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REVIEW ARTICLE

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Fatty pancreas: A possible risk factor for pancreatic cancer in animals and humans

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Obesity, type 2 diabetes mellitus (T2DM) and aging are associated with pancreatic cancer risk, but the mechanisms of pancreatic cancer development caused by these factors are not clearly understood. Syrian golden hamsters are susceptible to *N*-nitroso*bis*(2-oxopropyl)amine (BOP)-induced pancreatic carcinogenesis. Aging, BOP treatment and/or a high-fat diet cause severe and scattered fatty infiltration (FI) of the pancreas with abnormal adipokine production and promote pancreatic ductal adenocarcinoma (PDAC) development. The KK-A^y mouse, a T2DM model, also develops severe and scattered FI of the pancreas. Treatment with BOP induced significantly higher cell proliferation in the pancreatic ducts of KK-A^y mice, but not in those of ICR and C57BL/6J mice, both of which are characterized by an absence of scattered FI. Thus, we hypothesized that severely scattered FI may be involved in the susceptibility to PDAC development. Indeed, severe pancreatic FI, or fatty pancreas, is observed in humans and is associated with age, body mass index (BMI) and DM, which are risk factors for pancreatic cancer. We analyzed the degree of FI in the non-cancerous parts of PDAC and non-PDAC patients who had undergone pancreatoduodenectomy by histopathology and demonstrated that the degree of pancreatic FI in PDAC cases is significantly higher than that in non-PDAC controls. Moreover, the association with PDAC is positive, even after adjusting for BMI and the prevalence of DM. Accumulating evidence suggests that pancreatic FI is involved in PDAC development in animals and humans, and further investigations to clarify the genetic and environmental factors that cause pancreatic FI are warranted.

KEYWORDS
cancer susceptibility, fatty infiltration, obesity, pancreatic cancer, type 2 diabetes mellitus

1 | INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer death in Japan.[1] The phenomenon of Westernization, including the addition of more fat to diets, and an increase in the elderly population, are considered to be involved in the increasing pancreatic cancer incidence. Pancreatic cancer is difficult to detect in its early phases and tends to be intractable; thus, it is important to clarify its risk factors

and etiology and to develop prevention methods against it. We have studied the risk and preventive factors for pancreatic cancer using animal models.[2-4] Syrian golden hamsters are susceptible to chemically induced pancreatic carcinogenesis.[5] Screening of preventive agents for pancreatic cancer has been carried out using this animal model because mice and rats are not usually susceptible to chemically induced pancreatic carcinogenesis.[6] Recently, mouse models of pancreatic cancer, such as genetically engineered mouse models and patient-derived xenograft models, have been developed and used in preclinical studies for cancer therapy,[7] but these models may not be suitable for studying carcinogenic/anti-carcinogenic factors. There are species differences in pancreatic cancer susceptibility. If we can clarify the reason why Syrian golden hamsters are susceptible to pancreatic carcinogenesis, it may be helpful to understand the factors that are related to pancreatic cancer susceptibility and to develop preventive methods against them. Syrian golden hamsters develop hypertriglyceridemia and fatty infiltration (FI) of the pancreas, and the severity of FI increases along with the progression of carcinogenesis.[2] However, the association of FI with pancreatic cancer in other animals has not yet been clarified. We then investigated whether FI of the pancreas, or a pancreas with FI per se, was an essential modification factor for pancreatic carcinogenesis in both experimental animals and humans.

Epidemiological studies have shown that obesity and type 2 diabetes mellitus (T2DM) are risk factors for pancreatic cancer.[8] Obesity and T2DM accompany dyslipidemia and visceral fat accumulation,[9] and ectopic fats are observed in the liver, heart, muscle, and pancreas[10-12] and cause lipotoxicity in these organs.[13] In particular, hepatic steatosis, also known as non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH), promotes hepatocellular carcinoma and cholangiocarcinoma development.[14,15] Recently, lipid deposition in the pancreas (fatty pancreas) has been studied in relationship to non-alcoholic fatty pancreatic diseases (NAFPD),[10] and the involvement of fatty pancreas in pancreatic carcinogenesis has been suggested.[16,17] In this review, we focus on the contribution of pancreatic FI to pancreatic carcinogenesis in humans and animal models and discuss the putative mechanisms.

2 | WHAT IS FATTY PANCREAS?

2.1 | Histopathology and diagnosis of fatty pancreas in humans

Pancreatic FI can be assessed by a histological examination. Pancreatic tissue samples from humans who underwent pancreatoduodenectomy[18] revealed that pancreatic FI is different from fatty liver, in which fat accumulates within hepatocytes. Fatty pancreas is a fatty-infiltrated pancreas where adipocytes infiltrate the parenchyma with a scattered pattern (intralobular fat) and/or accumulate in the peri-lobular space; this pattern is mainly observed around large vessels (interlobular fat). Human pancreatic FI can be divided into four patterns: (a) a pancreas with both intralobular and interlobular FI (Figure 1A); (b) a pancreas with intralobular FI only (Figure 1B); (c) a pancreas with interlobular FI only (Figure 1C); and (d) a pancreas without FI (Figure 1D). To evaluate pancreatic fat in a non-invasive medical examination, image analysis, such as computed tomography (CT) or magnetic resonance imaging (MRI), is used. Ultrasonography is a non-invasive method that can detect fatty pancreas, which is diagnosed as a "bright pancreas" because fatty pancreas increases echogenicity.[19] Among these methods, we have shown that the area-based measurement of pancreatic fat by CT is useful for evaluating the degree of pancreatic fat.[20]

