

Mixed HCC-ICC Liver Cancer Derives From Hepatic Progenitor Cells- A Lineage Tracing Investigation in Mouse Liver Inflammation Model.

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1 INTRODUCTION

Primary liver cancer is the second leading cause of cancer-related death worldwide. Primary liver cancer includes: Hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC) and a mixed HCC-ICC tumor. Preceding the development of primary liver cancer, there is usually a prolonged period of chronic inflammation that leads to cirrhosis. It has been proposed that hepatic progenitor cells (HPCs) could contribute to hepatocarcinogenesis. However, this was not proven. These cells proliferate in response to injury and chronic inflammation in the liver. Although stem cells residing in highly proliferative tissues, such as skin, and are essential for sustaining normal tissue homeostasis, their contribution in quiescent tissues, such as liver, is still a matter of debate.

2 AIM

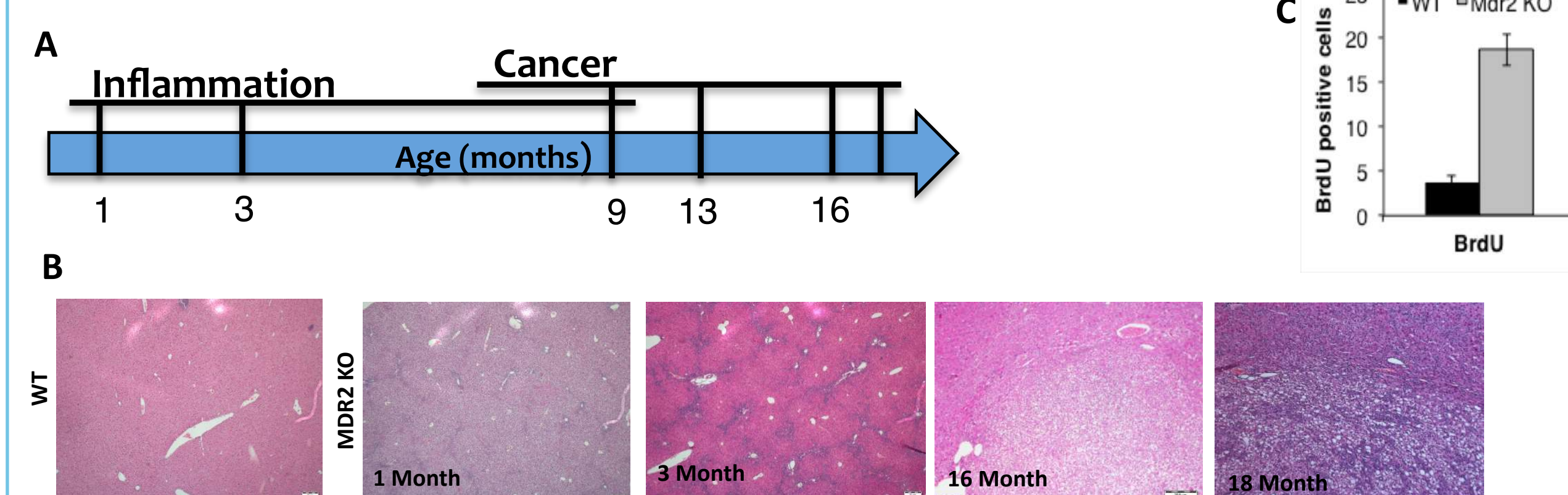
- To determine the role of hepatic progenitor cells in liver carcinogenesis.
- To unravel the mechanism of hepatic progenitor cells transformation that leads to generation of the mixed HCC-ICC liver tumors.

