Virchows Arch (2001) 438:442–450
DOI 10.1007/s004280000359

ORIGINAL ARTICLE

Motoyoshi Izumi · Koichi Suda · Akira Torii
Eisuke Inadama

Pancreatic ductal myofibroblasts

Proliferative patterns in various pathologic situations

Received: 5 April 2000 / Accepted: 31 October 2000 / Published online: 8 February 2001

Abstract Myofibroblasts in the periacinar area of the pancreas have been demonstrated to mediate fibrogenesis in pancreatic fibrosis. However, only a few reports have described myofibroblasts in the pancreatic duct. To elucidate the presence of myofibroblasts in the pancreatic ductal wall, we performed an immunohistochemical study, using immunostains for both α-smooth muscle actin (αSMA) and desmin, and an electron microscopic study on surgically resected pancreatic specimens from 10, 23, 23, and 56 cases of focal pancreatitis (FP), chronic pancreatitis (CP), pancreatic carcinoma (PCa), and carcinoma of the papilla of Vater (VPCa), respectively. All cases showed localized stenosis of the main pancreatic duct by means of preoperative pancreatography. As controls, 20 autopsy cases were studied. αSMA-positive and desmin-negative cells existed in the ductal walls of controls and were revealed as myofibroblasts by means of electron microscopy. In six FPs, proliferation of myofibroblasts was observed at the stenotic portion. In VPCas, myofibroblasts mainly proliferated in the pancreatic ductal wall. In CPs and PCas, no myofibroblast proliferation was observed at the stenotic portion. The proliferation of myofibroblasts might occur as a wound healing process in FP, while acting against elevation of intraductal pressure in VPCa. In conclusion, proliferation of myofibroblasts plays an important role in ductal changes in various pathological situations.

Keywords Myofibroblast · Smooth muscle actin · Focal pancreatitis · Localized stenosis of the pancreatic duct · Obstructive chronic pancreatitis

M. Izumi (✉) · A. Torii · E. Inadama
Division of Gastroenterology and Hepatology,
Department of Internal Medicine, Jikei University,
School of Medicine, 3-25-8 Nishi-Shinbashi, Minato-ku,
Tokyo 105-8461, Japan
e-mail: motoyosh@qj8.so-net.ne.jp

M. Izumi · K. Suda
Department of Pathology, Juntendo University,
School of Medicine, Tokyo, Japan

Introduction

The term ‘myofibroblasts’ was introduced by Majno et al. in 1971 to define cells that exhibit some of the ultrastructural features of both smooth muscle cells and fibroblasts in granulation tissue [21]. Some immunohistochemical and in situ hybridization studies have suggested that myofibroblasts consistently express α-smooth muscle actin (αSMA) [7, 44], and immunostaining for αSMA is useful to detect myofibroblasts [28, 36]. The presence of myofibroblasts has been shown in normal tissues [6, 17, 25, 27] and in various pathologic conditions [26, 31, 34, 37], such as liver cirrhosis [13, 30], lung fibrosis [1, 15, 16, 44], kidney fibrosis [9], and myocardial scar [40, 42]. Many investigators have also analyzed the role of myofibroblasts [25, 26].

Recent reports have revealed that myofibroblasts are also involved in pancreatic fibrosis [2, 3, 5, 20]. The identification of the pancreatic stellate cells (PSCs) was reported by Bachem et al. [4, 5], and these cells were morphologically and functionally similar to hepatic stellate cells, also called Ito cells [12], vitamin A-storing cells, or fat-storing cells. In that study, vitamin A-storing cells isolated from the pancreas were shown to differentiate into myofibroblast-like cells expressing αSMA and producing collagen types I and III, laminin, and fibronectin. It is therefore suggested that PSCs participate in the fibrogenic process of the pancreas.

Only a few reports have described myofibroblasts of the pancreatic ducts in various conditions. In this study, we showed immunohistochemically and ultrastructurally the existence of myofibroblasts in the normal pancreatic duct wall and examined the pancreatic duct walls in four pathological conditions: focal pancreatitis (FP), chronic pancreatitis (CP), invasive ductal carcinoma of the pancreas (PCa), and carcinoma of the papilla of Vater (VPCa).

Materials and methods

Materials

For this study, Jikei University and Juntendo University provided 112 surgically resected pancreas specimens with localized stenosis of the main pancreatic duct. Histologically, 10, 23, 23, and 56 specimens were diagnosed as FPs, CPs, PCas, and VPCas, respectively. In PCas, six were well-differentiated adenocarcinomas, 13 were moderately differentiated adenocarcinomas, and the remaining four were poorly differentiated adenocarcinomas. For controls, we randomly selected, from the 1998 autopsy files of Juntendo University, the pancreatic bodies of 20 people who had neither history of alcoholism nor pathological abnormalities of the liver, bile duct, or pancreas. These cases were matched by age and gender to the study cases. Surgical specimens of histologically normal pancreas tissues, downstream, not upstream, from the duct stenosis in six cases of PCa and three cases of FP, were also examined as controls. All materials were fixed with 10% formaldehyde solution and embedded in paraffin for microscopy. Serial sections were cut from each paraffin block at a thickness of 3 μm and were stained using hematoxylin and eosin (HE) and elastica van Gieson (EVG). They were also immunostained for αSMA and desmin.

Antibodies

The following antibodies were used:

1. Monoclonal mouse anti-αSMA, clone 1A4 (Dako A/S, Denmark), diluted 1:100, to detect myofibroblasts [27, 28]
2. Monoclonal mouse anti-human desmin, clone D33 (Dako A/S, Denmark), diluted 1:50

Immunohistochemistry

The avidin-biotin peroxidase method was performed for immunohistochemistry. Monoclonal antibodies, mentioned above, against αSMA and desmin were used as the primary antibodies. The specificities of these antibodies had been confirmed using an appropriate positive control series. Sections were deparaffinized, and endogenous peroxidase was blocked with 0.3% H_2O_2 in methanol for 20 min after dehydration. The slides were then incubated with anti-α-SMA or anti-desmin for 60 min and rinsed ten times in phosphate-buffered saline. After incubation with biotinylated secondary antibody, avidin–biotin peroxidase complex (Dako A/S, Denmark) was employed, and enzymatic activity was revealed using 3,3′-diaminobenzidine. Sections were finally counterstained with hematoxylin and covered in an aqueous mounting medium.

Electron microscopy

Main pancreatic ducts taken from the excised tissues were cut into 1 mm cubes and fixed for 2 h at 4°C in 2.5% glutaraldehyde (Merck, Darmstadt, Germany). They were then postfixed in 1% osmium tetroxide solution for 2 h at 4°C and embedded in Epon 812. Ultra-thin sections were cut using a Reichert ultramicrotome (Ultracut R/FCR; Wein, Austria) with a diamond knife and then double stained with uranyl acetate and lead citrate. They were examined and photographed using an H-7100 (Hitachi, Tokyo, Japan) at 75 kV.

