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Study questions 'cancer stem cell' hypothesis in breast cancer

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A Dana-Farber Cancer Institute study challenges the hypothesis that "cancer stem cells" – a small number of self-renewing cells within a tumor – are responsible for breast cancer progression and recurrence, and that wiping out these cells alone could cure the disease.

Instead, the scientists report in the March issue of *Cancer Cell* that they have identified two genetically distinct populations of cancer cells in samples of human breast tumors – one of the types being a cell recently proposed by other scientists to be a true breast cancer stem cell.

"If the breast cancer cells were all coming from a single cancer stem cell, you might be able to cure the disease with just one drug," said Kornelia Polyak, MD, PhD, of Dana-Farber, senior author of the paper. "But our findings suggest that the tumor cells come from a ‘stem-like’ progenitor cell, and then diverge genetically, so I think you have to treat both cell types."

The results suggest that both cell types, and probably others, are involved in the development of breast cancer. While analyzing the genetics of each cell type, the
researchers discovered that the proposed "cancer stem cells" were driven by an activated molecular pathway that makes them resemble normal stem cells. Women whose breast tumors are largely made up of these "stem-like" cells are at higher risk of recurrences.

On the positive side, the abnormal activated pathway in these cells,

known as the TGF-Beta1 signaling pathway, can be blocked by experimental drugs now entering clinical trials, said Polyak, who is also an associated professor at Harvard Medical School. Such inhibitors, in combination with other therapies, may improve the prognosis in breast cancers fueled by these cells.

Clonal evolution or cancer stem cells?

According to a longstanding cancer model, known as "clonal evolution," tumors arise from normal cells that mutate and generate abnormal offspring that also mutate, forming a mass of genetically varied cancer cells. However, there has been a new wave of interest in an alternative explanation – that tumors are initiated and driven by a single, abnormal type of adult stem cell found in, for example, breast tissue, resulting in a population of genetically identical tumor cells. Moreover, several pathways and genes required for normal stem cell function are activated in cancer cells and play essential roles in the development of tumors.

According to the cancer stem cell hypothesis, the few self-renewing stem cells that fuel the cancer are difficult to kill, and their persistence may explain why tumors so often recur following successful therapy.

In 2003, scientists purified what they proposed were breast cancer stem cells from patients' tumors. The distinctive molecule, or marker, on the cells' surface, known as CD44+, was identical to the marker on normal breast cells. When injected into mice lacking an immune system, the CD44+ cells demonstrated the ability to initiate breast tumors. The scientists also found closely related cells with a CD24+ marker and suggested that they were offspring of CD44+ cells.

The team led by Polyak and Michail Shipitsin, also of Dana-Farber and HMS, used gene activity analysis to clarify the relationship of the two cell types. They generated gene libraries from CD24+ and CD44+ cells

purified from normal mammary epithelium and fluids within the chest, and from primary invasive tumor samples collected from breast cancer patients.

The findings, the scientists reported, fit more closely with the clonal model than the cancer stem cell hypothesis. That is, the CD24+ cells were very similar to the CD44+ cells, but not always genetically identical – which they would have been if the CD44+ cells were true stem cells and the CD24+ their offspring.

"Although CD44+ cells appear to express many stem cell markers, the genetic difference between CD24+ and CD44+ cells within a tumor questions the validity of the cancer stem cell hypothesis in breast cancer, and suggests clonal evolution involving intra-tumoral heterogeneity as an alternative explanation," the authors wrote.

Moreover, the Polyak team found that the CD44+ cells, but not the CD24+ cells were driven by the activated TFG-Beta1 pathway. For that reason, they said, "tumors composed of mostly CD44+ cells may have worse clinical behavior than tumors mainly composed of CD24+ cells, and these patients may benefit from therapy targeting the TFG-Beta1 pathway."

Source: Dana-Farber Cancer Institute