CELLULAR ORIGINS OF HEPATOCELLULAR CARCINOMA

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Introduction

Activation, proliferation and differentiation of oval cells are observed after severe hepatic injuries in which mature hepatocytes are incapable of proliferation. Under these conditions, oval cells can act as bipotential progenitors of the two distinct epithelial cells of the liver, the hepatocytes and the bile ductular cells. Although native to the liver, data exists supporting a bone marrow origin for the putative hepatic stem cell, the oval cell. In concurrence with theories endorsing a stem cell origin of cancer, oval cells are believed to contribute to the development of hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCC), although no direct evidence exists to support this concept. This proposal will test the hypothesis that the oval cell is the predominant cell of origin for the development of HCC. In order to test this principle, the extent of oval cell participation in the development of HCC will be investigated utilizing various rodent carcinogenesis models in conjunction with transplantation and the assessment of tumor burden via MRI and gross/histologic analysis.

Experimental Preliminary Studies and Results

Initially, normal B6 mice were scanned in order to develop a protocol for the imaging of a mouse liver that will allow for the cardiac/respiratory pulsation of the liver. The preliminary studies also determined the greatest level of detail within the liver obtainable with the 4.7T. Following accurate protocol development, the analysis of normal mice livers was assessed as controls. Subsequently, aged mice (greater then 2 years old) were analyzed to determine the effectiveness of Teslascan vs. gadolinium in spontaneously formed hepatic lesions. We found one animal with a gadolinium positive hepatic lesion, however, histological examination revealed no gross lesion, and a morphologic preneoplastic lesion. Also development of the experimental animals was problematic, in that the donor animals did not respond to DEN exposure as expected.

Conclusions

In light of the problems initiating tumors with the experimental model, we will be forgoing further MRI usage until the HCC induction model is more consistent.

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