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Detection of genetic and epigenetic DNA markers in urine for the early detection of primary and recurrent hepatocellular carcinoma

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Introduction
Hepatocellular carcinoma (HCC) or liver cancer is an aggressive disease and one of the fastest growing cancers by incidence in the United States. Early detection is the key for effective treatment as the 5-year survival rate is 20% in early stage HCC as compared to only 2% when found onspread to distant organs. The current marker, alpha-fetoprotein (AFP) and its fucosylated glycolipid, GL3, are of limited utility as they are not sensitive or specific.

Objectives
Develop a urine test using a panel of genetic and epigenetic markers for the early detection of primary and recurrent HCC.

Methods
Urine samples were collected with informed consent and institutional review board approval from National Cheng Kung University (Tainan, Taiwan), Tzu Chi Hospital, (Hualien, Taiwan), and Thomas Jefferson University Hospital (Philadelphia, PA), at visits with a hepatologist. The samples from T.J.U. were barcoded for disease status as a blinded study. Total urine DNA was isolated (So, Wang et al. 2018) and from low molecular weight DNA, DNA was less than 1 kb, was obtained from total urine DNA using carbonyl-bonded magnetic beads (Agilent, Santa Clara, CA). The DNA isolated was then subjected to microarray analysis.

Results

Case 1: Detection of a primary HCC
Urine contains fragmented, cell-free, cancer-associated DNA, both mutated and methylated, derived from the circulation of cancer patients (Li, Dhillon et al. 2011). Samples were collected before TACE at the first time point. The DNA markers were undetectable but serum AFP was slightly elevated at 89 ng/ml and declined to baseline after TACE therapy. HCC recurrence was detected by MRI 11-13 months after TACE treatment. TERT 124 mutation levels were elevated 6 months prior to recurrence detection by MRI. mRASSF1A, TP53 249T mutation, and serum AFP levels rise with the appearance of recurrent nodule and declined post treatment. This recurrence was also treated with TACE. No, MRI at 11 months was not definitive. Urine mGSTP1, TERT 124 levels rose 4 months post repeat TACE with the appearance of a LRADS category 3 lesion on MRI.

Case 2: Detection of recurrent HCC
The urine sample from a patient with HCC recurrence was collected 12 months prior to post-MRI diagnosis of recurrence. The urine sample showed a 40% drop in mRASSF1A and 80% drop in TERT 124 levels. The urine sample was also positive for urine AFP.

Case 3: Detection of recurrent HCC
A patient with HCC recurrence was monitored with urine mRASSF1A, TERT 124, and urine serum AFP. The urine sample showed a 50% drop in mRASSF1A and 80% drop in TERT 124 levels. The urine sample was also positive for urine AFP.

Case 4: Detection of recurrent HCC
A patient with HCC recurrence was monitored with urine mRASSF1A, TERT 124, and urine serum AFP. The urine sample showed a 50% drop in mRASSF1A and 80% drop in TERT 124 levels. The urine sample was also positive for urine AFP.

Conclusion
• A total of 10 cases with treated HCC were monitored by serum AFP and urine DNA biomarkers in a blinded study. Of the 10, 4 developed recurrence during the study. HCC-specific urine DNA markers were detected in 3 of 4 patients six months prior to MRI diagnosis and in one patient concurrent with MRI diagnosis.
• Fifteen cirrhosis and nine hepatitis patients were monitored every six months for HCC. In this group, one patient developed primary HCC and the urine DNA biomarkers were detected six months prior to MRI diagnosis in a blinded study.
• The urine test could lead to a paradigm shift for screening and effective management of primary and recurrent HCC and for personalized disease management.

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