Study explains why drug may help more cancer patients

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(Medical Xpress)—Recently some intriguing data has suggested that breast cancer patients whose tumors appear insensitive to a class of drugs known as anti-HER2 medications (the drug trastuzumab, marketed as Herceptin, is a well-known example) may somehow still benefit from treatment with the medication.

There's an ongoing clinical trial to determine if Trastuzumab, given in combination with other treatments, really is beneficial to more patients than previously thought. But the reason why it could be has been a mystery.

Now, a study from the laboratory of Maximilian Diehn, MD, PhD, assistant professor of radiation oncology, has started to answer some of these questions. The study was published online Oct. 31 in *Cancer Research*.

Typically, only tumors in which the cells express abnormally high levels of a receptor molecule, HER2, on their surfaces—about 25 percent of all breast cancer cases—seem to shrink in the presence of the drugs, which bind to and inactivate the receptor. As a result, only these patients are given anti-HER2 agents.

"Trials of anti-HER2 agents like Herceptin in metastatic patients with HER2-negative tumors haven't shown tumor shrinkage or improved outcomes, which is why these drugs are only approved for use in HER2-positive tumors," Diehn said.

However, Diehn said that recent clinical studies have indicated the drugs may also help breast cancer patients with tumors that don't express high levels of HER2—once most of the tumor has been removed through surgery or killed with radiation or other types of chemotherapy. Although these patients are considered to be in remission, microscopic numbers of cancer cells can remain and cause the disease to recur; treatment with anti-HER2 agents appears to improve their chances of survival.

Diehn and postdoctoral scholar Cleo Yi-Fang Lee, PhD, the lead author of the study, wondered why this could be. How could Trastuzumab and other anti-HER2 agents effectively fight tumors that didn't overexpress HER2? They hypothesized that perhaps the drugs were targeting only a few important cells in the tumor: the cancer stem cells. Also called tumor-initiating cells, cancer stem cells are able to both renew themselves and to generate all the cells of the original tumor. Killing them is vital to ensure that a tumor does not recur after seemingly successful treatment with chemotherapy, radiation or surgery. Unfortunately, these cancer stem cells are uncommonly resistant to normal cancer therapies.

"Our hypothesis was that the clinical observations described above could be explained if the anti-HER2 drugs work against microscopic deposits of cancer stem cells in at least a subset of HER2-negative tumors," Diehn said. "Patients with visible metastases of these types of tumors do not respond since since only a small proportion of cells in tumor deposits are cancer stem cells. However, if most of the tumor has been killed or removed through standard approaches, anti-HER2 drugs may effectively target remaining cancer stem cells and possibly prevent recurrence."

To understand how this could occur, Diehn, Lee and their colleagues studied breast cancer cells in mice and humans. They learned that, in a subset of tumors with low expression of HER2, the stem cells produce

high levels of a molecule called neuregulin 1. Neuregulin 1 works by activating HER2 in these cancer stem cells to promote their growth and self-renewal. Blocking HER2 or another molecule in the pathway, EGFR, together or separately inhibited the growth of breast cancer cells grown in the laboratory and after transplantation into mice. It also made the stem cells more sensitive to the types of radiation used in cancer therapies.

The researchers hypothesize that a similar mechanism may exist in other types of cancers.

"Anti-HER2 therapies are already being used for esophageal and gastric cancers, and they have been explored for use in other cancers like those of the head and neck," Diehn said. "It will be interesting to see if there is a similar dependence by cancer stem cells on HER2 signaling in the absence of HER2 amplification in some of these tumors."

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