Gene therapy kills breast cancer stem cells, boosts chemotherapy

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Gene therapy delivered directly to a particularly stubborn type of breast cancer cell causes the cells to self-destruct, lowers chance of recurrence and helps increase the effectiveness of some types of chemotherapy, researchers at The University of Texas MD Anderson Cancer Center reported in the Sept. 13 edition of *Cancer Cell*.

In cellular and mouse studies, scientists found the gene mutation BikDD significantly reduced treatment-resistant breast-cancer initiating cells (BCICs), also known as breast cancer stem cells, by blocking the activity of three proteins in the Bcl-2 family. This genetic approach increased the benefits of lapatinib, one of the most common chemotherapy drugs for breast cancer.

"There are no effective methods to target BCICs, and they're urgently needed, especially for relapsed breast cancer patients," said senior author Mien-Chie Hung, Ph.D., vice president for basic research, professor and chair of MD Anderson's Department of Molecular and Cellular Oncology. "This research suggests a potential therapeutic approach to breast cancer stem cells that will minimize recurrence and drug resistance."

Special delivery system targets cells

Gene therapy was deposited directly into breast cancer cells with an innovative delivery system called VISA, short for versatile expression

vector, which was developed at MD Anderson. It includes a targeting agent, also called a promoter, two components that boost gene expression in the target tissue and a payload -- a Bik mutant gene called BikDD known to kill cancer cells. It's all packaged in a fatty ball called a liposome and delivered intravenously.

This system has been successfully applied in pancreatic, lung, liver and ovarian cancer preclinical models. MD Anderson clinical researchers are preparing a phase I clinical trial for pancreatic cancer.

Stem cells frequently stymie treatment

Breast cancer stem cells, often resistant to chemotherapy and radiotherapy, are a major obstacle for breast cancer treatment, Hung said. If any of these cells remain after treatment, a new tumor often forms. Although lapatinib, known commercially as Tykerb®, can stabilize the level of these cells, no drugs are available to reduce them.

The Bcl-2 family of proteins – especially the subtypes Bcl-2, Bcl-xL and Mcl-1 -- is essential for breast cancer tumor growth and treatment resistance. If too many of these three proteins are present, they can cause poor prognosis and resistance to chemotherapy drugs including lapatinib, as well as paclitaxel, doxorubicin and cisplatin.

This study shows that Bcl-2 proteins help breast cancer stem cells survive, causing resistance to treatment and likelihood of recurrence. However, using VISA to deliver BikDD can block the three key Bcl-2 proteins, eliminating the stem cells.

VISA-claudin4-BikDD cuts tumor burden

The researchers engineered a VISA that contained claudin4, a protein

over-expressed in breast cancer, as a targeting agent to preferentially express BikDD in breast cancer cells. This process silenced the three Bcl-2 proteins and caused the cancer cells to self-destruct. Since the VISA focused the BikDD on cancer cells, normal cells were not affected.

Treating mice with the VISA-claudin4-BikDD therapy reduced tumor volume by 75 percent compared to control mice.

They also compared VISA-claudin4-BikDD therapy to BikDD packaged with a non-specific strong promoter from cytomegalovirus. Both versions reduced tumor burden and extended survival of mice, but tumor volume in mice treated with VISA-claudin4-BikDD was half that of the CMV-BikDD-treated mice. In a safety study using an unusually high dose, 60 percent of mice treated with CMV-BikDD survived after three days; all mice treated with VISA-Claudin4-BikDD survived for the duration of the 14-day safety profile study.

In cell line experiments, the CMV-BikDD also invaded and destroyed normal cells, while the VISA-Claudin4-BikDD did not.

Agent energizes lapatinib, other drugs

BikDD made HER2-positive breast cancer cells more sensitive to lapatinib when all three Bcl-2 proteins were inhibited but not when they were inhibited separately. HER2-positive breast cancer is a particularly aggressive type that makes too much human epidermal growth factor 2; it accounts for about 20 percent of breast cancers. BikDD also sensitized EGFR+ (epidermal growth factor positive) breast cancer cells to lapatinib and several other breast cancer cells lines to paclitaxel.

Moving discovery forward

Hung said this approach is promising for breast cancer treatment, especially recurrent disease.

"VISA-claudin4-BikDD gene therapy may provide an effective strategy to inhibit breast tumor growth," he said. "It demonstrates virtually no toxicity in normal cells and produces a profound killing effect in multiple breast cancer cell lines and synergy with other agents."

Hung said the next step is to move VISA-claudin4-BikDD into a Phase I clinical trial to test its effect on patients with breast cancer.

Provided by University of Texas M. D. Anderson Cancer Center