News Release

Title

The mechanisms of the development of pancreatic cancer has been revealed.

Key Points

○Although the pancreatic cancer has been thought to arise from pancreatic precursor lesions, the mechanisms of this malignant transformation has been elusive. We clarified, at least partly, the mechanisms by which pancreatic cancer develops from its precursor.

○TFF1 is the secreted protein mainly expressed in gastrointestinal mucosa. We found that TFF1 act as tumor suppressor to inhibit the malignant transformation of pancreatic precursor lesions into pancreatic cancer.

○TFF1 might be useful as a new therapeutic agent against pancreatic cancer.

Summary

Prof. Masato Nagino (Division of Surgical Oncology, Department of Surgery) in Nagoya University Graduate School of Medicine (Dean: Dr. Kenji Kadomatsu) and Dr. Junpei Yamaguchi (assistant professor, Division of Surgical Oncology, Department of Surgery, Nagoya University Graduate School of medicine) revealed the relationship between TFF1 (Trefoil Factor Family 1) and pancreatic cancer development.

Pancreatic cancer is one of the most critical malignancies with the 5-year survival as low as 10%. Pancreatic cancer has been thought to develop by the malignant transformation of precursor lesions; however, the mechanisms underlying this transformation has not been clarified.

The team has been studying on the role of TFF1 in pancreatic carcinogenesis. TFF1 is the key element for the recovery of damaged gastrointestinal mucosa such as gastric ulcer, and studies indicate that TFF1 can act as tumor suppressor as well. In this study, they revealed that TFF1 can inhibit the EMT (Epithelial-Mesenchymal Transition) thus suppress the invasive ability of pancreatic cancer cells. The analysis on the transgenic mouse model also revealed that TFF1 can inhibit malignant transformation of pancreatic precursor lesions, PanIN (Pancreatic Intraepithelial Neoplasm). These results suggest that TFF1 can act as tumor suppressor to inhibit the development of pancreatic cancer, and TFF1 can be the new therapeutic target. This work was published online in *Journal of Clinical Investigation* on May 29th, 2018.

Research Background

Pancreatic caner is the 4th leading malignancy in terms of cancer death in Japan and its 5-year survival is as low as 10% (cancer statistics in Japan 2017; Foundation for Promotion of Cancer Research). The therapeutic strategy for advanced pancreatic cancer has been improved by the novel chemotherapy as FOLFIRINOX and gemcitabine plus nab-PTX, yet the median

survival time is less than 1-year. Thus, we need further improvement of the treatment for pancreatic cancer. The most important factor for the pancreatic carcinogenesis is the alterations of oncogene, especially KRAS mutation, which can be found in almost all pancreatic cancer. The KRAS mutation alone does not result in the development of pancreatic cancer, however, and an additional oncogenic alteration is necessary for the development of malignant tumor. To clarify the mechanisms of cancer development in the pancreas is needed to invent novel therapeutic strategy against pancreatic cacner.

Research Results

First, the surgically resected pancreatic specimens were analyzed by immunohistochemical analysis. TFF1 expression was not found in normal structure of pancreas, while PanIN (Pancreatic Epithelial Neoplasm) and IPMN (Intraductal Papillary Mucinous Neoplasm) showed abundant TFF1 expression. In contrast, TFF1 expression was lost in invasive component of pancreatic cancer (Figure 1). These data suggest that loss of TFF1 result in the invasive transformation of PanIN and IPMN.