2.2 | Risk factors

2.2.1 | Age-related physiological changes and fatty pancreas

There are multiple risk factors for fatty pancreas.[21] The degree of pancreatic fat is positively associated with age and body mass index (BMI).[22] It has been reported that pancreatic fat increases with age until ~60 years and then reaches a plateau, while the parenchymal pancreas volume increases with age until ~30 years and then gradually decreases; these factors increase the fat/parenchymal ratio in middle-aged and elderly people.[23] In the case of obesity, the parenchymal pancreas volume increases by approximately 10%-15%, whereas pancreatic fat mass increases by ~70% compared to that of lean subjects, resulting in an increase in the fat/parenchymal ratio.[23] Analysis of 685 subjects in a general population cohort study of adult Hong Kong Chinese volunteers revealed that the prevalence of fatty pancreas increased with age, in general, but there were also sex differences. The prevalence of fatty pancreas in men peaked from 40 to 49 years. On the other hand, the prevalence of fatty pancreas was very low in women <50 years old, but increased progressively to age 60.[24] These results suggest that the overweight/obesity in middle-aged men and the hypercholesterolemia in postmenopausal women may be involved in the development of fatty pancreas. Compared to adults, pancreatic fat levels were low in children, but the pancreatic fat ratio in overweight/obese children with fatty liver was higher than that in overweight/obese children without fatty liver (2.28% vs 1.77%).[25]

2.2.2 | Fatty pancreas-associated disease

Fatty pancreas is associated with abdominal obesity, insulin resistance, T2DM, dyslipidemia, arterial hypertension and metabolic syndrome.[26,27] In non-obese T2DM patients, a significant association between pancreatic steatosis and atherosclerosis has been reported.[28] In addition, fatty liver is one of the risk factors for fatty pancreas.[29] Infection and autoimmune diseases are also involved in the development of fatty pancreas.[22] Infection by *Helicobacter pylori* in humans and infection by Coxsackie B viruses in mice have been reported to cause severe pancreatitis and lead to the replacement of damaged acinar cells with adipocytes.[30,31] Human immunodeficiency virus-1 infection and/or antiretroviral therapy are also known to cause lipomatosis.[32]

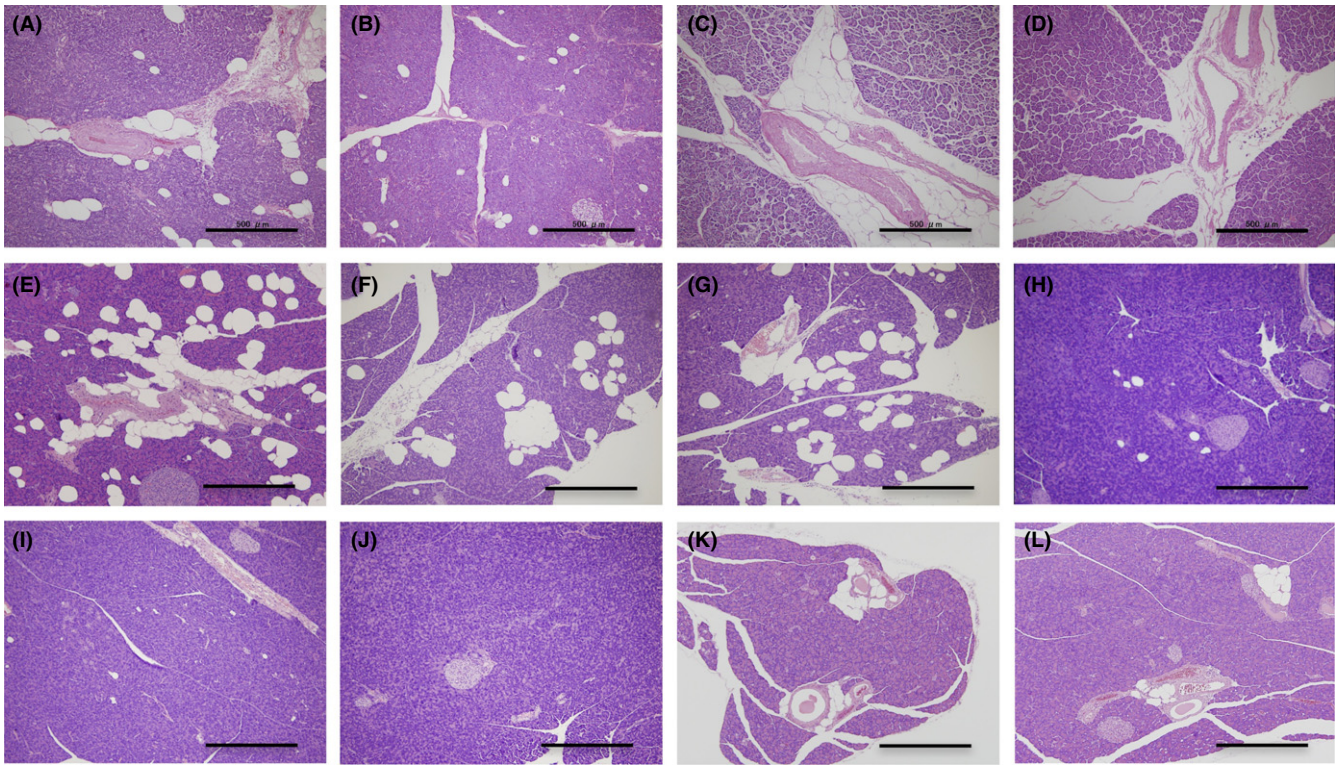

FIGURE 1 Pancreatic fatty infiltration (FI) in humans and animals. Hematoxylin and eosin-stained sections of the pancreas with intralobular FI and/or interlobular fat of pancreatic ductal adenocarcinoma (PDAC) patients (A-D), Syrian golden hamsters at 24 wk of age (E), KK-A^y(F), KK (G), C57BL/6J-A^y (H), ICR (I) and C57BL/6J mice (J) at 17 wk of age, and OLETF (K) and LETO rats (L) at 65 wk of age that were obtained from our previous studies.[18,36,39] Bar, 500 μm

