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BREAST CANCER: MORE INSIGHTS ON HOW HORMONAL THERAPY WORKS

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Treatable: Hormone therapy is a standard treatment for breast cancer and is often used in combination with other treatments such as surgery.

Work carried out by researchers from the Integrated Cancer Genomics Laboratory at the Advanced Centre for Training, Research, and Education in Cancer (ACTREC) in Mumbai's Tata Memorial Centre has shed more light on the molecular mechanism through which progesterone treatment prior to breast cancer surgery is quite likely to increase the survival rates of patients.

In 2018, a team led by Dr. Amit Dutt at the ACTREC found through in vitro studies that when breast cancer cell lines were treated with progesterone, two genes — SGK1 and NDRG1 — were produced in excess amount (overexpressed). They also found that the expression of a few microRNAs was reduced (down-regulated) in response to the hormone treatment. Two particular microRNAs that were down regulated were found to also regulate the expression of the SGK1 gene.

Since the normal function of the two microRNAs is to reduce the amount of SGK1 enzyme produced, when the level of microRNAs drops, the amount of SGK1 enzyme produced increases. Through the action of SGK1 and two other genes, and the two microRNAs, the ability of the breast cancer cells to migrate and invade is reduced, thus increasing the survival rates of patients undergoing hormone therapy prior to surgery.

In a recently published study in the journal, *Breast Cancer Research*, the team led by Neelima Yadav in Dr. Dutt's lab expanded the scope of their previous work to focus on the role of non-coding genes; non-coding genes do not produce any proteins but regulate the expression of other genes. The work was to uncover the molecular mechanism of any non-coding gene in providing therapeutic advantage of progesterone on breast cancer cells.

The study found that treatment of breast cancer cells with progesterone results in a down-regulation of a long non-coding linc RNA known as the Down Syndrome Cell Adhesion Molecule (DSCAM-AS1).

"As with progesterone therapy, we found that with silencing of DSCAM-AS1 expression, the ability of breast cancer cells to invade and migrate is slowed down," Ms. Yadav says.

In breast cancer patients, the amount of DSCAM-AS1 present is elevated. The team also found that DSCAM-AS1 behaves like a sponge and depletes the availability of another non-coding microRNA called the miR-130a. And the level of estrogen receptor in breast cancer cells is increased, which serves as an indicator to begin hormonal therapy.

But when progesterone is provided from externally, the amount of DSCAM-AS1 that is available reduces, and thereby the sponging effect of DSCAM-AS1 also sees a dip. This results in elevated levels of the microRNA (miR-130a) that are freely available. As the level of the microRNA increases, there is more of them binding to the estrogen receptor. “The study threw a surprise. We found that miR-130a is known to regulate the level of estrogen receptor in breast cancer cells,” says Dr. Dutt.

Dr. Dutt says the detection of DSCAM-1in blood or tumour tissue can likely provide information about the aggressiveness of breast cancer and prognosis. “Non-coding RNA-based diagnostic and screening methods are still in the early stages of development. We need further validation before using it in clinical practice,” he says.

“Our study identifies a three-tiered regulatory network wherein DSCAM- AS1 sponges off miR-130a to downregulate estrogen receptor expression in response to progesterone. We show that an increased expression of miR-130a or decreased expression of DSCAM-AS1 corresponds with improved survival outcomes in breast cancer patients, similar to the effects of progesterone treatment,” says Dr. Dutt. “When taken as a whole, our research represents the first step in describing the progesterone-responsive long non-coding RNAs and their mechanistic functional insight downstream of progesterone in breast cancer cells, parallel to other regulatory pathways.”

“The potential therapeutic benefit of progesterone and its mediators is the highlight of the current study,” he says.

Hormone therapy targets hormone receptors in breast cancer cells to slow or stop the growth of cancer. It is a standard treatment for breast cancer and is often used in combination with other treatments such as surgery, radiation, and chemotherapy. However, resistance to hormone therapy in breast cancer is a significant problem in treating hormone receptor-positive breast cancer.

One of the main mechanisms of resistance to hormone therapy is the presence of mutations in the hormone receptors themselves or through the down-regulation of its expression levels.

Another implication of the latest study is that when the microRNA miR-130a binds to the estrogen receptors, it might lead to cancer cells becoming resistant to hormone therapy.

“It is currently a hypothesis and has to be verified through further studies,” says Dr. Dutt.

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