Lipid metabolic reprogramming in tumor microenvironment: *Clostridium* cluster cocktail attenuate high-fat diet induced hepatocellular carcinoma.

Seol-Hee Song[1], Jeong-Su Kim[1], Jeong-Ha Park[1], Min-Ju Kim[1], Jung A Eom[1], Dong-Hoon Yang[1], Satya Priya Sharma[1], Hyunjoon Park[1], Jin-Ju Jeong[1], Sung-Min Won[1], Dong Joon Kim[1], Ki Tae Suk[1]**

[1]Institute for Liver and Digestive Disease, Hallym University, Chuncheon, Republic of Korea

INTRODUCTION & AIM

Metabolic reprogramming for adaptation to the tumor microenvironment (TME) has been recognized as a hallmark of cancer. In recent studies, lipid metabolism reprogramming has been shown to play an important role in TME. TME of progressed hepatocellular carcinoma (HCC) revealed inflammation-based lipid-rich background and deteriorated lipid metabolism. Clostridium cluster is known for reducing liver inflammation. This study focused on the regulatory mechanism of Clostridium cluster in lipid pathway of HCC TME.

MATERIAL & METHODS

For the hypothesis establishment, we collected fecal samples from healthy control (n=66), non-alcoholic fatty liver (n=67), hepatitis (n=100), and cirrhosis and cancer patients (n=21). We compared microbial diversity among human groups. In the HCC-animal study, C57BL/6J male mice received 20 mg/kg (i.p) of diethylnitrosamine (DEN) at 14 days of age. To accelerate the development of HCC, mice were fed a 60% high-fat diet and drinking water with 300 mg/L thioacetamide (TAA). Clostridium cluster cocktail was orally administered at a concentration of 10^9 CFU/day from 7 weeks to 32 weeks of age. We compared liver weight, body weight, liver enzymes, cholesterol, and triglyceride. We conducted the histopathological examination, fecal analysis, and markers for inflammation, lipogenesis, ¯¯'I growth factor, hypoxia pathway and β-oxidation in the liver.

RESULTS

Figure 1. Liver disease altered composition of C*lostridium*, lipid metabolites, and the expression levels of hypoxia related genes in patients.