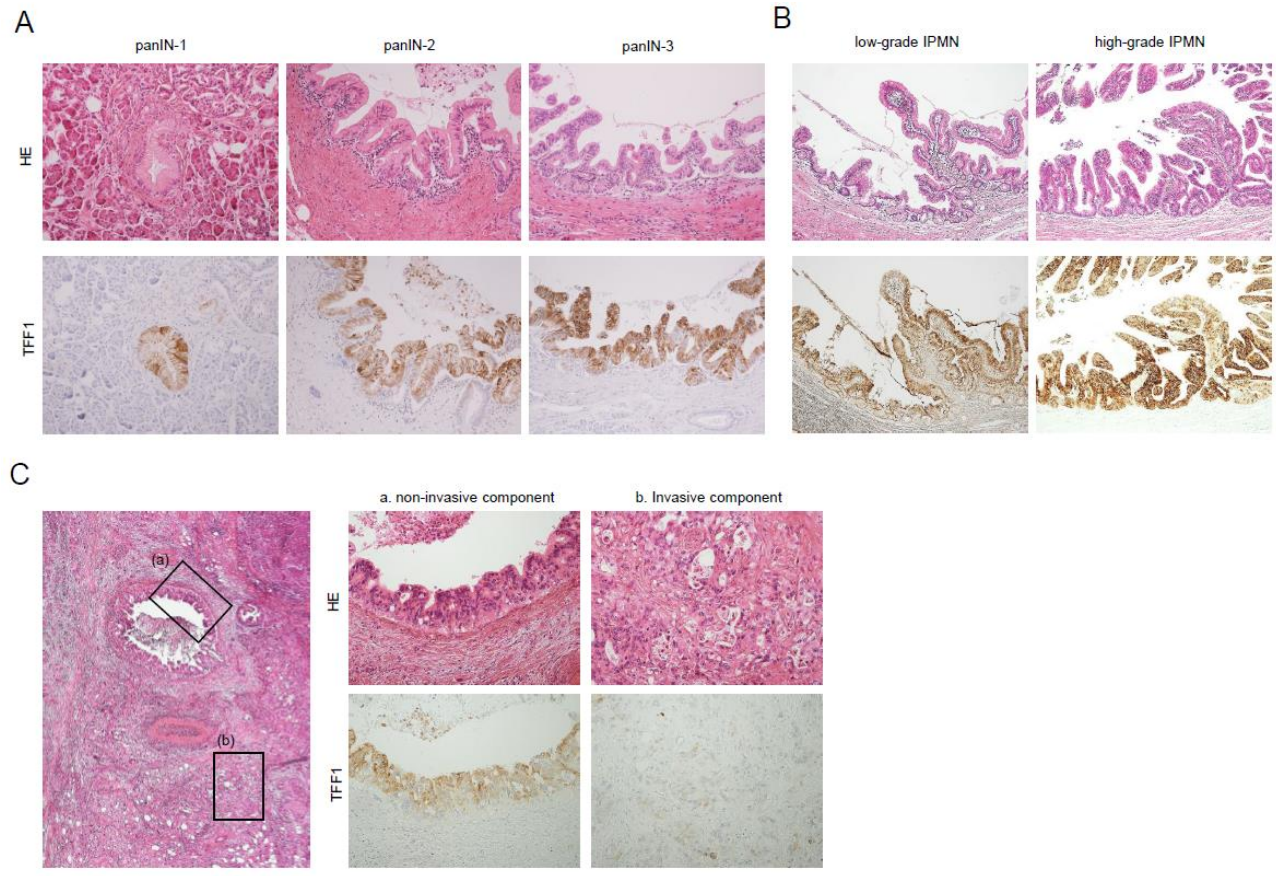

Figure 1: The expression of TFF1 in pancreatic precursor lesions and invasive pancreatic cancer. A: PanIN, B: IPMN, C: invasive cancer.

Next, the invasive ability of pancreatic cancer cells was evaluated after the suppression of TFF1 by siRNA, revealing that the invasive ability was strengthened by the suppression of TFF1 (Figure 2A, B). The invasive ability of cancer cells is supposed to depend on EMT

(Epithelial-Mesenchymal Transition). The expressions of EMT-related molecules were analyzed, revealing that EMT-promoting factor (Snail, Slug and Twist1) were upregulated, while the cell-cell adhesion molecules (E-cadherin, Occludin and Zo-1) were downregulated by the suppression of TFF1 (Figure 2C). These results suggest that TFF1 can inhibit invasion of pancreatic cancer cells via the suppression of EMT.

