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Mouse study: Triple-therapy cocktail shrinks triple-negative breast tumors

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In a new study using mice and lab-grown human cells, a scientific team led by Johns Hopkins Kimmel Cancer Center researchers show how a triple-drug cocktail can shrink triple-negative breast cancers by killing off cancer cells and halting new tumor growth.

The combination treatment, described in a paper published in the April 1 issue of *Cancer Research*, is composed of the chemotherapy drug doxorubicin; all-trans retinoic acid, or ATRA, which can cause a tumor to lose its self-renewing cells; and entinostat, which makes cancer cells more sensitive to retinoic acid treatment.

Led by Saraswati Sukumar, Ph.D., the Barbara B. Rubenstein Professor of Oncology at the Johns Hopkins Kimmel Cancer Center, the scientific team reports that EAD therapy—named for each of its component drugs—"significantly" reduced the size of triple-negative breast cancer tumors in mice and the number of lab-grown spheres of metastatic breast cancer cells harvested from patients and grown in the laboratory.

Specifically, Sukumar and her colleagues tested several pairings of drugs before determining that the EAD combination was the most potent against triple-negative tumors. For instance, doxorubicin alone was able to reduce the formation of tumor spheres grown in the laboratory by 32 percent, while entinostat alone or ATRA alone could reduce them only by 18 percent. However, the combination EAD therapy reduced the formation of spheres by 90 percent.

Triple-negative breast cancers account for 15 to 20 percent of all breast cancers. They are so named because they are negative for, or lack, estrogen and progesterone receptors and the HER2 protein—all of which are implicated in other types of breast cancer. Without hormonal or HER2 receptors to target, patients with aggressive triple-negative breast cancers are not likely to respond to drugs that target those molecules, says Sukumar. Combinations of chemotherapy drugs are the current standard treatments, but about one-quarter of patients with triple-negative breast cancers will not respond to them. Thus, she says, finding combinations that work better than those in common use is an ongoing endeavor.

Compared to the combination of entinostat and doxorubicin, EAD reduced by twofold the number of tumor-starting cells in the tumor spheres, suggesting that the addition of ATRA helped to move the tumor away from a "stem like" state to a more differentiated group of cells that are more responsive to drugs.

In spheres grown from six patients' metastatic triple-negative breast cancer cells, EAD was also the most effective at decreasing tumor growth, reducing the number of spheres formed by about 80 percent, compared to about 40 percent reduction by the next-best treatment of doxorubicin alone.

Previous research has shown that retinoic acid drugs such as ATRA can rid breast cancer stem cells of their ability to self-renew, multiply and develop into more differentiated, mature breast cells. When tumor cells lose their ability for self-renewal through stem cells, they are less likely to grow and become invasive, says Vanessa Merino, Ph.D., a research associate at the Johns Hopkins University School of Medicine, stem cell expert and co-author of the study.

"If the cancer is supplied with agents that can cause their differentiation

faster than their production, the tumor will shrink, since more cells are dying than are being produced to replace the dead ones," she says.

However, retinoic acids have had limited success as tumor suppressors, in part because their molecular partners within tumors are frequently "silenced." To alter this, the scientists decided to combine ATRA with entinostat, a drug that reverses gene "silencing"—a process known as epigenetic marking and revives ATRA's partner to make tumor cells more sensitive to retinoic acid treatment.

Sukumar says the next step for the triple therapy will be to test its safety and effectiveness in patients with triple-negative breast cancers.

More information: V. F. Merino et al, Combined Treatment with Epigenetic, Differentiating, and Chemotherapeutic Agents Cooperatively Targets Tumor-Initiating Cells in Triple-Negative Breast Cancer, *Cancer Research* (2016). DOI: 10.1158/0008-5472.CAN-15-1619

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