a result, the survival rate of patients with pancreatic cancer has not substantially improved over the last few decades. Therefore, it is very important to develop effective chemotherapeutic and chemopreventive agents and to elucidate causative factors and mechanisms underlying pancreatic carcinogenesis. Epidemiological studies have suggested that several agents may have a chemopreventive potential against pancreatic cancer [253]. Here, we focus on the inflammatory factors in pancreatic carcinomas and the chemotherapeutic and chemopreventive agents having anti-inflammatory activity.

Agents that inhibit COX-2

COX-2 selective inhibitors

As described, COX-2 expression is elevated both in CP and PDACs. Selective COX-2 inhibitors prevent the growth of cancer cells [254]. In addition, preclinical and clinical data suggest that selective COX-2 inhibitors have the potential to prevent pancreatic cancer prolongation [255, 256]. It is thus likely that increased expression of COX-2 is an important contributor to pancreatic tumor formation, and compounds that inhibit the activity and/or expression level of this enzyme are potentially of great interest as candidate chemopreventive agents against pancreatic carcinogenesis. On the other hand, although major efforts have been made to develop selective inhibitors of COX-2 as chemopreventive agents against pancreatic cancer, efforts to identify agents that can selectively suppress the expression of COX-2 at the gene level appear to be equally important. It is also likely that the combination of suppression of COX-2 gene expression and selective inhibition of its enzyme activity may provide a most effective approach to pancreatic cancer prevention. Therefore, developing a simple screening system, which could detect the suppression of COX-2 gene expression, might be useful in searching for novel chemopreventive agents.

Nimesulide (4-nitro-2phenoxymethanesulfonanilide), a preferential COX-2 inhibitor of non-steroidal anti-inflammatory drugs (NSAIDs) [257], is used clinically as an anti-inflammatory drug in several European countries. This compound is a potent anti-inflammatory agent with fewer ulcerogenic effects than other NSAIDs, and severe side effects have not been reported [257].

Nimesulide has been demonstrated to suppress the development of precancerous lesions (atypical hyperplasia) and PDACs in BOP-treated hamsters. Proliferating cell nuclear antigen labeling indices of pancreatic ducts were also significantly reduced by nimesulide [258]. Therefore, the mechanism underlying the chemopreventive effect of nimesulide was suggested to be the inhibition of cell growth.

Funahashi et al. also evaluated the efficacy of nimesulide in preventing the progression of mPanINs using a *LSL-KRAS^{G12D};PDX-1-Cre* mouse model. Treatment with nimesulide inhibited COX-2, significantly decreased PGE_2 levels in the pancreas, and led to reduced mPanINs, particularly later-stage lesions (mPanIN2 and mPanIN3) [259]. These data clearly suggest that COX-2 and COX-2-derived prostanoids are critical mediators in pancreatic carcinogenesis. Inhibition of COX-2 may represent an intriguing strategy to prevent pancreatic cancer in high-risk patients.

NSAIDs

NSAIDs are some of the most commonly used pharmaceuticals worldwide. They are used for the prevention and treatment of inflammatory diseases. Aspirin is the most frequently used NSAID and has been reported to reduce cancer risk in several organs such as the colon [260]. However, in the pancreas, epidemiological data on aspirin use are controversial. A cohort study of post-menopausal women has shown that current use of aspirin is associated with reduced risk of pancreatic cancer (the multivariate-adjusted RR=0.57) [261], whereas another cohort study of nurses demonstrated that more than 20 years of regular aspirin use is associated with increased risk (RR=1.58) [262]. It is difficult to understand these epidemiological data because regular users of aspirin possibly include CP patients.

In GEM models, aspirin treatment has been shown to delay the progression of PanINs in *LsL-KrasG12D;Pdx1-Cre* mice and to partially inhibit the development of invasive carcinomas in *LSL-KrasG12D;LsL-Trp53R172H;Pdx1-Cre* mice [263]. Meanwhile, the NF-κB pathway has been implicated in pancreatic cancer biology [264]. Aspirin is a surrogate pharmacological inhibitor of the NF-κB pathway, and aspirin treatment inhibited tumor formation in mice [265, 266].

Laboratory studies indicate that aspirin may inhibit pancreatic carcinogenesis, but epidemiologic data to support this finding are limited. To identify aspirin as an effective chemotherapeutic and chemopreventive agent against pancreatic cancer, further detailed studies of its role might be warranted.

Takahashi et al. investigated the effects of prostanoid synthesis inhibitors, such as indomethacin, phenylbutazone, and aspirin, on the development of BOP-initiated hamster pancreatic tumors [267]. The incidence of pancreatic carcinoma was significantly lower in hamsters receiving phenylbutazone than in the controls and the numbers of carcinomas per hamster were significantly reduced by indomethacin and phenylbutazone treatment compared with the control group value. Aspirin also showed a tendency to decrease pancreatic tumor incidence, although not significantly. Thus, inhibition of prostanoid synthesis might help reduce the development of pancreatic cancer.

Other (COX-2 specific and non-specific) NSAIDs, including etodolac, sulindac, ibuprofen, celecoxib, and NS-398,

have also shown efficacy in cellular and animal models [268–272], but they have not been fully evaluated for the prevention and/or treatment of pancreatic cancer.

For instance, some case report studies have also shown that NSAIDs such as aspirin, sulindac, indomethacin, ketoprofen diclofenac, and naproxen could induce acute pancreatitis [273–278]. To resolve the discrepancy, further investigation is needed to better elucidate how COX-2 inhibition might affect pancreatitis.

