The autotaxin-lysophosphatidic acid pathway emerges as a therapeutic target to prevent liver cancer

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The autotaxin-lysophosphatidic acid pathway emerges as a therapeutic target to prevent liver cancer

Derek J. Erstad, Andrew M. Tager, Yujin Hoshida, and Bryan C. Fuchs

Hepatocellular carcinoma (HCC) is a major cause of cancer death, with rising incidence worldwide. Cirrhosis is the main risk factor for HCC, regardless of underlying etiology. In the United States, obesity and Type II diabetes with accompanying non-alcoholic steatohepatitis (NASH) are predicted to supplant hepatitis C virus (HCV) as the major cause of HCC over the next decade. HCC 5-year survival is less than 15%, which is driven by multiple factors. Screening for early stage disease remains a challenge, and most cases are diagnosed at a late stage when potentially curative transplant or resection is no longer an option. HCC is also insensitive to many chemotherapeutics, as evidenced by Sorafenib remaining the only Food and Drug Administration (FDA)-approved therapy for advanced HCC after nearly a decade, despite its modest benefits. Early results with immunotherapy are encouraging, though response rates are still only approximately 20%. For these reasons, chemoprevention may currently be a more promising strategy, than increasing screening efforts, to reduce deaths attributable to the dismal prognosis of HCC.

Therapies that can both delay the progression of fibrosis to cirrhosis and prevent the development of HCC would therefore be of particular interest. Recently, a novel ectonucleotide pyrophosphatase/phosphodiesterase 2 (ENPP2, best known as autotaxin (ATX)) inhibitor PAT-505 was shown to reduce fibrosis progression and HCC development in animals, identifying ATX-LPA signaling as a novel chemoprevention strategy for cirrhosis and HCC.

Using transcriptome meta-analysis, we recently identified the autotaxin (ATX)-lysophosphatidic acid (LPA) pathway as a regulator of hepatocellular carcinoma (HCC) risk in human cirrhosis patients. Pharmacological targeting of this pathway reduced fibrosis progression and HCC development in animals, identifying ATX-LPA signaling as a novel chemoprevention strategy for cirrhosis and HCC.

AUTHOR'S VIEW

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collagen-secreting activated hepatic stellate cells, suggesting an integral link between the cell types that promote liver fibrosis and hepatocarcinogenesis. In fact, treatment of rats in a diethylnitrosamine (DEN) model of hepatic fibrosis and HCC, that has been shown to closely resemble human disease, with either an ATX inhibitor (AM063) or an LPAR1 antagonist (AM095) resulted in decreased histological fibrosis and reduced HCC development, establishing for the first time an association between ATX-LPA signaling and hepatocarcinogenesis. More recently, it was shown that hepatocyte-specific Atx-deficient mice are protected from both fibrosis development in response to carbon tetrachloride (CCl₄), and HCC development in response to a single injection of DEN and repeated administrations of CCl₄, thus confirming our original findings.

While results have not been reported yet, two trials examining LPA receptor antagonists have recently completed: a phase II trial in idiopathic pulmonary fibrosis of an LPAR1-selective antagonist BMS-986020 (NCT01766817), and a phase II trial in systemic sclerosis of an LPAR1, 3 antagonist SAR100842 (NCT01651143). In addition, an ATX inhibitor GLPG1690 is currently under investigation in a phase II trial for idiopathic pulmonary fibrosis (NCT02738801).

In summary, although more work is needed to characterize the role of other LPA receptors in chronic liver disease, and to determine whether ATX or LPA receptors are the better therapeutic objectives, this pathway is now an intriguing target in chronic liver disease. Based on our preclinical findings, treatment with ATX inhibitors and/or LPA receptor antagonists to reduce fibrosis in chronic liver disease patients may hold great promise for the prevention of HCC.

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