TGF-Beta Signaling Contributes To Liver Tumorigenesis in the Context of P53 Inactivation

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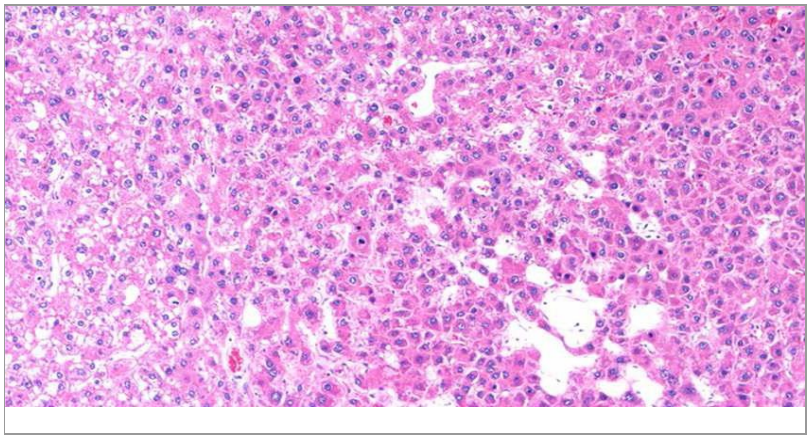
Hepatocellular carcinoma (HCC) is the most common type of liver cancer, and among the deadliest forms of all cancer types with a five-year survival rate of less than 5%. While currently uncommon in the United States, its incidence is rapidly increasing because of hepatitis C and alcohol- and obesity-related liver disease. In other parts of the world, including Sub-Saharan Africa and Southeast Asia where hepatitis infections are highly prevalent, HCC is one of the most prevalent cancers. A better understanding of the disease progression carries the promise to develop better screening methods for HCC or improved treatment strategies. Several studies have highlighted that p53 inactivation and inhibition of transforming growth factor-beta (TGF-beta) signaling are among the most common molecular disruptions in HCC. As a critical regulator of the cell cycle and apoptosis, p53 is frequently targeted for inactivation during liver tumorigenesis, through a variety of mechanisms. TGF-beta is a cytokine that controls a variety of processes in healthy cells including proliferation and differentiation. However, in several cancers including HCC, studies have shown that the cellular context can direct TGF-beta's function to be either tumor suppressive or oncogenic. In light of this, studying the role of TGF-beta in the presence of other gene mutations is relevant to understanding how TGF-beta affects HCC.

To study the role of TGF-beta signaling in the context of p53 inactivation within liver cells, postdoctoral fellow Dr. Shelli Morris and corresponding author Dr. William Grady together with colleagues in the Clinical Research Division have generated a new mouse model system to study how inactivation of p53 and TGF-beta signaling cooperate *in vivo* during HCC development. Drs. Morris and Grady used a conditional deletion mouse model to eliminate expression of *Tp53* and the TGF-beta receptor, type II (*Tgfbr2*) specifically in liver cells. While inactivation of *Tgfbr2* alone did not induce liver tumors, deletion of *Tp53* resulted in liver tumors in approximately 40% of mice within one year. However, coordinated loss of both *Tp53* and *Tgfbr2* reduced the frequency of tumors to 17% of mice, delayed tumor development, and impaired metastasis. Thus loss of p53 in the setting of intact TGF-beta signaling results in earlier tumor development, metastasis and lower survival rates relative to mice lacking both *Tp53* and *Tgfbr2*. To understand how TGF-beta promotes tumorigenesis in the setting of p53 inactivation, the authors examined how TGF-beta affected

downstream signaling and gene expression. Liver tumors from p53-deficient mice show increased levels of the clinical biomarker for HCC, alpha-fetoprotein, as well as greater TGF-beta 1 levels (the ligand for the TGF-beta receptor), relative to tumors from mice deficient in both *Tp53* and *Tgfbr2*. TGF-beta dependent and independent signaling pathways that contribute to gene expression, cell activation and growth are also more highly activated in mice lacking only p53. Together these data demonstrate that TGF-beta signaling and its downstream effects promote the formation of liver tumors and metastasis in the setting of p53 inactivation.

Morris SM, Baek JY, Koszarek A, Kanngurn S, Knoblaugh SE, Grady WM. 2011. TGF-beta signaling promotes hepatocarcinogenesis induced by p53 loss. *Hepatology*. Epub ahead of print, doi:10.1002/hep.24653.



Dr. William Grady

H&E stained section of a liver tumor from a mouse deficient for p53 and TGF-beta receptor (100x magnification).