Conditional loss of hepatocellular Hedgehog signaling in female mice leads to the persistence of hepatic steroidogenesis, androgenization and infertility.

Rennert C, Eplinius F, Hofmann U, Johänning J, Rolfs F, Schmidt-Heck W, Guthke R, Gebhardt R, Ricken AM, Matz-Soja M (2017) Conditional loss of hepatocellular Hedgehog signaling in female mice leads to the persistence of hepatic steroidogenesis, androgenization and infertility. *Arch Toxicol* 91(11), 3677-3687.

Abstract

The Hedgehog signaling pathway is known to be involved in embryogenesis, tissue remodeling, and carcinogenesis. Because of its involvement in carcinogenesis, it seems an interesting target for cancer therapy. Indeed, Sonidegib, an approved inhibitor of the Hedgehog receptor Smoothened (Smo), is highly active against diverse carcinomas, but its use is also reported to be associated with several systemic side effects. Our former work in adult mice demonstrated hepatic Hedgehog signaling to play a key role in the insulin-like growth factor axis and lipid metabolism. The current work using mice with an embryonic and hepatocyte-specific Smo deletion describes an adverse impact of the hepatic Hedgehog pathway on female fertility. In female SAC-KO mice, we detected androgenization characterized by a 3.3-fold increase in testosterone at 12 weeks of age based on an impressive induction of steroidogenic gene expression in hepatocytes, but not in the classic steroidogenic organs (ovary and adrenal gland). Along with the elevated level of

testosterone, the female SAC-KO mice showed infertility characterized by juvenile reproductive organs and acyclicity. The endocrine and reproductive alterations resembled polycystic ovarian syndrome and could be confirmed in a second mouse model with conditional deletion of Smo at 8 weeks of age after an extended period of 8 months. We conclude that the down-regulation of hepatic Hedgehog signaling leads to an impaired hormonal balance by the induction of steroidogenesis in the liver. These effects of Hedgehog signaling inhibition should be considered when using Hedgehog inhibitors as anti-cancer drugs.

Involved units

Microbiome Dynamics Gianni Panagiotou Read more

Leibniz-HKI-Authors

Reinhard Guthke

Details

Wolfgang Schmidt-Heck

Details

Identifier

doi: 10.1007/s00204-017-1999-5

PMID: 28560483