Oncogenic driver genes and the inflammatory microenvironment dictate liver tumor phenotype.

The majority of hepatocellular carcinoma develops in the background of chronic liver inflammation caused by viral hepatitis and alcoholic or nonalcoholic steatohepatitis. However, the impact of different types of chronic inflammatory microenvironments on the phenotypes of tumors generated by distinct oncogenes is largely unresolved. To address this issue, we generated murine liver tumors by constitutively active AKT-1 (AKT) and β-catenin (CAT), followed by induction of chronic liver inflammation by 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) and carbon tetrachloride. Also, the impact of DDC-induced chronic liver inflammation was compared between two liver tumor models using a combination of AKT-CAT or AKT-NRAS(G12V). Treatment with DDC and carbon tetrachloride significantly facilitated the adenoma-to-carcinoma conversion and accelerated the growth of AKT-CAT tumors. Furthermore, DDC treatment altered the morphology of AKT-CAT tumors and caused loss of lipid droplets. Transcriptome analysis of AKT-CAT tumors revealed that cellular growth and proliferation were mainly affected by chronic inflammation and caused
up-regulation of Cxcl16, Galectin-3, and Nedd9, among others. Integration with transcriptome profiles from human hepatocellular carcinomas further demonstrated that AKT-CAT tumors generated in the context of chronic liver inflammation showed enrichment of poor prognosis gene sets or decrease of good prognosis gene sets. In contrast, DDC had a more subtle effect on AKT-NRAS(G12V) tumors and primarily enhanced already existent tumor characteristics as supported by transcriptome analysis. However, it also reduced lipid droplets in AKT-NRAS(G12V) tumors. Our study suggests that liver tumor phenotype is defined by a combination of driving oncogenes but also the nature of chronic liver inflammation. (Hepatology 2016; 63:1888-1899).