The effect of dual COX-1/2 inhibitor sulindac on mPanIN and PDAC development was studied using caerulein-treated K-*Ras*$^{+/G12V}$;*Elas-tTA/tetO-Cre* mice. Sulindac treatment for 3 months after caerulein exposure for 3 months significantly reduced the numbers of high-grade PanIN lesions and PDACs [240]. These results suggest that inflammation is a key contributor to the effect of pancreatitis not only in promoting mPanIN formation but also in inducing progression to PDAC.

Agents that inhibit iNOS

As mentioned, increased expression of iNOS has been frequently detected in pancreatic cancers and severe AP patients [164, 165]. We have demonstrated that an iNOS inhibitor, ONO-1714, can effectively suppress the development of atypical hyperplasia and carcinomas, especially invasive adenocarcinomas, in hamster pancreas after treatment with BOP [167]. The results indicated that iNOS plays important roles in the development of pre-neoplastic lesions at an early stage of pancreatic carcinogenesis and also in carcinoma invasion and expansion in later stages. ONO-1714 also attenuated rat diaphragmatic dysfunction associated with cerulein-induced AP through the reduction of iNOS activity and lipid peroxidation [166]. These results could serve as basis of clinical research to assess whether the use of iNOS-selective inhibitors is a promising approach to the management of patients with pancreatitis and pancreatic cancer.

Agents that inhibit oxidative stress

There is increased oxidative stress in experimental animals as well as in patients with CP, and suppression of oxidative stress by antioxidative agents has been demonstrated to reduce the severity of pancreatitis in animals and humans. Moreover, suppressive effects of antioxidative agents on pancreatic cancer development have also been demonstrated in animals.

Treatment with the flavonoid quercetin markedly reduced the severity of cerulein-induced pancreatitis, malondialdehyde, and the serum levels of TNF-α, IL-1β, and IL-6 in mice [279]. Quercetin ameliorates the severity of cerulein-induced AP by acting as an anti-inflammatory and antioxidant agent. Treatment of mice with green tea polyphenol attenuates the degree of cerulein-induced mouse pancreatitis by reducing the activation of NF-κB, the production of pro-inflammatory cytokines, and the formation of lipid peroxidation [280]. Patients with topical pancreatitis received oral curcumin, which reduced erythrocyte malondialdehyde levels and increased the glutathione levels compared with a placebo [281]. When methionine was supplemented along with selenium, β-carotene, vitamin C, and vitamin E, CP symptoms were improved [282, 283].

Furthermore, treatment with the combined antioxidant supplement decreased the serum levels of the free radical marker 9-*cis*,11-trans linoleic acid, which was initially significantly higher in CP patients [282, 283]. A randomized clinical trial for combined antioxidant supplementation has been reported. One hundred twenty-seven CP patients were randomly assigned to receive either an antioxidant supplement, which contained selenium, ascorbic acid, β-carotene, α-tocopherol, and methionine, or a placebo. After 6 months, reduction in the levels of thiobarbituric acid-reactive substances and superoxide dismutase, which are markers of oxidative stress, was observed in the antioxidant group compared with the placebo group. Pain was also diminished in patients receiving the supplement. Significantly fewer painful days per month compared with the placebo group were reported by questionnaire [284]. Combined antioxidant supplementation might appear to be more promising for CP treatment than single antioxidant supplementation.

Protochatechuic acid, green tea extracts, and butylated hydroxyanisole are antioxidative agents which have demonstrated inhibitory effects on pancreatic cancer development during the post-initiation stage of the BOP-initiated hamster model [285–287]. Sarcophytol A, which is known to be an anti-tumor promoter, and methionine, which is an essential amino acid and associated with antioxidation, have also been shown to suppress pancreatic carcinogenesis in the BOP-treated hamster model [288, 289]. Woutersen et al. [290] reported that antioxidant products, such as β-carotene, selenium, and vitamin C, inhibit pancreatic carcinogenesis in azaserine-treated rat model. Therefore, it is considered that treatment with antioxidants may have practical application in chemoprevention of pancreatitis and pancreatic cancer.

Anti-hyperlipidemic/anti-type II diabetic agents

A high-calorie diet and low physical activity are associated with an increased risk of pancreatic cancer. Moreover, they are also closely associated with hyperlipidemia [291]. High serum TG levels are known to cause pancreatitis. It is also known that hypertriglyceridemia often precedes hyperglycemia in type II diabetes. Interestingly, Syrian golden hamsters are in a hyperlipidemic state even under normal diet conditions [211]. Thus, hyperlipidemia in hamsters may also be an enhancing factor for PDAC development.

Peroxisome proliferator-activated receptor γ (PPARγ) is a member of nuclear receptor superfamily of ligand-activated nuclear transcription factors, which prominently express in adipose tissue and in the immune system [292, 293]. Moreover, PPARγ is involved in the regulation of lipid and glucose homeostasis and also controls inflammation [294].

Thiazolidinediones (TZDs) are ligands for PPARγ, and one of the TZD derivatives, pioglitazone, has been clinically accepted as an anti-diabetic drug. Our previous study showed that dietary intake of pioglitazone improves hyperlipidemia and suppresses the incidence and multiplicity of pancreatic tumors in BOP-treated hamsters; the PDAC incidences in the BOP + 800 ppm pioglitazone group and the BOP-alone group were 38 vs 80 % ($P<0.01$) and the multiplicities were 0.55±0.15 vs 1.37±0.22 ($P<0.01$), respectively [211]. It is well established that administration of TZDs improves hyperlipidemia and hyperglycemia in animal models [295, 296]. Thus, anti-hyperlipidemic drugs may deserve more consideration as candidate chemopreventive agents against pancreatic cancer.

