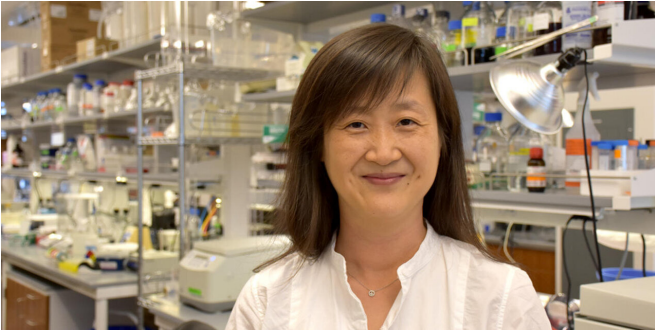


# New mechanism fueling brain metastasis discovered at Wistar

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Dr. Qing Chen of The Wistar Institute Credit: The Wistar Institute

Scientists at The Wistar Institute described a novel mechanism through which astrocytes, the most abundant supporting cells in the brain, also promote cancer cell growth and metastasis in the brain.

According to a study published online in the journal *Cancer Discovery*, astrocytes provide [fatty acids](#) that activate the PPAR-gamma pathway in [cancer cells](#), enhancing their proliferation.

Brain metastasis remains an important contributor to overall cancer mortality in patients with advanced-stage disease, especially lung, breast, colon and kidney carcinoma, and melanoma. Current therapeutic strategies have shown limited efficacy, underscoring the need to expand our knowledge of [brain metastasis](#) mechanisms to identify novel therapeutic targets.

"We know that cancer cells take advantage of the interaction with local cells, especially astrocytes, to survive and proliferate in the [brain](#) environment," said Qing Chen, M.D., Ph.D., assistant professor in the Immunology, Microenvironment & Metastasis Program and senior author of the study. "We wanted to understand the nature of this interaction

and what exactly astrocytes provide to support metastatic growth."

Chen and her collaborators focused on clinically relevant mouse models of melanoma brain metastasis and showed that astrocytes promoted cancer cell proliferation. By investigating the molecular mechanisms of this interaction, they found that the peroxisome proliferator-activated receptor-gamma (PPAR-gamma) pathway is activated in cancer cells that possess elevated ability to form brain metastasis, and it is even more active when these cells are co-cultured with astrocytes.

Genetic and pharmacologic blockade of PPAR-gamma signaling resulted in decreased [cancer cell growth](#) and a reduced response to [astrocyte](#)-induced proliferative effect, establishing the functional relevance of this pathway in brain metastasis.

The brain is the fattiest organ in the body, enriched in polyunsaturated fatty acids that are needed to support its functions. Astrocytes are a major cellular source of fatty acids. The team showed that polyunsaturated fatty acids released by astrocytes activate PPAR-gamma signaling in cancer cells, which in turn results in enhanced proliferation.

"Our data support that brain metastatic cells take advantage of the high fat supply provided by astrocytes as a nutrient source for their metabolism and growth," said Yongkang Zou, Ph.D., a postdoctoral fellow in the Chen lab and first author of the study.

Importantly, comparing normal skin, benign nevus, primary tumors, extracranial metastasis, and brain metastasis samples from melanoma patients, the team confirmed the highest PPAR-gamma levels in brain metastatic lesion.

Furthermore, treatment of mouse models of

melanoma and breast [cancer](#) brain metastasis with a PPAR-gamma inhibitor decreased the metastatic burden and was well tolerated.

"Previous studies have indicated a tumor-suppressive function for PPAR-gamma in primary tumors," said Chen. "Our work suggests that this pathway may play an opposite role in metastatic [cells](#), particularly in the lipid-rich brain environment, and highlights PPAR-gamma as a viable therapeutic target to control brain metastasis."

**More information:** YongKang Zou et al, Polyunsaturated Fatty Acids from Astrocytes Activate PPAR Gamma Signaling in Cancer Cells to Promote Brain Metastasis, *Cancer Discovery* (2019). [DOI: 10.1158/2159-8290.CD-19-0270](https://doi.org/10.1158/2159-8290.CD-19-0270)

Provided by The Wistar Institute

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