The Role of Spy1 in the Development of Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is among the most aggressive and prevalent forms of primary liver cancer. With an increasing incidence in Canada and only a five-year survival rate of 19%, a more comprehensive understanding of this debilitating disease is imperative in order to consider future treatment options. A variety of lifestyle factors may underlie HCC, including chronic alcoholism, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). These factors are known to elicit liver injury, inflammatory immune responses, and oxidative damage thereby imparting a regenerative response in this visceral organ. This regeneration is manifested as either fibrosis, in order to maintain structural integrity of the organ, or through hepatocyte proliferation, in order to restore functional mass. Progression through the cell cycle by the normally quiescent hepatocytes is thought to contribute to the proliferative response. Spy1 is a novel, cyclin-like protein, which binds and activates CDKs at the G1-S and G2-M checkpoints, leading to cell cycle progression independent of cyclin-based regulation. A serendipitous discovery in the transgenic MMTV-Spy1 murine model demonstrates that Spy1 significantly increases the incidence of fatty liver disease and HCC. Combined with a methionine-choline deficient (MCD) diet in order to elicit liver injury, the MMTV-Spy1 murine livers response to these factors through inflammatory, proliferative and fibrotic responses is analyzed. Preliminary evidence demonstrates Spy1’s role in favouring hepatic regeneration through a proliferative response rather than a fibrotic one, demonstrating a potential mechanism in the development of HCC. Through primary cultures of THLE-2 and Hep G2 cell lines, similar assays are conducted in order to determine Spy1’s role in causing liver cancer. These results will shed light on Spy1’s role in HCC, potentially allowing for determination of a diagnostic markers and pathways of therapeutic importance.