Metformin (1,1-dimethylbiguanide hydrochloride) is a biguanide class of oral hypoglycemic agents and it is the world's most widely used anti-diabetic drug for the treatment of type II diabetes mellitus. In a study using a hamster model, hamsters fed a high-fat diet and metformin had lower numbers of pancreatic carcinoma, proliferative lesions, and pre-neoplastic lesions than hamsters fed a high-fat diet alone [297]. In addition, administration of metformin significantly decreased the growth of pancreatic carcinoma cells xenografted into the flank of nude mice [298]. A large case–control clinical trial regarding the use of metformin for pancreatic cancer risk was conducted from 2004 to 2008 involving 973 pancreatic cancer patients (including 259 diabetes mellitus patients) and 863 controls (including 109 diabetes mellitus patients) [299]. Diabetes mellitus patients who were administrated metformin had a significantly lower risk of pancreatic cancer compared to those who did not receive metformin (OR, 0.38; 95 % confidence interval (CI), 0.22–0.69, $P=0.001$). These recent studies clearly suggest that the administration of metformin is positively associated with a decreased risk of pancreatic cancer in diabetes mellitus patients. Based on these positive associations between hyperinsulinemia, diabetes, and pancreatic cancer, therapeutic targets aimed at treating diabetes should decrease the risk of pancreatic malignancy. Metformin has been found to inhibit the production of inflammatory cytokines such as TNF-α and IL-6 as well as VEGF, probably via inactivation of NF-κB and HIF-1α [300–302]. Additionally, antioxidant and tumor growth inhibition activities have been shown for the potential function of metformin [303, 304]. These data imply that metformin may appear to exert a protective role

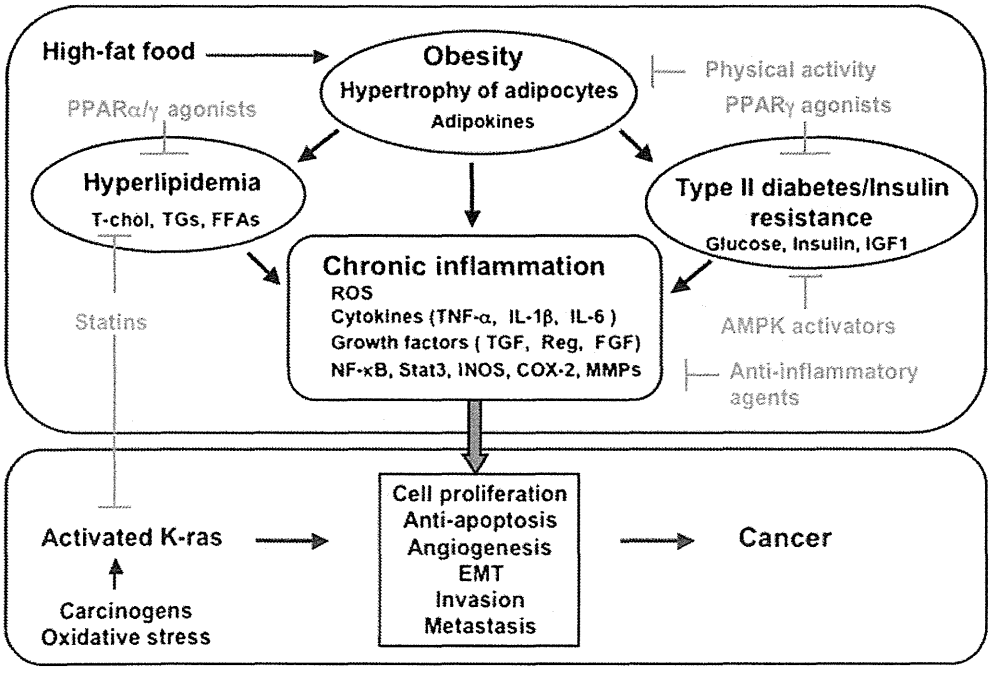

Fig. 2 Cancer promotion by chronic inflammation and its prevention by anti-inflammatory agents. K-*ras* mutations plus inflammatory status including CP, hyperlipidemia, type II diabetes/insulin resistance, and obesity effectively cause PDAC development. Chemopreventive agents targeting these inflammatory factors may prevent PDAC development. *TG* triglyceride, *FFA* free fatty acid, *ROS* reactive oxidative species, *TNF* tumor necrosis factor, *IL* interleukin, *TGF* transforming growth factor, *FGF* fibroblast growth factor, *NF-κB* nuclear factor-κB, *Stat3* signal transducer and activator of transcription 3, *iNOS* inducible nitric oxide synthase, *COX-2* cyclooxygenase-2, *MMP* matrix metalloproteinase, *EMT* epithelial to mesenchymal transition

against the development and progression of pancreatic cancer through improvement of inflammation.

Statins, inhibitors of 3-hydroxy-3-methylglutaryl coenzyme-A reductase, are widely used for the treatment of lipid disorders, especially hypercholesterolemia [305]. Furthermore, several preclinical studies revealed their pleiotropic actions, such as apoptosis induction, anti-angiogenesis, tumor growth suppression, metastasis suppression, anti-inflammation, and K-ras prenylation inhibition properties [306–308]. Thus, the use of statins as pancreatic cancer chemopreventive agents is expected.

