Stress hormones could undermine breast cancer therapy

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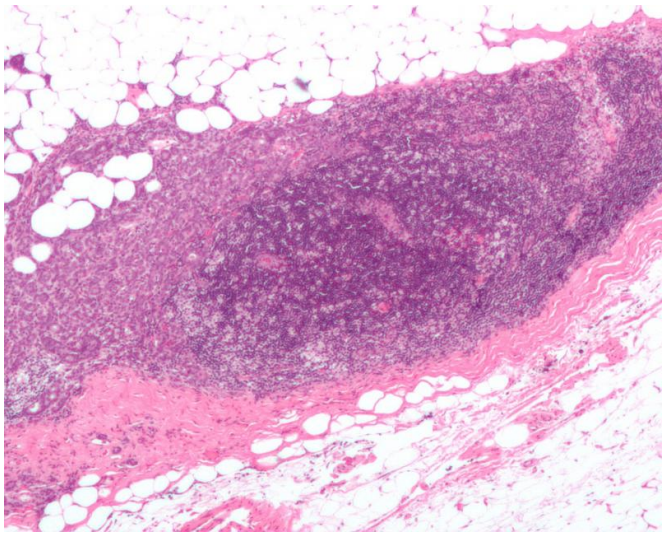

Micrograph showing a lymph node invaded by ductal breast carcinoma, with extension of the tumour beyond the lymph node. Credit: Nephron/Wikipedia

Recently, researchers have discovered that the hormone progesterone, an ingredient in contraceptives and menopausal hormone replacement therapies, might stimulate the growth of breast cancer cells that are resistant to anti-estrogen therapy and chemotherapy. Now, new research published June 22nd in the journal *Oncogene*, a *Nature* publication, shows that additional hormones, including stress hormones that are frequently used to treat the side effects of common chemotherapy, could make these effective cancer drugs fail sooner in some women with breast cancer. But there may be ways to counteract the effect.

"The data we have collected suggests that hormones used in breast cancer treatment, which are also produced by the body in response to stress, could have a major impact on disease progression and outcomes in some patients," says Hallgeir Rui, M.D., Ph.D., a Professor of Cancer Biology, Pathology and Medical Oncology at Thomas Jefferson University. "However, these studies must be confirmed in clinical trials with patients before any new treatment recommendations can be made."

About 70-80 percent of all invasive breast cancers are driven by the hormone estrogen; they are often called estrogen receptor (ER) positive disease. This group of women can successfully keep the growth of their cancer in check with therapies that block estrogen receptors, or block the production of estrogen in the body, essentially starving the cancer. While some women can use hormone blockers such as tamoxifen or aromatase inhibitors to control their cancer for a decade or more, one of four will develop resistance.

Researchers believe that some of this resistance is caused by a small subpopulation of cancer cells within the tumor called CK5 cells which harbor the ability to resist estrogen-blocking therapy and chemotherapy. When these cells become more abundant, tumors become therapy-resistant. Dr. Rui estimates that 10-15 percent of patients with ER+ disease harbor CK5 cells.

Earlier work by the Rui laboratory and others had shown that progesterone spurs the growth of CK5 cells in breast cancer. But since most ER-positive breast cancers are diagnosed after menopause when progesterone production has stopped, this wasn't a major concern. Progesterone, however, belongs to a family of hormones called 3-ketosteroids that are often produced by the body in times of stress. Dr. Rui and colleagues decided to test whether other members of the 3-ketosteroid family, including glucocorticoids used to treat nausea and other breast-cancer-treatment related symptoms, might also expand the population of CK5 cells.

Dr. Rui and colleagues exposed breast cancer cell

lines to four 3-ketosteroids. Two of the steroids, dexamethasone and aldosterone, boosted CK5-cell numbers by as much as four to seven times. The researchers also confirmed their results in human breast cancer grown in mice, showing increased growth of therapy-resistant tumors in mice treated with dexamethasone and aldosterone.

"Not only are these steroids sometimes used in cancer treatment, glucocorticoid hormones are also naturally produced by the body in response to stress," says first author Chelain Goodman, an M.D./Ph.D. student in Dr. Rui's lab. "Women with breast cancer experience greater levels of stress and studies have shown that this stress can negatively impact their treatment. Glucocorticoids are also widely prescribed for common diseases, including many chronic rheumatoid or autoimmune diseases which can co-occur with breast cancer. "This research helps pinpoint a new mechanism behind therapy-resistance in patients with this subtype of ER-positive breast cancer containing CK5 cells and suggests a way to counteract the effect," Ms. Goodman adds.

In order to counteract the effect of these stress hormones, Dr. Rui and colleagues turned to another hormone, called prolactin. Prolactin is best known for helping women produce milk after childbirth, but it also has the ability to maintain cell maturity. CK5 cells, on the hand, are cells that are less mature and more "primitive" or stem-cell like. Therefore, when Dr. Rui and colleagues added prolactin to the cells exposed to 3-ketosteroids, the expansion of CK5 cells was prevented. In other words, prolactin helped keep the breast cells mature, and made the environment unfavorable for growth of the immature-CK5 cells.

"Although prolactin appears to be an excellent candidate to counteract the effect of stress hormones on women with this subtype of breast cancer," says Dr. Rui, who leads the breast cancer program at the Sidney Kimmel Cancer Center at Jefferson, "the hormone can also drive other types of breast cancer, so we must proceed with caution. An alternative possibility supported by this research is inhibiting a protein called BCL6 that appears to be critical for steroid-induction of CK5 cells." Dr. Rui adds, "Perhaps the simplest solution would be to seek alternatives to steroids for controlling the side-effects of chemotherapy in patients with this tumor subtype."

The group has already found two potential biomarkers in clinical samples that would help identify ER-positive tumors with CK5 cells and are looking into validating their findings in clinical trials.

More information: C.R. Goodman, et al., "Steroid-induction of therapy-resistant cytokeratin-5-positive cells in estrogen receptor-positive breast cancer through a BCL6-dependent mechanism," *Oncogene*, 2015.

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