Development of prophylactic therapies and risk biomarkers for liver cancer in chronic liver disease

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Abstract

In patients with chronic liver disease, p53 is constitutively activated in hepatocytes. We found that p53 activation in hepatocytes causes hepatocyte cell death and senescence, leading to the emergence of hepatic progenitor cells and liver cancer development. This process is suppressed by acyclic retinoid, which also reduced liver cancer in a mouse model. Patients with chronic liver disease who have high hepatic expression levels of p21, a protein that increases with p53 activation, are more likely to develop liver cancer (Ref.1).

Senescence cells secrete various proteins, one of which is GDF15 (growth differentiation factor 15). In patients with steatotic liver disease, those with higher serum levels of GDF15 were found to be more likely to develop liver cancer later (Ref.2). Additionally, using proteomic analysis, we found that patients with steatotic liver disease who had high serum levels of Fibulin-3 were also more likely to develop liver cancer (Ref.3)

Background & Results

Patients with chronic liver disease progress from chronic hepatitis to cirrhosis, eventually leading to liver cancer. However, there are no preventive treatments for liver cancer. It is crucial to clarify the mechanisms of liver cancer development and establish preventive therapies based on these mechanisms, as well as biomarkers that can help identify patients at high risk of developing liver cancer.

In patients with chronic liver disease, p53 is constitutively activated in hepatocytes. Using a mouse model, we discovered that activating p53 in hepatocytes promotes liver cancer development. In these mice, we observed hepatocyte cell death and senescence, along with worsening inflammation, which led to emergence of hepatic progenitor cells. These progenitor cells were found to transform into cancer cells. When treated with acyclic retinoid, the emergence of hepatic progenitor cells was suppressed, and the incidence of liver cancer was reduced (Fig.1). In patients with chronic liver disease, those with higher hepatic expression of the p21—a marker of p53 activation—also had a higher incidence of liver cancer (Ref.1) (Fig2).

On the other hand, we focused on GDF15, a protein secreted by senescent cells, and found that patients with steatotic liver disease who had high serum levels of GDF15 were more likely to develop liver cancer (Ref.2). By combining the Fib-4 index, a liver stiffness risk index, we can more effectively narrow down patients at high risk of developing liver cancer, liver deterioration, or poor prognosis. (Fig.3) (Ref.2). Furthermore, through proteomic analysis aimed at discovering new biomarkers, we found that patients with steatotic liver disease who had high serum levels of Fibulin-3 were also more likely to develop liver cancer (Ref.3).

Significance of the research and Future perspective

Our research findings may lead to the development of new preventive methods for liver cancer in patients with chronic liver disease, using compounds such as acyclic retinoid. Furthermore, the establishment of new biomarkers to identify high-risk patients for liver cancer development is anticipated, with potential applications in selecting which chronic liver disease patients should receive preventive treatment for liver cancer.

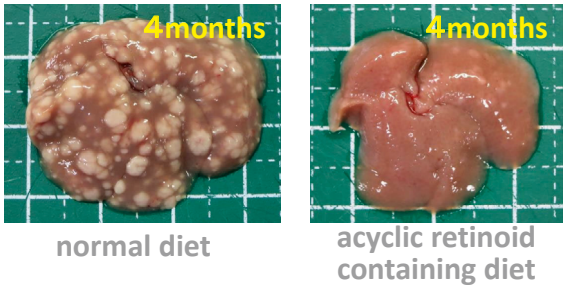

Fig.1 Suppression of liver cancer by acyclic retinoid administration to hepatocyte-specific p53-activated mice.

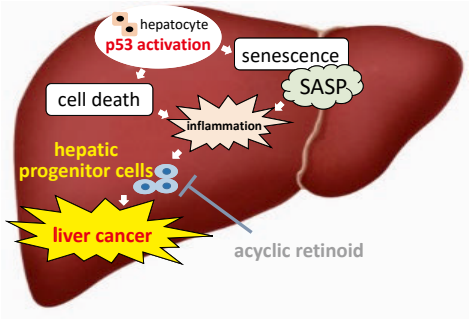

Fig.2 Mechanism of cancer promotion by p53 activation in the liver

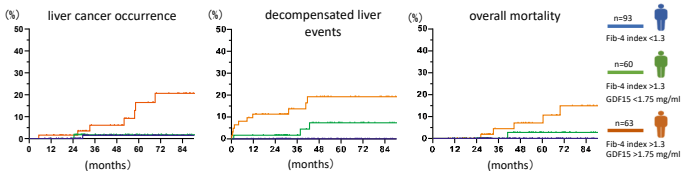

Fig.3 Incidence rates of liver cancer, liver deterioration, and overall mortality in 216 patients with steatotic liver

Patent	PCT/JP2022/ 28776, PCT/JP2023/022224
Treatise	1)Makino, Yuki; Hikita, Hayato; Takehara, Tetsuo et al. Constitutive activation of the tumor suppressor p53 in hepatocytes paradoxically promotes non-cell autonomous liver carcinogenesis. Cancer Res. 2022, 82(16), 2860-2873. doi: 10.1158/0008-5472.CAN-21-4390 2)Kumazaki, Shusuke; Hikita, Hayato; Takehara, Tetsuo et al. Serum growth differentiation factor 15 is a novel biomarker with high predictive capability for liver cancer occurrence in patients with MASLD regardless of liver fibrosis. Aliment Pharmacol Ther. 2024, 60(3), 327-339. doi: 10.1111/apt.18063 3)Sakane, Sadatsugu; Hikita, Hayato; Takehara, Tetsuo et al. Proteomic analysis of serum extracellular vesicles reveals Fibulin-3 as a new marker predicting liver-related events in MASLD. Hepatol Commun. 2024, 8(6), e0448. doi: 10.1097/HC9.0000000000000448
URL	https://www.med.osaka-u.ac.jp/eng/activities/results/2022year/takehara2022-6-13-2
Keyword	chronic liver disease, liver carcinogenesis, p53, prophylactic medicine for liver cancer, biomarker