Results

Controls

In all control cases, no or scant autolytic change was observed, and αSMA-positive cells, including vascular smooth muscle cells, existed mainly in the outer layer of the wall of the main pancreatic duct (Fig. 1A, C). Most of these cells, except vascular smooth muscle cells, were negative for desmin. Elastic fibers were distributed homogeneously over the ductal wall (Fig. 1B).

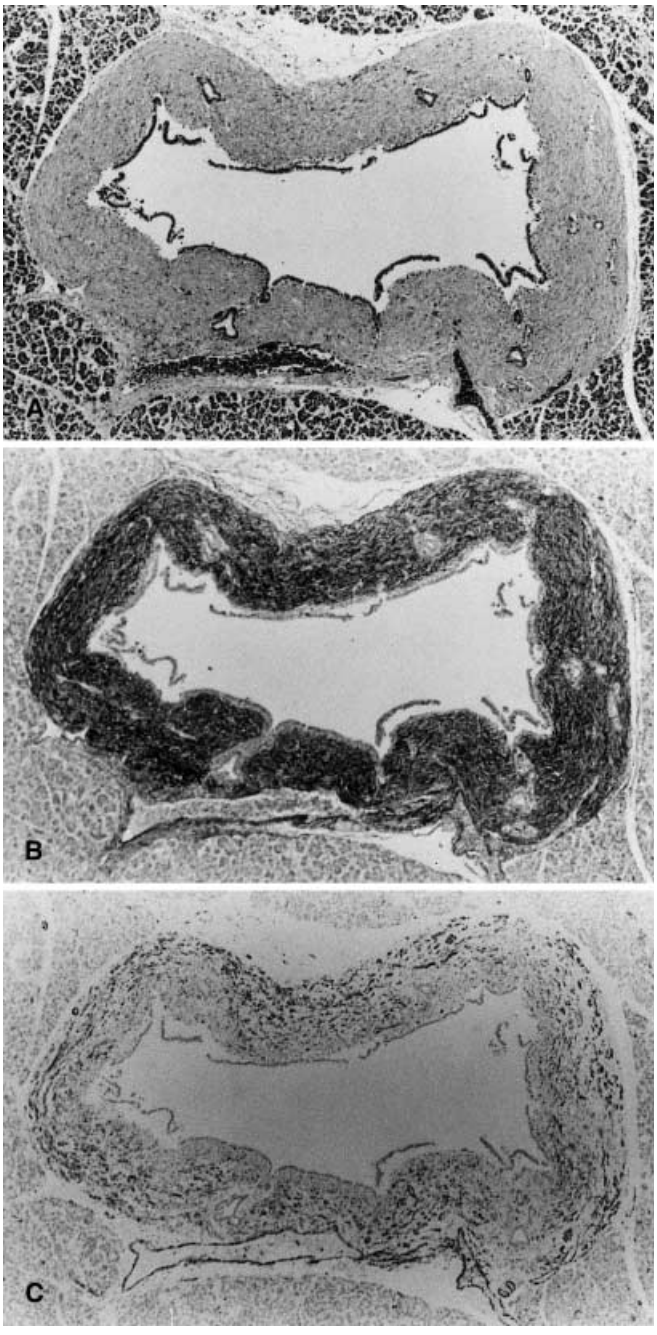

Fig. 1 The main pancreatic duct in a control. **A** No pathological change is identified (hematoxylin and eosin, ×60). **B** Elastic fibers distributed over the ductal wall (elastica van Gieson, ×60). **C** α-Smooth muscle actin-positive cells existed mainly in the outer region of the wall (immunostain for α-smooth muscle actin, ×60)

The electron microscopic study showed triangular shaped cells with cytoplasmic lipid droplets in the pancreatic ductal wall (Fig. 2A). These cells also contained a large notched nucleus, a prominent endo-

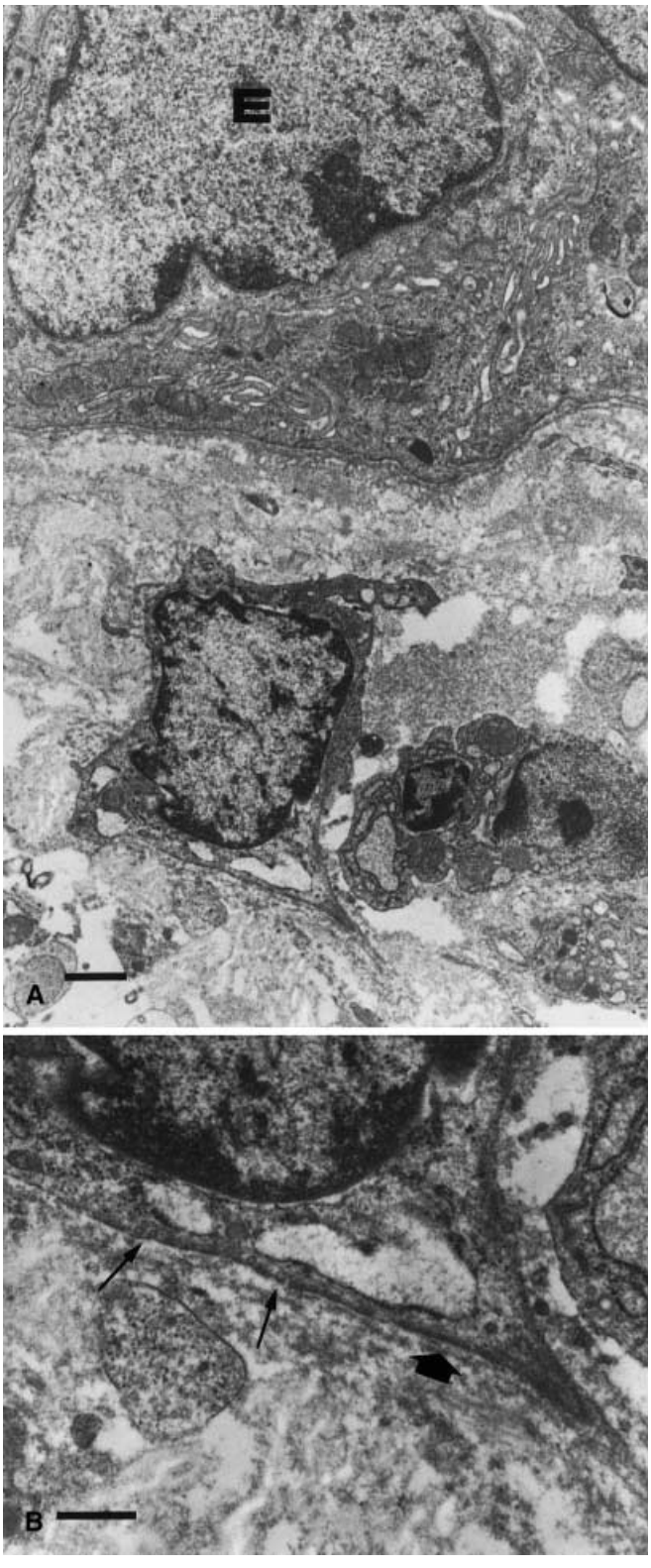

Fig. 2 Transmission electron micrograph illustrating a typical myofibroblast in the pancreatic duct of a control. **A** This cell shows a triangular shape, a large nucleus, and dilated cisternae of the rough endoplasmic reticulum. *E* Ductal epithelium. *Bar* 1 µm. **B** Bundles of microfilaments are observed throughout the cytoplasm (*bold arrow*), frequently forming dense bodies. Pinocytotic vesicles are observed at the cell membrane (*small arrow*). *Bar* 2 µm. (Uranyl acetate, lead citrate, and tannic acid stain)

