Role of nuclear receptors in regulation of cellular oxidative stress and inflammation in alcoholic liver diseases

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Alcoholic liver disease (ALD) is the common liver disease caused by alcohol abuse, which increases global burden of liver disease-related mortality. Chronic alcohol abuse triggers liver injury, which manifests as a broad spectrum of hepatic disorders including steatosis, alcoholic steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. With chronic alcohol consumption, cytochrome P450 2E1 (CYP2E1) is a key microsomal enzyme that induces the generation of reactive oxygen species (ROS) which exacerbate alcohol-induced oxidative stress. Increased cytochrome P450 2E1 (CYP2E1) expression is the main cause of oxidative stress, which exacerbates alcoholic liver diseases (ALDs). Estrogen-related receptor gamma (ERRg) induces CYP2E1 expression and contributes to enhancing alcohol-induced liver injury. Retinoic acid-related orphan receptor alpha (RORa) has antioxidative functions; however, potential cross-talk between ERRg and RORa in the regulation of CYP2E1 has not been studied. We report that RORa suppressed ERRg-mediated CYP2E1 expression. A physical interaction of RORa with ERRgat the ERRresponse element in the CYP2E1 promoter was critical in this suppression. At this site, coregulator recruitment of ERRg was switched from coactivator p300 to the nuclear receptor corepressor 1 in the presence of RORa. Cross-talk between ERRg and RORa was demonstrated *in vivo,* in that administration of JC1-40, a RORa activator, significantly decreased both CYP2E1 expression and the signs of liver injury in ethanol-fed mice, and this was accompanied by coregulator switching. Thus, this nonclassical RORa pathway switched the transcriptional mode of ERRg, leading to repression of alcohol-induced CYP2E1 expression, and this finding may provide a new therapeutic strategy against ALDs (Fig. 1) (1).

Chronic ethanol consumption causes hepatic steatosis and inflammation, which are associated with liver hypoxia. Monocyte chemoattractant protein-1 (MCP-1) is a hypoxia response factor that determines recruitment and activation of monocytes to the site of tissue injury. The level of MCP-1 is elevated in the serum and liver of patients with alcoholic liver disease (ALD); however, the molecular details regarding the regulation of MCP-1 expression are not yet understood completely. Here, we showed the role of liver X receptor a (LXRa) in the regulation of MCP-1 expression during the development of ethanol-induced fatty liver injury using an antagonist, 22-*s*-hydroxycholesterol (22-*s*-HC). First, administration of 22-*s*-HC attenuated the signs of liver injury with decreased levels of

MCP-1 and its receptor CCR2 in ethanol-fed mice. Second, hypoxic conditions or treatment with the LXRa agonist GW3965 significantly induced the expression of MCP-1, which was completely blocked by treatment with 22-*s*-HC or infection by shLXRa lentivirus in the primary hepatocytes. Third, overexpression of LXRa or GW3965 treatment increased MCP-1 promoter activity by increasing binding of hypoxia inducible factor-1a to the hypoxia response elements together with LXRa. Finally, treatment by recombinant MCP-1 increased the level of expression of LXRa and LXRa-dependent lipid droplet accumulation in both hepatocytes and Kupffer cells. We show that LXRa and its ligand-induced upregulation of MCP-1 and MCP-1-induced LXRa-dependent lipogenesis plays a key role in the autocrine and paracrine activation of MCP-1 in the pathogenesis of alcoholic fatty liver disease and this activation may provide a new promising target for ALD therapy (Fig. 2) (2).

