EBioMedicine 50 (2019) 3–4

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

Commentary

Cirrhosis-associated immune dysfunction: Novel insights in impaired adaptive immunity

Evaggelia Liaskou[a,b], Gideon M Hirschfield[c,d,*]

[a] Centre for Liver and Gastrointestinal Research, Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK
[b] NIHR Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[c] Toronto Centre for Liver Disease, University Health Network, Canada
[d] Department of Medicine, University of Toronto, Toronto, Canada

ARTICLE INFO

Article history:
Received 29 October 2019
Accepted 29 October 2019
Available online 11 November 2019

Keywords:
CD8 T cell
Chronic liver disease

The increasing burden faced from complications of cirrhotic liver disease represents a current international public health concern. Regardless of aetiology, patients with cirrhosis are at increased risk of developing a range of life-threatening complications, including severe infections that pose high morbidity and mortality rates, and often end in hospital admissions [1]. A major concern related to severe infections is the added growing global threat of multidrug-resistant bacteria, impervious to classical antibiotic strategies [2–4].

Cirrhosis and immune function have a bidirectional relationship; immune-mediated inflammatory mechanisms play a role in the pathogenesis of cirrhosis, and equally cirrhosis and portal hypertension contribute to dysregulated immune cell activation and immune impairment [5]. The dynamic spectrum of immunological perturbations that develop in patients with cirrhosis can be considered as cirrhosis-associated immune dysfunction (CAID). CAID is a dynamic phenomenon comprised of both increased systemic inflammation and immunodeficiency and is associated with substantial mortality risk [6]. CAID is associated with increased gut permeability, reduced gut motility, and altered gut flora, all of which can contribute to augmented bacterial translocation and consequent bloodstream infections that may lead to systemic inflammatory response syndrome, sepsis, multiorgan failure and even death [7]. Therefore, understanding the defective host immunity associated with CAID is relevant to gaining comprehensive and precise pathophysiology of this phenomenon and could facilitate the development of effective diagnostic and therapeutic tools, independent of the underlying liver disease aetiology.

The innate immune dysfunctions of CAID are well described, however, to date the adaptive immune abnormalities in cirrhotic patients have only partially been explored. In an article in *EBioMedicine*, Lebossé and colleagues studied $CD8^+$ T cells in patients with cirrhosis and for the first time, report the presence of an activated dysfunctional subset that may impact susceptibility to infection and correlate with poor disease outcome [8]. The authors demonstrate the expansion of an immunosuppressive HLA-DR expressing $CD8^+$ T cell subset, not only in circulation but also in peritoneal and intrahepatic compartments; an association was evident for this expanded immunosuppressive immune subset with development of infection.

Transcriptional characterisation of HLA-DR^+CD8^+ T cells revealed down-regulation of genes involving pro-inflammatory cytokine production and intracellular signaling pathways. Moreover, functional assays revealed that HLA-DR^+CD8^+ T cells from cirrhotic patients showed a diminished capacity to induce proliferation of autologous peripheral blood mononuclear cells. When the authors cultured $CD8^+$ T cells from healthy volunteers with 25% of plasma-derived from patients with acute decompensation, the cells acquired higher expression of HLA-DR, mimicking the ex- vivo phenotype. When these conditioned cells were co-cultured with autologous neutrophils, there was a reduction in cell activation markers, impaired phagocytic capacity, and a significant decrease in their ability to produce TNFα upon treatment with LPS.

These observations confirm existing evidence from previous work that showed neutrophils in patients with cirrhosis are

DOI of original article: 10.1016/j.ebiom.2019.10.011
* Corresponding author at: Toronto Centre for Liver Disease, University Health Network, Canada.
E-mail address: gideon.hirschfield@uhn.ca (G.M. Hirschfield).

https://doi.org/10.1016/j.ebiom.2019.10.056

chronically activated, exhibiting high resting ROS production, yet a reduced capacity to traffic to sites of infection and mount effective antimicrobial responses [9]. When these conditioned HLA-DR$^+$CD8$^+$ T cells were co-cultured with monocytes, it resulted in an immunosuppressive phenotype, characterised by elevated MERTK and PD-1 expression levels. These findings are consistent with previous reports that show increased expression of MERTK$^+$ monocytes in acute-on-chronic-liver disease patients that display impaired pro-inflammatory cytokine production correlating with disease severity [10]. The importance of an inflammatory microenvironment in driving the predominant HLA-DR$^+$CD8$^+$ T cell phenotype in cirrhosis was demonstrated in this study; the inflammatory milieu of cirrhosis contributes to this phenotype in suppressing the immune system and rendering individuals more susceptible to infections [8].