2.2.3 | Medications and alcohol

Steroid hormones and some chemical agents are involved in the development of fatty pancreas.[22] Antiretroviral therapy is also known to cause lipomatosis.[32] Rosiglitazone has been shown to exacerbate pancreatic FI in C57BL/6 mice fed a high-fat/high-sucrose diet.[33] Chronic ethanol feeding has been shown to increase pancreatic cholesteryl ester accumulation and to induce pancreatic steatosis in Wistar rats.[34]

2.3 | Fatty pancreas in experimental animals

In experimental animals, there are species- and strain-specific differences in the pancreatic FI patterns.

2.3.1 | Syrian golden hamsters

The Syrian golden hamster is a unique animal model that develops pancreatic ductal adenocarcinoma (PDAC) when given subcutaneous injections of *N*-nitroso*bis*(2-oxopropyl)amine (BOP).[35] Syrian golden hamsters have both severely scattered intralobular fat and accumulation of interlobular fat that is mainly observed around large vessels (Figure 1E),[2] similar to that seen in humans with severe pancreatic FI.[18]

2.3.2 | T2DM and hyperlipidemia models in mice and rats

In our study on colon carcinogenesis in T2DM model KK-A^y mice,[36] we found that KK-A^y and KK mice (Figure 1F,G)[36] had both severely scattered intralobular FI and an accumulation of interlobular fat that was mainly observed around large vessels. On the other hand, C57BL/6J-A^y mice, an obesity model, had fewer intralobular adipocytes in the pancreas (Figure 1H) and ICR mice had only small adipocytes in the pancreas (Figure 1I).[36] Scattered FI is rarely observed in the pancreas of C57BL/6J mice (Figure 1J). Interlobular fat is observed in C57BL/6J-A^y and ICR mice[36] and high-fat diet-induced obese C57BL/6 mice,[37] but is rare in lean C57BL/6J mice.[36] Apc^{Min} mice, a model of familial adenomatous polyposis, are insulin-resistant and develop hypertriglyceridemia with age.[38] Despite having high serum triglyceride levels, Apc^{Min} mice are lean, and scattered intralobular FI is not observed in the mouse pancreas (data not shown).

Otsuka Long-Evans Tokushima Fatty (OLETF) rats, a T2DM model accompanied by hypertriglyceridemia, and their controls (Long-Evans Tokushima Otsuka [LETO] rats) did not develop scattered intralobular FI, and only interlobular fat accumulation around large vessels was observed (Figure 1K,L).[39] Matsuda et al.[40] reported that intralobular fat increased with age and with a high-fat diet in

Zucker diabetic fatty rats, although pancreatic FI in these rats was moderate compared to that observed in Syrian golden hamsters.

2.4 | Possible etiology and genetic predisposition

2.4.1 | Possible etiology

The species- and strain-specific differences in the FI patterns described above suggest that the etiology of scattered intralobular FI is different from that of the interlobular fat accumulation that is mainly observed around large vessels in the pancreas. In the case of scattered intralobular fat, adipocytes appear independent from the vessels and are assumed to be produced by the transformation of fibroblasts or acinar cells to occupy the space created by the loss of damaged acinar cells. High levels of triglycerides and glucose, or ischemia induced by atherosclerosis, are considered to be cytotoxic effects. Scattered FI is only observed in a limited number of species or strains, and severe fatty pancreas often accompanies this scattered FI, so there may be genetic backgrounds related to the susceptibility to acinar cell damage. Of note, these speculations need to be proven by further experiments. On the other hand, interlobular fat accumulation, mainly observed around large vessels in the pancreas, is widely observed in most species and seems to be associated with obesity/T2DM. Similarly, perivascular fat of the liver has been observed in fatty liver subjects.[41] Perivascular fat is an ectopic fat and affects atherosclerosis.[42] Perivascular mesenchymal stem cells were shown to differentiate into adipocytes in an adipogenic differentiation medium containing dexamethasone, 3-isobutyl-1-methylxanthine, insulin and indomethacin.[43] Hyperinsulinemia in obesity/T2DM and stress-induced glucocorticoid production may prompt the differentiation of perivascular mesenchymal stem cells to adipocytes.

2.4.2 | Possible genetic predisposition for fatty pancreas

Genetic predisposition for fatty pancreas has not yet been clarified. Thus, we propose several speculations that are based on other diseases, such as NAFLD and DM, or derived from animal experiments.

Several causative genes of NAFLD have been proposed by case-control studies,[44] and there is a strong association of the Patatin-like phospholipase domain-containing 3 gene variant rs738409(C > G) (I148M) with the development and progression of NASH- and NAFLD-related hepatocellular carcinoma.[45] Fatty liver is one of the risk factors for fatty pancreas,[29] so causative genes for NAFLD may be involved in the development of fatty pancreas.

