Presence of tuft cells expressing haematopoietic prostaglandin D synthase in intraductal papillary mucinous neoplasms of the pancreas

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Abstract. Intraductal papillary mucinous neoplasm (IPMN) is the second most common pancreatic tumour and a common precursor lesion of invasive carcinoma. Tuft cells are chemosensory epithelial cells present in the gastrointestinal and respiratory tracts that serve roles in response to infection and tissue repair. In addition, tuft cells have pivotal roles in the carcinogenesis of pancreatic ductal adenocarcinoma (PDAC), especially in tumour suppression, by producing prostaglandin (PG)D_2; however, their role in IPMN remains unclear. The present study aimed to evaluate the presence of tuft cells producing PGD_2 in human IPMN. Consecutive patients with IPMN who underwent surgical resection were retrospectively enrolled. Dual immunohistochemical staining for POU domain class 2 transcription factor 3 (POU2F3), as a specific tuft cell marker, and haematopoietic PGD synthase (H-PGDS), as a useful marker for PGD_2 production, were performed. The present study included 21 patients with IPMN (11 women and 10 men; median age, 74 years). A total of 11, two and eight patients had IPMN with low-grade dysplasia, high-grade dysplasia and associated invasive carcinoma, respectively. POU2F3-positive tuft cells were noted in IPMN, and 20.0% of POU2F3-positive cells in IPMN without invasive carcinoma and the non-invasive regions of IPMN-associated invasive carcinoma expressed H-PGDS. Moreover, POU2F3-positive tuft cells and the ratio of H-PGDS expression in POU2F3-positive tuft cells were significantly lower in the invasive regions than in the non-invasive regions of IPMN-associated invasive carcinoma. These results indicated that POU2F3-positive tuft cells have possible roles in the tumourigenesis of IPMN, as well as in the carcinogenesis of PDAC, because tuft cells present in non-invasive IPMN may serve tumour-suppressive roles via production of PGD_2 and they were absent in the invasive carcinoma component. Notably, further analyses are required to clarify the role and importance of POU2F3-positive tuft cells in IPMN, which will lead to a better understanding of the pathogenesis of this tumour.

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Abbreviations: ADM, acinar-to-ductal metaplasia; COX1, cyclooxygenase 1; DCLK1, doublecortin-like kinase1; H-PGDS, haematopoietic PGD synthase; IPMN, intraductal papillary mucinous neoplasm; PanIN, pancreatic intraepithelial neoplasm; PDAC, pancreatic ductal adenocarcinoma; PG, prostaglandin; POU2F3, POU domain class 2 transcription factor 3; TRPM5, transient receptor potential melastatin 5

Key words: pancreas, IPMN, tuft cells, PGD, pancreatic tumour

Introduction

Intraductal papillary mucinous neoplasm (IPMN) is the second most common pancreatic neoplasm of the surgical specimens, because nearly 90% of adult pancreatic neoplasm are pancreatic ductal adenocarcinomas (PDACs) and cystic and intraductal neoplasms comprise 4-5%, in which 60% of cyst-forming neoplasms are IPMNs (1). Population-based incidence of pancreatic cysts are around 2%, and the incidence of IPMN is 0% in 20's, 0.2% in 30's, and 6.6% in 70's based on abdominal ultrasound screening study (2). The other report showed that estimated population prevalence of IPMN was 10.9% of persons aged 50 years or older (3), but more than 80% of IPMN have no worrisome or high-risk features, thus,

most of these patients are not for candidate for surgical resection (2,3). The exact data of the number of IPMN patient are not available, because most of IPMN patients are not for candidate for surgical resection. IPMN is characterised by grossly visible intraductal papillary proliferation of mucin-producing cells in the main pancreatic duct and/or its branches, leading to cystic dilatation of the pancreatic ducts by mucin accumulation (4). Invasive carcinoma can contiguously occur with IPMN, and these tumours are designated as IPMN-associated invasive carcinoma (2,4). IPMN is classified into low- and high-grade according to the highest degree of cytoarchitectural atypia in the neoplastic cells (4). Low-grade dysplasia progresses to high-grade dysplasia and eventually to IPMN associated with invasive carcinoma (5). Although IMPN frequently harbours *KRAS* and *GNAS* mutations (60-80% and 50-70%, respectively), the detailed pathogenesis of this tumour remains unclear (4).

