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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 PIK3CAH1047R (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.