

New models of drug-resistant breast cancer point to better treatments

December 12 2013, by Julia Evangelou Strait

Human breast tumors transplanted into mice are excellent models of metastatic cancer and are providing insights into how to attack breast cancers that no longer respond to the drugs used to treat them, according to research from Washington University School of Medicine in St. Louis.

The transplanted tumors maintain the genetic errors that caused the original cancer, even though they are growing in mice. As such, mice carrying human tumors can help identify drivers of [tumor growth](#) and serve as excellent test subjects for investigating new drugs. The mice are particularly good models of estrogen receptor-positive tumors (so named because they are fueled by estrogen) that have become resistant to the drugs used to treat them.

Matthew J. Ellis, MD, PhD, said the research, presented Dec. 12 at the San Antonio Breast Cancer Symposium, is a step toward precision medicine, allowing scientists to study tumors from patients whose treatment regimens are well-documented.

The researchers, including scientists from The Genome Institute at Washington University School of Medicine, presented the research titled, "Patient-derived xenograft study reveals endocrine therapy resistance of ER+ [breast cancer](#) caused by distinct ESR1 gene aberrations."

Building on research recently published in *Cell Reports*, the researchers

identified new mutations that appeared to be driving the strong drug resistance exhibited by these tumors. Specifically, they found mutations in the estrogen receptor.

"Research over the past 20 years has shown tantalizing hints that patients whose disease stops responding to anti-hormonal agents have changes in the estrogen receptor," said Ellis, who sees patients at Siteman Cancer Center at Barnes-Jewish Hospital and Washington University. "And we found all three types of 'gain-of-function' mutations in the estrogen receptor gene ESR1 in the tumor samples."

This study focused on estrogen receptor- (ER) positive breast cancer—the most common type—that also is resistant to standard treatment. Unlike ER-positive cancers that respond well to treatment, those that are drug-resistant spread elsewhere in the body even with aggressive therapy.

Typically, ER-positive tumor growth is driven by the presence of estrogen. Block or remove the estrogen with different types of drugs, such as the commonly prescribed tamoxifen or aromatase inhibitors, and the [tumor](#) stops growing. Some women with estrogen receptor-positive breast cancer do extremely well on such anti-hormone treatment. But others don't, and it's not clear why.

Perhaps shedding light on this mystery, the researchers found three different types of mutations in the estrogen receptor in patients whose cancer was resistant to anti-hormone therapy. One type of mutation is called gene amplification, in which multiple copies of the ESR1 gene are present. A second type is a point mutation in the part of the receptor that binds estrogen, causing the receptor to become active even without estrogen. And the third type is a translocation, in which half of the estrogen receptor gene is swapped for a completely unrelated gene from a different part of the genome.

Similar to the way [breast cancer patients](#) are told whether their tumors make estrogen receptor, Ellis envisions a clinical test that could tell a patient whether and how the estrogen receptor is mutated.

"We can now categorize estrogen receptor-positive breast cancer that has evolved resistance into four categories: point mutated, translocated, amplified and none of the above," he said. "We're planning clinical trials to study different treatment strategies for each of these types."

One strategy is already known to be effective for patients with the gene amplification. In fact, the discovery of the [gene amplification](#) may explain a long-known but mystifying paradox. Some women whose tumors become resistant to estrogen-lowering drugs actually do well when estrogen is reintroduced.

"Some hormone therapy-resistant cancers can be treated with estrogen," said Ellis. "This always confused everybody. Now we know that these tumors are most likely the gene amplified variety. They massively overexpress the [estrogen receptor](#) to compensate for a lack of estrogen. So if you reintroduce estrogen, you overstimulate the cell to such a degree that it becomes a toxic event. And you don't have to give very much estrogen to achieve that."

More information: Li S, et al. Endocrine therapy resistant ESR1 variants revealed by genomic characterization of breast cancer derived xenografts. *Cell Reports*. Sept. 19, 2013.

Provided by Washington University School of Medicine

Citation: New models of drug-resistant breast cancer point to better treatments (2013, December 12) retrieved 22 July 2023 from

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