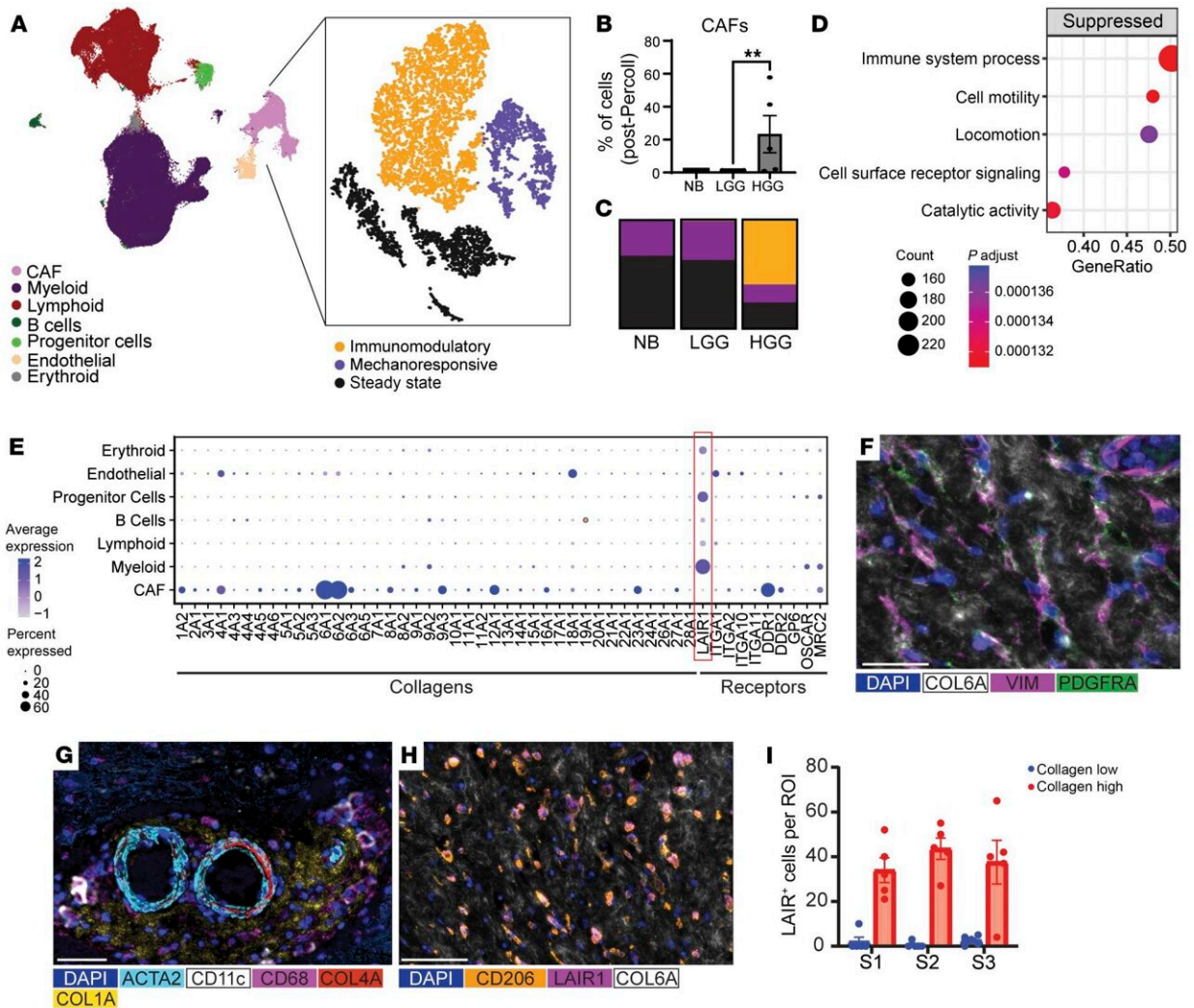


# Novel immune inhibitor associated with glioma progression

March 21 2024, by Melissa Rohman



CAFs are enriched in pediatric HGG relative to LGG and NB. (A) UMAP clustering from 21 pediatric brain samples. (B) The frequency of CAFs is a function of glioma grade. (C) Stacked histogram of CAF subtypes by glioma

