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Identification of early drivers of HBV associated hepatocarcinogenesis

There are more than 350 million people worldwide who are chronically infected with hepatitis B virus (HBV) and are at risk for the development of chronic liver diseases (CLD). CLD consists of hepatitis, fibrosis and cirrhosis, and finally the appearance of hepatocellular carcinoma (HCC). HCC is the 5th most common cancer and 2nd most deadly form of cancer worldwide. Although surgical resection and liver transplantation may be curative, clinical symptoms do not appear in most patients until the tumor is multinodular. The mechanisms underlying the pathogenesis of HCC have not been clearly elucidated, although the virus contribution to the development of cancer involves the expression of the hepatitis B x antigen (HBx). HBx is a trans-regulatory protein that activates many signaling pathways and alters the expression of numerous host genes, although it is not known which of these many pathways and genes drive tumorigenesis. To approach this problem, The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) were queried to identify genes and/or pathways that are differentially expressed in HCC compared to surrounding non-tumor liver. This identified over 2,700 genes that were differentially expressed. When the latter were compared to the 140 driver mutations in all cancers, 26 drivers had changes in expression levels among patients who developed HCC. Two of these drivers showed differential expression in the liver prior to the development of HCC that inversely correlated with DNA methylation activity. These were identified as the tumor suppressor, *Tet methylcytosine dioxygenase 2 (TET2)* and the oncogene, myeloproliferative leukemia protein (MPL). These two genes are known to be upstream regulators of other driver genes altered in HBV associated HCC. They reside in biochemical pathways known to be altered by HBx in hepatocarcinogenesis. These pathways also include genes that promote survival, growth, DNA repair, and regulate both cell cycle arrest and apoptosis. These findings imply that HBx epigenetic changes in driver gene expression appears to occur prior to the appearance of driver mutations recorded in the literature, and that changes in *TET2* and MPL expression may trigger subsequent changes in the expression/activity levels of many downstream molecules that are known to drive tumorigenesis.

Biography

Mark A Feitelson has completed his BS in Biology from the UCI. He was a graduate student in the Department of Microbiology and Immunology at the UCLA School of Medicine, where he began his studies in Viral Oncogenesis, and completed his PhD degree in 1979. He was then an American Cancer Society Postdoctoral Fellow in the Department of Medicine at Stanford University from 1979-1982. He then moved to the Fox Chase Cancer Center in Philadelphia, where he studied the Biology of hepatitis B virus (HBV) with Baruch S Blumberg, who won the Nobel Prize in Medicine (1976) for his discovery of HBV. In 1991, he moved to the Department of Pathology and Cell Biology at Thomas Jefferson University where he became a Professor. In 2007, he moved to Temple University, where he is a Professor with tenure. Currently, he is the Chair of the Professional Science Master's program in Biotechnology at Temple.

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