3 METHOD

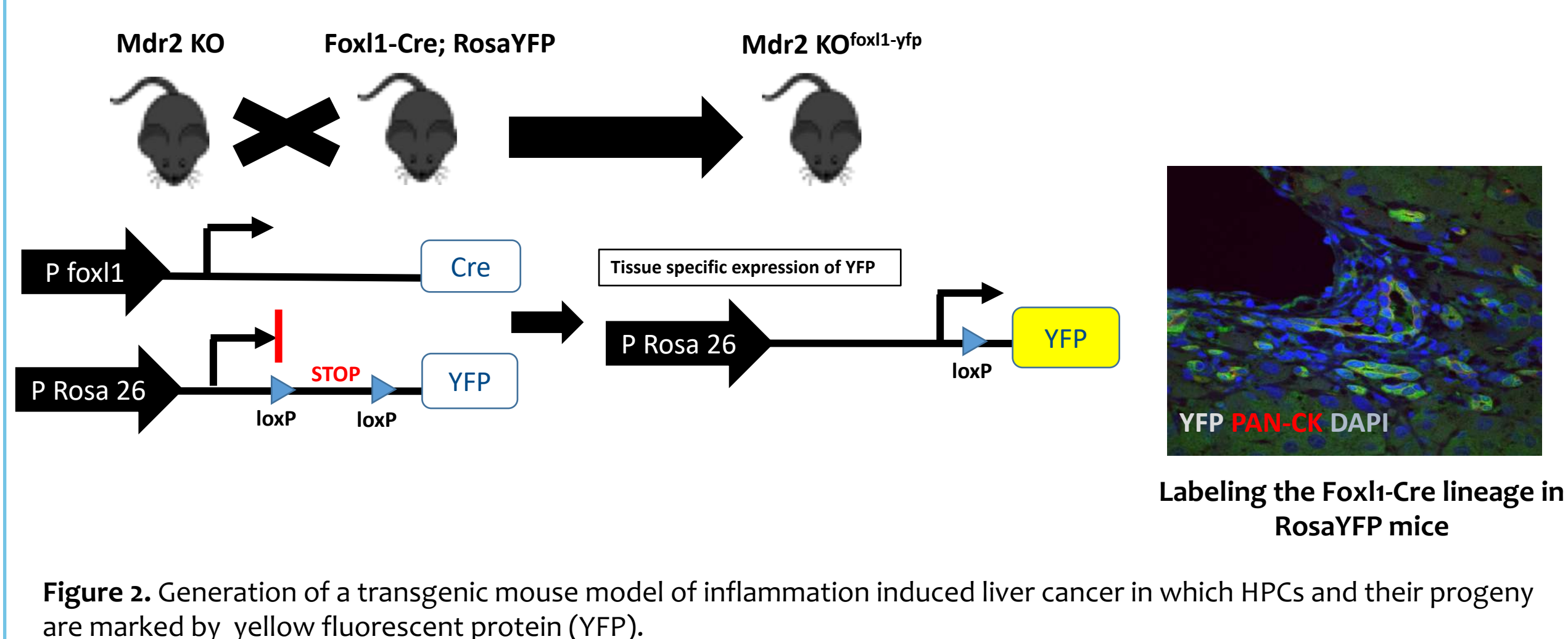
A mouse model for tracing of progenitor cells: a transgenic mouse strain based on the MDR2 KO background that harbors a YFP reporter gene driven by the liver progenitor-specific Foxl1 promoter. To ablate the HPCs we generated transgenic Mdr2 KO mice expressing the diphtheria toxin receptor under the Foxl1 promoter. Immunohistochemistry (IHC) and Immunofluorescence (IF): Staining was performed on liver sections from transgenic Mdr2 KO Foxl1-Cre;Rosa-YFP mice at 16 and 18 month old.

