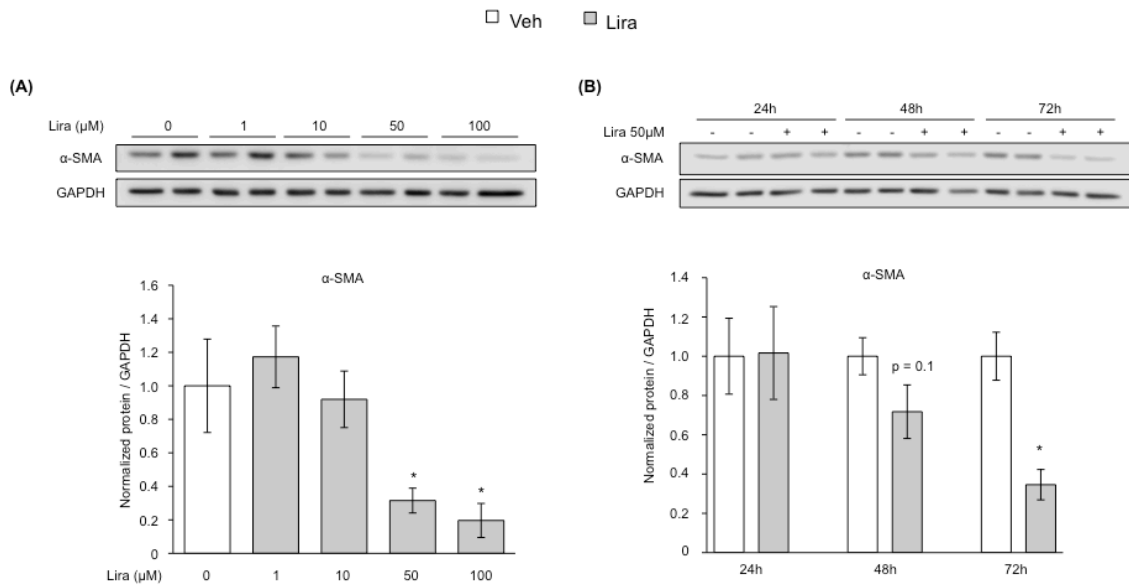


## **Liraglutide improves liver microvascular dysfunction in cirrhosis:**

### **Evidence from translational studies.**

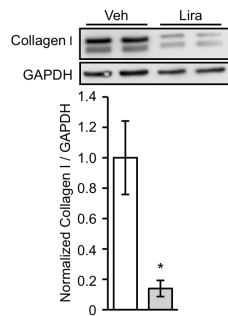
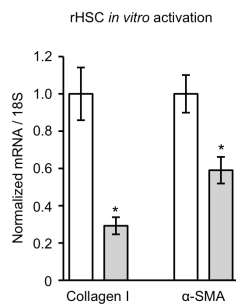
Fernanda Cristina de Mesquita, Sergi Guixé-Muntet, Anabel Fernández-Iglesias, Raquel Maeso-Díaz, Sergi Vila, Diana Hide, Martí Ortega-Ribera, José Luís Rosa, Juan Carlos García-Pagán, Jaime Bosch, Jarbas Rodrigues de Oliveira, Jordi Gracia-Sancho



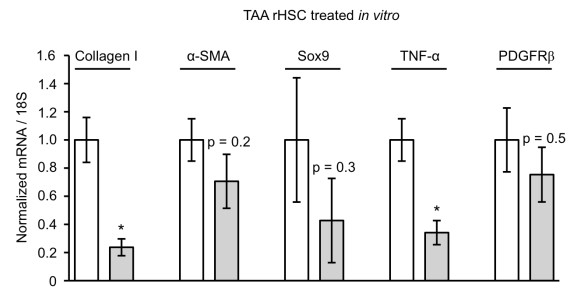
**Supplementary figure 1.** Analysis of LX-2 de-activation in terms of  $\alpha$ -SMA expression in response to liraglutide administered at different doses and times. n=3 per experimental condition. \*p<0.05 vs. vehicle.

