Award ID:
DP150077

Project Title:
Targeting the SWI/SNF chromatin-remodeling complex in liver cirrhosis and hepatocellular carcinoma

Award Mechanism:
Bridging the Gap: Early Translational Research Awards

Principal Investigator:
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Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

Hepatocellular carcinoma (HCC) is a significant cause of cancer-related death worldwide and Texas has the second highest HCC incidence rate in the US. Cirrhosis is the strongest risk factor for HCC, and without cirrhosis, there would be few cases of HCC. Thus, the challenge is twofold: 1) to develop effective therapies for cirrhosis, and 2), to develop effective HCC drugs that do not harm the cirrhotic liver. Recently, we identified a pathway that when suppressed, results in better liver regeneration and can potentially inhibit HCC. Mice defective for a gene called Arid1a, part of the SWI/SNF gene family that normally regulates the physical scaffold of the genome, showed increased liver cell growth, reduced damage, and improved function after surgical resection of the liver and multiple toxic injuries that mimic chronic liver diseases. Chronically injured KO mice were also highly resistant to liver cancer formation, suggesting that improving regeneration and blocking injury could prevent HCC in cirrhotic patients. Recent reports suggest that paradoxically, SWI/SNF mutant cancers (up to 20% of all cancers) are particularly dependent on remaining SWI/SNF components. For example, cancers with Arid1a mutations are inhibited by suppressing its partner, Arid1b. Thus, there is dual rationale for blocking SWI/SNF: 1) To promote liver health in the context of chronic injury, and 2) To kill SWI/SNF mutant cancers. Since there is no obvious way to make a drug against Arid1a, we examined other SWI/SNF members called Brg1 and Brm, enzymatic components of the complex that are potentially amendable to drug inhibition. Our initial in vivo tests of PFI-3, a potent inhibitor of Brg1/Brm, show that this drug also promotes regeneration after liver injury. We will use mouse models to validate the SWI/SNF pathway as a target in chronic liver disease and HCC. Using PFI-3 as a starting point, we will develop compounds for the simultaneous treatment of cirrhosis and cancer in the liver.