Asian Journal of Andrology (2015) 17, 435–436

www.asiaandro.com; www.ajandrology.com

Open Access

INVITED RESEARCH HIGHLIGHT

Prostate Cancer

Transcriptome sequencing in prostate cancer identifies inter-tumor heterogeneity

Janet Mendonca, Anup Sharma, Sushant Kachhap

Asian Journal of Andrology (2015) **17**, 435–436; doi: 10.4103/1008-682X.143750; published online: 02 December 2014

Given the dearth of gene mutations in prostate cancer,[1,2] it is likely that genomic rearrangements play a significant role in the evolution of prostate cancer. However, in the search for recurrent genomic alterations, "private alterations" have received less attention. Such alterations may provide insights into the evolution, behavior, and clinical outcome of an individual tumor. In a recent report in "Genome Biology" Wyatt *et al.*[3] defines unique alterations in a cohort of high-risk prostate cancer patient with a lethal phenotype. Utilizing a transcriptome sequencing approach they observe high inter-tumor heterogeneity; however, the genes altered distill into three distinct cancer-relevant pathways. Their analysis reveals the presence of several non-ETS fusions, which may contribute to the phenotype of individual tumors, and have significance for disease progression.

Predicting clinical outcome of prostate cancer, based on the differentiation status of tumors, is often limited. Hence, stratifying prostate cancer based on molecular characteristics is actively sought. Recent advances in next-generation sequencing technology have provided great insights into the molecular complexity of prostate cancer.[1,2] Besides revealing recurrent genomic alterations, these studies have also uncovered the occurrence of complex genomic rearrangements found in prostate cancer. However, the vast majority of genomic alterations in prostate cancer are nonrecurrent, contributing to inter-tumor heterogeneity.[4] These nonrecurrent alterations are unique to the patient and may dictate tumor progression and clinical outcome. Most of the above studies are based on genome or exome sequencing. In a recent report, Wyatt *et al.*[3] used transcriptome sequencing in a cohort of 25 high-risk prostate cancer patients, representing lethal phenotype. The high dynamic range and absolute quantification feature of transcriptome sequencing were leveraged by the authors to identify rare alterations unique to individual's tumor. To achieve this, the authors utilized "recurrent" outlier analysis that allowed the detection of alterations that were individual-specific and those that were more frequent. Using this strategy, 68% of tumors showed significant enrichment for genes within at least one of three major cellular pathways associated with metabolism: translation (EIF2, mammalian target of rapamycin [mTOR], ribosomal biogenesis), cell cycle (including PLK1, CDC25A and CDK1), and the immune system (T and B cell markers signifying lymphocyte infiltration). Such alterations that are unique to a given tumor, exemplify pathway reliance of the individual tumor and provide an opportunity for personalizing therapy. What is encouraging about these results is that many of the enriched pathways are druggable (e.g. PLK1, mTOR); some of the inhibitors of the pathways are presently undergoing clinical trials.[5,6] Stratifying patients, based on pathway affinity of the individual's tumor, and targeting the pathway with contemporary drugs, would arguably be a more rational approach, predicting better clinical outcome.

Prostate tumors are known to harbor complex chromosomal rearrangements through the process of chromoplexy.[7] Chromoplexy involves intricately weaved genomic rearrangements that involve breakage, shuffling, and rejoining of several chromosomal segments. A related phenomenon called chromothripsis that involves clustered rearrangement of one or two chromosomes, as opposed to six or more in chromoplexy, also occurs, albeit less frequently, in prostate cancer.[8] Many of the fusion transcripts that arise from this process disrupt tumor suppressors, although some may also be potentially oncogenic in nature. Demonstrating the power of transcriptome sequencing, the authors identified 242 fusion transcripts arising from genome rearrangement in their cohort, a feature that escapes conventional microarray analysis. Majority (69%) of the tumors harbored ETS fusions. However, several tumors expressed unique non-ETS fusion genes. Majority of the non-ETS fusion genes caused a loss of function through interruption and or truncation of one or both fusion partners. Understandably, many of these were known tumor suppressors such as TP53, RB1, and MRE11a, to name a few. The authors also found several in-frame fusion genes that were predicted to be functional and could serve as oncogenic drivers. Although the functional and clinical relevance of these non-ETS fusion genes need further evaluation, the study underscores the high degree of genomic rearrangements prevalent in prostate tumors. Intriguingly, there appears to be differences in the chromoplexy across molecular subtypes defined by the presence and absence of ETS fusions and the chromodomain helicase CHD1. Rearrangements in ETS^{+} $CHD1^{WT}$ tumors are predominantly interchromosomal, resembling chromoplexy, whereas ETS^{-} $CHD1^{del}$ tumors exhibit a higher frequency of intrachromosomal rearrangements, which more closely resemble chromothripsis.[7] In line with this, 2 of the 25 tumors that expressed the greatest number of genomic rearrangements were ETS^{-}. One of these tumors exhibited a novel "tandem duplicator genotype" which has been recently reported for breast and

Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Medical Institutions, Baltimore, MD 21231, USA.
Correspondence: Dr. S Kachhap (Kachhsu@jhmi.edu)

ovarian cancer.[9] This tumor had 25 fusion transcripts that were intrachromosomal and predicted to have arisen through tandem duplication. Overlapping focal copy gains with genome rearrangement predictions in this tumor further revealed an additional 216 tandem duplications spread across the entire genome. Particularly noteworthy, among these tandem duplications, was a high focal genome amplification of the MDM2 gene loci caused by serial tandem duplication events across a ~3 Mb region of chromosome 12. This tumor harbored an intact *TP53* gene, and since MDM2 drives proteolytic degradation of TP53,[10] it is likely that tandem *MDM2* duplications have a functional role in keeping the tumor suppressor function of p53 under check. This finding is also interesting in the context of a second tumor, also with an intact *TP53* gene, that harbored an androgen responsive *SLC45A3-UBE3A* fusion gene. *UBE3A* (also called *E6AP*) also promotes degradation of *TP53*,[11] and together with the MDM2 amplification suggests a wider role for ubiquitin ligase-mediated suppression of TP53 in prostate cancer. Unique alterations may not only define the evolution of an individual tumor but also offer opportunities for personalized therapy. However, not all alterations may have biological, or clinical significance and functional analysis in the future will shed some light towards this aspect. Nonetheless, exploiting individual tumor profile to tailor existing therapy or design novel therapeutic strategies with reduced toxicities will undoubtedly benefits patients and change clinical practice in future. Such knowledge will allow patient stratification for drug trials as well as treatment regimen, and explain the biology of response/resistance of prostate cancer to therapy. Along with whole genome sequencing, deep transcriptome sequencing is a step forward in personalized medicine for prostate cancer.

REFERENCES

1 Barbieri CE, Bangma CH, Bjartell A, Catto JW, Culig Z, *et al.* The mutational landscape of prostate cancer. *Eur Urol* 2013; 64: 567–76.
2 Grasso CS, Wu YM, Robinson DR, Cao X, Dhanasekaran SM, *et al.* The mutational landscape of lethal castration-resistant prostate cancer. *Nature* 2012; 487: 239–43.
3 Wyatt AW, Mo F, Wang K, McConeghy B, Brahmbhatt S, *et al.* Heterogeneity in the inter-tumor transcriptome of high risk prostate cancer. *Genome Biol* 2014; 15: 426.
4 Beltran H, Yelensky R, Frampton GM, Park K, Downing SR, *et al.* Targeted next-generation sequencing of advanced prostate cancer identifies potential therapeutic targets and disease heterogeneity. *Eur Urol* 2013; 63: 920–6.
5 Stadler WM, Vaughn DJ, Sonpavde G, Vogelzang NJ, Tagawa ST, *et al.* An open-label, single-arm, phase 2 trial of the Polo-like kinase inhibitor volasertib (BI 6727) in patients with locally advanced or metastatic urothelial cancer. *Cancer* 2014; 120: 976–82.
6 Templeton AJ, Dutoit V, Cathomas R, Rothermundt C, Bärtschi D, *et al.* Phase 2 trial of single-agent everolimus in chemotherapy-naive patients with castration-resistant prostate cancer (SAKK 08/08). *Eur Urol* 2013; 64: 150–8.
7 Baca SC, Prandi D, Lawrence MS, Mosquera JM, Romanel A, *et al.* Punctuated evolution of prostate cancer genomes. *Cell* 2013; 153: 666–77.
8 Lapuk AV, Wu C, Wyatt AW, McPherson A, McConeghy BJ, *et al.* From sequence to molecular pathology, and a mechanism driving the neuroendocrine phenotype in prostate cancer. *J Pathol* 2012; 227: 286–97.
9 McBride DJ, Etemadmoghadam D, Cooke SL, Alsop K, George J, *et al.* Tandem duplication of chromosomal segments is common in ovarian and breast cancer genomes. *J Pathol* 2012; 227: 446–55.
10 Momand J, Zambetti GP, Olson DC, George D, Levine AJ. The mdm-2 oncogene product forms a complex with the p53 protein and inhibits p53-mediated transactivation. *Cell* 1992; 69: 1237–45.
11 Johnson ES, Ma PC, Ota IM, Varshavsky A. A proteolytic pathway that recognizes ubiquitin as a degradation signal. *J Biol Chem* 1995; 270: 17442–56.