Treatment-naïve, locally advanced prostate cancer contains numerous subclonal clinically significant alterations

David J. VanderWeele1,2, Richard Finney3, Kotoe Katayama4, Marc Gillard5, Gladell Paner6, Seiya Imoto4, Rui Yamaguchi7, David Wheeler3, Maggie Cam3, Kazuhiro Maejima7, Aya Sasaki-Oku7, Kaoru Nakano7, Hiroko Tanaka4, Andrea Pontier2, Dmitry Grigoryev1, Michiaki Kubo7, Mark J. Ratain2, Satoru Miyano4, Hidewaki Nakagawa7

Affiliations:
1Laboratory for Genitourinary Pathogenesis, National Cancer Institute, Bethesda, MD
2Department of Medicine, University of Chicago, Chicago, IL
3Center for Cancer Research Collaborative Bioinformatics Resource, National Cancer Institute, Bethesda, MD
4Human Genome Center, Institute of Medical Science, University of Tokyo, Tokyo, Japan
5Department of Surgery, University of Chicago, Chicago, IL
6Department of Pathology, University of Chicago, Chicago, IL
7Laboratory for Genome Sequencing Analysis, RIKEN Center for Integrative Medical Sciences, RIKEN, Kanagawa, Japan

Abstract

Background Primary prostate cancer is genetically heterogeneous with few recurrent alterations, whereas advanced, therapy-resistant disease has recurrent alterations in clinically significant pathways. The timing of the accumulation of these alterations is unknown.

Methods We performed multiregion genomic analysis on 74 regions from ten cases of treatment-naïve, localized or locally advanced node positive prostate cancer.

Results Exome sequencing and copy number analysis demonstrated branched evolution with >90% of point mutations being subclonal and broad spatial occupancy by comingled subclones. Compared to localized disease, locally advanced disease contained higher number of mutations in cancer genes (0.6 vs 2), higher fraction of genome altered by amplifications and deletions (0.05 vs 0.19), and more co-occurring subclonal alterations in CRPC pathways (3 vs 20, p<0.05 for all comparisons). Locally advanced cases demonstrated predicted susceptibility to up to 20 targeted therapies, but within biomarker-positive cases, 60% of regions were biomarker-negative.

Conclusions Our data are consistent with a model whereby progression to locally advanced disease is coincident with the accumulation of numerous subclonal clinically significant alterations; advanced, therapy-resistant disease emerges from enrichment of these subclones.

Conflict of Interest
None

Funding Acknowledgement
This work was supported by the Office of the Assistant Secretary of Defense for Health Affairs, through the Prostate Cancer Research Program under Award No. W81XWH-13-1-0451, the University of Chicago Cancer Center Support Grant P30 CA014599, and the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research. Exome sequencing analysis was performed in the super-computing resource “SHIROKANE” in Human Genome Center, The University of Tokyo.