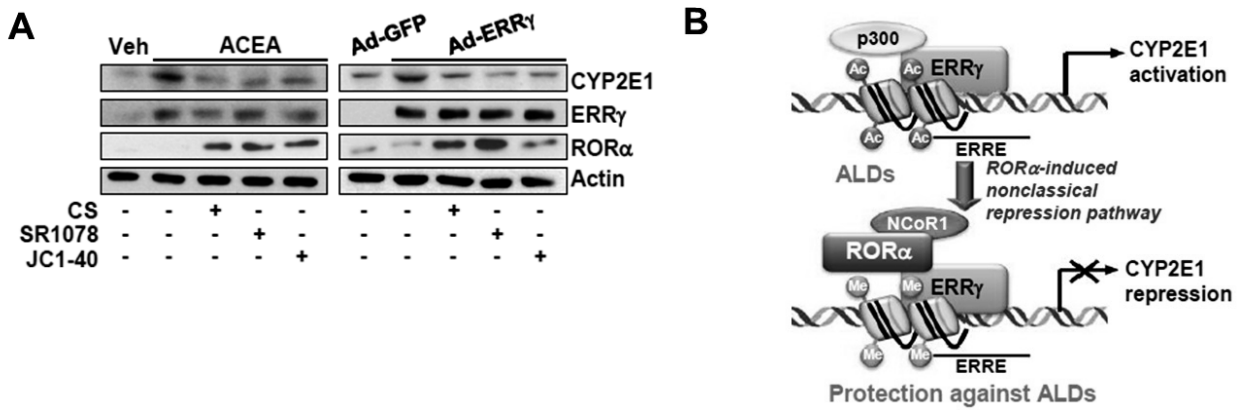

Figure 1. A non-classical RORa pathway suppresses the ERRg-mediated induction of CYP2E1 gene expression. A. Primary cultures of mouse hepatocytes were treated with ACEA in the presence or absence of CS, SR1078, or C1-40 for 24 h. Or the hepatocytes were infected by Ad-GFP or Ad-ERRgand then underwent the same treatment. The protein levels were measured by western blotting. B.Schematic model for repression of the ERRg-induced CYP2E1 gene expression by RORa-induced cofactor switchin the hepatocytes under ethanol exposure.

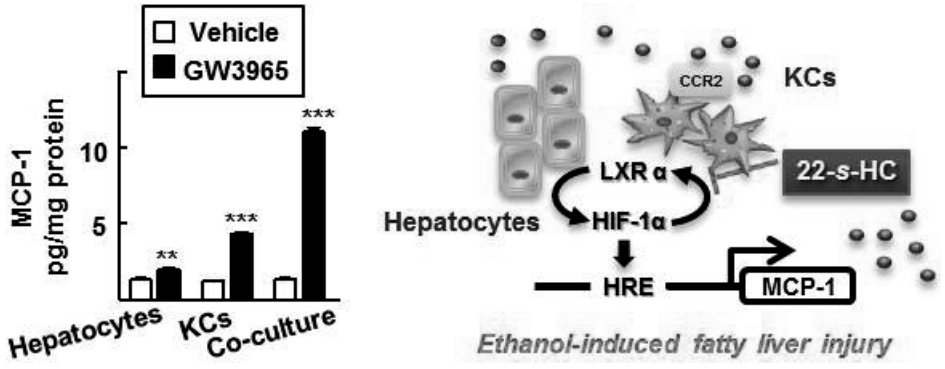

Figure 2. LXRainduces the autocrine and paracrine activation of MCP-1 in the pathogenesis of ALDs. A. The primary hepatocytes were cultured with or without Kupffer cells for 4 h. And the cells weretreated with vehicle or GW3965 for 48 h. MCP-1 protein secreted into the culture supernatants was quantified by ELISA.B.Schematic model for the activation of MCP-1 by LXRa and HIF-1a, which mediates the ethanol-induced fatty liver injury.

References

1. Han YH, Kim DK, Na TY, Ka NL, Choi HS, Lee MO. RORαswitches transcriptional mode of ERRγthat results intranscriptional repression of CYP2E1 under ethanol-exposure.Nucleic Acids Res. 2015. [Epub ahead of print]
2. Na TY, Han YH, Ka NL, Park HS, Kang YP, Kwon SW, et al. 22-S-Hydroxycholesterol protects against ethanol-induced liver injury by blocking the auto/paracrine activation of MCP-1 mediated by LXRα. Na TY, Han YH, Ka NL, Park HS, Kang YP, Kwon SW, Lee BH, Lee MO. J Pathol. 2015;235:710-20.