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Reply: Rho-Kinase inhibition is beneficial in fibrosis

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We thank Gortzen and Trebicka for their interest in our work (1). Studies suggest that mechanical force regulates RhoA mainly at the level of activity, by increasing the amount of activated GTP-bound RhoA, modulating guanine nucleotide exchange factors, and/or coupling GTP-RhoA to Rho-kinase (ROCK) (2–4). How RhoA mRNA expression affects the downstream effectors of the RhoA/ROCK pathway is less established. An interesting finding from our study is that there appears to be a threshold effect at the lower limit of fibrotic liver stiffness (1kPa), at which point albumin production and hepatocyte nuclear factor 4 alpha (HNF4 α) expression are inhibited (1). These results suggest that in determining the severity of hepatic dysfunction of a fibrotic liver, the gradient of stiffness in the liver tissue may be less important than the proportion of liver mass that reaches the threshold stiffness. We believe that the RhoA/ROCK pathway likely plays multiple cell-type specific roles that are important in modulating the progression and pathophysiology of liver fibrosis. In stellate cells, RhoA/ROCK activation may regulate fibrogenesis. In hepatocytes, as we have shown (1), RhoA/ROCK activation inhibits hepatocyte function in part through downregulation of HNF4 α . The challenge for translating these discoveries into clinical therapies that benefit patients with liver fibrosis will be to identify efficacious RhoA or ROCK inhibitors that have minimal adverse systemic effects (5).

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