News Release

Title

The development of hepatocellular carcinoma can be inhibited by TFF1.

Key Points

・Hepatocellular carcinoma (HCC) develops in the liver with chronic hepatitis or cirrhosis. Surgical resection is the only one treatment to make a full recovery, but it is impossible in the severely-damaged liver.

・We found that TFF1 (Trefoil Factor Family 1) functions as tumor suppressor for HCC.

・TFF1 might be a novel therapeutic option to inhibit the development of HCC.

Summary

Prof. Masato Nagino (Division of Surgical Oncology, Department of Surgery) in Nagoya University Graduate School of Medicine (Dean: Dr. Kenji Kadomatsu), Dr. Junpei Yamaguchi (assistant professor, Division of Surgical Oncology, Department of Surgery, Nagoya University Graduate School of medicine) and Yosuke Ochiai (Graduate Student, Division of Surgical Oncology, Department of Surgery, Nagoya University Graduate School of medicine) revealed that TFF1 (Trefoil Factor Family 1) can inhibit the development of hepatocellular carcinoma (HCC).

HCC develops in the liver with chronic hepatitis or cirrhosis. Surgical resection is the only one treatment to make a full recovery; however, it is impossible in the severely damaged liver. Thus, it is important to prevent the development of HCC, while there is no such treatment so far. We focused on a secreted protein, TFF1, which is supposed to inhibit cancer development in gastric carcinogenesis. As a result, we found that TFF1 inactivates β-catenin and increased the apoptosis of HCC cells. In addition, we found that TFF1-KO mice developed HCC frequently, indicating HCC-preventing function of TFF1. Also, TFF1 protein itself could inhibit the Wnt signaling pathway, suggesting the possible novel treatment for HCC as preventive therapy. This work was published online in *Hepatology* on November 16th, 2019.

Research Background

HCC develops in the liver with chronic hepatitis and cirrhosis. While HBV (Hepatitis B Virus), HCV (Hepatitis C Virus) and alcohol abuse can cause hepatitis, nonalcoholic fatty liver disease (NAFLD) can also result in hepatitis and cirrhosis. Once HCC develops in their liver, surgical resection is the only one treatment to make a full recovery. However, the liver function of the patients is frequently less than ideal and the surgery is impossible in the severely damaged liver. Thus, it is of great importance to prevent the development of HCC in damaged liver, while there is no such treatment so far.

Research Results

First of all, TFF1-expressing plasmid was transfected into HCC cell lines, revealing that TFF1 inhibits the proliferative ability and induces apoptosis of HCC cells. Further investigation revealed that TFF1 inactivates β-catenin. Interestingly, the promoter lesion of TFF1 gene was found to be highly methylated in human HCC.

Next, we employed HCC-developing mouse model, KC (Alb-Cre/LSL-KRAS^{G12D}). In this mouse model, HCC develops at the age of one-year old. When TFF1 was deleted from these mice, HCC develops at the age of 6-months-old, and almost all mice developed large HCC within one year (Fig. 1). These results proved that TFF1 function as tumor suppressor to inhibit the development of HCC.

The important point here is that TFF1 can function as protein itself. Recombinant TFF1 treatment was found to inhibit the Wnt/β-catenin pathway if administered to HCC cells. These results suggest that TFF1 protein have the therapeutic potential to inhibit HCC development in the patients of chronic hepatitis and liver cirrhosis.

Research Summary and Future Perspective

We are now trying to find how to treat the patients, including oral administration, injection and intravenous infusion. In addition, it might be possible to modify TFF1 protein to henhance the effect on HCC.

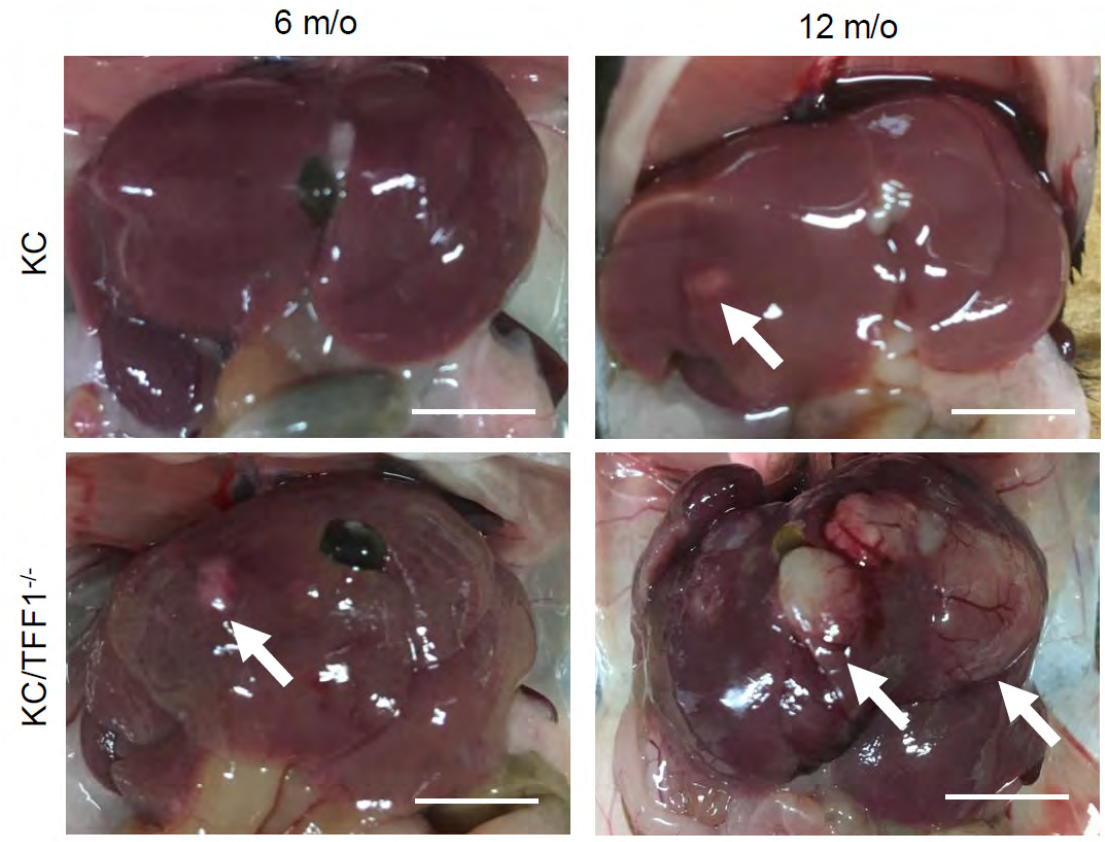

Figure 1. the development of HCC in KC mice. Arrows: HCC.

Publication

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Trefoil factor 1 functions as a tumor suppressor to inhibit the development of hepatocellular carcinoma by regulating β-catenin activation.

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