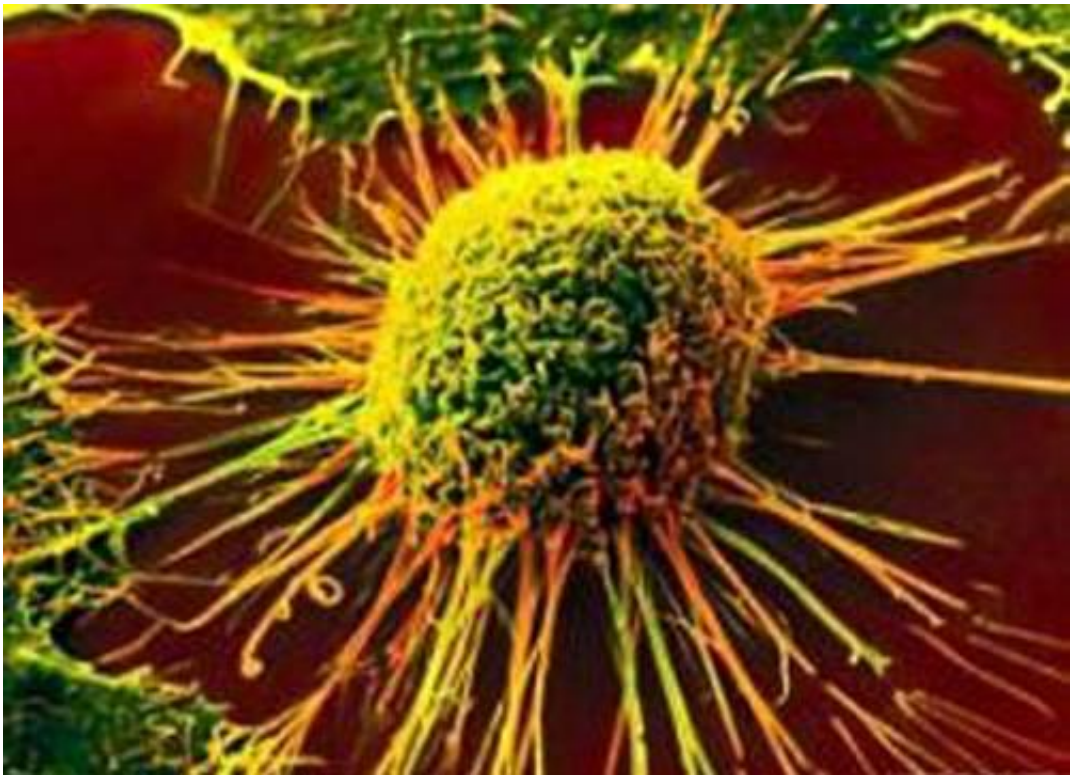
MedicalXpress

# Research team identifies master switch for cancer-causing HER2 protein

April 28 2015



Herceptin has been touted as a wonder drug for women with HER2-positive breast cancer, an aggressive form of the disease that is fueled by excess production of the HER2 protein. However, not all of these patients respond to the drug, and many who do respond eventually acquire resistance.

A team of researchers led by Mayo Clinic has found a promising way to circumvent this obstacle. They identified a small site in the HER2 protein that enables it to form a molecular switch that sets off a cascade of events that turn normal cells cancerous. The researchers showed that disrupting this site can stem the growth of breast cancer cells, even more effectively than drugs currently used in the clinic. Their study is published in the *Journal of the National Cancer Institute*.

"This study is the first to look at the specific sequences for dimerization of HER2 as a possible anti-cancer target," says the study's senior author Ruth Lupu, Ph.D., a professor of experimental pathology and laboratory medicine and biochemistry and molecular biology at Mayo Clinic. "This finding could be beneficial not only for breast cancer, but also for other cancers with abnormal HER2 levels, such as ovarian, stomach and prostate cancer."

One in every five breast cancers is HER2-positive, meaning that they have too many copies of the HER2 gene and/or produce too much of its product, the human epidermal growth factor receptor 2 (HER2) protein. A receptor like HER2 sits idle on the surface of the cell, becoming active only after pairing up with itself or other members of the protein family. These pairings create a kind of molecular key that opens up communication channels into the cell for stimulating proliferation and growth. When there is too much HER2 around, the protein pairs up even when it should not and that sends in a constant stream of signals telling the cell to grow out of control.

The discovery of HER2 and its role in breast cancer has led to the development of several therapies that specifically target its ability to transform cells. Trastuzumab (known commercially as Herceptin), pertuzumab and cetuximab have together significantly extended the lives of women with HER2-positive breast cancer. But none of the treatments has specifically targeted the ability of HER2 cells to join together or

with other proteins, an essential first step in tumor growth.

Dr. Lupu hypothesized that HER2 activation occurs through a "functional site," a section of protein that is ultimately responsible for forming pairs with itself or other proteins of the same receptor family. If such a site exists, then blocking it would deactivate HER2, stopping tumor growth and metastasis. Dr. Lupu and her colleagues studied the protein sequence of HER2 and found a region that appeared to be involved in its dimerization.

They introduced a series of deletions into this region and eventually zeroed in on a section that contained just a short stretch of 16 amino acids, the building blocks of proteins. The researchers showed that unlike the wild-type HER2, a mutant protein that was missing this short sequence could not transform normal cells into cancer. Most importantly, when they added this mutant protein to HER2-positive breast cancer cells they showed that it halted the growth of these cells, overcoming the molecular makeup that made them aggressive. At the same time, they treated HER2-positive cells with the drugs trastuzumab, pertuzumab and cetuximab and found that the HER2-mutant outperformed all three HER2-targeted therapies.

"Our study demonstrates that this protein sequence is a druggable target," says Dr. Lupu. "Targeting this sequence could have a much broader impact than other drugs that are currently available because it does not just disrupt HER2, but it actually gets in the way of HER2's dimerization to itself and other family members. As a result, this approach could block many of the different pathways by which cancer-causing signals get sent into the cell."

Dr. Lupu and her colleagues are now confirming the anti-tumor activity of the HER2 mutant in relevant animal models, a necessary step before studies can move on to clinical testing. They are also investigating

drugs—such as mimetic agents, targeted antibodies and small molecules—that could specifically block this site responsible for HER2's oncogenic potential.

Provided by Mayo Clinic