Breast cancer cells become invasive by changing their identity

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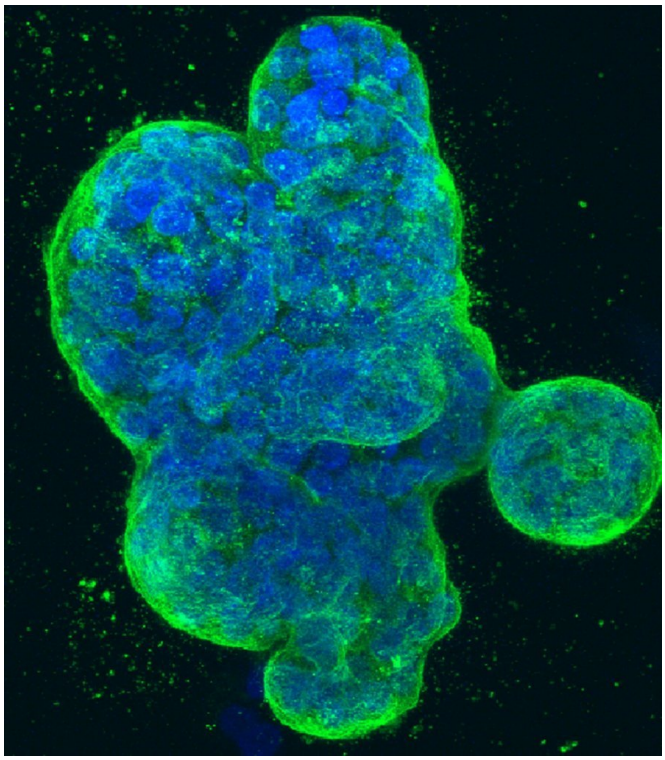

Three-dimensional culture of human breast cancer cells, with DNA stained blue and a protein in the cell surface membrane stained green. Image created in 2014 by Tom Misteli, Ph.D., and Karen Meaburn, Ph.D. at the NIH IRP.

Researchers from Karolinska Institutet in Sweden have identified a protein that determines the identity and invasive properties of breast cancer cells. The finding could lead to the development of new therapeutic and diagnostic strategies to target breast cancer invasion and metastasis. The study is published in the scientific journal *Cancer Research*.

Cancer cell invasion of the surrounding tissue is the first step in metastasis, the major cause of death in cancer. Our knowledge of how cancer cells acquire invasive and metastatic properties is incomplete, and consequently, there is a lack of treatment for cancer patients with metastatic disease. The current study sheds new light on this area.

"In recent years, it has become evident that a change in a cancer cell's identity may contribute to its invasive and metastatic behaviour," says Jonas Fuxe, Associate Professor at the Department of Microbiology, Tumor and Cell Biology at Karolinska Institutet, who led the study.

For a long time, it was believed that a cell's identity, which is created during embryonic development, is a permanent feature. Thus, once a cell has been instructed to become, for example, a muscle cell, a nerve cell or a skin cell, it will remain this type of cell no matter what.

Today, however, we know that a cell's identity is not necessarily fixed, and can change under pathological conditions such as cancer. Cancer cells mostly originate from a cell type called epithelial cells that form the skin, the inner surfaces of our tubular organs, and glands, for example in the breast. Recent studies show that breast cancer cells may lose their epithelial identity and acquire invasive and metastatic properties through a process termed epithelial-mesenchymal transition (EMT).

"Induction of EMT may be described as a process resembling how boats in a harbour being unhitched from their anchoring points become ready to move out," says Dr. Fuxe. "This is where a protein called CXADR, or CAR, comes in."

CAR was originally identified as a virus receptor, but its normal function has not been understood. CAR is often lost during cancer progression towards invasive and metastatic disease, but the implications of this have not been clear.

"What we show in this study is that CAR is an important anchoring point for breast cancer cells, preventing them from losing their epithelial cell identity and becoming invasive," says Dr. Fuxe.

What was also interesting was that, when CAR was reintroduced into breast cancer cells with low CAR levels, it was possible to change cells back to a more epithelial (normal) identity and thereby repress their invasive properties. The results may open up the way to target CAR as a new strategy for inhibiting breast cancer invasion and metastasis.

More information: Azadeh Nilchian et al, CXADR-Mediated Formation of an AKT Inhibitory Signalosome at Tight Junctions Controls Epithelial-Mesenchymal Plasticity in Breast Cancer, *Cancer Research* (2018). DOI: 10.1158/0008-5472.CAN-18-1742