A new tumor-suppressive gene that boosts personalized treatment response in breast cancer

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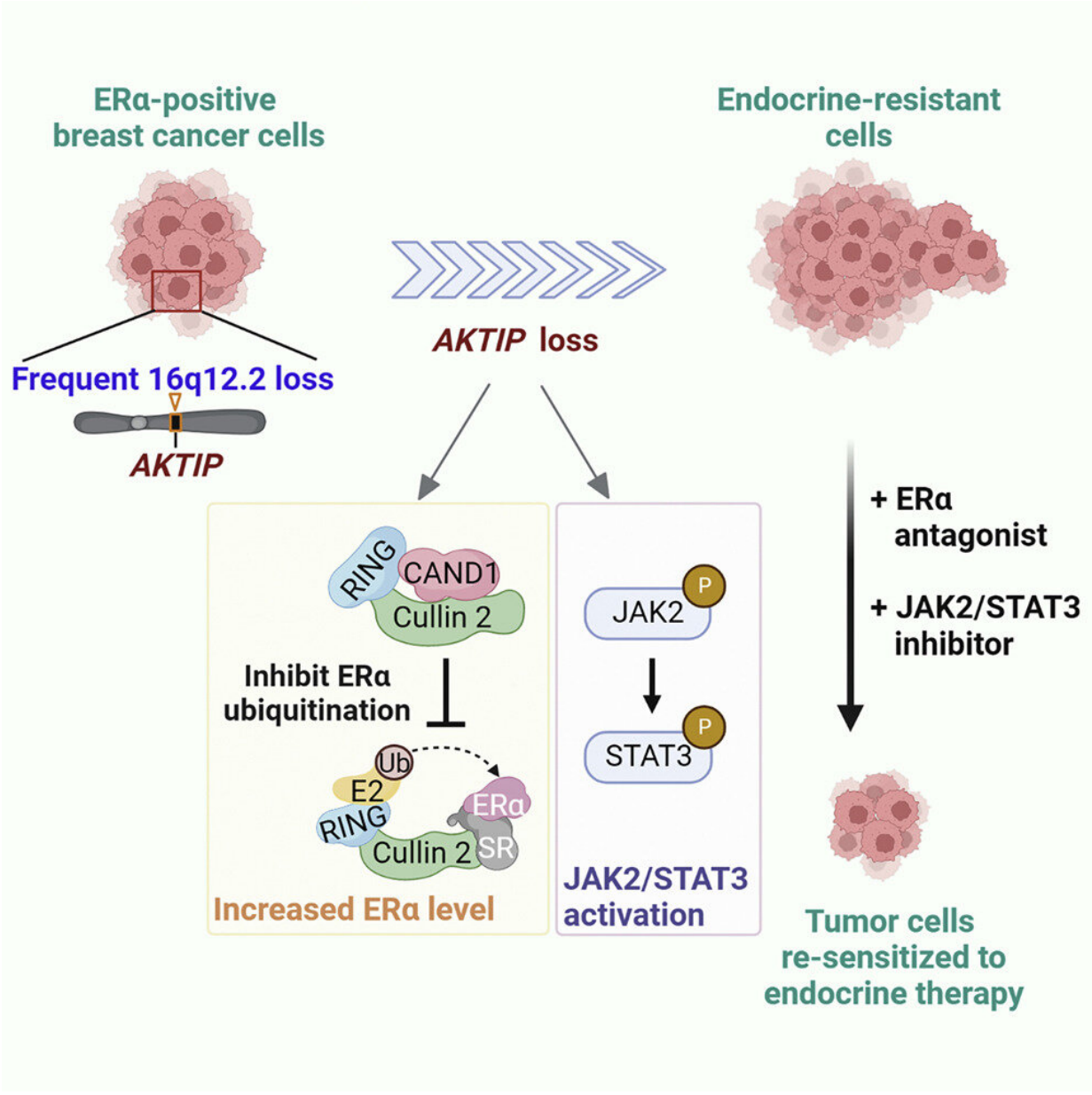

Graphical Abstract. Credit: *Cell Reports* (2022). DOI: 10.1016/j.celrep.2022.111821

A research team from LKS Faculty of Medicine, the University of Hong Kong (HKUMed) discovered that somatic deletion of a tumor suppressor gene AKTIP promotes luminal breast cancer development and resistance to endocrine therapy. The findings are now published in *Cell Reports*.

Breast cancer is the most common cancer and the third leading cause of cancer death among women in Hong Kong, and can be classified into several molecular subtypes. Each subtype has distinct clinical characteristics, genetic profiles and treatment guidelines. While the disease can be hereditary with inherited mutations in genes such as BRCA1, the majority of the breast cancer cases are somatic resulted from non-inherited mutations that are acquired during one's lifetime.

The luminal breast cancer, which expresses a hormone receptor called estrogen receptor α (ERα), is the most common subtype and constitutes 60-70% of all breast cancer cases. Because the cancer cells express ERα which fuels cancer development, targeting ERα by therapeutic agents (endocrine therapy) is the cornerstone of management for luminal breast cancer.

However, one-third of luminal breast cancer patients who initially respond to endocrine therapy eventually develop resistance to the therapy. Deletion of the AKTIP gene is observed in about 55% of luminal breast cancer cases. Despite the high occurrence, the consequence of the gene deletion was unknown.

Through multi-omics and molecular biology approaches using breast cancer cell lines, clinical samples, mouse model and cancer patient-derived organoids, the team made an intriguing discovery that loss of the AKTIP gene promotes breast cancer through increasing the protein expression level of ERα. Consistent with the pro-cancer consequences observed in these experimental models, an analysis of patient data showed that luminal breast cancer patients with AKTIP gene deletion has worse survival.

Importantly, breast cancer cells with AKTIP loss are resistant to endocrine therapy. This endocrine resistance is due to a concurrent activation of another survival pathway JAK2/STAT3, which represents an alternative escape pathway utilized by the cancer cells when ERα is inhibited. Building on this finding, the team further found that blocking this alternative escape pathway by the addition of JAK2/STAT3 inhibitor can overcome the resistance.

This study identified a new driver aberration of luminal breast cancer and the therapeutic possibilities targeting breast tumors with AKTIP gene deletion.

"We present clear evidence that deletion of AKTIP is a prognostically and therapeutically relevant chromosomal mutation in luminal breast cancer. Our findings that JAK2/STAT3 inhibitor can reverse the endocrine resistance caused by AKTIP deletion need to be further investigated. Genomic data from tumor DNA profiling are increasingly guiding cancer care in which tailored therapy can be formulated based on the gene status of the cancer patient. This precision medicine approach can kill tumor cells efficiently with less toxic side effects. The incorporation of AKTIP gene status as predictive biomarker may refine the treatment strategy for luminal breast cancer," explained Dr. Lydia Cheung Wai-ting, Assistant Professor of School of Biomedical Sciences, HKUMed.

More information: Angel S.N. Ng et al, AKTIP loss is enriched in ERα-positive breast cancer for tumorigenesis and confers endocrine resistance, *Cell Reports* (2022). DOI: 10.1016/j.celrep.2022.111821