MedicalXpress

Inflammatory pathway spurs cancer stem cells to resist HER2-targeted breast cancer treatment

July 19 2012

Breast cancer treatments such as Herceptin that target a marker called HER2 have dramatically improved outcomes for women with this type of cancer. But nearly half of these cancers are resistant to Herceptin from the start and almost all of them will eventually become resistant.

Now, researchers at the University of Michigan Comprehensive Cancer Center have discovered one reason why the cancer cells become resistant: They turn on a completely different pathway, one that is involved in inflammation, fueling the cancer independently of HER2.

The pathway at work involves a protein called Interleukin-6, or IL-6. The researchers also showed in mice that a drug that blocks IL-6 can stop this effect and overcome the Herceptin resistance.

"Resistance to HER2-targeted therapies remains a major challenge in treating breast cancer. Our study suggests that an IL-6 inhibitor in combination with Herceptin may be a valuable addition for treating HER2-positive breast cancer," says senior study author Max S. Wicha, M.D., Distinguished Professor of Oncology and director of the U-M Comprehensive Cancer Center.

Results of the study will be published in the Aug. 24 issue of *Molecular Cell*.

Not only are these cells resistant to Herceptin, but they develop higher proportions of cancer stem cells, the small number of cells within a tumor that fuel the growth and spread. This makes the tumor extremely aggressive and likely to spread throughout the body. The IL-6 inhibitor also was shown to prevent this increase in cancer stem cells.

"There is evidence that patients with a lot of IL-6 tend to do poorly. What we found now is that in many of the Herceptin-resistant breast cancers, the IL-6 inflammation loop is driving the cancer stem cell," says lead study author Hasan Korkaya, D.V.M., Ph.D., research assistant professor of internal medicine at the U-M Medical School.

The researchers found that blocking the IL-6 inflammatory loop almost completely blocked the cancer and the stem cells. Mice treated with the IL-6 blocker along with Herceptin immediately after the cancer developed never became resistant to Herceptin.

IL-6 is known to play a role in inflammatory diseases such as rheumatoid arthritis, as well as obesity and cancer. Tocilizumab, a drug that targets this protein, is approved by the U.S. Food and Drug Administration to treat rheumatoid arthritis.

The researchers are developing a clinical trial to test the IL-6 blocker along with Herceptin. That trial will likely open early in 2013.

Breast cancer statistics: 229,060 Americans will be diagnosed with breast cancer this year and 39,920 will die from the disease, according to the American Cancer Society

More information: Korkaya et al.: "Activation of an IL6 Inflammatory Loop Mediates Trastuzumab Resistance in HER2+ Breast Cancer by Expanding the Cancer Stem Cell Population," *Molecular Cell*, Aug. 24, 2012

Provided by University of Michigan Health System