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Titel des Beitrags: Increased liver carcinogenesis and enrichment of stem cell properties in livers of Dickkopf 2 (Dkk2) deleted mice.

Abstract: Dkk2 a antagonist of the Wnt/?-catenin-signaling pathway was shown to be silenced in diverse cancers. More recent data indicate that Dkk family members may also possess functions independent of Wnt-signaling during carcinogenesis. The detailed biological function of Dkks and its relevance for liver cancer is unknown. We analyzed the effects of a genetic deletion of Dkk2 (Dkk2-/-) in a hepatocarcinogenesis model using DEN/Phenobarbital. Untreated Dkk2-/- animals, showed considerable atypia with variation of hepatocyte size and chromatin density. In livers of Dkk2-/- mice nodule formation was seen at 9 months of age with focal loss of trabecular architecture and atypical hepatocytes and after DEN induction Dkk2-/- mice developed significantly more liver tumors compared to controls. Whole transcriptome analysis of untreated Dkk2-/- liver tissue revealed a Dkk2-dependent genetic network involving Wnt/?-Catenin but also multiple additional oncogenic factors, such as e.g. Pdgf-b, Gdf-15 and Hnf4a. Dkk2-/- tumor cells showed a significant deregulation of stemness genes associated with enhanced colony forming properties. Integration of the Dkk2-/- signature into human data was strongly associated with patients survival. Dkk2 deletion results
in alterations of liver morphology leading to an increased frequency of liver cancer. The associated genetic changes included factors not primarily related to Wnt/?-Catenin-signaling and correlated with the clinical outcome of HCC-patients.

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