Grappling with the Androgen Receptor: A New Approach for Treating Advanced Prostate Cancer

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In this issue of *Cancer Cell*, Andersen et al. report on a small molecule that interacts with and blocks transactivation of the androgen receptor amino-terminal domain. This agent can overcome the shortcomings of clinically used antiandrogens, an important advance in the development of effective therapy for advanced prostate cancer.

Experimental androgen-deprivation therapy (ADT) for prostate cancer in the form of estrogen treatment or surgical castration was first reported nearly 70 years ago (Huggins and Hodges, 1941). The results of these initial studies were translated to the clinic, where ADT was shown to retard the inexorable progression of prostate cancer. Subsequent research yielded significant improvements in ADT through the development of more effective pharmacologic agents, including inhibitors of androgen-synthetic pathways, that are currently being tested in clinical trials (Vis and Schroder, 2009). The relative success of ADT and the exquisite sensitivity of the prostate and prostate cancer to androgens have sustained the androgen axis, and particularly the androgen receptor (AR), as the premier therapeutic target for prostate cancer. An early approach to improving ADT by using AR targeting was the development of competing androgen antagonists (bicalutamide, flutamide) that interact with the carboxyl-terminal ligand-binding domain (LBD) of the AR.

Unfortunately, however, the development of so-called castrate-resistant prostate cancer (CRPC) limits the effects of ADT. CRPC is believed to emerge after genetic and/or epigenetic changes in prostate cancer cells render them insensitive to ADT. CRPC is characterized partly by overexpression of AR (Taplin and Balk, 2004). In addition, the use of antiandrogens that target the LBD can lead to selection of prostate cancer cells that harbor AR mutations in the LBD. In some cases, these mutations can cause prostate cancer cells to acquire the capacity to convert those antiandrogens from antagonists to agonists (Chen et al., 2008; Steinkamp et al., 2009). Recently, a second-generation antiandrogen was built on the chemical scaffold of the nonsteroidal agonist RU59063, which also interacts with the AR LBD (Van Dort et al., 2000). This therapeutic agent, MDV3100, has notable advantageous biologic properties, including increased affinity of the AR; suppression of AR nuclear translocation, DNA binding, and coactivator recruitment; proapoptotic activities; and lack of detectable agonistic effects (Tran et al., 2009).

However, CRPC can also exhibit ligand-independent AR activation through various signaling pathways (Chen et al., 2008; Vis and Schroder, 2009). Further, CRPC can express AR-splicing variants that lack the carboxyl terminus, including the LBD (Nacusi and Tindall, 2009; Vis and Schroder, 2009). These activities could provide a means of escape from the effects of agents that target the AR LBD.

The report by Andersen et al. in this issue of *Cancer Cell* shows that EPI-001, which is a BADGE (*B*isphenol *A* *D*iglycidic *E*ther) analog, may have the potential to overcome the "Achilles' heel" of the antiandrogens that target the AR LBD (Andersen et al., 2010). The authors present impressive results demonstrating that EPI-001 interacts with the activation function (AF)-1 region in the amino-terminal domain (NTD) of the AR and does not interfere with ligand binding. Additionally, EPI-001 does not inhibit the transcriptional activity of progesterone receptor or glucocorticoid receptor. These results suggest that EPI-001 is specific to the AR without inhibiting the transcriptional activities of other steroid receptors. These unique properties, elegantly demonstrated by Andersen and colleagues, may partly explain the lack of any significant toxicity associated with administration of EPI-001 in preclinical animal studies. They further underscore that resistance to EPI-001 through mutations in the LBD is not likely to occur via any known mechanism(s).

The results showing that EPI-001 blocks the AR amino-carboxyl terminal (N/C) interactions, and protein-protein interactions with the AR provide a molecular mechanism through which EPI-001 inhibits both androgen-dependent and, importantly, selective androgen-independent AR transactivation. It is interesting that many, but not all, androgen-regulated genes were inhibited by EPI-001, suggesting that the molecular constraints imposed on the AR by EPI-001 translate into a unique inhibitory gene profile. In turn, this suggests that additional experiments to define the downstream genetic pathways suppressed by EPI-001 may reveal new therapeutic targets.

Andersen and colleagues also show that EPI-001 can block transactivation of a constitutively active AR deletion mutant containing the NTD, DNA-binding domain, and hinge region, but not the LBD. In light of recent data that show CRPC expresses such AR mutants (Nacusi and Tindall, 2009; Vis and Schroder, 2009), it is difficult to overstate the importance of this capacity of EPI-001.

