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Targeting cholesterol metabolism to suppress prostate cancer metastasis

Metastatic prostate cancer is the second leading cause of cancer death in men worldwide. Prostate cancer itself is one of the most common cancers in men. At the early stages, localized prostate cancer usually grows slowly and has nearly 100% 5-year survival rate. However, once cancer cells spread to nearby tissues, or metastasize to other parts of the body, the 5-year survival rate drops to 29%. Several treatment approaches are available, such as androgen deprivation therapy, enzalutamide or abiraterone, but progression into treatment-resistant cancer is often inevitable. To date, metastatic prostate cancer is still considered not curative and there is a critical need for new treatment approaches.

Prostate cancer has been known to have aberrant lipid accumulation. In fact, cancer lipid metabolism is gaining increasing attention for its potential in cancer prognosis or therapy. Still, the composition and spatial distribution of lipid in cancer are unclear. The incomplete understanding of lipid metabolism obscures the functional roles of lipid in cancer progression and hinders the clinical applications. To address such challenges, we developed and applied a novel technique to perform quantitative analysis of lipid compositions at single-cell level in human patient tissues.

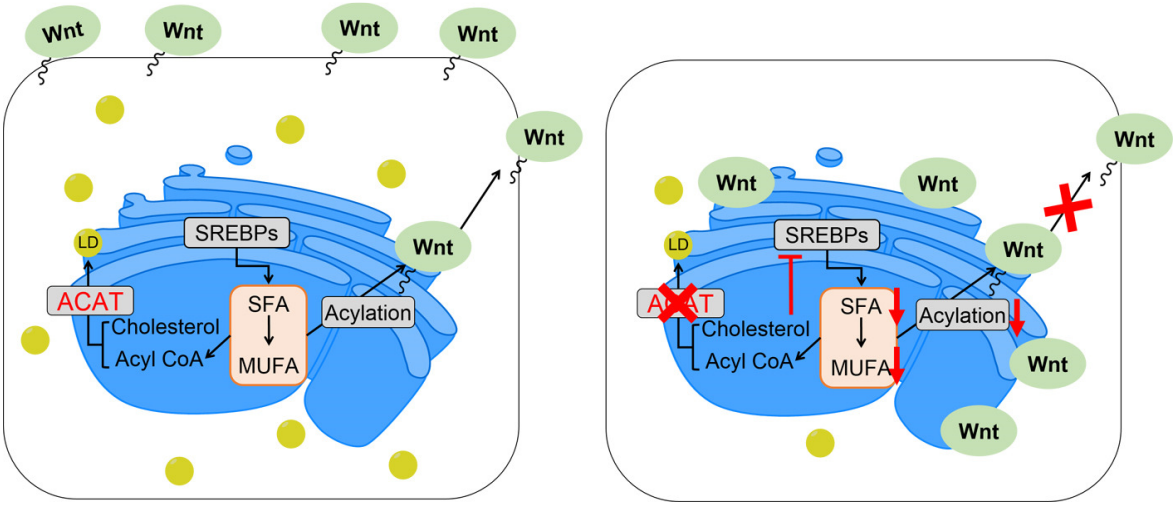

Fig. 1. Molecular mechanism of suppressing prostate cancer metastasis by cholesteryl ester depletion. Adopted from Mol Cancer Res (2018) 16(6), 974-985.

Using spectroscopic imaging of human specimen, we identified unexpected, aberrant accumulation of esterified cholesterol in lipid droplets as a metabolic signature of metastatic prostate cancer. We applied Raman spectromicroscopy to analyze individual lipid droplets found in metastatic tissue samples from patients. Surprisingly, we found high amount of cholesteryl ester inside these lipid droplets. These cholesterol metabolites came from cholesterol esterification by Acyl-Coenzyme A:Cholesterol Acyltransferase 1 (ACAT-1, also known as Sterol O-Acyltransferase 1), which is an important buffering mechanism for detoxifying excess intracellular cholesterol. Cholesterol esterification process can be inhibited by a potent ACAT

inhibitor, avasimibe. Indeed, when we treated metastatic prostate cancer cells with avasimibe, we found a significant reduction of cholesteryl ester in lipid droplets. Importantly, we discovered that cholesteryl ester accumulation is linked to migration capacity of the cancer cells. These observations triggered us to test therapeutic potential of targeting cholesterol esterification to suppress metastasis using preclinical mouse models.

In the prostate cancer orthotopic mouse model, we found a significant reduction of metastasis after depleting cholesteryl ester in the primary prostate cancer. In the control mice, primary prostate tumor shows invasive phenotype. To deplete cholesteryl ester *in vivo*, we previously developed a systemically injectable neoformation of avasimibe, named avasimin. When the cholesteryl ester is depleted by avasimin, primary prostate tumor shows clear tumor margins, indicating reduced invasiveness. Most excitingly, the number of metastasis developed in the avasimin-treated mice reduces dramatically at the same time. Using another metastatic cancer mouse model, we also found significantly inhibition of metastatic prostate cancer growth by depleting cholesteryl ester. These studies support that cholesterol esterification is a potential therapeutic target for suppressing metastatic cancer development and growth. Importantly, no detectable toxicity from the cholesteryl ester depletion treatment by avasimin was observed in the mouse models. As most normal cell types do not accumulate high level of cholesteryl ester, enhanced cholesterol esterification is a cancer-specific metabolic signature, and this metabolic target can be used to suppress cancer progression without causing unfavorable disturbance to the cholesterol homeostasis in other normal cells.

To further unveil the functional role of cholesteryl ester accumulation in metastatic prostate cancer, we combined Raman spectroscopy with gene expression analysis. After confirming cholesteryl ester depletion by avasimibe in human metastatic prostate cancer, the same cells are collected for RT-PCR profiler array. We found several metastasis-related genes that are significantly changed upon cholesteryl ester depletion in metastatic prostate cancer cells, which supports our preclinical animal studies. Among these genes, we identified Wnt/β-catenin as one of major oncogenic signaling pathways regulated by altered cholesterol metabolism. In this pathway, Wnt lipid modification and membrane localization are required for its activation. For lipid modification of proteins, intracellular fatty acid availability is important. Combining spectroscopic imaging with mass spectrometry, we found that lipogenic potential of prostate cancer cells is suppressed when cholesteryl ester is depleted. This observation triggered us to test whether Wnt lipid modification is regulated by cholesterol metabolism. Indeed, inhibition of cholesterol esterification blocks membrane localization and secretion of Wnt through reducing its lipid modification. We further showed that such regulation is essential for enhancing migration capacity of the prostate cancer cells. Collectively, the mechanism study demonstrates an important crosstalk between lipid metabolism and oncogenic signaling to promote prostate cancer metastasis.

To summarize, we show that cholesterol esterification is a promising therapeutic target for prostate cancer intervention and effective treatment for late-stage metastatic cancer. We also incorporated spectroscopic imaging technique with conventional molecular biology studies to reveal one important function of aberrant lipid metabolism – regulation of Wnt/β-catenin pathway to promote cell migration. This study paves the foundation for future clinical studies using drugs targeting cholesterol esterification to suppress prostate cancer metastasis.

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Publication

Cholesterol Esterification Inhibition Suppresses Prostate Cancer Metastasis by Impairing the Wnt/β-catenin Pathway.
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