Cancer Biology & Therapy 10:11, 1079-1080; December 1, 2010; © 2010 Landes Bioscience

Prostate cancer genomic signature offers prognostic value

Sarah M. Troutman,[1] Douglas K. Price[1] and William D. Figg[1,2,*]

[1]Molecular Pharmacology Section; [2]Clinical Pharmacology Section; Medical Oncology Branch; National Cancer Institute; Bethesda, MD USA

Previous attempts to link prostate cancer progression to genetic alterations have been unsuccessful, and consequently, there is still no reliable predictor of prognosis for men with this disease. A recent study by Taylor et al. published in *Cancer Cell*, assesses copy number alterations, mutations and transcriptomes in 218 tumors and 12 prostate cancer cell lines and xenografts. Their analysis identifies frequencies of *ERG* alterations, 8p loss and 8q gain similar to previous findings. It also reveals novel genetic factors in prostate cancer progression, including the androgen receptor coactivator, *NCOA2*, which serves as an oncogene in about 11% of tumors, and a deletion at chromosome 3p14, which was associated with *TMPRSS-ERG* fusion. The copy number alteration data demonstrates six distinct subgroups of prostate cancer with considerable variation in time to biochemical relapse. Classification of prostate cancer into these genetic subgroups may help clinicians predict the likelihood of disease progression in newly diagnosed men, ultimately guiding treatment decisions and therapy development.

Key words: prostate cancer, pharmacogenetics, prognosis, copy number alterations, androgen receptor, TMPRSS-ERG, PI3K pathways, NCOA2

Submitted: 11/02/10

Accepted: 11/02/10

Previously published online: www.landesbioscience.com/journals/cbt/article/14086

DOI: 10.4161/cbt.10.11.14086

*Correspondence to: William D. Figg; Email: wdfigg@helix.nih.gov

The aggressiveness of prostate cancer is highly heterogeneous; some tumors are indolent and never progress while others rapidly metastasize and are ultimately lethal. Unfortunately, clinicians are currently unable to accurately predict prognosis in newly diagnosed men. Specific genomic signatures with prognostic value have been identified in other types of cancers, such as the 21 gene score assay for breast cancer,[1,2] but efforts to find a comparable assay for prostate cancer have so far been unsuccessful.[3,4]

Previous reports implicated the *TMPRSS2-ERG* fusion,[5] and 8p loss and 8q gain[6,7] as factors in the progression of prostate cancer. In addition, *MYC* and *PTEN* are both commonly altered in men with prostate cancer.[6,7] However, the impact of these studies is limited by the relatively low association between genomic variation and clinical outcome, as well as small samples sizes or use of low resolution platforms.

In a study recently published in *Cancer Cell,* Taylor et al.[8] assess genomic variation and clinical outcome in prostate cancer. They examine copy number alterations (CNAs), mutations and transcriptomes in 218 prostate tumors (181 primaries and 37 metastases) and 12 prostate cancer cell lines and xenografts. The CNA and transcriptome analysis reveals several common alterations in prostate cancer. The *ERG* alteration frequency and rates of chromosome 8p loss and 8q gain are consistent with previous reports.[5-7] Additional alterations include *PTEN* on 10q23.31, *RB1* on 13q14.2, *TP53* on 17p31.1, and an interstitial deletion, 21q.22.2-3, which spans *ETV6*, *DUSP16* and *CDKN1B*. According to their findings, the most commonly amplified loci are *MYC* on 8q24.21 and *NCOA2* on 8q13.3.

Several patterns of alterations offer the potential to differentiate between primary and metastatic tumors based on genomic differences. The authors report that metastatic tumors generally exhibit greater levels of alteration compared with primary tumors, though a wide range of alteration levels is detected in both tumor types. In addition, their data indicate that only patients with metastatic prostate cancer demonstrate mutation, gene amplification or overexpression of the *AR* gene.

Alterations of specific genes contribute to the understanding of prostate cancer, but researchers are beginning to look to gene pathways for a more comprehensive explanation of the genetic components of the disease. Taylor et al. conduct a pathway analysis of several genes that have been implicated in prostate cancer or other types of cancers. They find that PI3K, RAS/RAF and RB, all common cancer pathways, are often altered in prostate cancer tumors. Of particular interest, their results show alteration of the PI3K pathway in 50% of primary tumors and 100% of metastatic tumors. In addition, 56% of primary tumors display an alteration in the AR pathway (including *AR* coactivators and repressors), whereas 100% of metastatic tumors are altered. More specifically, the authors find overexpression or mutation of 8q13.3 in 8% of primary tumors versus 37% of metastatic tumors. 8q13.3 spans *NCOA2*, an *AR* coactivator gene. An in vitro study demonstrates that *NCOA2* is capable of priming the AR to respond to lower concentrations of androgens as well as enhance AR transcriptional output. Based on these findings, they suggest that *NCOA2* serves as an oncogene by increasing *AR* signaling. *AR* amplification, which appears to be limited to metastatic tumors, may be a mechanism of drug resistance. These findings demonstrate the involvement of entire gene pathways in prostate cancer and open the door for predicting prognosis and individualizing therapy.

