Discovery of biomarkers to predict therapeutic efficacy of pharmacotherapy for hepatocellular carcinoma

Department of Gastroenterology and Hepatology, Graduate School of Medicine

Assistant Professor Takahiro Kodama Researchmap https://researchmap.jp/takahirokodama

Professor Tetsuo Takehara Researchmap https://researchmap.jp/takeharatetsuo

Abstract

Patients with chronic liver disease are known to develop hepatocellular carcinoma (HCC) as the disease progresses, and its development has a significant impact on their prognosis. The efficacy of various molecular targeted therapies currently used for advanced HCC is less than 30%, but there are no useful biomarkers that can predict the efficacy of drugs. HCC is known to have a variety of genetic abnormalities that vary from patient to patient. But the impact of this inter-tumor heterogeneity on the effecacy of drug therapy is not well understood. We have developed a screening model in which the inte-tumor heterogeneity of oncogenes is recapitulated in mice, and found that FGF19-driven HCC is malignant but highly sensitive to lenvatinib, a molecular targeted therapy used in HCC. In addition, we identified that serum levels of ST6GAL1, which is regulated by the FGF19 gene, are useful for detecting FGF19-driven HCC and lenvatinib-sensitive HCC.

Background & Results

Early detection of HCC is extremely important, especially for highly malignant HCC, but the sensitivity of currently used tumor markers is not sufficient. In addition, the efficacy of various molecular targeted therapies currently used for advanced HCC is less than 30%, but there are no useful biomarkers that can predict the efficacy of drugs and serve as indicators for drug selection. HCC is known to have a variety of genetic abnormalities that vary from patient to patient. On the other hand, the impact of this inter-tumor heterogeneity on the therapeutic effect of drug therapy is not well understood. We hypothesized that inter-tumor heterogeneity due to differences in oncogenes affects the grade of cancer and the therapeutic effect of drug therapy. First, we established a method to introduce multiple oncogenes into hepatocytes at once, and succeeded in creating a novel mouse model that develops HCC with high inter-tumor heterogeneity in which oncogenes are randomly activated. The percentage of tumors expressing the FGF19 gene was significantly reduced when this model was treated with lenvatinib, indicating that FGF19-driven HCC is highly sensitive to lenvatinib. Next, we identified ST6GAL1, a secreted protein whose expression is regulated by FGF19. We also found that serum ST6GAL1 can be used to select HCC with poor prognosis that express high levels of FGF19. Furthermore, by stratifying patients based on serum ST6GAL1 levels, we found that the prognosis of patients in the high ST6GAL1 group treated with lenvatinib was significantly longer than that of patients treated with other drugs. These results indicate that serum ST6GAL1 levels may be useful as a biomarker for the identification of high-grade HCC and the selection of optimal drugs in liver cancer drug therapy.

Significance of the research and Future perspective

The clinical application of the biomarker ST6GAL1 is expected to contribute to the detection of highly-malignant HCC and to the selection of the most appropriate drug for patients with advanced HCC, thereby improving their prognosis.

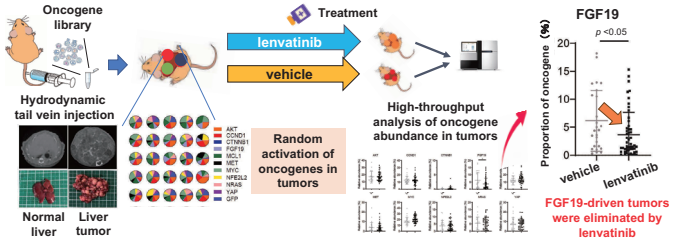

Figure 1. The novel mouse model that reproduces the inter-tumor oncogene heterogeneity of liver tumors and discovery of high susceptibility of FGF19-driven tumors to lenvatinib treatment

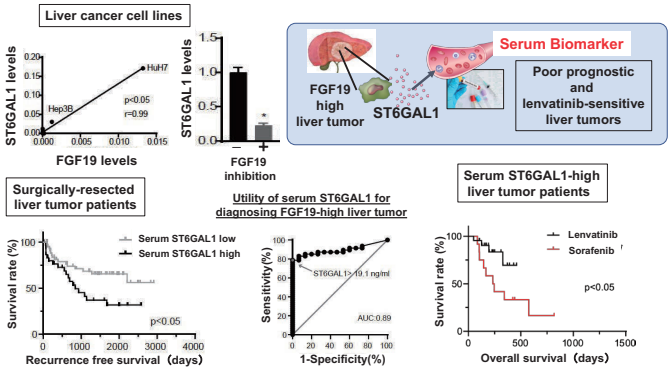

Figure 2. Serum ST6GAL1 is a novel biomarker for predicting the poor prognostic and lenvatinib-sensitive liver cancer

Patent	Japanese Patent Application No. 2020-165604
Treatise	Myojin, Y; Kodama, T; Maesaka, K et al. ST6GAL1 is a Novel Serum Biomarker for Lenvatinib-susceptible FGF19-driven Hepatocellular Carcinoma. Clin Cancer Res. 2021 Feb 15; 27(4): 1150-1161. doi: 10.1158/1078-0432.CCR-20-3382.
URL	https://www.med.osaka-u.ac.jp/activities/results/2020year/2020myojin-kodama https://www.amed.go.jp/news/release_20201208-01.html
Keyword	hepatocellular carcinoma, mouse model, FGF19, ST6GAL1, molecular targeted therapy