Tuft cells are chemosensory epithelial cells located on normal luminal surfaces of the respiratory and gastrointestinal tracts and act as luminal sensors (6). These cells play various important roles in these organs, such as in the response to parasitic or bacterial infection and tissue injury and repair (6). Tuft cells also play a pivotal role in tumourigenesis, and their significance in the carcinogenesis of PDAC has been reported (7,8). Tuft cells emerge in lesions of acinar-to-ductal metaplasia (ADM), a possible precursor lesion of pancreatic intraepithelial neoplasm (PanIN), which are not detected in the normal pancreatic acini of either the human or mouse pancreas (7-9). ADM is a regenerative process resulting from pancreatic acinar injury and can progress to PanIN and PDAC in a mouse model (7). DelGiorno *et al* (7) clearly demonstrated that tuft cells appeared in ADM and gradually decreased from ADM to PanIN and that there were no tuft cells in PDAC in a *Kras*-induced pancreatic tumourigenesis mouse model. They also showed that tuft cells inhibited the development and acceleration of PanIN to PDAC by producing prostaglandin D_2 (PGD_2), a lipid mediator that suppresses inflammation and tissue repair (7). Moreover, our previous study revealed that tuft cells emerged in human ADM lesions and that the number of tuft cells was significantly higher in low-grade PanIN than in high-grade PanIN in the human pancreas (8). Thus, tuft cells may play a pivotal role in the development of PanIN lesions in both mice and humans. However, only one report has addressed the presence of tuft cells in IPMN. Qiu *et al* (10) showed that tuft cells were present in mouse IPMN in approximately the same number as those in PanIN and ADM and demonstrated that these cells were also present in human IPMN lesions. However, it remains unclear whether tuft cells present in human IPMN lesions produce PGD_2 and whether they are present in the invasive lesions of IPMN associated with invasive carcinoma. This study aimed to clarify the role of tuft cells in human IPMN.

Materials and methods

Patient selection. We selected consecutive patients with IPMN who underwent surgical resection at the Department of General and Gastroenterological Surgery of Osaka Medical and Pharmaceutical University Hospital (Takatsuki, Japan) between January 2022 and December 2023. Patients who received neoadjuvant chemotherapy and/or radiation therapy were excluded, because these therapies may have influenced the presence and/or number of tuft cells. We assessed the information of the medical records and tissue samples in July 2025.

This retrospective, single-institution study was conducted in accordance with the tenets of The Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Osaka Medical and Pharmaceutical University Hospital (approval no. 2023-198). All data were anonymised. Informed consent was obtained from the patients using the opt-out method because of the retrospective study design, as medical records and archived samples were used with no risk to the participants. Moreover, the present study did not include minors. Information regarding this study, such as the inclusion criteria and opportunity to opt out, was provided via the institutional website (https://www.ompu.ac.jp/u-deps/path/img/file34.pdf).

Histopathological analysis. Surgically resected specimens were fixed in 10% buffered neutral formalin, sectioned, and stained with haematoxylin and eosin. Two researchers (KN and MI) independently evaluated the histopathological features of all the slides.

The diagnostic criteria for IPMN are based on the recent World Health Organization classification (4). IMPN is characterised by the intraductal proliferation of columnar neoplastic cells with intracytoplasmic mucin and is classified into low- and high-grade based on the highest degree of cytoarchitectural atypia of the neoplastic cells (4). Low-grade IPMN is characterised by mild-to-moderate nuclear atypia and may or may not have papillary projections and mitoses. High-grade IPMN is characterised by severe nuclear atypia, nuclear stratification with loss of polarity, papillary structures with irregular branches, and numerous mitoses (4). IPMN associated with invasive carcinoma is defined as infiltrative neoplastic proliferation of glandular cells with or without abundant stromal mucin deposition contiguous with IPMN (4).