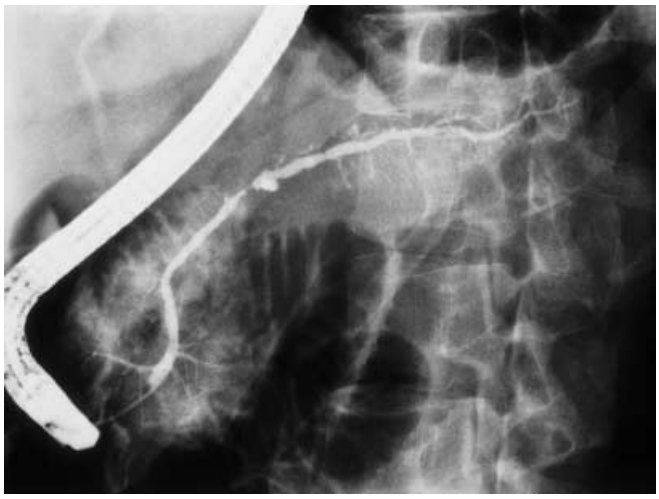

Fig. 3 Endoscopic retrograde pancreatography of a case of focal pancreatitis. Endoscopic retrograde pancreatography showed localized stenosis (*arrow*) of the main pancreatic duct in the body of the pancreas with dilatation of the distal ductal system

plasmic reticulum, bundles of microfilaments with dense bodies, partial investment by basal lamina, and a few mitochondria. Microfilaments were oriented parallel to the long axis of the cell, commonly located beneath the cell membrane. Pinocytic vesicles were sometimes observed at the cell membrane (Fig. 2B).

Focal pancreatitis

In this study, cases categorized into FPs showed localized stenosis of the main pancreatic duct on endoscopic retrograde pancreatography (Fig. 3) and histological findings of localized acinar atrophy with massive fibrosis and scanty inflammatory cell infiltration. No pathological change was observed in the pancreatic tissue downstream from the ductal stenosis. The tissue upstream from the stenosis showed no or slight inter- and intralobular fibrosis, which was compatible with obstructive CP [35, 39]. Additionally, none of the cases had either history of alcohol abuse or immunological abnormality. Therefore, these cases could not be distinctively classified into both non-alcoholic duct destructive CP [10] and early stage alcoholic pancreatitis [18]. In six of ten cases, myofibroblasts massively proliferated around the ductal epithelium at the stenotic portion of the main pancreatic duct, resulting in dissociation of elastic fibers from the ductal epithelium, as shown in Table 1 and Fig. 4. The irregularity of the ductal lumen at the stenosis was thus positively correlated with the non-uniform width of the subepithelial zone of proliferating myofibroblasts. In the other four cases, there was a hypocellular area composed of collagen fibers between the ductal epithelium and the elastic fibers band, but proliferation of myofibroblasts was not observed. In all cases, the main pancreatic duct on the duodenal side of the stenosis showed a similar pattern to that of the controls. In the tissue upstream

Table 1 Histological findings of the main pancreatic duct wall at stenosis in focal pancreatitis (FP) and chronic pancreatitis (CP). *Dissociated* preexisting elastic fiber band was dissociated from ductal epithelia; *Loose* elastic fibers were dissociated from each other by an increase of collagen fibers; *H* head; *B* body; *BT* body and tail; *T* tail

Case	Age (years)/gender	Portion	Inflammatory cell[b]	Elastic fiber	Myofibroblast[c]
Control	65.1[a]	B	–	Diffuse	+
FP1	55/Male	B	–	Dissociated	+++
FP2	55/Female	BT	+	Dissociated	+++
FP3	69/Female	B	–	Dissociated	+++
FP4	51/Male	T	+	Dissociated	+++
FP5	50/Female	BT	–	Dissociated	+++
FP6	69/Female	BT	–	Dissociated	+++
FP7	51/Female	B	+	Dissociated	+
FP8	74/Male	BT	–	Dissociated	+
FP9	76/Male	BT	–	Dissociated	+
FP10	65/Female	H	–	Dissociated	+
CP1	50/Male	H	++	Disrupted	+
CP2	49/Male	BT	++	Disrupted	+
CP3	68/Male	H	++	Disrupted	+
CP4	49/Male	BT	++	Disrupted	+
CP5	63/Male	H	+++	Disrupted	+
CP6	76/Male	BT	+++	Disrupted	+
CP7	60/Male	H	+++	Disrupted	+
CP8	59/Male	H	+++	Disrupted	+
CP9	47/Male	BT	+	Disrupted	+
CP10	51/Male	H	+	Disrupted	+
CP11	42/Male	BT	+	Dissociated	+
CP12	39/Male	BT	+	Dissociated	+
CP13	69/Male	H	+	Dissociated	+
CP14	43/Male	BT	+	Dissociated	++
CP15	43/Male	BT	+	Dissociated	++
CP16	63/Female	BT	+	Loose	+
CP17	52/Male	H	+	Loose	+
CP18	70/Male	H	+	Loose	+
CP19	70/Female	T	+	Loose	+
CP20	45/Male	H	+	Loose	+
CP21	47/Male	B	+	Loose	+
CP22	43/Male	BT	+	Loose	+
CP23	72/Male	BT	+	Loose	++

[a] Mean age
[b] – No cell, + few and focal, ++ massive and diffuse, and +++ massive cells in duct lumen
[c] – No cell, + same as control, ++ slight proliferation, and +++ subepithelial massive proliferation

from the stenosis, myofibroblasts slightly proliferated in the ductal wall and fibrous area, but the proliferating state was different from that seen in the stenotic ductal wall, as described later in the result of VPCas.

Chronic pancreatitis

All cases of CP had history of alcohol abuse and showed no immunological abnormality in various clinical examinations. Histologically, all cases were advanced stage, and ten cases contained focal necrosis. Inflammatory cell infiltration at various degrees was observed over the ductal wall at the stenotic portion of the main pancreatic duct (Fig. 5A), resulting in disruption of elastic fibers in ten cases (Fig. 5B). The other five cases showed dissociation of elastic fibers from the ductal epithelium and, in the remaining eight cases, the elastic fibers became loose and wide, resulting from an increase of collagen fibers among them, as shown in Table 1. No case showed proliferation of myofibroblasts in the stenotic ductal wall (Fig. 5C).

