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Genes found linked to breast cancer drug resistance could guide future treatment choices

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Researchers at Dana-Farber Cancer Institute have discovered a gene activity signature that predicts a high risk of cancer recurrence in certain breast tumors that have been treated with commonly used chemotherapy drugs.

Despite their resistance to drugs of the anthracycline class, the breast cancers bearing this gene signature will probably still be vulnerable to other types of chemotherapy agents, say scientists in a letter to be published in *Nature Medicine* on its Web site and later in a print edition. Thus, the findings could lead to a genetic test of breast cancers to help physicians choose the best initial treatment for an individual patient.

With this guidance, physicians could avoid the current trial-and-error approach that in some cases exposes patients to the toxic side effects of a cancer drug that is destined to be ineffective. The new report underscores the potential of personalized cancer care, in which knowing the specific molecular features of a patient's cancer helps direct the course of care.

The investigators from the Dana-Farber Women's Cancers Program undertook the studies to search for molecular traits in tumors that cause some patients to suffer recurrences in the wake of breast cancer surgery despite post-surgery, or "adjuvant," chemotherapy, while other patients do well for many years.

Led by Andrea Richardson, MD, PhD, and Zhigang Charles Wang, MD, PhD, the investigators identified two genes that, when abnormally active, enabled cancer cells to resist the effects of drugs called anthracyclines. This class of agents includes doxorubicin, daunorubicin, and epirubicin, which are often used as adjuvant therapy in breast cancer.

The scientists probed stored breast tumor specimens from 85 patients and found the gene signature associated with drug resistance in about 1 in 5 samples, according to the report. Clinical records on file showed that those patients had poorer outcomes than those without the culprit gene signature.

However, the overexpression of the two genes did not protect laboratory-grown breast cancer cells against other classes of drugs, including paclitaxel and cisplatin, reported Richardson, Wang, and the first author, Yang Li, PhD.

"These results suggest that tumors resistant to anthracyclines may still be sensitive to other agents," said Richardson, who is also on faculty at Brigham and Women's Hospital and Harvard Medical School. "So this would be very useful as a test to help pick the therapy that's going to be most effective for these patients."

Such a tool should not be difficult to develop, she said, and could be available for clinical testing within a year or two.

It's been known that some breast tumors acquire, during the course of treatment, altered genes or chromosomes that make them resistant to many cancer drugs. But with one or two exceptions, "No tests are done before treatment begins to predict who's going to be resistant or sensitive to different compounds," says Richardson. "Most breast cancer patients are initially given the same drugs."

Exceptions include patients whose tumors are spurred by estrogen and are often less sensitive to any chemotherapy; hormonal treatment is generally prescribed in that case. Also, breast cancers found to be HER2-positive are treated with the antibody trastuzumab - another example of "personalized" or tailored therapy.

In search of genetic alterations that might explain disease recurrence despite treatment with adjuvant chemotherapy in some breast cancer patients, the Dana-Farber scientists scanned the genome (all the DNA) of stored breast cancer samples from patients who had been treated according to modern guidelines, including the use of anthracyclines. The samples had been taken in the operating room during breast surgery - before any drug therapy had begun - and thus enabled the scientists to look for DNA alterations that could be linked to the patients' subsequent disease recurrence.

Richardson and Wang's laboratory team sifted the tumor DNA and spotted a region on chromosome 8 that contained many redundant, or amplified, copies in the drug-resistant tumors. They found that this small region, labeled 8q22, was associated with a poor outcome in the breast cancer patients. In parallel, they discovered that 12 genes in that region were consistently "overexpressed" - making abnormal amounts of protein - as a result of amplification. "This was the only region of the genome that was tightly associated with poor outcomes despite the adjuvant chemotherapy treatment," Wang noted.

Wang, Richardson, and colleagues singled out the genes in the region that might be involved in tumors' drug resistance, based on their structures and functions. They then experimentally narrowed the field to two likely candidates - LAPTM4B and YWHAZ.

When the researchers knocked out the two genes' function in cancer cells grown in the laboratory, the cells became vulnerable to

anthracycline compounds. Conversely, when the genes were overexpressed, the cells resisted anthracycline compounds, but were killed by other agents, cisplatin and paclitaxel.

To clinch their case, the researchers needed to carry out a blind test in which they didn't know ahead of time which patients' tumors had responded well to drug therapy. Fortunately, they learned of a Belgian clinical trial in which breast cancer patients had been treated prior to surgery with epirubicin - one of the anthracyclines - and their tumors were studied to determine the drug's effectiveness. Among other things, the researchers had obtained gene expression data from the tumors. The Dana-Farber researchers used that data to predict the degree of patients' tumors' response to the drug by measuring the LAPTM4B and YWHAZ activity in the tumors.

When their predictions were matched with the Belgian outcome data, "it turned out that the expression level of these two genes was highly associated with anthracycline resistance in the tumors," said Richardson.

Eric Winer, MD, director of the Breast Oncology Center at Dana-Farber, commented, "While this work remains preliminary, it may ultimately help us use the anthracyclines in a much more thoughtful manner and allow us greater ability to personalize our breast cancer treatments to the tumor and the patient."

Provided by Dana-Farber Cancer Institute

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