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A subtle increase in wild-type RTK levels provides a permissive context allowing multiple signaling cooperators to initiate liver cancer

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Aberrant receptor tyrosine kinase (RTK) signaling is essential during liver cancer evolution and resistance to therapies. Using mouse genetics, we recently demonstrated that a subtle increase of wild-type RTK levels leads to cancer in sensitive tissues, illustrating how the shift towards cancerogenesis can stem from a slight perturbation of signaling dosage. In particular, when the Met RTK is slightly enhanced in liver, mice (namely Alb-R26^{Met}) spontaneously develop hepatocellular carcinoma (HCC), which belong to the so called "proliferative progenitors" subclass (*Fan et al. Hepatology 2017 Nov;66(5):1644-1661*). To uncover new genes that cooperate with RTKs during tumor initiation, we combined the clinically-relevant *Alb-R26^{Met}* mice with the *Sleeping Beauty (SB)* transposon (*T2/ONC)* mutagenesis system. Whereas neither *Alb-R26^{Met}* nor T2/onc-Alb-R26SB/+ mice developed tumors at 30 weeks of age, *T2/onc-Alb-R26SB/^{Met}* mice (with enhanced Met in liver in addition to active SB-driven mutagenesis) developed multiple liver tumors, each carrying distinct genomic insertions. Analysis of 251 independent tumors led to the identification of 285 putative cancer-related genes: some of them correspond to known proto-oncogenes or tumor suppressors, thus validating the overall strategy we employed for cancer gene discovery; other genes have not previously linked to cancer. Integrative analysis with human data revealed that a large proportion of identified genes are also altered in HCC patients. Moreover, we compared our screen outcomes with those performed in other tumor-sensitizing contexts and found 71 genes that emerged specifically in our RTK-sensitized background. *In vivo* assays established the functional relevance of several new putative tumor suppressors. Overall, our screen strategy identifies new functional mechanisms destabilizing liver homeostasis and illustrates how a subtle increase in wild-type RTK levels provides a permissive context for several types of cooperative mechanisms leading to liver tumor initiation.