genes were mutated in more than one tumor, the authors estimated that only ten genes were mutated at statistically significant rates. However, they attached significance to identical mutations occurring in different tumors, functionally related mutations in a pathway (e.g., NFKB-activating mutations), clinically relevant mutations (e.g., BRAF, including some that were V600E), histone-modifying enzymes, and mutations that might impact microenvironment interactions.

Finally, a recent study used whole-transcriptome paired-end sequencing to identify fusion transcripts (Steidl et al., 2011). The authors initially identified 14 and five predicted fusion transcripts, respectively, in two Hodgkin's lymphoma (HL) cell lines. They then focused on fusions involving *CIITA* and identified recurrent translocations that fused the 5′ end of *CIITA* to multiple partner genes in 15% of HL and 38% of primary mediastinal B cell lymphoma (PMBCL), which phenotpically is related to HL, but in only 3% of DLBCL. Additional studies showed that the hybrid protein made from the fusion transcripts had several potential effects on tumor-microenvironment interactions that favored survival of the tumor.

Comprehensive genome analysis is identifying important genetic abnormalities in hematologic malignancies. Regardless, distinguishing driver and passenger mutations remains a daunting task. In these early studies of hematopoietic tumors, most putative driver mutations are present in only a small fraction of tumor cells, suggesting great molecular diversity even for an apparently single clinical disease. Clearly, many additional samples will need to be sequenced to obtain a more complete picture. However, it will be important to focus also on changes other than nonsynonymous coding changes, e.g., mutations in regulatory regions, structural variations with long-rang effects on gene expression, and changes in the expression and forms of noncoding RNA. Ultimately, to make sense of all these findings, it will be critical to perform multidimensional analysis of large cohorts of patients, ideally uniformly treated, with serial samples collected longitudinally at different disease stages, and comprehensively analyzed in terms of DNA (including epigenetic modifications), RNA, and protein structure and function.

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Beefing up Prostate Cancer Therapy with Performance-Enhancing (Anti-) Steroids

William G. Nelson,[1,*] Michael C. Haffner,[1] and Srinivasan Yegnasubramanian[1,*]
[1]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, 400 North Broadway Street, Baltimore, MD 21231-1000, USA
*Correspondence: bnelson@jhmi.edu (W.G.N.), syegnasu@jhmi.edu (S.Y.)
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In the May 26th issue of the *New England Journal of Medicine*, de Bono et al. report that the inhibition of androgen synthesis by abiraterone acetate prolonged the survival of men with prostate cancer previously treated by androgen suppression.

Huggins and Hodges presented the results of what may be the first translational clinical trial of targeted therapy for cancer in 1941, when circulating androgen levels were reduced by bilateral orchiectomy in men with progressive metastatic prostate cancer (Huggins and Hodges, 1941). To test the benefit of castration, changes in serum acid phosphatase, a biomarker of prostate cancer, and in alkaline phosphatase, a biomarker of bone destruction at metastatic sites, were monitored, revealing marked decreases that accompanied improvements in bone pain and other disease-related symptoms. In the

seven decades since, androgen suppression, now accomplished via the use of gonadotropin-releasing hormone (GnRH) analogs, has remained the mainstay treatment for advanced prostate cancer. Yet despite its utility, androgen suppression almost always ultimately fails to control the disease.

More recently, new insights into the molecular pathogenesis of prostate cancer, along with a progressive understanding of the mechanisms underlying prostate cancer progression despite androgen suppression, have led to a new generation of drugs targeting the androgen signaling axis for prostate cancer. In normal prostate epithelial cells, circulating androgens such as testosterone and dihydrotestosterone bind to the androgen receptor (AR) to initiate a transcription program that drives terminal differentiation to a columnar secretory phenotype. Prostate cancer cells coopt androgen signaling to support growth, survival, and invasiveness. Additionally, in a large subset of prostate cancers, chromosomal translocations and deletions involving androgen-regulated differentiation genes, such as *TMPRSS2*, *SLC45A3*, and others, create fusions between the androgen-regulated genes and oncogenes, rendering the expression of these malignancy genes under the control of the AR (Kumar-Sinha et al., 2008; Palanisamy et al., 2010). Androgen suppression acts as targeted therapy for prostate cancer therefore, at least in part by suppressing the transcription of fusion oncogenes.

