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Potential new therapy for triple-negative breast cancer shows promise in lab studies

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Recent laboratory findings provide novel insight into potential new therapeutic approaches for triple-negative breast cancer, a particularly difficult to treat and aggressive form of the disease.

In a recent study published online in the journal *Clinical Cancer Research*, scientists from Van Andel Research Institute (VARI) and Wayne State University demonstrated in preclinical experiments that the drug cabozantinib inhibits growth of several triple-negative breast cancer subtypes.

"Triple-negative breast cancer accounts for 15 to 20 percent of all breast cancer cases, yet is responsible for a disproportionate number of cancer-related deaths," said Carrie Graveel, Ph.D, VARI research assistant professor and corresponding author on the paper. "This higher mortality rate is due to a lack of targeted therapies, the disease's aggressive nature and the diverse cell population that comprises the tumor. It is crucial we develop better diagnostic tests and an array of targeted therapies to better classify cancer subtypes and effectively treat the disease on a patient-by-patient basis."

Triple-negative breast cancer and the lack of treatment options

Triple-negative breast cancer is resistant to many current therapies because it lacks three major receptors—proteins that receive and

transmit messages to and from the cell—that are present in other forms of the disease. These proteins—the human epidermal growth factor receptor 2 (HER2), and receptors for the hormones estrogen and progesterone—are targets for many common breast cancer treatments. Their absence in triple-negative cases eliminates many of the treatment options available to patients with other types of breast cancer, underscoring the importance of developing new, more targeted therapies.

"In this study we used two complementary preclinical models to analyze drug responses of the tumor in the context of interactions with its microenvironment, which is known to contribute to malignancy," said co-senior author Bonnie Sloane, Ph.D., of Wayne State University. "These types of analyses may identify novel pathways for therapeutic intervention."

MET in cancer

One target of cabozantinib is the MET protein, which drives many of the processes that make cancer aggressive and challenging to treat, including invasion of other tissues, proliferation and survival of cancer cells. MET is overexpressed in 20 to 30 percent of all breast cancer cases, and is typically associated with poor outcome. In a 2009 paper, Graveel and VARI's George Vande Woude, Ph.D., demonstrated that MET is expressed in triple-negative breast cancer and is a potential therapeutic target.

Discovered and developed by Exelixis, Inc., cabozantinib also is the subject of ongoing clinical trials in advanced kidney and liver cancers, and is approved to treat metastatic medullary thyroid cancer.

Translational impact

In preclinical experiments, the team demonstrated that cabozantinib impedes triple-negative breast cancer progression and spread by inhibiting the MET protein. Graveel and Sloane's laboratories used unique cancer models that include both breast cancer cells and the connective tissue cells that often support cancer growth. Their findings not only provide evidence for cabozantinib's therapeutic potential for triple-negative breast cancer, but also imply that MET plays a crucial role in growth and invasion by triple-negative cancer cells.

Future directions

Graveel and Sloane plan to continue exploring the potential of MET inhibitors as therapies for triple-negative breast cancer in addition to conducting further analysis on their models to define characteristics that may be used as diagnostic tools.

"Currently, we're determining the efficacy of combination treatments of MET and EGFR inhibitors in triple-negative breast cancer as well as investigating signaling pathways that drive sensitivity or resistance to targeted therapy such as MET inhibitors," Graveel said. "By analyzing the signaling pathways in our preclinical models, we are identifying changes in triple-negative cases that could serve as tools for determining whether a patient will respond favorably or not to targeted therapy. We're hopeful that these discoveries will lead to new treatments for patients battling these tough-to-treat cancers."

More information: Sameni M, Tovar EA, Essenburg C, Chalasani A, Linklater ES, Borgman A, Cherba DM, Anbalagan A, Winn ME, Graveel CR*, Sloane BF*. In press. Cabozantinib (XL184) inhibits growth and invasion of preclinical TNBC models. *Clin Cancer Res.* clincancerres.aacrjournals.org … 5-0187.full.pdf+html