Lactococcus A phages predict ACLF while Enterococcus B phages predict bacterial infection in decompensated cirrhosis

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Abstract

Background & Aims

As portal hypertension progresses in cirrhosis, bacterial translocation across a compromised gut barrier leads to endotoxemia, systemic inflammation and immune dysfunction. Gut phages play a key role in these processes by influencing bacteria-host interactions. This study explores the role of the human gut virome in acute decompensation of cirrhosis and acute-on-chronic liver failure (ACLF).

Methods

The fecal virome was longitudinally assessed by metagenomic sequencing in two independent cohorts: 93 patients (292 samples) with acute decompensation or ACLF from the PREDICT study, and 94 patients (94 samples) with decompensated cirrhosis undergoing TIPS (transjugular intrahepatic portosystemic shunt) surgery collected in a tertiary care setting. Besides descriptive analysis, phages were grouped according to their predicted bacterial host and lifestyle, and associated with clinical parameters.

Results

Phage alpha-diversity was higher in patients with ACLF and correlated with ACLF severity. In the absence of ACLF, the phageome was dominated by virulent phages, but in ACLF, temperate phages became more prevalent. Genus-level analysis showed that phageomes were highly patient-specific. Lactococcus A phages were the only phage-host group predicting ACLF development (odds ratio [OR] = 14; Fisher test p = 0.0129). Enterococcus B phages (OR = 14.7; p = 0.0015; adj. p = 0.037) and their bacterial hosts (OR = 2.8; p = 0.020) were significantly more prevalent in cases of proven systemic bacterial infection. The presence of both phage families was linked to increased 90-day mortality rates.

Conclusion

ACLF is characterized by increased fecal virome diversity and a shift from virulent toward temperate phages at disease onset. Our study links Lactococcus A phages to ACLF development, and Enterococcus B phages to bacterial infection, while both are associated with increased 90-day mortality.

Clinical trial number

NCT03056612.

Impact and implications

The human gut virome is a poorly investigated part of the human gut microbiome, especially in the context of decompensated cirrhosis and acute-on-chronic liver failure. This study identified two phage groups (Lactococcus A phages and Enterococcus B phages) with particular prognostic value. In the future, virome analysis of fecal samples could be useful for patient stratification in clinical practice.