News Release

Title

Discovery of the Inhibitory Effect on Liver Tumor Development by Bile Acid Transporter Inhibitor (Elobixibat) in Non-alcoholic Steatohepatitis Model Mice

Key Points

- There is currently no effective method for suppressing liver cancer that originates from NASH (Non-alcoholic Steatohepatitis).
- Previous research has indicated that bile acids play a role in the development of liver tumors. However, we are the first to demonstrate that by using a drug to inhibit the reabsorption of these bile acids, it's possible to suppress liver tumor growth in a mouse model.
- Furthermore, we reported that inhibiting the reabsorption of bile acids leads to a decrease in the proportion of Gram-positive bacteria in the gut.

Summary

A research group composed of Dr. Yoshiaki Sugiyama, Assistant Professor Kenta Yamamoto, Lecturer Takashi Honda, Professor Hiroki Kawashima (Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine), Lecturer Tomomi Asano (College of Human Life and Environment, Kinjo Gakuin University), Professor Atsushi Enomoto (Department of Pathology, Nagoya University Graduate School of Medicine), Professor Kei Zaitsu (Multimodal Informatics and Wide-Data Analytics Laboratory (MiWA-Lab.), Department of Computational Systems Biology, Faculty of Biology-Oriented Science and Technology, Kindai University), Professor Mitsuhiro Fujishiro (Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo) and their colleagues, reported that the drug Elobixibat, which inhibits the reabsorption of bile acids, reduces the incidence of liver tumors originating from a Non-alcoholic Steatohepatitis (NASH) mouse model.

A research group from Dr. Yoshiaki Sugiyama, Dr. Kenta Yamamoto, Dr. Takashi Honda, and Prof. Hiroki Kawashima (the Nagoya University Graduate School of Medicine, Department of Gastroenterology and Hepatology) has reported that Elobixibat, a drug that inhibits the reabsorption of bile acids, reduces the incidence of liver tumors originating from a Non-alcoholic Steatohepatitis (NASH) mouse model.

Recent years have witnessed a surge in liver cancer cases attributed to fatty liver conditions and Non-Alcoholic Steatohepatitis (NASH). Despite the growing

incidence, effective treatments have been elusive. Some studies have suggested that elevated levels of bile acids in the liver may contribute to tumor initiation and growth. Bile acids are produced in the liver, secreted into the intestines, metabolized by gut bacteria, and then reabsorbed into the liver—a process known as enterohepatic circulation.

Our research team has recently focused on the potential of Elobixibat, a drug typically used as a laxative, to inhibit the reabsorption of these bile acids. In mouse models genetically predisposed to develop liver tumors as a result of NASH, we found that the administration of Elobixibat led to decreased levels of bile acids in both the bloodstream and the liver. Remarkably, this is the first study to report a decrease in tumor incidence related to such conditions.

Moreover, our research identified a significant alteration in the gut microbiota within the colon due to suppressed bile acid reabsorption. This pivotal finding opens the door for the development of new strategies aimed at inhibiting bile-acid mediated carcinogenesis, and could also provide crucial insights into the mechanisms underlying tumor formation.

The research findings have been published in an online advance edition of Hepatology International, the esteemed scientific journal of the Asia-Pacific Association for the Study of the Liver, dated September 4th, 2023.

Research Background

Even without excessive alcohol consumption, some individuals develop Non-Alcoholic Fatty Liver Disease (NAFLD). A small percentage of these patients not only experience fat accumulation but also suffer from liver damage, including inflammation and fibrosis. This advanced stage of the condition is known as Non-Alcoholic Steatohepatitis (NASH), which can eventually lead to liver cancer in some cases. Current medical science offers no effective prevention methods for these conditions.

The complexity of mechanisms behind the onset of liver cancer—ranging from lipid metabolism disorders and gut microbiota imbalance to bile acid fluctuations and oxidative stress—has made it challenging to identify the most critical factors involved. Our research team took notice of prior studies showing that mice fed a high-fat diet developed fatty liver and increased levels of bile acids in the liver, both of which are linked to tumor development. We also considered reports suggesting that the use of antibiotics to suppress gut microbiota led to a reduced incidence of tumor formation.

Focusing on these insights, our team evaluated the potential tumor-suppressing effects of Elobixibat—a drug commonly used as a laxative and known to inhibit bile acid reabsorption—whose relation to tumor suppression has not been extensively reported on.

Research Results

Diethylnitrosamine was administered to mice at three weeks of age, followed by a 20-week course of a high-fat diet lacking choline from week 8 to week 28. This protocol established a mouse model that develops liver tumors originating from NASH. In the Elobixibat group, we administered a high-fat diet mixed with the drug from week 8 to week 28 and compared the incidence of liver tumors.

Both groups showed no significant differences in weight gain or fibrosis levels. However, the Elobixibat group exhibited more than a 50% reduction in tumor incidence. We observed a decrease in total bile acid concentrations in the blood, and within the liver, the levels of key bile acids like cholic acid, glycocholic acid, and taurocholic acid were markedly reduced. Additionally, the ratio of Gram-positive bacteria in the gut microbiota was significantly lowered. Bile acids have been reported to inhibit the growth of Gram-positive bacteria. Our findings indicate that Elobixibat suppresses bile acid reabsorption, thus reducing bile acid levels in both the serum and liver while increasing them in the colon. The changes in microbiota showed a trend similar to that induced by vancomycin, a known tumor-suppressing agent, suggesting that shifts in microbiota may also be associated with tumor-suppressive effects.

Research Summary and Future Perspective

This study is the first to demonstrate the potential of reducing tumor incidence by using a drug that inhibits bile acid reabsorption. While humans and mice have different types of bile acids and gut microbiota, the discovery of a mechanism that lowers the likelihood of tumor formation by inhibiting the absorption of bile acids in the liver is significant. This research provides valuable insights for the development of new treatments in cancer prevention, an area where effective therapies are currently lacking.

Publication

Sugiyama Y, Yamamoto K, Honda T, Kato A, Muto H, Yokoyama S, Ito T, Imai N, Ishizu Y, Nakamura M, Asano T, Enomoto A, Zaitsu K, Ishigami M, Fujishiro M, Kawashima H. Impact of elobixibat on liver tumors, microbiome, and bile acid levels in a mouse model of nonalcoholic steatohepatitis. Hepatol Int. 2023 Sep 4. doi: 10.1007/s12072-023-10581-2. Epub ahead of print. PMID: 37666952.

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