Hepatic Hedgehog Signaling Participates in the Crosstalk between Liver and Adipose Tissue in Mice by Regulating FGF21

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Abstract

The Hedgehog signaling pathway regulates many processes during embryogenesis and the homeostasis of adult organs. Recent data suggest that central metabolic processes and signaling cascades in the liver are controlled by the Hedgehog pathway and that changes in hepatic Hedgehog activity also affect peripheral tissues, such as the reproductive organs in females. Here, we show that hepatocyte-specific deletion of the Hedgehog pathway is associated with the dramatic expansion of adipose tissue in mice, the overall phenotype of which does not correspond to the classical outcome of insulin resistance-associated diabetes type 2 obesity. Rather, we show that alterations in the Hedgehog signaling pathway in the liver lead to a metabolic phenotype that is resembling metabolically healthy obesity. Mechanistically, we identified an indirect influence on the hepatic secretion of the fibroblast growth factor 21, which is regulated by a series of signaling cascades that are directly transcriptionally linked to the activity of the Hedgehog transcription factor GLI1. The results of this study impressively show that the metabolic balance of the entire organism is maintained via the activity of morphogenic signaling pathways, such as the Hedgehog cascade. Obviously, several pathways are orchestrated to facilitate liver metabolic status to peripheral organs, such as adipose tissue.