

## Interactions Between Vitamin D and Androgen Receptor Signaling in Prostate Cancer Cells

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Prostate cancer is an androgen-dependent disease, and androgen blockade is the primary treatment for metastatic prostate cancer. However, the tumors become resistant within a relatively short time. The recurrent tumors, surprisingly, typically overexpress androgen receptor and a subset of androgen-regulated genes including prostate-specific antigen (PSA). The mechanism for this reactivation is unknown, but alternate therapies that target androgen receptor or other pathways are needed.

There is good evidence that vitamin D reduces risk for prostate cancer. Increased exposure to sunlight (our primary source of vitamin D<sub>3</sub>) is correlated with a decreased incidence of prostate cancer.<sup>1</sup> A more recent study comparing exposure to sunlight and vitamin D receptor (VDR) polymorphisms in advanced prostate cancer patients and controls showed that increased VDR activity decreased risk for prostate cancer.<sup>2</sup> The active form of vitamin D<sub>3</sub>, 1,25-dihydroxyvitamin D<sub>3</sub>, abbreviated 1,25(OH)<sub>2</sub>D, is produced by sequential hydroxylations of the 25 and 1 positions in vitamin D<sub>3</sub>. In a large study of nearly 20,000 men, the risk of subsequently developing a more aggressive form of prostate cancer was higher in men with low levels of 25(OH)D.<sup>3</sup> Almost all prostate cancer cell lines and primary prostate cancer cells express VDR, and most are inhibited by 1,25(OH)<sub>2</sub>D.<sup>4–6</sup> 1,25(OH)<sub>2</sub>D-mediated growth inhibition in various types of cancer has been associated with G<sub>0</sub>/G<sub>1</sub> accumulation,<sup>7–11</sup> and, in some cases, with apoptosis.<sup>12,13</sup> 1,25(OH)<sub>2</sub>D also reduces invasiveness of DU145 prostate cancer cells,<sup>14</sup> and reduces expression of MMP-9 and cathepsins, proteases that facilitate motility and invasion.<sup>15</sup>

Although most prostate cancer cells contain VDR,

the extent to which they are growth inhibited varies greatly. The androgen receptor-positive LNCaP cells are much more responsive than the androgen receptor-negative PC-3 or DU145 cells<sup>4</sup> and somewhat more responsive than some other androgen receptor-positive cell lines such as LAPC-4 and 22RV1.<sup>16</sup> A report by Zhao et al.<sup>17</sup> showed that the growth-inhibitory effects of 1,25(OH)<sub>2</sub>D in the androgen-dependent prostate cancer cell line LNCaP were reduced by treatment with the androgen receptor antagonist Casodex, although Casodex has some growth inhibitory actions of its own. We sought to determine whether this response was a general phenomenon in prostate cancer cell lines, as well as to determine the basis for this differential action. We found that other cells derived from the LNCaP lineage showed the same response, but two other independently derived androgen receptor-containing cell lines (LAPC-4 and 22RV1) did not.<sup>16</sup> Activation of a transiently transfected VDR-responsive reporter was unaffected by treatment with Casodex, so the effect was indirect. Although combined Casodex and 1,25(OH)<sub>2</sub>D treatment inhibits the growth of LNCaP cells to the same extent as Casodex alone, an examination of some of the effects of 1,25(OH)<sub>2</sub>D (down-regulation of bcl-2, down-regulation of c-myc, and G<sub>0</sub>/G<sub>1</sub> arrest) revealed that each of these responses was only partially inhibited.

The question arises as to whether antagonist-bound androgen receptor has a unique function. In androgen-independent C4-2 cells, a derivative of the androgen-dependent LNCaP cells, 1,25(OH)<sub>2</sub>D does inhibit the growth of the cells in medium depleted of androgens. However, this line exhibits some hormone-dependent androgen receptor activity, and PSA is expressed in the absence of androgens. Under these conditions, Casodex partially reverses the growth inhibition caused by 1,25(OH)<sub>2</sub>D, suggesting a unique function for the antagonist-bound receptor. In an analysis of 1,25(OH)<sub>2</sub>D action in LNCaP cells, we found that an androgen-induced gene that inhibits cell growth (AS3/APRIN) was also induced by 1,25(OH)<sub>2</sub>D.<sup>16</sup> Moreover, Casodex reduced induction by 1,25(OH)<sub>2</sub>D. In contrast, AS3 is not induced by either androgens or 1,25D in 22RV1 cells and there is no Casodex reversal of 1,25(OH)<sub>2</sub>D-mediated

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doi: 10.1301/nr.2007.aug.S116–S117

growth inhibition.<sup>16</sup> The LNCaP lineage is more responsive to 1,25(OH)<sub>2</sub>D than are most other prostate cancer cell lines. Thus, there appear to be both androgen-dependent and androgen-independent actions of 1,25(OH)<sub>2</sub>D that contribute to growth inhibition in prostate cancer cells.

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