TRIGLYCERIDE RICH ADENOCARCINOMA OF THE PROSTATE (TRAP): A HIGH-GRADE TUMOR VARIANT ASSOCIATED WITH AN IMBALANCE OF LIPID REGULATING PROTEINS DGAT1 & ATGL

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Background:
Lipogenesis and lipolysis are tightly regulated to maintain adequate flux of triglycerides to meet the metabolic needs of a tissue. An adaptive mechanism to promote growth, tumor cells undergo metabolic reprogramming to favor increased neutral lipid accumulation. We postulated that the neutral lipid imbalance could be the result of altered expression of diacylglycerol O-acyltransferase 1 (DGAT1), a key lipogenesis protein, and adipose triglyceride lipase (ATGL), the rate-limiting enzyme in lipolysis.
Methods:
We analyzed protein expression for DGAT1 and ATGL in prostate tumors (n=46) from varying Gleason grades, scored the staining intensity (grade 1-4), and assessed the quantity of vacuoles within the epithelial and stromal compartments. Prostate cancer (PC) cells were co-cultured with human periprostatic fat (PPF) to simulate an obesogenic microenvironment and intracellular lipid evaluated by Oil-Red-O staining and immunofluorescence.
Results:
We found that higher intratumoral DGAT1 protein expression correlated with higher Gleason scores while ATGL often resided on the surface of the vacuoles or lipid droplets (LDs) in both the tumor epithelial and stromal muscle cells. The co-culture of PC cells with PPF exacerbated the intratumoral lipid content. Interestingly, a distinctive histologic phenotype emerged in a subset of tumors (9/46). We termed this tumor subtype as triglyceride-rich adenocarcinoma of the prostate (TRAP). Microscopically, TRAP was characterized by diffuse vacuoles streaming through the stroma, especially the smooth muscle cells and fibroblasts. Grape-like clusters of vacuoles were observed within the cytoplasm of most tumors cells. These vacuoles stained for DGAT1 > ATGL. All TRAP tumors had lipogenesis and lipolysis proteins on the surface of LDs and correlated with higher Gleason scores (8-9).
Conclusion:
These data suggest that lipid re-programming in PC can create nutrient sources to support high-grade tumor growth. Recognition of histologic TRAP tumor subtype could assist in identifying a group of patients who would benefit from DGAT1 inhibition therapy.