News Release

Title

The novel tumor suppressor to inhibit cholangiocarcinogenesis.

Key Points

- **Cholangiocarcinoma is one of the most lethal malignancies.**
- **We found that TFF2 functions as tumor suppressor to inhibit cholangiocarcinogenesis.**
- **TFF2 can be a novel therapeutic approach for treating cholangiocarcinoma.**

Summary

Prof. Tomoki Ebata (Division of Surgical Oncology, Department of Surgery) in Nagoya University Graduate School of Medicine (Dean: Dr. Kenji Kadomatsu), Dr. Junpei Yamaguchi (Lecturer, Division of Surgical Oncology, Department of Surgery, Nagoya University Graduate School of medicine) and Dr. Keiji Hasebe (Graduate School Student, Division of Surgical Oncology, Department of Surgery, Nagoya University Graduate School of medicine) revealed that TFF2 functions as tumor suppressor to inhibit cholangiocarcinogenesis.

Cholangiocarcinoma is the second most common primary hepatic cancer that accounts for 3% of annual cancer-related deaths and has a high mortality rate and a poor prognosis. There are many risk factors such as sclerosing cholangitis and liver cirrhosis, whereas precise mechanisms of cholangiocarcinogenesis is still unclear. We found that TFF2 (Trefoil Factor Family 2) inhibits proliferation and invasion, and promotes apoptosis of cholangiocarcinoma cells. These tumor-suppressive function was supposed to depend on the activation of PTEN. In addition, TFF2-defficient mice developed BilIN and cholangiocarcinoma, indicating that TFF2 function as tumor suppressor to inhibit the development of cholangiocarcinoma. This work was published online in *Carcinogenesis* on October 13, 2021.

Research Background

Cholangiocellular carcinoma (CCC) is the second most common primary hepatic cancer that accounts for 3% of annual cancer-related deaths and has a high mortality rate and a poor prognosis. The median survival time of CCC patients is less than 24 months after diagnosis, indicating the lethal potential of CCC. There are many risk factors for CCC, such as primary sclerosing cholangitis, liver cirrhosis, and liver fluke infection. Underlying chronic inflammation of the bile duct caused by these conditions is supposed to induce genetic aberrations and eventual development of CCC. Although surgical resection is the only curative treatment for CCC, the advanced nature at initial presentation precludes this approach. Even in cases without distant metastasis, the long-term outcomes remain unsatisfactory, with a 5-year survival rate of 20% to 40%. Multidrug chemotherapy is the second therapeutic option for CCC patients; however, the efficacy remains limited.

Research Results

By analyzing cholangiocarcinoma cell lines, we found that TFF2-expressing cancer cells showed slow proliferation, frequent apoptosis, and less invasive ability. In addition, TFF2 promoted activation of PTEN (Figure 1).

