MOLECULAR & CELLULAR ONCOLOGY
2017, VOL. 4, NO. 3, e1311827 (2 pages)
https://doi.org/10.1080/23723556.2017.1311827

Taylor & Francis
Taylor & Francis Group

AUTHOR'S VIEW

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

Derek J. Erstad[a], Andrew M. Tager[b], Yujin Hoshida[c], and Bryan C. Fuchs[a]

[a]Division of Surgical Oncology, Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA; [b]Center for Immunology and Inflammatory Diseases, Fibrosis Research Center, Division of Pulmonary and Critical Care Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; [c]Division of Liver Diseases, Department of Medicine, Liver Cancer Program, Tisch Cancer Institute, Graduate School of Biomedical Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA

ABSTRACT

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.

ARTICLE HISTORY
Received 15 March 2017
Revised 22 March 2017
Accepted 22 March 2017

KEYWORDS
ATX; chemoprevention; cirrhosis; fibrosis; HCC; hepatocellular carcinoma; LPA; LPAR1; NASH; non-alcoholic steatohepatitis

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.[1] 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%.[2] 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.[3]

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 in two animal models of NASH: the Stelic Mouse Animal Model (STAM) developed by Stelic Institute, and a choline-deficient, L-amino acid-defined, high-fat diet (CDAHFD) containing 60 kcal %fat and 0.1% methionine.[4] ATX is a secreted enzyme that converts lysophosphatidylcholine (LPC) to the bioactive phospholipid lysophosphatidic acid (LPA). LPA signals through a family of at least 6 G protein-coupled receptors designated LPA receptors 1–6 (LPAR1-LPAR6). Signaling through these receptors has been implicated in the pathogenesis of fibrosis and cancer in several organs, through effects on cell proliferation, migration, and survival.[5]

HCV infection has recently been shown to increase ATX expression to support viral replication,[6] and consistently, serum ATX levels are known to be increased in chronic HCV patients where they correlate with fibrosis stage,[7] a known risk factor for HCC. The role of ATX-LPA signaling in liver carcinogenesis had not been examined until recently however. To explore pan-etiology targets for HCC chemoprevention, we performed regulatory gene network modeling by synthesizing genome-wide transcriptome profiles of clinical fibrotic/cirrhotic liver tissue (n = 523).[8] The transcriptome meta-analysis identified 31 tightly co-regulated gene modules forming two major groups connected by three central hub modules. One of these central hub modules was uniquely activated in association with increased risk of *de novo* HCC recurrence. To identify functional regulators of this module, we systematically surveyed enrichment of experimental genetic perturbation transcriptome signatures defined by small hairpin RNA (shRNA) library-based knockdown of 5,272 genes in an unbiased manner (NIH Library of Integrated Cellular Signatures [LINCS] project). We identified five upstream regulator genes that were highly associated with the HCC risk gene module including *LPAR1*.

Interestingly, while *Atx* expression is mainly confined to the hepatocytes in the liver, *Lpar1* was highly expressed in the

CONTACT Bryan C. Fuchs bfuchs@mgh.harvard.edu Division of Surgical Oncology, Massachusetts General Hospital Cancer Center and Harvard Medical School, 55 Fruit Street, WRN 401, Boston, MA 02114, USA.

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,[9] 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.[8] More recently, it was shown that hepatocyte-specific *Atx*-deficient mice are protected from both fibrosis development in response to carbon tetrachloride (CCl_4), and HCC development in response to a single injection of DEN and repeated administrations of CCl_4, thus confirming our original findings.[10]

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 the liver. Moreover, while local production of LPA is certainly a key determinant in driving fibrosis, serum ATX activity could be a useful, non-invasive biomarker to identify patients for treatment and to monitor response to therapy, given the observed increase in serum ATX activity in patients with 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.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Funding

DJE was supported by the National Cancer Institute under grant T32CA071345; AMT was supported by the National Heart, Lung, and Blood Institute under grant R01HL133153; YH was supported by the National Institute of Diabetes and Digestive and Kidney Diseases under grant R01DK099558, the European Union under grant ERC-2014-AdG-671231 HEPCIR, the Irma T. Hirschl Trust, and the US Department of Defense under grant number W81XWH-16–1–0363; BCF was supported by the National Cancer Institute under grant K01CA140861, and the National Institutes of Diabetes and Digestive and Kidney Diseases under grants R01DK104956 and U01DK104302.

