Study finds inflammation caused by radiation can drive triple-negative breast cancer

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While radiation is successfully used to treat breast cancer by killing cancer cells, inflammation caused as a side-effect of radiation can have a contrary effect by promoting the survival of triple-negative breast cancer

cells, according to research published online in the *International Journal of Radiation Biology* by Jennifer Sims-Mourtada, Ph.D., director of Translational Breast Cancer Research at ChristianaCare's Helen F. Graham Cancer Center & Research Institute.

Accounting for 15-20% of all breast cancers, triple-negative breast cancer is faster growing than other types of breast cancers.

Dr. Sims-Mourtada's latest study, "Radiation induces an inflammatory response that results in STAT3-dependent changes in cellular plasticity and radioresistance of breast cancer stem-like cells," brings scientists closer to understanding the mechanisms behind this aggressive and hard-to-treat cancer. It shows that inflammation caused by radiation can trigger stem-cell-like characteristics in non-stem breast cancer cells.

"This is the good and the bad of radiation," Dr. Sims-Mourtada said. "We know radiation induced inflammation can help the immune system to kill tumor cells—that's good—but also it can protect cancer stem cells in some cases, and that's bad."

She added, "What's exciting about these findings is we're learning more and more that the environment the tumor is in—its microenvironment—is very important. Historically, research has focused on the genetic defects in the tumor cells. We're now also looking at the larger microenvironment and its contribution to cancer."

The term triple-negative breast cancer refers to the fact that the cancer cells don't have estrogen or progesterone receptors and also don't make too much of the protein called HER2. The cells test "negative" on all 3 tests. These cancers tend to be more common in women under age 40, who are African-American, Latina or who have a BRCA1 mutation.

"My work focuses on cancer stem cells and their origination," Dr. Sims-

Mourtada said. "They exist in many cancers, but they're particularly elusive in triple-negative breast cancer. Their abnormal growth capacity and survival mechanisms make them resistant to radiation and chemotherapy and help drive tumor growth."

She and her team applied radiation to triple-negative breast cancer stem cells and to non-stem cells. In both cases, they found radiation induced an inflammatory response that activated the Il-6/Stat3 pathway, which plays a significant role in the growth and survival of cancer stem cells in triple-negative breast cancers. They also found that inhibiting STAT3 blocks the creation of cancer stem cells. Still unclear is the role IL-6/STAT3 plays in transforming a non-stem cell to a stem-cell.

For women living in Delaware, Dr. Sims-Mourtada's research is especially urgent: The rates of triple-negative breast cancer in the state are the highest nationwide.

"At ChristianaCare, we are advancing cancer research to help people in our community today, while we also advance the fight against cancer nationwide," said Nicholas J. Petrelli, M.D., Bank of America endowed medical director of the Helen F. Graham Cancer Center & Research Institute. "Dr. Sims-Mourtada's research is a dramatic step toward better treatments for triple-negative breast cancer."

To advance her research on inflammation, last year Dr. Sims-Mourtada received a $659,538 grant from the Lisa Dean Moseley Foundation. The three-year grant will enable her and her team at the Cawley Center for Translational Cancer Research to continue investigating the role of cells immediately around a tumor in spurring the growth of triple-negative breast cancer and a possible therapy for this particularly difficult cancer.

"Our next step is to understand the inflammatory response and how we might inhibit it to keep new cancer stem cells from developing," Dr.

Sims-Mourtada said.

Dr. Sims-Mourtada's research team previously identified an anti-inflammatory drug, currently used to treat rheumatoid arthritis, that has the potential to target and inhibit the growth of cancer stem cells and triple-negative breast cancer tumors. That research could set the stage for clinical investigation of the drug, alone or in combination with chemotherapy, to improve outcomes for patients with triple-negative breast cancer.

More information: Kimberly M. Arnold et al, Radiation induces an inflammatory response that results in STAT3-dependent changes in cellular plasticity and radioresistance of breast cancer stem-like cells, *International Journal of Radiation Biology* (2019). DOI: 10.1080/09553002.2020.1705423

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