The study reported by Lebossé and colleagues has inherent challenges due to the difficulty of accessing sufficiently representative clinical samples, adequate study power and meaningful cohort constituency that is needed to reduce the variability introduced by clinical heterogeneity, as well as inconsistencies arising from the handling and other technical issues. As a validation, this immune-phenotype should be measured in a larger prospective patient cohort, accounting for therapy status and disease aetiology. Limitations of this study include access to all disease stages, variable medication use (e.g. antibiotics, corticosteroids, proton pump inhibitors, statins), heterogeneous nutritional status, and potential confounding from microbiome variability at the time of sampling. Disease aetiology, relative degrees of portal hypertension, and associated lifestyle factors may impact gut permeability and immune function, and thus need to be accounted for when designing future CAID studies. Beyond validation, follow up studies will need to focus on the nature of circulating soluble factors that may drive the expansion of HLA-DR$^+$CD8$^+$ T cells, and to identify targets to counteract adaptive immune defects in cirrhosis.

Establishment of biomarkers that can better stratify patients with cirrhosis by their risk of developing immune dysfunction and infection at an early stage is an ongoing need. Impaired adaptive immunity may affect innate immune cells and could lead to increased susceptibility to infections in patients with cirrhosis. With the growing threat of multi-therapy resistant infectious agents in clinical practice, novel interventions arising from these observations thus become not only an idealistic hope but a necessary advance.

Acknowledgments

EL is supported by NIHR Biomedical Research Centre. GMH is supported by the Lily and Terry Horner Chair in Autoimmune Liver Disease Research. GMH has consulted for Cymabay, Intercept, GSK, Roche, Genfit and Pliant.

This paper presents independent research funded and supported by the NIHR Birmingham Biomedical Research Centre at the University Hospitals Birmingham NHS Foundation Trust and the University of Birmingham. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

References

[1] Irvine KM, Ratnasekera I, Powell EE, Hume DA. Causes and consequences of innate immune dysfunction in cirrhosis. Front Immunol 2019;10:293.
[2] Fernandez J, Prado V, Trebicka J, et al. Multidrug-resistant bacterial infections in patients with decompensated cirrhosis and with acute-on-chronic liver failure in Europe. J Hepatol 2019;70(3):398–411.
[3] Piano S, Singh V, Caraceni P, et al. Epidemiology and effects of bacterial infections in patients with cirrhosis worldwide. Gastroenterology 2019;156(5):1368–80 e10.
[4] Arvaniti V, D'Amico G, Fede G, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. Gastroenterology 2010;139(4):1246–56 e1-5.
[5] Tuchendler E, Tuchendler PK, Madej G. Immunodeficiency caused by cirrhosis. Clin Exp Hepatol 2018;4(3):158–64.
[6] Tandon P, Garcia-Tsao G. Bacterial infections, sepsis, and multiorgan failure in cirrhosis. Semin Liver Dis 2008;28(1):26–42.
[7] Wiest R, Lawson M, Geuking M. Pathological bacterial translocation in liver cirrhosis. J Hepatol 2014;60(1):197–209.
[8] Lebossé F, Gudd C, Tunc E. CD8+ t cells from patients with cirrhosis display a phenotype that may contribute to cirrhosis-associated immune dysfunction. EBioMedicine 2019. doi:10.1016/j.ebiom.2019.10.011.
[9] Fiuza C, Salcedo M, Clemente G, Tellado JM. In vivo neutrophil dysfunction in cirrhotic patients with advanced liver disease. J Infect Dis 2000;182(2):526–33.
[10] Bernsmeier C, Pop OT, Singanayagam A, et al. Patients with acute-on-chronic liver failure have increased numbers of regulatory immune cells expressing the receptor tyrosine kinase Mertk. Gastroenterology 2015;148(3):603–15 e14.