

Knockdown of hepatic GnRH reduces liver fibrosis in a mouse model of PSC

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Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by progressive inflammation and fibrosis of intrahepatic and extrahepatic bile ducts. [1]. Cholangiocyte proliferation occurs in all pathologic conditions of liver injury where it is associated with inflammation and regeneration. During these processes, biliary cells start to secrete different cytokines, growth factors, neuropeptides and hormones which represent potential mechanisms for cross talk with other liver cells [2]. Gonadotropin-releasing hormone (GnRH) is a trophic peptide hormone synthesized by hypothalamic neurons and biliary epithelium and exerts its biological effects on cholangiocytes by interaction with the receptor subtype, GnRHR1, expressed by both cholangiocytes and HSCs [3]. Studies have shown that microRNA-200b is associated with the progression of hepatic fibrosis. However, the role of GnRH/GnRHR1/miR-200b axis in the progression of hepatic fibrosis in PSC is unknown. Using a mouse model of PSC (Mdr2^{-/-}), we found that hepatic knockdown of GnRH decreased IBDM and liver fibrosis. *In vivo*, treatment with GnRH increases the expression of miR-200b and markers of fibrosis with an upregulation of the GnRH/GnRHR1 axis and miR-200b in human PSC samples. *In vitro*, inhibition of miR-200b decreases fibrotic gene expression in cultured murine cholangiocyte and HSC lines. In conclusion, these findings provides novel insights that the modulation of the GnRH/GnRHR1/miR-200b axis may regulates the progression of liver fibrosis in PSC.

References

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Keywords

Cholangiocytes, fibrosis, GnRH, PSC