholesterol. These findings suggest that targeting astrocyte immunometabolic signalling may be useful in treating this uniformly lethal brain tumour.

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DOI: 10.1093/brain/awac222

PMID: 35899587