Immunohistochemical analyses. Immunohistochemical staining was performed using an autostainer (Leica Bond-MAX; Leica Biosystems GmbH), according to the manufacturer's instructions. The BOND Polymer Refine Detection Kit (DS9800; Leica) and BOND Polymer Refine Red Detection Kit (DS9390; Leica) were used for dual immunohistochemical staining, as the same method as previously reported (11). Rabbit monoclonal antibodies against POU domain class 2 transcription factor 3 (POU2F3) (E5N2D; Cell Signalling Technology; diluted 1:200) and rabbit polyclonal antibodies against haematopoietic PGD synthase (H-PGDS) [(11), diluted 1:4,000] were used. In the present study, POU2F3, also known as Oct11 or Skn1, was used to detect human tuft cells because it is the master regulator of tuft cell identity and is useful marker of human tuft cells (6,11,12). PGD_2 is synthesised by PGDS, and immunohistochemical analysis of PGDS is a useful method for demonstrating PGD_2 synthesis (7,11,13,14). H-PGDS expression has been reported in tuft cells present in the human salivary glands and tumour lesions (11).

Squamous cells of the skin were used as positive controls for POU2F3 (15), and placental trophoblasts were used for H-PGDS (16). These skin and placental tissues were obtained from Osaka Medical and Pharmaceutical University Hospital. Negative controls were prepared without primary antibodies. Nuclear and cytoplasmic staining were recognised as positive immunoreactivity for POU2F3 (11,15) and H-PGDS (11,14,16), respectively.

Two authors (KN and MI) independently evaluated the immunohistochemical features. POU2F3$^+$/H-PGDS$^+$ (nuclei stained black and cytoplasm stained red), POU2F3$^+$/H-PGDS$^-$ (only nuclei stained brown), and POU2F3$^-$/H-PGDS$^+$ cells (both nuclei and cytoplasm stained red) were separately counted in five high-power fields (x400) within the IPMN and invasive carcinoma regions (if present) in each tumour and in the non-neoplastic pancreatic tissues around the tumour.

Statistical analyses. Differences between the two groups were analysed using the Mann-Whitney U test or Wilcoxon signed-rank test, using Statcel 5 (OMS Ltd., Tokyo, Japan). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient and histopathological characteristics. Table I summarises the clinicopathological features of the study cohort. This study included 11 women (52.4%) and 10 men (47.6%). The median age at the time of surgery was 74 (range, 61-81 years). The tumour locations were as follows: pancreatic head in eight (38.1%) patients and body and tail in 13 (61.9%) patients. Eleven (52.4%), two (9.5%), and eight (38.1%) patients had IPMN with low-grade dysplasia, high-grade dysplasia, and IPMN associated with invasive carcinoma, respectively.

Immunohistochemical characteristics. In non-neoplastic pancreatic tissues, POU2F3-positive tuft cells were present in the pancreatic ducts (from the interlobular ducts to the main pancreatic ducts). The median number of POU2F3-positive cells present in non-neoplastic pancreatic ducts was 10 cells/5-high power fields (range, 3-28 cells). More than half of these POU2F3-positive tuft cells expressed H-PGDS (Fig. 1A), because the median ratio of (POU2F3$^+$/H-PGDS$^+$)/[(POU2F3$^+$/H-PGDS$^+$) + (POU2F3$^+$/H-PGDS$^-$)] was 66.7% (range, 25-92.9%). Neither POU2F3-positive tuft cells nor H-PGDS-positive cells were observed in the non-neoplastic acini.

POU2F3-positive tuft cells were observed among the neoplastic glandular cells in the lesions of IPMN with low- and high-grade dysplasia (IPMN without invasive carcinoma) (Fig. 1B, C) and in the non-invasive regions of IMPN associated with invasive carcinoma (Fig. 1D). The median number of POU2F3-positive cells present in IPMN without invasive carcinoma and in the non-invasive regions of IMPN associated with invasive carcinoma was 12 cells/5-high power fields (range, 0-96 cells). There was no significant difference in POU2F3-positive tuft cells between IPMN without invasive carcinoma (median, 10 cells; range, 2-41 cells) and non-invasive regions of IPMN associated with invasive carcinoma (median, 12.5; range, 0-96 cells) (P=0.085) (Fig. 2A). The median ratio of (POU2F3$^+$/H-PGDS$^+$)/[(POU2F3$^+$/H-PGDS$^+$) + (POU2F3$^+$/H-PGDS$^-$)] was 20.0% (range, 0-58.8%) in IPMN without invasive carcinoma and in the non-invasive regions of IMPN associated

Table I. Clinicopathological characteristics of the present cohort (n=21).

