

Effect of Probiotic Mixture “Prohep” on Hepatocellular Carcinoma Development

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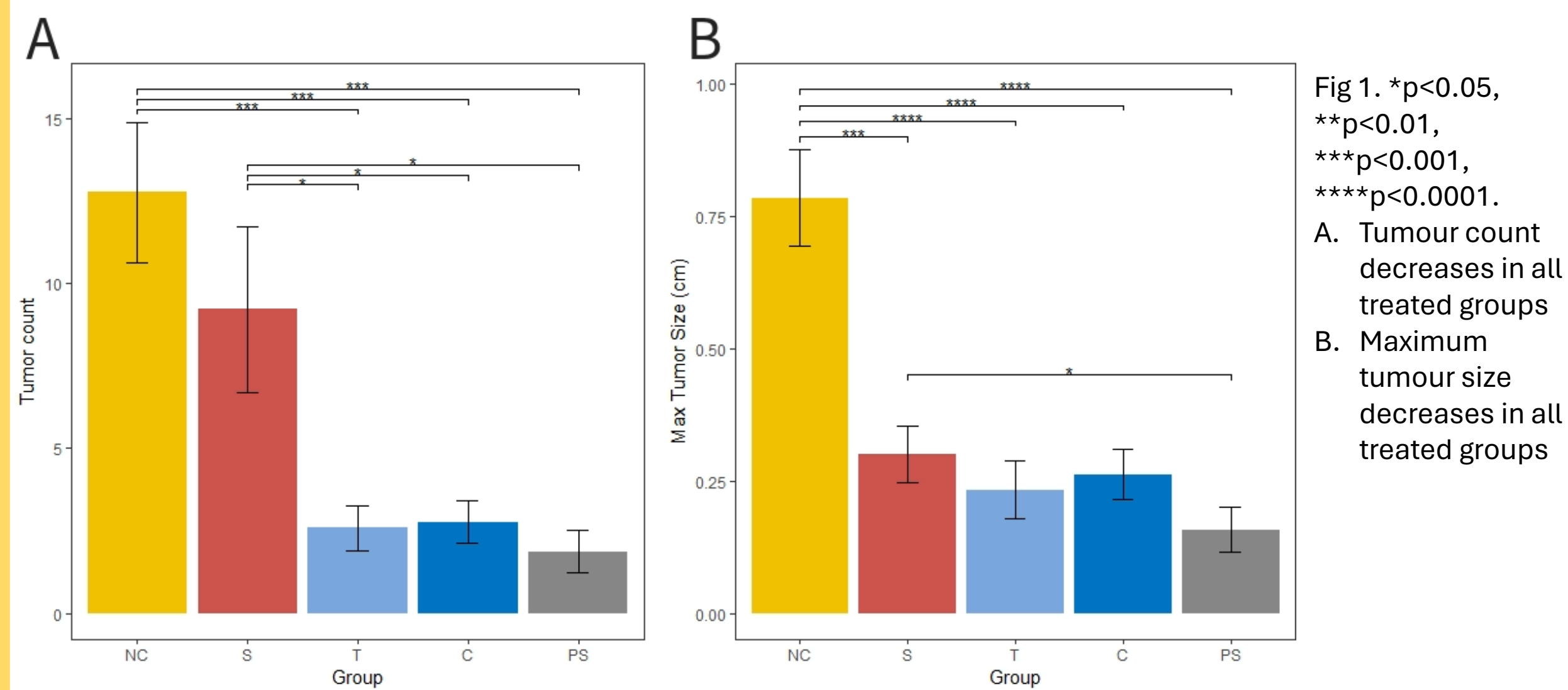
Introduction

Liver cancer is one of the most prevalent cancers globally, ranked at the eighth most prevalent cancer with over 900,000 annual diagnoses. Among all types of liver cancers, Hepatocellular Carcinoma (HCC) is diagnosed in over 90% of the cases. The gut-liver axis is one of the most popular targets in HCC treatment since the modulation of the gut microbiota occupies a crucial role in the modulation of tumour microenvironment and contributes to the repression of HCC development.