References

1. El-Serag HB, Kanwal F. Epidemiology of hepatocellular carcinoma in the United States: where are we? Where do we go?. Hepatology. 2014; 60(5):1767-75; PMID:24839253; https://doi.org/10.1002/hep.27222
2. Kudo M. Immune checkpoint inhibition in Hepatocellular Carcinoma: Basics and ongoing clinical trials. Oncology. 2017; 92 Suppl 1:50-62; PMID:28147363; https://doi.org/10.1159/000451016
3. Hoshida Y, Fuchs BC, Tanabe KK. Prevention of hepatocellular carcinoma: potential targets, experimental models, and clinical challenges. Curr Cancer Drug Targets. 2012; 12(9):1129-59; PMID:22873223; https://doi.org/CCDT-EPUB-20120803-4 [pii]
4. Bain G, Shannon KE, Huang F, Darlington J, Goulet L, Prodanovich P, Ma GL, Santini AM, Stein AJ, Lonergan D, et al. Selective inhibition of Autotaxin is efficacious in mouse models of liver Fibrosis. J Pharmacol Exp Ther. 2017; 360(1):1-13; PMID:27754931; https://doi.org/10.1124/jpet.116.237156
5. Aikawa S, Hashimoto T, Kano K, Aoki J. Lysophosphatidic acid as a lipid mediator with multiple biological actions. J Biochem. 2015; 157 (2):81-9; PMID:25500504; https://doi.org/10.1093/jb/mvu077
6. Farquhar MJ, Humphreys IS, Rudge SA, Wilson GK, Bhattacharya B, Ciaccia M, Hu K, Zhang Q, Mailly L, Reynolds GM, et al. Autotaxin-lysophosphatidic acid receptor signalling regulates hepatitis C virus replication. J Hepatol. 2017; 66(5):919–929; PMID:28126468; https://doi.org/10.1016/j.jhep.2017.01.009
7. Nakagawa H, Ikeda H, Nakamura K, Ohkawa R, Masuzaki R, Tateishi R, Yoshida H, Watanabe N, Tejima K, Kume Y, et al. Autotaxin as a novel serum marker of liver fibrosis. Clin Chim Acta. 2011; 412(13–14): 1201-06; PMID:21419756; https://doi.org/10.1016/j.cca.2011.03.014
8. Nakagawa S, Wei L, Song WM, Higashi T, Ghoshal S, Kim RS, Bian CB, Yamada S, Sun X, Venkatesh A, et al. Molecular liver cancer prevention in cirrhosis by organ transcriptome analysis and lysophosphatidic acid pathway inhibition. Cancer Cell. 2016; 30(6):879-90; PMID:27960085; https://doi.org/10.1016/j.ccell.2016.11.004
9. Fuchs BC, Hoshida Y, Fujii T, Wei L, Yamada S, Lauwers GY, McGinn CM, DePeralta DK, Chen X, Kuroda T, et al. Epidermal growth factor receptor inhibition attenuates liver fibrosis and development of hepatocellular carcinoma. Hepatology. 2014; 59(4):1577-90; PMID:24677197; https://doi.org/10.1002/hep.26898
10. Kaffe E, Katsifa A, Xylourgidis N, Ninou I, Zannikou M, Harokopos V, Foka P, Dimitriadis A, Evangelou K, Moulas AN, et al. Hepatocyte autotaxin expression promotes liver fibrosis and cancer. Hepatology. 2017; e65(4):1369–1383; PMID:27981605; https://doi.org/10.1002/hep.28973