Licochalcone A Reprograms SREBP1-dependent Lipogenesis and Inflammation in High-Risk Breast: a Novel Path to Cancer Prevention

Atieh Hajirahimkhan[1,2], Elizabeth T. Bartom[2,3,4], Carolina H Chung[5], Xingyu Guo[6], Kyli Berkley[6], Oukseub Lee[1,2], Ruohui Chen[2,4], Wonhwa Cho[6], Sriram Chandrasekaran[5], Susan E. Clare[1,2], Seema A. Khan[1,2].

[1]Department of Surgery, Feinberg School of Medicine, Northwestern University, Chicago, IL. USA; [2]Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL. USA; [3]Department of Biochemistry and Molecular Genetics, Northwestern University, Chicago, IL. USA; [4]Department of Preventive Medicine, Northwestern University, Chicago, IL. USA; [5]Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI. USA; [6]Department of Chemistry, University of Illinois Chicago, IL. USA

Adverse effects of anti-estrogens have led to low acceptance, resulting in minimal impact on breast cancer (BC) risk reduction. Further, they do not reduce the risk of estrogen receptor negative (ER-) BC. Novel agents with broader efficacy and reduced adverse effects are needed.

We demonstrated that an established anti-inflammatory agent, licochalcone A (LicA) reduced proliferation in 7 pre-malignant and malignant breast cell lines, and significantly suppressed tumor growth in xenograft models of luminal and triple negative BC. We confirmed these observations *ex vivo* in microstructures from the contralateral unaffected breast (CUB) of 12 women with unilateral sporadic BC, and ER+ and ER- BC cells using diverse molecular mechanistic approaches. In addition, we developed proprietary oral formulations of LicA promising pharmacokinetic profiles in female mice and rats, sufficient for efficacy. We find that LicA targets sterol regulatory element binding protein 1 (SREBP1) with subsequent metabolic-inflammatory changes, lowering spatiotemporally resolved cholesterol levels inside malignant cells to the levels in normal mammary cells. SREBP1 is a central regulator of lipogenesis and inflammation and is an adverse prognostic factor in BC.

Mechanistic studies in CUBs using RNA sequencing and metabolic flux modeling revealed profound downregulation of PI3K-AKT-SREBP1-dependent lipogenesis and the NF-kB-dependent inflammatory pathways. Additionally, the NAD(P)H regenerating pentose phosphate shunt, which supports the latter, was upregulated in a direction unfavorable to de novo nucleotide biosynthesis and proliferation. NanoString metabolism panel evaluations in microstructures from additional subjects, and ER+ and ER- BC cells showed suppression of SREBP1-dependent pivotal lipogenesis enzymes such as *ACAT2*, *ACLY*, *FASN*, *SCD*, mediator of inflammation prostaglandin E2, *PRPS1*-catalyzed de novo nucleotide biosynthesis, and downregulation of proliferative markers *MKI67*, *RRM2,* and the survival gene *BCL2.* Western blots demonstrated suppression of p-PI3K and p-AKT in ER+ and ER- BC cells and the suppression of SREBP1, consistent with a significant reduction in cholesterol biosynthesis in the inner leaflet of the plasma membrane.

Our data demonstrate that LicA is a promising non-endocrine candidate agent for BC risk reduction by targeting SREBP1, reducing pro-tumorigenic aberrations in lipid homeostasis and inflammation. Future studies with oral LicA in immunocompetent models of BC prevention are warranted.