Characteristic	Value
Median age, years (range)	74 (61-81)
Sex, n (%)	
Male	10 (47.6)
Female	11 (52.4)
Tumour location, n (%)	
Head	8 (38.1)
Body and tail	13 (61.9)
Tumour pathology, n (%)	
IPMN with low-grade dysplasia	11 (52.4)
IPMN with high-grade dysplasia	2 (9.5)
IPMN with associated invasive carcinoma	8 (38.1)

IPMN, intraductal papillary mucinous neoplasm.

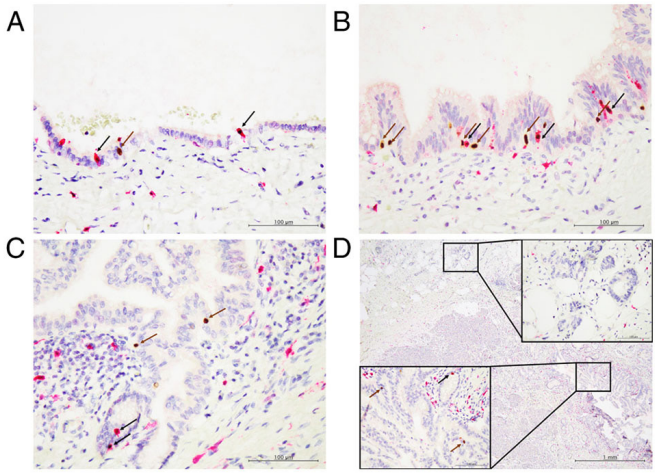

Figure 1. Immunohistochemical features using dual immunohistochemical staining for POU2F3 (brown) and H-PGDS (red). (A) In non-neoplastic pancreatic tissue, a few POU2F3-positive tuft cells expressing H-PGDS (black arrows) are present in the interlobular pancreatic duct. POU2F3-positive tuft cell without H-PGDS expression (brown arrow) is also noted (original magnification, x400). (B) In IPMN with low-grade dysplasia, POU2F3-positive tuft cells with and without H-PGDS expression (black and brown arrows, respectively) are observed among the neoplastic glandular cells (original magnification, x400). (C) In IPMN with high-grade dysplasia, POU2F3-positive tuft cells with and without H-PGDS expression (black and brown arrows, respectively) are observed among the neoplastic glandular cells (original magnification, x400). (D) IPMN associated with invasive carcinoma. In non-invasive carcinoma region, a few POU2F3-positive tuft cells with or without H-PGDS expression (black and brown arrows, respectively) are observed among the neoplastic glandular cells (left lower). No POU2F3-positive tuft cells are noted in the invasive carcinoma portion (right upper) [original magnification, x40, x400 (inset)]. H-PGDS, haematopoietic prostaglandin D synthase; IPMN, intraductal papillary mucinous neoplasm; POU2F3, POU domain class 2 transcription factor 3.

