OPEN

Clinical & Translational Immunology (2017) 6, e164; doi:10.1038/cti.2017.53
Australasian Society for Immunology Inc.
www.nature.com/cti

EDITORIAL

The immune system of the liver: 50 years of strangeness

Clinical & Translational Immunology (2017) **6,** e164; doi:10.1038/cti.2017.53; published online 8 December 2017

It is half a century since Roy Calne, a transplant surgeon, published his work revealing the distinct nature of immune responses in the liver.[1] These results from studies of 'Strange English Pigs', showing unexpected tolerance, were pivotal in the field.[2] Fifty years on, liver transplantation has moved on enormously but the liver itself remains a very difficult organ to study. The lessons learned from these landmark studies have been very influential in other settings (both in health and disease) and the 'tolerogenic environment' of the liver is thought to have a role in infection, inflammation and cancer. In this special issue, a range of authors discuss the balance that is struck in the liver between tolerance and reactivity, and importantly discern the critical cell types and mediators involved in this complex biology. The anatomical structure of the liver vasculature allows for constant screening of the blood for systemic and gut-based pathogens. This vasculature consists of a slow-flowing capillary network, the sinusoids, which contain unique subsets of immune and endothelial cells, critical for the liver's and ultimately the host's defence. Thus, understanding liver immunology means exploring and experimentally dissecting this unique microenvironment. This issue covers the key areas of clinical liver disease and condenses the emerging evidence for the roles that liver-resident cells have in liver pathology and protection.

The selected reviews emphasize the role of the diverse immune cell populations present in the liver, with particular focus on mucosal-associated invariant T (MAIT) cells, monocyte-derived macrophages and tissue-resident T cells that act in concert with structural cells of the liver such as liver sinusoidal cells and Kupffer cells. These cell populations, poised for action, take centre stage in regulating the fine balance between immediate responses against invading pathogens and prevention of systemic inflammation and auto-immunity.

In 2010, two seminal papers showed that MR1-restricted MAIT cells have a potential role in the protective immunity against various bacteria and yeasts.[3,4] MAIT cells were found to be highly enriched in the human liver and one of the most dominant lymphocyte types found in both health and disease. Kurioka *et al.*[5] summarise the evidence for the function of this abundant and distinctive population of hepatic T cells. Based on multiple published studies, they build the case that liver MAIT cells are one of the critical players in the first line of defence described as the liver 'firewall'.[6]

Another cell type infiltrating the liver, in response to tissue injury, is the monocyte-derived macrophage. Brempelis *et al.*[7] discuss the dual role of these cells in non-infectious liver injury, where they promote inflammation to allow for efficient clearance of damaged tissue, whereas also stimulating physiological wound healing. As rapid and effective tissue repair is one of the hallmarks of the liver, the balanced activities of these cells may be crucial for liver health.

The review by Wohlleber *et al.*[8] emphasizes the role of other liver sinusoidal cells, specifically liver sinusoidal endothelial cells (LSECs) and Kupffer cells, in liver-specific pathogen responses. These cells serve as unique physical platforms for circulating immune cells to be retained in the liver and enable efficient antigen-specific retention of effector CD8 T cells. This is likely to be critical in the protection of the liver from invading pathogens. However, the exact nature of the interactions of MAIT cells or other innate lymphocytes present in the liver sinusoids, such as natural killer T (NKT) cells and gamma-delta T cells, with LSECs and Kupffer cells will require further investigation.

McNamara *et al.*[9] delve deeper into the retention and recruitment of innate and adaptive lymphocyte populations (NKT, NK, CD8+ and CD4+ T cells) in the liver. A particular focus of their review is on the molecular and cellular interactions that allow for the transition of a circulating cell to a cell that takes up residency in the liver and their motility within the liver. Modulating these interactions (blocking or enhancing) may be one way of shifting the balance of the liver immune system from inflammation to protection.

The reviews by Holz *et al.*[10] and Wong *et al.*[11] both focus on the critical role of liver-resident CD8+ T cells, one in the context of malarial infection, the other highlighting their role in tolerance to allografts. The review by Holz *et al.* highlights how the liver phase of malarial infection represents a bottleneck for overt malaria. Emerging evidence suggests that liver-resident memory CD8+ T cells are particularly effective in providing protection against the spread of malaria parasites to the blood, thus holding the promise to be amenable to achieve sterilising immunity. Wong *et al.* explain the unexpected role for CD8+ T cells in the establishment of liver allograft tolerance, adding further molecular and cellular detail to the phenomenon. Thus, both reviews highlight the critical roles of liver-resident CD8+ T cells in liver protection.

The final three reviews of this special issue are more clinically orientated. Ban-Hok Toh[12] provides an overview of the diagnostic antibodies that differentiate the various subtypes of auto-immune liver disease, emphasising that further definition and stratification of these pathologies—as well as better understanding of the underlying immune processes—is needed to bring forward better therapies for this complex group of severe chronic diseases.