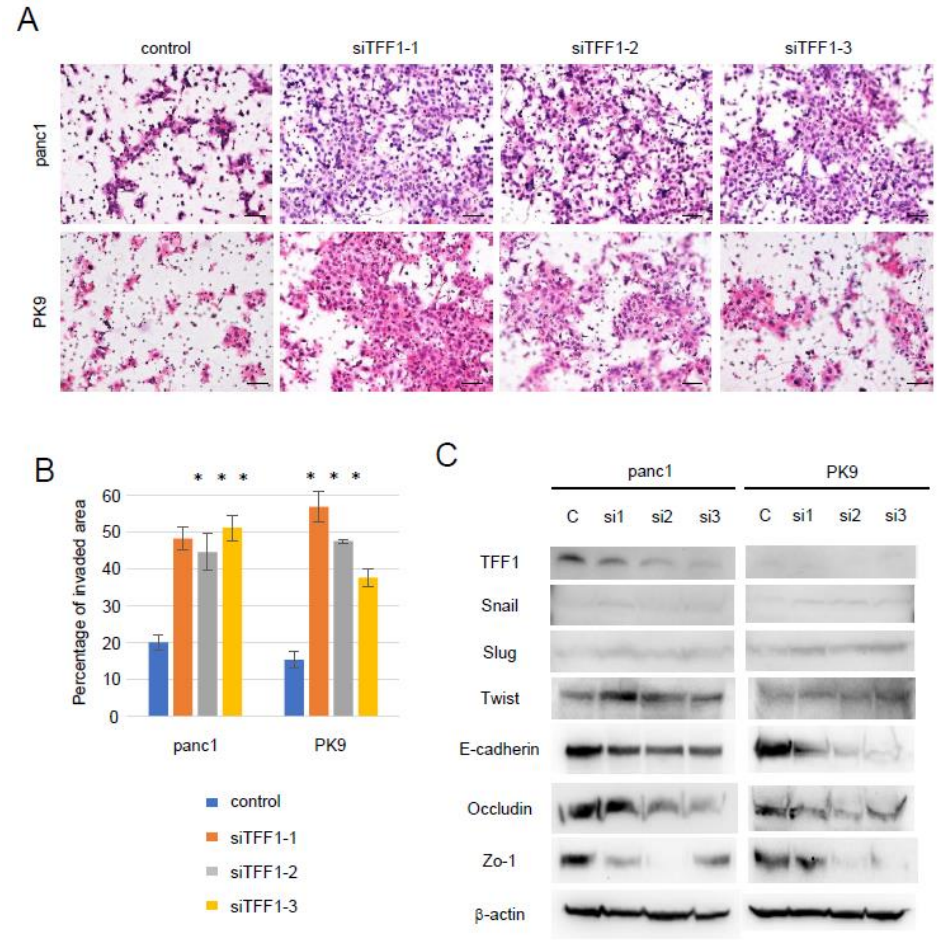

Figure 2: The invasive ability of pancreatic cancer cells (panc1, PK9) was enhanced by the suppression of TFF1. A: Invading pancreatic cancer cells, B: Quantification of invasive ability, C: Expression of EMT-related factors.

To further investigate the relationship between TFF1 and pancreatic cancer, genetically-engineered mice were employed. The mice with KRAS mutation in their pancreas (KC mice) developed PanIN but no pancreatic cancer was found. TFF1 expression was abundantly found in PanIN in KC mice. Furthermore, KC mice were bred with TFF1-knockout mice to generate KC/TFF1-/- mice. The PanIN in KC/TFF1-/- were found to have frequent high-grade atypia more than that in KC mice (Figure 3), and eventually, KC/TFF1-/- mice developed invasive pancreatic cancer with poor survival rate of the mice (Figure 4). These data revealed that TFF1 can inhibit malignant transformation of pancreatic precursor lesions.