Pancreatic carcinoma

At the stenotic portion of the main pancreatic duct, carcinoma cells destroyed the ductal wall and disrupted the band of elastic fibers (Fig. 6A, B) without massive proliferation of myofibroblasts in all 23 cases of PCa (Fig. 6C, Table 2). Additionally, no case showed myofibroblast proliferation in the ductal wall where carcinoma cells spread only in the epithelial layer, and no invasion was observed.

Carcinoma of the papilla of Vater

The pancreatic tissue of patients with VPCa showed various degrees of inter- and intralobular fibrosis with acinar atrophy, which correspond to obstructive CP [35, 39]. In most pancreatic specimens of VPCa, proliferation of αSMA-positive cells, which showed negative for desmin, was identified. The 56 specimens were classified into five patterns of myofibroblast distribution, as follows: “same as controls (*n*=6)”, “proliferation only in the ductal wall (*n*=10)”, “proliferation in the ductal wall and periductal area (*n*=15)”, “proliferation in interlobular and periacinar areas in addition to the ductal wall (*n*=15)”, and “diffuse proliferation in the parenchyma (*n*=10)”, as shown in Fig. 7. In all cases, the distribution of myofibroblast fitted with distribution of fibrosis, as shown in Table 3. Furthermore, myofibroblasts that proliferated in the pancreatic ductal wall were distributed mainly in the subepithelial area, resulting in dissociation of elastic

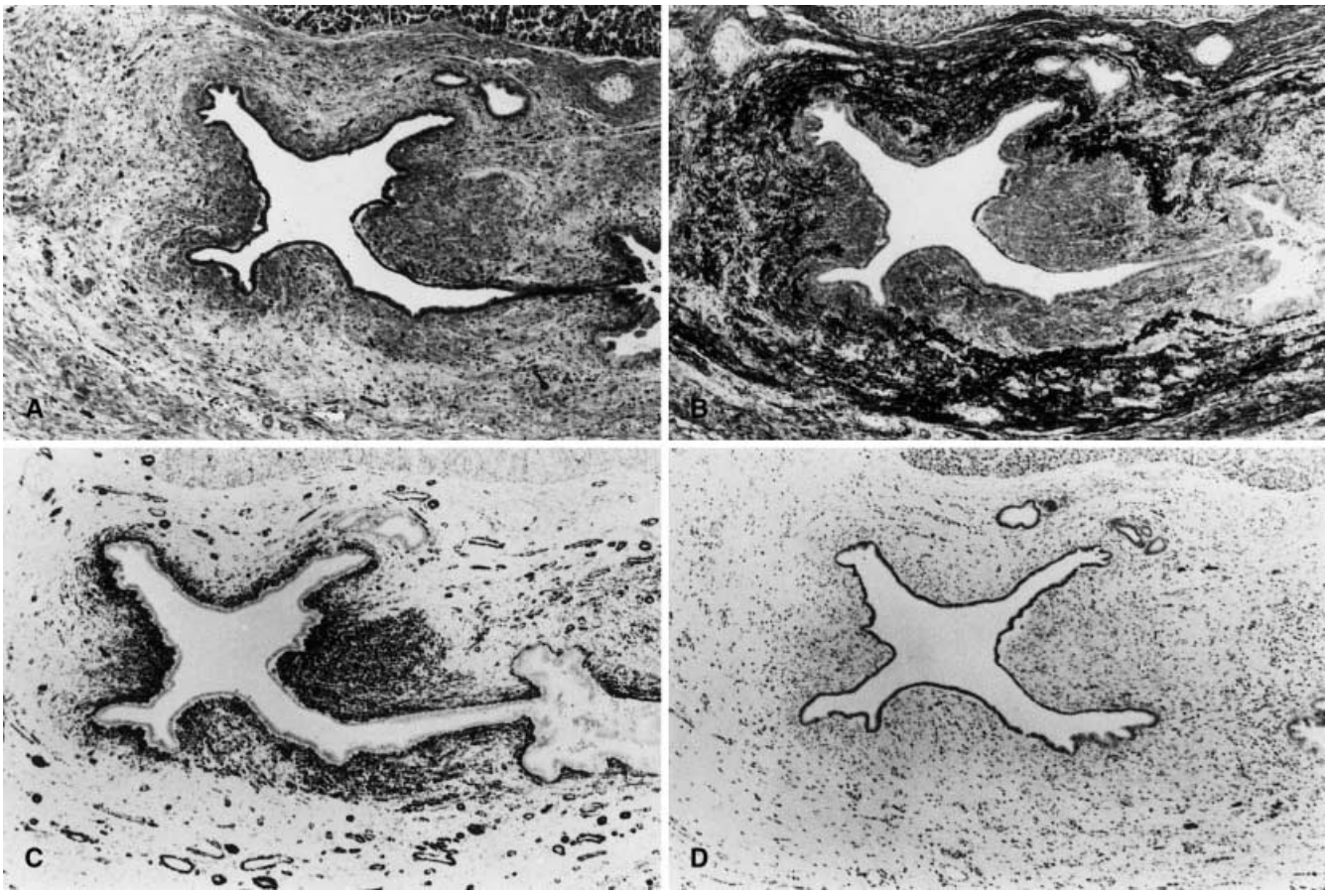

Fig. 4 A stenotic portion of the main pancreatic duct in a patient with focal pancreatitis. **A** The main pancreatic duct is surrounded by fibrous tissue (hematoxylin and eosin, ×80). **B** Elastic fibers are dissociated from ductal epithelium (elastica van Gieson ×80). **C** Massive proliferation of myofibroblast is observed in the subepithelium (immunostain for α-smooth muscle actin, ×80). **D** No proliferation of desmin-positive cells is identified (immunostain for desmin, ×80)

fibers from the ductal epithelium, as seen in the stenotic ductal wall in FP. However, the width of proliferating myofibroblast zone around the ductal epithelium in VPCa was rather more uniform and narrower than that seen in the stenotic ductal wall in FP.

In FP and PCa, the pancreatic tissue upstream, not downstream, from the stenotic portion showed various degrees of fibrosis and acinar atrophy, which were also compatible with obstructive CP, and the same distribution patterns of proliferating myofibroblasts as in VPCa were observed. However, the pancreatic tissues of PCa tended to show a more advanced stage of parenchymal fibrosis than those of VPCa, and the myofibroblast proliferation patterns of most cases were classified into "proliferation in interlobular and periacinar areas in addition to the ductal wall (*n*=12)" and "diffuse proliferation in the parenchyma (*n*=8)".

