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Marauding monocytes, macrophages, and microglia in gliomas

Daniel W. Fults

Department of Neurosurgery, University of Utah School of Medicine and Huntsman Cancer Institute, Salt Lake City, Utah (D.W.F.)

Correspondence: Daniel W. Fults, M.D., Department of Neurosurgery, Clinical Neurosciences Center, University of Utah, 175 North Medical Drive East, Salt Lake City, UT 84132, USA (daniel.fults@hsc.utah.edu).

See the article by Lee et al in this issue, pp. 1463–1473.

The perverse tendency of gliomas to progress through stages of increasing malignancy over time has moved the thinking among neuro-oncologists away from a watchful waiting approach toward earlier therapeutic intervention. This shift has heightened the need to identify molecular markers that distinguish quiescent tumors from those likely to become more aggressive. Analyzing the genome of 90 malignant gliomas that had progressed from a lower histopathological grade, a research team headed by Ganesh Rao at The MD Anderson Cancer Center in Houston, Texas, found a positive correlation between prolonged patient survival and an inherited variant of the chemokine receptor protein CX3CR1 (V249I amino acid substitution) (Lee, 2020).[1] The ligand for this cell surface receptor is fractalkine (CX3CL1), a dual-function protein that mediates adhesion to or migration of CX3CR1-expressing leukocytes, depending upon whether fractalkine is in a membrane-anchored or secreted (soluble) state, respectively.[2,3]

Citing literature that peripheral blood monocytes carrying the I249 variant of CX3CR1 have reduced binding affinity for fractalkine,[4] Rao and colleagues hypothesized that suppressed fractalkine–CX3CR1 signaling might make gliomas less aggressive. Earlier work by Rodero et al showed that in glioblastomas arising de novo (without apparent progression from a less malignant stage), CX3CR1-I249 correlated with longer overall survival times for patients and reduced infiltration of tumors by microglial cells.[5] Microglia are phagocytosing immune cells that permanently reside in the brain, whereas macrophages are interlopers that arise by differentiation of monocytes entering the brain from the bloodstream.[6] In a mouse model of neurofibromatosis type I, decreased expression of CX3CR1 delayed the formation of low-grade gliomas in the optic nerve, accompanied by decreased accumulation of microglia.[7] Taken together, these findings suggested that fractalkine–CX3CR1 signaling plays a causal role in the malignant progression of low-grade gliomas by creating an inflammatory tumor microenvironment.

To test this hypothesis, Rao's team used a mouse model of glioma in which platelet-derived growth factor B (PDGF-B) was overexpressed in neural progenitor cells by retroviral gene transfer. This model system is an effective testing platform for tumor progression genes because 70% of the PDGF-B–induced gliomas have low-grade histologic features and 30% have high-grade features. Ectopic expression of the active 249V form of CX3CR1 in combination with PDGF-B reversed the distribution to 70% high-grade and 30% low-grade tumors, with a corresponding downturn in animal survival. Consistent with observations in human tumor specimens, CX3CR1 expression in the mouse tumors increased the accumulation of cells showing positive immunostaining for ionized calcium–binding adapter molecule 1, a marker for macrophages and microglia.

Fractalkine–CX3CR1 signaling is not the only mechanism for generating an inflammatory, oncogenic microenvironment in gliomas. Blood-borne monocytes home to glioblastomas in genetically engineered mice completely lacking CX3CR1.[8] In fact, loss of CX3CR1 in bone marrow–derived inflammatory monocytes increased expression of interleukin-1β and cysteine-cysteine motif chemokine ligand 2 (CCL2), cytokine molecules that strongly attract monocytes from the bloodstream to inflamed tissue sites. Although CX3CR1 has different physiological effects in gliomas of different malignancy stages and genetic backgrounds, a unifying theme is emerging that accumulation of inflammatory cells promotes glioma growth.

The close association between inflammation and cancer is a basic tenet of oncology. Inflammatory monocytes and their derivative macrophages create an oncogenic tissue environment through multiple mechanisms.[9] Activated macrophages generate reactive oxygen molecules, like nitric oxide, which cause DNA damage and consequently accelerate mutagenesis. They secrete large quantities of proteolytic enzymes, like cathepsins and matrix metalloproteinases, which create migratory paths

for cancer cells by digesting the extracellular matrix.[10] Macrophages also secrete vascular endothelial growth factor, which induces angiogenesis, without which tumor growth is limited by an organ's normal blood supply.

Hope for targeting the inflammatory microenvironment therapeutically requires a clear understanding of the specific types of immune cells that accumulate in gliomas. Feng and colleagues warn us that the common descriptor *tumor-associated macrophages* refers to a heterogeneous cell population comprising not only macrophages, but also infiltrating blood monocytes and brain-resident microglia.[8] Overlapping expression of the common determinant antigens (CD molecules), which scientists use to define specific immune cells, frustrates attempts to identify these cell types accurately.

The idea that an inflammatory microenvironment promotes glioma progression raises concern about mobilizing the immune system to attack gliomas through immunotherapy and vaccination. An important goal for future neuro-immunology research will be to elicit a cytotoxic T-cell response against glioma cells without attracting microglia, monocytes, and macrophages.

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References

1. Lee S, Latha K, Manyam G, Yang Y, Rao A, Rao G. Role of CX3CR1 signaling in malignant transformation of gliomas. *Neuro Oncol.* 2020;22(10):1463–1473.
2. Bazan JF, Bacon KB, Hardiman G, et al. A new class of membrane-bound chemokine with a CX3C motif. *Nature.* 1997;385(6617):640–644.
3. Imai T, Hieshima K, Haskell C, et al. Identification and molecular characterization of fractalkine receptor CX3CR1, which mediates both leukocyte migration and adhesion. *Cell.* 1997;91(4):521–530.
4. Moatti D, Faure S, Fumeron F, et al. Polymorphism in the fractalkine receptor CX3CR1 as a genetic risk factor for coronary artery disease. *Blood.* 2001;97(7):1925–1928.
5. Rodero M, Marie Y, Coudert M, et al. Polymorphism in the microglial cell-mobilizing CX3CR1 gene is associated with survival in patients with glioblastoma. *J Clin Oncol.* 2008;26(36):5957–5964.
6. Sevenich L. Brain-resident microglia and blood-borne macrophages orchestrate central nervous system inflammation in neurodegenerative disorders and brain cancer. *Front Immunol.* 2018;9:697.
7. Pong WW, Higer SB, Gianino SM, Emnett RJ, Gutmann DH. Reduced microglial CX3CR1 expression delays neurofibromatosis-1 glioma formation. *Ann Neurol.* 2013;73(2):303–308.
8. Feng X, Szulzewsky F, Yerevanian A, et al. Loss of CX3CR1 increases accumulation of inflammatory monocytes and promotes gliomagenesis. *Oncotarget.* 2015;6(17):15077–15094.
9. Qian BZ, Pollard JW. Macrophage diversity enhances tumor progression and metastasis. *Cell.* 2010;141(1):39–51.
10. Egeblad M, Werb Z. New functions for the matrix metalloproteinases in cancer progression. *Nat Rev Cancer.* 2002;2(3):161–174.