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CO-REGULATION OF FIBROGENIC AND LIVER PROGENITOR CELL RESPONSES IN BOTH PRE- AND POST-LIVER TRANSPLANT RECURRENT CHRONIC HEPATITIS C INFECTION

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BACKGROUND: There is co-regulation of fibrogenic and liver progenitor cell (LPC) responses in a range of human chronic liver diseases including chronic hepatitis C virus (HCV) infection, which is the commonest indication for orthotopic liver transplantation (OLT) in western countries. Recurrent and accelerated hepatitis C infection in grafted livers is a frequent cause of graft loss. LPC numbers increase significantly with progression of fibrosis severity in pre-transplant chronic HCV disease, however it is not known whether LPCs proliferate following recurrent HCV infection post-OLT and contribute to accelerated fibrosis in this setting. The aim of this study was to determine whether LPCs are detected and associated with inflammation and fibrosis in recurrent HCV disease following OLT. **METHODS:** Liver biopsies were available from 16 pre-OLT and 16 post-OLT subjects with chronic HCV. De-identified specimens underwent blind evaluation following haematoxylin/eosin (histology) and Masson's trichrome staining (fibrosis) as well as pan cytokeratin (LPCs) and CD45 (inflammation) immunohistochemistry. Fibrosis was scored according to the Metavir system and digital whole slide scanning was conducted to evaluate numbers of positively stained cells. Results were expressed semi-quantitatively using a 0-4+ scoring system and confirmed by algorithm-based positive pixel count per area. Statistical analyses were conducted using SPSS version 17. **RESULTS:** In pre-OLT biopsies, the number of LPCs increased with advancing fibrosis



and inflammation. Seven of 16 pre-OLT subjects had severe F3 or F4 fibrosis and these had a median score of 4+ for numbers of CKpan+ LPCs. This was significantly higher ($p = 0.012$) than for subjects with only mild F0-F2 fibrosis, who showed a median score of only 2.5+ for LPC numbers. Increasing numbers of CD45+ cells were also associated with increasing LPC proliferation and fibrosis severity in pre-OLT livers. Similarly, in post-OLT subjects, increasing levels of inflammation and fibrosis were associated with increased numbers of LPCs. Five of 16 post-OLT subjects had severe F3 or F4 fibrosis and these had a median score of 3.5+ for CKpan+ LPCs. In contrast, post-OLT subjects with mild F0-F2 fibrosis had a significantly lower median score of 2.5+ for LPC proliferation ($p = 0.019$). **CONCLUSION:** Hepatic fibrosis occurring in chronic HCV disease either before or after OLT is associated with increasing numbers of LPCs suggesting co-regulation of the fibrogenic and LPC responses. Thus, targeting of the LPC compartment after OLT might be a novel treatment strategy to prevent accelerated fibrosis progression to cirrhosis and hepatocellular carcinoma.

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