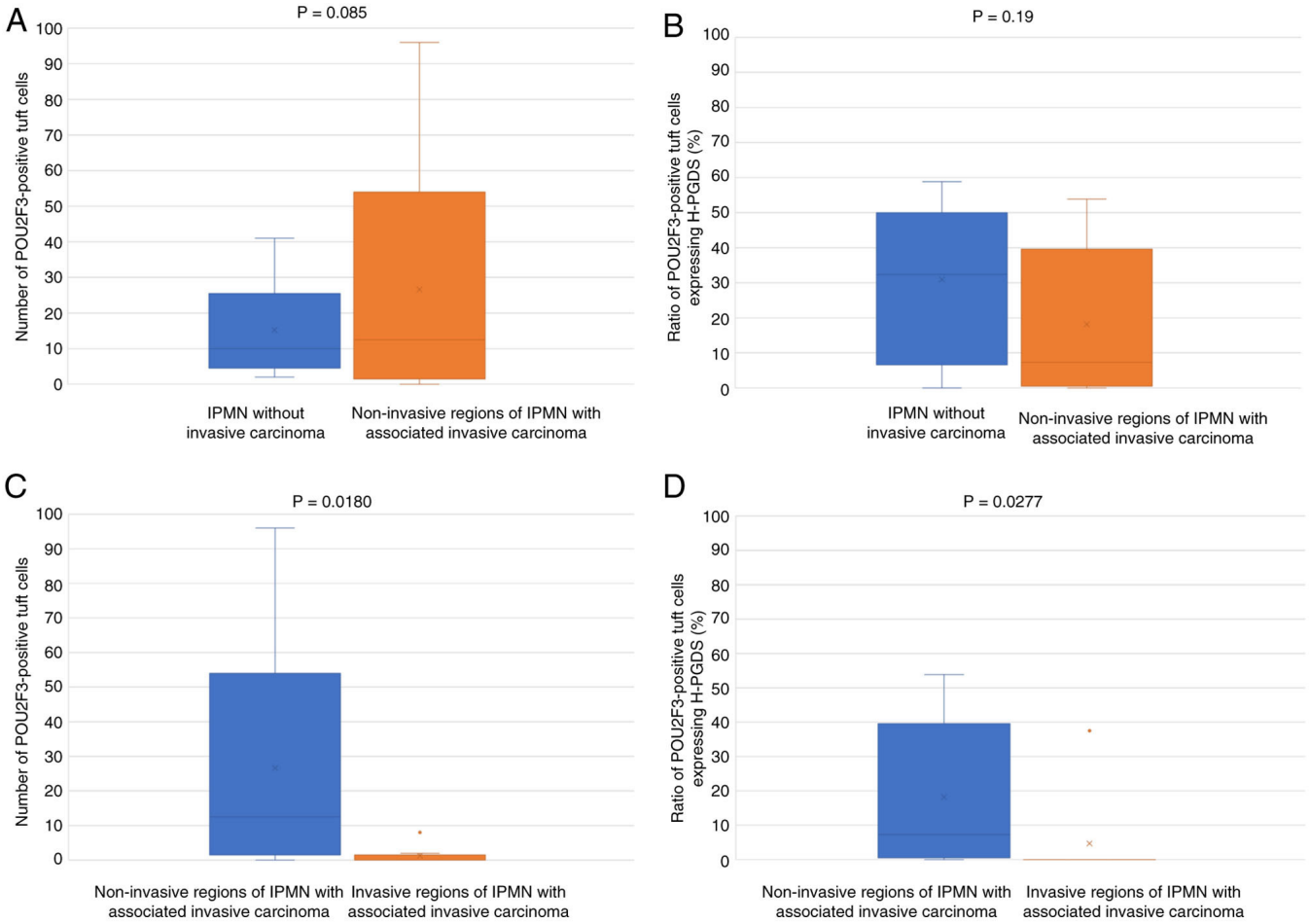

Figure 2. Number of total POU2F3-positive tuft cells and the ratio of POU2F3-positive tuft cells expressing H-PGDS/total POU2F3-positive tuft cells in IPMN. (A) Number of total POU2F3-positive tuft cells between the lesions of IPMN without carcinoma and the non-invasive regions of IPMN associated with invasive carcinoma. (B) Ratio of POU2F3-positive tuft cells expressing H-PGDS/total POU2F3-positive tuft cells between the lesions of IPMN without carcinoma and the non-invasive regions of IPMN associated with invasive carcinoma. (C) Number of total POU2F3-positive tuft cells between the non-invasive and invasive regions of IPMN associated with invasive carcinoma. (D) Ratio of POU2F3-positive tuft cells expressing H-PGDS/total POU2F3-positive tuft cells between the non-invasive and invasive regions of IPMN associated with invasive carcinoma. H-PGDS, haematopoietic prostaglandin D synthase; IPMN, intraductal papillary mucinous neoplasm; POU2F3, POU domain class 2 transcription factor 3.

with invasive carcinoma. There was no significant difference in this ratio between IPMN without invasive carcinoma (median, 32.4%; range, 0-58.8%) and non-invasive regions of IPMN associated with invasive carcinoma (median, 7.3%; range, 0-53.8%) (P=0.190) (Fig. 2B).