Treatment with pravastatin started after the induction of CP attenuates progression of pancreatic inflammation in a rat experimental model. Pravastatin also downregulated the expression level of pro-inflammatory cytokines such as TNF-α and markedly increased the production of anti-inflammatory cytokines such as IL-10 [309]. In experimental data, statins were associated with a decreased risk of pancreatic cancer [310, 311]. Furthermore, one case–control study demonstrated 67 % risk reduction in incidence of pancreatic cancer among statin users (adjusted OR, 0.33; 95 % CI, 0.26–0.41; $P<0.01$) [312]. However, other observational studies suggested that there is no association between statin use and pancreatic cancer risk [313]. Thus, the use of statins as a chemopreventive agent remains a matter of debate.

Still some studies have declared the availability of statins for adjuvant chemotherapy. A dramatic synergism between lovastatin and troglitazone (a TZD-type PPARγ agonist and used for improving insulin sensitivity in type II diabetes mellitus patients) in anti-cancer at clinically achievable concentrations has been indicated [314]. The combination of fluvastatin with the anti-cancer agent gemcitabine (the cytosine arabinoside analog 2′,2′-difluorodeoxycytidine) is an effective cytotoxic, proapoptotic treatment in vitro and in vivo against MIAPaCa-2 cells harboring a mutated K-*ras* by a mechanism of action mediated, at least in part, by the inhibition of prenylation of K-ras and rhoA proteins [315]. These results support the probability of statins for the adjuvant chemotherapy treatment of pancreatic cancer. Further investigations may be needed to ensure the combination chemotherapy of anti-diabetic drugs or anti-cancer agents and statins for pancreatic cancer.

Conclusions

Epidemiological studies and animal model studies have shown an increase of pancreatic cancer risk by inflammatory status, such as CP, hyperlipidemia, type II diabetes, and obesity (Fig. 2). Acinar/ductal cell damages caused by exposure to alcohol, carcinogens derived from tobacco, lipids, high amounts of glucose, pancreatic enzyme/bile reflux by ductal obstruction, and following cellular proliferation stimulated by further exposure to pro-inflammatory cytokines, chemokines, adipokines, and growth factors are considered to favor the development of pro-tumorigenic environments. In addition, K-*ras* activating mutations, which can be induced by tobacco carcinogens or ROS, are essential for pancreatic cancer development. Indeed animal model studies have demonstrated that chemical or genetic induction of K-*ras* mutations plus inflammation effectively causes PDAC development.

In humans, a number of epidemiological studies have suggested reduced pancreatic cancer risk with the use of anti-inflammatory agents. However, this is difficult to prove in randomized control studies because of the relatively low incidence of pancreatic cancer in humans and the absence of early biomarkers to predict pancreatic cancer. Thus, in vivo carcinogenesis studies using animal models are important to support the epidemiological findings and provide direct evidence. Some anti-inflammatory agents that target COX-2, iNOS, oxidative stresses, insulin resistance, and hyperlipidemia have indeed been shown to exert suppressive effects on pancreatic carcinogenesis in animal models, indicating that factors related to inflammation are candidate targets for pancreatic cancer prevention.

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In Vivo SPECT Imaging with ^{111}In-DOTA-c(RGDfK) to Detect Early Pancreatic Cancer in a Hamster Pancreatic Carcinogenesis Model

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Early detection of pancreatic cancer is key to overcoming its poor prognosis. $\alpha_v\beta_3$-integrin is often overexpressed in pancreatic tumor cells, whereas it is scarcely expressed in normal pancreatic cells. In this study, we investigated the usefulness of SPECT imaging with ^{111}In-1,4,7,10-tetraazacylododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid-cyclo-(Arg-Gly-Asp-D-Phe-Lys) [^{111}In-DOTA-c(RGDfK)], an imaging probe of $\alpha_v\beta_3$-integrin, for the early detection of pancreatic cancer in a hamster pancreatic carcinogenesis model. **Methods:** Hamsters were subcutaneously injected with the pancreatic duct carcinogen *N*-nitrosobis(2-oxopropyl)amine to induce pancreatic cancer. *N*-nitrosobis(2-oxopropyl)amine–treated hamsters underwent in vivo SPECT with ^{111}In-DOTA-c(RGDfK). After imaging, the tumor-to-normal pancreatic tissue radioactivity ratios in excised pancreatic samples were measured with autoradiography (ARG) and compared with the immunopathologic findings for $\alpha_v\beta_3$-integrin. In a mouse model in which inflammation was induced with turpentine, the uptake of ^{111}In-DOTA-c(RGDfK) in inflammatory regions was evaluated with ARG and compared with that of ^{18}F-FDG. **Results:** ^{111}In-DOTA-c(RGDfK) was clearly visualized in pancreatic cancer lesions as small as 3 mm in diameter. ARG analysis revealed high tumor-to-normal pancreatic tissue radioactivity ratios (4.6 ± 1.0 [mean ± SD] in adenocarcinoma and 3.3 ± 1.4 in atypical hyperplasia). The uptake of ^{111}In-DOTA-c(RGDfK) strongly correlated with $\alpha_v\beta_3$-integrin expression. In the inflammatory model, inflammation-to-muscle ratios for ^{18}F-FDG and ^{111}In-DOTA-c(RGDfK) were 8.37 ± 4.37 and 1.98 ± 0.60, respectively. These results imply that ^{111}In-DOTA-c(RGDfK) has a lower rate of false-positive tumor detection than ^{18}F-FDG. **Conclusion:** Our findings suggest that SPECT with ^{111}In-DOTA-c(RGDfK) has great potential for the early and accurate detection of pancreatic cancer.