4 RESULTS

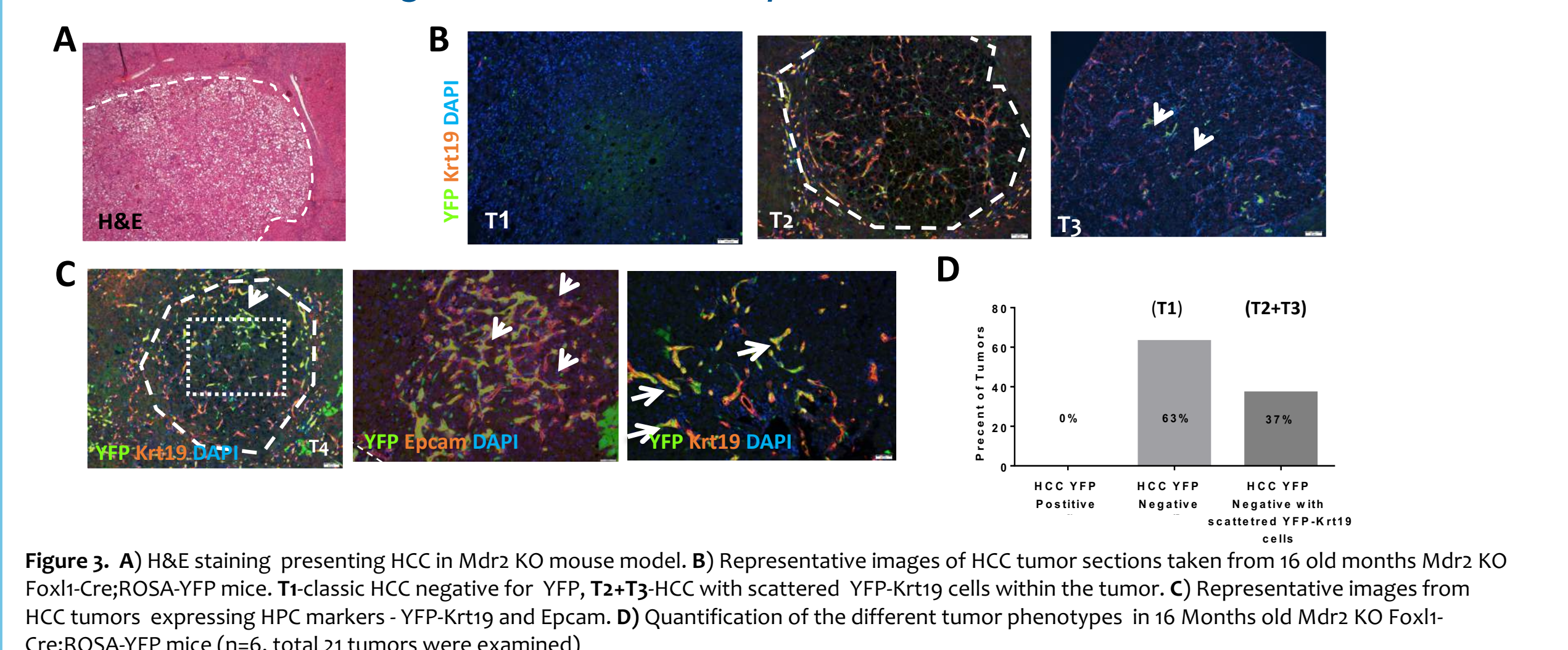
1. The Mdr2 KO Model: inflammation induced liver cancer



