OS-2158: Interferon lambda 4 is associated with dysfunctional antibacterial immunity during alcohol-related liver disease.

Jennifer M Ryan[1,2,3], Huyen Adams[1,4,5], Dhruti Devshi[1,4], Stephen Atkinson[6], Luke Tyson[6], Debbie L Shawcross[3], Gavin Wright[7], Sarah Fairclough[7], Alex Evans[5], Marieta Simonova[8], Krum Katzarov[8], Tanya Hadzhiolova[8], Slava Pavlova[8], Jasmohan Bajaj[9], Andrew Fagan[9], Mark Thursz[6], Roger Williams[1,4], Andrew McQuillin[10], Marsha Y Morgan[11], Antonio Riva[1,4], Shilpa Chokshi*[1,4]

1 Institute of Hepatology London, Foundation for Liver Research, London, UK
2 Department of Hepatology, Royal Free Hospital, London, UK
3 Institute of Liver Studies, King's College London, London, UK
4 Faculty of Life Sciences and Medicine, King's College London, London, UK
5 Department of Gastroenterology, Royal Berkshire Hospital, Reading, UK
6 Department of Hepatology, Imperial College London, St Mary's Hospital, London, UK
7 Basildon and Thurrock University Hospitals, Basildon, UK
8 Department of Gastroenterology, Hepatobiliary surgery and Transplantology, Military Medical Academy, Sofia, Bulgaria
9 Virginia Commonwealth University and Hunter Holmes McGuire VA Medical Centre, Richmond VA (US)
10 Molecular Psychiatry Laboratory, Division of Psychiatry, University College London, UK
11 UCL Institute for Liver & Digestive Health, Royal Free Campus, University College London, UK
* Corresponding author

Background and aims. Advanced alcohol-related liver disease (ALD) is associated with a defective antibacterial immunity Consequently, patients face is an increased vulnerability to bacterial infection, which may worsen organ failure and increase the risk of death. The interferon lambda family (IFN-λ1/λ2/λ3/λ4) are important mediators of anti-pathogen immunity, but their role in ALD remains unexplored.

Methods. Genetic variants in IFN-λ1/λ2/λ3/λ4 and their associations with infection were explored in 814 STOPAH participants with severe alcoholic hepatitis (SAH) and >11000 disease and healthy controls. Liver and colon expression of IFN-λ4 was measured in a public ALD liver microarray dataset and in ALD colonic biopsies. Systemic plasma IFN-λ4 concentrations and production of IFN-λ4 during *in vitro* bacterial challenge of peripheral blood mononuclear cells (PBMC) were measured in patients with ALD and healthy controls (HC) by ELISA. IFN-λ4 gene expression was assessed in a large PBMC transcriptomics dataset (30 alcohol-related cirrhosis (ARC), 15 SAH, 12 HC). Finally, the impact of recombinant IFN-λ4 on antibacterial immune responses in *E. coli* stimulated PBMC cultures from ALD patients and HC was measured by flow cytometry and Luminex.

Results., The only variant associated with bacterial infection in patients with SAH at presentation (p = 0.03) was the loss of function rs117648444 in *IFNL4* . IFN-λ4 was not expressed in the liver or colon of patients with ALD but plasma IFN-λ4 was lower in these patients compared with HC. PBMC IFN-λ4 production was lower in patients with ARC and undetectable in SAH, compared to HC, and was completely abolished following *E. coli* challenge. In the PBMC transcriptomics dataset, *IFN-λ4* expression was lower in ARC and SAH patients compared to HC (p = 0.005), and *in vitro* treatment of ALD and HC PBMC with recombinant IFN-λ4 modulated the antibacterial immunity.

Conclusion. IFN-λ4 is involved in the immunopathogenesis of ALD and may be a novel attractive target for immunomodulation of antibacterial responses in patients with advanced disease.