

Genomic Characterization of Circulating Tumor Cells in De Novo Metastatic Prostate Cancer

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Background:

The absence of biomarkers that identify clinically meaningful biological subsets of prostate cancer results in the homogeneous application of systemic therapies to a heterogeneous disease and hampers therapy development. This heterogeneity may become more evident at the molecular level under the pressure of androgen withdrawal. Here, we longitudinally characterized peripheral blood circulating tumor cells (CTCs) from patients with de novo metastatic prostate cancer to examine the phenotypic and genomic changes induced by androgen suppression.

Methods:

Peripheral blood samples were collected at MD Anderson Cancer Center from a cohort of DNM1PCa patients under clinical trial NCT01751438. Timepoints of collection includes baseline (BSL, before treatment) and 6 months (6mo, after 6 months of systemic therapy). We used the High-Definition Single Cell Assay (HD-SCA) workflow for CTC enumeration, morphology (nuclear size, DAPI intensity, cytokeratin (CK), androgen receptor (AR) intensity) and genomics (whole-genome copy number aberration analysis) evaluation. This workflow utilizes an enrichment-free fluorescence based (DAPI/ CK/ CD45/ AR) CTC identification system and single-cell genomic sequencing.

Results:

Twenty-nine of the 58 available blood samples contained CTCs: 15 of the 28 (53.6%) collected at BSL (median 2.00 CTCs/mL, range 0.84-74.15) and 14 of the 30 (46.7%) collected at 6mo (median 2.43 CTCs/mL, range 0.96-13.85). However, at the 6mo timepoint, the CTCs had undergone a significant morphological shift in nuclear area local ratio (BSL vs 6mo: 1.036 vs 1.165, $p=0.039$), DAPI intensity (0.199 vs 1.030, $p=0.036$), CK intensity (18.978 vs 15.651, $p=0.006$), AR intensity (0.681 vs -0.468, $p=0.037$) and AR+ percentage (36.25% vs 15.38%, $p=0.020$). Further, genomic analysis of two patients at BSL indicated copy number aberrations including PTEN, TP53, RB1 and BRCA2 loss and MYC gain.

Discussion:

This study aims at characterizing changes induced by systemic therapies in CTC potential biomarkers that identify distinct subsets of disease biology. The changes observed in patient

subsets may serve as clinically relevant biomarkers to optimize treatment and improve prognosis.

Conflicts of Interest:

The HD-SCA technology described here is licensed to Epic Sciences. AK and PK have ownership in Epic Sciences. JH is on the Advisory Board for Epic.

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