Impact of Hedgehog modulators on signaling pathways in primary murine and human hepatocytes in vitro: insights into liver metabolism

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Abstract

The Hedgehog (Hh) signaling pathway is essential for maintaining homeostasis during embryogenesis and in adult tissues. In the liver, dysregulation of this pathway often leads to liver cancer development. Recent studies also suggest that disturbances in the Hh pathway can affect liver metabolism in healthy livers through interactions with other signaling pathways, such as the Wnt/β-catenin pathway. As a result, the Hh pathway has emerged as a promising target for therapeutic intervention. However, little is known about the effects of Hh modulators on healthy hepatocytes. In our study, we investigated the effects of the Hh agonists SAG (300 nM) and triamcinolone acetonide (40 µM), as well as the antagonists RU-SKI 43 (100 nM), cyclopamine (5 µM), budesonide (25 µM), GANT61 (0.5 µM), and vismodegib (1 µM) on healthy mouse and human primary hepatocytes in vitro. We employed toxicological, transcriptomic, proteomic, and functional assays, including proliferation and Seahorse assays. Our results show that these compounds significantly impact metabolic pathways such as lipid and glucose metabolism at both transcriptional and protein levels. Mechanistically, our data suggest the involvement of both canonical and non-canonical Hedgehog pathways, a phenomenon not previously described in hepatocytes. These findings highlight the diverse effects of these compounds on signaling and key metabolic functions in the liver, which emphasizes the need to investigate the hepatic Hh cascade and its metabolic control in depth. As the compounds regulate different aspects of metabolism, they need to be carefully studied in appropriate model systems for specific therapeutic use.