

EASL Abstract

Title: Progression of cirrhotic liver disease towards acute-on-chronic liver failure triggers changes in innate immune cell phenotype and their response to pro-inflammatory stimuli.

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Background & Aims

Bacterial infection is a major cause of hospital admission in cirrhosis and patients are highly prone to nosocomial infection. Innate immune dysfunction is implicated in these patients. As there are no current strategies to reverse immune dysfunction, antibiotics are liberally used to treat patients in an era of increasing anti-microbial resistance.

We aimed to determine whether progression to ACLF triggers a change in the receptor phenotype on innate immune cells reflecting impaired function. We also explored the response to inflammatory stimuli. Any changes in profile may reveal novel targets for immune therapy.

Methods

Peripheral whole blood of healthy volunteers (HV), ambulant outpatients attending for drainage of ascites and acute decompensated (AD) cirrhotic patients was studied. Cells were analysed by flow cytometry for activation and cell type.

Whole blood was stimulated *ex vivo* with 1ng/ml lipopolysaccharide for 4 hours. Supernatant was analysed for cytokines. Cells were analysed by flow cytometry.

Results

In neutrophils there was a significant decrease in CD88 ($p=0.0304$) from HV to ACLF, with decreasing trends of CD11b, CD54, CD66b and CD16 and an increasing trend of CD62L observed as disease severity increased. When stimulated with LPS, increases in CD11b ($p=0.008$) and CD66b ($p=0.0436$) were reduced in ACLF compared to HV. This was not seen in ambulant patients. In ACLF the response to LPS was reduced (trend), particularly in CD54 and CD88. In mononuclear phagocytes HLA-DR was significantly reduced between HV and both ambulant ($p=0.0197$) and ACLF ($p=0.0110$). There were also trends of increased CD16, CD62L and CD64, with decreasing CD88 and CD66b. When stimulated, there was a significant reduction in CD11b ($p=0.161$), CD16 ($p=0.0355$), CD54 ($p=0.0174$), CD88 ($p=0.0397$) and CD64 ($p=0.0004$) in ACLF patients. Significant differences were also observed between HV and stable patients in CD54 ($p=0.0387$) and CD64 ($p=0.0167$). TNF levels in the supernatants of the stimulated blood were reduced in both ambulant and AD patients.

Conclusions

The phenotype of innate immune cells in ACLF was altered reflecting immune dysfunction and explaining increased rates of bacterial infection. The response of innate cells to stimulation was also modified. These changes reflect a reduced capacity to migrate to sites of infection, as well as reduced bactericidal potential. This is mirrored by the reduced production of TNF- α by whole blood stimulation. Overall, we see an immune-fatigued phenotype in innate immunity.