As a functional candidate gene for T2DM, CD44 has been identified by an expression-based genome-wide association study.[46] CD44 variant expression is known to be associated with poor prognosis in pancreatic cancer.[47] In addition, CD44 expression is increased in inflammatory cells in obese adipose tissue, and anti-CD44 antibody treatment lowers hyperglycemia and improves insulin resistance, adipose inflammation, and hepatic steatosis in diet-induced obese mice.[48] In hypoxia, CD44 is co-expressed with Sca-1 in adipose tissue-derived mesenchymal stem cells and enhances adipogenic differentiation.[49] In addition, a diabetes-related gene variant, rs1501299(A > C) in the *ADPIOQ* gene, has been shown to be positively associated with pancreatic cancer in Japanese patients.[50] This variant is correlated with adiponectin levels, and low adiponectin levels contribute to insulin resistance.

KK-A^y mice, established by cross-breeding diabetic KK mice with obese A^y mice, exhibit severe hypertriglyceridemia, which is derived from KK mice.[36] Non-insulin-dependent T2DM is polygenic in KK mice, and Suto et al.[51] reported quantitative trait loci (QTLs) that are responsible for hyperlipidemia in these mice. An apolipoprotein A-II gene polymorphism was identified as the cause of cholesterol QTLs in KK mice.[52] Serum levels of apolipoprotein A-II are decreased in patients with pancreatic cancer.[53] Thus, apolipoprotein A-II deficiency could be involved in the etiology of fatty pancreas. As Yazdi et al.[54] reviewed, many gene mutations/single nucleotide polymorphisms are associated with obesity in mice/humans, and leptin-melanocortin pathway-related genes, in particular, are associated with monogenic obesity via food intake and energy expenditure. Some of these genes could also be involved in the development of fatty pancreas.

It has been reported that transgenic mice overexpressing serine/threonine protein kinase 25, a critical regulator of ectopic fat storage, inflammation and fibrosis in liver tissue and skeletal muscle, have aggravated diet-induced lipid storage in the pancreas.[55]

Gotoh et al.[56] have shown that spleen-derived interleukin (IL)-10, an anti-inflammatory cytokine, has a protective role in the development of NAFPD and that high-fat diet-induced obesity decreases IL-10 synthesis ability of the spleen and aggravates fat accumulation and inflammatory responses in the pancreas of mice. Thus, IL-10 deficiency could also be involved in the etiology of fatty pancreas.

3 | ASSOCIATION BETWEEN PANCREATIC CARCINOGENESIS AND FI OF THE PANCREAS

3.1 | Animal experiments

3.1.1 | Chemically induced pancreatic carcinogenesis in Syrian golden hamsters

We have shown that pancreatic intralobular FI increases with age in Syrian golden hamsters (14 weeks vs 25 weeks with saline + standard diet: 4.4 ± 0.3% vs 14.7 ± 0.9%; Student's *t* test: $P < .001$) and that a high-fat diet and treatment with BOP, a pancreatic carcinogen, enhance the severity (Table 1).[2] Syrian golden hamsters have hyperlipidemia, and the hepatic lipoprotein lipase activity in Syrian golden hamsters is lower compared with that of C57BL/6J mice and F344/Wistar rats.[4] A high-fat diet elevates serum lipid levels and exacerbates pancreatic FI in Syrian golden hamsters.[2] The developmental period of BOP-induced PDAC was shortened, and the numbers of PDAC at 25 weeks of age were increased 2-fold by the consumption of a high-fat diet (Table 1).[2] BOP induces a K-*ras* gene mutation,

TABLE 1 Pancreatic fatty infiltration (FI) and pancreatic ductal adenocarcinoma (PDAC) development in Syrian golden hamsters[†]

Treatment	Diet	Age (wk)	Intralobular adipocyte area (%)	PDAC development	
				Incidence (%)	Multiplicity
Saline	Standard	14	4.4 ± 0.3	0	0
Saline	High-fat	14	7.9 ± 0.7[a]	0	0
BOP	Standard	14	7.4 ± 4.0	0	0
BOP	High-fat	14	14.5 ± 4.4[b]	67[d]	1.14 ± 0.69[d]
Saline	Standard	25	14.7 ± 0.9	0	0
Saline	High-fat	25	24.9 ± 5.0[a]	0	0
BOP	Standard	25	27.3 ± 4.0[c]	80	1.66 ± 1.37
BOP	High-fat	25	41.9 ± 2.8[b,d]	86	3.19 ± 3.54[e]

Female Syrian golden hamsters were subcutaneously injected with *N*-nitrosobis(2-oxopropyl)amine (BOP) (at a dose of 10 mg/kg body weight, 4 times a week) or vehicle (saline) at 6 wk of age and were fed a high-fat diet or standard diet from 1 wk after the last injection for 6 or 17 wk.[2]

[a]$P < .05$ vs saline + standard diet with the same age; [b]$P < .01$ vs saline + high-fat diet with the same age; [c]$P < .01$ vs saline + standard diet with the same age; [d]$P < .01$ vs BOP + standard diet; [e]$P < .05$ vs BOP + standard diet with the same age.

