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Glioma

Major finding: The primitive oligodendrocyte precursor cell (OPC) lineage is a primary contributor to gliomagenesis.

Mechanism: Reprogramming OPC intermediates to a stem-like state increases cell cycling and drives tumor growth.

Impact: Targeting factors that specify glial fate may serve as a potential therapy in patients with glioma.

DISTINCT TRANSITIONAL STATES OF GLIAL PROGENITORS DRIVE GLIOMAGENESIS

Previous attempts to uncover the molecular connections between normal glial progenitors and tumor cells have yielded limited success, largely due to high tumor heterogeneity. Weng, Wang, Wang, and colleagues exploited single-cell RNA sequencing (scRNA-seq) from neonatal mouse cortices and a murine model of glioblastoma to demonstrate that oligodendrocyte precursor cells (OPC) are a major contributor to glioma formation. Gene ontology analysis of neonatal astrocyte lineage cells identified nine clusters with distinct gene-expression signatures and corresponding subpopulations, including astrocytes and OPCs. Within the OPC cluster were two distinct subclusters, OPCs and a primitive OPC subpopulation (pri-OPC). scRNA-seq of the OPC population of the neonatal cortex revealed eight distinct groups of cells, the most abundant of which were OPCs, pri-OPCs, and cycling OPCs. In a murine model of glioma, pri-OPC–like cells were the most abundant population in malignant tissue. Within tumor tissue, pri-OPC–like cells expressed high levels of cell stemness and stress-associated and hypoxia-associated gene signatures, harbored increased chromosomal aberrations, and exhibited higher rates of cell-cycle progression as tumors developed, suggesting that genomic instability in pri-OCP–like cells leads to acquisition of stem cell–like properties that subsequently fuel tumor growth. Analysis of differentially expressed genes identified the transcription factor gene *Zfp36l1* as the primary driver of the OPC lineage commitment and glioma growth. In neonatal cortices and during glioma development, deletion of *Zfp36l1* resulted in reduced OPC and pri-OPC populations, reduced glioma cell proliferation and tumor burden, and extended overall survival. In human glioma, expression of *ZFP36L1* was enhanced compared to normal brain, and depletion of ZFP36L1 *in vitro* reduced spheroid formation and impaired cell-cycle progression. Taken together, these results identify pri-OPCs as the predominant contributors to gliomagenesis and show that disruption of lineage commitment to this cell type may serve as an effective therapy against glioma. ■

Weng Q, Wang J, Wang J, He D, Cheng Z, Zhang F, et al. Single-cell transcriptomics uncovers glial progenitor diversity and cell fate determinants during development and gliomagenesis. Cell Stem Cell 2019;24:707–23.

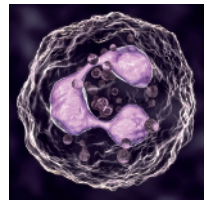
Immunology

Major finding: Fatty-acid transport protein 2 is required for the immunosuppressive activity of PMN-MDSCs.

Concept: FATP2 mediates immunosuppression via uptake of arachidonic acid and synthesis of prostaglandin E_2.

Impact: Inhibition of FATP2 may be a potential strategy to improve the efficiency of cancer therapy.

FATTY ACID TRANSPORT REGULATES NEUTROPHIL FUNCTION IN TUMORS



Polymorphonuclear myeloid-derived suppressor cells (PMN-MDSC) are pathologically activated neutrophils that contribute to failure of immunotherapy in cancer and are associated with poor clinical outcome. Despite similar origin and differentiation pathways, the mechanisms that drive distinct features of neutrophils and PMN-MDSCs remain poorly defined. Veglia and colleagues report that PMN-MDSCs upregulate fatty-acid transport protein 2 (FATP2) to alter lipid metabolism and drive immunosuppressive function. PMN-MDSCs isolated from the spleens of tumor-bearing mice expressed higher levels of *Slc27a2*, the gene encoding FATP2. Total or conditional deletion of *Slc27a2* from mice or PMNs, respectively, resulted in slower growth of transplantable mouse tumor models. Tumors established in mice reconstituted with bone marrow from *Fatp2*-knockout mice grew more slowly than in mice reconstituted with wild-type bone marrow, and depletion of $CD8^+$ T cells from tumor-bearing mice restored tumor growth in *Slc27a2*-knockout mice. *Fatp2* knockout from PMN-MDSCs resulted in decreased total and free arachidonic acid, reduced arachidonoyl-containing phospholipids, and lower intracellular and secreted levels of the FATP2 metabolite prostaglandin E_2 (PGE_2). Treatment of PMNs with arachidonic acid favored expansion of PMN-MDSCs that expressed increased levels of PGE_2 and suppressed antigen-specific T-cell responses. Treatment of PMNs with GM-CSF resulted in increased phosphorylation of STAT5, which bound the *Fatp2* promoter and upregulated its transcription. PMN-MDSCs from human patients with various cancers accumulated more lipids, expressed higher levels of FATP2, and contained significantly higher levels of free triglycerides, arachidonic acid, and PGE_2 compared with healthy donors. Inhibition of FATP2 significantly delayed tumor growth in several tumor models, and combined inhibition of FATP2 with either anti-CTLA4 or anti-CSF1R antibodies resulted in potent antitumor effects. Taken together, these findings identify FATP2 as a critical regulator of the immunosuppressive functions of PMN-MDSCs and present a highly specific method for targeting PMN-MDSCs in cancer. ■

Veglia F, Tyurin VA, Blasi M, De Leo A, Kossenkov AV, Donthireddy L, et al. Fatty acid transport protein 2 reprograms neutrophils in cancer. Nature 2019;569:73–8.

AACR American Association for Cancer Research

CANCER DISCOVERY

Fatty Acid Transport Regulates Neutrophil Function in Tumors

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