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PROGRESS REPORT

Project / Program Title		The role of mucosal associated invariant T (MAIT) cell and gut microbiota in the pathogenesis of paediatric autoimmune liver disease (AILD)
Name		Dr Jeremy Rajanayagam
Award Received		2017 RACP NHMRC CRB Blackburn Scholarship
Report Date		1 July 2019
Chief Investigator / Supervisor		Professor Jim McCluskey, Dr Alexandra Corbett, Professor Winita Hardikar
Administering Institution		The University of Melbourne
Funding Period	Start Date:	1 July 2017
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PROJECT SUMMARY

Primary sclerosing cholangitis (PSC) is a rare liver disorder characterised by an “onion skin” pattern of scarring (peri-ductal fibrosis) of the small, medium and/or large bile ducts leading to multifocal bile duct narrowing (stricturing) and progressive biliary cirrhosis. Comorbid presentation of Ulcerative Colitis (UC), a chronic inflammatory condition affecting the colon, is a hallmark of PSC, along with a high risk for developing bile duct cancer (cholangiocarcinoma) and colorectal cancer. To date, no effective medical treatment is available for patients with PSC. Consequently, patients with PSC continue to encounter early clinical end-points including, liver transplantation, cancer and death. The development of effective primary therapy in PSC is therefore a high priority. Bile duct obstruction is a major driving force that causes chronic cholestasis and eventually progressive liver fibrosis in PSC. By exploring the pathogenesis of inflammation and fibrosis in a bile duct ligation model, we hope to further elucidate the host immune cell/s critical in this pathway.

Mucosal-associated invariant T (MAIT) cells (CD3+, Vα7.2+, CD161++) are a recently identified T-cell subset with features of innate and adaptive immunity. MAIT cells have anti-bacterial functions, but may also drive immune pathology in several conditions. Their potential involvement in PSC is proposed based on key observations: (1) MAIT cells are abundant in human liver and intestinal mucosa; (2) they recognise conserved microbial metabolites produced by many bacteria and fungi, including commensal gut flora, (3) accumulation of MAIT cells has been shown within the liver in patients with chronic liver disease (4) hepatic MAIT cell frequencies have been correlated with stages of fibrosis in chronic liver disease. The role of MAIT cells in the pathogenesis of biliary inflammation and fibrosis however, has not been investigated.

PROJECT AIMS / OBJECTIVES

The aims of this project are to investigate the in vivo role of MAIT cells in a mouse model of progressive biliary disease; to explore the links between liver inflammation and fibrosis; and the activation signals that drive MAIT cell responses in the liver.

Aim 1: To determine whether MAIT cells abrogate or intensify inflammation/and or fibrosis in the liver in a bile-duct ligation model.

- C57BL/6 and MR1-/- (lack MAIT cells) mice will be compared using blood markers for inflammation and using liver histopathology.

Aim 2: To investigate alterations in MAIT cell phenotype and function during stages of progressive liver fibrosis

- MAIT cells will be characterised by flow cytometry in the liver after bile duct ligation.

This project also aims to investigate the in vivo role of MAIT cells in known models of colitis and hepatic translocation; to explore the link between colitis and liver inflammation; and the activation signals that drive MAIT cell responses in the liver.

Aim 3: To investigate the role of MAIT cells in a mouse model for colitis (dextran sulfate sodium [DSS] model)

- MAIT cells will be characterised by flow cytometry in both the bowel and liver after induction of colitis.

SIGNIFICANCE AND OUTCOMES

With an understanding of the role of hepatic unconventional T-cells (e.g. MAIT cells) in progressive biliary fibrosis we hope to identify specific immune targets for future therapeutic trials. In addition, by exploring the etiopathogenesis of Ulcerative colitis and PSC (possibly related to the entero-hepatic translocation of bacterial metabolites producing effector T cell (MAIT) response leading to biliary inflammation and cholangiocyte senescence) we also hope to identify methods to prevent the onset of PSC.

The optimised models developed during this project will additionally be useful for the analysis of other cell types and in combination with other laboratory models (e.g. bacterial infection and vaccination models)

PUBLICATIONS / PRESENTATIONS

None to date