The Genetics of Castration-Resistant Prostate Cancer: What Can the Germline Tell Us?

Nima Sharifi,1 William L. Dahut,2 and William D. Figg2

Abstract
Androgen deprivation therapy (ADT) is the cornerstone treatment for advanced prostate cancer. Despite frequent responses, the majority of metastatic tumors will progress to castration-resistant prostate cancer. Numerous molecular and genetic perturbations have been described in castration-resistant prostate cancer, which are attributable for gain-of-function changes in the androgen receptor, allowing for cell survival and proliferation with castrate levels of testosterone. The utility of these somatic perturbations, which are selected for in the tumor after ADT, for prognostication of response and response duration in metastatic prostate cancer, is problematic. Here, we discuss recent studies that describe germline polymorphisms that determine the response to ADT. Coding and noncoding germline polymorphisms in genes involved in the androgen pathway affect the response to ADT. These polymorphisms require further study and validation. However, they have the potential to be useful for prognosticating the response to ADT, designing clinical trials for patients who have poor germline prognostic features and designing novel therapies targeted against genes that influence the response to ADT.

Androgen Deprivation Therapy
Growth and proliferation of prostate cancer cells is dependent on the androgen receptor (AR), which is expressed in almost all prostate cancers (1). Depriving prostate cancer of testosterone generally reverses AR-dependent growth and proliferation, explaining the effectiveness of this therapy. Androgen deprivation therapy (ADT) is used in several clinical scenarios. First, ADT is upfront therapy in the metastatic setting and responses occur in the majority of patients (2). Second, ADT given as adjuvant therapy along with radiation therapy for high-risk or locally advanced prostate cancer gives a survival advantage (3, 4). Third, immediate ADT given to men with lymph node–positive disease after radical prostatectomy improves survival (5).

Castration-Resistant Prostate Cancer
Although the majority of men with metastatic prostate cancer will initially respond to ADT, the development of castration-resistant prostate cancer (CRPC) almost always occurs. Clinical factors that influence the response to ADT include Gleason score, pretreatment prostate-specific antigen, visceral metastases, and presence of distant lymphadenopathy (6). Although these factors in part account for disease burden and some of the biology inherent to individual cancers, they are imperfect and there is still a large variation in the response to ADT.

There is abundant evidence that the road to CRPC is paved by AR reactivation and the reexpression of androgen-responsive genes. Androgens control the expression of hundreds of genes through AR (7). Although the gene expression pattern of prostate cancer initially shows a down-regulation of androgen-responsive genes, a subset of these genes are later reexpressed when tumors progress as CRPC (8, 9). This suggests that AR is reactivated by a gain-of-function in a ligand-sensitized manner, other ligands substitute as activators of AR, or that androgen ligands are up-regulated. There is evidence for all of these scenarios (10, 11).

Gain-of-function in AR in CRPC occurs by AR gene amplification (12), phosphorylation-dependent mechanisms with growth factors and growth factor receptors (13, 14), as well as by changes in the balance of steroid receptor coregulators (15). Mutations occur in the AR ligand–binding domain, which broaden the specificity for steroid hormone ligands (16). Furthermore, molecular changes in CRPC allow for the enzymatic conversion of other steroids to androgens in the local tumor environment (17). This leads to an increase in the concentration and availability of androgens for the tumor (18). These characteristics all reflect genetic or epigenetic changes that occur from within the tumor, after the tumor undergoes selection with ADT. Therefore, knowledge of these somatic changes is generally not useful for determining a priori how patients will respond to ADT.
Germline Determinants of Response to Androgen Deprivation

Two recent studies have shown that germline DNA polymorphisms can influence the response to ADT. The first study was conducted in 529 patients with advanced prostate cancer with and without radiographic evidence of metastatic disease. The investigators examined 129 DNA polymorphisms associated with 20 genes that are involved in androgen metabolism (19) and an association with CRPC as determined by two increases in prostate-specific antigen after the initiation of ADT. Three single nucleotide polymorphisms (SNP) were found to be significantly associated with response duration to ADT. The first SNP is 5 kb upstream of CYP19A1, which encodes for the aromatase protein, and is involved in the conversion of testosterone to estrogen. The second SNP is 13 kb upstream of HSD3B1, which encodes for proteins involved in deactivating dihydrotestosterone and the production of androstenedione. The third SNP is within an intron in HSD17B4, which is involved in regulating the production of DHEA. Notably, none of these SNPs that are associated with response duration to ADT are in known protein coding sequences.

