Transcriptome differences in prostate cancer highlight racial disparities and vitamin D

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The results of clinical studies by investigators at the Medical University of South Carolina (MUSC) and the Ralph H. Johnson VA Medical Center (VAMC), reported in the July 2016 issue of *Pharmacogenomics*, demonstrate transcriptome-level linkages between racial disparities in circulating levels of vitamin D and expression of pro-inflammatory genes in African American (AA) patients with prostate cancer compared to European American (EA) patients.

Racial disparities in prostate cancer are well documented with AA men having significantly higher risk of developing prostate cancer and significantly higher mortality rates than EA men. In addition, among patients presenting at the same disease stage, AA men often have higher prostate-specific antigen (PSA) levels and higher-grade tumors than EA men. However, the biological mechanisms underlying these substantial and persistent disparities are unclear.

Researchers at MUSC and VAMC noticed that racial disparities in prostate cancer mirror differences in circulating levels of vitamin D between AA and EA patients. Vitamin D3 is known to have multiple anti-cancer actions including suppression of cyclo-oxygenase-II (an independent predictor of cancer recurrence) and inhibition of IL-8 (an angiogenic, pro-inflammatory cytokine). Prostate cells express the vitamin D receptor, vitamin D-25-hydroxylase, 25 hydroxyvitamin D-1-alpha-hydroxylase, and 25-hydroxyvitamin D-24-hydroxylase. Thus, normal prostate cells can synthesize 25(OH)D3 (calcidiol) from vitamin D (cholecalciferol), and 1,25(OH)2D3 (calcitriol) from 25(OH)D3.

1,25(OH)2 D3 (calcitriol) is the bioactive, hormonal, and most potent form of vitamin D and facilitates cell-to-cell communication via paracrine/autocrine pathways.

Sebastiano Gattoni-Celli, M.D., Professor of Radiation Oncology at MUSC, and senior author on the article, explains how his team came to explore the therapeutic potential of vitamin D supplementation in prostate cancer, "A lot of previous work shows that D3 levels are much lower in African Americans than in European Americans and it's well established that prostate cells are very sensitive to vitamin D levels. So this raised the possibility that long-term vitamin D deficiency may contribute to the progression of prostate cancer, especially among African American men. We began to wonder whether eliminating racial disparities in circulating levels of vitamin D, through supplementation, could help reduce the disparities we see in prostate cancer outcomes."

The team designed a prospective, placebo-controlled, clinical study to investigate the effects of a daily 4,000 IU vitamin D3 supplementation over a two-month period among 27 men (10=AA, 17=EA) who had elected to treat their prostate cancer via prostatectomy. A trial length of two months was chosen to leverage the recommended, standard-of-care recovery period between their biopsy and surgery procedures. Using high-throughput RNA sequencing, they performed a series of genome-wide expression profiling experiments to generate transcriptional profiles of patients' prostate tissue samples and assessed them using systems-level analyses. Their primary aims were to: (1) illuminate any molecular differences in gene expression that may be related to prostate cancer disparities between AA and EA men; and (2) investigate any effects vitamin D supplementation may have on the prostate transcriptome.

Not only did the team find significant differences in gene expression between AA and EA men but also between AA men receiving vitamin D supplements and AA men receiving placebo. Due to the size of the RNA

sequencing dataset, results are reported as adjusted p-values (or q-values) which represent the smallest 'false discovery rate' at which a result can be called significant. A total of 3,107 prostate genes were differentially expressed between the AA and EA groups (q