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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Swimming Against the Current: MAIT Cell Function Is Preserved in the Peritoneum of Advanced Liver Disease Patients

Mucosal-associated invariant T (MAIT) cells are a population of unconventional T cells displaying features of both the adaptive and the innate arms of the immune system. They are characterized by the expression of an evolutionary highly conserved invariant alpha chain (Vα7.2-Jα33 in humans) in combination with a biased repertoire of beta chains and respond to bacterial and yeast riboflavin metabolite ligands presented by the major histocompatibility complex Ib-molecule MR1. MAIT cells are enriched in the human liver and also account for 1%–10% of the T cells found in peripheral blood.[1]

In the context of chronic inflammatory disorders, particularly advanced liver disease, the number of circulating MAIT cells drops and the remaining cells in blood and tissue were shown to display varying degrees of functional impairment. Microbial translocation from the gut is a common feature of chronic inflammatory diseases regardless of their origin, and it has been suggested that the constant exposure to bacterial riboflavin metabolites could result in hyperactivation, exhaustion, and ultimately cell death of MAIT cells.[2–6] While MAIT cell dysfunction in blood and liver tissue during advanced liver disease is well established, it is less clear how and if MAIT cells would respond within other parts of the body when facing bacterial pathogens. This is a relevant question, as spontaneous bacterial peritonitis (SBP) represents one of the leading causes of death in liver cirrhosis patients.

In the current issue of *Cellular and Molecular Gastroenterology and Hepatology*, Ibidapo-Obe et al[7] address this question by analyzing the abundance and functionality of MAIT cells in the blood and peritoneal cavity of patients suffering from decompensated cirrhosis in combination with SBP. Confirming previous studies, they show a reduction of circulating MAIT cells in cirrhosis patients, as well as a reduced capacity of the remaining cells to mount responses against *Escherichia coli* in vitro. In contrast, MAIT cells in the peritoneal cavity transiently increased in frequency during SBP. Peritoneal MAIT cells did not seem to proliferate preferentially compared with conventional T cells and expressed high levels of the chemokine receptors CCR6, CCR5, and CXCR3, enabling them to respond and migrate along gradients of CCL20, CCL5, and CXCL10, respectively. Importantly, the ascitic fluid of cirrhosis patients with SBP contained higher levels of these chemokines compared with SBP-free cirrhosis patients and induced preferential migration of blood-derived MAIT cells in transwell assays, overall suggesting a model of MAIT cell redistribution during SBP. Strikingly, in contrast to the functional deficits seen in circulating MAIT cells, Ibidapo-Obe et al went on to show that the peritoneal MAIT cells in these patients seemed to be fully functional, as indicated by the expression of effector molecules like interferon γ, tumor necrosis factor, and perforin at levels similar to those observed in circulating MAIT cells isolated from healthy control subjects. This finding is especially important, as the authors also showed that the ascitic fluid from SBP patients contained MAIT cell ligands, as it could activate MAIT cells in an MR1-dependent manner. Finally, the group demonstrated that the activation of MAIT cells in the peritoneum as measured by CD69 expression correlated with the Model for End-Stage Liver Disease score (a measure of liver disease status), hinting at a potential relationship between disease progression and peritoneal MAIT cell activation.

How does this study add to our understanding of MAIT cell biology in the context of chronic inflammatory disease? Ibidapo-Obe et al's data suggest the possibility that in the context of bacterial peritonitis, MAIT cells redistribute from other compartments into the peritoneum. Currently, it remains unclear whether the increase in peritoneal MAIT cells represents the consequence of the migration of MAIT cells from other tissues or results from local proliferation. However, such a redistribution could partially explain the repeatedly observed loss of circulating MAIT cells during advaced liver disease. Furthermore, while most previous analyses demonstrated MAIT cell loss and functional impairment in blood and liver of cirrhosis patients, Ibidapo-Obe et al showed clearly that in the same patients, the subset in the peritoneum is fully functional and capable of responding to the presence of ligand-bearing pathogens. Hence, MAIT cells, whose role in the immune responses against various pathogens is increasingly recognized,[8–10] could still contribute to host defense in cirrhosis patients. Notably, while behaving differently from MAIT cells in the blood, peritoneal MAIT cells still seem to be affected by systemic events, as their activation was correlated with disease severity in cirrhosis patients in general and systemic inflammation in SBP patients in particular. However, it remains to be elucidated in future studies what role this MAIT cell activation plays in disease progression or whether it is only a bystander effect.

Overall, this study raises some important new questions about MAIT cell function during chronic liver disease. In particular, it would be important to determine whether MAIT cell accumulation and activation in the context of SBP is beneficial or detrimental to the outcome of disease and also whether the results here can be translated into other disease settings. Importantly, it adds an interesting new twist to the rapidly evolving story of MAIT cells and host defense and suggests that there is still much more to learn about these potent unconventional T cells.

CARL-PHILIPP HACKSTEIN, PhD
PAUL KLENERMAN, FMedSci
Translational Gastroenterology Unit
Nuffield Department of Medicine
University of Oxford
Oxford, United Kingdom

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Correspondence
Address correspondence to: Carl-Philipp Hackstein, PhD, University of Oxford, Translational Gastroenterology Unit, Department of Medicine, Peter Medawar Building for Pathogen Research, South Parks Road, Oxford OX1 3SY, United Kingdom. e-mail: carl-philipp.hackstein@ndm.ox.ac.uk; fax: (+44) 1865 281531.

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The authors disclose no conflicts.

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