An RNA-based digital circulating tumor cell signature is predictive of drug response and early dissemination in prostate cancer

David T. Miyamoto, Richard J. Lee, Mark Kalinich, Joseph LiCausi, Yu Zheng, Tianqi Chen, Anita Giobbie-Hurder, Ben S. Wittner, Sarah Javaid, Tanya T. Kwan, Xin Hong, Douglas M. Dahl, Jason Efstathiou, Chin-Lee Wu, Matthew R. Smith, David T. Ting, Sridhar Ramaswamy, Mehmet Toner, Shyamala Maheswaran, and Daniel A. Haber

Massachusetts General Hospital Cancer Center and Departments of Radiation Oncology, Medicine, Urology, Pathology and Surgery, Harvard Medical School, Boston, MA 02129.

Background: Circulating tumor cells (CTCs) in the bloodstream provide a noninvasive source of material to monitor the presence and composition of prostate cancer. The development of microfluidic CTC isolation technologies allows for the efficient, tumor epitope-independent isolation of CTCs with intact RNA.

Methods: We performed whole cell isolation of CTCs from patient blood samples using the microfluidic CTC-iChip, which performs efficient depletion of hematopoietic cells and tumor-epitope independent enrichment of untagged CTCs. Isolated CTCs were subjected to RNA extraction and mRNA transcript quantitation using droplet digital PCR. This combination of the microfluidic CTC-iChip with a digital assay for expression of multiple prostate-lineage-specific and cancer-specific RNA transcripts enabled the establishment of a high throughput, quantitative, and highly specific assay for the detection of prostate cancer cells in the blood.

Results: A digital CTC score was derived that detected signal in the blood from a majority of patients with metastatic prostate cancer, a subset of cases with localized cancer, and in no healthy individuals without a diagnosis of cancer. Compared to immunofluorescence-based microscopic imaging, the digital CTC assay showed increased sensitivity and specificity for the detection of CTCs. In a prospective study of 27 men with metastatic castration-resistant prostate cancer receiving first-line abiraterone, pre-treatment elevation of the digital CTC score and individual markers including HOXB13 and AR-V7 were predictive of radiographic progression and overall survival. Furthermore, in 34 patients with clinically localized prostate cancer, an elevated pre-operative digital CTC score predicted for pathologic seminal vesicle invasion and lymph node involvement identified at the time of radical prostatectomy.

Conclusions: Combined with microfluidic CTC isolation, the highly sensitive and specific digital quantitation of transcripts derived from CTCs enables noninvasive interrogation of cancer markers predictive of treatment response in metastatic prostate cancer, as well as prediction of early dissemination of disease in clinically localized prostate cancer.

Conflict of Interest Statement: MGH has applied for patent protection for the CTC-iChip

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