Liver Sinusoidal Endothelial Cells Suppress Bone Morphogenetic Protein 2 Production in Response to TGFβ Pathway Activation

Info

PUBLISHED DATE
2021-08-24

JOURNAL
Hepatology

LINK
https://doi.org/10.1002/hep.31900

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Abstract

Background and aims: TGFβ/bone morphogenetic protein (BMP) signaling in the liver plays a critical role in liver disease. Growth factors, such as BMP2, BMP6, and TGFβ1, are released from LSECs and signal in a paracrine manner to hepatocytes and hepatic stellate cells to control systemic iron homeostasis and fibrotic processes, respectively. The misregulation of the TGFβ/BMP pathway affects expression of the iron-regulated hormone hepcidin, causing frequent iron overload and deficiency diseases. However, whether LSEC-secreted factors can act in an autocrine manner to maintain liver homeostasis has not been addressed so far.

Approach and results: We analyzed publicly available RNA-sequencing data of mouse LSECs for ligand-receptor interactions and identified members of the TGFβ family (BMP2, BMP6, and TGFβ1) as ligands with the highest expression levels in LSECs that may signal in an autocrine manner. We next tested the soluble factors identified through in silico analysis in optimized murine LSEC primary cultures and mice. Exposure of murine LSEC primary cultures to these ligands shows that autocrine responses to BMP2 and BMP6 are blocked despite high expression levels of the required receptor complexes partially involving the inhibitor FK-506-binding protein 12. By contrast, LSECs respond efficiently to TGFβ1 treatment, which causes reduced expression of BMP2 through activation of activin receptor-like kinase 5.

Conclusions: These findings reveal that TGFβ1 signaling is functionally interlinked with BMP signaling in LSECs, suggesting druggable targets for the treatment of iron overload diseases associated with deficiency of the BMP2-regulated hormone hepcidin, such as hereditary hemochromatosis, β-thalassemia, and chronic liver diseases.