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Three San Antonio studies target androgen in breast cancer

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Three studies presented by University of Colorado Cancer Center researchers at the San Antonio Breast Cancer Symposium 2014 demonstrate the effects of blocking androgen receptors in breast cancer. One shows that, counterintuitively, blocking the action of androgen receptors reduces the growth of estrogen-positive (ER+) breast cancers. The second study found that even triple-negative breast cancers (TNBCs), which are without known hormone drivers and carry the poorest prognosis, are dependent on androgen receptor activation. And the third study finds that targeting androgen receptors along with known cancer drivers HER2 or mTOR has a synergistic effect in which more cancer cells are killed by the combination than the sum of the cells killed by both drugs, combined.

"We're on the cusp of a major revolution in the way we treat breast cancer. We've known for years that prostate cancer is driven by androgens and now it's increasingly clear that androgens and androgen receptors can influence many breast cancers as well. AR is actually even more prevalent in breast cancer than estrogen or progesterone receptors. Targeting androgen receptors in breast cancer gives us an new way to attack the disease," says Jennifer Richer, PhD, investigator at the CU Cancer Center and head of the Richer Laboratory that produced the results.

"Drugs like tamoxifen that target estrogen-positive breast cancer are pretty effective, but resistance and recurrence are still big problems," says Nicholas D'Amato, postdoc in the Richer lab and first author of one

of the studies. Previous work showed that presence of the androgen receptor on breast cancer cells is a major predictor of resistance to tamoxifen, a drug that blocks the effects of the hormone estrogen. D'Amato's work shows why: when androgen receptors are activated, they move to the cell's nucleus where they can regulate the cell's actions. It seems that this "nuclear localization" of androgen is required for breast cancers to grow in response to estrogen. D'Amato showed that drugs like enzalutamide that block the nuclear localization of androgen also prevent the binding of estrogen, and decrease the growth and proliferation of breast cancer cells that depend on estrogen. (Poster number: P3-04-06, Thursday 5-7pm, "Inhibiting androgen receptor nuclear localization decreases estrogen receptor (ER) activity and tumor growth in ER+ breast cancer.")

Triple negative breast cancers account for about 15 percent of breast cancer diagnosed. Because triple negative breast cancer has no known hormonal driver, it hasn't been able to be treated by drugs that block the cancer's access to the hormones it needs. However, while triple negative breast cancer may not depend on known drivers like estrogen, progesterone or the gene HER2, work by Valerie Barton, Cancer Biology graduate student in the Richer Lab, shows that many subtypes of triple negative breast cancer are dependent on the androgen receptor. Specifically, her paper presented this week shows that androgen receptors regulate the production of the protein amphiregulin, which previous work has pinpointed as a driver of cancer.

"When you use drugs like enzalutamide to block the action of androgen receptors, you decrease the production of amphiregulin and therefore kill triple negative breast cancer cells," Barton says. (Poster number: P3-04-02, Thursday 5-7pm, "Multiple subtypes of triple negative breast cancer are dependent on androgen receptor.")

Finally, work by postdoc Michael Gordon in the Richer Lab shows

explores the use of anti-androgen-receptor drugs in combination with other drugs in cancers driven by the gene HER2 and the signaling pathway mTOR. When Gordon added the drug trastuzumab, which targets HER2, along with the drug enzalutamide, which targets the androgen receptor, to breast cancer cells dependent on HER2, more cells were killed than the sum of the cells killed by both drugs, individually. The same was true when enzalutamide was added to the drug evorolimus, which targets the mTOR signaling pathway.

"Evorolimus has side effects that can limit its use," Gordon says. "Our hope is that if we can increase its effectiveness by adding enzalutamide, we could reduce the dose of both drugs."

Gordon explains that evorolimus has been shown to increase the expression of androgen receptors, perhaps as mechanism by which breast cancer can acquire resistance to the drug. By blocking androgen receptors along with mTOR signaling, Gordon hopes to block the primary pathway driving mTOR-dependent cancer and also its "escape route". (Poster number - P6-03-07, Saturday 7:30-9am, "Targeting multiple pathways in breast cancer: androgen receptor, HER2, and mTOR.")

"Our work and others show that in, many subtypes of breast cancer, targeting androgen receptors can be a powerful therapy, sometimes alone and sometimes as a way to increase the effectiveness of existing drugs," Richer says.

Provided by University of Colorado Denver