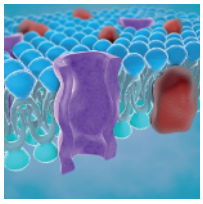
Breast Cancer

Major finding: High expression of LLGL2 promotes proliferation and drug resistance in ER$^+$ breast cancer.

Concept: LLGL2 mediates a nutritional stress response by trafficking the leucine transporter SLC7A5 to the cell surface.

Impact: LLGL2 and SLC7A5 represent potential therapeutic targets in tamoxifen-resistant, ER$^+$ breast cancers.

LLGL2 PROMOTES ADAPTATION TO NUTRIENT STRESS IN ER$^+$ BREAST CANCER



Resistance to endocrine therapy and metastatic progression is a leading cause of death in patients with estrogen receptor–positive (ER$^+$) breast cancer. Saito and colleagues report that the scaffolding protein LLGL2, the human ortholog of a *Drosophila* tumor suppressor that regulates cell polarity, is overexpressed in ER$^+$ breast cancer and promotes cellular proliferation under conditions of nutrient stress. High expression of *LLGL2* was specific to ER$^+$ breast cancer cell lines, breast cancer tissue samples, and patients with ER$^+$/PR$^+$ breast cancer, correlating with poor survival. In settings of nutrient stress, overexpression of *LLGL2* promoted cell proliferation *in vitro*, and depletion of *LLGL2* impaired proliferation *in vitro* and *in vivo*. Stimulation of ER$^+$ breast cancer cells with estrogen induced expression of *LLGL2* and restored proliferation under nutrient stress conditions, whereas deletion of an ER binding site within *LLGL2* ablated these effects. Depletion of *LLGL2* resulted in loss of multiple essential amino acids, but reintroduction of leucine rescued the proliferative defect observed in these cells. In response to nutrient stress, LLGL2 formed a trimeric complex with the leucine transport protein SLC7A5 and the SNARE protein YKT6 to stabilize SLC7A5 localization to the cell surface. Like LLGL2, high expression of SLC7A5 correlated with poor prognosis in patients with ER$^+$/PR$^+$ breast cancers, and depletion or pharmacologic inhibition of SLC7A5 impaired proliferation *in vitro* and *in vivo*. In patients with ER$^+$ breast cancer who received tamoxifen treatment, high expression of LLGL2 and SLC7A5 correlated with poor survival. Tamoxifen-resistant cells expressed high levels of *SLC7A5* and were insensitive to nutrient stress conditions, yet depletion of *LLGL2* or inhibition of SLC7A5 was sufficient to restore sensitivity to tamoxifen under nutrient stress. Collectively, these data demonstrate that LLGL2 mediates cellular adaptation to nutritional stress and that SLC7A5 represents a potential therapeutic target to overcome endocrine resistance in breast cancer. ■

Saito Y, Li L, Coyaud E, Luna A, Sander C, Raught B, et al. LLGL2 rescues nutrient stress by promoting leucine uptake in ER$^+$ breast cancer. Nature 2019;569:275–9.

Metabolism

Major finding: Ovarian cancer cells promote cholesterol efflux from tumor-associated macrophages (TAM).

Concept: Cholesterol efflux from TAMs stimulates IL4 signaling to promote tumor growth.

Impact: Targeting cholesterol efflux from TAMs represents an opportunity for therapeutic intervention.

TUMOR CELLS SCAVENGE CHOLESTEROL FROM TUMOR-ASSOCIATED MACROPHAGES

Although macrophages are known to exhibit tumoricidal activity, tumor-associated macrophages (TAM) adopt alternative signaling mechanisms to promote tumor growth and suppress antitumor immune responses. Goossens and colleagues show that cancer cells actively promote plasma membrane cholesterol efflux from TAMs, which enhances IL4 signaling and inhibits IFNγ-induced gene expression to contribute to tumor progression. Seeding of ovarian cancer cells in the mouse peritoneal cavity was followed by blood monocyte–mediated, CCR2-dependent accumulation of peritoneal macrophages. Following tumor seeding, global gene-expression analysis of TAMs revealed upregulation of genes associated with IL4 signaling and cholesterol metabolism and efflux. Co-culture of bone marrow–derived macrophages (BMDM) with ovarian cancer cells or ovarian cancer cell–conditioned medium resulted in decreased cholesterol-rich membrane microdomains and a reduction in total cholesterol levels in BMDMs. Pretreatment of the conditioned medium with hyaluronidase (HAase) or deletion of the ABC transporter *Abca1* in TAMs abrogated depletion of cholesterol in macrophages, indicating that active cholesterol efflux is responsible for the decrease in plasma membrane cholesterol levels. Following stimulation with IL4 or IFNγ, conditioned medium–pretreated BMDMs showed increased expression of IL4-induced genes and inhibited expression of IFNγ-induced genes. IL4 treatment also resulted in increased levels of activated STAT6 and phosphorylated AKT, and pharmacologic inhibition of PI3K abrogated these changes. Depletion of membrane cholesterol elicited similar effects, but not in cells lacking the ABC transporters or following incubation with HAase-treated conditioned medium. Inhibition of mTORC1 and mTORC2 also blocked phosphorylation of AKT, indicating that mTORC activity is required for macrophage reprogramming. *In vivo*, treatment with an IL4 receptor–blocking antibody or hematopoietic deficiency in *Stat6*, *Pik3cd*, or ABC receptors reduced ovarian cancer xenograft growth. Taken together, these data demonstrate that cholesterol efflux plays an important role in TAM reprogramming and tumor progression and may represent a potential therapeutic target. ■

Goossens P, Rodriguez-Vita J, Etzerodt A, Masse M, Rastoin O, Gouirand V, et al. Membrane cholesterol efflux drives tumor-associated macrophage reprogramming and tumor progression. Cell Metab 2019 Mar 28 [Epub ahead of print].