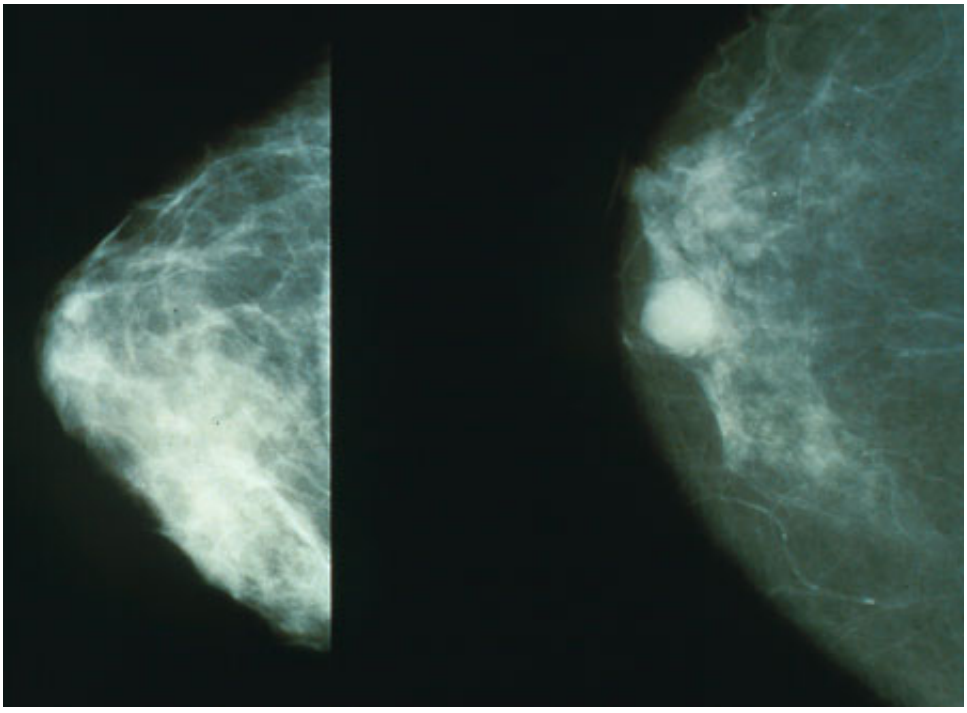
MedicalXpress

Metastatic breast cancer cells turn on stem cell genes

September 23 2015



Mammograms showing a normal breast (left) and a breast with cancer (right). Credit: Public Domain

It only takes seconds: one cancerous cell breaks off from a tumor, slips into the bloodstream and quickly lodges elsewhere in the body. These colonizers may bloom into deadly metastatic cancer right away or lie dormant for years, only to trigger a recurrence decades after the primary tumor is removed.

Metastases cause the vast majority of cancer deaths, but their tiny seeds are so difficult to track that few researchers have managed to study them. Now, scientists from UC San Francisco describe capturing and studying individual metastatic cells from human breast cancer tumors implanted into mice as the cells escaped into the blood stream and began to form tumors elsewhere in the body.

The researchers discovered that genetic programs expressed in these cells were quite distinct from the primary tumors in which they originated and included genes typically expressed in mammary stem cells. The findings, published online Sept. 23, 2015 in *Nature*, could change the way researchers think about how cancer spreads and suggest new drugs to track down and disable its deadly seeds.

For the most part, modern cancer drugs ignore differences between primary and metastatic tumors, said Zena Werb, PhD, professor and vice-chair of anatomy at UCSF, and a senior author on the new study.

"We test drugs for their ability to make primary tumors shrink, but most just don't work on metastases, and this leaves patients open to recurrence," Werb said. "Patients have their original tumor treated or removed, but then the cancer comes back 20, 30, 40 years later because there were just a few metastatic cells sitting around."

Catching metastatic cancer cells in the act

No one really knows how dormant metastatic cells can survive incognito for decades, said Devon Lawson, PhD, who led the research team as a UCSF post-doctoral researcher and is now an assistant professor of physiology and biophysics at UC Irvine.

"It's a big black box in the cancer field - mostly because it's very difficult to study," she said.

