ERRγ-inducible FGF23 promotes alcoholic liver injury through enhancing CYP2E1 mediated hepatic oxidative stress

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Abstract

Fibroblast growth factor 23 (FGF23) is a member of endocrine FGF family, along with FGF15/19 and FGF21. Recent reports showed that under pathological conditions, liver produces FGF23, although the role of hepatic FGF23 remains nebulous. Here, we investigated the role of hepatic FGF23 in alcoholic liver disease (ALD) and delineated the underlying molecular mechanism. FGF23 expression was compared in livers from alcoholic hepatitis patients and healthy controls. The role of FGF23 was examined in hepatocyte-specific knock-out (LKO) mice of cannabinoid receptor type 1 (CB1R), estrogen related receptor γ (ERRγ), or FGF23. Animals were fed with an alcohol-containing liquid diet alone or in combination with ERRγ inverse agonist. FGF23 is mainly expressed in hepatocytes in the human liver, and it is upregulated in ALD patients. In mice, chronic alcohol feeding leads to liver damage and induced FGF23 in liver, but not in other organs. FGF23 is transcriptionally regulated by ERRγ in response to alcohol-mediated activation of the CB1R. Alcohol induced upregulation of hepatic FGF23 and plasma FGF23 levels is lost in ERRγ-LKO mice, and an inverse agonist mediated inhibition of ERRγ transactivation significantly improved alcoholic liver damage. Moreover, hepatic CYP2E1 induction in response to alcohol is FGF23 dependent. In line, FGF23-LKO mice display decreased hepatic CYP2E1 expression and improved ALD through reduced hepatocyte apoptosis and oxidative stress. We recognized CBIR-ERRγ-FGF23 axis in facilitating ALD pathology through hepatic CYP2E1 induction. Thus, we propose FGF23 as a potential therapeutic target to treat ALD.