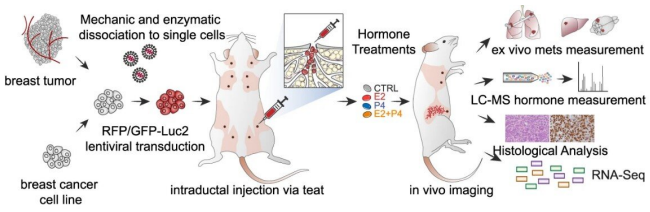
Breakthrough study of hormone 'cross-talk' in breast cancer

16 June 2022



Experimental workflow of the study. Freshly collected breast tumor samples are dissociated into single cells and genetically labeled with reporter genes to allow cell detection and tracking. Shortly after, tumor cells are injected into the milk ducts of mice to form mammary tumors. Hormone treatments are administered to the animals to study their effects on breast cancer growth and metastasis. Credit: *Nature Communications* (2022). DOI: 10.1038/s41467-022-30898-0

Scientists led by EPFL have successfully engrafted breast cancer cells on mice, allowing them to study in vivo the cross-talk between the estrogen and progesterone receptors that hampers hormone therapies. Their findings suggest that endocrine therapy may need to be personalized, and that abrogating progesterone receptor expression can be a therapeutic option.

"Breast cancer affects 1 in 7 women," says Professor Cathrin Brisken at EPFL's School of Life Sciences. "More than two thirds of the cases are hormone-sensitive and express the receptor for estrogen in more than 1% of the tumor cells." In fact, biological signaling by the estrogen receptor is a key driver of breast carcinogenesis and blocking it is a standard pursuit of hormone therapies, which have substantially improved survival rates of patients.

The problem is that tumors that are positive for the estrogen receptor have been understudied because the field lacks adequate animal models. "Mammary carcinomas that develop in genetically engineered mouse models are not sensitive to hormones, and the rates for successful estrogen receptor-positive breast cancer xenografts are extremely low."

Previous studies have revealed an important "cross-talk" between the estrogen receptor with another sex hormone, progesterone. Specifically, the biological signaling pathways of the estrogen and progesterone receptors seem to interfere with each other both on a genomic and protein level.

However, the lack of adequate cell lines and animal models has prevented scientists from studying this cross-talk under clinically relevant hormone levels. As the gene for the progesterone receptor is affected by the estrogen receptor, hormone therapies that target the latter can block the expression of the former. This complexity makes it hard to study the role of either receptor independently and, subsequently, optimize treatment strategies.

Now, working with researchers and clinicians at the Lausanne University Hospital (CHUV), the Réseau Lausannois du Sein, and the International Cancer Prevention Institute (ICPI), Brisken's lab has successfully grafted human estrogen receptor-positive breast cancer cells to the milk ducts of immunocompromised mice. The breakthrough allowed them to study the effect of both estrogen and progesterone on breast cancer development.

The scientists found that both hormones, estrogen and progesterone can increase tumor growth and combined treatments can actually enhance metastasis.

But there is a way forward. "We found that tumors from different patients have different responses to the two hormones, suggesting that endocrine therapy may be improved by personalizing it," says Brisken. "In addition, abrogating the expression of the progesterone receptor can be a therapeutic

option," she adds. "While it has been proposed that progesterone may help women with breast cancer, we show that the hormone has tumor-promoting effects, and provide evidence that the progesterone receptor acts as a mediator of estrogen receptor signaling, making this receptor attractive as a potential therapeutic target."

The study, which is published in *Nature Communications*, was featured by the director of the Endocrine Society at the recent ENDO 2022 meeting, attended by more than seven thousand clinicians and scientists.

More information: Valentina Scabia et al, Estrogen receptor positive breast cancers have patient specific hormone sensitivities and rely on progesterone receptor, *Nature Communications* (2022). DOI: 10.1038/s41467-022-30898-0

Provided by Ecole Polytechnique Federale de Lausanne