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Research team identifies mechanism of chemotherapy resistance in inflammatory breast cancer

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Researchers at Roswell Park Cancer Institute (RPCI) have identified a mechanism of breast cancer cells that leads to chemotherapy resistance in inflammatory breast cancer. These preclinical findings, published online ahead of print in the International Journal of Oncology, provide evidence for a potential therapeutic approach that will restore sensitivity to chemotherapy and improve treatment of inflammatory breast cancer tumors.

"This study forms the basis for future research in patients with breast cancer and offers hope for targeted therapy for patients with aggressive triple-negative inflammatory breast cancer," said lead researcher Mateusz Opyrchal, M.D., Ph.D., Assistant Professor of Oncology at RPCI.

Inflammatory breast cancer is the most aggressive type of advanced breast cancer and is characterized by rapid development, resistance to chemotherapy, early metastases and a poor prognosis. Inflammatory breast cancer cells display a triple-negative breast cancer phenotype that lacks the receptors needed to promote tumor growth. Therefore, common treatments such as endocrine therapy and molecular targeting of the HER-2 receptor are not effective for this breast cancer subtype. No targeted therapy has been approved for noninflammatory and inflammatory triple-negative breast cancer tumors, and the standard of therapy for these tumors is a combination of conventional cytotoxic

chemotherapeutic agents.

In the laboratory, Dr. Opyrchal and colleagues used breast cancer cell lines to determine the extent to which chromosomal instability and resistance to chemotherapy—characteristics of inflammatory breast cancer—are linked to the CD44+/CD24–/^{Low} stem-like phenotype. They found that CD44+/CD24–/^{Low}cancer stem cells (CSCs) were resistant to conventional chemotherapy but were sensitive to SU9516, which is a specific cyclin-dependent kinase 2 (Cdk2) inhibitor. The researchers concluded from these findings that aberrant activation of cyclin E/Cdk2 oncogenic signaling is essential for maintaining and expanding the CD44+/CD24–/Low subpopulation in inflammatory breast cancer. Therefore, a novel therapeutic approach in inflammatory breast cancer could involve a combination of conventional chemotherapy with small-molecule inhibitors of the Cdk2 cell cycle kinase.

"Cdk2 cell cycle kinase seems to play a role in the ability of cancer cells to be more aggressive and resistant to standard chemotherapy," Dr. Opyrchal said. "Blocking its function resulted in the improved ability of the chemotherapy drugs to kill cancer cells. Cancer stem cells will need to be identified and treated in a different manner than the bulk tumor."

Dr. Opyrchal noted that these results will have to be confirmed before human trials can be planned. His laboratory continues to work on identifying the cancer stem cells and signaling pathways that play a role in growth, metastatic potential and resistance to standard therapies.

More information: "Inhibition of Cdk2 kinase activity selectively targets the CD44+/CD24-/^{Low} stem-like subpopulation and restores chemosensitivity of SUM149PT triple-negative breast cancer cells." Opyrchal M, et al. *Int J Oncol*. 2014 Sep;45(3):1193-9. DOI: 10.3892/ijo.2014.2523. Epub 2014 Jun 25.

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