Valaydon *et al.*[13] examine the role of tumor necrosis factor (TNF) in chronic hepatitis B virus (HBV) infection, a disease claiming over one million lives per year. Despite our advances in understanding HBV biology, treatment options are limited and rarely curative. Appropriately termed the 'Jekyll and Hyde' cytokine, TNF contributes significantly to viral immune control within in the liver; however, this may come at the cost of collateral damage of tissue injury and possible

induction of hepatocellular carcinoma (HCC). Recently, immune modulation in a mouse model of chronic HBV with antagonists of cellular inhibitors of apoptosis has shown promising results. These antagonists augment TNF-mediated apoptosis of virally infected cells, thus promoting viral clearance while ameliorating tissue damage.

Elsegood *et al.*[14] summarise the latest studies on the treatment of HCC. With the emergence of cancer immune checkpoint inhibition, significant advances have been made in cancer therapy. However, data about the use of these therapies in HCC therapies are just emerging. Given the difference of liver immunology compared with conventional adaptive responses outside the liver, immunotherapy against HCC may be not straightforward.

Overall, these reviews highlight the complexity of liver biology in health and disease. The distinct organisation and composition of the liver's immune system has evolved to safeguard this vital organ, which has unique physiologic roles but also serves as a gateway to systemic infections. Although the mucosal immune system of the gut and its associated microbiome has been the subject of an enormous number of studies, the similarly complex and tightly linked environment of the liver has received less attention. However, given the new tools and models described in these reviews, there is reason for optimism. Fifty years on from Roy Calne and his 'strange pigs', the liver still has plenty to teach us and likely has further surprises in store.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

Michaela Lucas[1,2,3,4], Axel Kallies[5,6] and Paul Klenerman[7,8]
[1]Department of Immunology, Sir Charles Gardiner Hospital and Princess Margaret Hospital for children, Perth, WA, Australia; [2]School of Medicine and Pharmacology, The University of Western Australia, Perth, WA, Australia; [3]Institute for Immunology and Infectious Diseases, Murdoch University, Perth, WA, Australia; [4]PathWest Laboratory Medicine, Perth, WA, Australia; [5]Department of Microbiology and Immunology, The University of Melbourne, The Peter Doherty Institute for Infection and Immunity, Melbourne, VIC, Australia; [6]The Walter and Eliza Hall Institute of Medical Research, Melbourne, VIC, Australia; [7]Peter Medawar Building for Pathogen Research, University of Oxford, Oxford, UK and [8]National Institute for Health Research, Biomedical Research Centre, University of Oxford, Oxford, UK
E-mail: Michaela.Lucas@health.wa.gov.au

1 Calne RY, White HJ, Yoffa DE, Binns RM, Maginn RR, Herbertson RM. Prolonged survival of liver transplants in the pig. *Br Med J* 1967; **4**: 645–648.
2 'Strange english PIGS'. *Lancet* 1969; **2**: 940–941.
3 Gold MC, Cerri S, Smyk-Pearson S, Cansler ME, Vogt TM, Delepine J *et al.* Human mucosal associated invariant T cells detect bacterially infected cells. *PLoS Biol* 2010; **8**: e1000407.
4 Le Bourhis L, Martin E, Peguillet I, Guihot A, Froux N, Core M *et al.* Antimicrobial activity of mucosal-associated invariant T cells. *Nat Immunol* 2010; **11**: 701–708.
5 Kurioka A, Walker LJ, Klenerman P, Willberg CB. MAIT cells: new guardians of the liver. *Clin Trans Immunol* 2016; **5**: e98.
6 Balmer ML, Slack E, de Gottardi A, Lawson MA, Hapfelmeier S, Miele L *et al.* The liver may act as a firewall mediating mutualism between the host and its gut commensal microbiota. *Sci Transl Med* 2014; **6**: 237ra66.
7 Brempelis KJ, Crispe IN. Infiltrating monocytes in liver injury and repair. *Clin Trans Immunol* 2016; **5**: e113.
8 Wohlleber D, Knolle PA. The role of liver sinusoidal cells in local hepatic immune surveillance. *Clin Trans Immunol* 2016; **5**: e117.
9 McNamara HA, Cockburn IA. The three Rs: recruitment, retention and residence of leukocytes in the liver. *Clin Trans Immunol* 2016; **5**: e123.
10 Holz LE, Fernandez-Ruiz D, Heath WR. Protective immunity to liver-stage malaria. *Clin Trans Immunol* 2016; **5**: e105.
11 Wong YC, McCaughan GW, Bowen DG, Bertolino P. The CD8 T-cell response during tolerance induction in liver transplantation. *Clin Trans Immunol* 2016; **5**: e102.
12 Toh BH. Diagnostic autoantibodies for autoimmune liver diseases. *Clin Trans Immunol* 2017; **6**: e139.
13 Valaydon Z, Pellegrini M, Thompson A, Desmond P, Revill P, Ebert G. The role of tumour necrosis factor in hepatitis B infection: Jekyll and Hyde. *Clin Trans Immunol* 2016; **5**: e115.
14 Elsegood CL, T-P J, Olynyk JK, Yeoh GCT. Immune checkpoint inhibition: prospects for prevention and therapy of hepatocellular carcinoma. *Clin Trans Immunol* 2017; **6**: e161; doi:10.1038/cti.2017.47.