

JUNE 26, 2003

Distinctive Genetic Program Guides Breast Cancers Deadly Spread

Researchers have peered inside breast cancer's toolbox and identified a set of rogue genes that accelerates the spread of cancer from its primary site in the breast to a secondary location in bone marrow. The genes identified by the scientists are distinct from those that spawn the initial tumor, which invites speculation about whether different cancers bear unique "gene expression signatures" that increase the probability that a cancer will spread in a process called metastasis.

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 therefore researchers have been looking for specific genes that propel metastasis. If they can identify distinctive metastatic gene programs for different cancers, it may be possible to slow or halt metastases by targeting the proteins produced by those genes.

"Our finding is that above and beyond the genetic signature that has created this tumor, there is a toolbox of overexpressed genes that the cancer cell will need."

— Joan Massagué

In the June 2003 issue of the journal *Cancer Cell*, researchers led by Howard Hughes Medical Institute investigator Joan Massagué at Memorial Sloan-Kettering Cancer Center, published a report showing that breast cancer metastasis to bone is mediated by a specific set of genes. Massagué collaborated on the studies with colleagues from the University of Texas Health Science Center.

"There has been a raging controversy in the cancer research field between two hypotheses," said Massagué. "One is the classical view that says that only a few cells in a tumor acquire alterations that render them increasingly metastatic. And of the millions of tumor cells that enter the circulation, the patient only gets a handful of metastases from these cells."

“By contrast, there has been recent evidence that primary tumors that go on to develop metastases already possess a ‘poor prognosis signature’ involving a group of genes whose high level of activity is indicative of the potential for metastasis,” he said.

To attempt to distinguish between these two models, Massagué and his colleagues used a precise technique to isolate specific cells from cultures of cells from a breast cancer patient who had died from metastatic disease. The researchers explored whether some of these types of isolated cells were better than others at metastasizing to bone - a major site of breast-cancer metastasis.

“Indeed, we did find that certain of these cells were more adept at metastasizing to bone when injected into mice,” said Massagué. “And when we analyzed the gene expression in these cells, we found a set of genes whose activity was specifically associated with this enhanced metastatic ability.”

These overexpressed genes enabled tumor cells to home in on bone, to trigger growth of blood vessels, and to recruit bone cells in the metastatic process, said Massagué. Furthermore, he said, the bone-metastasis genes were distinct from those in cells that metastasize to the adrenal gland.

“We also asked the question of whether these bone-metastasis genes were among the genes previously identified as part of the ‘poor prognosis signature,’ and the answer was zero, not a one,” said Massagué.

“This means that the metastatic gene signature defines and forms a violent society—a large group of cells in a tumor that are competent to become metastatic cells.” However, said Massagué, discovery of these metastatic genes does not invalidate the classical model that tumor cells require additional genetic mutations to metastasize.

“In and of themselves, these genes may not be mediators of metastases,” he said. “Our finding is that above and beyond the genetic signature that has created this tumor, there is a toolbox of overexpressed genes that the cancer cell will need; that will be the mediators for the cell to thrive in the bone marrow. So the poor-prognosis signature is bad news, but that signature is not enough.”

Massagué and his colleagues conducted two types of experiments to demonstrate that the metastatic-related genes were, indeed, causative in triggering cancer spread to the bone. In one series, they engineered poorly metastatic cells to overexpress different numbers of the genes they had identified as being necessary for metastasis to bone. They found that cells in which more of the genes were overexpressed showed more aggressive metastasis in mice.

In the second set of experiments, the researchers analyzed existing cultured breast cancer cells to determine which ones had more of the overexpressed genes they had found associated with metastasis. When they injected those cells into mice, the researchers found that that the more of the mutant genes

the cells possessed, the more aggressively metastatic they were.

Massagué said the findings indicate “we have basically identified a Darwinian process of selection at work. These cells just happen to accumulate the ‘winning combination’ of hyperactive genes that enables them to thrive in bone marrow. And once the traveling tumor cells pass through bone marrow, they are incredibly successful at attaching to and invading bone.”

According to Massagué, additional studies will be required to understand whether distinct collections of “metastatic genes” exist in other metastatic tumors, including breast cancers.

While the presence of these telltale proteins in the blood of cancer patients could give clues to the specific identities of the cancers, “I cannot be sure that such analyses will have major value in diagnosis,” said Massagué. “Imaging technologies for metastases are already very effective at detecting them. Nevertheless, some of these factors might be expressed at such high level by micro-metastases that they might become a first line of diagnosis.

“The much more conceivable possibility is that we could determine precisely what particular combination of genes is driving a patient's metastasis. And with that profile, we might be able to use specific blockers to attack and silence enough of these proteins to render the ‘metastatic toolbox’ ineffective, and to ameliorate metastatic growth.”