Human breast tumors' 'microenvironment' primes them for metastasis

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The environment within primary breast tumors can “empower” cells that break free and enter the bloodstream to successfully invade other organs, researchers report in the April 4th *Cell*, a publication of Cell Press.

Specifically, through studies of hundreds of human breast tumors, the researchers found evidence that the cytokine TGFß in the tumor microenvironment primes breast cancer cells for metastasis to the lungs, one of the most common sites for the spread of breast and other cancers. TGFß signaling is often activated within tumors as a natural response to the oxygen starved and inflammatory conditions that come with tumor progression.

“ The microenvironment of a tumor is not just cancer cells, but all other cell types that congregate there,” said Joan Massague of Memorial Sloan-Kettering Cancer Center in New York. In recent years, he said, increasing attention has been paid to the impact those other body cells can have on the tumor locally, through their affects on blood vessel growth, the ability of cancer cells to enter the circulation, and so on.

“ Our study shows that it doesn’t end there,” he said. “The cancer cells can come out with instructions that serve them in the long run.”

The research team analyzed the expresssion of all 20,000 genes in the human genome within hundreds of primary breast tumors. Those tumors fell within two classical groups based on whether their estrogen receptor status was positive or negative (ER+ or ER-). In both tumor groups, the

researchers found that about 40 percent of the tumors bore the genetic signature of TGFß's influence.

They found that TGFß exposure didn't seem to make any difference to the risk of cancer spread in ER+ tumors. In ER- tumors, however, TGFß correlated markedly with an increased risk for metastasis to the lung, but not to bone. In other words, Massague said, "context matters."

The researchers continued to dig, ultimately uncovering the "fascinating biology" behind that correlation. They found that the TGFß exposure in ER- tumors leads to an increase in a second cytokine within the tumor cells, called angiopoietin-like 4 (ANGPTL4). Once those cells escape the tumor and lodge in the lungs, ANGPTL4 disrupts the connections between cells in the thin capillaries there. That separation of cell-cell contacts allows the cancer cells to cross the vessel wall and pass into the lung proper, Massague said.

The findings suggest that TGFß, or perhaps even better ANGPTL4, might serve as targets for drugs aimed at preventing the spread of breast cancer to the lungs. The TGFß signature could also offer a means of predicting those breast cancer patients at particularly high risk for developing metastatic lung cancer so that they might be monitored more closely and treated more aggressively with existing drugs.

Massague said he suspects the new findings are but one example of a more general cancer phenomenon.

"Entering and colonizing an organ requires of a tumor cell a number of special abilities," he said. After all, "our bodies are not made up of cells that are allowed to go anywhere as tumor cells [sometimes] manage to do. We've shown that factors within primary tumors can act on cancer cells to enhance their ability" to selectively spread to other tissues.

Source: Cell Press