

Unraveling and targeting the lipidome of clinical prostate cancer.

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Background. Metabolic rewiring is both a hallmark feature of prostate cancer cells and a potential therapeutic vulnerability, but remains a critical gap in the molecular profiling of this disease. Herein, we detail and spatially visualize the lipidomic landscape of clinical prostate cancer.

Experimental Design. Mass spectrometry-based imaging and lipidomics were used to measure and spatially visualize the lipidome of a cohort of prostate tumors and matched benign tissues (n=21), an independent validation cohort (n=47), and primary prostate explants cultured in the absence or presence of a clinical AR antagonist, enzalutamide (n=43).

Results. Significant differences in phospholipid (PL) composition were evident in tumors compared to matched benign samples. Notably, tumors featured higher proportions of monounsaturated lipids across all PL classes and elongated fatty acid chains specifically in phosphatidylinositol and phosphatidylserine-based lipids. Associations between abundance of individual PLs and malignancy were identified for both patient cohorts, and PL composition was characteristically altered in patient tissues that responded to AR inhibition. Moreover, targeting of the observed tumor-related changes in lipid synthesis, saturation and elongation, via inhibition of acetyl-CoA carboxylase or stearyl-CoA desaturase, significantly reduced cellular proliferation.

Conclusion. This first characterization of the prostate cancer lipidome in a clinical tissue context revealed enhanced fatty acid synthesis, elongation and desaturation as tumor-defining features, with potential for therapeutic targeting to improve patient outcomes.