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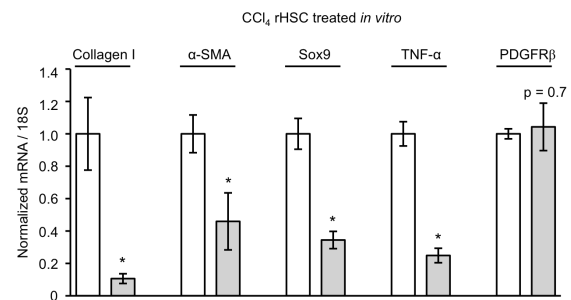
(A)



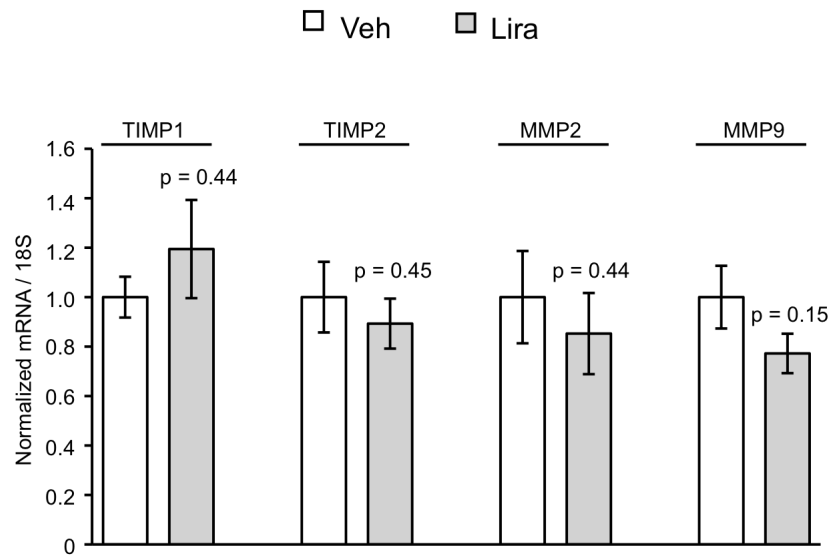
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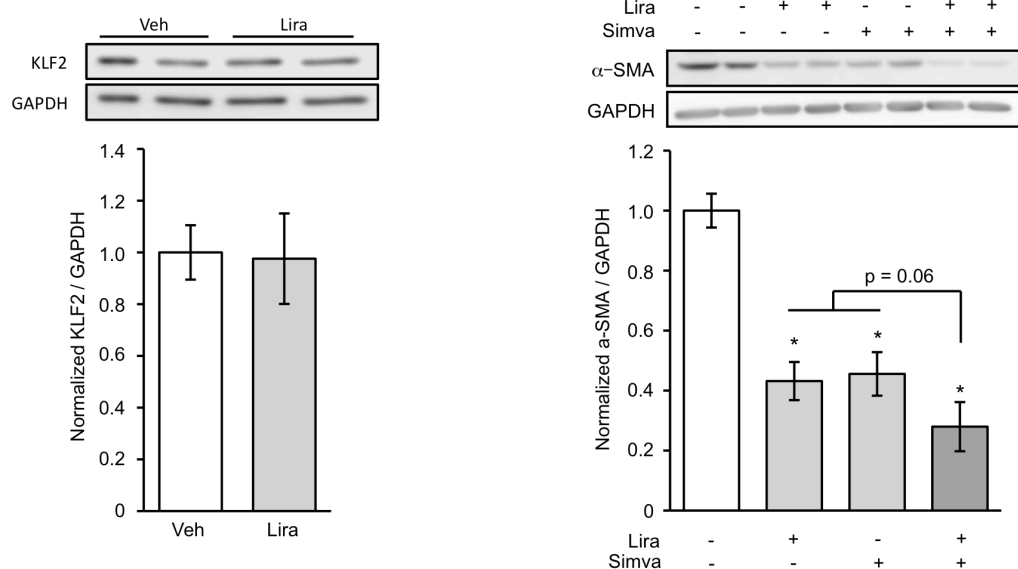
(C)