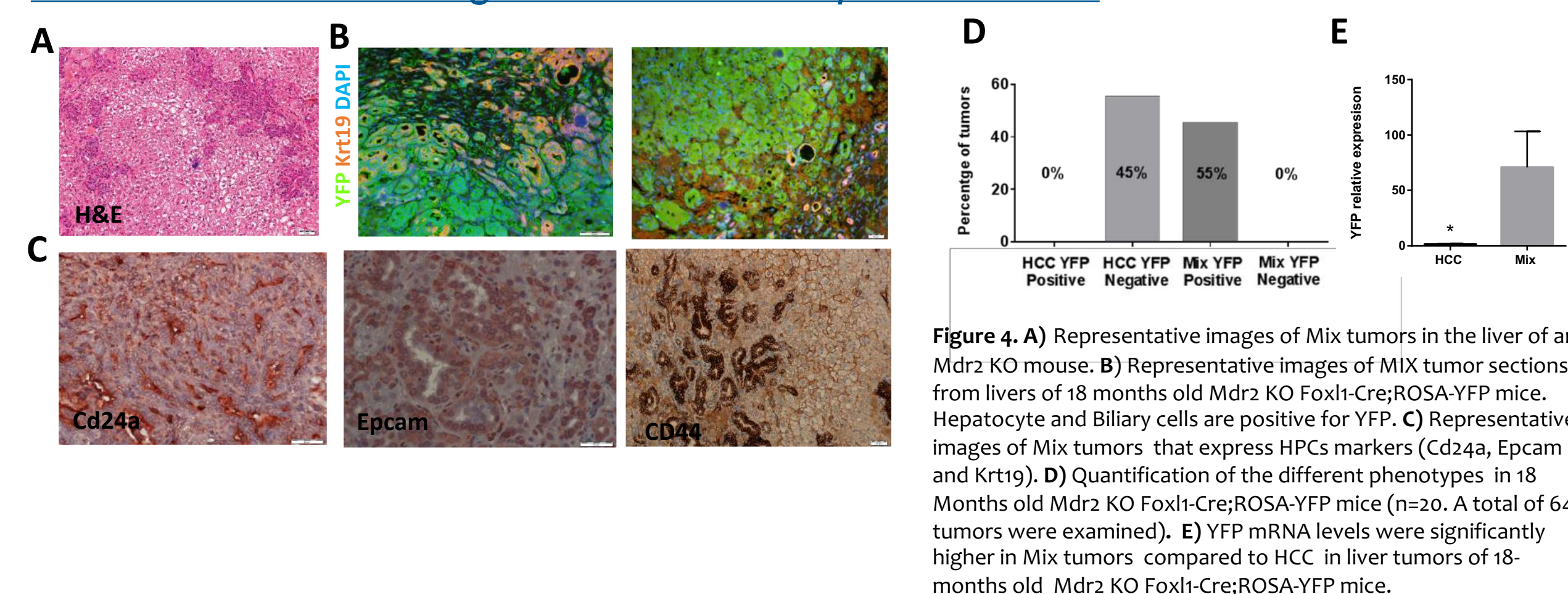
2. Lineage tracing of HPCs (Hepatic Progenitor Cells) in Mdr2 KO mice



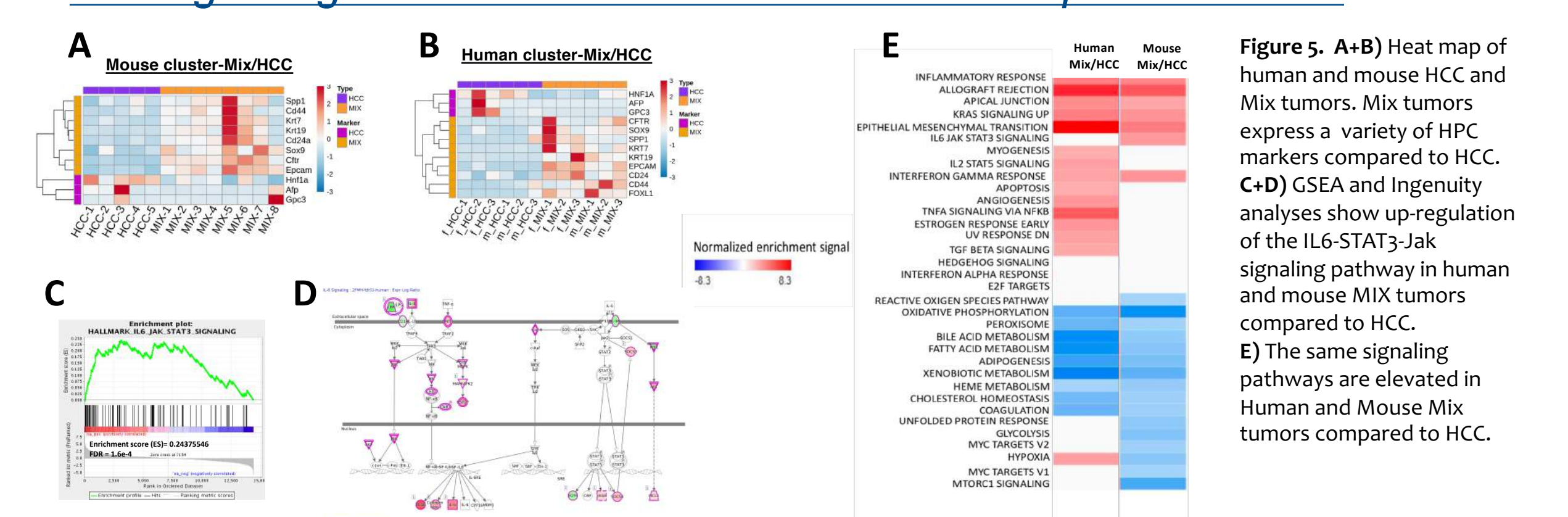
3. HCC do not originate from Foxl1 positive cells



