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Hepatocyte-specific deletion of Tristetraprolin family of RNA Binding Proteins result in the development of Hepatocellular Carcinomas

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Tristetraprolin family of RNA binding proteins, including tristetraprolin (TTP), zinc finger protein 36 like 1 (ZFP36L1), and zinc finger protein 36 like 2 (ZFP36L2) regulate mRNA levels by binding to AU-rich elements on the 3'untranslated regions of specific mRNAs and enhancing their turnover. Reduced TTP expression levels and activity have been associated with a diverse range of aggressive human cancers, however, experimental evidence for the role of TTP family proteins in cancer is lacking. Here, using Cre-loxP technology, we independently and simultaneously (triple KO) deleted the three TTP family proteins in mouse liver and characterized the phenotype of the resulting mice strains using clinical, histopathological, immunohistochemical, and transcriptomics approaches. The triple KO mice exhibited significantly increased serum levels of bile acids, bilirubin, and liver function enzymes. Histological analysis of the adult livers showed severe, chronic active, peri-portal hepatitis, bile duct hyperplasia, and portal fibrosis. Immunohistochemically, increased numbers of T cells, B cells, and macrophages, with few neutrophils were detected within the peri-portal areas. Increased expression of alpha-smooth muscle actin, a marker of hepatic stellate cell activation and heme-oxygenase-1, a marker of reactive oxygen species was also found. Most interestingly, at a later age (between 6 and 12 months), these mice spontaneously developed hepatocellular carcinomas. We conclude that dysregulated post-transcriptional regulation of gene expression upon loss of the three TTP family proteins results in the development of hepatocellular carcinoma. In summary, our study provides strong evidence that TTP family of RNA binding proteins act as tumor suppressors in the liver.