CANCER PREVENTION & RESEARCH
INSTITUTE OF TEXAS

Award ID:
RP120138

Project Title:
Nuclear receptors and Hippo signaling in liver cancer

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
Baylor College of Medicine

Lay Summary:

The incidence of hepatocellular carcinoma (HCC) in the US is increasing rapidly and has more than tripled since the mid 1980s. In contrast to the major gains made against many other cancers, progress against HCC has been poor and therapeutic options are limited. Its major risk factors are more common in minority and disadvantaged populations, and Texas has the second highest rate of death from HCC in the US. We will study exciting new mechanisms for liver carcinogenesis and potential therapeutic targets that we have discovered in a novel mouse model. The nuclear hormone receptors FXR and SHP function coordinately to control production of potentially toxic bile acids in the liver. This important liver protective mechanism is lost in mutant mice lacking both receptors (FSKO). Elevated bile acid levels have been linked to increased liver cancer in both mice and man, and the FSKO mice spontaneously get multiple liver tumors. We have discovered 2 very different mechanisms that drive their tumor formation. The first is based on activation of another nuclear receptor, CAR, which we have shown promotes liver tumorigenesis. The second is based on inactivation of a negative growth regulatory cascade called the Hippo pathway. Repressing this pathway increases the activity of a proliferation inducer called Yap. Both CAR and Yap are fully activated in the FSKO mice before they get tumors, and both responses are due to elevated bile acid levels. The unexpected activation of YAP by bile acids is a major new discovery, and we will study its specific molecular mechanisms. We will also critically test the impact of inactivating CAR or Yap in bile acid induced tumorigenesis. This project will continue to produce exciting new insights into hepatocellular carcinogenesis. Particularly because the nuclear receptors are natural targets for therapeutic intervention, it also has the potential for dramatic clinical impact by providing critically needed new targets for HCC treatment.