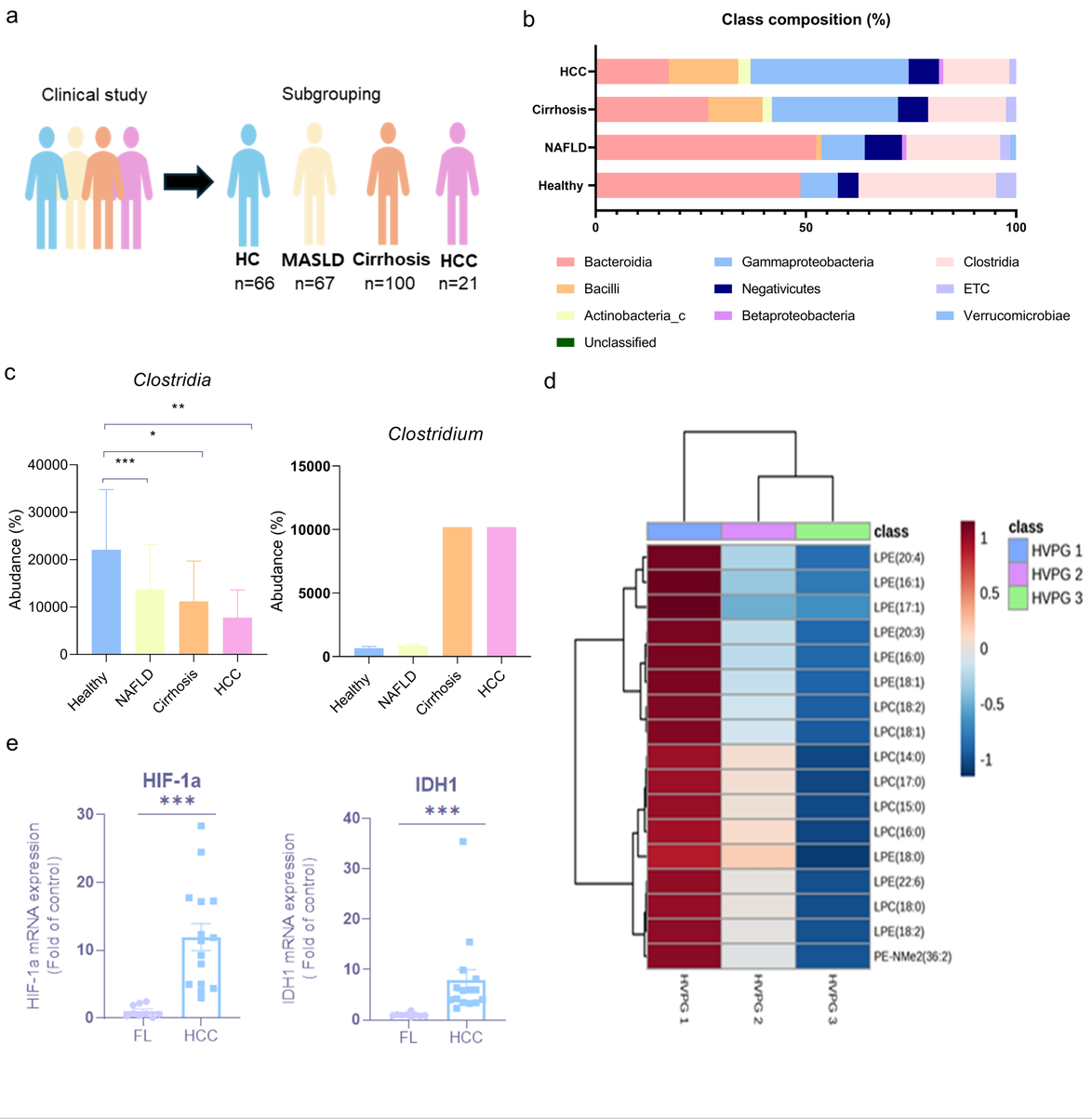
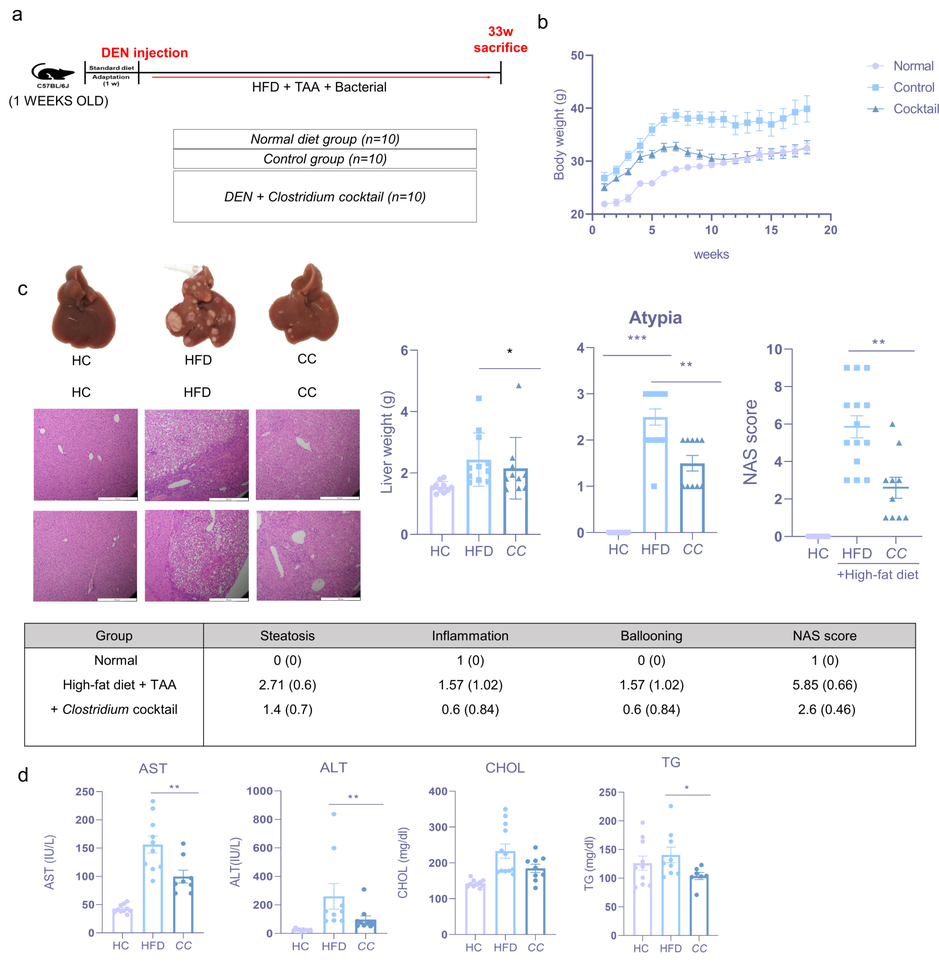


