43 The bone microenvironment drives upregulation of the pentose phosphate pathway in prostate cancer, improving antioxidant properties

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Introduction & Objectives: Metabolic changes are a hallmark of malignant transformation, and to facilitate this cancer cells develop a metabolic relationship with their surrounding stroma. Prostate cancer (PCa) has an unusually high propensity for metastasizing to bone, and interactions between PCa cells and the bone microenvironment promote tumour growth and survival and drug resistance. These processes require energy, reducing power and a source of biosynthetic precursors. The pentose phosphate pathway (PPP) runs parallel to glycolysis and is advantageous for rapidly dividing cells as it provides nucleotide precursors and is the main source of NADPH, which is vital for the detoxification of free radicals. We hypothesise the bone microenvironment drives upregulation of the PPP and this could drive tumour resistance to currently used therapies.

Materials & Methods: In silico analysis performed via CBioPortal with analysis in Prism 5 and GSEA (Broad Institute). Metabolite changes analysed using capillary electrophoresis time-of-flight mass spectrometry (CE-TOFMS). Real-time PCR and Western blotting used to confirm expression levels of selected targets. GSH and ROS measured using Promega kits.

Results: In silico analysis of PCa cells isolated from patients with primary and metastatic disease revealed that the PPP, including the rate limiting enzyme, glucose-6-phosphate-dehydrogenase (G6PD), is upregulated in metastatic samples, and in particular in bone metastatic samples. High expression of G6PD correlated with shorter progression free survival. Bone metastatic PCa cell lines (PC3, MDA-2a) were found to have higher expression of G6PD compared to non-bone metastatic (22RV1, LNCaP) and benign (PNT1a) cell lines. PPP metabolites and G6PD protein and mRNA were more highly expressed in PCa cells after co-culture with or conditioned media (CM) from HS-5 bone marrow stromal cells (BMSC's) suggesting the bone microenvironment can drive this upregulation of the PPP. We found HS-5 cells secrete high interleukin-6 (IL-6) and blocking IL-6 in BMSC CM abrogated the upregulation of G6PD. PCa cells with increased G6PD induced by BMSCs have improved anti-oxidant ability with an increased NADPH/NADP ratio, and raised glutathione (GSH) levels. Inhibiting G6PD increases cellular reactive oxygen species (ROS), and improves response to chemotherapy in vitro.

Conclusions: In this study we have identified G6PD is significantly upregulated in patients with metastatic prostate cancer and correlates negatively with progression free survival. IL-6 secreted from BMSCs can drive this upregulation in PCa cells, and lead to increased anti-oxidant ability. Targeting this pathway could sensitize PCa to the oxidative damage caused by currently used radio- and chemo-therapy, and thereby provide benefit to patients with advanced prostate cancer.