Discussion

In the present study, the existence of the myofibroblasts in the pancreatic ductal wall was elucidated in normal and various pathological conditions. In the normal pancreas, myofibroblasts were scattered and distributed mainly in the outer layer of the ductal wall. In the normal condition, the role of ductal myofibroblasts may be the regulation of intraductal pressure for smooth drainage of the pancreatic juice, similar to that of the Ito cells, which control the blood flow in the sinusoids of the liver [11].

There are many studies comparing pancreatography with pathological findings at the stenotic portion of the main pancreatic duct [24], but many cases are surgically treated without an accurate preoperative diagnosis [19, 23, 38, 41]. In these cases, no detailed histological or immunohistochemical analyses of the ductal wall deformities were seen, and the causes of such pathological changes were thought to be early stage chronic diffuse pancreatitis, ductitis, state after acute pancreatitis, or abdominal trauma [12, 14, 23, 38, 41, 43]. In this study, however, in six cases with FP, myofibroblasts massively and non-uniformly proliferated between the ductal epithelium and elastic fibers in the stenotic ductal wall. It is common knowledge that myofibroblasts play an important role in wound healing [7, 22, 33]. Therefore, such phenomena at the stenotic portion might indicate a

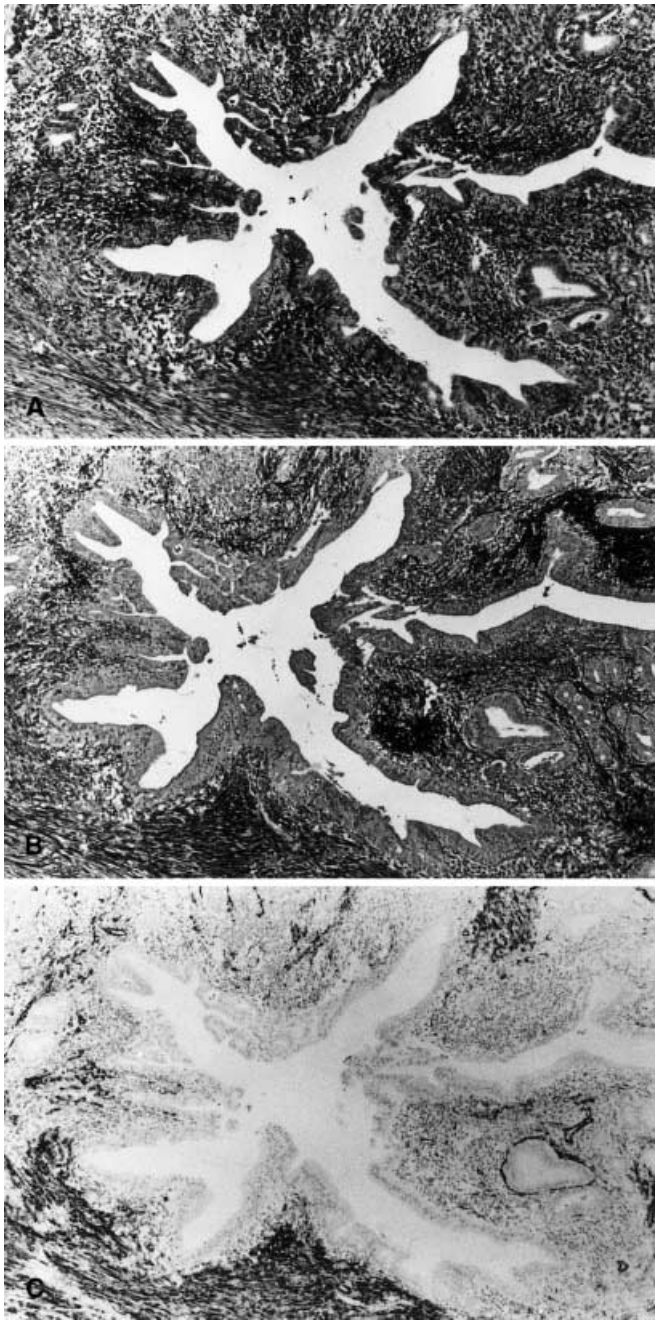

Fig. 5 The main pancreatic duct in a patient with chronic pancreatitis. **A** Massive infiltration of inflammatory cells is observed over ductal wall (hematoxylin and eosin, ×80). **B** Elastic fibers are disrupted by inflammatory infiltration (elastica van Gieson, ×80). **C** No proliferation of α-smooth muscle actin (αSMA)-positive cells is identified in the ductal wall (immunostain for αSMA, ×80)

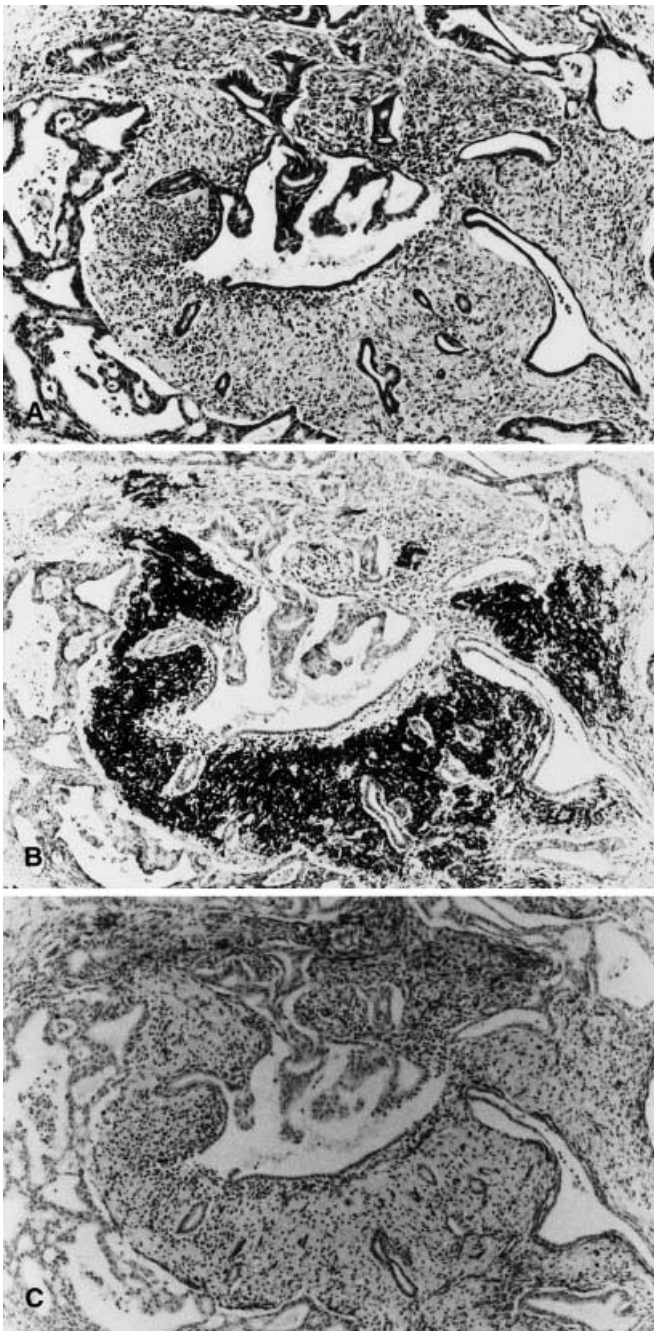

Fig. 6 The main pancreatic duct in a patient with pancreatic carcinoma. **A** Carcinoma cells invaded and destroyed the ductal wall, resulting in stenosis of the duct (hematoxylin and eosin, ×80). **B** Elastic fibers are disrupted by invasion of carcinoma cells (elastica van Gieson, ×80). **C** No proliferation of α-smooth muscle actin (αSMA)-positive cells is identified in the ductal wall (immunostain for αSMA, ×80)