Prohep is a probiotic mixture containing multiple strains of bacteria (*Lactobacillus acidophilus*, *Lactobacillus paracasei*, *Lactobacillus rhamnosus*, *Lactobacillus plantarum*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *Lactobacillus helveticus*, *Bifidobacterium animalis ssp. Lactis*)

Sorafenib is a multi-target tyrosine kinase inhibitor. Studies shown Sorafenib treatment has increased the survival time in advanced HCC patients. Sorafenib can suppress HCC development by targeting growth factor receptors (PDGFR- β , VEGFR). However, the efficacy of Sorafenib treatment is not high, effective reports occupies about 30% of patients. Resistance towards Sorafenib is also developed quickly in these patients. Thus, various studies have paired Sorafenib treatment with other pharmaceuticals or natural substances to enhance the efficacy of the drug or reduce resistance.

Previously, we have observed decreases in tumor counts (Fig.1A) and maximum tumor size (Fig.1B) in all treated groups. Thus, we would like to explore the mechanisms involved in the repression of HCC. In this study, Oil Red O (ORO) staining has been performed to investigate the accumulation of lipid in livers. Then, RT-PCR was performed to disclose the genes being modulated by our treatments and possible mechanisms are proposed.



Aim & Hypothesis

Aims:

- To investigate the role of Prohep treatment in the modulation of lipid in HCC
- To test the efficacy of combinational treatment of Prohep and Sorafenib treatment of inhibition of HCC development.
- To explore the possible mechanisms of Prohep-associated modulation of HCC development

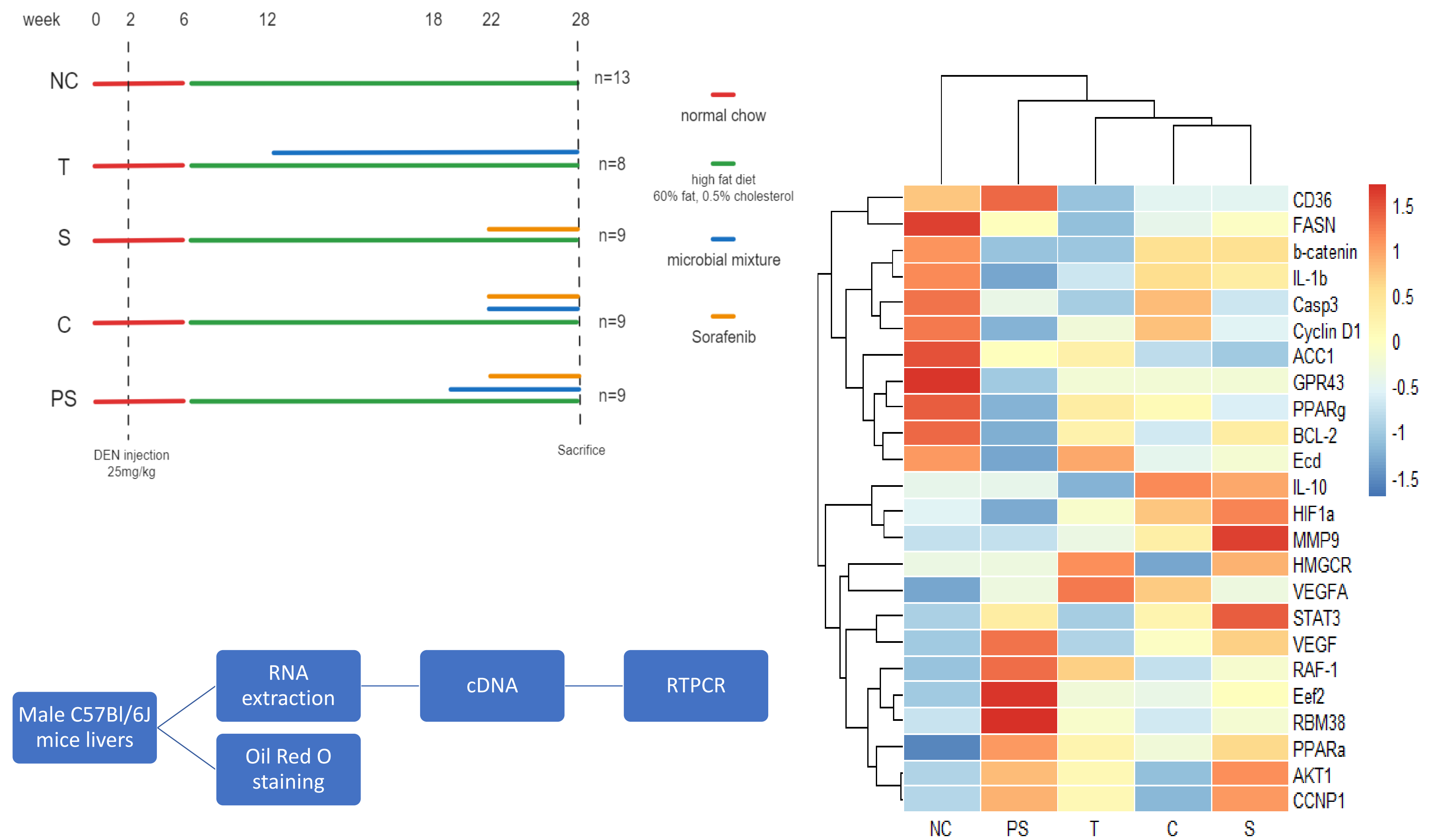
Hypothesis:

Combinational treatments with Prohep improves efficacy of Sorafenib on the repression of HCC development.

Summary

- Prohep and Sorafenib treatments reduced the lipid accumulation in livers of HCC mouse models.
- The efficacy of the combined treatment can be enhanced with early administration of Prohep.
- The possible mechanisms of regulation of HCC by Prohep are modulating lipid metabolism, increasing apoptosis, and inhibiting inflammation in the liver.

Method



Results & Discussion

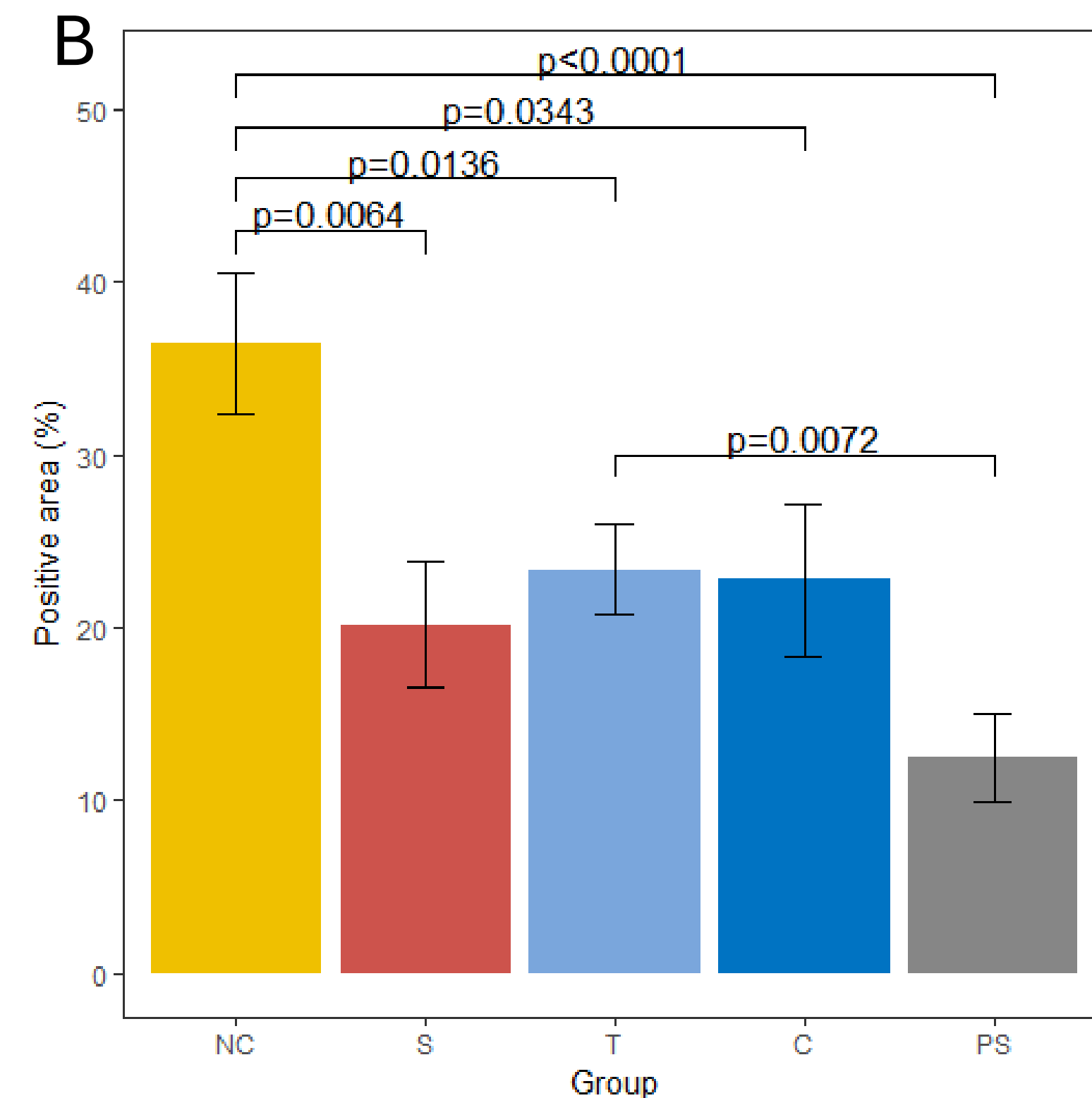
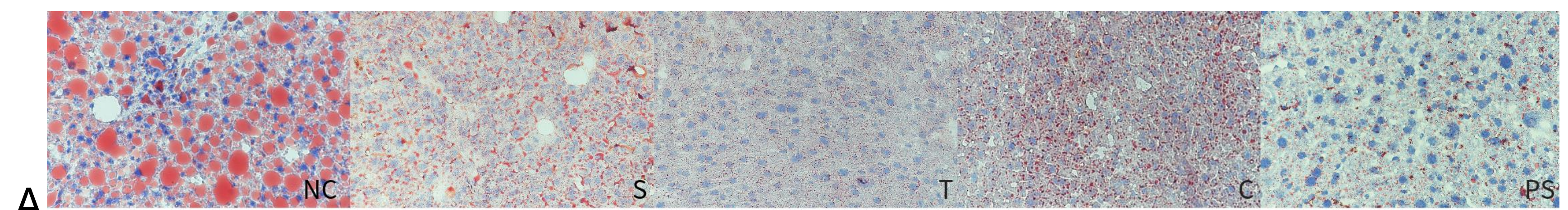


Fig.2

- ORO stained samples.
- Average positive area in ORO staining. Treatment groups reduces lipid accumulation in liver significantly.

