Regulation of megalin by vitamin D as the mechanism for differential levels of intra-prostatic androgens between African American and Caucasian men

J Garcia, Z Richards, M Zenner, Y Wang, P Gann, G Prins, L Nonn

Prostate cancer (PCa) is a hormonally driven cancer and is currently the third most common cancer in the US. African American (AA) men are disproportionately at risk for both PCa and vitamin D (vitD) deficiency compared to white men. The numerous chemopreventative properties of vitD and epidemiological relationship of vitD status with PCa aggressiveness and mortality has led to the hypothesis that vitD deficiency is a biological contributor to PCa disparity in AA men. Our lab recently reported an unexpected relationship between serum and intraprostatic vitD metabolites 25-hydroxyvitamin D (25(OH)D) and 1,25-dihydroxyvitamin D in AA men. We also observed that Megalin, a multi-liganded endocytic membrane receptor encoded by the gene *LRP2,* was expressed in the prostate epithelium and is regulated by vitD. Extra-renal activity of Megalin has not been well studied as the widely accepted Free Hormone Hypothesis assumes passive diffusion of circulating free hormones into tissues. The presence of megalin suggests that globulin bound hormones from the circulation, including 25(OH)D bound to vitamin D binding protein (DBP) and testosterone (T) bound to sex hormone binding globulin (SHBG), are imported into the prostate in a regulated manner. Here we examine megalin as a potential mechanism to regulate globulin bound hormone import into the prostate. 25(OH)D decreased expression of *LRP2* in primary prostate epithelial cells and fresh human prostate tissue slice explants. DBP-bound 25(OH)D and SHBG-bound T were imported into these prostate models and transcriptionally active. Lastly, we quantified T and its active metabolite dihydrotestosterone (DHT) in the patient cohort from our prior study. Prostatic DHT levels inversely correlated with serum 25(OH)D status. AA men had higher levels of DHT in prostate tissue compared to white men. These clinical findings support our hypothesis that vitD status regulates intraprostatic hormone levels. In summary, we report the presence of a negative feedback loop in which vitD deficiency increases hormone import into prostate epithelium via megalin. Therefore, the upregulation of megalin in the setting of vitamin D deficiency may facilitate increased import of circulating sex steroids into the prostate contributing to carcinogenesis in AA men.