A second study was based on preclinical work with a gene that codes for a protein that is a transmembrane transporter of testosterone and other steroids. SLCO1B3 is a gene that codes for the OATP1B3 protein and has two SNPs in the protein coding region of this gene. 334T>G encodes for a serine to alanine substitution, and 699G>A encodes for a methionine to isoleucine change. These SNPs are in complete linkage disequilibrium. Expression of the allele containing 334T and 699G (T allele) confers an increase in testosterone uptake when compared with cells that express the 334G and 699A allele (G allele; ref. 20). OATP1B3 protein is also overexpressed in prostate cancer compared with nonmalignant prostate. Furthermore, of Caucasian patients who died of CRPC, those who carry one or two copies of the T allele, which is a more active testosterone transporter, have a shorter survival from diagnosis compared with patients who carry two copies of the G allele (20). The unequal distribution of the T allele and G allele among different ethnicities (21) precluded a meaningful analysis in other patient ethnicities. On the premise that the shorter survival with the T allele is due to the effect that increased testosterone import would have on perturbing the response to ADT, time from CRPC to ADT as determined by first sustained prostate-specific antigen increase was assessed (22). In an analysis of Caucasian patients with advanced prostate cancer with and without radiographic evidence of metastatic disease treated with ADT, patients with one or two copies of the T allele had a shorter time to CRPC compared with patients with two copies of the G allele.

These two studies show evidence that SNPs in four genes are involved in the response duration to ADT. The SNPs in CYP19A1, HSD3B1, and HSD17B4 occur in noncoding regions and presumably affect the level of expression of these genes that are involved in androgen metabolism. The SNP in SLCO1B3 occurs in a protein coding region. The increase in testosterone uptake and effective increase in intracellular testosterone concentrations conferred by the wild-type T allele indicates that this gene is involved in yet another mechanism of AR gain-of-function in CRPC. These studies associating DNA polymorphisms with response to ADT require validation in other patient cohorts. Functional validation of germline polymorphisms affecting the response to ADT are possible by studying the expression of androgen-responsive genes in prostate cancer after ADT. However, obtaining tissue in patients with advanced disease is often problematic. Genome scale approaches to finding other SNPs that determine response to ADT, such as those in studies on prostate cancer risk, are possible and may provide evidence for a role in SNPs that are not necessarily hypothesis driven. However, a limitation is that the numbers of patients with CRPC are low compared with total cases of prostate cancer. Furthermore, data on the clinical course is needed to perform these studies, as opposed to genetic studies on prostate cancer risk.

These recent findings are remarkable for the fact that they complement the evidence on somatic genetic changes in CRPC that lead to AR reactivation and suggest that germline genetic changes may likewise contribute to AR activation as a common end point that is critical for the development of CRPC. Furthermore, the utility of understanding germline determinants of the response to ADT is that this could be used, along with known and established clinical factors, before the administration of hormonal therapy, to prognosticate clinical course. In addition, poor prognostic germline genetic factors could be used to select patients for clinical trials before ADT or in combination with ADT. Finally, germline polymorphisms may be used to further understand the biological basis of CRPC and to ultimately tease out targets for therapy to add to the pharmacologic armamentarium for the treatment of prostate cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

10. Sharifi N, Farrar WL. Androgen receptor as a...
Genetics of Castration-Resistant Prostate Cancer


The Genetics of Castration-Resistant Prostate Cancer: What Can the Germline Tell Us?

Nima Sharifi, William L. Dahut and William D. Figg


Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/14/15/4691

This article cites 20 articles, 6 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/14/15/4691.full#ref-list-1

Sign up to receive free email-alerts related to this article or journal.

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

To request permission to re-use all or part of this article, use this link http://clincancerres.aacrjournals.org/content/14/15/4691. Click on "Request Permissions" which will take you to the Copyright Clearance Center's Rightslink site.