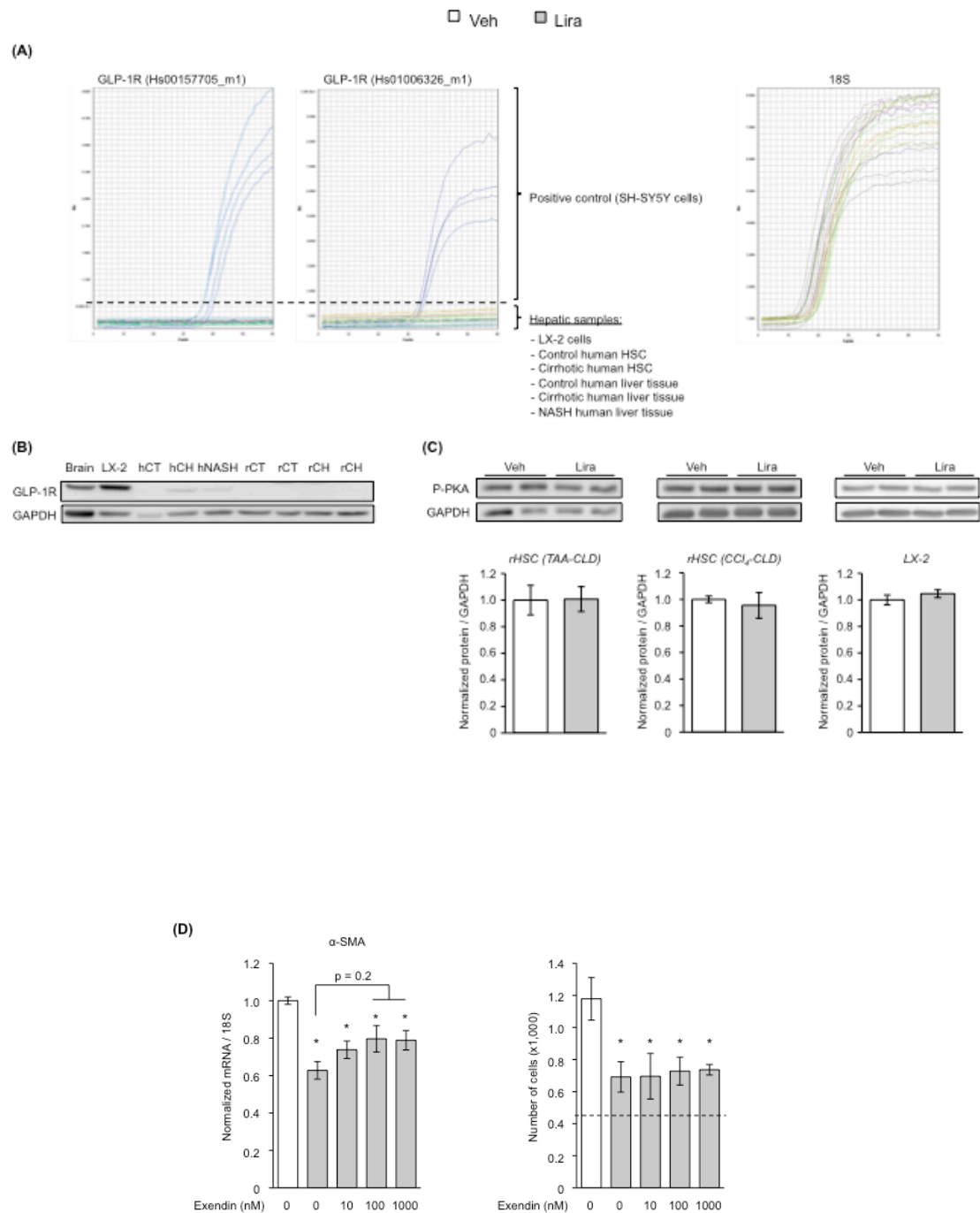
**Supplementary figure 2.** Effects of 72h-liraglutide on the *in vitro* activation of primary quiescent HSC isolated from healthy rats **(a)**, and in the amelioration of activated HSC isolated from TAA-CLD **(b)** and CCl<sub>4</sub>-CLD **(c)** rats. n=3 per group. \*p<0.05 vs. vehicle.



