

# Androgen Suppression: The Good, The Bad and The Ugly

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Prostate cancer is a significant health problem for men in the USA and worldwide. Nearly thirty thousand American men die each year of advanced prostate cancer. The androgen receptor, a member of the family of nuclear receptors, is a key modulator in development of prostate cancer and of prostate cancer progression. Therefore the androgen receptor is a well-established target for therapeutic intervention in prostate cancer.

Androgen suppression has been a mainstay of prostate cancer treatment since 1941. Prostate cancer begins as an androgen-dependent tumor that responds favorably to androgen suppression but after the initial response, prostate cancer in due course progresses to a castration-resistant metastatic tumor that is invariably fatal. While there is some evidence that androgen suppression increases survival, this treatment is not curative. A common assumption is that the persistence of androgen receptor signaling accounts for the failure of androgen suppression [1-4]. Convincing evidence that androgen receptor activity is involved in the stimulation of castration-resistant prostate cancer growth has been recently published. Androgen receptor activity was disrupted using anti-androgen receptor mRNA ribozymes, microinjection of anti-androgen receptor antibodies, and androgen receptor shRNA transfection into androgen-sensitive and castration-resistant prostate cancer cells inhibiting proliferation of both cell types [5,6]. Given the persistence of androgen receptor function in castration-resistant prostate cancer, the androgen receptor remains a primary target in castration-resistant prostate cancer. Therefore the prevailing clinical strategy in advanced prostate cancer is to achieve a more complete blockade of androgen receptor signaling. Developing specific and between specific and effective inhibitors of the intracellular events that underlie androgen receptor signaling has been a major focus of recent prostate cancer research. Strategies to inhibit androgen receptor function with improved antagonists and inhibitors of synthesis of adrenal and intra-tumoral androgens are being developed and tested in preclinical and clinical settings.

## Why Does Androgen Suppression Fail?

Androgen suppression causes significant decreases in serum levels of testosterone and dihydrotestosterone. However, despite the large decrease in levels of circulating androgen levels during androgen suppression therapy, androgens remain present in prostatic tissues at levels sufficient to activate the androgen receptor. A recent report shows that treatment with a GnRH antagonist decreased serum testosterone by 94%, while intra-prostatic testosterone and dihydrotestosterone fell only 70% and 80%, respectively [7]. Moreover, despite these decreases in prostate tissue androgens, there were no detectable differences in prostate epithelial proliferation, apoptosis, and prostate-specific antigen and the androgen receptor expression. In another study testosterone levels in castration-resistant prostate cancer tissue were normal, whereas intra-prostatic dihydrotestosterone levels were reduced by 75% [8]. Furthermore, despite the undetectable levels of androgens in serum of castrated male mice, androgens were detected in the castration-resistant LuCaP 35V prostate cancer xenografts, with similar levels of testosterone and dihydrotestosterone also detected in metastatic prostate cancer tissue from patients [9]. These results clearly demonstrate that serum androgen concentrations

do not reflect those found within prostate cancer tissue, and suggest that manipulation of serum androgens may not affect target-tissue androgens proportionately. Undoubtedly, the presence of androgens in the tumor environment is one of the factors contributing to active androgen receptor signaling in androgen-suppressed patients. Other mechanisms which contribute to continued androgen receptor activity in castration-resistant prostate cancer are androgen receptor amplification, androgen receptor mutations, altered expression of androgen receptor co-activator and co-repressor proteins, and activation of other pathways that can enhance androgen receptor function [1,2]. These data together indicate that inhibition of testicular androgen production alone is insufficient to suppress all androgen receptor-mediated signaling in prostate tumors.

To increase the efficacy of androgen suppression, a range of novel inhibitors of androgen receptor signaling are being developed that block adrenal androgens action, as well as intra-prostatic synthesis of androgens. A novel inhibitor of androgen receptor signaling, abiraterone (CYP17 inhibitor), has recently been approved as a treatment for castration-resistant prostate cancer resulting in survival benefit, and preclinical studies also demonstrate decreases in intra-tumoral androgen levels [10]. Additional new agents are being evaluated in preclinical and clinical setting (e.g., MDV3100, TOK001, HE3235, and EPI001) [11-14]. We have recently shown that a new steroidal compound, HE3235, decreases tissue levels of testosterone and dihydrotestosterone as well as levels of androgen receptor mRNA which leads to inhibition of castration-resistant prostate cancer growth *in vivo* [15]. Unfortunately, these new agents and strategies have failed to eradicate castration-resistant disease and treatment resistance develops similarly to primary androgen ablation.

