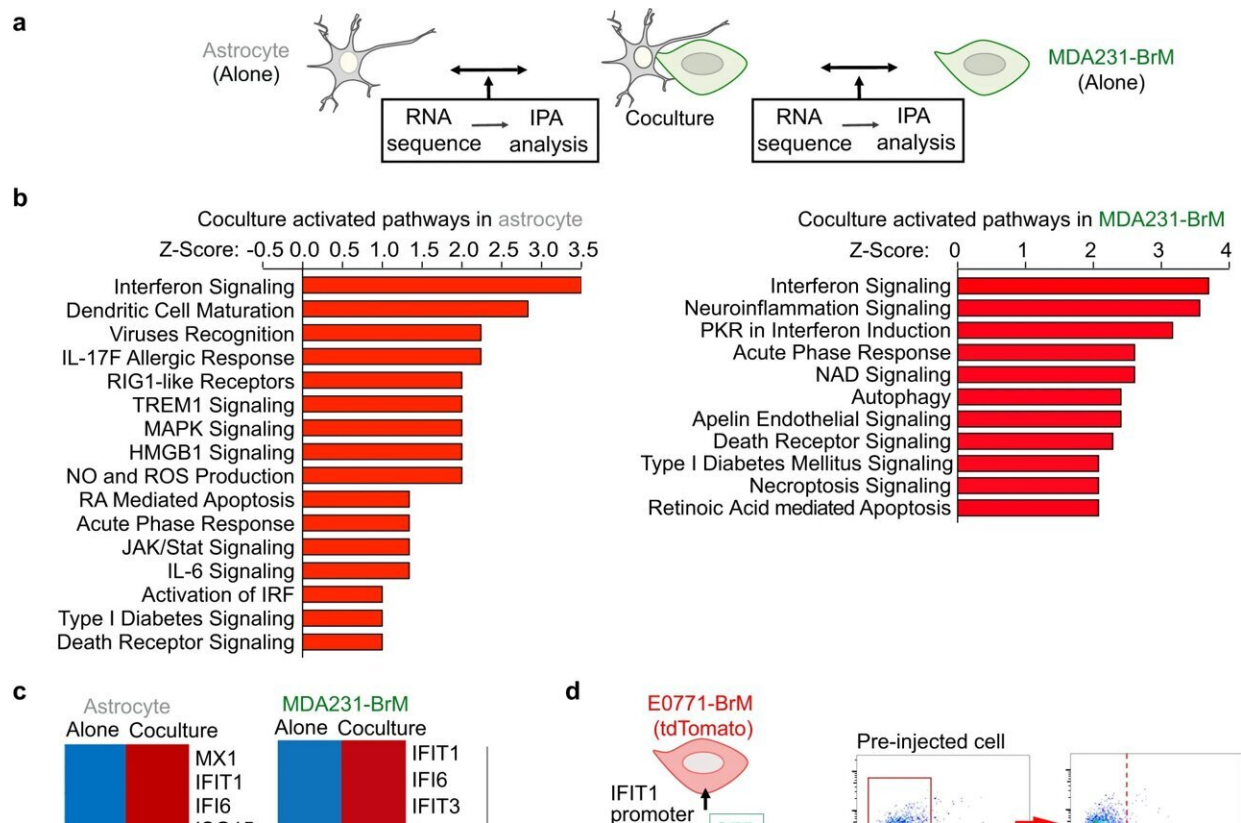


Study gives new insight into how cancer metastasizes to the brain

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IFN signaling is activated in brain metastasis. **a–c** IFN signaling is activated in both human astrocytes and MDA231-BrM cells by coculture in vitro. $N = 2$ biologically independent experiments per condition. **a** Scheme of RNA sequencing experiment setup. **b** Ingenuity Pathway analysis (IPA) comparing BrM-induced changes in astrocytes and astrocyte-induced changes in BrM cells. **c** Heatmaps of genes in IFN signaling pathway from IPA in astrocytes and BrM cells. **d, e** IFN pathway is activated in brain metastatic lesions in vivo. IFIT1-GFP reporter structure is expressed in E0771-BrM cells. The reporter

