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Hepatocellular Cancer Genome and Transcriptome Analysis Validates Clinically Significant Mutational Signatures with the TGF-? Pathway

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Hepatocellular Cancer Genome and Transcriptome Analysis Validates Clinically Significant Mutational Signatures with the TGF-β Pathway

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Development of hepatocellular carcinoma (HCC) is associated with alterations in the TGF-β signaling pathway, which regulates liver inflammation and can have tumor suppressor as well as promoter activities. Little is known about the roles of specific members of this pathway at specific of HCC development. We performed transcriptome analyses for 488 human HCCs that include TCGA data to identify and validate the effects of this pathway in HCC and identify potential therapeutic targets. Our data reveals that decreased levels of TGF-β–related genes, associated with loss of TGF-β tumor suppressor function and a significantly poorer survival as compared to the group with increased levels of TGF-β related genes (P=.0129). About 38% of HCC samples showed somatic mutations in at least one of the TGF-β members. These alterations correlate with DNA repair genes such as FancD2 but irrespective of known risk factors such as HBV, HCV and alcohol. SPTBN1, a Smad3 adaptor, was mutated in the largest proportion of samples (12/202, 6%). Further functional validation identified a loss of function mutation of SPTBN1-D1089Y, which leads to decreased FancD2 levels and increased sensitivity to DNA crosslinking agents. Interestingly, we also observed strong correlations between the inactivated TGF-β signature and deregulation of Sirtuin pathways. Additional analysis of Sirtuins in TGF-β deficient cells revealed positive feedback regulation of Sirtuins by TGF-β. Loss of TGF-β signaling inhibits Sirt1 and Sirt6 expression and *vice versa.* Overall, our findings provide new insight into how disruption of the TGF-β pathway correlates with deregulation of DNA repair pathway and Sirtuins, which lead to increased genomic instability, epigenetic changes and thereby promotes liver cancer progression.