Chromosomal instability (CIN) in diagnostic prostate biopsies predicts prostate cancer metastases

Eric T. Miller, MD[1], Sungyong You, PhD[2], Radu M. Cadaneanu, BS[1], Sandy T. Liu, MD[1,3], Xinmin Li, PhD[4,5], Lorna Kwan, MS[1], Jennelle Hodge, PhD[2], Michael S. Lewis, MD[6], Beatrice S. Knudsen, MD, PhD[2], Michael R. Freeman, PhD[2], and Isla P. Garraway, MD, PHD[1,5,7*].

1. Department of Urology, David Geffen School of Medicine at UCLA, Los Angeles, California, United States of America
2. Department of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, California, United States of America
3. Department of Medicine, Division of Hematology-Oncology, David Geffen School of Medicine at UCLA, Los Angeles, California, United States of America
4. Department of Pathology, David Geffen School of Medicine at UCLA, Los Angeles, California, United States of America
5. Jonsson Comprehensive Cancer Center, David Geffen School of Medicine at UCLA, Los Angeles, California, United States of America
6. Department of Pathology, Greater Los Angeles Veterans Affairs Health System, Los Angeles, California, United States of America
7. Division of Urology, Greater Los Angeles Veterans Affairs Healthcare Center, Los Angeles, California, United States of America

Background: Chromosomal instability (CIN) is a vicious cycle of defective chromosomal separation resulting in aneuploidy, copy number aberrations (CNAs) and micronuclei. CIN is often lethal to cells, and its tolerance in cancer may represent a critical bottleneck in tumor evolution that yields metastatic subclones. We evaluated CIN via transcriptome analysis in diagnostic prostate needle biopsies (PNBX) from untreated men with high-grade localized or de novo metastatic prostate cancer (PC).

Methods: PC outcomes were determined in a racially diverse cohort (n=2134) treated between 2000 and 2016. Cases were designated as localized, oligometastatic or polymetastatic based upon tumor burden on cross-sectional imaging. Archival PNBX from select cases (n=99) were annotated and tumor regions procured for transcriptome and/or CNA analysis.

Results: A 157-gene signature, identified through comparison of PNBX transcriptome data and previously published castration-resistant metastases datasets, separated metastatic from non-metastatic cases. Metastatic cases displayed significant enrichment of CIN genes and frequent CNAs. CIN enrichment score of PCs in the cancer genome atlas showed similar correlation with CNA frequency. Seven CIN genes (CIN7) comprising the leading edge of differentially expressed genes in polymetastatic cases accurately predicted recurrence in multiple independent PC cohorts. Specific immune cell signatures, including a dysfunctional T-cell signature, correlated with CIN gene enrichment scores in PNBX.

Conclusions: Transcriptome evaluation of a unique, untreated PC cohort reveals CIN as a predominant feature in primary PC that is shared with CRPC metastases. CIN predicts progression in men diagnosed with localized PC and is associated with dysfunctional T-cell infiltration in primary tumors of men with polymetastases.

Conflicts of Interests: None

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