[†]Modified from reference 2.

which plays an essential role in pancreatic carcinogenesis.[57] Fatty pancreas itself cannot induce PDAC development (Table 1), but reactivity to BOP may be associated with a pancreas that is susceptible to damage and easily infiltrated by adipocytes. Indeed, a single high dose of BOP activated pancreatic ductal cell proliferation.[58] Furthermore, the enhancement of pancreatic FI induced by a high-fat diet can promote PDAC development via the elevation of adipokine/cytokine expression.[2] A combination of BOP treatment and a high-fat diet increased the amount of adipocytes infiltrating PDAC tissues compared to BOP treatment only.[2] When the PDACs were classified according to the degree of FI, the number of PDAC with FI within PDAC and its surrounding tissue was increased by a high-fat diet, but the number of PDACs without FI was unchanged.[2]

3.1.2 | Animal models of T2DM and hypertriglyceridemia

Initially, we hypothesized that hyperlipidemia and obesity might contribute to the susceptibility of hamsters to pancreatic cancer development, and we then attempted to develop PDAC in mice and rats with hyperlipidemia/T2DM. In our preliminary study, Apc^{Min} mice were treated with BOP, but did not develop PDAC (data not shown). OLETF rats also did not develop scattered FI in the pancreas and failed to develop PDAC after treatment with BOP.[39] These data indicated that T2DM with hypertriglyceridemia and/or hyperinsulinemia is not sufficient to increase susceptibility to pancreatic carcinogenesis. The pancreas of mice and rats seems to be resistant to lipotoxicity and chemical damage compared to that of hamsters, so we realized the importance of scattered intralobular FI in the pancreas for pancreatic carcinogenesis.

We then examined whether the mouse pancreas with intralobular FI was sensitive to BOP-induced pancreatic ductal proliferation. A single high dose of BOP treatment increased pancreatic ductal cell proliferation in KK-A^y mice, but not in ICR, C57BL/6J and C57BL/6J-A^y mice (Figure 2A).[58] In addition, cell proliferation in common bile ducts was enhanced by BOP treatment in KK-A^y and C57BL/6J-A^y mice (Figure 2B).[58] These data suggest that scattered FI in the pancreas may be an important factor for carcinogenesis. However, our attempt to develop pancreatic tumors in KK-A^y mice treated with BOP failed. In contrast to Syrian golden hamsters, the number and size of the islets in KK-A^y mice were significantly increased at 46 weeks of age (data not shown). KK-A^y mice resemble Syrian golden hamsters in their development of scattered intralobular FI and sensitivity to BOP-induced ductal cell proliferation, but those are not sufficient factors to cause the development of pancreatic cancer, and other contributing factors may exist. To activate BOP as a carcinogen, drug-metabolizing enzymes are needed. There is a wide species variation in the presence and cellular localization of enzymes in the pancreas.[59] K-ras mutations were detected in pancreatic tumors of Syrian golden hamsters. We speculate that K-ras mutations cannot be induced by BOP in KK-A^y mice due to the species differences in the expression of drug-metabolizing enzymes, but we have no data on the mutation patterns in the pancreas of BOP-treated KK-A^y mice. Further studies are needed to clarify the reasons for the species differences in the pancreatic carcinogenicity of BOP.

There is another species difference related to pancreatic carcinogenesis in glucocorticoid hormone production. Glucocorticoids are stress hormones that play anti-inflammatory, but immune-suppressive, roles.[60] There are species differences in the substrate affinity for 11beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1), which catalyzes the intracellular activation of glucocorticoids.[61] Corticosterone is the major glucocorticoid in mice and rats, whereas cortisol is the major glucocorticoid in humans. Hamsters secrete both cortisol and corticosterone, and chronic stress increases cortisol.[62] Immune suppression caused by cortisol may also be involved in the pancreatic cancer susceptibility of hamsters.

3.2 | Clinical studies

3.2.1 | Pancreatic cancer

To clarify the association between fatty pancreas and PDAC in humans, we used histopathology to analyze the degree of FI in the non-cancerous part of PDAC/non-PDAC patients who had undergone pancreatoduodenectomy.[18] The adipocyte-infiltrated areas in the pancreas are significantly greater in the cases than in the controls (median 25.8% vs 15.0%, $P < .001$).[18] In these cases, the types of differentiation and stages of tumors are not associated with the degree of FI. The areas of FI in the pancreas are positively correlated with BMI and serum HbA1c levels in both cases and controls, but are associated with age only in cases, although the observed correlations are not that strong (Figure 3). Many patients with an area of FI ≥40% were observed in cases, while there were few observed in controls (cases vs controls: 26/102, 25.5% vs 3/85, 3.5%; Chi-square test: $P < .0001$). Even among those with a BMI <25 kg/m^2 or an HbA1c of <6%, the areas of FI ≥40% in the pancreas were more prevalent in cases than in controls (BMI: 21/84, 25.0% vs 3/74, 4.1%; $P < .001$, HbA1c: 13/65, 20.0% vs 1/73, 1.4%, $P < .001$). Cases tended to have severe FI even if their BMI or HbA1c levels were normal. The proportion of subjects with an area of FI <10%, 10%-20%, and ≥20% in the pancreas were almost the same in controls, but more than 60% of cases had an area of FI ≥20% in the pancreas (Figure 4). The degree of FI of the pancreas is positively associated with PDAC, even after adjusting for BMI, the prevalence of DM and other confounding factors (odds ratio [OR], 6.1; P trend <.001).[18] This result indicates that pancreatic FI is a possible risk factor for PDAC, independent of obesity and DM. In addition, severe fibrosis was often observed in the pancreatic tissue areas without FI in PDAC patients. It has been reported that fibrosis is another predisposing factor for PDAC.[63] Fibrosis is also associated with age-related changes of the pancreas. Damaged tissues may be occupied by fibroblasts or adipocytes. Mesenchymal stem cells have the potential to differentiate into adipocytes and fibroblasts, and environmental factors affect cell differentiation. The quantitative relationship between pancreatic fibrosis and FI levels was not examined in our previous study, and further analyses are needed.

