Study finds new explanation for resistance to breast cancer treatment

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Breast cancers that initially respond to hormone therapies such as tamoxifen eventually become resistant to treatment, and a new study finds this may be because of a mutation in the receptor present in the cancer cell to which tamoxifen binds, according to data published in *Cancer Research*, a journal of the American Association for Cancer Research.

"Virtually all patients with metastatic breast cancer who initially respond to endocrine [hormone] treatments eventually develop resistance to these treatments," said Ido Wolf, M.D., head of the medical oncology department at the Tel Aviv Sourasky Medical Center in Israel. "We identified a new mutation in the estrogen receptor, which is the target for endocrine treatments, and the mutation makes the receptor more active and resistant to endocrine treatments. Importantly, we identified the mutation in 38 percent of our patients. Thus, our findings may be relevant to many of the patients who develop resistance."

The only treatment option available currently for patients whose breast cancers develop resistance to endocrine therapies is chemotherapy, which is highly toxic and less effective compared with endocrine therapies.

"We discovered a very simple and straightforward mechanism of resistance, but we were able to do it only by the use of modern sequencing techniques," said Wolf. "Using these high-throughput techniques is likely to decipher simple mechanisms of treatment resistance and uncover many other mysteries."

Wolf and colleagues used breast cancer samples collected from breast, as well as from liver, to which the tumor had spread, in 13 patients. All patients had received endocrine therapy initially, but subsequently failed multiple lines of treatment. Wolf's team conducted genomic analyses of the primary breast and metastatic liver tumors by a sophisticated method called deep sequencing using the Foundation One platform, with the primary goal of identifying novel targets for treatment.

The team, however, stumbled upon an interesting finding: In five samples, the receptor, called the estrogen receptor, to which tamoxifen binds, was found to be mutated. They found that this mutation, called D538G, was not present in the primary tumor samples obtained from the breast, but was only present in the metastatic tumor samples obtained from the liver.

Because of this mutation, the structure of the receptor changed in such a way that it could no longer bind to tamoxifen, which is necessary for the drug to act. With further experiments using breast cancer cells in the laboratory, Wolf and colleagues found that because of the change in its structure, the receptor functioned independently and caused uncontrolled multiplication of the cancer cells, making the tumors more aggressive and unresponsive to treatments.

"Previous studies mostly looked at either the primary tumor or metastases before treatment, which may be why this mutation was never detected. We were able to detect it because we sampled tumors at the right time," said Wolf. "Tumors evolve with treatments, and only the most recent sample can accurately represent the 'new' tumor," he explained. This finding needs to be examined in a larger cohort of patients at different time points of the disease, according to Wolf.

"We now need to find ways to inhibit this mutated receptor and develop therapies that will be more effective and less toxic than chemotherapy," Wolf added.

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