

# Arresting Prostate Cancer Growth by Targeting the Androgen Receptor and MAGE-A11

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Important questions concerning the hormonal regulation of prostate cancer growth include: Can the androgen receptor (AR) drive prostate tumor growth independent of androgen, and can drug therapies that target androgen biosynthetic enzymes provide a long term cure for prostate cancer?

Prostate cancer begins as a hormone-dependent tumor driven by dihydrotestosterone (DHT), the most potent naturally occurring androgen. DHT is produced locally in the prostate primarily by the action of 5 $\alpha$ -reductase that converts testosterone, the major circulating but less potent form of androgen [1]. DHT is also produced by a backdoor pathway from androstenediol [2-4]. AR bound to DHT activates androgen-dependent genes by binding androgen response element DNA in enhancer and promoter regions. A key step in AR transactivation of target genes is the androgen-dependent AR NH<sub>2</sub>- and carboxyl-terminal (N/C) interaction mediated by AR NH<sub>2</sub>-terminal FXXLF motif binding to activation function 2 in the carboxyl-terminal AR ligand binding domain [5-7]. AR function as a ligand-activated transcription factor requires the coordinated actions of coregulatory proteins.

The requirement for androgen in AR mediated prostate cancer growth is indicated by the temporary remission of tumor growth after androgen deprivation therapy. The eventual regrowth of castration-recurrent prostate cancer refractory to antihormonal therapies suggests that AR signaling is restored during prostate cancer progression. Many lines of evidence support this and suggest that AR continues to drive castration-recurrent tumor growth despite the ineffectiveness of antiandrogen therapy. However, it is not clear how the low circulating androgen environment of prostate cancer cells enhances AR signaling and how this can be blocked.

The effectiveness of small inhibitory RNA knockdown of AR in blocking prostate cancer cell growth in culture has helped maintain a focus on AR as a key target for the development of new prostate cancer therapies [8,9]. Recent evidence states that prostate tumor cells produce their own active androgen that involves up-regulation of genes in the biosynthetic pathway supports the idea that AR remains dependent on androgen for its transcriptional activity [3,4,10, 11]. Increased intratumoral androgen production provides a mechanism for continued AR signaling in the low circulating androgen environment resulting from androgen deprivation therapy. The ineffectiveness of antiandrogens in arresting the growth of castration-recurrent prostate cancer may be explained by locally produced high affinity active androgens that out-compete lower affinity antiandrogens delivered from the circulation.

Worldwide efforts continue to identify new inhibitors of AR mediated gene transcription and the intratumoral production of androgen. However, whether targeting androgen biosynthetic enzymes will ultimately be effective in curing the patient remains elusive. The recent success of the FDA approved abiraterone acetate, an irreversible inhibitor of 17 $\alpha$ -hydroxylase/17,20 lyase (P450c17) [12,13], has provided only temporary remission with the eventual regrowth of the

tumor. Enzyme inhibitors such as abiraterone acetate may incompletely inhibit their target enzymes and allow sufficient androgen production to maintain AR function. Alternatively, AR may acquire the ability to activate genes and drive prostate cancer growth in a relative deficiency of androgen.

Prostate cancers acquire a variety of survival mechanisms in the hypoxic environment associated with androgen deprivation therapy to enhance the development of castration-recurrent growth. Amplification of the AR gene and increased expression of coactivators allows AR to function in a low androgen environment [14-16]. In a few cases, AR mutations in the ligand binding domain expand the range of steroids that can activate AR. These mechanisms maintain AR as the central molecule driving the growth and progression of prostate cancer. However, is it possible that a sufficiently high level of an AR coregulator can bypass the requirement for AR?

An example of increased AR coactivator expression that appears to supplant the requirement for AR in the growth of castration-recurrent prostate cancer is melanoma antigen-A11 (MAGE-11). MAGE-11 was first identified as a cancer- testis antigen expressed solely in primates. MAGE-11 interacts with the AR FXXLF motif, the same motif that mediates the androgen-dependent AR N/C interaction [17]. MAGE-11 amplifies AR transcriptional activity through its interactions with p300 and p160 coactivators [18,19]. The levels of MAGE-11 increase during prostate cancer progression due to hypomethylation of a CpG island at the transcription start site of the MAGE-11 gene [20,21]. This is evident both in the CWR22 xenograft model of human prostate cancer that undergoes a similar pattern of tumor remission and regrowth after castration, as well as in approximately 1/3 of a relatively small cadre of castration-recurrent prostate cancer patients [20]. In both systems, the increase in MAGE-11 mRNA greatly exceeded the increase in AR mRNA. Moreover, one patient had several orders of magnitude higher levels of MAGE-11 mRNA measured by quantitative real-time RT-PCR, yet there was no detectable AR mRNA. This suggests that sufficiently high levels of MAGE-11 can substitute for a functional AR in promoting the growth and progression of prostate cancer.

The studies point to a need to identify the mechanisms amplified

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in a given prostate cancer patient, be it AR or coregulator, and develop a multi-pronged therapeutic approach that targets AR, the enzymes required for androgen biosynthesis, as well as MAGE-11 or other coregulators. The carboxyl-terminal region of MAGE-11 that interacts with the AR FXXLF motif is predicted to have an ordered structure with multiple  $\alpha$ -helices. The ordered structure of MAGE-11 may provide a new target for drug therapy needed to establish a cure for prostate cancer.

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