Key Words: ^{111}In-DOTA-c(RGDfK); SPECT; $\alpha_v\beta_3$-integrin; pancreatic cancer; early detection

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Pancreatic cancer is a leading cause of cancer-related mortality in developed countries, with an increasing incidence (*1*). The 5-y survival rate is poor (*2,3*). Surgical resection remains the only curative option. The postoperative 5-y survival rate has been recorded to be high as 40%–50%, whereas only 15%–20% of tumors are found to be resectable at the time of diagnosis (*4*). Tumor size is an important prognostic factor for pancreatic cancer because better prognosis and postsurgical survival have been reported for small pancreatic cancers (≤2 cm) than for large ones (>2 cm) (*5,6*). Given the incidence and high mortality rate of pancreatic cancer, the development of novel diagnostic technologies is essential for overcoming this type of cancer.

Currently, ^{18}F-FDG PET is widely used in the diagnosis of malignant tumors. ^{18}F-FDG PET is more accurate in detecting relatively large pancreatic adenocarcinomas than conventional imaging techniques (*7–9*). However, it has some limitations in detecting pancreatic cancer (*10*). ^{18}F-FDG can accumulate in chronic and acute pancreatitis, and this fact often yields false-positive interpretations for PET (*11,12*). It is also well known that the sensitivity of ^{18}F-FDG PET in hyperglycemic patients tends to be lower than that in euglycemic patients because elevated serum glucose levels suppress ^{18}F-FDG uptake in tumors by up to 50% as a result of competitive inhibition (*13,14*). New imaging agents that are not influenced by these factors are essential for the detection of small pancreatic cancers.

Integrins are cell adhesion molecules that mediate cell–cell and cell–matrix interactions and contribute to angiogenesis, tumor invasion, and metastasis. $\alpha_v\beta_3$-integrin is a well-characterized integrin that is overexpressed in endothelial cells and various tumor cells (*15–17*). Immunohistochemical analysis demonstrated that $\alpha_v\beta_3$-integrin was expressed in 60% of invasive pancreatic ductal carcinomas of stages I–IV, and patients with $\alpha_v\beta_3$-integrin–positive carcinomas showed shorter survival times than those with $\alpha_v\beta_3$-integrin–negative carcinomas (mean survival times, 12.3 vs. 21.4 mo) (*18*). Thus, $\alpha_v\beta_3$-integrin would be an excellent target for the early detection of malignant pancreatic cancer.

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For investigating the mechanisms of the development of pancreatic cancer, an experimental pancreatic ductal carcinogenesis model has been established with the carcinogen *N*-nitrosobis(2-oxopropyl)amine (BOP) in hamsters (*19–22*). This model provides unique characteristics that are similar to a sequence of well-characterized morphologic changes in the human pancreatic duct and frequently shows point mutations in codon 12 of the K-*ras* gene, in accordance with human findings (*23,24*). We found that $\alpha_v\beta_3$-integrin was overexpressed not only in adenocarcinomas but also in atypical hyperplasia in this hamster model (*25*). Therefore, this model is useful in the development of imaging probes for the early detection of pancreatic carcinogenesis.

Radiolabeled Arg-Gly-Asp (RGD) peptides are widely used as $\alpha_v\beta_3$-integrin imaging agents (*26–28*). In a previous study, ^{111}In-1,4,7,10-tetraazacylododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid-cyclo-(Arg-Gly-Asp-D-Phe-Lys) [^{111}In-DOTA-c(RGDfK)] showed high uptake in tumors with strong expression of $\alpha_v\beta_3$-integrin, low uptake in normal pancreas, and extremely rapid clearance from the blood (*29*). These characteristics are favorable for pancreatic cancer imaging. In the present study, we investigated the usefulness of SPECT imaging with ^{111}In-DOTA-c(RGDfK) for the early and accurate detection of pancreatic cancer in a chemically induced hamster pancreatic cancer model.

MATERIALS AND METHODS

Experimental Animal Models

Ten 5-wk-old female Syrian golden hamsters were obtained from Japan SLC. For the induction of pancreatic cancer, hamsters were subcutaneously injected with BOP (Nacalai Tesque) in saline at 10 mg/kg of body weight 4 times every other day. Palpation and laparotomy were occasionally performed after BOP treatment to confirm the induction of pancreatic cancer.

Eight 6-wk-old male ddY mice (Japan SLC) were intramuscularly injected with 50 μL of turpentine oil (Kanto Chemical) in the right thigh to induce inflammation (*30,31*).

Animal studies were performed in compliance with the guidelines set for animal experiments by the Committee for Ethics of Animal Experimentation at the National Cancer Center.

SPECT with ^{111}In-DOTA-c(RGDfK) in Hamster Pancreatic Cancer Model

DOTA-c(RGDfK) was labeled with ^{111}In as described previously (*29*). Hamsters were injected via the subclavian vein with 17.5–37.0 MBq of ^{111}In-DOTA-c(RGDfK) 16 wk after treatment with BOP. They were maintained under anesthesia with isoflurane (Dainippon Sumitomo Pharmaceutical) throughout the experiment. Just before the acquisition of CT images, the hamsters were injected with 500 μL of iopamidol (Iopamiron 370; Bayer Schering Pharma).

