Study shows biomarkers can predict which ER-positive breast cancer patients respond best to first-line therapy

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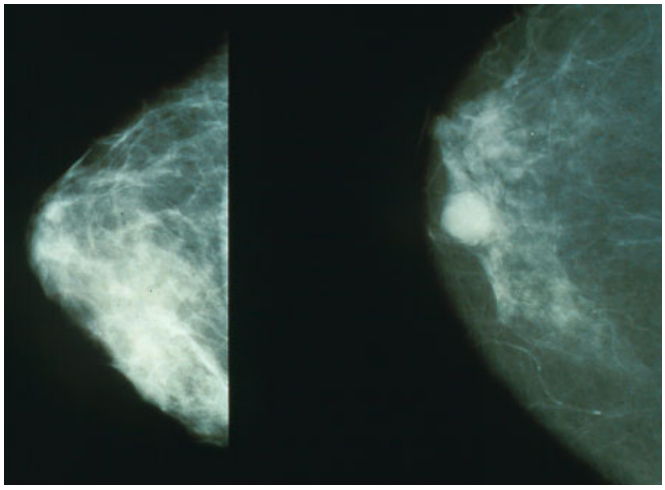

Mammograms showing a normal breast (left) and a breast with cancer (right). Credit: Public Domain

Two challenges in treating patients with estrogen-positive breast cancer (ER+) have been an inability to predict who will respond to standard therapies and adverse events leading to therapy discontinuation. A study at The University of Texas MD Anderson Cancer Center revealed new information about how the biomarkers retinoblastoma protein (Rb) and cytoplasmic cyclin E could indicate which patients will respond best to current first-line therapies.

The study also discovered that combining the current therapy with autophagy inhibitors will result in using one-fifth of the dosage of the standard treatment, which could significantly reduce side effects associated with this therapy. Findings were published in the June 27 issue of *Nature Communications*.

Standard treatment, consisting of palbociclib, often has adverse side effects and not all ER+ patients respond to the therapy. Palbociclib inhibits proteins called CDK4 and CDK6 (CDK4/6) and tumor cells escape this inhibition by activating autophagy, a process allowing cancer cells to thrive even when starved of nutrients. By combining palbocicilb with autophagy inhibitors in cells that express normal Rb and nuclear cyclin E, the dose of palbociclib was significantly reduced.

Khandan Keyomarsi, Ph.D., professor of Experimental Radiation Oncology, led a team that demonstrated how CDK4/6 and autophagy inhibitors synergistically induce cell senescence in Rb-positive cytoplasmic cyclin E-negative cancers. CDK4/6 inhibitors are approved by the Food and Drug Administration (FDA).

"Our findings could impact the majority of ER+ and HER2-negative breast cancers accounting for about 60 percent of advanced breast cancers," said Keyomarsi. "We demonstrated for the first time evidence that Rb and cytoplasmic cyclin E status have a very strong effect on predicting response to the current standard first-line therapy for this population of patients, hormonal therapy plus palbociclib.We also discovered that by inhibiting the pathway such as autophagy that causes tumor cells to escape palbociclib growth inhibition, CDK4/6 inhibitor was more effective."

Deregulation of cell cycle checkpoint proteins, such as CDK4/6, is a key hallmark of cancer, resulting in uncontrolled cellular growth and tumor formation. Some CDK4/6 inhibitors, including palbociclib, ribociclib and abemaciclib, have shown potential in pre-clinical and clinical studies in numerous solid tumors. Palbociclib has demonstrated benefits in Phase II and III trials in advanced ER+ breast cancers, doubling progression-free survival compared to drugs such as letrozole or fulvestrant,

and is currently being evaluated clinically in other solid tumors.

"Data provided through The Cancer Genome Atlas revealed alterations in the CDK4/6/cyclin D pathway in about 35 percent of the patients, making them an ideal population for targeting CDK4/6," said Keyomarsi. "Our study revealed that inhibition of CDK4/6 and autophagy pathways cooperate to induce sustained growth inhibition and senescence in vitro and in vivo, in breast and other solid tumors and showed how autophagy inhibition can significantly decrease the dose of palbociclib required to treat breast cancer patients. We believe this new strategy can improve the efficacy of other CDK4/6 inhibitor treatments like ribociclib and abemaciclib."

The team's findings indicated how Rb and cyclin E status predicts response to a combination of CDK4/6 and autophagy inhibition in pre-clinical models and that autophagy blockade is successful in reversing resistance to palbociclib.

"Palbociclib resistance is a significant limitation of this treatment which is not curative and does not prolong survival even though transient responses and prolongation of response have formed the basis of FDA approval," said Keyomarsi. "Our study provides evidence that models of hormone receptor-negative cancer and even non-breast cancer malignancies can respond to the combination of palbociclib and autophagy inhibition, when selected based on Rb and cyclin E isoform status, representing a completely new therapeutic opportunity for these cancers."

Keyomarsi and colleagues anticipate future clinical studies based on this pre-clinical and clinical evidence with the aim of developing translational and clinical applications.

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