In the invasive carcinoma regions of IPMN associated with invasive carcinoma, few POU2F3-positive cells were observed (median, 0 cells; range, 0-8 cells/5-high power fields) (Fig. 1D). There was a significant difference in the number of POU2F3-positive tuft cells between the non-invasive and invasive regions in IPMN associated with invasive carcinoma (P=0.0180) (Fig. 2C). The median ratio of ($POU2F3^+$/$H\text{-}PGDS^+$)/[($POU2F3^+$/$H\text{-}PGDS^+$) + ($POU2F3^+$/$H\text{-}PGDS^-$)] in the invasive regions of IPMN associated with invasive carcinoma was 0% (range, 0-37.5%). The ratio was significantly different between the non-invasive and invasive regions in patients with IPMN associated with invasive carcinoma (P=0.0277) (Fig. 2D).

In addition, the number of tuft cells were not significantly different depending on the tumour location and the clinical histories (such as comorbidities and smoking history).

Discussion

This study demonstrated that POU2F3-positive tuft cells were present in human IPMN and that 20.0% of POU2F3-positive cells in IPMN without invasive carcinoma and in non-invasive regions of IPMN associated invasive carcinoma expressed H-PGDS. Moreover, POU2F3-positive tuft cells and the ratio of H-PGDS expression in POU2F3-positive tuft cells were significantly lower in the invasive regions than in the non-invasive regions of IPMN-associated invasive carcinoma.

Tuft cells play important roles in bacterial and parasitic infections of the gastrointestinal and respiratory tracts as chemosensory cells express taste receptors by producing various types of physiologically active substances (6). Recent studies have demonstrated the significance of tuft cells in tumourigenesis of some organs, including gastric cancer (17-19) and PDAC (7-9). In pancreatic carcinogenesis, POU2F3-positive tuft cells emerge in ADM, a possible precursor of PanIN, but not in normal acini in both the human and mouse pancreas (7,8). ADM is thought to be the trans-differentiation or de-differentiation of pancreatic acinar

cells after injury, and the possible role of tuft cells in ADM lesions is to facilitate tissue repair from the injury (6,20). Damaged acinar cells form ADM, in which some of cells within ADM lesions are speculated to differentiate into tuft cells in response to tissue injury, and the alternative mechanism of presence of tuft cells, such as *de novo* development from acinar cells, has not been considered (20). These tuft cells within ADM could facilitate tissue repair (20). Tuft cells are present in PanIN, a possible precursor lesion of PDAC, and their levels are significantly higher in low-grade PanIN than in high-grade PanIN in the human pancreas (8), as well as in the mouse pancreas using *Kras*^{G12D} transgenic models (7). Tuft cells present in PanIN lesions have been speculated to suppress tumour progression by producing PGD_2 in a mouse model (7). Moreover, tuft cells have also been paid attention in their oncogenic roles, because carcinomas with tuft cell-like gene signatures, including POU2F3, namely 'tuft cell-like carcinoma' has been reported (21). Small cell carcinomas of the lung are the first to show tuft cell-like signatures, and it has been demonstrated that thymic squamous cell carcinomas and a proportion of other extra-thoracic carcinomas, such as breast and uterine cervical carcinomas, show these signatures (21). Tuft cell-like gene signatures shows oncogenic roles, because these signatures have important roles in carcinogenesis of these malignant neoplasms (21). In contrast, tuft cells may have suppressive roles in tumourigenesis of PDAC and IPMN via production of PGD_2 (7). Moreover, in gastric tumourigenesis, tuft cells are present in dysplastic lesions, but rarely present in the adenocarcinoma (19), as the same line of the results of PanIN, PDAC (7), and IPMN. In pancreatic and gastric tumourigenesis, tuft cells show tumour-suppressive roles (7,19), although PGD_2 plays important roles in tumour-suppressive function in PanIN, PDAC, as well as IPMN (7), but its roles in gastric tumourigenesis remains unresolved (19). These key findings appear to be dual-faceted of tuft cells, having both tumour-promoting and tumour-suppressive roles (22). Although the reason of these different roles of tuft cells remains controversial, it might depend on the organ or molecular context roles of tuft cells and tumour microenvironment might influence the function of tuft cells (22). Tuft cells are present both in the normal respiratory and gastrointestinal tracts, and the thymus (6,23), and functions of tuft cells may be different among organs (23). These original function of tuft cells depending on the organs and their tumour microenvironment might influence the oncogenic or tumour-suppressive function of tuft cells (22,23). Additional studies are needed to clarify the roles of tuft cells in various types of tumours.