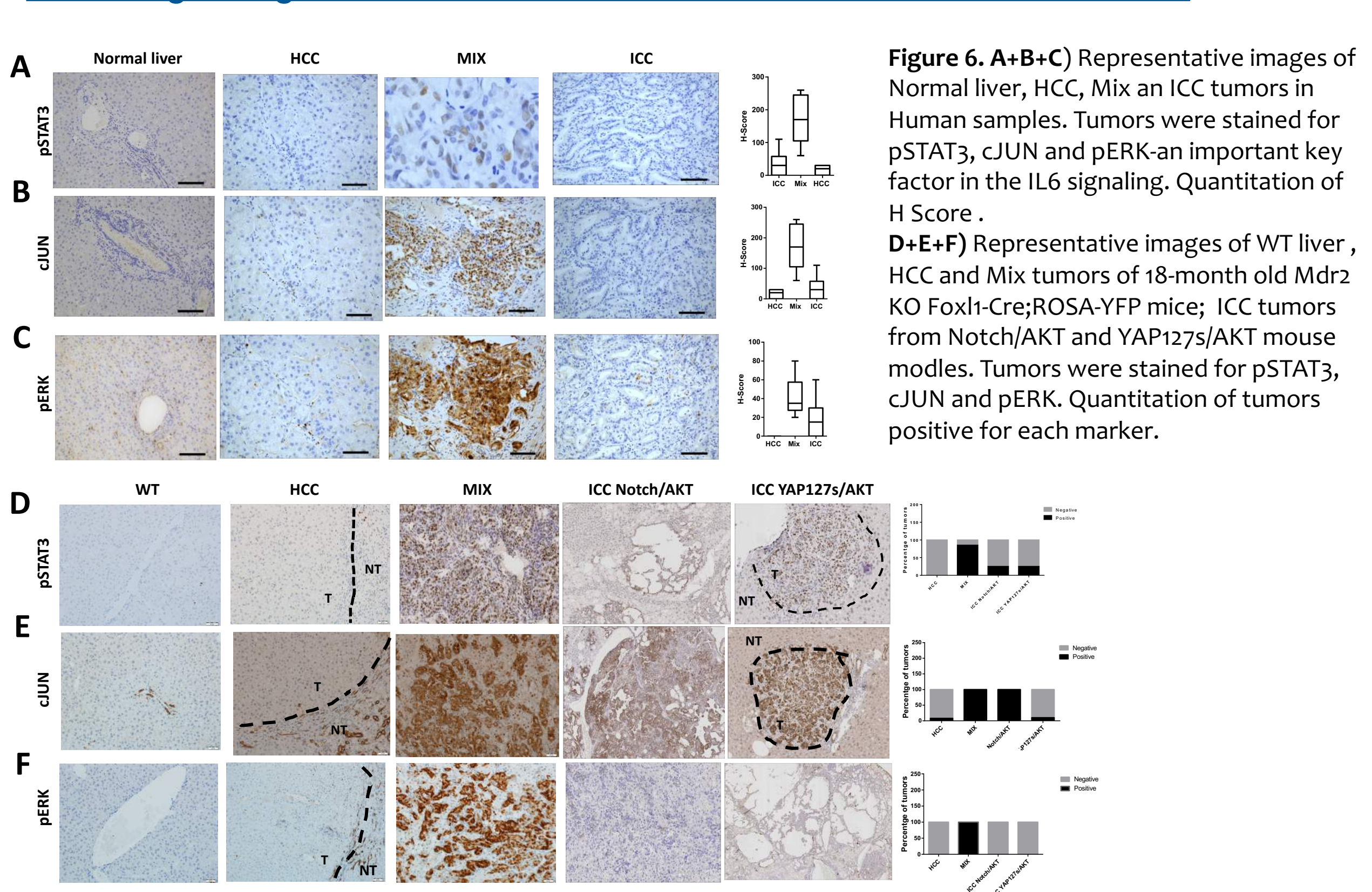
4. Mix liver tumors originate from Foxl1 positive cells



