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The Hedgehog signaling pathway in nonalcoholic steatohepatitis and hepatocellular carcinoma: Fueling the fire?

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Introduction: The global "obesity epidemic" has thrust non-alcoholic steatohepatitis (NASH) and the metabolic syndrometo the forefront of health-related concerns, and both are linked to the rising incidence of hepatocellular carcinoma (HCC). Successful treatments are lacking. Deeper insights into the cellular signaling mechanisms driving these processes are needed and may shed light on possible therapeutic targets. The Hh signaling pathway was first discovered in 1980 as an embryonic morphogen regulating *Drosophila* segmentation patterning. Over the past decade, however, the importance of Hh signaling in human liver disease has been recognized. Hh pathway activity has been identified in adult and pediatric NASH and HCC. For example, Hh signaling has been linked to NASH ballooning; Hh ligands are released from ballooned hepatocytes and act as damage associated molecular pattern molecules (DAMPs) to drive myofibroblastic fibrogenesis. The Hh pathway has been linked to the ductular reaction and fibrosis progression in adult NASH. Furthermore, Hh pathway signaling was recently shown to be downregulated in NASH following successful Vitamin E therapy. Finally, Hh signaling has also been linked to hepatocellular carcinogenesis via the Warburg effect. Tumor cells release Hh ligands which act in a paracrine manner to drive the production of lactate in neighboring stellate cells. The stellate cell lactate is then used by tumor cells to fuel aerobic glycolytic activity and ATP production.

Conclusions: Recent advances in our understanding of the importance of Hh signaling in NASH and HCC may provide insights into potential therapeutic targets for these emerging worldwide diseases.

Biography

Cynthia D Guy completed her MD degree from the Medical University of South Carolina in Charleston, SC in 1993 and completed her AP/CP training at Emory University in Atlanta, GA 1998. She then completed a Cytopathology Fellowship at Duke University in Durham, NC in 1999. She is currently an Associate Professor and the Chief of the Liver and GI Section in the Department of Pathology at Duke University. She has published more than 75 peer-reviewed manuscripts. She enjoys a busy clinical practice and participation in translational research.

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