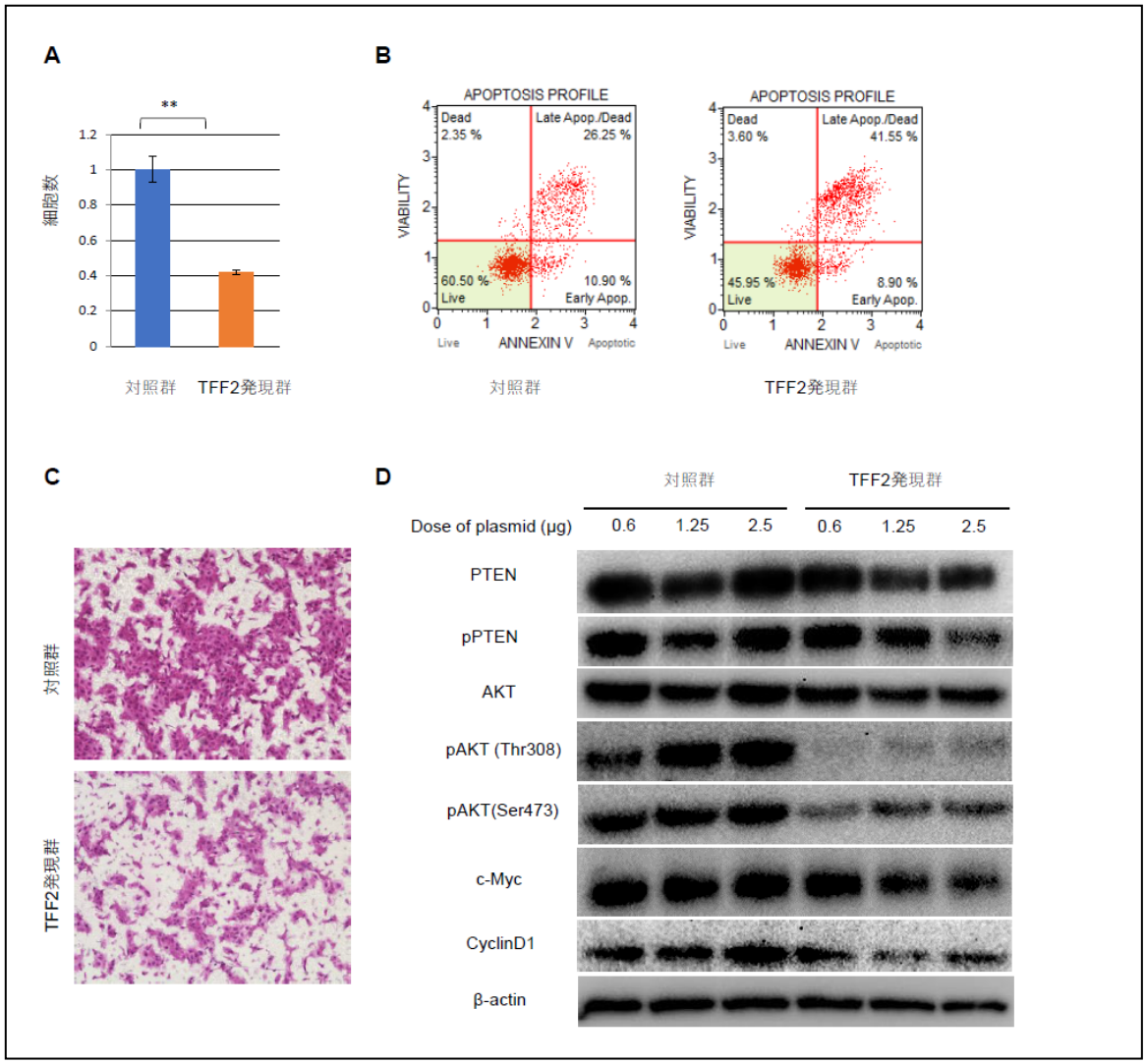

Figure 1. The tumor-suppressive role of TFF2 in cholangiocarcinoma cells.
TFF2 inhibits proliferation (A), promotes apoptosis (B), and inhibits invasion of cancer cells (C). PTEN is activated by TFF2 (D).

Next, KRAS-mutation and TFF2-deficiency was induced in mouse liver. As a result, TFF2-deficient mice developed BilIN (precursor lesion of cholangiocarcinoma) and some mice developed cholangiocarcinoma (Figure 2). These results suggest that TFF2 function as tumor suppressor to inhibit the development of cholangiocarcinoma.

