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Tumor-Associated Microglia Secrete Extracellular ATP to Support Glioblastoma Progression

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Abstract

Glioblastoma (GBM) is a highly aggressive brain tumor with poor prognosis and high recurrence rates. The complex immune microenvironment of GBM is highly infiltrated by tumor-associated microglia and macrophages (TAM). TAMs are known to be heterogeneous in their functional and metabolic states and can transmit either protumoral or antitumoral signals to glioma cells. Here, we performed bulk RNA sequencing and single-cell RNA sequencing on samples from patients with GBM, which revealed increased ATP synthase expression and oxidative phosphorylation activity in TAMs located in the tumor core relative to the tumor periphery. Both in vitro and in vivo models displayed similar trends of augmented TAM mitochondrial activity, along with elevated mitochondrial fission, glucose uptake, mitochondrial membrane potential, and extracellular ATP (eATP) production by TAMs in the presence of GBM cells. Tumor-secreted factors, including GM-CSF, induced the increase in TAM eATP production. Elevated eATP in the GBM microenvironment promoted glioma growth and invasion by activating the P2X purinoceptor 7 (P2X7R) on glioma cells. Inhibition of the eATP-P2X7R axis attenuated tumor cell viability in vitro and reduced tumor size and prolonged survival in glioma-bearing mouse models. Overall, this study revealed elevated TAM-derived eATP in GBM and provided the basis for targeting the eATP-P2X7R signaling axis as a therapeutic strategy in GBM. Significance: Glioblastoma-mediated metabolic reprogramming in tumor-associated microglia increases ATP secretion that supports cancer cell proliferation and invasion by activating P2X7R, which can be inhibited to attenuate tumor growth.