cells are injected into the experimental mice to track the activated IFN signaling in the brain metastasis microenvironment. **d** Macrometastatic lesions are isolated based on the luciferase signals in bioluminescent images (BLI), defined as BrM+ tissues. GFP expression in tdTomato⁺ BrM cells is detected by flow cytometry. **e** Representative images of intravital microscopy (IVM) observation of GFP expression in tdTomato⁺ BrM cells through an implanted cranial chamber. Vascular structure is outlined by orange dotted line. In the enlarged images, individual BrM cells are outlined by blue dotted line. Scale bar, 50 μ m. Representative data shown of three biologically independent experiments. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-38252-8

When cancer that starts in the body metastasizes to the brain, it is almost always lethal, in part because so few treatment options exist. Now a new study by Wistar scientists published in *Nature Communications* shows that a type of brain cell called astrocytes plays an important role in promoting brain metastasis by recruiting a specific subpopulation of immune cells.

The finding could be a first step toward identifying potential targets for therapies to fight cancers that metastasize to the brain. This would fill a significant unmet need, said researcher Qing Chen, M.D., Ph.D., assistant professor, Immunology, Microenvironment & Metastasis Program, Ellen and Ronald Caplan Cancer Center at The Wistar Institute. because [treatment options](#) for brain metastasis have lagged behind, even as advances in other [cancer](#) therapies have made enormous strides, making those cancers much more treatable.

"It can be devastating for patients and their families, because they go through so much treatment, they survive the [breast cancer](#), they all celebrate, and then it shows up in the brain," leading to a terminal diagnosis, she said.

Several types of cancer are known for metastasizing to the brain, including breast, lung, carcinoma, and melanoma. One reason conventional treatments do not work on these cancers after they reach the brain is because the brain is such a different environment from the rest of the body, with unique brain cells (neuron and glia cells) providing different support to the metastatic cancer cells.

For the study, researchers wanted to better understand the cancer-brain interactions that trigger metastasis when cancer cells enter the brain. They focused on astrocytes, a type of star-shaped cell that helps form connections between neurons.

Using brain metastasis mouse models, researchers showed that when the astrocytes were exposed to cancer cells, they began to activate type I [interferon](#) pathways. Type I interferon, the cytokines associated with regulating inflammation, have been shown to have anti-tumor effects. However, more and more evidence suggest controversial effects of type I IFN signaling in chronic inflammation and cancer.

"That was an exciting surprise," Chen said, adding that it was the first time the type I [interferon response](#) had been implicated to promote brain metastasis.

They found that the interferon response was being activated at a low level but for a prolonged period of time. This could explain why a process that is normally associated with helping the immune system was actually causing harm by supporting tumor growth. Previous studies have found that low-level, chronic interferon response can cause negative health outcomes, she noted.

When they took a closer look, researchers found that the interferon signaling was activating production of a chemokine called CCL2, which in turn attracted harmful immune cells called monocytic myeloid cells.

These cells promote tumor growth.

Researchers then studied mice that were genetically altered to abolish the type I interferon activation in astrocyte cells. They found that mice that were missing this pathway had fewer brain metastases.

"That shows the type I interferon response in astrocyte cells actually promotes metastasis," Chen said.

She noted researchers found a similar result with both melanoma and breast cancer cells, showing that the process—and potential therapeutic targets—occur across different cancer types.

Chen hoped the findings encouraged more researchers to study the interactions that lead cancers to metastasize in the [brain](#).

"It's an urgent need to have more people pay attention to this problem, and hopefully we'll have more basic researchers and clinicians participate in future studies, as well as more resources," she said.

Next, Chen's team is applying for a federal grant from the National Cancer Institute (NCI) for a follow up study to better understand the mechanism and timing of how astrocytes and the interferon response promote [brain metastasis](#), with a goal of identifying the best therapeutic window for treating and stopping this process.

More information: Weili Ma et al, Type I interferon response in astrocytes promotes brain metastasis by enhancing monocytic myeloid cell recruitment, *Nature Communications* (2023). [DOI: 10.1038/s41467-023-38252-8](https://doi.org/10.1038/s41467-023-38252-8)

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