Hedgehog signaling is a potent regulator of liver lipid metabolism and reveals a GLI-code associated with steatosis

Matz-Soja M, Rennert C, Schönefeld K, Aleithe S, Boettger J, Schmidt-Heck W, Weiss TS, Hovhannisyan A, Zellmer S, Klöting N, Schulz A, Kratzsch J, Guthke R, Gebhardt R (2016) Hedgehog signaling is a potent regulator of liver lipid metabolism and reveals a GLI-code associated with steatosis *eLife* 5, e13308.

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in industrialized countries and is increasing in prevalence. The pathomechanisms, however, are poorly understood. This study assessed the unexpected role of the Hedgehog pathway in adult liver lipid metabolism. Using transgenic mice with conditional hepatocyte-specific deletion of Smoothened in adult mice, we showed that hepatocellular inhibition of Hedgehog signaling leads to steatosis by altering the abundance of the transcription factors GLI1 and GLI3. This steatotic 'Gli-code' caused the modulation of a complex network of lipogenic transcription factors and enzymes, including SREBP1 and PNPLA3, as demonstrated by microarray analysis and siRNA experiments and could be confirmed in other steatotic mouse models as well as in steatotic human livers. Conversely, activation of the Hedgehog pathway reversed the "Gli-code" and mitigated hepatic steatosis. Collectively, our results reveal that dysfunctions in the Hedgehog pathway play an

important role in hepatic steatosis and beyond.

Involved units

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