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**Fueling survival: Adipocyte-mediated modulation of iron metabolism and oxidative stress pathways in bone metastatic prostate cancer**

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Fueling survival: Adipocyte-mediated modulation of iron metabolism and oxidative stress pathways in bone metastatic prostate cancer

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Prostate cancer (PCa) commonly metastasizes to the bone marrow, where cancer cells interact with a variety of cell types that compose the bone tumor microenvironment. The interaction of interest for this research is between metastatic PCa cells and adipocytes, a major cell type in bone marrow. Numbers of marrow adipocytes increase with age, obesity and metabolic pathologies, and their impact on tumors that grow in bone is being increasingly recognized. The PCa cells in bone marrow have increased survivability and chemoresistance that may be related to their communication with bone marrow adipocytes. One mechanism of interest is the balance of lipid peroxides and iron stores within PCa during adipocyte exposure. The aim of this research is to test the hypothesis that bone marrow adipocytes support PCa survival in the bone tumor microenvironment through the modulation of iron stores and lipid peroxides. Our analysis of single-cell RNaseq data from patients with PCa bone metastases demonstrated changes in genes related to the regulation of iron and lipid peroxides, suggesting their possible role in PCa survival. Specifically, high expression of ferritin (FTH1), an iron storage protein, and low levels of nuclear receptor coactivator 4 (NCOA4), a ferritin degradation protein, were observed in tumor clusters, along with high expression of glutathione peroxidase 4 (GPX4), an enzyme that protects cells from lipid peroxides. Interestingly, when PCa cells were exposed to bone marrow-derived adipocytes in vitro, similar patterns of expression were observed (i.e., increased levels of FTH1 and GPX4, but reduced levels of NCOA4), indicating the potential role of marrow adipocytes in the regulation of iron storage and ferritin turnover. IHC staining of tumor sections from mice fed either high fat (HFD) or low fat (LFD) diet showed increased FTH1 expression in tumors from HFD mice. Notably, particularly high FTH1 presence was observed in the areas rich in adipocytes, demonstrating a potential relationship between the iron storage protein and lipids. In addition, tumor areas with augmented FTH1 showed increased expression of heme oxygenase 1 (HO-1), an antioxidant enzyme responsible for the breakdown of heme into iron and biliverdin. This was in line with our in vitro results showing an increase in HO-1 levels with adipocyte exposure, and a high FTH1 expression in cells stably overexpressing HO-1. One notable observation is that PCa cells exposed to adipocytes in Transwell co-culture in vitro, showed initially increased lipid peroxidation levels, which declined upon prolonged interaction with adipocytes. This suggests an adaptive mechanism present in PCa cells, potentially involving modulation of iron stores and HO-1 and GPX4 activity. Upon treatment with iron citrate, FTH1 protein levels increased while GPX4 protein levels decreased particularly in PCa cells cultured with adipocytes, indicating a potentially more direct relationship between FTH1 levels and GPX4 activity. To further explore this relationship, PCa cells were cultured alone or exposed to adipocytes in the presence or absence of GPX4 inhibitor, RSL3. Inhibition of GPX4 led to an increase in FTH1 and HO-1 protein levels in PCa cells, suggesting their possible roles in reducing oxidative stress from lipid peroxides during adipocyte exposure. Collectively, our data indicate that the modulation of iron storage and lipid peroxides in PCa cells by bone marrow adipocytes may play a role in the survival of metastatic PCa within the harsh bone marrow microenvironment.