## Androgen Receptor-Too Much of a Good Thing?

While inhibition of the androgen receptor results in decreased growth of prostate cancer cells, other lines of evidence suggest that prostate cancer cells with little or no androgen receptor activity are more aggressive and have higher proliferative potential. Under some circumstances, therefore, the androgen receptor may negatively regulate growth of prostate cancer cells and impede development of these aggressive phenotypes. For example, androgen suppresses the growth of ARCaP cells in a dose-dependent manner *in vivo* and *in vitro*. ARCaP cells are tumorigenic and highly metastatic to lymph nodes, lung, pancreas, liver, kidney, and bone. However, these cells express little or no androgen receptor mRNA, PSA mRNA, and PSA protein. Another example of outgrowth of aggressive prostate cancer cells from originally

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Received February 15, 2012; Accepted February 17, 2012; Published February 20, 2012

Citation: Corey E (2012) Androgen Suppression: The Good, The Bad and The Ugly. Andrology 1:e106. doi:10.4172/2167-0250.1000e106

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androgen-sensitive, androgen receptor-positive cells are the CL-1 and CL-2 prostate cancer cells. CL-1 and CL-2 cells were established by androgen deprivation of LNCaP cells and are castration-resistant, express little to no androgen receptor and no PSA. These sublines grow faster than LNCaP and possess metastatic potential to bone, liver, and lymph nodes [16]. Additional results suggesting growth-inhibitory roles of the androgen receptor were published recently; over expression of androgen receptor in PC-3 cells was shown to inhibit proliferation of these cells [17]. Thus, lines of aggressive prostate cancer cells have been developed on several occasions, evidently as a result of selection by androgen deprivation.

Further evidence that androgen receptor signaling is not always required for growth of castration-resistant prostate cancer is found in observations of variable androgen receptor expression in prostate cancer bone metastases obtained from patients that died of advanced prostate cancer. Published results show significant heterogeneity in androgen receptor expression among 153 bone metastases from 15 patients who had been treated with androgen suppression and progressed to castration-resistant disease. Androgen receptor immunoreactivity ranged from 0-100% of the metastatic cells [18]. These and other published results reveal a decrease in the proportion of androgen receptor-positive cells in castration-resistant prostate cancer bone metastases vs. primary prostate cancer. Furthermore these results indicate clearly that prostate cancer cells can survive and proliferate without expressing androgen receptor, and therefore, it is not likely that total androgen receptor signaling blockade could ever eradicate cells with this phenotype.

We can also draw an analogy with breast cancer. Estrogen receptor blockade is used very successfully to treat patients with estrogen receptor-positive breast tumors. Unfortunately, this strategy is ineffective against estrogen receptor-negative tumors. Furthermore, the most aggressive tumors are the triple negative breast tumors that do not express estrogen receptor, progesterone receptor or Her2. Clearly something other than estrogen is driving the growth and spread of these cancer cells. Studies showed that tumors adapt to aromatase inhibitor treatment, which blocks the synthesis of estrogen, by activating alternate signaling pathways, thus enabling them to proliferate in the absence of estrogen. If these alternative growth-stimulatory pathways can be identified, treatments for estrogen receptor-negative breast cancer may become a reality. Since our basic understanding of breast cancer is more advanced than that of prostate cancer in many ways, this example may represent a model for future progression in prostate cancer as well. For example, an androgen receptor signature has been identified using LNCaP cells and applied to patient samples to investigate activation of oncogenic pathways correlating with androgen receptor signaling activity. The analyses showed that tumors with low activity of androgen receptor had significant increases in activity of Src, implicating Src signaling in growth of castration-resistant prostate cancer cells with low androgen receptor activity [19].

## Summary

Persistent androgen receptor signaling is involved in outgrowth and progression of advanced prostate cancer and novel agents that have the capabilities to suppress androgen receptor signaling in castration-resistant prostate cancer are of significant value. Inhibition of androgen receptor signaling is an effective palliative therapy, but to date, it has failed to eradicate the disease. Reduction of androgen receptor signaling is desirable to eradicate androgen receptor-positive cells that are dependent on this signaling, and present results indicate

that this leads to prolonged survival. Still, contrary evidence indicates that androgen receptor may also act as an inhibitor of proliferation of prostate cancer cells with an androgen suppressive phenotype, possibly by inhibiting signaling pathways associated with tumor progression, such as Src and Wnt. Therefore the total ablation of androgen receptor signaling may lead to an outgrowth of cells that are no longer dependent on androgens to support their growth. Therefore in a challenge to the prevailing model that total androgen-receptor signaling suppression might cure prostate cancer, one could put forward a theory that complete abolishment of androgen receptor signaling might result in clonal selection of aggressive androgen receptor-signaling negative prostate cancer cells, rather than cure of the disease. This theory by no means calls into question the significant value of androgen suppression for control of prostate cancer. Rather, it is directed to the virtually unexplored issue of what might happen when "total" androgen-receptor signaling ablation is achieved and what molecular mechanisms control growth in the androgen receptor-negative castration-resistant, aggressive cells that are not responsive to endocrine therapy.

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