For many years, the propensity for prostate cancer to progress despite androgen suppression was attributed to the emergence of "androgen-independent" prostate cancer cell clones. However, more recent evidence has revealed that the cells that foil GnRH treatment have often remained substantially addicted to androgen signaling, adopting a "castration-resistant" phenotype that is not necessarily androgen-independent. By ablating production of testosterone in the testes, GnRH analogs and bilateral orchiectomy tend to reduce circulating androgens to a fraction of physiologic levels but not eliminate the hormones. Prostate cancer cells addicted to androgen signaling overcome this treatment by: (1) amplification or mutation of the gene encoding the AR, permitting increased receptor expression or altered function, (2) activation of other cell-signaling pathwaysthat augment AR transcriptional *trans*-activation, and/or (3) directly synthesizing androgenic hormone ligands (Scher and Sawyers, 2005). Clinical evidence of this androgen addiction phenotype in the setting of prostate cancer progression despite androgen suppression is provided by progressive increases in the serum prostate cancer biomarker prostate-specific antigen (PSA), which requires AR function for expression.

To exploit the persistent addiction of many prostate cancers to androgen signaling despite GnRH treatment, de Bono et al. (2011) conducted a clinical trial of abiraterone acetate, a prodrug for the cytochrome p450 c17 (CYP17) inhibitor abiraterone, in men with castration-resistant prostate cancer who had also been treated with docetaxel chemotherapy. CYP17 is the critical enzyme necessary for the synthesis of androgenic hormones in the testes and elsewhere; previous studies had revealed that the castrate circulating androgen levels seen in men on GnRH analogs could be even further lowered by abiraterone acetate administration. The trial enrolled 1195 men with prostate cancer who were randomized in a 2:1 ratio to receive 1 g of abiraterone acetate or a placebo daily along with a replacement dose of corticosteroid. Results strongly favored the abiraterone acetate treatment arm, prompting early study termination after an interim analysis, with an improvement in overall survival (with a hazard ratio of 0.65 and a 95% confidence interval of 0.54–0.77), progression-free survival, and serum PSA response rate (29% versus 6%). Side effects, which were generally tolerable, included mineralocorticoid-like