Preclinical results using subcutaneous and orthotopic xenograft models showed that EPI-001 can effectively block both

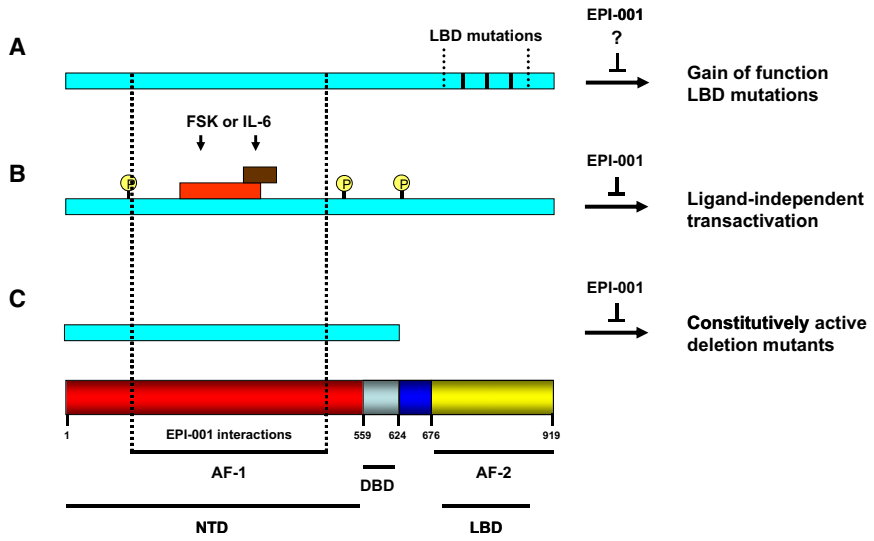

Figure 1. Potential of EPI-001 to Inhibit Specific Aberrant Androgen Receptor Transactivation Activities that Contribute to Castrate-Resistant Prostate Cancer

(A) On the basis of its interaction with the AF-1 region of the AR amino-terminal domain (NTD), EPI-001 would not be expected to reduce the selection pressure for AR amplification and/or mutations in the AR NTD that are associated with CRPC. However, because EPI-001 does not interact with the ligand-binding domain (LBD) or reduce ligand binding, it is unlikely that treatment would impose selection for gain-of-function LBD mutations that allow for AR-mediated activities in the presence of reduced or altered ligands.

(B) EPI-001 can block forskolin (FSK)- or IL-6-mediated ligand-independent AR transactivation activities.

(C) EPI-001 can inhibit a constitutively active AR deletion mutant that lacks the LBD. P, possible AR phosphorylation sites; filled rectangles, proteins that interact with AR to promote FSK- or IL-6–mediated ligand-independent AR transactivation; DBD, DNA-binding domain; AF-1, activation function-1; AF-2, activation function-2. AR protein domains are not drawn to scale.

androgen-dependent and CRPC prostate cancer growth. Additional experiments showed that EPI-001 can also significantly reduce the weight of the prostate in intact male mice. Of considerable importance is that no significant toxicity was observed. Overall, these impressive results strongly support the therapeutic potential of EPI-001 or its derivatives in vivo.

The novel mechanism of action (interaction with the AR NTD) through which EPI-001 inhibits AR transactivation suggests unique advantages of EPI-001 for inhibiting CRPC. First, EPI-001's capacity to interact with and inhibit AR function without affecting the LBD defines a new level of pharmacologic specificity, which may suppress selection pressure for mutations in the AR LBD that allow CRPC to become resistant to currently used antiandrogens (Figure 1). However, previous investigators have suggested a relationship between AR overexpression and altered normal responses to AR antagonists (Chen et al., 2008). Further testing of EPI-001 or its derivatives for the development of gain-of-function mutations in the AR LBD will likely clarify this important question.

Second, EPI-001's capacity to inhibit the ligand-independent AR transactivation mediated by forskolin (FSK), which stimulates PKA activity, or IL-6 breaks new ground in the pharmacologic suppression of AR (Figure 1). Certainly, the mechanisms underlying ligand-independent AR transactivation are poorly defined. In this regard, it is important that the authors demonstrated that EPI-001 inhibited interactions between AR-AF-1 and CBP or RAP74 and inhibited N/C interactions through its interaction with the NTD AF-1. Although these results have important therapeutic implications, other mechanisms of ligand-independent AR transactivation may permit an escape from EPI-001's effects. Additional studies to analyze EPI-001's capacity to inhibit pathways of ligand-independent AR transactivation other than FSK and IL-6 that lead to CRPC will be necessary to address this issue and perhaps lead to important information related to AR structure-activity relationships.

Third, recent reports of the expression of AR splicing variants lacking the carboxyl terminus, including the LBD, reveal a new mechanism of antiandrogen resistance and represent a considerable threat to the efficacy of currently used antiandrogens. EPI-001's capacity to block transactivation of a constitutively active AR deletion mutant that contains the NTD, the DNA-binding domain, and the hinge region, but not the LBD, is a unique and critical function that will, we hope, have a substantial effect in CRPC. Further studies that test additional AR deletion mutants that contain the NTD, but not other AR domains, will generate a more comprehensive picture of this important and unique activity of EPI-001.

CRPC is biologically complex and certainly presents new and unforeseen difficulties in the medical management of advanced prostate cancer. The molecular and cellular interactions that contribute to prostate cancer growth, and its resistance to ADT and antiandrogen therapy within the bone microenvironment are just beginning to be understood. However, it is a rare occasion in prostate cancer research when such a unique and promising therapeutic agent for advanced prostate cancer is developed. We all wait with interest the further preclinical and possible clinical testing of EPI-001 or its derivative(s).

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