healing process for localized inflammation or ulceration of the ductal wall. Furthermore, myofibroblasts participate in the contraction of tissues [28, 29, 32, 33]. In our FP cases, circular contraction of the ductal wall by proliferating myofibroblasts might induce the stenosis of the main pancreatic duct and block the efflux of pancreatic juice from branch pancreatic ducts at the stenotic portion, following localized acinar atrophy and fibrosis. Although FP seems to be due to focal damage to the pancreatic duct, we could not identify the initial cause of such ductal damage in this study. The question of whether FP is an entity thus remains to be solved. The remaining four FP cases showed hypocellular area composed of collagen fibers distributed between the ductal epithelium

Table 2 Histological findings of the main pancreatic duct wall at stenosis in pancreatic carcinomas. *H* head; *B* body; *BT* body and tail; *T* tail; *Wel* well differentiated type; *Mod* moderately differentiated type; *Por* poorly differentiated type; *ts* tumor size; *PCa* invasive ductal carcinomas of the pancreas

Case	Age (years)/gender	Portion	Histology	ts[b]	Elastic fiber	Myofibroblast[c]
Control	65.1[a]	B	–	–	Diffuse	+
PCa1	55/Male	H	Wel	2	Disrupted	+–
PCa2	66/Male	H	Wel	2	Disrupted	+–
PCa3	54/Male	H	Wel	2	Disrupted	+–
PCa4	53/Male	B	Wel	3	Disrupted	+–
PCa5	65/Male	H	Wel	2	Disrupted	+–
PCa6	73/Male	B	Wel	2	Disrupted	+–
PCa7	59/Male	B	Mod	2	Disrupted	+–
PCa8	57/Male	H	Mod	3	Disrupted	+–
PCa9	67/Male	B	Mod	1	Disrupted	+–
PCa10	64/Male	H	Mod	2	Disrupted	+–
PCa11	40/Male	H	Mod	1	Disrupted	+–
PCa12	72/Male	H	Mod	4	Disrupted	+–
PCa13	61/Male	H	Mod	2	Disrupted	+–
PCa14	72/Male	BT	Mod	3	Disrupted	+–
PCa15	61/Male	H	Mod	2	Disrupted	+–
PCa16	72/Female	H	Mod	2	Disrupted	+–
PCa17	68/Male	T	Mod	3	Disrupted	+–
PCa18	74/Male	B	Mod	1	Disrupted	+–
PCa19	72/Female	T	Mod	4	Disrupted	+–
PCa20	69/Male	H	Por	2	Disrupted	–
PCa21	69/Male	H	Por	2	Disrupted	–
PCa22	54/Male	H	Por	3	Disrupted	–
PCa23	70/Male	B	Por	2	Disrupted	–

[a] Mean age
[b] Maximum diameter of tumor size; ts1≤2 cm, 2 cm<ts2≤4 cm, 4 cm<ts3≤6 cm, and 6 cm<ts4
[c] – No cell; +–fewer cells identified than control

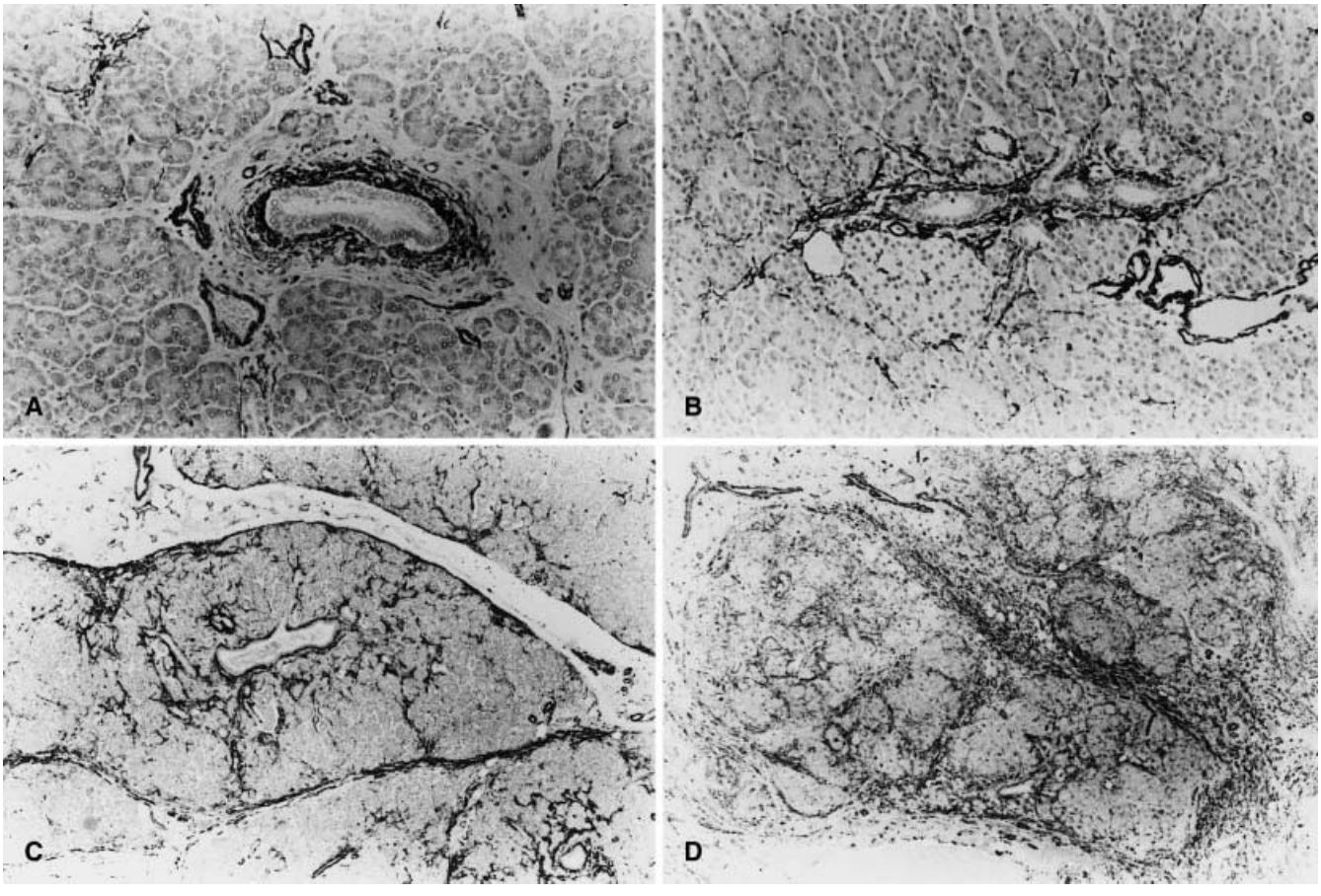

Fig. 7 Myofibroblasts, α-smooth muscle actin (αSMA)-positive cells, proliferating in patients with carcinomas of the papilla of Vater. The proliferation of αSMA-positive cells is seen only in the ductal wall (**A**), in the ductal wall and the periductal area (**B**), in the interlobular and the periacinar area (**C**), and in the parenchymal fibrotic area (**D**) (immunostain for αSMA; **A** and **B** ×100, **C** ×40, and **D** ×20)