Similar to pathway analysis, Taylor et al. examine how the interaction of multiple genes may explain why the *TMPRSS-ERG* fusion is the most common lesion in prostate cancer despite failure to implicate it as an oncogene in functional studies.[5] They predict that the involvement of other genes may be necessary for *TMPRSS-ERG* fusion to produce an oncogenic effect. Their analysis reveals three regions of copy-number loss associated with the *TMPRSS-ERG* fusion. Two regions span the tumor suppressor genes, *PTEN* and *TP53*, and the third region spans an eight-gene region at 3p14, a previously unidentified region. Additional assessment of 3p14 implicates the involvement of the genes *FOXP1*, *RYBP* and *SHQ1*. This is the first evidence that alterations in other genes operate in a cooperative manner with *TMPRSS-ERG* lesions to produce an oncogenic effect.

Finally, the authors examine whether or not the genomic profile of prostate cancer is correlated with clinical outcome. Their mRNA and microRNA data fails to identify specific subgroups of prostate cancer. However, the CNA data provide evidence for six distinct prostate cancer subgroups based on time to biochemical relapse. First, they divide the prostate cancer cases into two major groups, those with minimal CNA (clusters 1–4) and those with substantial CNA (clusters 5–6). Cluster 1–4 tumors are associated with a positive prognosis in most cases, particularly cluster 2 tumors, which generally have an unaltered genome. Cluster 1 shows a pattern of deletions, particularly on chromosome 6q. Cluster 3 is characterized by deletions mostly limited to 13q, and cluster 4 tends to have deletions primarily on chromosome 8p. Most cases of metastatic prostate cancer are in cluster 5 or cluster 6. Cluster 5 is characterized by genome wide CNAs, whereas the genomic alterations in cluster 6 tumors are generally limited to 8q or chromosome 7 gains.

To demonstrate the prognostic value of these prostate cancer clusters, Taylor et al. provide evidence that the prognostic power of the categories is due to specific genomic alterations, not simply genomic instability. For example, even though more alterations are associated with cluster 6 and cluster 4, cluster 4 tumors are associated with a higher probability of biochemical recurrence. Additionally, the genome appears to be altered systematically, not randomly. They also demonstrate that Gleason scores cannot fully explain the association between CNA and biochemical relapse, which further supports the use of CNA assessment to guide prostate cancer therapy.

Confirmational studies are necessary before utilizing these criteria in a clinical setting, but the work of Taylor et al. provides considerable insight into the genomic contributions to prostate cancer progression. Their findings may be used to help clinicians determine appropriate therapy for individual patients as well guide the development of new therapeutics.

References

1. Paik S, Shak S, Tang G, Kim C, Baker J, Crornin M, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004; 351:2817-26.
2. Albain KS, Barlow WE, Shak S, Hortobagyi GN, Lingston RB, Yeh IT, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, estrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomized trial. Lancet Oncol 2010; 11:55-65; DOI: 10.1016/S14702045(09)70314-6.
3. Lapointe J, Li C, Higgins JP, van de Rijn M, Blair E, Montgomery K, et al. Gene expression profiling identifies clinically relevant subtypes of prostate cancer. Proc Natl Acad Sci USA 2004; 101:811-6; DOI: 10.1073/pnas.0304146101.
4. Singh D, Febbo PG, Ross K, Jackson DG, Manola J, Ladd C, et al. Gene expression correlates of clinical prostate cancer behavior. Cancer Cell 2002; 1:203-9.
5. Tomlins SA, Rhones DR, Perner S, Dhanasekaran SM, Mehra R, Sun XW, et al. Recurrent fusion of TMPRSS and ETS transcription factor genes in prostate cancer. Science 2005; 310:644-8; DOI: 10.1126/science.1117679.
6. Kim JH, Dhanasekara SM, Mehra R, Tomlins SA, Gu W, Yu J, et al. Integrative analysis of genomic aberrations associated with prostate cancer progression. Cancer Res 2007; 67:8229-39; DOI: 10.1158/0008-5472.CAN-07-1297.
7. Lieberfarb ME, Lin M, Lechpammer M, Li C, Tanenbaum DM, Febbo PG, et al. Genome-wide loss of heterozygosity analysis from laser capture microdissected prostate cancer using single nucleotide polymorphic allele (SNP) arrays and a novel bioinformatics platform dChipSNP. Cancer Res 2003; 63:4781-6.
8. Taylor BS, Schultz N, Hieronymus H, Gopalan A, Xiao Y, Carver BS, et al. Integrative genomic profiling of human prostate cancer. Cancer Cell 2010; 18:11-22; DOI: 10.1016/j.ccr.2010.05.026.