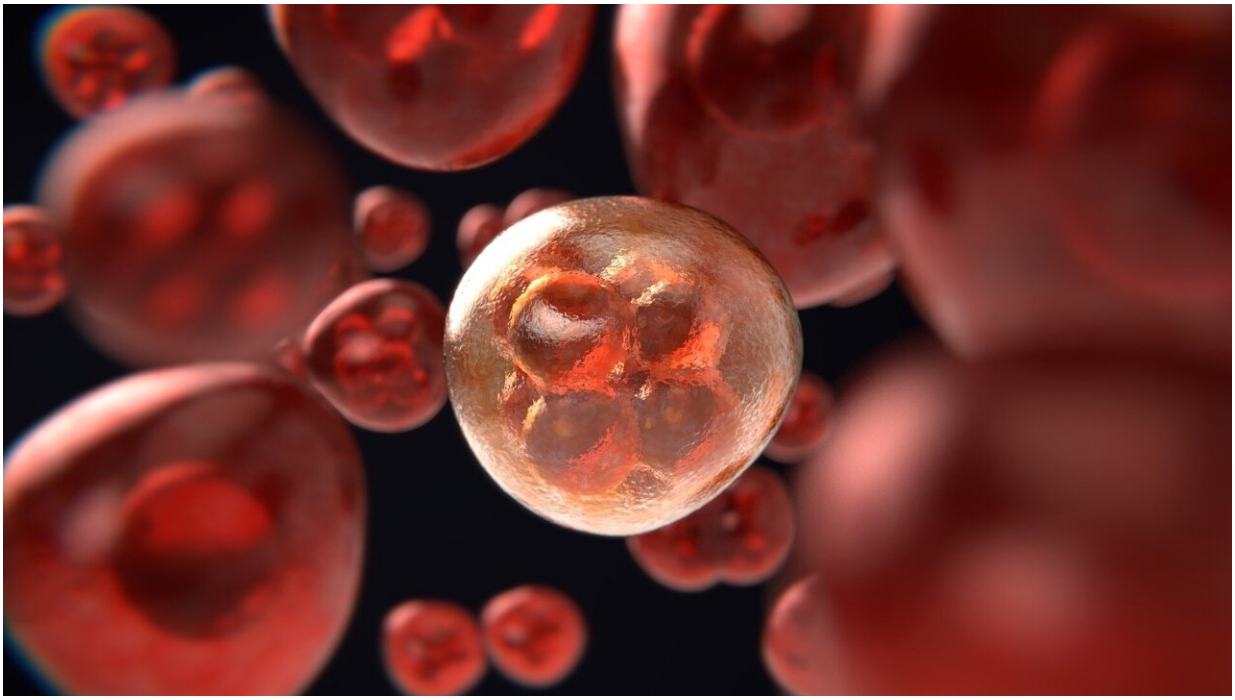
Discovering targetable vulnerabilities in endocrine therapy-resistant breast cancer

May 17 2023, by Ana María Rodríguez



Credit: Pixabay/CC0 Public Domain

When it comes to cancer, developing resistance to therapy and metastasis, the ability to spread outside the organ of origin, are issues of major concern as they give cancer the upper hand.

In the case of breast cancer, researchers have found that mutations in the gene for estrogen receptor alpha (*ESR1*) can contribute to resistance to

therapy and subsequent metastasis. At Baylor College of Medicine, one of the goals of the lab of Dr. Charles E. Foulds and colleagues has been to identify ways to control the progression of these advanced cancers. They report in the journal *Cancer Research* pre-clinical evidence for an actionable target for the treatment of a type of ESR1 variant-driven, endocrine therapy-resistant breast cancer.

"We studied a type of breast cancer with alterations in the *ESR1* gene caused by fusion to other genes. Fusion genes can be made naturally by joining parts of two different genes during the process of cell division," said first author Dr. Xuxu Gou, postdoctoral associate in the Foulds lab while she was working on this project. Currently, Gou is a postdoctoral scholar at the University of California, San Francisco. "*ESR1* fusion genes give rise to ESR1 fusion proteins whose structure and function is different from those of the original non-fused protein."

The researchers focused on breast cancer with *ESR1* fusion genes that confer tumor resistance to endocrine therapy, the gold standard treatment for estrogen receptor-positive breast cancer.

"The cancer cells are resistant to the therapy because the altered ESR1 fusion proteins no longer bind to the therapy drugs, effectively escaping their neutralizing effect," said Foulds, assistant professor in the Lester and Sue Smith Breast Center and member of Baylor's Dan L Duncan Comprehensive Cancer Center. "We searched for other ways to control this cancer's growth, specifically we looked into therapeutically targeting a type of enzyme called kinases."

"Currently, there are many kinase inhibitor drugs available and already approved by the Food and Drug Administration (FDA) for human use, so we concentrated on identifying which kinases were produced by these tumors," Gou said.

The researchers developed a laboratory method they called kinase inhibitor pull-down assay (KIPA) that significantly sped up the process of kinase identification. The strategy consists of coating tiny beads with selective kinase inhibitors, then breaking down the cells and mixing them with the beads. Each kinase binds to its specific inhibitor, effectively separating them from other cell components. Then, the researchers collect and wash the beads, obtain the kinases and use mass spectrometry to identify each one of them. This approach revealed that many therapy-resistant breast cancer cells with *ESR1* fusion genes naturally kinases that normal cells do not produce without the hormone estrogen.

"However, among all the candidates, RET stood out as a common kinase overproduced by a variety of endocrine therapy-resistant breast cancers with *ESR1* fusion genes," Gou said. "There is already an FDA-approved small molecule inhibitor for this kinase called pralsetinib for lung and thyroid cancer, and we tested its effect on this cancer's growth."

"The results were encouraging," Foulds said. "Praseltinib suppressed the growth of cancer cells in a wide variety of pre-clinical models, including cells grown in the lab as well as human cancer cells grown in mouse models. Altogether, our findings support further clinical evaluation of RET inhibition for the treatment of this type of ESR1 fusion-driven, endocrine therapy-resistant breast cancer."

More information: Xuxu Gou et al, Kinome reprogramming is a targetable vulnerability in ESR1 fusion-driven breast cancer, *Cancer Research* (2023). DOI: 10.1158/0008-5472.CAN-22-3484

Provided by Baylor College of Medicine