Figure 2. C*lostridium* cocktail alleviated liver cancer in murine model.



Group	Steatosis	Inflammation	Ballooning	NAS score
Normal	0 (0)	1 (0)	0 (0)	1 (0)
High-fat diet + TAA	2.71 (0.6)	1.57 (1.02)	1.57 (1.02)	5.85 (0.66)
+ *Clostridium* cocktail	1.4 (0.7)	0.6 (0.84)	0.6 (0.84)	2.6 (0.46)

Figure 3. Transcriptome analysis revealed *Clostridium* cocktail dependent regulation of G2M pathway in murine model.

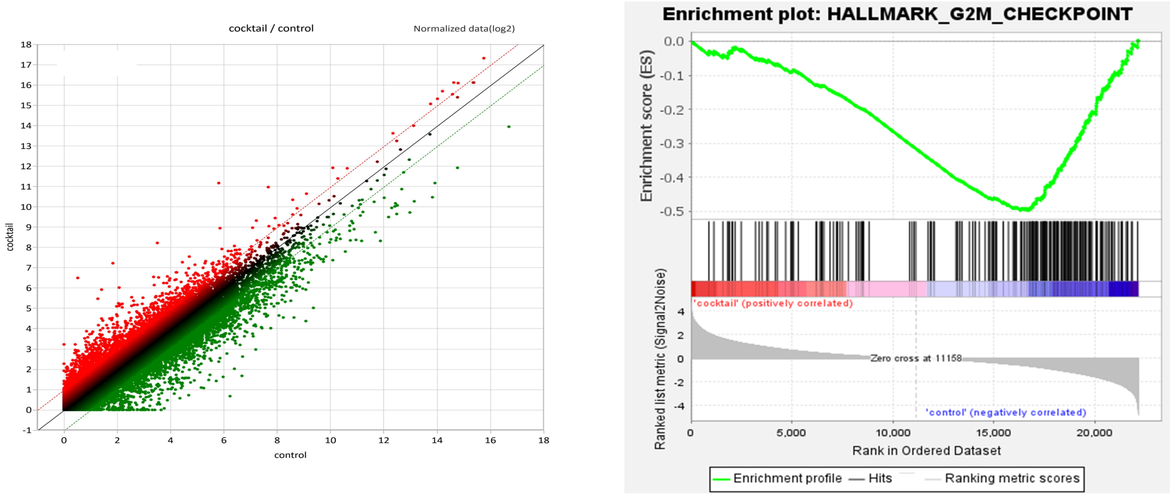
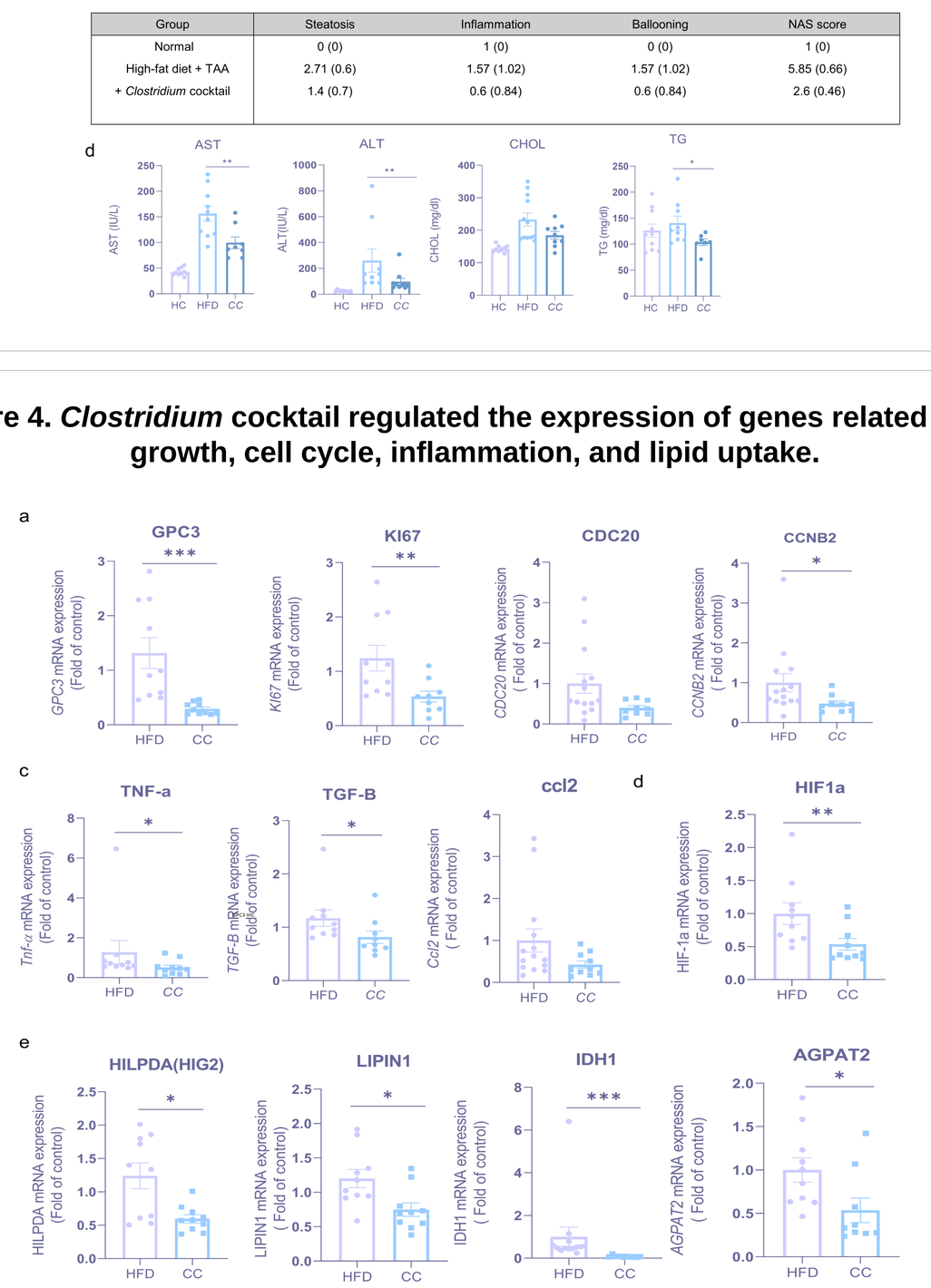


Figure 4. *Clostridium* cocktail regulated the expression of genes related to cell growth, cell cycle, inflammation, and lipid uptake.



CONCLUSION

This study revealed that hypoxia pathway plays an important role in the development of HCC. Oral administration of Clostridium cluster cocktail inhibited hypoxia pathway in murine liver disease model. The result of this study will contribute to the development of novel prevention method of HCC.

ACKNOWLEDGEMENTS

We would like to thank Professor Tae-Seok Ki (K.T.S.) and Professor Dong-Jun Kim (D.J.K) for providing this wonderful research opportunity. Funded by National Research Foundation of Korea