Table 3 Distribution of myofibroblast in the pancreatic tissue of carcinoma of the papilla of Vater. *I* no fibrosis, *II* periductal fibrosis, *III* periductal, interlobular and intralobular fibrosis, *IV* diffuse fibrosis; – no cell; + same as control; ++ slight proliferation; +++ massive proliferation

Fibrosis	Number of case (%)	Ductal wall	Periduct	Intralobule	Interlobule
Control		+	–	–	–
I	16 (28.5)	+/++	–	–	–
II	15 (26.8)	++	++	–	–
III	15 (26.8)	++	++	++	++
IV	10 (17.9)	++	++	+++	+++

and elastic fibers zone without myofibroblast proliferation. Possible mechanisms of such pathological change include not only apoptosis, as seen in the late phases of wound healing [8], but also cytoskeletal transformation to be negative for αSMA after collagen fiber synthesis.

The pancreatic tissue of VPCas and tissue upstream from the stenotic portion of both FPs and PCas showed interlobular and intralobular fibrosis in various degrees, with or without acinar atrophy. These changes were caused by disturbance of the flow of pancreatic juice and were recognized as obstructive CP [35], and characteristic fibrosis was observed in both periacinar and interlobular areas [39]. In this study, all cases with such fibrosis showed myofibroblast proliferation in the ductal wall. Additionally, ten VPCa cases without parenchymal fibrosis showed proliferation of myofibroblasts in the pancreatic ductal wall. Sections downstream, not upstream, from the stenotic portion, which were obtained from PCas and FPs, did not show either parenchymal fibrosis or myofibroblast proliferation in the ductal wall. Furthermore, in contrast to the stenotic ductal wall of FPs, the width of the proliferating myofibroblast zone was relatively uniform, following no ductal stenosis. Therefore, proliferation of myofibroblasts over the ductal wall in our study might be a phenomenon against the elevation of intraductal pressure by disturbance of the flow of pancreatic juice. Once the intraductal pressure becomes higher than the limitation of the compensation by contractile force of myofibroblasts, however, both atrophy of the acini and fibrosis may occur. Such varying patterns of fibrosis and myofibroblast proliferation in cases of obstructive CP may depend on the difference in intraductal pressure in each case.

In both CPs and PCas, stenosis of the pancreatic duct is due to intraluminal factors, such as protein plugs or neoplasia, and extraluminal factors, such as inflammatory cell or carcinoma cell infiltration with fibrosis. However, no proliferation of myofibroblasts in the ductal wall was observed at the duct stenotic portion. These results suggested that myofibroblast proliferation in the fibrotic area is non-specific, while that in the ductal wall is a specific phenomenon.

Finally, we elucidated the existence of ductal myofibroblasts in this study. To elucidate the role of ductal myofibroblasts, further studies, such as analyses of coculture models of ductal epithelial cells and myofibroblasts, should be performed. However, our pathological study can explain the roles of myofibroblasts if we take into account the findings of previous studies [7, 17, 21, 25, 26, 44], as follows: ductal myofibroblasts may take part in (1) control of the intraductal pressure for smooth flow of pancreatic juice, (2) epithelial cell restitution and duct remodeling in healing of ductal injury, and (3) epithelial proliferation and differentiation [26]. In conclusion, we demonstrated that myofibroblasts in the ductal wall proliferated in various pathological situations and occasionally caused ductal stenosis.

Acknowledgements This work was supported by a research grant from the Ministry of Health and Welfare, Japan. The authors are indebted for the positive technical assistance given by Hiroshi Abe and Yoshinori Hosokawa, Department of Pathology, Juntendo University.

References

1. Adler KB, Low RB, Lesile KO, Mitchell J, Evans JN (1989) Biology of disease. Contractile cells in normal and fibrotic lung. Lab Invest 60:473–485
2. Apte MV, Haber PS, Applegate TL, et al (1998) Periacinar stellate shaped cells in rat pancreas: identification, isolation, and culture. Gut 43:128–133
3. Apte MV, Haber PS, Rodgers SC, McCaughan GW, Korsten MA, Pirola RC, Wilson JS (1999) Pancreatic stellate cells are activated by proimflammatory cytokines: implications for pancreatic fibrogenesis. Gut 44:534–541
4. Bachem MG, Sell KM, Melchior R, Kropf J (1993) Tumor necrosis factor alpha (TNFα) and transforming growth factor β 1 (TGFβ1) stimulate transdifferentiation of fat-storing cells into myofibroblasts and fibronectin synthesis. Virchows Arch 63:123–130
5. Bachem MG, Schneider E, Groβ H, et al (1998) Identification, culture, and characterization of pancreatic stellate cells in rats and humans. Gastroenterology 115:421–432
6. Czernobilky B, Shezen E, Lifschitz-Mercer B, et al (1989) Alpha smooth muscle actin (αSM actin) in normal human ovaries, in ovarian stromal hyperplasia and in ovarian neoplasm. Virchows Arch 57:55–61
7. Darby I, Skalli O, Gabbiani G (1990) α-Smooth muscle actin is transiently expressed by myofibroblasts during experimental wound healing. Lab Invest 63:21–29
8. Desmoulière A, Redard M, Darby I, Gabbiani G (1995) Apoptosis mediates the decrease in cellularity during the transition between granulation tissue and scar. Am J Pathol 146:56–65
9. Diamond JR, van Goor H, Ding G, Engelmyer E (1995) Myofibroblasts in experimental hydronephrosis. Am J Pathol 146:121–129
10. Ectors N, Maillet B, Aerts R, Geboes K, Donner A, Borchard F, Lankisch P, Stolte M, Lütteges J, Kremer B, Klöppel G (1997) Non-alcoholic duct destructive chronic pancreatitis. Gut 41:263-268
11. Enzan H, Himeno H, Iwamura S, Saibara T, Onishi S, Yamamoto Y, Hara H (1994) Immunohistochemical identification of ito cells and their myofibroblastic transformation in adult human liver. Virchows Arch 424:249–256
12. Feller ER (1988) Stenosis of the main pancreatic duct in acute pancreatitis of unknown etiology. Gastrointest Endosc 34: 131–133
13. Friedmann SL (1993) The cellular basis of hepatic fibrosis. Mechanisms and treatment strategies. New Engl J Med 328: 1828–1835
14. Furukawa T, Tsukamoto Y, Naitoh Y, Hirooka Y, Hayakawa T (1994) Differential diagnosis between benign and malignant

