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Reply to: "Is the pathway of energy metabolism modified in advanced cirrhosis?"

To the Editor:

We would like to thank Ganapathy-Kanniappan *et al.*, for relating to our work to suggest an interesting hypothesis for the origin of hepatocellular carcinoma (HCC). Based on the recent and historical findings that HCC is associated with elevated glycolysis [1,2], they propose an interesting hypothesis that metabolic adaptations in early stages of liver cirrhotic hepatocytes could be linked to the origin of tumorigenesis in liver and that end-stage failing cirrhotic hepatocytes undergoes metabolic adaptations leading to HCC. However, the mechanistic links between liver cirrhosis and HCC are unclear and identification of pathways connecting both remains elusive. The focus of our recent work was the study of adaptive energy metabolic changes during liver cirrhosis to understand hepatic failure in the terminal stages of chronic injury [3]. Even though the letter to the editor from Ganapathy-Kanniappan *et al.*, is not completely related to the study we designed, it is recognized that liver cirrhosis is considered as a precursor to HCC.

In addition to hepatocytes, it is important to consider the role of the tumor microenvironment in regulating the metabolism of cancer cells. Recent studies have shown that cells in the tumor microenvironment generate energy rich metabolites (e.g., lactate, beta-hydroxybutyrate) that are used by cancer cells for meeting their energetic demand through mitochondrial tricarboxylic acid cycle [4,5]. Based on the compelling recent results [6], one possibility is that microenvironment may induce metabolic transformations in early cirrhotic hepatocytes and when in contact with stromal cells to sustain their nutrient demand. Early cirrhotic hepatocytes may alter the surrounding cells metabolic phenotype to secrete high-energy metabolites for their energetic requirements. Metabolic alterations and adaptations are thus an exciting area of investigation.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Cost-effectiveness of upcoming treatments for hepatitis C: We need to get the models right

To the Editor:

We read with great interest the recent article on cost-effectiveness of current and future treatments of patients with HCV genotype 1 by Younossi and colleagues [1]. Although the authors explore a very pertinent issue regarding treatment decisions in such patients, there are certain aspects that somewhat decrease the validity of their findings.

Firstly, the authors assume that the health-related utility/quality of life is similar to all patients with HCV infection irrespective of fibrosis stage. The critical question is whether patients with F0/F1 could be left without treatment. There is a bias favoring a treat-all strategy if higher utilities are not ascribed to patients with F0/F1 [2].

Secondly, the SVR rates of the all-oral therapy combination are unclear and sourced from abstract publications in 2012. With huge steps in HCV treatment since then, we would expect more up to date source data. Moreover, we would favor a more