Characterization of an inducible alcoholic liver fibrosis model for hepatocellular carcinoma investigation in a transgenic porcine platform
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Introduction

• Hepatocellular Carcinoma (HCC) is a deadly tumor that spans more than 780,000 new diagnoses and causes 750,000 annual deaths worldwide.
• Alcoholic liver disease represents a common progressive chronic liver ailment that incites liver cirrhosis—a precancerous state of liver scarring—that increases the risk for HCC development.
• The health status of the liver affects HCC tumor biology and treatment responses; therefore, a large animal model capable of exhibiting both HCC and alcohol induced liver cirrhosis would be a valuable resource for preclinical research investigating HCC in its native comorbid cirrhotic microenvironment.
• Pigs represent ideal human disease models due to their similar size, anatomy, metabolism, genetics, and epigenetics compared to humans.
• This study utilized the innovative Oncopig Cancer Model (OCM)—a transgenic swine model that recapitulates human cancer through development of site and cell specific tumors via induced expression of heterozygous KRASG12D and TP53R167H transgenes—to develop alcohol induced fibrosis in a porcine model capable of developing HCC tumors.

Materials and Methods

• Liver injury was induced in Oncopigs (Cohort 1 n=5; Cohort 2 n=5) via transcatheater infusion of absolute ethanol and ethiodized oil (1:3 v/v dosed at 0.75 mL/kg) into the hepatic arterial circulation.

Results

• This study successfully validated a protocol to develop a pre-cirrhotic METAVIR F2-F3 model of alcoholic liver disease within 8 weeks using transarterial ethanol-ethiodized oil infusion.
• Induction of alcoholic liver injury resulted in METAVIR stage F2-F4 fibrosis, stage A2-A3 inflammation, and elevated fibrosis levels compared to age matched controls after 8 weeks.
• METAVIR stage F1-F3 fibrosis was observed as early as 2 weeks post induction.
• As observed clinically for patients presenting with pre-cirrhotic alcohol induced liver damage, a lack of persistent alcohol exposure resulted in liver recovery based on temporal profiling up to 20 weeks post induction.
• No behavioral or biochemical abnormalities were observed during the monitoring period to suggest liver decompensation.
• These results support the OCM's capability to serve as a model for HCC in a cirrhotic liver background.
• In an effort to develop an irreversible METAVIR stage F4 porcine model of cirrhosis, further studies will closely mimic human alcoholic liver disease in two important ways: (1) prolonged and repetitive exposure of the liver parenchyma to alcohol, and (2) simultaneous administration of an immune antigen to catalyze immune-mediated biochemical processes involved in cirrhosis.

Conclusions and Future Work

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