THE ROLE OF MONOCYTE CHEMOTAXIS PROTEIN-1 AND THE DUCTULAR REACTION IN INITIATING FIBROGENESIS IN PEDIATRIC CHOLESTATIC LIVER DISEASE

Tamara N. Pereira1, Peter J. Lewindon2, Ross W. Shepherd1, Meagan J. Walsh1, Janina E. Tirnitz-Parker1, John K. Olynyk3, George Yeoh3, Grant A. Ramm1; 1Hepatic Fibrosis Group, Queensland Institute of Medical Research, Brisbane, QLD, Australia; 2Department of Gastroenterology, University of Queensland, Brisbane, QLD, Australia; 3School of Medicine and Pharmacology, University of Western Australia, Perth, WA, Australia

The ductular reaction is proposed to initiate liver fibrosis but the causal mechanisms are not known. Monocyte chemotaxis protein-1 (MCP-1) is expressed in both hepatocytes and cholangiocytes in pediatric cholestatic liver diseases and induces chemotaxis of hepatic stellate cells (1). This study aimed to characterise the ductular reaction in pediatric cholestasis and to assess its role in hepatic MCP-1 expression and thus in the development of hepatic fibrosis. Methods: Liver from patients with cystic fibrosis associated liver disease (CFLD) (n=65), biliary atresia (n=3) neonatal hepatitis (n=5) and control subjects (n=5) were immunohistochemically stained for cytokeratin-7 (CK-7) to assess the ductular reaction and for MCP-1. The results were correlated with the degree of hepatic fibrosis (Scheuer). Dual immunofluorescence was used to determine if CK-7 and MCP-1 co-localised to cells of the ductular reaction. Hepatic progenitor cell lines (BMOL and PIL-2) were treated with the bile acid taurocholic acid (TCA) and MCP-1 mRNA expression determined by real-time RT-PCR. Migration assays were performed using hepatic stellate cells and conditioned-media from the progenitor cells ±TCA. Migration inhibition assays were performed using an anti-MCP-1 antibody. Results: The ductular reaction was increased in pediatric cholestatic liver disease and consisted of expanded reactive bile ducts, hepatic progenitor cells and intermediate hepatocytes. This was most pronounced in patients with acute liver diseases such as biliary...
atresia (P=0.05) and neonatal hepatitis (P=0.04). In CFLD, where it was possible to stratify specimens according to the degree of fibrosis, the ductular reaction increased with increasing fibrosis (Spearman r=0.59, P<0.0001). Dual immunofluorescence confirmed that cells of the ductular reaction express both CK-7 and MCP-1. Progenitor cells treated with 150µM TCA showed increased MCP-1 mRNA expression. Significant chemotaxis of hepatic stellate cells was induced by conditioned-media from BMOL (1.7 fold, P=0.01) and PIL-2 (1.9 fold, P=0.0084) progenitor cells treated with TCA. This migration was inhibited by an anti-MCP-1 antibody. Conclusion: The ductular reaction correlates with increasing stage of hepatic fibrosis in pediatric cholestasis. MCP-1 is expressed by hepatic progenitor cells. In vitro, progenitor cells exposed to the bile acid TCA secrete MCP-1, which is chemoattractive to stellate cells. Thus, MCP-1 derived from progenitor cells of the ductular reaction may recruit stellate cells and initiate fibrosis in pediatric cholestatic liver diseases. (1) Ramm et al Hepatology 2009:49:533-544.

Disclosures:
John K. Olynyk - Grant/Research Support: Roche, Bayer
The following people have nothing to disclose: Tamara N. Pereira, Peter J. Lewindon, Ross W. Shepherd, Meagan J. Walsh, Janina E. Tirnitz-Parker, George Yeoh, Grant A. Ramm