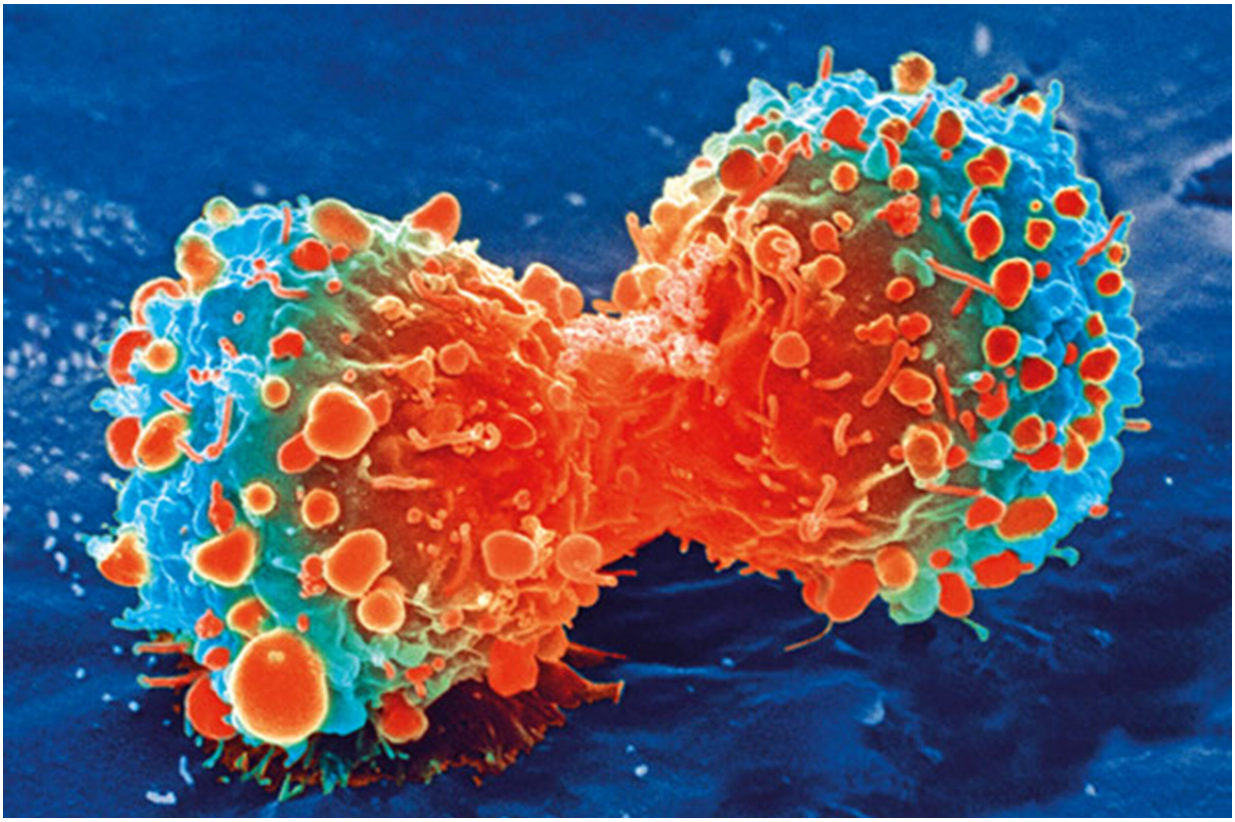
MedicalXpress

Genomic analysis of liver cancer reveals unexpected genetic players

June 16 2017



Cancer cell during cell division. Credit: National Institutes of Health

Liver cancer has the second-highest worldwide cancer mortality, and yet there are limited therapeutic options to manage the disease. To learn more about the genetic causes of this cancer, and to identify potential

new therapeutic targets for HCC, a nation-wide team of genomics researchers co-led by David Wheeler, Director of Cancer Genomics and Professor in the Human Genome Sequencing Center (HGSC) at Baylor College of Medicine, and Lewis Roberts, Professor of Medicine at the Mayo Clinic, analyzed 363 liver cancer cases from all over the world gathering genome mutations, epigenetic alteration through DNA methylation, RNA expression and protein expression. The research appears in *Cell*.

Part of the larger Cancer Genome Atlas project (TCGA), this work represents the first large scale, multi-platform analysis of HCC looking at numerous dimensions of the tumor. "There have been large-cohort studies in liver cancer in the past, but they have been limited mainly to one aspect of the tumor, genome mutation. By looking at a wide variety of the tumor's molecular characteristics we get substantially deeper insights into the operation of the cancer cell at the molecular level," Wheeler said.

The research team made a number of interesting associations, including uncovering a major role of the sonic hedgehog pathway. Through a combination of p53 mutation, DNA methylation and viral integrations, this pathway becomes aberrantly activated. The sonic hedgehog pathway, the role of which had not been full appreciated in liver cancer previously, is activated in nearly half of the samples analyzed in this study.

"We have a very active liver cancer community here at Baylor, so we had a great opportunity to work with them and benefit from their insights into liver cancer," Wheeler said. Among the many critical functions of the liver, hepatocytes expend a lot of energy in the production of albumin and urea. It was fascinating to realize how the liver cancer cell shuts these functions off, to its own purpose of tumor growth and cell division.

"Intriguingly, we found that the urea cycle enzyme carbamyl phosphate synthase is downregulated by hypermethylation, while cytoplasmic carbamyl phosphate synthase II is upregulated," said Karl-Dimiter Bissig, Assistant Professor of Molecular and Cellular Biology at Baylor and co-author of the study. "This might be explained by the anabolic needs of liver cancer, reprogramming glutamine pathways to favor pyrimidine production potentially facilitating DNA replication, which is beneficial to the cancer cell."

"Albumin and apolipoprotein B are unexpected members on the list of genes mutated in liver cancer. Although neither has any obvious connection to cancer, both are at the top of the list of products that the liver secretes into the blood as part of its ordinary functions," explained Dr. David Moore, professor of molecular and cellular biology at Baylor. "For the cancer cell, this secretion is a significant loss of raw materials, amino acids and lipids that could be used for growth. We proposed that mutation of these genes would give the cancer cells a growth advantage by preventing this expensive loss."

Multiple data platforms coupled with clinical data allowed the researchers to correlate the molecular findings with clinical attributes of the tumor, leading to insights into the roles of its molecules and genes to help design new therapies and identify prognostic implications that have the potential to influence HCC clinical management and survivorship.

"This is outstanding research analyzing a cancer that's increasing in frequency, especially in Texas. Notably, the observation of gene expression signatures that forecast patient outcome, which we validate in external cohorts, is a remarkable achievement of the study. The results have the potential to mark a turning point in the treatment of this cancer," said Dr. Richard Gibbs, director of the HGSC at Baylor. The HGSC was also the DNA sequence production Center for the project.

Wheeler says they expect the data produced by this TCGA study to lead to new avenues for therapy in this difficult cancer for years to come. "There are inhibitors currently under development for the sonic hedgehog pathway, and our results suggest that those inhibitors, if they pass into phase one clinical trials, could be applied in liver cancer patients, since the pathway is frequently activated in these patients," added Wheeler.

More information: Adrian Ally et al. Comprehensive and Integrative Genomic Characterization of Hepatocellular Carcinoma, *Cell* (2017). DOI: 10.1016/j.cell.2017.05.046

Provided by Baylor College of Medicine