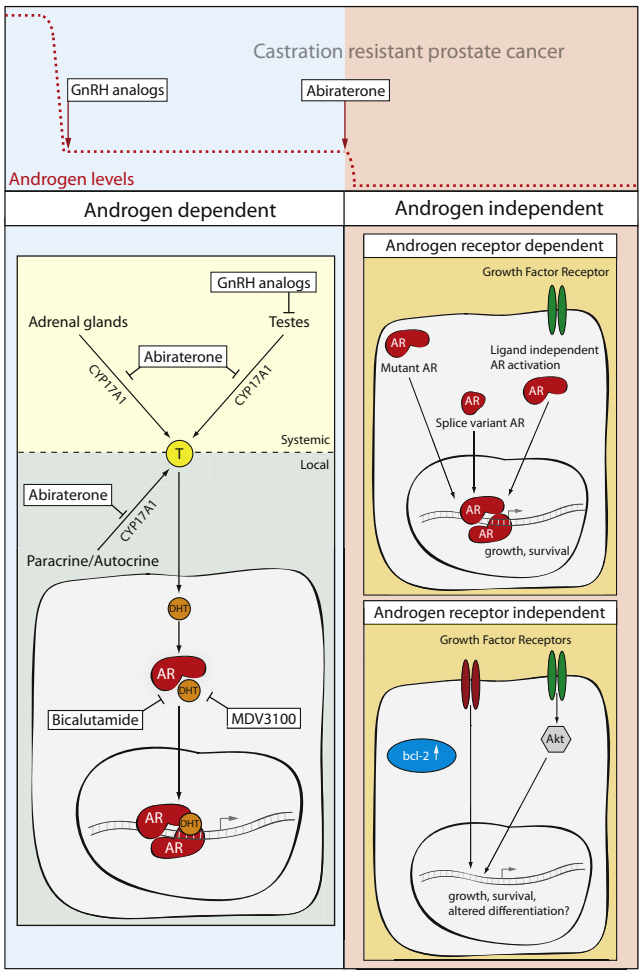

Figure 1. Androgen-Dependent versus Androgen-Independent Prostate Cancer

The CYP17A inhibitor, abiraterone, can improve outcomes in castration-resistant prostate cancer by further reducing castration levels of androgens. This provides evidence that castration-resistant prostate cancer can often still be androgen-dependent. However, ultimately, prostate cancer cells can emerge that are resistant to abiraterone. Such cells are likely to have a truly androgen-independent phenotype, in which resistant prostate cancer cells could continue to express growth and survival pathways through AR-dependent (e.g., via mutation of AR to allow other ligands to stimulate signaling, via production of constitutively active AR isoforms lacking the ligand binding domain, or via subversion of other growth factor receptor pathways for activating AR signaling), or AR-independent mechanisms. T, testosterone; DHT, dihydrotestosterone.

effects, such as fluid retention, elevated blood pressure, and low serum potassium levels. With these data, on April 28, 2011, the United States Food and Drug Administration (FDA) approved abiraterone acetate for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer that is progressing despite docetaxel chemotherapy.

The utility of abiraterone for castration-resistant prostate cancer is reminiscent of the ongoing development of a new generation of androgen-receptor antagonists, which attempt to better thwart androgen-signaling in prostate cancer cells than existing receptor blockers, including bicalutamide, flutamide, nilutamide, and cyproterone acetate. One of these new drugs, MDV3100, interacts with the AR in castration-resistant prostate cancer cells in such a way as to interfere with AR translocation to the cell nucleus, binding to target genes, and activation of target gene transcription, effectively undermining addiction to androgen signaling. In a clinical trial of this drug for 140 men with castration-resistant prostate cancer, MDV3100 exhibited encouraging anticancer activity, with significant serum PSA declines in 56% of the men treated (Scher et al., 2010). The clinical development of MDV3100 has progressed to pivotal phase 3 trials.

The experience with abiraterone and MDV3100 underscores the promise of new drugs targeting androgen signaling for castration-resistant prostate cancer. One general limitation of such drugs will likely be the adverse consequences of prolonged androgen ablation, including bone loss and increased cardiovascular risk that has bedeviled GnRH treatment (Saylor and Smith, 2010). The major ultimate challenge, however, will almost certainly be the inevitability of disease progression despite drug treatment. Prostate cancer cells that emerge despite abiraterone administration may well display a true androgen-independentphenotype, manifest in two major mechanisms: those that continue to use androgen receptor signaling in an androgen-independent fashion for growth and survival, and those that are entirely independent of androgen receptor signaling (Figure 1). Evidence for androgen-receptor-independent signaling has been seen in autopsies of men dying of prostate cancer, where disease deposits have been found to contain cancer cells devoid of the AR and its target gene products such as PSA (Shah et al., 2004). For prostate cancer cells which are truly androgen-independent, other signaling pathways will need to be targeted to control disease progression.

The availability of abiraterone, which reversibly reduces circulating androgen levels much more rapidly than do GnRH analogs, may facilitate the development of cyclical approaches to manipulate androgen signaling in prostate cancer cells to improve treatment effectiveness. Already a clinical study of such an approach, in which GnRH analogs and testosterone were rapidly cycled along with docetaxel chemotherapy in men with non-castrate-resistant prostate cancer, has been reported (Rathkopf et al., 2008). The recognition that the initiation of transcription at AR target genes in prostate cancer cells triggers DNA double strand breaks mediated by TOP2B, a type 2 DNA topoisomerase, has prompted the idea that the targeted induction of such genome damage might kill prostate cancer cells (Haffner et al., 2011). A treatment approach in which abiraterone administration liberates AR from its sites in the genome, and then a subsequent androgen bolus drives AR back to such sites, creating DNA strand breaks, could lead to an opportunity for the use of agents that sensitize cells containing DNA strand breaks to apoptosis, such as poly(ADP-ribose) polymerase (PARP) inhibitors and other DNA repair antagonists (Haffner et al., 2011). In this way, when sequenced with an androgen signaling antagonist, AR agonists might become targeted drugs for castration-resistant prostate cancer.

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