3.2.2 | Pancreatic intraepithelial neoplasia (PanIN)

Recently, Rebours et al.[64] reported the correlation of pancreatic FI with PanINs known as precancerous lesions. Non-tumor areas of

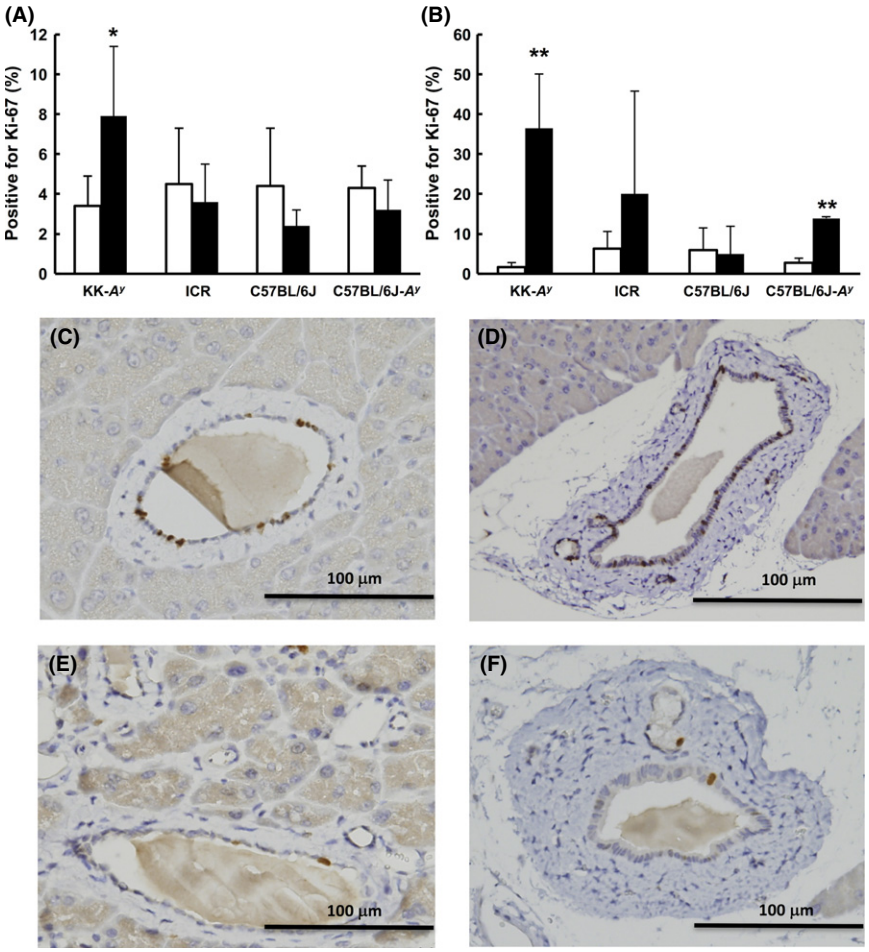

FIGURE 2 *N*-nitroso*bis*(2-oxopropyl) amine (BOP)-enhanced cell proliferation in pancreatic ducts (A) and common bile ducts (B) in KK-A^y mice. Modified from reference 58. KK-A^y, ICR, C57BL/6J and C57BL/6J-A^y mice were intraperitoneally injected with saline (white column) or BOP (black column) at a dose of 80 mg/kg of body weight, and the ratio of Ki-67-positive cells in pancreatic ducts (A) and common bile ducts (B) was examined 2 d later. In BOP-treated KK-A^y mice, the enhancement of proliferation in both pancreatic (C) and common bile ducts (D) was observed, but not in BOP-treated C57BL/6J mice (E,F).[58] Data are the mean ± SD. *$P < .05$ and **$P < .01$ vs saline-treated. Bar, 100 μm

