Mixed Signals: The Liver's Perspective

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Liver cancer is one of the main causes of cancer-related deaths in men and women around the world, with its high mortality rate attributed to its advanced stage at presentation and the lack of effective medical therapies. Most cases (75–80%) are classified as hepatocellular carcinomas (HCC), which typically develops secondary to a viral hepatitis B or C infection or cirrhosis. Among non-HCC liver cancers, cancer of the bile duct (cholangiocarcinoma; CC) is the most common type (10%). Increased incidence of CC over the last 30 years, along with identification of rare mixed HCC-CC tumors, have highlighted a knowledge gap regarding the molecular mechanisms behind the formation of liver tumors. More information is therefore needed to improve the treatments for these cancers. Drs. Shelli Morris and William Grady in the Clinical Research Division addressed this issue in a recent publication in *Oncogene*, specifically looking at the interplay between phosphatase and tensin homolog (Pten), a protein that inhibits signaling through the PI3K pathway, and transforming growth factor β (TGF-β).

The PI3K/Pten pathway has been shown to regulate the internal conditions in many organs and to affect tumor formation in various tissues in mouse models, for instance controlling normal liver development and differentiation of liver cells such as hepatocytes and cholangiocytes. In humans, the expression of the *PTEN* gene, which encodes the protein PTEN, is suppressed in almost half of all liver cancers, and about 4–5% of all liver cancers have mutant *PTEN*. Another key player in the liver is TGF-β, which together with its cell signaling family members affects the formation of liver cancer in a complex and sometimes contradictory manner; it appears to be able to either suppress or promote liver tumors, depending on the tissue microenvironment and parallel concurrent gene mutations.

Together with colleagues at University of Washington and the National Cancer Center in Goyang, Republic of Korea, the Fred Hutch investigators developed a new mouse liver cancer model and carried out a series of studies to analyze how HCCs and CCs that are established through *Pten* inactivation are affected by TGF-β signaling. They found that when TGF-β receptor 2 (*Tgfbr2*) was inactivated in mice with simultaneous liver-specific Pten loss, the overall incidence of tumors increased to 86% (25/29), as compared to 67% (20/30) of mice with *Pten* deletion alone. In addition to the increased tumor incidence, they observed a dramatic shift in the distribution of tumor

types for the double-inactivated livers; more specifically, the number of CCs was significantly greater. The latter finding spurred the researchers to look more closely at the expression of a subset of markers for liver progenitor/stem cells, i.e. cells that can develop into specialized cell types and divide to produce more stem cells. They discovered that the markers *c-Kit* and *CD133* were notably increased in mice with inactivated TGF-β signaling. In the double knock-out mice the same was also true for the markers Scf and EpCam. This suggests that the histologic shift in tumor types was influenced by the deregulated signaling pathways, which in turn influenced the destiny of the cancer stem cells.

"Our results highlight the role that alterations in factors that regulate stem cell fate has on the formation of hepatocellular carcinoma and of cholangiocarcinoma," said Dr. Morris. "Furthermore, this work highlights the cooperation of multiple signaling pathways in controlling the specification of the ultimate tumor type that develops."

Besides increasing knowledge about the signaling pathways that affect the formation of various forms of liver cancer, the developed mouse model provides insights into tumor formation resulting from chronic inflammation in the liver. Drs. Morris, Grady and colleagues concluded that *Pten* inactivation likely contributed to the development of inflammatory fatty changes in the liver that may have affected the development of HCC, CC and other tumors.

The research team will continue to investigate the influence of cell signaling proteins and growth factors on tumor formation, hopefully leading to more effective targeted therapies. Dr. Morris concludes: "Understanding how different signaling pathways control cell specification may help us target cancers of a certain lineage more specifically. Our results also suggest that TGF-β signaling and PI3K signaling alterations may play a role in the etiology of hepatocellular carcinoma and cholangiocarcinoma, which may lead to novel liver cancer prevention strategies."

Morris SM, Carter KT, Baek JY, Koszarek A, Yeh MM, Knoblaugh SE, Grady WM. 2014. TGF-beta signaling alters the pattern of liver tumorigenesis induced by Pten inactivation. *Oncogene*. doi: 10.1038/onc.2014.258. [Epub ahead of print]

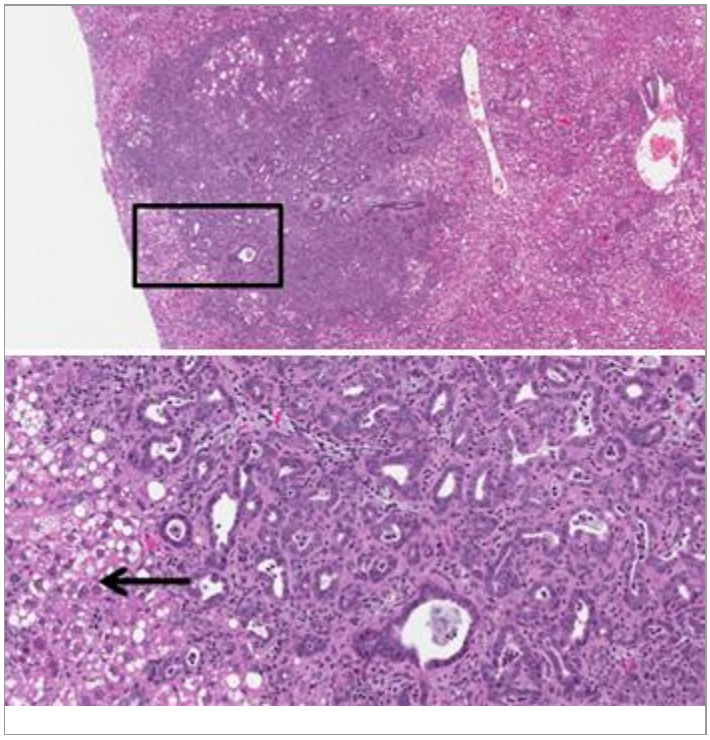

Image provided by Dr. Shelli Morris.

A representative liver section from a Pten;Tgfbr2 double-knockout specimen exhibiting focal cholangiocarcinoma with invasion into the neighboring hepatic parenchyma (arrow). The upper panel shows a low power (5×) view; the lower panel shows a high power (20×) view of the boxed area.