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Shp2/Ptpn11 Deletion Suppresses Liver Tumorigenesis Driven by MET, β-Catenin and PIK3CA

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Most recent experimental data demonstrated a liver tumor-suppressing effect for *Shp2/Ptpn11*, as ablating Shp2 in hepatocytes triggered spontaneous development of hepatocellular adenoma (HCA) in aged mice and also aggravated hepatocellular carcinoma (HCC) induced by chemical carcinogen or Pten deletion. Herein we report surprisingly that despite the induction of hepatic injuries, inflammation, and fibrosis, Shp2 deletion in hepatocytes suppressed liver tumorigenesis driven by overexpression of oncogenic proteins MET and ΔN90-β-catenin (MET/CAT), or MET and PIK3CA^{H1047R} (MET/PIK). Shp2 loss inhibited proliferative signaling from MET, Wnt/β-catenin, Erk and PI3K/Akt pathways, but induced cell senescence following exogenous expression of the oncogenes. These results clearly distinguish a requirement for Shp2 in mediating and amplifying the oncogenic signals of these oncoproteins from a tumor-promoting hepatic microenvironment resulting from Shp2 deficiency. Based on these data, we propose a new molecular targeted therapy by inhibiting Shp2 for HCCs driven by oncogenic signals emanating from RTKs and other upstream molecules. However, to achieve optimal and lasting therapeutic effect, it is necessary to suppress the tumor-enhancing environmental factors produced secondary to Shp2 inhibition. This simultaneous targeting approach may be developed into a widely used clinical recipe, as long as the cell-intrinsic drivers and the stromal factors are identified for a given liver cancer patient in the precision medicine era.

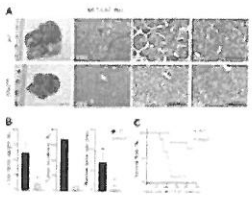

Fig. 1. Shp2 deletion suppresses MET/CAT-induced hepatocellular cancer.

1. A. Macroscopic images and H&E staining of *WT* and *Shp2$^{hep-/-}$* mouse livers at week-8 post-hydrodynamic injection of *hMET* and Dδ-*Catenin* constructs.
2. B. Liver versus body weight ratios, tumor incidences and maximal tumor sizes (n=8) were measured for *WT* and *Shp2$^{hep-/-}$* mice at the time of sacrifice.
3. C. Survival rates were determined for *WT* and *Shp2$^{hep-/-}$* mice after MET/CAT transfection (n=8-10).

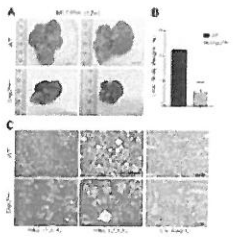

Fig. 2. Shp2 ablation inhibits MET/PIK3CA-induced liver tumorigenesis.

1. A. Representative macroscopic images of *WT* and *Shp2$^{hep-/-}$* mouse livers at week-12 post-hydrodynamic injection of *hMET* and *PIK3CA* (MET/PIK) constructs.
2. B. Liver versus body weight ratios of MET/PIK-transfected *WT* and *Shp2$^{hep-/-}$* mice at the time (12 weeks) of sacrifice.
3. C. H&E and Oil-Red-O staining of MET/PIK-transfected livers at week-12 post-injection.

Figure 3. Shp2 deletion disturbs multiple signaling events upon MET/CAT or MET/PIK transfection

A. Ingenuity pathway analysis (IPA) of top positively regulated pathways in untreated Shp2$^{hep-/-}$ compared to WT livers .

B-C. Ingenuity pathway analysis of differentially expressed genes in MET/PIK-transfected WT or Shp2$^{hep-/-}$ livers at day 3 compared to WT or Shp2$^{hep-/-}$ untreated liver(B), MET/CAT-transfected WT or Shp2$^{hep-/-}$ livers at day 3 compared to WT or Shp2$^{hep-/-}$ untreated liver (C).