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The genetics of castrate-resistant prostate cancer: What can the germline tell us?

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Abstract

Androgen deprivation therapy (ADT) is the cornerstone treatment for advanced prostate cancer. Despite frequent responses, the majority of metastatic tumors will progress to castrate-resistant prostate cancer (CRPC). Numerous molecular and genetic perturbations have been described in CRPC, which are attributable for gain-of-function changes in the androgen receptor (AR), 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 which 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. 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).

Castrate Resistant Prostate Cancer

Although the majority of men with metastatic prostate cancer will initially respond to ADT, the development of castrate-resistant prostate cancer (CRPC) almost always occurs. Clinical factors which influence the response to ADT include Gleason score, pretreatment PSA, 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.

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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 downregulation 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 upregulated. 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 rises in PSA 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 dehydroepiandrosterone. 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 to cells that express the 334G and 699A allele (G allele) (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 to 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 ADT to CRPC as determined by first sustained PSA rise 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 4 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 which 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 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 to 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 endpoint 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.

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References

1. Gelmann EP. Molecular biology of the androgen receptor. *J Clin Oncol* 2002;20:3001–15. [PubMed: 12089231]
2. Sharifi N, Gulley JL, Dahut WL. Androgen deprivation therapy for prostate cancer. *Jama* 2005;294:238–44. [PubMed: 16014598]
3. D'Amico AV, Chen MH, Renshaw AA, Loffredo M, Kantoff PW. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. *Jama* 2008;299:289–95. [PubMed: 18212313]
4. Bolla M, Descotes JL, Artignan X, Fournieret P. Adjuvant treatment to radiation: combined hormone therapy and external radiotherapy for locally advanced prostate cancer. *BJU international* 2007;100 (Suppl 2):44–7. [PubMed: 17594359]
5. Messing EM, Manola J, Sarosdy M, Wilding G, Crawford ED, Trump D. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. *The New England journal of medicine* 1999;341:1781–8. [PubMed: 10588962]
6. Hussain M, Tangen CM, Higano C, et al. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from

- Southwest Oncology Group Trial 9346 (INT-0162). *J Clin Oncol* 2006;24:3984–90. [PubMed: 16921051]
7. DePrimo SE, Diehn M, Nelson JB, et al. Transcriptional programs activated by exposure of human prostate cancer cells to androgen. *Genome biology* 2002;3:RESEARCH0032. [PubMed: 12184806]
 8. Mousses S, Wagner U, Chen Y, et al. Failure of hormone therapy in prostate cancer involves systematic restoration of androgen responsive genes and activation of rapamycin sensitive signaling. *Oncogene* 2001;20:6718–23. [PubMed: 11709706]
 9. Holzbeierlein J, Lal P, LaTulippe E, et al. Gene expression analysis of human prostate carcinoma during hormonal therapy identifies androgen-responsive genes and mechanisms of therapy resistance. *The American journal of pathology* 2004;164:217–27. [PubMed: 14695335]
 10. Sharifi N, Farrar WL. Androgen receptor as a therapeutic target for androgen independent prostate cancer. *American journal of therapeutics* 2006;13:166–70. [PubMed: 16645434]
 11. Scher HI, Sawyers CL. Biology of progressive, castration-resistant prostate cancer: directed therapies targeting the androgen-receptor signaling axis. *J Clin Oncol* 2005;23:8253–61. [PubMed: 16278481]
 12. Edwards J, Krishna NS, Grigor KM, Bartlett JM. Androgen receptor gene amplification and protein expression in hormone refractory prostate cancer. *British journal of cancer* 2003;89:552–6. [PubMed: 12888829]
 13. Weber MJ, Gioeli D. Ras signaling in prostate cancer progression. *Journal of cellular biochemistry* 2004;91:13–25. [PubMed: 14689577]
 14. Heinlein CA, Chang C. Androgen receptor in prostate cancer. *Endocrine reviews* 2004;25:276–308. [PubMed: 15082523]
 15. Heemers HV, Tindall DJ. Androgen receptor (AR) coregulators: a diversity of functions converging on and regulating the AR transcriptional complex. *Endocrine reviews* 2007;28:778–808. [PubMed: 17940184]
 16. Veldscholte J, Ris-Stalpers C, Kuiper GG, et al. A mutation in the ligand binding domain of the androgen receptor of human LNCaP cells affects steroid binding characteristics and response to anti-androgens. *Biochemical and biophysical research communications* 1990;173:534–40. [PubMed: 2260966]
 17. Stanbrough M, Bubley GJ, Ross K, et al. Increased expression of genes converting adrenal androgens to testosterone in androgen-independent prostate cancer. *Cancer research* 2006;66:2815–25. [PubMed: 16510604]
 18. Titus MA, Schell MJ, Lih FB, Tomer KB, Mohler JL. Testosterone and dihydrotestosterone tissue levels in recurrent prostate cancer. *Clin Cancer Res* 2005;11:4653–7. [PubMed: 16000557]
 19. Ross RW, Oh WK, Xie W, Pomerantz M, Nakabayashi M, Sartor O, Taplin M, Regan MM, Kantoff PW, Freedman M. Inherited variation in the androgen pathway is associated with the efficacy of androgen-deprivation therapy in men with prostate cancer. *J Clin Oncol*. In press
 20. Hamada A, Sissung T, Price P, Danesi R, Chau C, Sharifi N, Venzon D, Maeda K, Nagao K, Sparreboom A, Mitsuya H, Dahut WL, Figg WD. Effect of SLCO1B3 haplotype on testosterone transport and clinical outcome in Caucasian patients with androgen-independent prostatic cancer. *Clin Cancer Res*. In press
 21. Smith NF, Marsh S, Scott-Horton TJ, et al. Variants in the SLCO1B3 gene: interethnic distribution and association with paclitaxel pharmacokinetics. *Clinical pharmacology and therapeutics* 2007;81:76–82. [PubMed: 17186002]
 22. Sharifi N, Hamada A, Sissung T, et al. A polymorphism in a transporter of testosterone is a determinant of androgen independence in prostate cancer. *BJU international*. In press