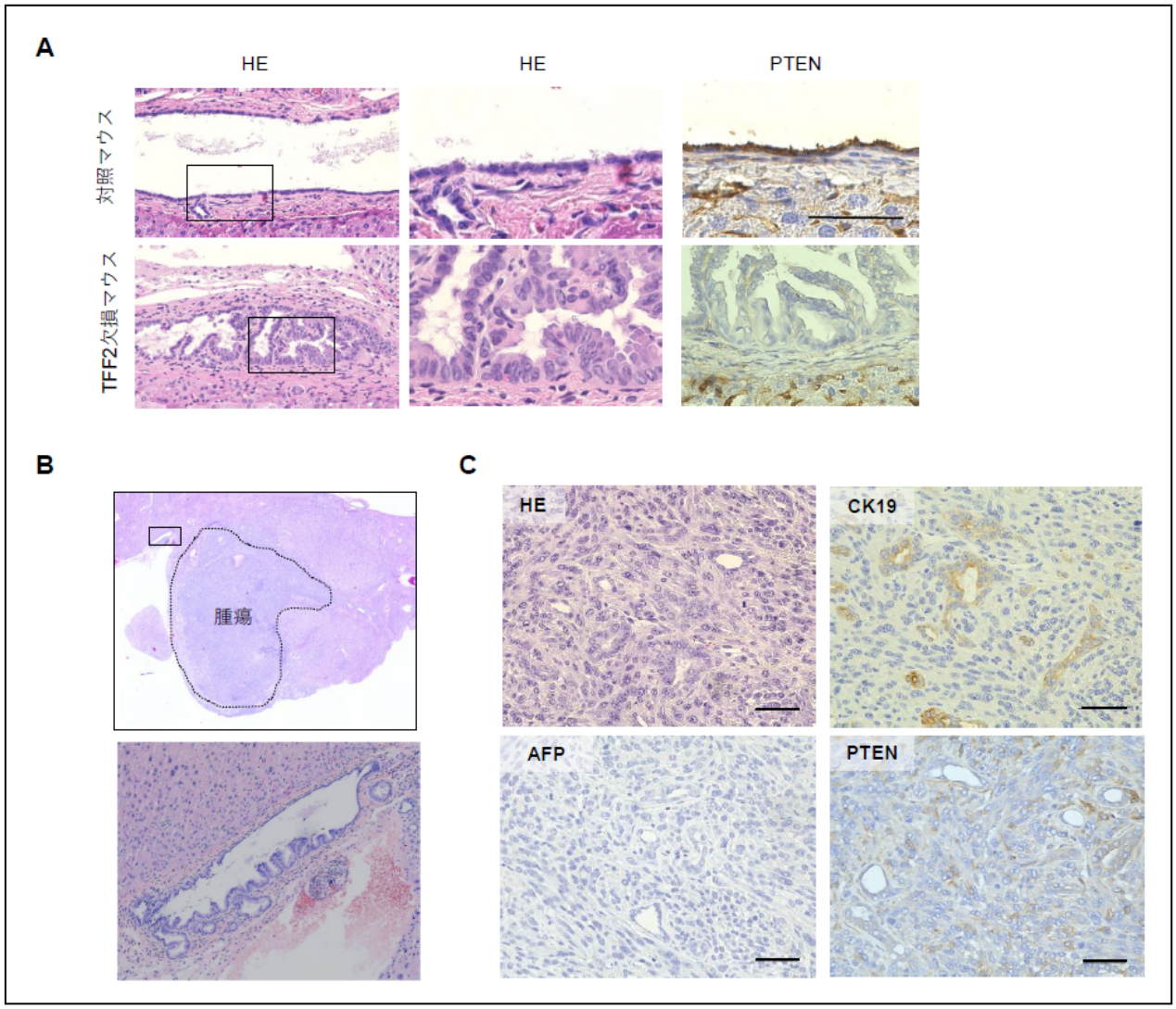

Figure 2. TFF2-deficient mice developed BilIN (A) and cholangiocarcinoma (B).

Research Summary and Future Perspective

Surgical resection is the only curative option for cholangiocarcinoma, and chemotherapy is not ideally effective. We are trying to find the novel therapeutic approach to treat cholangiocarcinoma by TFF2.

Publication

Keiji Hasebe, Junpei Yamaguchi, Toshio Kokuryo, Yukihiro Yokoyama, Yosuke Ochiai, Masato Nagino, and Tomoki Ebata. Trefoil factor family 2 inhibits cholangiocarcinogenesis by regulating the PTEN pwathway in mice. *Carcinogenesis* (in press)
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Japanese ver. https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Carcin_211013.pdf