# Exploring the Role of Peripheral Macrophages in Glioma Progression: The Metabolic Significance of Cyclooxygenase-2 (COX-2)


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## Abstract


Glioblastoma (GBM) is the most aggressive form of malignant gliomas, with the eicosanoid-synthesizing enzyme cyclooxygenase-2 (COX-2) playing a pivotal role in its progression via the COX-2/prostaglandin E2/4 axis. COX-2 upregulations in tumor cells induces a pro-inflammatory tumor microenvironment (TME), affecting the behavior of invading bone marrow-derived macrophages (Mϕ) and brain-resident microglia (MG) through unclear autocrine and paracrine mechanisms. Using CRISPR/Cas9 technology, we generated COX-2 knockout U87 glioblastoma cells. In spheroids and in vivo xenografts, this resulted in a significant inhibition of tumorigenic properties, while not observed in standard adherent monolayer culture. Here, the knockout induced a G1 cell cycle arrest in adherent cells, accompanied by increased ROS, mitochondrial activity, and cytochrome c-mediated apoptosis. In spheroids and xenograft models, COX-2 knockout led to notable growth delays and increased cell death, characterized by features of both apoptosis and autophagy. Interestingly, these effects were partially reversed in subcutaneous xenografts after co-culture with Mϕ, while co-culture with MG enhanced the growth-suppressive effects. In an orthotopic model, COX-2 knockout tumors displayed reduced proliferation (fewer Ki-67 positive cells), increased numbers of GFAP-positive astrocytes, and signs of membrane blebbing. These findings highlight the potential of COX-2 knockout and suppression as a therapeutic strategy in GBM, particularly when combined with suppression of infiltrating macrophages and stabilization of resident microglia populations to enhance anti-tumor effects.