RNA profiling of circulating tumor cells to monitor prostate cancer

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Circulating tumor cells (CTCs) provide a non-invasive strategy to identify and serially monitor molecular characteristics of metastatic prostate cancer, as it initially responds and ultimately progresses following therapeutic intervention. We have developed and applied increasingly sophisticated and automated microfluidic technologies, capable of depleting normal hematopoietic cells from blood samples, leaving behind CTCs without the selection bias inherent in the use of tumor-specific epitopes. The unmanipulated and viable CTCs contain high quality RNA, which may be interrogated at the single cell level. We first established single cell RNA sequencing profiles of 77 CTCs isolated from 13 patients with castration resistant prostate cancer (CRPC), demonstrating considerable inter-patient as well as intra-patient heterogeneity in expression of critical genes, including the Androgen Receptor (AR) gene and its splicing variants. Retrospective analysis of patients progressing under anti-androgen therapy revealed activation of non-canonical Wnt5a signaling (P=0.0064), a pathway that we showed can mitigate the effect of androgen depletion in cultured prostate cancer cells. To extend these studies, we established a molecular signature of prostate cancer-derived CTCs, directly applied to CTC-enriched blood fractions. In a pilot cohort, serial monitoring of both lineage-specific transcripts and the aberrant AR-v7 splice variant are predictive of response to androgen-targeted therapy as early as the first disease recurrence.

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