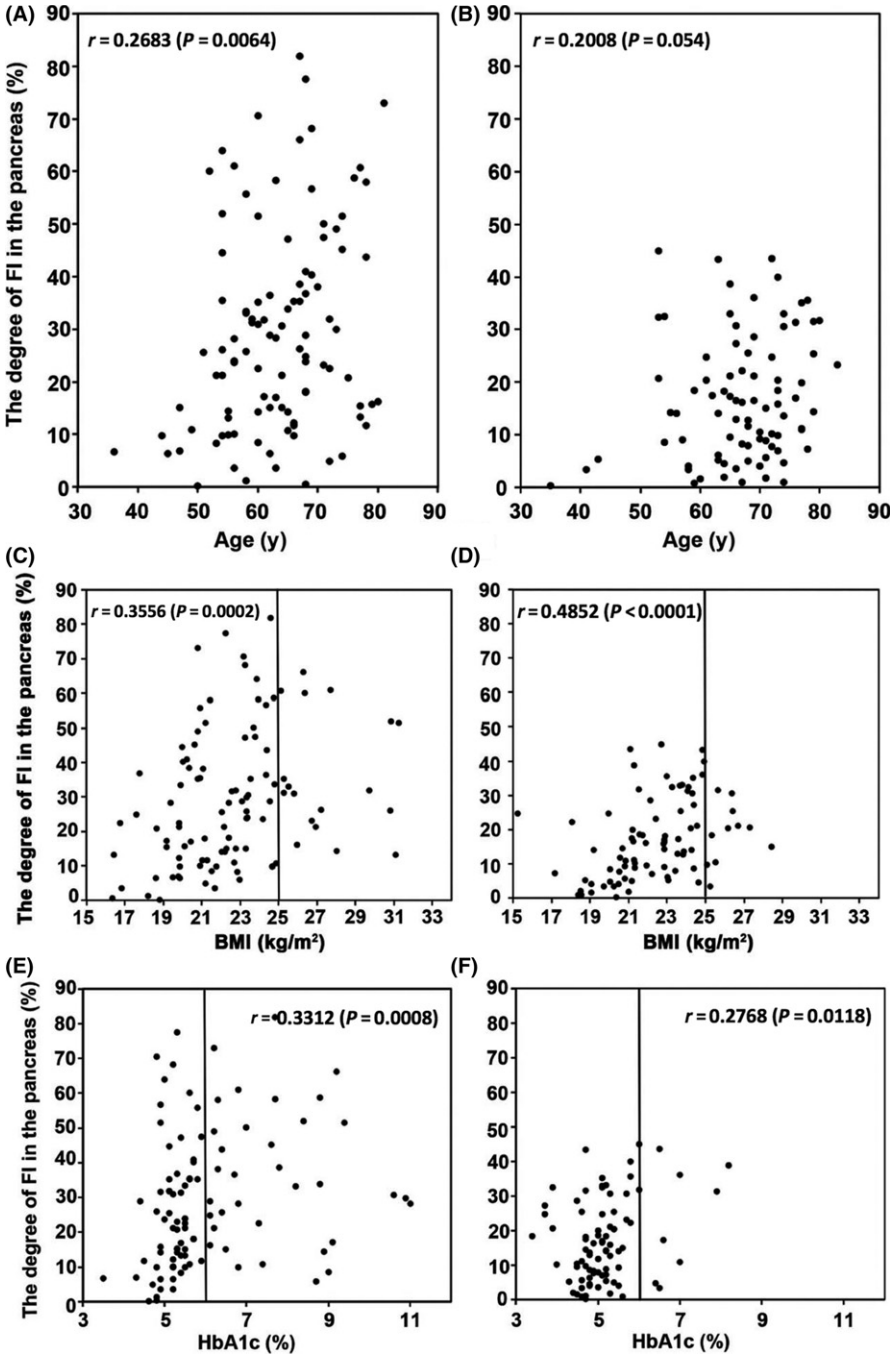

FIGURE 3 Associations of age (A,B), body mass index (BMI) (C,D) and HbA1c (E,F) levels with pancreatic fatty infiltration (FI) areas in pancreatic cancer cases (n = 102) and controls (n = 85). The data were obtained from our previous study.[18] Scatter plots of FI of the pancreas against age for cases (A) and controls (B), BMI for cases (C) and controls (D), and HbA1c for cases (E) and controls (F). *r*, Spearman's rank correlation coefficient

pancreatic tissue from surgical specimens of patients with well-differentiated neuroendocrine tumors (grade 1 or 2) were histologically analyzed for FI, fibrosis in intra- and extralobular locations, and PanINs. Pancreatic FI was observed in 51% and 30% of patients in intralobular and extralobular sites, respectively, and PanINs were found in 65% of patients. The presence of PanINs is associated with intralobular and extralobular FI, intralobular fibrosis, high BMI, and subcutaneous and intravisceral fat. In a multivariate model, PanINs were associated with intralobular FI (OR, 17.86; $P < .0001$) and intralobular fibrosis (OR, 5.61; $P = .057$).[64] These findings also indicate the importance of intralobular FI in the precancerous phase of pancreatic carcinogenesis.

3.2.3 | Dissemination and poor prognosis

Mathur et al.[65] conducted a case-control analysis in node-positive/negative patients who had resected PDAC. The mean number of adipocytes in the pancreas of cases was significantly high ($P < .02$), and the fibrosis score was significantly low ($P < .02$) compared with those of controls. The mean survival was reduced in cases (18.9 months vs 30.8 months; $P < .04$).[65] Cases had increased visceral fat, but not subcutaneous fat, compared to controls, and the mean survival in cases with a perineal fat pad ≥10 mm was poorer than that of controls with a perineal fat pad <10 mm (7 months vs 16 months; $P < .01$).[66] These observations suggest that pancreatic FI promotes the dissemination and lethality of PDAC.

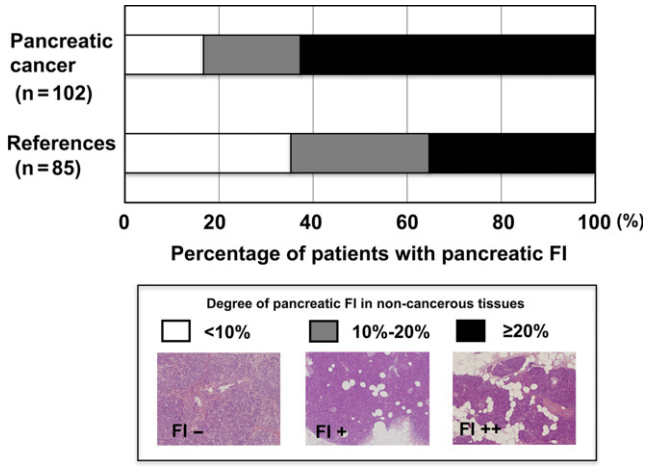

FIGURE 4 Association of pancreatic fatty infiltration (FI) with pancreatic ductal adenocarcinoma (PDAC). Modified from reference 18. The rate of severe FI (FI area ≥ 20%) is higher in PDAC cases than in the controls[18]