IPMN is the second common precursor lesion of invasive carcinoma of the pancreas (3). Although previous studies have revealed the significance of tuft cells in tumourigenesis from PanIN to PDAC (7,8), only one study has addressed the presence of tuft cells in IPMN (10). In that report, tuft cells were present in IPMN and were rarely observed in invasive carcinoma components in a mouse model, although doublecortin-like kinase1 (DCLK1) was used as an immunohistochemical marker for detecting tuft cells (10). The results of the present study showed that IPMN with low- and high-grade dysplasia and non-invasive regions of IPMN associated with invasive carcinoma had POU2F3-positive tuft cells, and the number of tuft cells between these lesions was not significantly different. These results are consistent with those of a previous study (10), although the immunohistochemical markers used to detect tuft cells were different. POU2F3 was used as a tuft cell marker in the present study because it is considered a more specific marker for human tuft cells owing to the nature of the master regulator of this type of cell (6,12,24).

PGs are lipid mediators involved in inflammation and smooth muscle and vascular dilatation in various types of tissues (25). PGD_2 is a PG that plays a pivotal role in inflammation and tissue injury (13,25). PGD_2 is synthesised from two different types of PGDS: H-PGDS and lipocalin-type PGDS (25). H-PGDS is expressed in certain types of immune cells, including macrophages, mast cells, and a subset of T lymphocytes (13,26). Immunohistochemical staining is a useful method for demonstrating PGD_2 production (7,11,13,14). Our previous study clearly demonstrated that tuft cells expressing H-PGDS were present in Warthin's tumour, the second most common benign salivary gland tumour, and its expression might be related to tissue injury within the tumour (10). The present study clearly demonstrated that 20.0% of POU2F3-positive tuft cells present in IPMN without invasive carcinoma and the non-invasive regions of IPMN associated with invasive carcinoma expressed H-PGDS and POU2F3-positive tuft cells and that the ratio of POU2F3-positive tuft cells expressing H-PGDS were significantly lower in the invasive portions compared with the non-invasive regions in IPMN associated with invasive carcinoma for the first time. It has been recognized that PGD_2 secreted from tuft cells in PanIN lesions shows tumour-suppressive functions from PanIN to PDAC, and these tuft cells are thought to be differentiated from PanIN lesions, however, carcinoma cells in PDAC have no potential to differentiation into tuft cells and production of PGD_2, thus, tuft cells are hardly present in PDAC lesions (7,27). The results of the present study were fundamentally the same line of those of PanIN and PDAC, because tuft cells were hardly present in the invasive carcinoma component of IPMN, but present in non-invasive regions. Non-invasive IPMN could have potential to differentiate into tuft cells, which play possible tumour-suppressive roles via production of PGD_2, but most of invasive carcinoma cells of IPMN might lack potential to differentiate into tuft cells. These results suggest that POU2F3-positive tuft cells have roles in progression to carcinoma in IPMN, similar to tuft cell function in PanIN and PDAC (7,8). No detailed molecular mechanism regarding the lack of potential to differentiate to tuft cells in tumourigenesis of PDAC, as well as invasive carcinoma component of IPMN, has been elucidated (7,27), therefore, further studies are needed to clarify this issue. In the present study, we did not perform a statistical analysis to compare the number of POU2F3-positive tuft cells and the ratio of H-PGDS expression between IPMN with low- and high-grade dysplasia because only two patients with IPMN with high-grade dysplasia were included. Therefore, additional studies with larger cohorts are required to clarify the differences in tuft cells between IPMN with low- and high-grade dysplasia. Moreover, although the presence of tuft cells in the non-neoplastic human pancreatic duct has been recognised (8), the present study showed that more than half of POU2F3-positive tuft cells present in the non-neoplastic pancreatic duct expressed H-PGDS. Although