SPECT/CT was performed with a 4-head, multiplexing, multipinhole NanoSPECT/CT scanner (Bioscan, Inc.) 1 h after the injection of ^{111}In-DOTA-c(RGDfK). First, CT scans were obtained with a tube voltage of 60 kV and a tube current of 0.12 mA. Next, SPECT scanning was performed at 300 s/projection, and 24 projection views were obtained. After imaging, the SPECT data were reconstructed with an ordered-subset expectation maximization algorithm, dedicated software (Invivoscope; Bioscan, Inc.), and Mediso InterViewXP (Mediso). SPECT and CT images were automatically superimposed with Invivoscope. The accuracy of the superimposition was regularly calibrated with phantoms. A researcher experienced in the evaluation of small-animal SPECT/CT images visually evaluated pancreatic uptake.

Autoradiography (ARG) with ^{111}In-DOTA-c(RGDfK) in Hamster Pancreatic Cancer Model

After SPECT/CT, the pancreas from each hamster was excised and macroscopically surveyed to detect pancreatic lesions. Samples were then embedded in Cryo Mount II (Muto Pure Chemicals Co., Ltd.) and frozen in liquid nitrogen. Frozen sections were cut with a cryostat to thicknesses of 20 μm for ARG and 10 μm for histologic analysis and mounted on glass slides. For ARG, glass slides were placed on an imaging plate (BAS-MS 2040; Fujifilm Co. Ltd.), and then the exposed plate was scanned with a bioimaging analyzer (FLA-7000; Fujifilm Co. Ltd.) to detect radioactivity. On the basis

TABLE 1
SPECT Detection Ratios and Tumor-to-Normal Pancreas (T/N) Ratios Calculated by ARG Analysis

Condition	Hamster	Size (mm)	Detection by SPECT	T/N ratio
Adenocarcinoma	4	2.0	ND	5.1
	5	3.0	Detected	4.0
		4.4	Detected	5.2
	6	3.0	Detected	4.5
		5.0	Detected	6.7
	7	2.0	ND	4.5
	9	3.5	ND	3.5
		5.0	Detected	4.2
	10	8.0	Detected	3.7
Atypical hyperplasia	3	1.5	ND	4.9
	7	0.7	ND	5.4
	9	0.8	ND	2.6
		1.3	ND	2.7
	10	0.9	ND	2.4

For adenocarcinoma and atypical hyperplasia, respective sizes (mean ± SD) were 4.0 ± 1.9 and 1.0 ± 0.3 mm; respective percentages detected by SPECT were 66.7% and 0%; and respective T/N ratios (mean ± SD) were 4.6 ± 1.0 and 3.9 ± 1.5. ND = not detected.

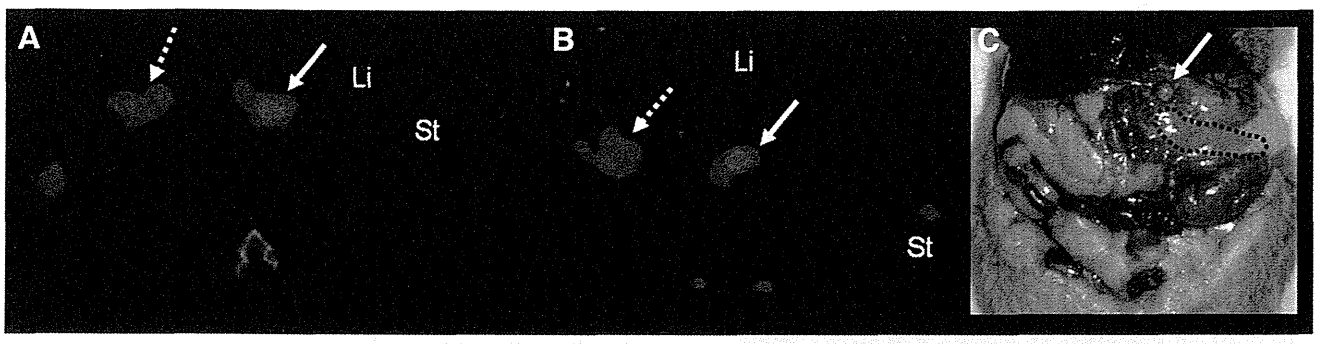

FIGURE 1. (A and B) SPECT images of pancreatic tumor in hamster 6 (A, axial; B, coronal). SPECT was performed 1 h after injection of ^{111}In-DOTA-c(RGDfK). Intense uptake was found in tumor (solid arrow). Slight uptake of ^{111}In-DOTA-c(RGDfK) was observed in intestine (dotted arrow). (C) Anatomic image of hamster abdomen. Tumor (5 mm) in pancreatic head is indicated by arrow; its position was identical to that of region of high uptake of ^{111}In-DOTA-c(RGDfK). Pancreatic gastric lobe is indicated by dotted line. Li = liver; St = stomach.

of microscopic observation of sections stained with hematoxylin and eosin, regions of interest were placed on both tumor and normal pancreatic samples. ImageQuant software (Fujifilm Co. Ltd.) was used to quantify the intensity of radioactivity.

ARG with ^{111}In-DOTA-c(RGDfK) and ^{18}F-FDG in Mouse Inflammatory Model

Three days after turpentine oil injection, ARG analysis of inflammatory regions was performed. Eight mice were divided into 2 groups. Each group was injected via the tail vein with 740 kBq of ^{111}In-DOTA-c(RGDfK) and 925 kBq of ^{18}F-FDG. Inflammatory tissue, including the surrounding tissue, was excised 1 h after injection. ARG analysis was performed as described earlier. Regions of interest were placed on both inflammatory and muscle regions.

