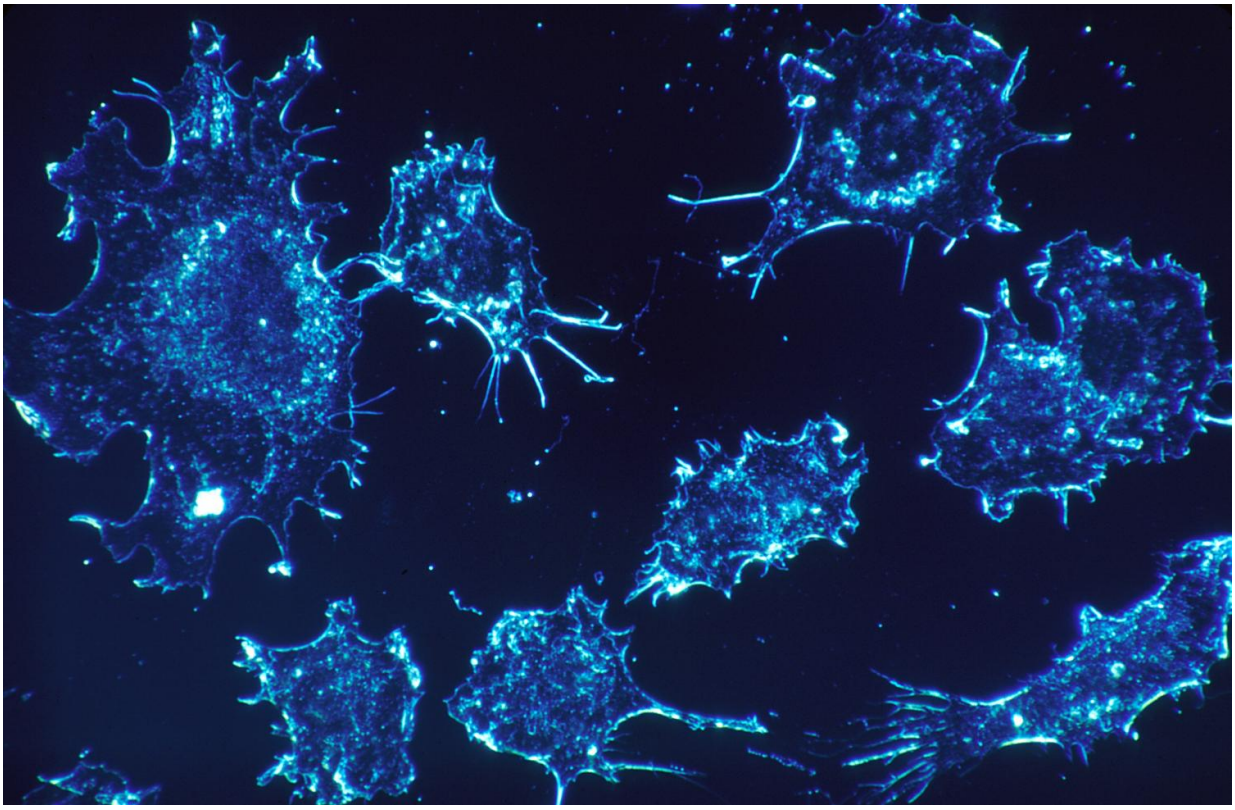
MedicalXpress

Liquid biopsy may be new way to detect liver cancer earlier, easier

October 9 2017



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An international team of researchers at University of California San Diego School of Medicine and Moores Cancer Center, with colleagues at Sun Yet-sun University Cancer Center and other collaborating institutions, have developed a new diagnostic and prognosis method for

early detection of hepatocellular carcinoma (HCC), based on a simple blood sample containing circulating tumor DNA.

The findings are published in the October 9 issue of *Nature Materials*.

HCC is the most common type of primary liver cancer in adults and among the leading causes of cancer mortality in the world, with more than 780,000 new cases and 740,000 deaths each year. More than 40,000 new cases are diagnosed in the United States annually, with approximately 29,000 deaths annually. Liver cancer incidence rates are rising.

"HCC and its precursor, nonalcoholic steatohepatitis, have increased markedly during the past decade and disproportionally affect Hispanic males," said Scott Lippman, MD, director of Moores Cancer Center. "California has one of the highest rates of liver cancer in the U.S. This novel report has major implications locally and globally on this devastating disease. It's also the first report to support the potential of ctDNA for early detection for any cancer."

Like many cancers, early detection improves prognosis and survival rates, in part due to greater efficacy of localized treatment versus systemic treatments. But current detection methods for HCC primarily rely upon imaging and a blood test for a non-specific tumor marker called alpha-fetoprotein (AFP), which is usually elevated when the disease is significantly advanced.

"Non-invasive blood tests or liquid biopsies present a better alternative," said Kang Zhang, MD, PhD, founding director of the Institute for Genomic Medicine and co-director of biomaterials and tissue engineering at the Institute of Engineering in Medicine, both at UC San Diego, "However, there has been little success in developing effective blood-based methods for screening HCC. The only blood test, AFP, has

limited clinical utility due to low sensitivity."

Many liquid biopsies work by detecting circulating tumor DNA (ctDNA), which are fragments of genetic material shed into the blood by tumor cells. These biopsies offer several potential advantages over other methods of cancer detection, according to Zhang. They are minimally invasive. They can be done at any time during therapy, allowing physicians to monitor molecular changes in tumors in real-time. They may detect tumors not apparent or indeterminant based upon imaging. And finally, ctDNA potentially represents the entire molecular picture of a patient's malignancy while a tumor biopsy may be limited to just the tested portion of the tumor.

DNA methylation is a process that can regulate gene expression and extensive DNA methylation of a gene usually leads to a gene being turned off. Increased methylation of tumor suppressor genes is an early event in tumor development, suggesting that altered DNA methylation patterns may be a good indicator of an emerging tumor.

In their study, Zhang and colleagues looked at hundreds of thousands of methylation profiles of HCC patients and healthy controls. The researchers identified a specific panel of methylation markers that correlated to HCC, then used a variety of machine learning and statistical methods to examine their efficacy at detecting and assessing HCC in 1,098 HCC patients and 835 normal controls.

"Our results were very encouraging," said Zhang. "In a large clinical cohort, our blood-based HCC diagnosis highly correlated with tumor burden, treatment response and stage of cancer. Right now, oncologists are quite limited in how they detect HCC and evaluate treatment. Our study is a great demonstration of proof-of-concept for a new, more effective approach that applies to solid malignancies, HCC and beyond."

More information: Circulating tumour DNA methylation markers for diagnosis and prognosis of hepatocellular carcinoma, *Nature Materials* (2017). nature.com/articles/doi:10.1038/nmat4997