

Liver Cancer Research at UIC

Liver cancer is one of the most rapidly increasing causes of malignancy in the United States. The rise in liver cancer is largely related to hepatitis C infection. The epidemic of diabetes and obesity is an important contributing cause. A number of different pathways have been implicated in the development of liver cancer in basic research studies using cell lines and animal models. The Section of Hepatology at UIC has focused on evaluating whether various pathways play a role in the development of liver cancer in humans.

Some of our most important clinical and translational research has been related to the AKT-mTOR pathway, which is an insulin signaling pathway that is activated by certain hepatitis C proteins. This pathway provides a potential mechanistic link between hepatitis C, diabetes, and the development of liver cancer. We found evidence in human liver cancer specimens that the AKT-mTOR pathway is activated in precancerous liver lesions and that activation increases with progression to liver cancer (1). We have also identified a link between diabetes, oxidative stress—which causes tissue injury, and progression of liver damage in hepatitis C (2). We are continuing our work in this area, studying various aspects of the AKT-mTOR pathway. In another study, we found that staining liver tissue for AMACR, which plays a role in oxidation of fatty acids can distinguish pre-malignant and malignant liver cells (3).

Liver transplantation can be curative for small liver cancers that have not spread outside the liver. We have worked to identify factors involved in the development of liver cancer that might predict which tumors will recur after liver transplantation. We found evidence that expression of an abnormal form of the tumor suppressor gene p53 and increased activity of Ki67, a marker for cell proliferation, are associated with recurrence after liver transplantation (4). Vasculogenic mimicry, or fluid conducting channels implicated in tumor spread, was also present in more aggressive tumors (5). Ultimately, we would like to be able to achieve a comprehensive profile of liver tumors in potential transplant candidates to improve patient management.

The Section of Hepatology is now working closely with faculty in the Departments of Biochemistry and Molecular Genetics, Microbiology and Immunology, and Pathology to clarify the underlying molecular events that lead to the development of liver cancer. This collaboration is supported by the Guild. Dr. Robert H. Costa, a world renowned liver researcher who worked in the Department of Biochemistry and Molecular Genetics at UIC identified a transcription factor named FoxM1 that plays a critical role in activating genes that promote the development of liver cancer. He showed that disruption of the FoxM1 gene prevented the development of liver cancer in mice treated with carcinogens that promote liver tumor formation. After his untimely death in 2006, three faculty in the department, Drs. Angela Tyner, Pradip Raychaudhuri, and Lester Lau have continued his work to understand the mechanisms by which FoxM1 promotes liver tumor formation

and progression. In addition, the laboratories of Dr. Raychaudhuri and Dr. Andrei Gartel in the Department of Medicine are focusing on developing drugs that target FoxM1 in liver cancer.

In collaboration with the Section of Hepatology, the basic research faculty are investigating the potential of new biomarkers for determining prognosis and/or predicting responses of liver cancer to therapy. These include the proteins CCN1, CUL4, AKT and PTK6. Dr. Lau identified CCN1, which is a protein expressed in human liver tumors that appears to contribute to cirrhosis, a risk factor for liver cancer. Dr. Raychaudhuri is doing research on Cullin 4 (CUL4) a protein that targets the destruction of growth inhibitors that are normally expressed in the liver. The growth inhibitors that are destroyed by CUL4 are important factors that prevent abnormal growth and development of liver tumors. Dr. Nissim Hay is one of the world's leading experts on AKT, a protein activated in many types of cancer, including liver cancer. He has been altering AKT expression in mouse liver stem cells to determine how AKT contributes to liver cancer and if it might be a good specific target for drug therapies. Dr. Tyner's group identified a breast cancer gene encoding PTK6, a tyrosine kinase that promotes breast tumor growth. Although PTK6 is not expressed in the normal liver, it appears to be induced in liver cells infected with the hepatitis C virus. Expression of CCN1, CUL4, AKT and PTK6 are currently being examined in normal and malignant human liver biopsy samples. Activities and contributions of these proteins to liver cancer are also being investigated.

Drs. Susan Uprichard and Alan MacLachlan are investigating the impact that hepatitis virus infection has on liver cells. They have developed unique tissue culture systems and animal models for studying the course of viral infection in liver cells. They are collaborating with the investigators listed above to determine if viral infection has an impact on FoxM1, CCN1, CUL4, AKT and PTK6 expression and/or activities.

With the support of the Guild, researchers at UIC are focusing on gaining a better understanding of the molecular and cellular mechanisms that lead to the development of liver cancer. The work is critical for understanding the processes that cause liver cancer and the studies are necessary for the development of successful preventive and therapeutic modalities. In addition, we are currently developing chemoprevention studies.

References

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