The HER2 paradox: HER2-positive stem cells found in HER2-negative breast cancer

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A multicenter study led by researchers at UC Davis describes new, paradoxical characteristics of the most common type of breast cancer. The findings shed light on how the disease can evade treatment and could improve diagnosis and treatment of breast cancer.

The research, led by Jian Jian Li, director of translational research in the UC Davis Department of Radiation Oncology, examined breast tumors previously thought to lack the HER2 protein, which, when over-expressed, is associated with disease recurrence. Instead, researchers found in the tumors small groups of aggressive, treatment-resistant HER2-positive breast cancer stem cells (BCSCs). The findings will be published Dec. 15 in Clinical Cancer Research.

"These BSCSs are very resistant to traditional treatments, which can lead patients to relapse," said Li, the study lead author. "Despite chemotherapy, radiotherapy or even surgery, the cancer is still recurrent. These findings change our concept of breast cancer because now we know HER2-negative breast cancers can be treated effectively with anti-HER2 treatments."

In the past decade scientists and clinicians have developed a better understanding of how breast cancers differ on the cellular level. Whether a tumor contains HER2, an estrogen receptor protein, a progesterone receptor protein or all three or none can have an enormous impact on the tumor's aggressiveness, the patient's overall prognosis and treatment choices.

HER2-positive breast cancers are routinely treated with drugs that target the HER2 protein, such as Herceptin or Tykerb, with good results. However, until recently, there has been little reason to administer these targeted treatments to patients with HER2-negative cancer.

The team, which included researchers from the University of Michigan Comprehensive Cancer Center, the Holden Comprehensive Cancer Center at the University of Iowa, Emory University School of Medicine and MD Anderson Cancer Center, isolated the HER2-positive BCSCs from irradiated, HER2-negative breast tumors. They also analyzed the stem cells for CD44 and CD24, cell surface proteins that indicate cancer aggressiveness and act as BCSC markers.

The team found that the HER2-positive, CD44 positive, CD24 negative/low BCSCs were more aggressive and highly resistant to radiotherapy. These characteristics were significantly reduced by Herceptin or short interfering RNA. HER2 and CD44 positive BCSCs were found in 57.1 percent of primary tumors and 84.6 percent of recurrent tumors.

In addition to identifying this previously hidden group of HER2-positive stem cells, further examination provided new insights into how these BCSCs maintain their resistance to treatment. A complex network of proteins, including HER2 and STAT3, modulate metastasis, programmed cell death and other functions. As a result, these cells survive the gamut of traditional anti-cancer therapies.

"We feel this research will have a major scientific, as well as clinical, impact," says Li. "We now have a better understanding of how BCSCs resist radiation and other treatments."

While recent research has shown that patients with HER2-negative breast cancer can indeed benefit from HER2 treatments, prior to this

work no one understood the mechanisms. This research provides detailed confirmation that HER2 treatment can potentially improve outcomes in HER2-negative breast cancers.

In addition to opening up new treatment options for HER2-negative patients, the research also provides a diagnostic pathway. Markers, such as CD44, could help clinicians identify aggressive, HER2-positive BCSCs in cancers that are ostensibly HER2-negative, individualizing treatment to match each patient's needs. These findings may also advance treatment for other cancers.

"This may open the possibility of treating HER2-positive stem cells in bone, lung or brain cancers, which are all difficult to treat in the later stages," says Li.

Provided by UC Davis