**Supplementary figure 3.** Expression of TIMPs and MMPs in livers from TAA-CLD-rats treated for 15 days with liraglutide, or vehicle. n=8 per group.

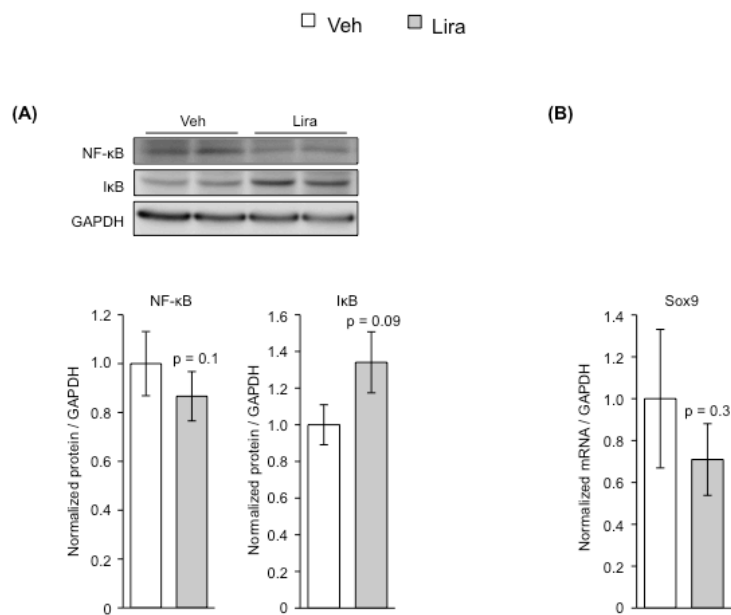


**Supplementary figure 4. (a)** Expression of the transcription factor KLF2 in LX-2 cells treated with 50  $\mu$ M liraglutide, or vehicle. **(b)** Expression of  $\alpha$ -SMA in LX-2 cells treated with 50  $\mu$ M liraglutide, or vehicle, in combination with 10 $\mu$ M simvastatin, or its vehicle. n=3 per experimental condition. \*p<0.05 vs. vehicle



**Supplementary figure 5. (a)** 60-cycle amplification charts of GLP-1R mRNA expression analyzed in human liver & cells samples using the human cell line SH-SY5Y as positive control. **(b)** Western blot of different hepatic samples using a GLP-1R antibody (Abcam ab189397). From left to right, brain tissue as positive control, LX-2 cells, human liver tissue (control, cirrhotic, NASH) and rat

liver tissue (control, cirrhotic). **(c)** p-PKA protein expression in primary cirrhotic HSC from TAA-CLD (left), CCl<sub>4</sub>-CLD (middle) and in LX-2 cells (right) in response to 50 $\mu$ M liraglutide. **(d)** Effects of the GLP-1R antagonist exendin 9-39 on  $\alpha$ -SMA mRNA expression (left) and proliferation (right) in LX-2 cells. n=3 per experimental condition. \*p<0.05 vs. vehicle.



**Supplementary figure 6. (a)** Protein expression of NF- $\kappa$ B and its inhibitor I $\kappa$ B and **(b)** mRNA expression of Sox9 in livers from TAA-CLD-rats treated with liraglutide, or vehicle. n=8 per group.