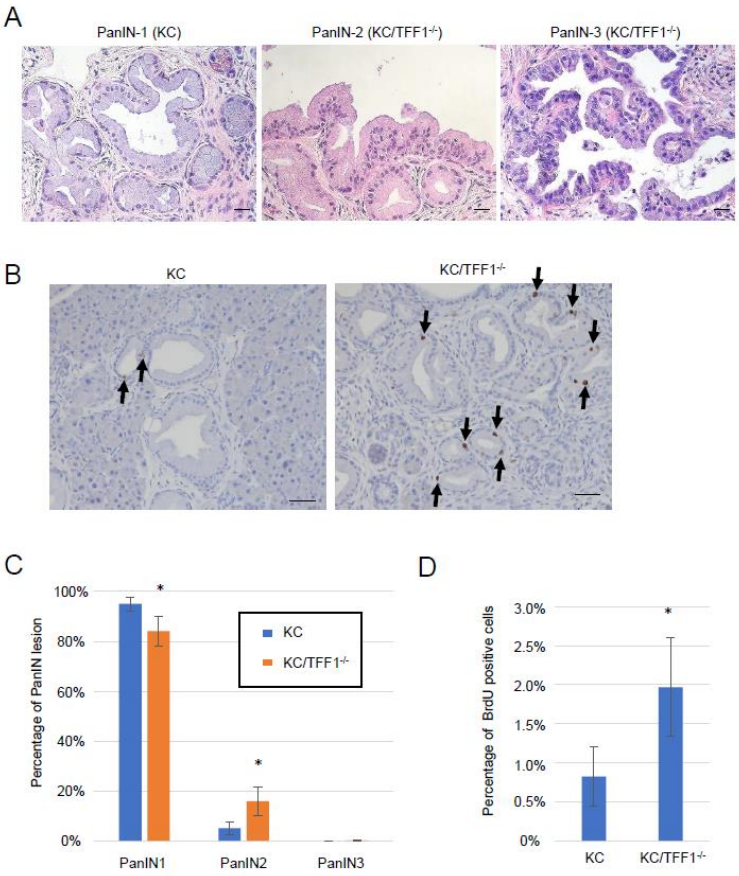

Figure 3: Appearance of PanIN in KC/TFF1-/- mice. A, C: high-grade atypia was found in PanIN in KC/TFF1-/-. B, D: BrdU incorporation (indicating the proliferative ability of the cells) was more frequently found in KC/TFF1-/-.

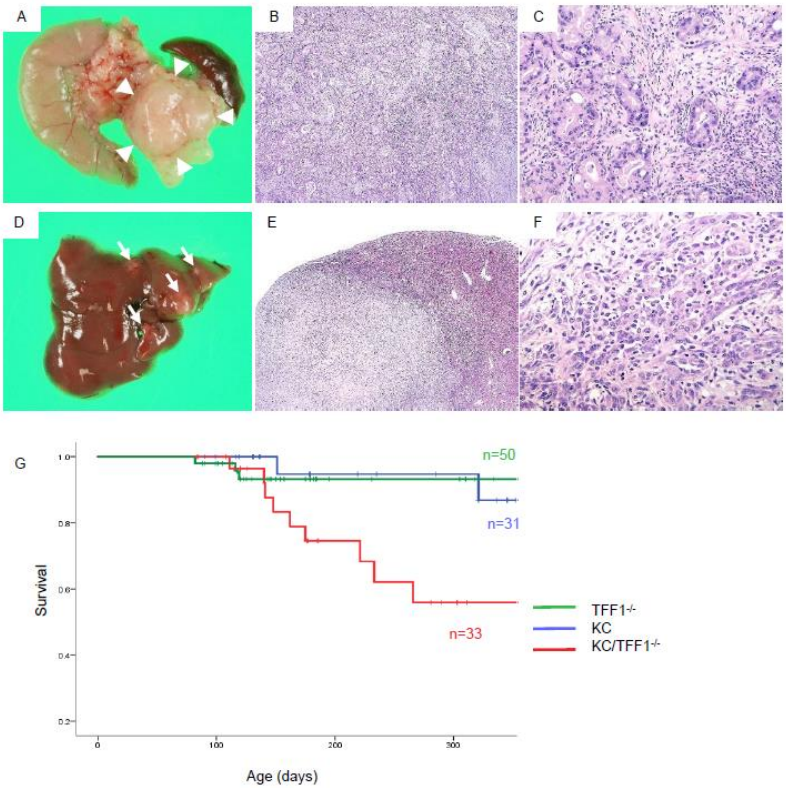

Figure 4: Pancreatic cancer developed in KC/TFF1-/- mice. A-C: Pancreatic cancer found in KC/TFF1+/- mice. D-F: Liver metastasis of pancreatic cancer. G: Survival curve of the mice.

Research Summary and Future Perspective

Pancreatic cancer is highly-malignant disease and hard to be treated successfully. To develop the therapeutic strategy for pancreatic cancer, it is of great importance to clarify the mechanisms of its carcinogenesis. This study revealed that TFF1 can act as tumor suppressor to inhibit malignant transformation of pancreatic precursor lesions, PanIN and IPMN. If applied for the cancer treatment, TFF1 might be able to invent the development of pancreatic cancer, and moreover, to treat pancreatic cancer patient effectively.

This research group are trying not only to apply TFF1 in the treatment of cancer patients, but also to investigate the role of TFF2 in pancreatic cancer. They also have found the evidences that indicate TFFs can inhibit liver carcinogenesis as well. The ultimate goal of this group is to develop TFF treatment for all kinds of gastrointestinal malignancies.

Publication

Junpei Yamaguchi, Yukihiro Yokoyama, Toshio Kokuryo, Tomoki Ebata, Atsushi Enomoto, and Masato Nagino. Trefoil factor 1 inhibits epithelial-mesenchymal transition of pancreatic intraepithelial neoplasm. *Journal of Clinical Investigation*, May 29, 2018.

Japanese ver.

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