BMP-9 modulates the hepatic responses to LPS

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We and others have previously shown that Bone Morphogenetic Protein (BMP-9) is constitutively produced and secreted by hepatic stellate cells (HSC). Upon acute liver damage BMP-9 expression is transiently down-regulated and blocking BMP-9 under conditions of chronic damage ameliorates liver fibrogenesis. Thereby BMP-9 acts pro-fibrogenic on liver but without directly inducing HSC in vitro. LPS, an endotoxin derived from the membrane of gram-negative bacteria in the gut, is known to be essential in the pathogenesis of diverse kinds of liver diseases. Aim of the present work was therefore to investigate how high levels of BMP-9 in the context of LPS signaling might result in enhanced liver damage.

Primary liver cells were isolated from mouse or human livers and were directly lysed for RNA isolation. Expression of the BMP-9 or LPS receptors were determined by real-time PCR. BMP-9 expressing human LSEC were cultured using conditioned medium and were used for subsequent LPS treatment.

Aim: (HSC): Bone morphogenetic protein (BMP-9) modulates the hepatic responses to LPS.

Schematic presentation of the possible cellular crosstalk between liver stellate/stellate cells (LSEC), hepatic myofibroblasts (MF), hepatic stellate cells (HSC), and hepatic Kupffer cells (Kupffer cells). BMP-9 upon exposure to endotoxin (LPS) activates hepatic Kupffer cells (Kupffer cells) with subsequent expression of pro-inflammatory genes (IL-6, IL-1β, TNFα) and thus provokes inflammation through activation of tumor necrosis factor receptors (TNFR). BMP-9 also blocks the expression of this cytokine by the macrophages (Fig. 3). BMP-9 also blocks the expression of this cytokine by the macrophages (Fig. 3). BMP-9 also blocks the expression of this cytokine by the macrophages (Fig. 3). BMP-9 also blocks the expression of this cytokine by the macrophages (Fig. 3). BMP-9 also blocks the expression of this cytokine by the macrophages (Fig. 3).

**Summary and Conclusions:**

- The BMP-9 receptor Alk-1 as well as the LPS receptor TLR-4 are expressed in LSEC and macrophages in mouse and man.
- Upon stimulation with LPS, LSECs secrete factor(s), including IL-6, that lead to up-regulated BMP-9 expression in human liver myofibroblasts.
- The increased BMP-9 in turn induces crosstalk of LSECs and enhances pro-inflammatory responses of macrophages.
- These data imply that LSEC control the hepatic response to LPS at least in part via regulating the BMP-9 levels in the neighbouring cells. Our hypothesis is that too much BMP-9 might induce fibrosis by promoting crosstalk and by provoking too intense inflammatory reactions. Too little BMP-9 on the other hand might make the sinusoidal layer too permissive for LPS leading to exposition of the hepatocytes in the parenchyma. Thereby the direct cross-talk between the non-parenchymal cells, including the LSEC, fine-tunes major hepatic responses with BMP-9 being a central homeostasis-factor.

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