the functions of these cells remain unclear, they are thought to modulate immune reactions or tissue repair. Additionally, one of the interesting findings of the present study was the presence of POU2F3-positive tuft cells in the invasive carcinoma region of IPMN associated with invasive carcinoma. It has been reported that POU2F3-positive tuft cells were not present in PDAC in a mouse model (7); however, our provisional study revealed that a few POU2F3-positive tuft cells were noted in PDAC in some cases (unpublished data), which is similar to the results of the present study. Thus, POU2F3-positive tuft cells may be present in invasive pancreatic carcinomas (both PDAC and IPMN associated with invasive carcinoma); thus, the clinicopathological features of POU2F3-positive tuft cells in invasive pancreatic carcinomas must be clarified.

This study has some limitations. First, this study included relatively few patients with pancreatic IPMN, especially those with IPMN with high-grade dysplasia, which could have led to a selection bias. Moreover, the number of tuft cells and the ratio of tuft cells expressing H-PGDS showed relative variations among the tumours. The possibility that tumours locations or clinical histories may influence the number of tuft cells cannot be ruled out, because these factors were not controlled in the present study. Although the number of tuft cells were not significantly different depending on the tumour location and the clinical histories, the possibility that these factors may influence the degree or extent of obstructive pancreatitis and tissue repair, leading to the changes of the number of tuft cells, cannot be excluded. Second, although IPMN are subclassified by immunohistochemical analyses for mucin into gastric, intestinal, and pancreatobiliary types (4), this subclassification was not performed in the present study. The possibility of differences in the number of tuft cells and the ratio of tuft cells expressing H-PGDS among these subclassifications cannot be ruled out. Validation studies with larger numbers of patients with IPMN are required to overcome statistical bias. Third, the present study showed the presence of POU2F3-positive tuft cells expressing H-PGDS in IPMN; however, the function of PGD_2 production in IPMN and the differences between H-PGDS-positive and H-PGDS-negative tuft cells remain unclear. Further analyses using mouse models are required to elucidate the function of tuft cells in IPMN, leading to the elucidation of IPMN. Fourth, POU2F3 was used as a human tuft cell marker in the present study, and immunohistochemical analysis using other markers, including DCLK-1, transient receptor potential melastatin 5 (TRPM5), and cyclooxygenase 1 (COX1), were not performed. Although these markers have been used as a marker for tuft cells, DCLK-1 is specific for mouse tuft cells, but not for human ones (6). TRPM5 is also expressed in pancreatic beta cells and taste buds (28), and COX1 expression is not specific for tuft cells (29). Moreover, as described-above, POU2F3 is a master regulator of tuft cell identity, thus, we used it as a human tuft cell marker in the present study (8). Finally, we did not perform the experiment using animal model, which might provide new information regarding the function of tuft cells in IPMN, because the aim of the present study was to show the roles of tuft cells in human IPMN tissues.

In conclusion, this study showed that POU2F3-positive tuft cells expressing H-PGDS were present in human IPMN and were hardly detected in the invasive regions of IPMN associated with invasive carcinoma. POU2F3-positive tuft cells producing PGD_2 might play a role in tumourigenesis in IPMN. Further analyses are required to clarify the function of tuft cells in IPMN, resulting in the resolution of the pathogenesis of IPMN.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

KN and MI conceived and designed the study. KN, MI, and KH analysed the histological and immunohistochemical staining. KN, MI, KH, KT, JA, AT, MA, YM, KF, YH and SWL analysed the data. KN and MI performed the statistical analyses. KN and MI wrote the manuscript, and prepared the figures and tables. KN and MI confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This retrospective, single-institution study was conducted in accordance with the tenets of The Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Osaka Medical and Pharmaceutical University Hospital (approval no. 2023-198). All data were anonymised. Informed consent was obtained from the patients using the opt-out methodology because of the retrospective study design, as medical records and archived samples were used with no risk to the participants. Moreover, the present study did not include minors.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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