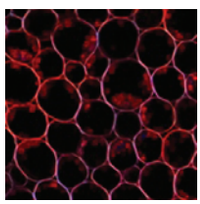
## Prostate Cancer

**Major finding:** Cholesteryl ester accumulates in *PTEN*-null prostate cancer cells and supports growth and invasion.

**Approach:** Lipid composition was quantitatively analyzed at the single-cell level in intact prostate tissues.

**Impact:** Altered cholesterol metabolism may be a diagnostic feature and therapeutic target in prostate cancer.

### ADVANCED PROSTATE CANCER IS DISTINGUISHED BY CHOLESTERYL ESTER ACCUMULATION



Accumulation of lipids within enlarged intracellular lipid droplets (LD) has been observed in several cancer types. However, the role of LD formation in cancer cell biology remains poorly understood, partly because so little is known about LD composition. Yue and colleagues evaluated a spectrum of prostate pathologies and observed enlarged LDs in high-grade or metastatic prostate cancer samples, but not in normal prostate, benign prostatic hyperplasia, or prostatic intraepithelial neoplasia tissues. Examination of LDs using Raman spectromicroscopy, a recently developed approach that allows quantitative analysis of LD lipid composition at the single-cell level in intact tissues, revealed specific enrichment of cholesteryl ether (CE) within LD in all stages of prostate cancer tissue. CE accumulation was not associated with increased androgen signaling but was increased in a prostate cancer cell line lacking the tumor suppressor PTEN, suggesting that PTEN loss drives CE accumulation. Indeed, PTEN reintroduction or inhibition of downstream PI3K–AKT–mTOR signaling significantly reduced CE accumulation in prostate cancer cells. Hyperactive PI3K–AKT–mTOR signaling caused by PTEN loss led to activation of the sterol regulatory element-binding protein (SREBP) transcription factors, which sustain cholesterol biogenesis, and the low-density lipoprotein (LDL) receptor, which increased cellular uptake of the exogenous LDLs that are subsequently hydrolyzed into free cholesterol and converted into CE within lysosomes by acyl coenzyme A: cholesterol acetylase-1 (ACAT-1). Strikingly, pharmacologic inhibition of ACAT-1 with the clinically available inhibitor avasimibe not only prevented LDL uptake and increased levels of free nonesterified cholesterol, but impaired *PTEN*-null prostate cancer cell viability, migration, and invasion *in vitro*. Moreover, ACAT-1 inhibition also suppressed growth of *PTEN*-null prostate cancer xenografts in mice without causing toxicity. Collectively, these data demonstrate a role for CE accumulation in prostate cancer progression and suggest that CE may represent a potential therapeutic target. ■

*Yue S, Li J, Lee SY, Lee HJ, Shao T, Song B, et al. Cholesteryl ester accumulation induced by PTEN loss and PI3K/AKT activation underlies human prostate cancer aggressiveness. Cell Metab 2014;19:393–406.*

## Drug Discovery

**Major finding:** Small-molecule agonists of GPR39, an orphan GPCR, are SMO-independent Hedgehog pathway inhibitors.

**Mechanism:** GPR39 activates $IP_3$-mediated second messenger signaling to activate MAPK signaling and inhibit GLI1/2.

**Impact:** GPR39 is a potential therapeutic target in SMO inhibitor-resistant Hedgehog-driven tumors.

### THE ORPHAN RECEPTOR GPR39 IS A REGULATOR OF HEDGEHOG SIGNALING

The Hedgehog signaling cascade is a key regulator of cell fate during development and is aberrantly activated in human cancers. Inhibitors of Smoothened (SMO), a G protein-coupled receptor (GPCR)–like mediator of Hedgehog signaling, have therapeutic potential in Hedgehog pathway–driven cancers, but acquired resistance can arise through reactivation of the downstream GLI transcription factors. To identify SMO-independent Hedgehog pathway inhibitors, Bassilana and colleagues performed a high-throughput cell-based reporter screen of a large compound library and found that cyclohexylmethyl aminopyrimidines (CMAP) suppressed GLI-driven luciferase cassette expression in the presence of a SMO agonist or GLI1 overexpression and reduced expression of Hedgehog pathway target genes independently of SMO binding. Identification of the target(s) of the CMAP compounds focused on GPCRs, as membrane permeability was not essential for CMAP activity and the CMAP scaffold resembled previously characterized GPCR antagonists. However, CMAP treatment stimulated production of the second messenger inositol triphosphate ($IP_3$), an indicator of GPCR activation. GPCR mRNA profiling in human and murine cell lines revealed a candidate target, G protein-coupled receptor 39 (GPR39), which was highly expressed in CMAP-responsive cell types. Overexpression of GPR39 sensitized nonresponsive cells to CMAP treatment, with GPR39 activation stimulating $IP_3$ production and reducing GLI1/2 activity in a MAPK pathway–dependent manner. Moreover, GPR39 depletion reduced CMAP potency without affecting SMO inhibitor activity. The identification of CMAPs as SMO-independent inhibitors of Hedgehog signaling that act as GPR39 agonists implicates the orphan receptor GPR39 as a modulator of the Hedgehog pathway and suggests that GRP39 may represent a potential therapeutic target for Hedgehog pathway–driven tumors, including those with acquired SMO inhibitor resistance. ■

*Bassilana F, Carlson A, DaSilva JA, Grosshans B, Vidal S, Beck V, et al. Target identification for a Hedgehog pathway inhibitor reveals the receptor GPR39. Nat Chem Biol 2014 Mar 16 [Epub ahead of print].*