Scientists reveal aggressive breast cancer's metastatic path

January 14 2013

Scientists at Weill Cornell Medical College have discovered the molecular switch that allows aggressive triple negative breast cancer cells to grow the amoeba-like protrusions they need to crawl away from a primary tumor and metastasize throughout the body. Their findings, published in *Cancer Cell*, suggest a novel approach for developing agents to treat cancer once it has spread.

"Metastasis can be lethal, and our findings point to potential targeted treatments to stop the spread of this aggressive breast cancer," says the study's senior investigator, Dr. Vivek Mittal, an associate professor of cell and developmental biology and director of the Lehman Brothers Lung Cancer Laboratory at Weill Cornell Medical College.

According to researchers, if such agents were developed, they would perhaps be the first to specifically treat cancer metastasis, importantly in patients whose tumors have already spread. They would also be among the first designed to restore the function of a microRNA (miRNA), a small, non-coding RNA that regulates gene expression, which is crucial to cancer spread. While distinct miRNA "signatures" have been found for many tumor types, including different breast cancers, their specific roles in later steps of cancer metastasis has been unclear, Dr. Mittal says.

In the study, researchers set out to identify a miRNA that impacts metastasis without affecting primary tumor growth, as well as address its underlying molecular mechanisms and therapeutic potential against metastatic breast cancer. They discovered that a miRNA known as

miR-708 is inhibited in metastatic triple negative breast cancer. They found that miR-708 acts as a metastatic tumor inhibitor, and when its function is restored, the tumors do not spread or form lethal macrometastases.

Silenced miRNA Inhibitor Molecule Can Be Switched Back On

Triple negative breast cancer has the worst outcome of all breast cancer subtypes because of its high recurrence rate and metastatic spread. This is why the research team chose to examine the role of miRNAs in the spread of triple negative breast cancer, which accounts for 15-25 percent of all breast tumors. The cancer is named "triple negative" because its tumor cells do not display two hormone receptors (estrogen and progesterone) or HER2/neu growth factor, which each form the basis of current targeted breast cancer treatments.

Using genome wide miRNA sequencing, Dr. Mittal and his research team found in human samples of triple negative breast cancer that miR-708 was significantly down-regulated with its normal expression curtailed. In both laboratory cells and in animal studies, the researchers identified that the normal role of miR-708 is to suppress the protein neuronatin, which is located on the membrane of a cell's endoplasmic reticulum—an organelle that stores calcium. Neuronatin helps control how much calcium leaves that organelle.

"It is calcium that provides legs to cancer cells to help them escape a tumor. So miR-708 acts as a suppressor of metastasis by keeping neuronatin in check," Dr. Mittal says. "If miR-708 is itself suppressed, there is an increase in production of neuronatin proteins, which then allows more calcium to leave the endoplasmic reticulum and activate a cascade of genes that turn on migratory pathways leading to metastasis."

Researchers found that delivering synthetic miR-708, carried by bubbles of fat, blocked metastatic outgrowth of triple negative breast cancer cells in the lung of mice. This makes miR-708 a promising therapeutic against metastatic breast cancer. The researchers also discovered that polycomb repressor complex proteins are responsible for silencing miR-708. These proteins remodel the way DNA is packaged in order to epigenetically silence genes.

Dr. Mittal adds that the findings suggest that pharmacological agents now being tested in lymphoma cancer cells may also help to restore miR-708 in triple negative breast cancer. These drugs are designed to inhibit histone-lysine N-methyltransferase EZH2, the member of the polycomb group that directly silences miR-708.

"It is exciting that there are now drugs that can turn off the silencing of these critical genes. They could very well work for this aggressive breast cancer," says Dr. Mittal. "Finding that there may be a way to shut down the spread of an aggressive breast cancer—which is the only way that triple negative breast cancer can be controlled and lives spared—is very promising."

"These study results are terrific," says co-author Dr. Linda Vahdat, director of the Breast Cancer Research Program, chief of the Solid Tumor Service and professor of medicine at Weill Cornell Medical College and medical oncologist at the Iris Cantor Women's Health Center at NewYork-Presbyterian Hospital/Weill Cornell Medical Center. "It not only offers us an avenue to treat metastatic triple negative breast cancer in the short-term, but also gives us the roadmap to prevent metastases in the long-run. We are anxious to get this into the clinic and are working as quickly as possible towards that end."

Provided by Weill Cornell Medical College