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Trefoil factor family 1 expression in the invasion front is a poor prognostic factor associated with lymph node metastasis in pancreatic cancer

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ABSTRACT

Objectives: Trefoil Factor Family protein 1 (TFF1) is secreted from mucus-producing cells. The relationship between TFF1 expression and clinical outcome in pancreatic ductal adenocarcinoma (PDAC) remains unknown. We aimed to evaluate the prognostic significance of TFF1 expression in PDAC.
Methods: TFF1 expression was examined on paraffin-embedded sections from 91 patients with resected PDAC using immunohistochemistry. The relationships between TFF1 expression and clinicopathological features were analyzed.
Results: Among 91 PDAC patients, 71 patients (79.7%) showed TFF1 expression in cancer cells. In a subgroup of 71 patients, TFF1 expression was predominantly observed in the central part of the tumor, whereas TFF1 expression in the invasion front was reduced in 33 patients (46.4%). A significant correlation between preserved TFF1 expression in the invasion front and lymph node metastasis was observed. Univariate survival analysis revealed that preserved TFF1 expression in the invasion front, positive lymphatic invasion, lymph node metastasis and R1 resection was a significant poor prognostic factor in TFF1-positive PDAC patients.
Conclusions: TFF1 expression is frequently lost or decreased in the invasion front of human PDAC, and preserved TFF1 expression in the invasion front might predict poor survival in patients with PDAC.
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Introduction

Pancreatic cancer remains a highly lethal cancer worldwide, ranking as the fourth leading cause of cancer-related deaths in the Western world, and the morbidity is expected to increase in future years [1,2]. Although complete surgical resection provides a cure, the recurrence rate of pancreatic cancer after resection is high [3,4]. Tumor size and lymph node involvement have been characterized as the strongest predictors of survival after the resection of pancreatic cancer [5–7]. In addition to these clinicopathological factors, several molecular markers have been investigated and identified as important prognostic parameters. Despite these advances, the mechanisms by which Pancreatic ductal adenocarcinoma (PDAC) can invade and metastasize, thereby impacting prognosis, have not been fully understood.

Pancreatic ductal adenocarcinoma (PDAC), a histological type of pancreatic cancer, develops from three distinct precursor lesions: pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasm (MCN) [8]. These precursor lesions and PDAC share distinct characteristics and are associated with each other. Particularly, the apomucins, including Mucin 1 (MUC1), Mucin 2 (MUC2), and Mucin 5AC (MUC5AC), are overexpressed in the epithelial cells of pancreatic neoplasms [9,10]. These observations suggest significant roles for mucins in pancreatic carcinogenesis.

Trefoil Factor Family 1 (TFF1, pS2), together with TFF2 and TFF3, is a member of the trefoil factor family [11,12]. Although the putative role of TFF1 is the protection and recovery of damaged gastrointestinal mucosa, there has been studies which indicate the tumor suppressive role of TFF1 in gastric carcinogenesis. TFF1 is not detected in the normal healthy pancreas without neoplastic or inflammatory changes. However, during inflammatory injury such as

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pancreatitis, TFF1 expression is predominantly observed in pancreatic duct glands (PDG), a potential progenitor compartment for pancreatic ductal epithelium [13]. In addition, TFF1 is abundantly expressed in the pancreatic premalignant lesions such as PanIN and IPMN [14–18], indicating that the TFF1 expression are closely associated with the development of PDAC, and that TFF1 might function as a tumor suppressor in pancreatic carcinogenesis. TFF1 expression in malignant disease has been reported in various types of adenocarcinomas. Clinicopathologically, TFF1 expression is a favorable prognostic factor in gastric, breast and gallbladder carcinomas [19–21] and a poor prognostic factor in ovarian mucinous carcinoma [22]. The relationship between TFF1 expression and prognosis in human cancer has been controversial to date [23]. Although the physiological functions and the clinical significance of TFF1 expression in PDAC remains unclear, Thiruvengadam et al. reported that TFF1 accelerated the metastasis of pancreatic cancer cells in a xenograft model [24]. Although these studies also suggested a putative role for TFF1 in the development of PDAC, the clinical significance of TFF1 expression remains unclear in human PDAC.

In the present study, TFF1 expression in PDAC was observed in almost 80% of the central region of PDAC. TFF1 expression was frequently lost or decreased in the invasion front of PDAC, and TFF1-positive invasion is associated with high lymph node metastasis and poor prognosis. These results suggest that TFF1 might have oncogenic significance in the invasion front of human PDAC.

