Reprogramming SREBP1-dependent metabolism and inflammation in high-risk breast with licochalcone A for the prevention of breast cancer

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BACKGROUND

- Proven breast cancer prevention drugs have side effects that are not acceptable to 85% of women at high risk for breast cancer.[1] There is no drug which prevents ER negative breast cancer.
- **Prevention strategies with optimal efficacy and less toxicity are needed.**
- We have shown that licochalcone A (LicA), a naturally occurring compound with antioxidant and anti-inflammatory properties[2,3,4,5] significantly reduces lipogenesis and inflammation in high-risk women's breast microstructures, proliferation of 7 pre-malignant and malignant breast cell lines, and mammary tumor growth in animals.[6]

OBJECTIVES

1. What is the mechanism through which LicA reduces cell proliferation and mammary tumor growth?
2. Pharmacokinetics: is LicA orally bioavailable?

METHODS

- **Xenografts** were established in female **athymic nude mice by inoculation** with luminal or triple negative breast cancer cells, treated with LicA or vehicle for 28 days at a dose of 80 mg/kg.day and the rate of tumor growth evaluated.
- **RNA sequencing of** mammary tumors, **thermal shift proteomics and spatiotemporal measurement of cholesterol** were performed in breast cancer cells following 24 h treatment with LicA (10 μM).
- **Oral bioavailability** in plasma, liver, and mammary tissue of BALB/c female mice and Sprague-Dawley rats was studied using LC-MS/MS and SAMII analysis.

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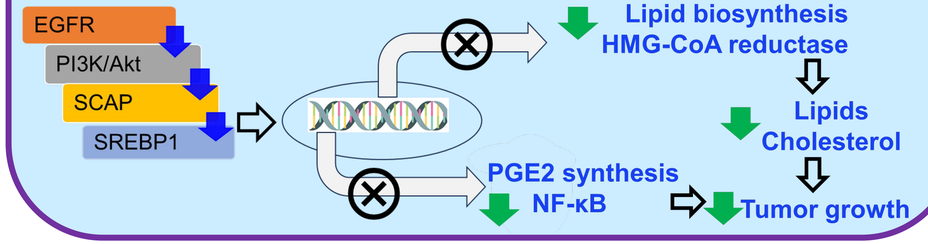
Licochalcone A (LicA): A promising ER agnostic candidate for the prevention of breast cancer

✓In high-risk women's breast microstructures

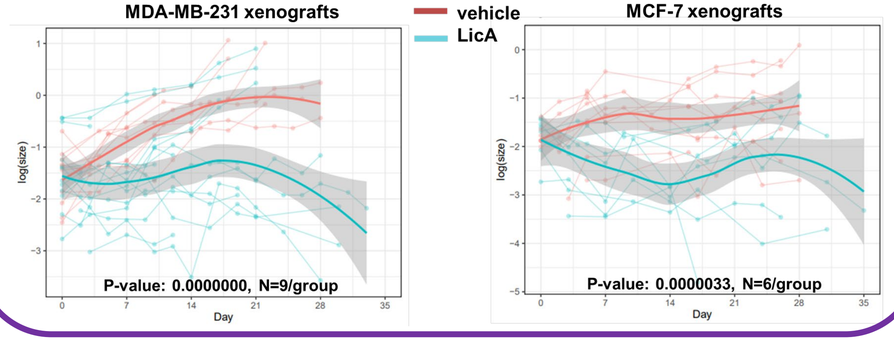
✓In ER+ and ER- pre-malignant and malignant breast cells

✓In mouse models of luminal and TNBC

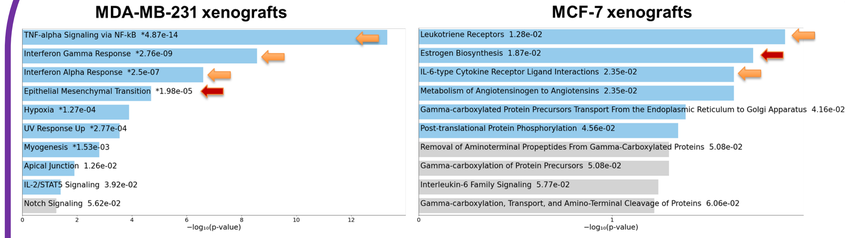


RESULTS

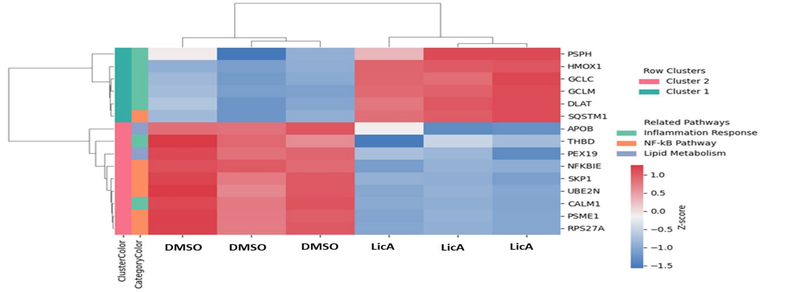
LicA reduces the growth of mammary tumors



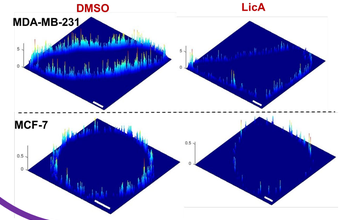
LicA downregulated inflammatory mediators in ER- and ER+ tumors, EMT in ER- and estrogen biosynthesis in ER+ tumors.



Thermal shift proteomics: LicA decreases inflammation and lipogenesis.



LicA decreases the levels of cholesterol in the inner leaflet of plasma membrane.



LicA is orally bioavailable