Farnesoid X receptor regulates cystathionase

May 13 2009

The expression and activity of Cystathionase is reduced in rodent models of liver injury, leading to hyper-homocysteinemia and impaired generation of hydrogen sulphide, two factors that contribute to endothelial dysfunction and increased intrahepatic resistance.

In the present study the analysis of the human Cystathionase gene promoter demonstrates the presence of an inverted repeat sequence. Administration of an FXR ligand to carbon tetrachloride treated mice protected against down-regulation of Cystathionase expression, increased hydrogen sulphide generation, reduced portal pressure and attenuated the endothelial dysfunction of isolated and perfused livers.

A research article to be published on May 7, 2009 in the *World Journal of Gastroenterology* addresses this question. The research team led by Dr. Barbara Renga and her colleagues in the University of Perugia, Italy used luciferase transfection assay, Electrophoretic Mobility Shift Assay (EMSA), Chromatin Immunoprecipitation Assay and Real-Time PCR to confirm the role of FXR in the regulation of CSE transcription.

The molecular mechanism of the CSE activation by FXR was revealed by identifying a sequence in the 5' flanking region of CSE gene containing a potential IR1 binding site. Co-transfection of HepG2 cells with luciferase reporter vector containing four copies of this putative IR1 resulted in transactivation of the CSE promoter in presence of an FXR ligand, while the mutation of the IR1 binding site abrogates this response. The functionality of this IR1 site was also confirmed by EMSA and CHIP assay.

In the normal liver the CSE expression was significantly increased when mice were fed a chow diet supplemented with 5 mg/kg body weight of 6E-CDCA while the FXR ligand failed to up-regulate CSE mRNA expression in FXR knock-out mice.

Contraction of presinusoidal myofibroblasts has relevance in regulating intrahepatic resistance and short term administration of 6E-CDCA regulates CSE expression in normal mice, therefore the authors have investigated whether acute administration of an FXR ligand effectively modulates CSE expression in CCl4 treated mice. The author demonstrated that CSE liver expression was down-regulated in an animal model of liver damage induced by CCl4 and that treatment with 6E-CDCA resulted in a robust induction of CSE expression only in FXR +/+ mice

The reduction of CSE expression in the cirrhotic liver contributes to the development of increased intrahepatic resistance and portal hypertension. The authors therefore investigated whether in vivo administration of an FXR ligand modulates hepatic resistance in cirrhotic rats.

In conclusion, they have shown that CSE is an FXR-regulated gene. By linking the deficiency of CSE to the FXR activity the present study provides a new molecular explanation to the pathophysiology of portal hypertension. It also proposes the concept that FXR agonists might correct for the altered generation of endogenous hepatic vasodilators that takes place in chronic liver diseases.

More information: Renga B, Mencarelli A, Migliorati M, Distrutti E, Fiorucci S. Bile-acid-activated farnesoid X receptor regulates hydrogen sulfide production and hepatic microcirculation. *World J Gastroenterol* 2009; 15(17): 2097-2108 www.wjgnet.com/1007-9327/15/2097.asp

Source: World Journal of Gastroenterology (news : web)