Nat Cancer. 2024 Jan;5(1):147-166. doi: 10.1038/s43018-023-00658-0. Epub 2024 Jan 3.

Lymphatic endothelial–like cells promote glioblastoma stem cell growth through cytokine–driven cholesterol metabolism

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PMID: 38172338 DOI: 10.1038/s43018-023-00658-0

Abstract

Glioblastoma is the most lethal primary brain tumor with glioblastoma stem cells (GSCs) atop a cellular hierarchy. GSCs often reside in a perivascular niche, where they receive maintenance cues from endothelial cells, but the role of heterogeneous endothelial cell populations remains unresolved. Here, we show that lymphatic endothelial-like cells (LECs), while previously unrecognized in brain parenchyma, are present in glioblastomas and promote growth of CCR7-positive GSCs through CCL21 secretion. Disruption of CCL21-CCR7 paracrine communication between LECs and GSCs inhibited GSC proliferation and growth. LEC-derived CCL21 induced KAT5-mediated acetylation of HMGCS1 on K273 in GSCs to enhance HMGCS1 protein stability. HMGCS1 promoted cholesterol synthesis in GSCs, favorable for tumor growth. Expression of the CCL21-CCR7 axis correlated with KAT5 expression and HMGCS1^{K273} acetylation in glioblastoma specimens, informing patient outcome. Collectively, glioblastomas contain previously unrecognized LECs that promote the molecular crosstalk between endothelial and tumor cells, offering potentially alternative therapeutic strategies.