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Hepatocyte Deletion of IGF2 Prevents DNA Damage and Tumor Formation in Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide with a 18% 5-year survival rate. Mice lacking the splicing factor SRSF3 in hepatocytes (SKO mice) overexpress IGF2 and are predisposed to developing HCC with age. Loss of Igf2 in the SKO background prevented hepatic fibrosis and inflammation, and completely prevented tumor formation. This was associated with decreased proliferation, apoptosis and DNA damage, and restored DNA repair enzyme expression. Mechanistically, IGF2 treatment of HepG2 cells in vitro caused DNA damage and decreased DNA repair enzyme expression, and tumors from the SKO mice show mutational signatures consistent with double strand break and defective mismatch repair. Looking at human data, HCC patients with high IGF2 mRNA expression had worse survival compared to patients with normal IGF2 expression. The patients also showed a switch in IGF2 promoter usage that correlated

with increased expression. HCC patients having high SRSF3 mRNA expression also showed poor survival as did patients with alterations in known SRSF3-dependent splicing events. The level of SRSF3 protein was decreased 6-fold in human HCC tissues compared with normal liver tissues. The results indicate that IGF2 overexpression in conjunction with reduced SRSF3 splicing activity could be a major cause of DNA damage and driver of liver cancer.

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