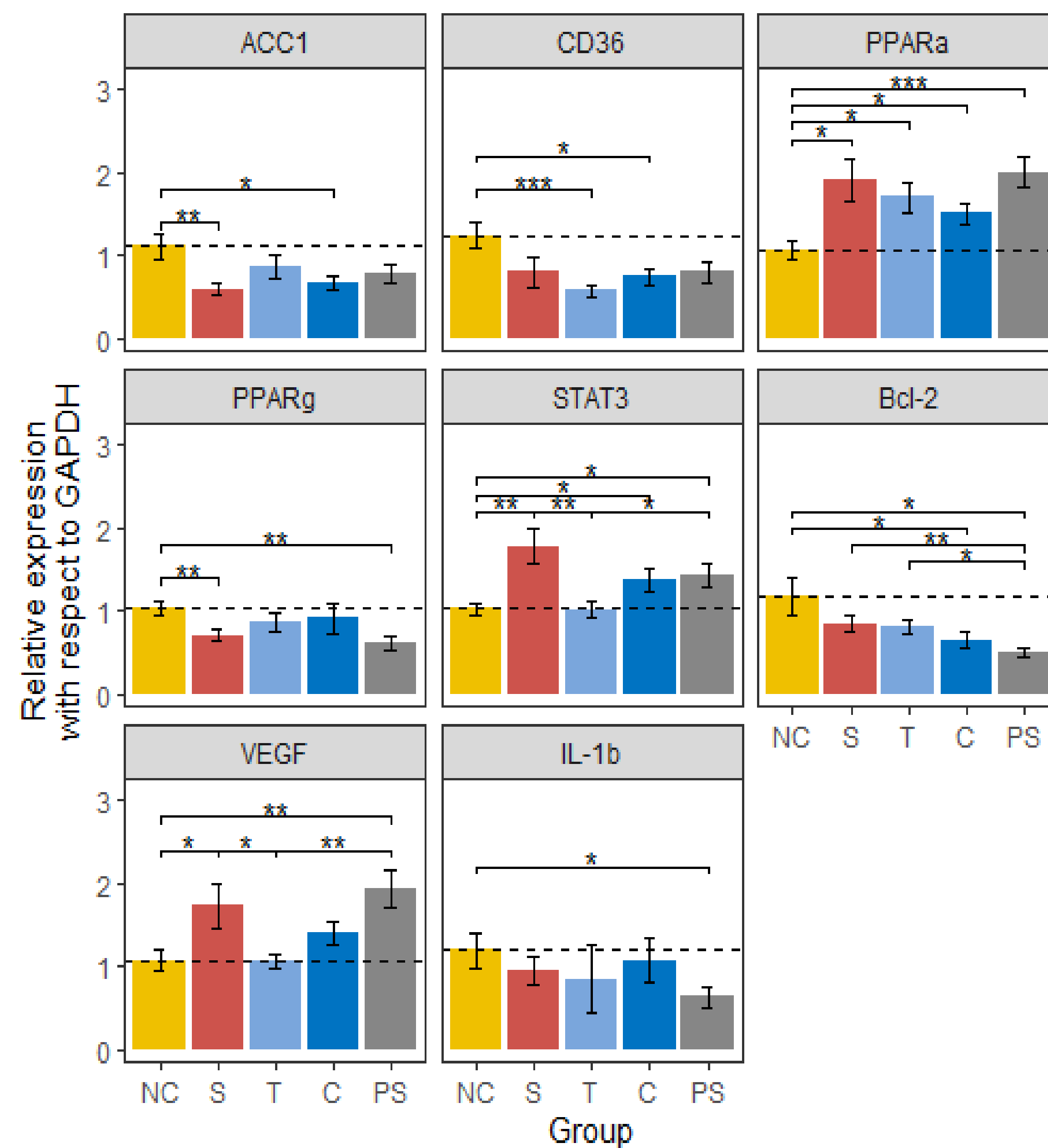


Fig.4 Relative expressions of genes with significant changes after treatment.

*p<0.05, **p<0.01, ***p<0.001.

Possible mechanisms:

Reducing lipid accumulation

- reduce building blocks of cellular compartments
- reduce fuel molecules under hypoxic environment with low glucose content
- reduce free FA uptake
- reduce lipogenesis

Promoting apoptosis

- inhibit pro-survival genes

Inhibiting inflammation

- inhibit inflammatory cytokines

Sorafenib resistance:

Continuous Sorafenib treatments leads to hypoxia, thus increasing the production of HIF-1 α , an angiogenic factor. The increase in STAT3 and VEGF indicates Prohep may not be effective in opposing the resistance against Sorafenib in hypoxic environment.