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Researchers discover a key to aggressive breast cancer

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In trying to find out why HER2-positive breast cancer can be more aggressive than other forms of the disease, UC Davis Cancer Center researchers have surprisingly discovered that HER2 itself is the culprit. By shutting down its own regulator gene, HER2 creates a permissive environment for tumor growth.

Building on recent research showing that the regulator — labeled LRIG1 and commonly called "Lig-1" — limits the growth-promoting signals of HER2, the research team set out to clarify the role of Lig-1 in breast cancer.

They found that, when compared to healthy breast tissue, the regulator is significantly suppressed.

"This suppression assists HER2 in its own over-expression and in driving the growth of cancer cells," said Colleen Sweeney, associate professor of biochemistry and molecular medicine and senior author of the study, which appears in this month's issue of *Cancer Research*. "HER2 is clearly taking an active role its own ability to be successful in promoting cancer."

Sweeney added that the study results could lead to new treatments aimed at restoring or replacing functions of the regulator. This is good news for patients because, in addition to being more aggressive, HER2-positive breast cancer tends to be less responsive to currently available treatments. The gene is over-expressed in about one-quarter to one-third

of breast cancer cases.

Sweeney and colleagues began by studying mouse models of breast cancer with genomes that carry extra copies of HER2. They noticed an excess of HER2 protein in the resulting tumors, but it was not over-expressed in adjacent healthy tissues that also carried extra copies of the HER2 gene.

"That suggested to us that extra copies of HER2 alone are not enough to explain its over-expression. If it was, HER2 would have been over-expressed in both normal and tumor tissues from these mice," she said.

Given that observation, the team set out to determine what, exactly, created the permissive environment for HER2 over-expression. Given its tumor-suppressor role, Lig-1 levels were compared in the mouse models.

They found that Lig-1 was greatly diminished in tumor tissues when compared to the normal tissues. The researchers next conducted a series of laboratory experiments using human breast cancer cell lines and a technique called RNA interference that allows for selective depletion of cellular proteins.

Interestingly, they found the same results in the human breast cancers that they found in mice. In fact, 60 percent of 67 tumors analyzed showed a loss of the Lig-1 protein and its levels were, on average, 33 percent lower in tumor tissue versus healthy breast tissue.

"There was a clear inverse relationship between Lig-1 and HER2," said Sweeney. "When we depleted Lig-1, cancer cells grew almost 50 percent faster, while the opposite occurred when we restored Lig-1 to healthy levels. We also found that depleting HER2 levels resulted in an increase in Lig-1 levels, while activating HER2 resulted in Lig-1 depletion."

According to Sweeney, the results may help explain why, even among patients with HER2-positive breast cancer, the disease process can vary dramatically.

"We think Lig-1 levels could be linked to prognosis. Patients with more of the regulator gene's functions intact are going to have a better outcome than those with less," she said.

Results of the current study further support the notion that Lig-1 serves as a tumor suppressor gene, though more work is needed to confirm this outcome. Sweeney and her team are gathering more evidence to support this theory and to determine whether or not Lig-1 levels are truly predictive of outcome for HER2-positive patients. If so, it will suggest that, while this type of test is not available today, these patients should in the future be screened for Lig-1 activity in order to better define treatment subgroups.

"It's clear that stratifying breast cancer patients as either HER2-positive or HER2-negative is not telling the whole story. This research takes us a step further in the right direction toward better understanding types of breast cancer and treatment targets for those different types," Sweeney said.

Source: University of California - Davis