Vitamin D Inhibition of the Prostaglandin Pathway as a Therapy for Prostate Cancer

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Inflammation has been associated with carcinogenesis and progression of a number of cancers including prostate cancer. Prostaglandins are an important element in the inflammatory process associated with many cancers, produced either in the epithelial cancer cells or in the infiltrating immune cells. Expression of cyclo-oxygenase-2 (COX-2), the enzyme that synthesizes prostaglandins, has been associated with worse prognosis of prostate cancer. We have found that calcitriol inhibits COX-2 expression suggesting that this action contributes to the anti-cancer activities of calcitriol. We further showed that calcitriol stimulates the expression of 15-prostaglandin dehydrogenase (15-PGDH), the enzyme that degrades prostaglandins. In addition, we found that calcitriol inhibits EP and FP prostaglandin receptors. Thus, calcitriol has three actions to inhibit prostaglandin action. Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to have activity in preventing and treating prostate cancer but have not been vigorously pursued after the finding that COX-2 selective NSAIDs increased cardiovascular risk. When we combined calcitriol with a non-selective NSAID like naproxen, we found that the combination was synergistic, even at lower concentrations of both drugs. We started a trial of men with early recurrent prostate cancer using the combination of high-dose intermittent calcitriol (DN-101) and naproxen in men with early recurrent prostate cancer. The ongoing study shows that many of the men respond with a substantial increase in the time it takes to double their PSA. This change in the PSA, although a surrogate marker, appears to indicate that calcitriol plus naproxen may have efficacy in preventing progression in men with early recurrent prostate cancer.