Immunohistochemical Analysis of $\alpha_v\beta_3$-Integrin

Frozen sections (10 μm) were fixed in methanol at −20°C. After 2 washes with phosphate-buffered saline containing 0.05% polysorbate 20 (PBS-T), endogenous peroxide was blocked with 3% H_2O_2 in methanol for 10 min. After 2 washes with PBS-T, sections were masked with 2% normal goat serum in PBS-T for 1 h at room temperature and then incubated overnight with anti-$\alpha_v\beta_3$-integrin (clone LM609; Millipore) at 4°C. Sections were incubated with biotinylated anti–mouse IgG (Dako Cytomation); this step was followed by reaction with streptavidin–biotin–horseradish peroxidase complex (StreptABComplex/HRP; Dako Cytomation). Horseradish peroxidase was detected with diaminobenzidine (Phoenix Biotechnologies) substrate. All sections were counterstained with hematoxylin.

Statistical Analysis

Data analysis was performed with GraphPad Prism (GraphPad Software). Unpaired t testing was used for ARG analysis in the mouse inflammatory model. The results were considered statistically significant at $P < 0.05$.

RESULTS

SPECT with ^{111}In-DOTA-c(RGDfK) in BOP-Treated Hamsters

Adenocarcinomas or atypical pancreatic hyperplasia was macroscopically or microscopically found in 7 of 10 BOP-treated hamsters (Supplemental Table 1) (supplemental materials are available online only at http://jnm.snmjournals.org). There were 9 adenocarcinoma lesions in 6 BOP-treated hamsters and 5 atypical hyperplasia lesions in 4 BOP-treated hamsters. Both adenocarcinomas and atypical hyperplasia were observed in 3 BOP-treated hamsters. The average size (mean ± SD) of the adenocarcinomas was 4.0 ± 1.9 mm, and SPECT with ^{111}In-DOTA-c(RGDfK) detected 6 of the 9 lesions (66.7%) (Table 1). The average size of the atypical hyperplasia lesions was 1.0 ± 0.3 mm, and SPECT with ^{111}In-DOTA-c(RGDfK) could not detect any such lesion.

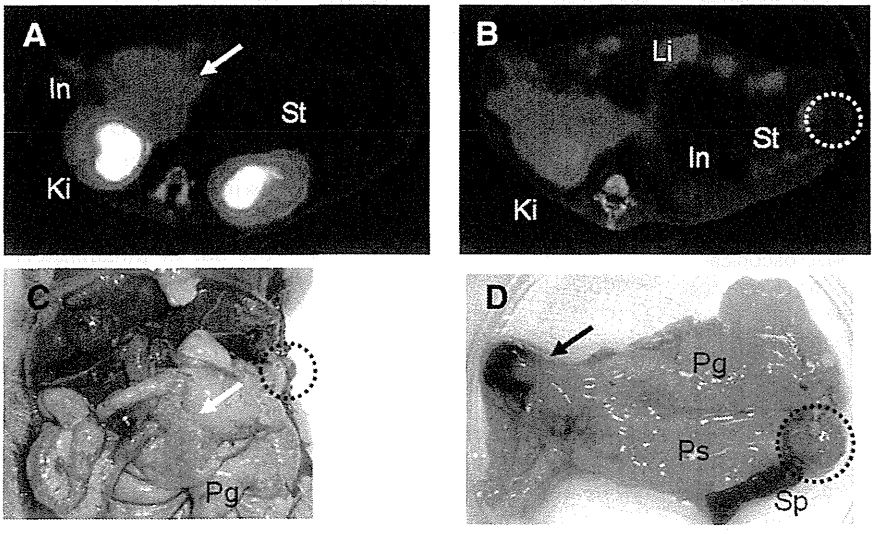

FIGURE 2. (A and B) SPECT axial images of pancreatic tumor (A) and purulent inflammatory lesion (B) in hamster 10. (C and D) Anatomic images of abdomen (C) and excised pancreas (D). Tumor (8 mm) in pancreatic head is indicated by arrow. Inflammatory lesion is indicated by dotted circle. In = intestine; Ki = kidney; Li = liver; Pg = pancreatic gastric lobe; Ps = pancreatic splenic lobe; Sp = spleen; St = stomach.

