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## Researchers Identify Genes that Drive Breast Cancer's Spread to the Brain

Researchers have uncovered the first genetic clues that suggest how invasive breast cancer cells pry their way into the tightly protected interior of the brain, where they can grow into new and lethal tumors.

Howard Hughes Medical Institute researcher Joan Massagué and colleagues at Memorial Sloan-Kettering Cancer Center have identified three genes that work together to fuel the spread of breast cancer to the brain. Their studies indicate that those renegade cancer cells use some of the same strategies that other breast cancer cells rely on to invade the lungs – but also need more specialized molecular tools to infiltrate the brain. The study is reported in an advance online publication on May 6, 2009, in the journal *Nature*.

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"This is the first paper of its kind that opens up a window into what it takes for cancer cells to attack the brain," Massagué said. "It shows that is possible to start deconstructing this problem. Until now we knew almost nothing about it."

Metastasis occurs when cells from a primary tumor break off and invade another organ. It is the deadliest transformation that a cancer can undergo, and is the cause of 90 percent of all cancer deaths. Metastases to the brain – usually from breast or lung cancers -- can be particularly devastating. Even with treatment, patients usually survive only six to 10 months after diagnosis. Despite its clinical impact, Massagué says, metastasis is poorly understood.

"Metastasis is what we fight with post-operative therapies, such as chemotherapy and radiation therapy, yet very little is known about the mechanisms that drive it," he said. "That inspired me and others to isolate metastatic cells from patients, and ask what these cells have -- above and beyond just being tumor cells -- that allows them to infiltrate and survive in distant organs."

Some cancerous cells, such as lung cancer cells, seem well equipped to invade multiple tissues soon after a tumor develops. But for breast cancer cells, metastasis takes time. When breast cancer spreads to distant organs, new tumors may not appear until years – or even decades -- after the original tumor has been removed from the breast. Massagué says this indicates that breast cancer cells do not become fully metastatic until they accumulate the genetic alterations that allow them to infiltrate new tissues and survive in that environment. “If metastasis occurs, the primary tumor must have released cells that were competent to be

released and to hide away,” he said. “However, when they were released, they evidently did not yet have everything that it takes to grow in the bones, or the lungs, or the brain. It may take years to acquire that capacity.”

Breast cancer metastases to the brain develop even more slowly than metastases to other organs. Massagué says this suggests that cells need a particularly specialized set of tools to enter and grow in the brain. This should not come as a surprise, he says, because the brain is well protected by a tightly woven, double-layered network of cells called the blood-brain barrier.

Massagué’s lab had already demonstrated that metastatic breast cancer cells acquire certain genetic characteristics that permit them to invade and survive in different organs, such as bone or lung. He likens cancer cells’ adaptation to these tissues to the evolution of different species of finches in the Galápagos Islands. Like the birds, whose beaks are shaped to best exploit the food source on individual islands, metastatic breast cancer cells acquire the specific properties they need to survive in a particular environment, Massagué says.

To find out which genetic adaptations are associated with brain metastases, the group implanted tumor cells from a patient with advanced breast cancer into mice. They later isolated cells that generated tumors in the brains of the mice. The scientists measured gene activity in the metastatic cells and found 243 genes whose expression appeared abnormal. They next measured the activity of those 243 genes in clinical tumor samples and narrowed their focus to 17 genes associated with brain metastases. “Cells that have these genes activated are better ready to invade the brain of a mouse,” Massagué explained. “We also found that patients whose primary tumors have these genes activated have a higher rate of brain metastases.”

“These results show that for entry into the brain tissue, breast cancer cells use some of the genes that they use to penetrate into the lung, but then some more. They are also using genes that are more specialized for the blood-brain barrier,” he said.

The next step, he says, is to see if they can determine the biological roles of these genes in cancer cells. His team has already done these kinds of studies for three of the candidate genes identified in their study. When they reduced the activity of any of the three genes in cells grown in the laboratory, those cells were not as effective at infiltrating a cellular model of the blood-brain

barrier. Two of the genes, COX2

and HBEGF, also help breast cancer invade the lungs. The third gene, ST6GALNAC5, appears to specifically enable metastasis to the brain. ST6GALNAC produces a protein that normally modifies the surface of cells in the brain. The cancer cells appear to use it to insinuate themselves into the brain “like a wolf in sheep’s clothing,” Massagué says.

Further characterization of the other genes Massagué’s group identified could provide new ideas for cancer therapy, or new markers to predict which cancers are most likely to spread to the brain, Massagué says. But importantly, their findings are already providing a new glimpse into the mechanisms that control metastasis to the brain.