Methods

Patients

A total of 125 patients with PDAC who underwent surgical resection between January 2005 and December 2014 at Nagoya University Hospital were enrolled in the present study. As overall survival was the main outcome determinant, patients with incomplete resection were excluded. For example, pM1 means pathologically revealed distant metastasis, including distant lymph node metastasis, and R2 resection means macroscopic residual tumor. On the other hand, R1 means microscopic residual tumor, which does not necessarily mean incomplete resection. Thus, we defined curative resection as R0/R1 resection and the patients with pM1 and/or R2 resection were excluded (n = 34), resulting in a cohort of 91 patients for the final analysis. Clinicopathological features were obtained from retrospectively collected data. The pathological features of resected specimens, including T and N factor and tumor differentiation, were determined in accordance with the 7th edition TNM classification of malignant tumors [25]. Fig. 1 shows a flow chart for the analyzed patients. This retrospective study was approved by the ethics committee of Nagoya University Graduate School of Medicine.

Immunohistochemical analysis

Formalin-fixed paraffin-embedded sections were sliced at a thickness of 4 μm, deparaffinized in Hemo-Clear (SASCO Chemical Group, Albany, GA) and rehydrated in a graded series of ethanol. For antigen retrieval, the sections were immersed in citrate buffer, pH 6, for 15 min in a microwave. Subsequently, the sections were washed with PBS, and 3% hydrogen peroxidase in ethanol was used for 15 min to inactivate the endogenous peroxidase activity. The sections were incubated with 10% normal goat serum (Nichirei Bioscience, Tokyo, Japan) for 30 min to avoid nonspecific reactions. Mouse monoclonal anti-pS2/pNR-2 estrogen-regulated protein (GE2) antibody (Thermo Scientific, Wilmington, DE) was diluted in 1% BSA/PBS (1:50) and applied overnight at 4 °C. The sections were incubated with the secondary antibodies EnVision + System-HRP Labeled Polymer Anti-Mouse (Dako, Hamburg, Germany) for 30 min at room temperature. The signals were visualized using the Liquid DAB$^+$ substrate-chromogen system (Dako) and nuclear counterstaining using hematoxylin.

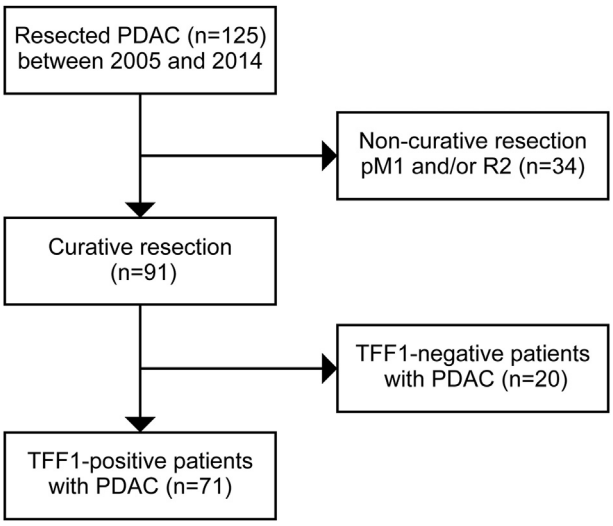

Fig. 1. Flow chart of the selection process for patients with PDAC.

We categorized TFF1 expression status into three groups: no expression (-; complete absence of membrane and cytoplasmic staining), moderate expression (+; faint and partial staining), or strong expression (++; strong and complete staining) according to staining intensity (Fig. 2A).

Statistical analysis

The association between TFF1 expression and clinicopathological features in patients with PDAC was assessed using $\chi 2$-test or Fisher's exact test, as appropriate. Patient survival was defined as the time from surgery to death or the most recent follow-up. The survival curves were calculated using the Kaplan-Meier method and subsequently compared using the log-rank test. The prognostic significance of the clinicopathological features and TFF1 expression was determined using a univariate Cox regression analysis. Cox proportional hazard models were applied for multivariate analysis. A value of $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS 23.0 software (SPSS Inc., Chicago, IL) or JMP version 9 (SAS Institute Inc., Cary, NC).

Results

Demographic characteristics of the study patients

A total of 91 PDAC patients were included in the present analysis (Fig. 1). The patients included 52 (57.1%) males and 39 (42.9%) females, ranging in age between 36 and 85 years (median, 67 years). A total of 86 (94.5%) patients had invasive cancer in the extrapancreatic region, and R0 resection was achieved in 63 (69.2%) patients. Lymph node metastasis was observed in 56 (61.5%) patients. Adjuvant chemotherapy was preoperatively and/or postoperatively performed in 66 (72.5%) patients. Five patients (5.5%) had cancer-related pancreatitis. The median overall survival time was 30 months.

The expression of TFF1 in PDAC

Immunohistochemical analysis was performed in the paraffin-

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