

Manipulating mitochondrial shape may limit metastatic cancer, study finds

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Study leader Srinivas Malladi, Ph.D., (left) worked with postdoctoral researcher Pravat Kumar Parida, Ph.D., to investigate the changing shape of mitochondria in breast cancer cells that migrate to the brain. Credit: UT Southwestern

Mitochondria that power cellular activity fragment and change shape in breast cancer cells that migrate to the brain, an adaptation that appears necessary for the cells to survive, UT Southwestern Medical Center researchers report in a new study. The findings, published in *Nature*

Cancer, could lead to new ways to prevent brain metastases, or the spread of cells from primary tumors to the brain.

"Through mitochondrial plasticity, these cancer cells undergo metabolic reprogramming that aids their survival in the brain niche that otherwise would not be available to them. Exploiting this vulnerability could offer a way to prevent brain metastases," said study leader Srinivas Malladi, Ph.D., Assistant Professor of Pathology at UT Southwestern and a member of the Harold C. Simmons Comprehensive Cancer Center.

Metastatic cancer, which is treated as stage IV cancer, is responsible for the majority of cancer deaths.

The Malladi lab focuses on understanding how cells that escape from a primary tumor can live in different locations in the body, often for years, before emerging as [metastatic cancer](#). Using [breast cancer](#), a disease that commonly metastasizes to the brain, as a model, Dr. Malladi and his colleagues discovered that cancer cells that migrate to the brain reprogram their metabolism to depend on fatty acids rather than carbohydrates as a main energy source.

This switch is necessary to survive in the brain, which is a completely different environment, Dr. Malladi explained. But how the cells accomplish this metabolic switch was unclear.

To answer this question, Dr. Malladi and his team isolated latent metastatic (Lat) cells—cancer cells that had migrated from the primary tumor but had not begun actively forming new tumors—from the brains of mouse models. They observed that these Lat cells have distinctly shaped "punctate," or dot-like, mitochondria compared to the primary tumor cells with elongated tubular mitochondria. Moreover, the Lat cells readily used fatty acids. This suggested that the mitochondrial shape change or plasticity was necessary for [fatty acid metabolism](#).

Further experiments showed that the fragmentation was driven by an increase in a protein known to be involved in mitochondrial fission called dynamin-related protein 1 (DRP1). When the researchers used a genetic technique to decrease the amount of DRP1, the Lat cells' mitochondria regained their tubular shape and lost the ability to metabolize fatty acids. Similarly, when they used a chemical that inhibited DRP1, Lat cells residing in mouse brains formed fewer metastases and were significantly less likely to survive.

A separate examination of metastatic tumors that formed in breast cancer patients showed that a phosphorylated form of DRP1 was elevated, suggesting that this phenomenon occurs in humans as well, Dr. Malladi said.

He and his colleagues plan to test DRP1 inhibitors to determine whether they might prevent, slow, or reverse metastatic disease, an important next step toward developing a treatment.

More information: Pravat Kumar Parida et al, Limiting mitochondrial plasticity by targeting DRP1 induces metabolic reprogramming and reduces breast cancer brain metastases, *Nature Cancer* (2023). [DOI: 10.1038/s43018-023-00563-6](https://doi.org/10.1038/s43018-023-00563-6)

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