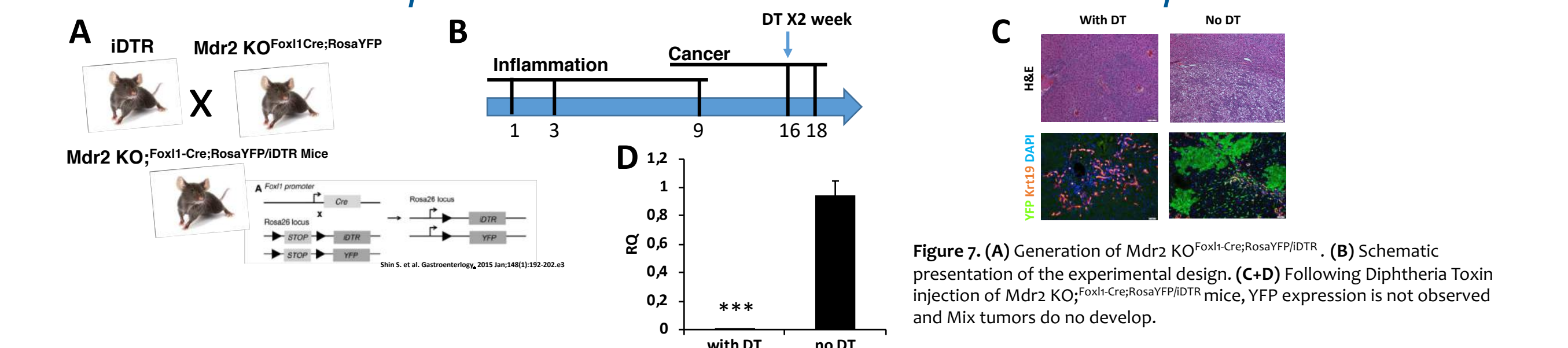
5. IL6 signaling is enriched in Mix liver tumors compared to HCC



6. IL6 signaling is enriched both in human and mouse Mix tumors



7. Ablation of Foxl1 positive cells inhibits Mix tumors development



5 CONCLUSIONS

Mdr2 KO mice develop liver tumors on the background of chronic portal inflammation similar to human liver tumors that are induced by chronic inflammatory processes. This model allows us to study the mechanisms responsible for liver tumor development.

Importantly, we detect a small scattered population of HPCs within the Mdr2 KO mice HCCs. These HPC cells express progenitor markers such as Epcam and Cd24a in both, mouse and human liver tumors.

Taken together, our results suggest that Mix tumors originate from HPCs in the mice model of inflammation-induced liver cancer, and that the IL6 signalling pathway is an important driver of this process.

6 ACKNOWLEDGEMENTS

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