Boosting pigment epithelial-derived factor: a promising approach for the treatment of early portal hypertension

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Portal hypertension (PHT) is a heterogeneous clinical entity which develops in patients with cirrhosis. It is responsible for many of the complications that occur in cirrhosis, including gastroesophageal varices, hepatorenal syndrome, ascites, hepatic encephalopathy and hypersplenism. 1 There are three principal factors responsible for the development of PHT, namely (1) purely mechanical obstruction resulting from hepatic fibrosis and regenerative nodules; (2) contraction of sinusoidal and perisinusoidal contractile cells due to an imbalance between intrahepatic vasoconstrictory and vasodilatory mediators and (3) splanchnic sinusoidal contractile cells due to an imbalance between intrahepatic vasoconstrictory and vasodilatory mediators resulting from the development of PHT, namely (1) purely mechanical obstruction resulting from hepatic fibrosis and regenerative nodules; (2) contraction of sinusoidal and perisinusoidal contractile cells due to an imbalance between intrahepatic vasoconstrictory and vasodilatory mediators and (3) splanchnic sinusoidal contractile cells due to an imbalance between intrahepatic vasoconstrictory and vasodilatory mediators resulting from the development of PHT, namely (1) purely mechanical obstruction resulting from hepatic fibrosis and regenerative nodules; 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pressure from the subclinical to the clinically significant range would prevent many of the sequelae we observe.

Since neoangiogenesis actively contributes to PHT from the first steps of its development, drugs with antiangiogenic properties are attractive candidates to prevent PHT. However, the development of clinical studies to investigate this has been hampered by drug toxicity and the concerns about interfering with physiological angiogenesis. The results presented by Mejias launches PEDF as a promising agent with the potential ability to affect portal pressure by specifically targeting pathological angiogenesis. Conversely, the significantly lower activity demonstrated by PEDF when given in a more advanced phase of liver disease raises some doubts concerning its potential to add something for the treatment of clinically significant PHT. However, since a modest effect on portal pressure is observed even in advanced cirrhosis, the combination of PEDF with vasoactive drugs deserves further experimental investigation, with the hope that working simultaneously on more therapeutic targets will maximise the impact on portal pressure.

In conclusion, the data presented in this study highlights again the importance of targeting VEGF-driven angiogenesis and reveals new important insights into the molecular working mechanism of PEDF as a possible antiangiogenic and antifibrotic agent in the treatment of early phase PHT. Hence, the next step should be trying to translate these findings into clinical practice, where PEDF needs to confirm its capability to halt the rise of portal pressure, and to prove it can add something, eventually in association with or without non-selective β-blockers (NSBB) and/or anti-inflammatory agents, before clinical significant PHT has developed.

Competing interests None.

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