localized stenosis of the main pancreatic duct by intraductal ultrasound of the pancreas. Am J Gastroenterol 89:2038–2041
15. Kapanci Y, Burgan S, Pietra GG, Conne B, Gabbiani G (1990) Modulation of actin isoform expression in alveolar myofibroblasts (contractile interstitial cells) during pulmonary hypertension. Am J Pathol 136:881–889
16. Kapanci Y, Ribaux C, Chaponnier C, Gabbiani G (1992) Cytoskeletal features of alveolar myofibroblasts and pericytes in normal human and rat lung. J Histochem Cytochem 40: 1955–1963
17. Kapanci Y, Assimacopoulos A, Irle C, Zwahlen A, Gabbiani G (1974) Contractile interstitial cells in pulmonary septa. J Cell Biol 60:375–392
18. Klöppel G (1999) Progression from acute to chronic pancreatitis. Surg Clin North Am 79:801-814
19. Kruse A, Thommesen P, Frederiksen P (1978) Endoscopic retrograde cholangiopancreatography in pancreatic cancer and chronic pancreatitis-differences in morphologic changes in the pancreatic duct and the bile duct. Scand J Gastroent 13:513–517
20. Kuroda J, Suda K, Hosokawa Y (1998) Periacinar collagenization in patients with chronic alcoholism. Pathol Int 48: 857–868
21. Majno G, Gabbiani G, Hirschel B J, Ryan G B, Statkov P R (1971) Contraction of granulation tissue in vitro: similarity to smooth muscle. Science 173:548
22. Nakatsuji S, Yamate J, Kuwamura M, Kotani T, Sakuma S (1997) In vivo responses of macrophages and myofibroblasts in the healing following isoproterenol-induced myocardial injury in rats. Virchows Arch 430:63–69
23. Neff CC, Simeone JF, Wittenberg J, Mueller PR, Ferrucci JT, Jr. (1984) Inflammatory pancreatic masses. Radiology 150:35–38
24. Oi I (1998) ERCP imaging. Pancreas 16:402–407
25. Powell DW, Mifflin RC, Valentich JD, Crowe SE, Saada JI, West AB (1999) Myofibroblasts. I. Paracrine cells important in health and disease. Am J Physiol 277:1–19
26. Powell DW, Mifflin RC, Valentich JD, Crowe SE, Saada JI, West AB (1999) Myofibroblasts. II. Intestinal subepithelial myofibroblasts. Am J Physiol 277:183–201
27. Sappino AP, Dietrich PY, Skalli O, Widgren S, Gabbiani G (1989) Colonic pericryptal fibroblasts. Differentiation pattern in embryogenesis and phenotypic modulation in epithelial proliferative lesions. Virchow Arch 415:551–557
28. Sappino AP, Schürch W, Gabbiani G (1990) Differentiation repertoire of fibroblastic cell: expression of cytoskeletal proteins as marker of phenotypic modulations. Lab Invest 63: 144–161
29. Schmitt-Gräff A, Skalli O, Gabbiani G (1989) α-Smooth muscle actin is expressed in a subset of bone marrow stromal cells in normal and pathological conditions. Virchows Arch 57:291–302
30. Schmitt-Gräff A, Krüger S, Bochard F, Gabbiani G, Denk H (1991) Modulation of alpha smooth muscle actin and desmin expression in perisinusoidal cells of normal and diseased human liver. Am J Pathol 138:1233–1242
31. Schmitt-Gräff A, Desmoulière A, Gabbiani G (1994) Heterogeneity of myofibroblast phenotypic features – an example of fibroblastic cell plasticity. Virchows Arch 425:3–24
32. Schürch W, Lagacé R, Seemayer TA (1982) Myofibroblastic stromal reaction in retracted scirrhous carcinoma of the breast. Surg Gynecol Obstet 154:351–358
33. Schürch W, Seemayer TA, Gabbiani G (1998) The myofibroblast. A quarter century after its discovery. Am J Surg Pathol 22:141–147
34. Seemayer TA, Lagacé R, Schürch W, Thelmo WL (1980) The myofibroblast: biologic, pathologic, and theoretical considerations. Pathol Annu 15:443–470
35. Shahel J, Sarles H (1984a) Chronic calcifying and obstructive pancreatitis: two entities. In: Gyr KE, Singer MV, Sarles H (eds) Pancreatitis: concepts and classification. Excepta Medica, Amsterdam, pp 47–49
36. Skalli O, Ropraz P, Trzeciak A, Benzonana G, Gillessen D, Gabbiani G (1986) A monoclonal antibody against α-smooth muscle actin – a new probe for smooth muscle differentiation. J Cell Biol 103:2787–2796
37. Skalli O, Schürch W, Seemayer TA, Lagacé R, Montandon D, Pittet B, Gabbiani G (1989) Myofibroblasts from diverse pathologic settings are heterogeneous in their content of actin isoforms and intermediate filament proteins. Lab Invest 60: 275–285
38. Smith CD, Behrns KE, Van Heerden JA, Sarr MG (1994) Radical pancreato-duodenectomy for misdiagnosed pancreatic mass. Br J Surg 81:585–589
39. Suda K, Mogaki M, Oyama T, Matsumoto Y (1990) Histopathologic and immunohistochemical studies on the alcoholic and chronic obstructive pancreatitis-special emphasis on ductal obstruction and genesis of pancreatitis. Am J Gastroenterol 85:271–276
40. Sun Y, Weber KT (1996) Angiotensin converting enzyme and myofibroblasts during tissue repair in the rat heart. J Mol Cell Cardiol 28:851–858
41. Van Gulik TM, Reeders JWAJ, Bosma A, et al. (1997) Incidence and clinical findings of benign, inflammatory disease in patients resected for presumed pancreatic head cancer. Gastrointest Endosc 46:417–423
42. Vracko R, Thorning D (1991) Contractile cells in rat myocardial scar tissue. Lab Invest 65:214–227
43. Watanabe T, Morimoto H, Suzuki K, et al. (1993) Fibrous thickening of the main pancreatic duct wall showing localized stenosis on endoscopic retrograde cholangiopancreatography. Pancreas 8:652–654
44. Zhang K, Rekhter MD, Gordon D, Phan SH (1994) Myofibroblasts and their role in lung collagen gene expression during pulmonary fibrosis. A combined immunohistochemical and in situ hybridization study. Am J Pathol 145:114–125