Study Discovers Key Switch in Breast Cancer Metastases

By Mike Fillon

Researchers from the University of Michigan may have discovered a small, but potentially mighty, piece of the metastasis puzzle.

In a preclinical study published in the Oct. 15, 2011, issue of Cancer Research, Sofia Merajver, M.D., Ph.D., scientific director of the breast oncology program at the University of Michigan Comprehensive Cancer Center in Ann Arbor, and colleagues, identified the molecule p38 mitogen-activated protein kinase (p38). This molecule affects breast cancer cells’ ability to spread to distant parts of the body: the hallmark of deadly, aggressive cancer. According to the National Cancer Institute, only 23.3% of women with metastatic breast cancer survive for more than 5 years.

"Motion is a key component in aggressive cancers, which is why it’s very important to understand what the key switches are for this motion,” said Merajver.

Merajver and colleagues conducted live cell studies across multiple cell lines precisely engineered to modulate expression of p38. The researchers also validated the results on the role of p38γ in human tissue samples. Results revealed that p38γ acts as a switch between mesenchymal motility and the less directed or minimal motility that flattened-out cells exhibit.

Specifically, p38γ-mediated cytoskeletal changes appear to control cell motility, according to a computational mechanical model. The cytoskeleton, present in all cells, is cellular scaffolding contained within the cytoplasm and made from protein.

Previous studies have shown that elevated expression of p38γ is associated with lower overall survival of patients with breast cancer. “Taken together, our results offer a detailed characterization of how p38γ contributes to breast cancer progression.”

The Mathematics of Movement

Merajver explained that the p38 molecule is an important player in metastasis because it sits at the hub of multiple signaling pathways. She elaborated, “p38γ in particular has received very little attention and yet it is as crucial—it makes a crucial decision to reorganize. By minimizing p38γ, the cell basically moves inefficiently, spends a lot of energy putting out feelers to move in multiple directions but doesn’t actually make much physical progress.”

In previous research, Merajver and her colleagues discovered that the cancer gene RhoC promotes metastasis. By following the pathway back to see what controls the cells to make them so aggressive, the team found that aggressive breast cancer expresses high levels of the p38 molecule. They inhibited p38γ in cell cultures and discovered the changes in shape and motion. This relationship persisted across multiple cell lines and in clinical breast cancer tissue samples.

Merajver said that besides the discovery of p38γ as a potentially important therapeutic target to keep aggressive breast cancers from moving rapidly, the new combination of live cell phenotyping, signaling studies, and mathematics is promising.

Collaborators in the University of Michigan College of Engineering developed the mathematical model to show how these changes would modulate cell motion. The computational models used the finite-element method to solve the partial differential equations governing the mechanics of cell motility.

The physical model of the cell, based on principles of continuum fluid mechanics, predicted the motion in the cell cultures. Furthermore, the model revealed that the observed cytoskeletal architectures in live cells that express high and low levels of p38γ determined the motion characteristics.

Merajver believes the model can be applied to other cancer types and will improve understanding of how all cancer cells move. She added that identifying p38γ’s role in breast cancer could lead to drug therapies that target only p38γ without affecting other pathways.

“The paper reveals a key component of the motility apparatus of an invading cancer cell,” says Robert A. Weinberg, Ph.D., professor of biology at the
Whitehead Institute for Biomedical Research in Cambridge, Mass. But that’s only one component in a multicomponent circuit board. It really does not deal with metastasis in general, but only a small part of it.”

So Much To Learn

Biologists know much about the steps that transform a normal cell into a cancer cell, but metastasis, which is responsible for 90% of cancer deaths, remains largely a mystery. Some snippets of understanding about metastasis have emerged. A study published in the June 25, 2004, issue of *Cell* reported that breast cancer tumor cells’ ability to travel through the body and form distant tumors appears to rely on their ability to appropriate a “sleeper protein” that plays an important role in early embryonic development. Weinberg, who cowrote the study, said that tumors spread by reactivating and hijacking a sleeper gene regulator protein called Twist. Twist determines when genes turn on or off. Twist is active only during embryonic development and enables cells to move from one part of the embryo to another; then it distributes these cells to different tissues.

But knowledge about metastasis remains sketchy at best, partly because although initial stages can be analyzed in vitro, metastasis is a multicomponent process, with potentially different tumor cell properties and molecules playing critical roles in different steps that must be studied in vivo.

Researchers know that metastasis is a cascade of linked sequential steps involving multiple host–tumor interactions. To grow at the metastatic site, a cell or group of cells must be able to leave the primary tumor, invade the local host tissue, and survive. Once invasive, it can spread through lymphatic channels, vascular channels, or both. Alissa Weaver, M.D., Ph.D., in the cancer biology department at Vanderbilt University Medical Center in Nashville, Tenn., said one thing that is not well understood is why cells grow into tumors only at selected organs. Another is dormancy. Often, cells will not grow out for many years. For example, a primary breast cancer might be taken out and the patient may develop metastasis more than 10 years later. “It is still unclear why some tumors would lay dormant apparently for a long time and suddenly grow into a new tumor. I can presume only that something changed in the microenvironment, but what that might be, we don’t really know,” said Weaver.

But according to Katrina Podsypanina, director of the Laboratory of Breast Cancer Biology at IRCM in Montreal, Canada, much is already known about metastasis—knowledge which has led only to more questions. “We actually understand more about metastasis than we can chew,” she said. “For example, we know that an important issue in metastatic behavior of cells is that most tumors do descend into circulation. A patient diagnosed with malignant tumor of any origin will have evidence of circulating tumor cells in the blood.”

Podsypanina said that what’s more important is determining which circulating cells will grow at the distant site and why not all of them do. “Until we know that specifically, we probably will not be able to treat patients with metastatic disease.”

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