Researchers show how brain's micro-environment fuels metastatic tumor growth

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James Driscoll, MD, PhD.

When a cancer cell breaks off from a tumor in the breast, lung or other part of the body and flows through the bloodstream to the brain, trouble erupts. Like a dandelion seed landing in the most fertile of soils, the tumor cell takes root, multiplies and rapidly grows into an often lethal metastatic brain tumor.

Why this happens with such deadly force in the brain is not completely understood. But how the process unfolds is vividly described by cancer researchers at the Brain Tumor Center at the University of Cincinnati (UC) Neuroscience Institute and UC Cancer Institute in a paper published [online today] in the Nature Publishing Group journal *Scientific Reports*.

The process is fueled by the interaction between cancer cells and brain cells, with the cancer cell acting as the seed and the brain tumor cells acting as the soil, says James Driscoll, MD, PhD, assistant professor in

the UC Department of Internal Medicine's Division of Hematology Oncology and the study's lead investigator.

"Our focus is on the brain and specifically these cell-to-cell interactions in the tumor microenvironment, where the tumor cell—the seed—usurps the surrounding beneficial effects of the normal, healthy cells in the brain tissue to actually flourish and blossom within that environment," Driscoll says.

In their paper, the researchers describe a kind of domino effect that begins when cancer cells come in physical contact with astrocytes, the most common type of brain cell. When that occurs, a small molecule known as microRNA 768-3p is reduced inside the tumor cell, and a signaling molecule known as K-ras increases. With elevated levels of K-ras acting like a kind of fertilizer, tumor growth blossoms while chemotherapy drugs are stifled.

"This only happens when cancer cells and brain cells are in direct contact," Driscoll says. "MicroRNA 768 regulates K-ras. When 768 goes down, the levels of K-ras go up. K-ras is the major player that drives tumor growth."

The research carries significant clinical promise. If microRNA-768 is a tumor suppressant that is battered and diminished during its contact with invading cancer cells, a synthetic, better-armored replacement for the molecule could potentially stand up to the cancer and prevent the rise of K-ras and tumor growth.

"The ultimate focus of our studies is to try to block or overcome the growth-promoting effect of the tumor micro-environment, just as you might block the growth of dandelions in your yard," Driscoll says. "We hope to advance these studies eventually to phase-1 and 2 clinical trials, in which we evaluate the efficacy on the overall survival of patients with

brain metastases."

The investigator-initiated study was funded by a pilot grant from the Brain Tumor Center Molecular Therapeutics Program and the Mayfield Education & Research Foundation. The Molecular Therapeutics Program, believed to be the first translational, metastasis-specific initiative of its kind in the United States, is a collaboration between the UC Neuroscience Institute and the UC Cancer Institute.

More than 170,000 people are diagnosed with metastatic brain tumors in the United States each year. Despite advances in surgical treatments, chemotherapy and targeted radiation treatment (radiotherapy), survival of brain metastasis remains limited.

Driscoll says researchers initially blamed the blood brain barrier and a cell membrane protein for blocking the effectiveness of chemotherapy drugs on metastatic tumors in the brain. But further research indicated that other, unidentified mechanisms were promoting the stubborn survival of these tumors.

Driscoll and other researchers have recently turned their attention to MicroRNAs. "These are newly discovered, evolutionary preserved small molecules that exist in normal and tumor cells," Driscoll says. "When deregulated, they can promote tumor initiation and metastasis."

In their study, Driscoll and his colleagues first combined lung, breast and melanoma cancer cells with healthy astrocytes in the laboratory. They found that cancer cells that had been "fertilized" with nutrients from the astrocytes showed heightened resistance to chemotherapy in a petri dish.

Moving from the lab to the real world, the researchers used 20 samples of metastatic tissue from the UC Brain Tumor Center's tissue bank to test their hypothesis that tumor cells that had comingled with astrocytes

had a diminished level of microRNA 768 compared to normal brain cells.

"We found microRNA-768 to be 100 times lower in metastatic tissue than in normal tissue," Driscoll says. "In one case of melanoma tissue, it was 600 times lower. This supported our premise that the brain micro-environment reduces 768 in real metastatic tumors."

Taking their research a step further, the researchers compared levels of microRNA 768 in both the primary and metastatic brain tumors of 10 patients.

"This was a rare, highly valuable study in which we looked at matched samples of different tumors in the same patient," Driscoll says. "Only through the highly coordinated efforts of surgeons, research teams and a tissue bank could you have such a controlled analysis of such precious tissue. We were able to demonstrate that this microRNA is reduced in metastatic tissue relative to the primary tumor tissue as well.

"We are also indebted to the patients who participated in our study," he adds. "Without them, our advancement of the molecular steps in brain metastases would not have been possible."

Driscoll and his team are now working to introduce a suppressor that blocks the reduction of microRNA-768.

"Our goal is to come back with synthetically engineered microRNA's as replacement therapy, to suppress the tumor cell growth," says Ronald Warnick, MD, medical director of the UC Brain Tumor Center and the John M. Tew, Jr., MD, Chair in Neurosurgical Oncology at UC. "The next step in our program is to evaluate microRNA replacement therapy for brain metastasis in a mouse model. If we can achieve that, we would then move rapidly toward our goal of human clinical trials and a phase-1

study."

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