4 | PUTATIVE MECHANISMS THAT EXPLAIN THE MODULATION OF PANCREATIC CARCINOGENESIS THROUGH FATTY PANCREAS

4.1 | Secretion of adipokines and growth factors

Adipocytes secrete pro-inflammatory adipokines/cytokines, such as leptin and monocyte chemotactic protein-1 (MCP-1).[67] Leptin has been reported to increase cancer cell proliferation via the up-regulation of Notch signaling,[68] and MCP-1 induces inflammation via macrophage recruitment.[67] Adipocytes also secrete insulin-like growth factor (IGF-1), which regulates the differentiation and growth of tissues,[69] and angiotensin II, which regulates lipogenesis.[70] Leptin and angiotensin II increase the angiogenesis and lymphatic metastasis of PDAC by producing vascular endothelial growth factor (VEGF).[71,72] A high-fat diet increased the expression of these genes in the pancreas of BOP-treated hamsters.[2] These proliferation and inflammatory factors derived from infiltrated adipocytes may be involved in tumor promotion. In addition, it has been reported that the C-X-C motif ligand 5 (CXCL5) secreted by adipose tissue-derived mesenchymal stem cells has neurotrophic effects[73] and is involved in inflammation and insulin resistance in adipose tissue.[67] Overexpression of CXCL5 induced angiogenesis and was associated with poor survival in PDAC patients.[74]

4.2 | Others

Meyer et al.[75] reported that a co-culture of murine 3T3L1 adipocytes with PanIN/PDAC cells derived from PKCY mice, which had pancreas-specific mutant K-ras expression and *p53* deletion, promoted PanIN/PDAC cell proliferation in nutrient-poor conditions via glutamate transfer. Zoico et al.[76] reported that cancer cell-derived WNT5a caused dedifferentiation/reprogramming of adipocytes into fibroblast-like cells in co-cultures of human pancreatic cancer cells MiaPaCa2 with murine 3T3L1 adipocytes and that this may influence the tumor microenvironment and cancer progression.

Tang et al. visualized the neuro-insular network around human pancreatic islets with 3D histology and identified the formation of adipose-ganglionic complexes in the peri-lobular space and an enlargement of ganglia around adipocytes. An increase in the number of nerve projections from the intra-parenchymal ganglia has been shown to be associated with severe FI.[77] A neurotrophic microenvironment created by FI may be involved in pancreatic cancer promotion. In obesity, cortisol secretion is increased by 11β-HSD1 in adipocytes[78] and may increase tumor development and metastasis through its immuno-suppressive actions.[79]

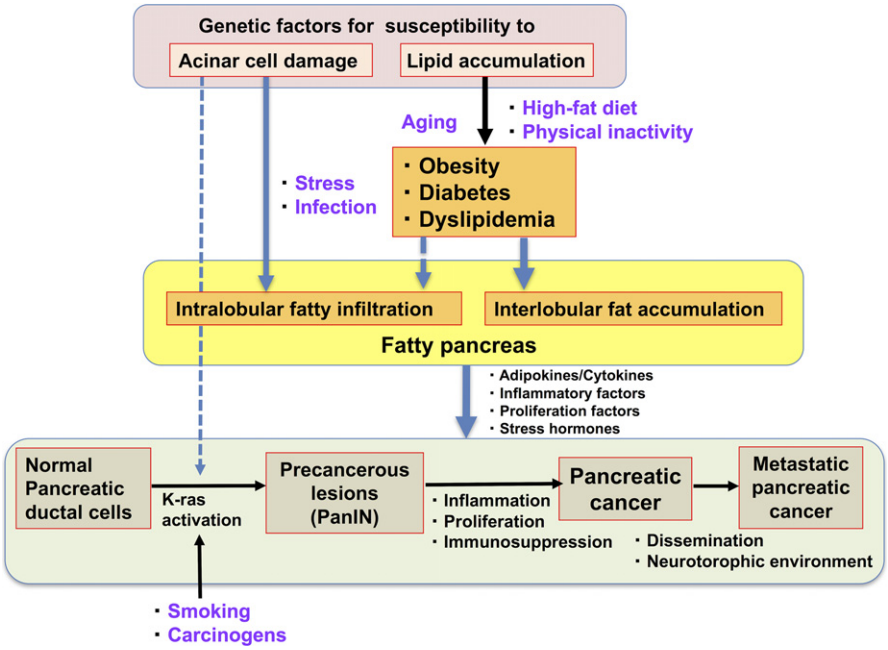

FIGURE 5 Involvement of fatty pancreas in pancreatic carcinogenesis. Modified from the figure in reference 16

5 | CONCLUSION

Based on these observations, the involvement of fatty pancreas, especially scattered intralobular FI, in pancreatic carcinogenesis is indicated (Figure 5). Pancreas with FI per se may play an essential role in pancreatic carcinogenesis. Recently, NAFPD has been studied, and data from fatty pancreas analyzed by non-invasive methods are accumulating.[10] Pancreatic FI is a candidate marker for individuals who have a high risk of pancreatic cancer. To clarify the direct causal relationship between fatty pancreas and pancreatic cancer, further studies to reveal the prevalence of fatty pancreas in the general population and to reveal its genetic backgrounds are warranted.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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