As a result, Lawson said, only about 7 percent of all breast cancer funding goes to studying metastatic cancer, despite the fact that it causes virtually all breast cancer deaths.

Previous work by Werb's group had found a subset of cells at the edges of breast cancer tumors that seemed primed to metastasize. Their close contact with the bloodstream and with proteins in the surrounding tumor microenvironment seemed to turn on genetic programs akin to those of mammary stem cells - the cells that allow breasts to form during puberty and grow during lactation. These genes for self-replication could make these cells particularly apt to generate new tumors elsewhere in the body. But the researchers had yet to catch the cells in the act.

In the new paper, the researchers used a technique called patient derived xenograft (PDX), which involves transplanting human tumor cells into mice. Against the backdrop of healthy mouse tissue, rogue metastatic cells from the human tumor stick out like flares. The researchers developed a new method using flow cytometry that let them capture individual human metastatic cancer cells traveling through the mouse's blood or lodged elsewhere in its body, then used newly-developed microfluidic technology to characterize the active genes in these rare cells.

"We were able to look at gene expression at a whole new level of resolution," Lawson said. "We could pull 12 metastatic cells out of the brain and tell you what is special about those 12 cells. Or the two cells we found in the blood. And we discovered there's something really unique about metastatic cells as they arrive in distant tissues."

Metastases show stem cell qualities

The team compared patterns of gene expression in human cancer cells lodged in different organs of the PDX mice and found stark differences

between early-stage and more advanced metastatic colonies. In metastases that had already grown and spread throughout an organ, the cancer cells' gene activity looked much like that of the primary tumor that had been transplanted into the mice, though with subtly different features specific to the new organ, whether lymph, liver, lung or brain.

In contrast, early-stage metastases and cancer cells traveling through the blood expressed genes typically active in mammary stem cells and quite distinct from primary tumor cells. In addition, these seed cells expressed specific genes that would be expected to keep them in a dormant, undifferentiated state and relatively immune to cell death, which the researchers surmised might help metastatic colonies survive in new and hostile environments.

Remarkably, the same signature pattern of gene activity was found in metastatic cells in mice whose tumors came from genetically and clinically diverse human patients. In other words, the genetic program that makes a cell metastatic did not depend on the genetics of its tumor of origin - suggesting that new techniques might allow researchers to find and specifically target these cells throughout the body in a variety of patient populations.

Insights could lead to targeted therapies

The research team performed a proof of principle experiment to demonstrate how valuable information about metastatic gene expression could be for drug development. Since metastatic cells that were beginning to differentiate into secondary tumors showed high expression of genes cMYC and CDK2, the researchers treated 24 PDX mice with dinaciclib, a CDK inhibiting drug known to kill off cells with high MYC levels. Whereas 44 percent of control mice (11 of 25) developed secondary tumors within four weeks, researchers could only find metastatic cells in one drug-treated mouse (4 percent).

Werb emphasized that this test was just a proof of principal and that dinaciclib itself may or may not prove be the ideal drug to target metastases. The key point, she said, was that the drug managed to nearly eliminate metastases without shrinking the primary tumor.

"If this drug had only been tested on primary tumors, we would have said it doesn't work," she said. "This tells us you actually have to look at metastases if you want drugs that treat them."

Preventing metastatic cells from invading other parts of the body has been a priority for cancer researchers for many years, said Andrei Goga, MD, PhD, professor of cell and tissue biology, and of medicine at UCSF and a co-corresponding author on the new study. "But practically speaking, by the time you've detected the tumor, that horse is either already out of the barn or it isn't. This new study is exciting because if you know the genetics of these early metastatic cells you can go after them specifically, wherever they are in the body. And that's the name of the game."

The researchers say the single-cell genomics they used in this study - which a consortium of researchers at UCSF are applying to diverse biological and clinical questions - could have a major impact on the emerging field of precision medicine.

"It's definitely a brave new world," Lawson said. "We couldn't have done this even five years ago. And this paper is just the tip of the iceberg."

More information: Single-cell analysis reveals a stem-cell program in human metastatic breast cancer cells, *Nature*, DOI: 10.1038/nature15260

Provided by University of California, San Francisco