grade. (D) Bubble plot depicting gene ontology (GO) analysis of functions that are suppressed by CAFs. (E) Dot plot displaying collagen and receptor expression within pediatric gliomas. (F) Multiplex imaging demonstrates PDGFRA<sup>+</sup>VIM<sup>+</sup>PDGFRB<sup>+</sup>ACTA2<sup>+</sup> CAFs embedded in COL6A1/A2 (white) within HGG. (G) ACTA2<sup>+</sup>COL4A<sup>+</sup> arteries were embedded in a COL1A1/A2 matrix infiltrated with immune cells. (H) LAIR1<sup>+</sup> myeloid cells embedded in COL6A1/A2<sup>+</sup> areas. (I) Quantification of LAIR1<sup>+</sup> cells in COL6A1/A2<sup>+</sup> areas versus areas without COL6A1/A2 in HGG. Credit: *Journal of Clinical Investigation* (2024). DOI: 10.1172/JCI1176613

Northwestern Medicine investigators led by Amy Heimberger, MD, Ph.D., the Jean Malnati Miller Professor of Brain Tumor Research and vice chair for Research in the Department of Neurological Surgery, have discovered a new mechanism in which cancer-associated fibroblasts mediate immune suppression in glioma tumors.

The findings, [published](#) in the *Journal of Clinical Investigation*, may also inform future immunotherapy strategies for patients who don't respond to standard treatment options.

In [solid tumors](#), cancer-associated fibroblasts (CAFs)—cells that form connective tissue—contribute to tumor formation and growth. CAFs have been known to reside in many solid tumor cancers and form a barrier around [cancer cells](#) to prevent them from being detected by T-cells.

Recent work has shown that CAFs are also present in glioblastoma, the most common and most aggressive primary brain cancer. This discovery prompted Heimberger's team to investigate whether CAFs are a function of glioma grade or aggressiveness.

In collaboration with Michael DeCuypere, MD, Ph.D., assistant

professor of Neurological Surgery in the Division of Pediatric Neurosurgery, the investigators used RNA sequencing to measure CAF frequency in low- and high-grade pediatric gliomas.

In high-grade gliomas, the investigators identified a higher frequency of a subtype of CAFs—immune modulatory cancer-associated fibroblasts.

"This study represents a unique look into the [tumor microenvironment](#) of pediatric high-grade gliomas, a previously understudied entity, and may open new avenues for immune-mediated therapy," DeCuypere said.

Multiplex staining revealed that these high-frequency CAFs were embedded in and produced collagen, which promotes tumor growth by triggering immunosuppressive mechanisms.

"These cancer-associated fibroblasts produce and are embedded in collagen, and this collagen contributes to the stiffness of the tumor," Heimberger said.

Next, by analyzing single-cell RNA sequencing data from both pediatric low and [high-grade gliomas](#), the investigators discovered that myeloid cells express an established immunosuppressive inhibitor, the LAIR1 protein, which is a key receptor for collagen. This receptor activates an immune inhibitory signal in myeloid cells (blood cells derived from [bone marrow](#)), which are frequent in gliomas, causing the myeloid cells to become unresponsive.

According to Heimberger, the findings could inform a new immunotherapy strategy for patients who don't respond to traditional immune checkpoint inhibitors.

"Since the expression of PD-1 and PD-L1 in gliomas is very low and since these tumors do not typically respond to these types of

immunotherapy, we have a new target that we can therapeutically consider," Heimberger said.

Shashwat Tripathi, a student in the Medical Scientist Training Program (MSTP), and Hinda Najem, MD, MS, a postdoctoral fellow in the Heimberger laboratory, were co-lead authors of the study.

**More information:** Shashwat Tripathi et al, Cancer-associated fibroblast–secreted collagen is associated with immune inhibitor receptor LAIR1 in gliomas, *Journal of Clinical Investigation* (2024).  
[DOI: 10.1172/JCI176613](https://doi.org/10.1172/JCI176613)

Provided by Northwestern University

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