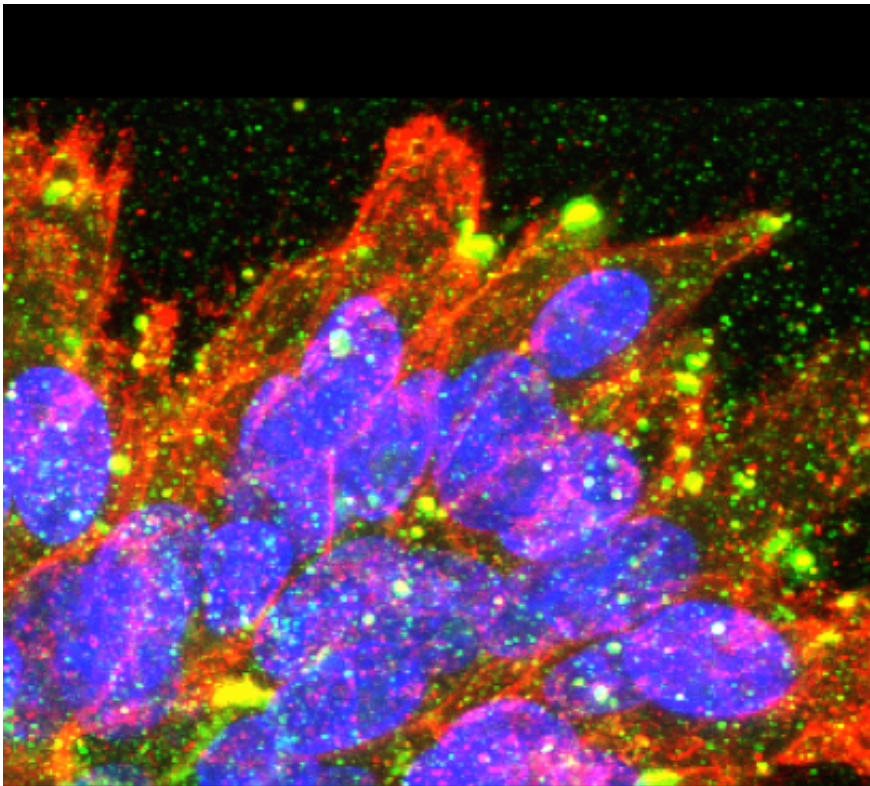


How breast cancer cells become more aggressive in response to targeted therapies

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Detail of breast cancer cells in 3D-culture, collectively invading into the surrounding extracellular matrix. Credit: Diana Dragoi / Helmholtz Zentrum München

Researchers at Helmholtz Zentrum München describe how breast cancer cells challenged with a small-molecule inhibitor targeting specific invasive properties switch to an alternative mode-of-action, rendering

them even more aggressive. The results may impair future therapeutic approaches in the TGF-beta pathway and are published in the journal *Oncotarget*.

As breast cancer develops, [tumor cells](#) begin to breach the tissue compartment that normally confines the mammary gland and actively invade and spread into the surrounding tissue. The research team, led by Dr. Christina Scheel attempted to block this process by exposing [cancer cells](#) to a small-molecule inhibitor targeting the TGF-beta Receptor Type I (TGFR1). TGFR1 is a crucial relay-protein in a signaling cascade known to endow [breast cancer cells](#) with the ability to invade.

Indeed, by doing so the scientist of the Institute of [stem cell research](#) were able to prevent a master regulator of genes involved in this process from initiating a cellular program that results in invasive behaviour of cancer cells. This master regulator, Twist1, has long been implicated in breast cancer progression, but constitutes a type of protein that is currently not amenable to therapeutic targeting. Therefore, the researchers aimed to inhibit other, targetable signaling pathways that Twist1 depends on in order to mediate invasiveness.

Surprising results reveal the adaptiveness of breast cancer cells

"Initially, using conventional in vitro tissue culture techniques, our results indicated that we were indeed successful, as many of the previously described effects of Twist1-activation were prevented by simultaneously blocking TGFR1" says Diana Dragoi, PhD student at ISF and first author on the study. However, when the researchers transferred the breast cancer cells to a more physiological, 3D-environment, they discovered to their great surprise that Twist1 was able to render breast cancer cells invasive even while TGFR1 signaling was

blocked.

The breast cancer cells had simply switched to an alternative mode of invasion, spreading through the 3D-environment as cohesive strands of cells, instead of [single cells](#). Moreover, these cells had significantly higher rates of proliferation, suggesting they were better equipped to launch secondary tumors after disseminating to distant sites. This latter process, termed metastasis, is the major course of morbidity for [breast cancer patients](#): systemic dissemination and subsequent growth of breast cancer cells in vital organs such as the brain, bone marrow or liver eventually leads to their destruction.

"Taken together, our study suggests that the inhibition of TGFBR1 does not simply block the ability of master regulator Twist1 to induce invasiveness in breast cancer cells, but redirects the actions of Twist1 to generate breast cancer cells that may be even more aggressive" adds co-author Anja Krattenmacher (ISF). "These data highlight the importance of diligent preclinical tests that aim to approximate in vivo conditions as much as possible and to test many different parameters. This is especially important when aiming to interfere with such a complex, multi-step process as metastasis" concludes Dr. Scheel. In the complexity of [breast cancer](#) progression, the devil is in the detail.

More information: Diana Dragoi et al. Twist1 induces distinct cell states depending on TGFBR1-activation, *Oncotarget* (2015). [DOI: 10.18632/oncotarget.8878](#)

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