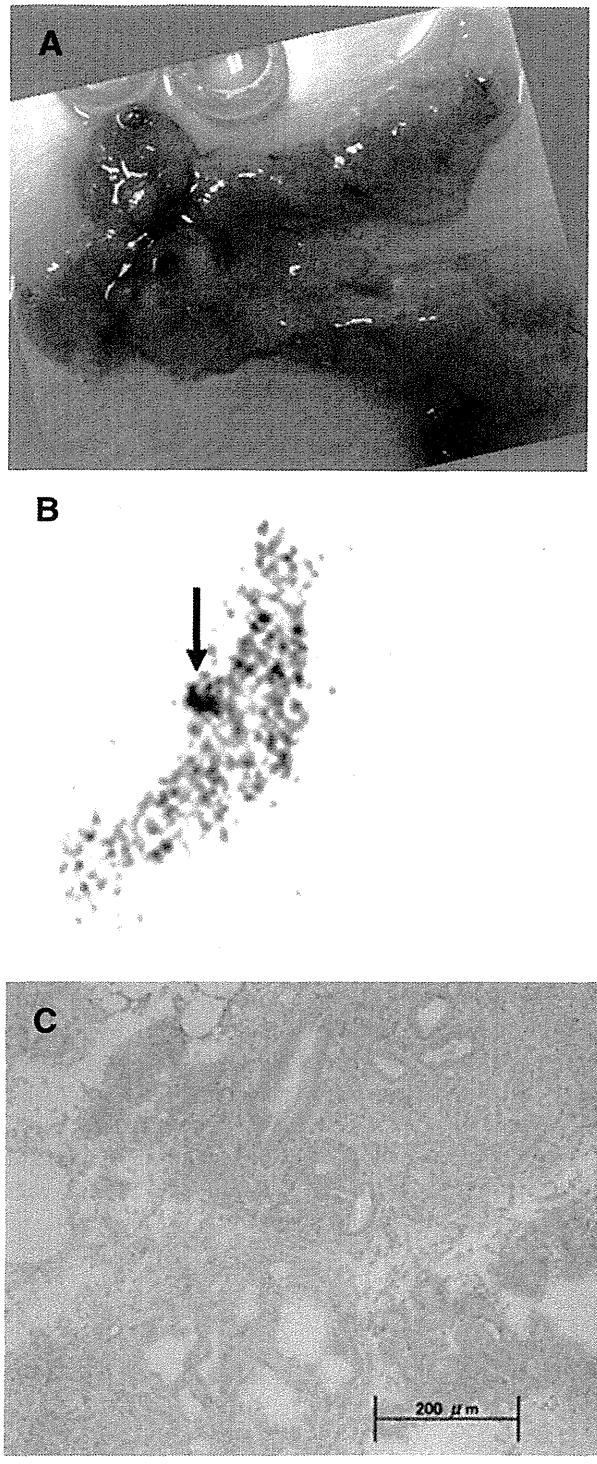

FIGURE 3. Ex vivo autoradiography and histopathologic analysis of atypical hyperplastic region in hamster 3. (A) Macroscopically, there was no lesion in pancreas. (B) One hot spot (arrow) was found in gastric lobe by ARG, but SPECT could not detect this small lesion. (C) Hematoxylin–eosin staining in region of hot spot.

Abdominal CT images of hamsters successfully depicted the liver, stomach, intestine, and kidneys. The anatomic relationships among these organs successfully indicated the location of the pancreas, although the actual pancreatic contours were not delineated. Because SPECT images were accurately superimposed on CT images, pathologic accumulation in the pancreas could be judged from the SPECT/CT fusion images. Representative SPECT/CT fusion images are shown in Figure 1 and Figure 2. Figures 1A and 1B show SPECT images of the pancreatic tumor in hamster 6. A tumor that was 5 mm in diameter and that was located near the pyloric region was clearly visualized with ^{111}In-DOTA-c(RGDfK). Although there was slight uptake in the intestine, this kind of uptake never interfered with the detection of pancreatic tumors because superimposed CT images clearly indicated that the uptake was not located in the pancreas. All tumors depicted by ^{111}In-DOTA-c(RGDfK) SPECT were verified by laparotomy findings (Figs. 1B and 1C).

In hamster 10, 1 pancreatic tumor (8 mm in diameter) in the pancreatic head and an artificially induced purulent inflammatory/foreign-body granulomatous nodule that was located in the splenic lobe of the pancreas and that was adherent to abdominal muscle were found (Figs. 2C and 2D, Ps). SPECT with ^{111}In-DOTA-c(RGDfK) accurately depicted the tumor in the pancreatic head (Fig. 2A),but the inflammatory lesion was not detected (Figs. 2B and 2D). There was intense uptake in the kidneys because of urinary excretion.

Ex Vivo ARG and Histopathologic Analysis of Excised Pancreas

ARG successfully depicted all adenocarcinoma and atypical hyperplasia lesions, but SPECT failed to detect atypical hyperplasia. The T/N ratios for adenocarcinomas and atypical hyperplasia were 4.6 ± 1.0 and 3.9 ± 1.5, respectively (Table 1). There was strong $\alpha_v\beta_3$-integrin expression in all adenocarcinoma lesions.

The contrast in ^{111}In-DOTA-c(RGDfK) accumulation on ARG images between tumors and the normal pancreas was quite good (Supplemental Figs. 1A and 1B). Strong positive results for $\alpha_v\beta_3$-integrin in tumor tissues on immunohistochemical analysis validated these results satisfactorily (Supplemental Fig. 1C).

Although SPECT failed to detect atypical hyperplasia lesions, ARG successfully depicted all of them, even when they were not macroscopically visualized. In hamster 3 (Fig. 3), the T/N ratio was 4.9—similar to that for adenocarcinoma (4.6). However, SPECT could not detect this lesion, likely because of its small size.

In hamster 10, the uptake of ^{111}In-DOTA-c(RGDfK) in the inflammatory lesion was not demonstrated even by ARG (Supplemental Fig. 2). In agreement with the in vivo SPECT findings (Fig. 2), ARG images revealed significant uptake of ^{111}In-DOTA-c(RGDfK) in tumors but not in inflammatory lesions. The T/N ratio was 3.7, and the ratio of inflammation to the normal pancreas was 0.9. These accumulation patterns were verified by the absence of $\alpha_v\beta_3$-integrin expression in inflammatory lesions.

Accumulation of ^{111}In-DOTA-c(RGDfK) and ^{18}F-FDG in Inflammatory Lesions

The uptake of ^{111}In-DOTA-c(RGDfK) was compared with that of ^{18}F-FDG in inflammatory lesions in the mouse

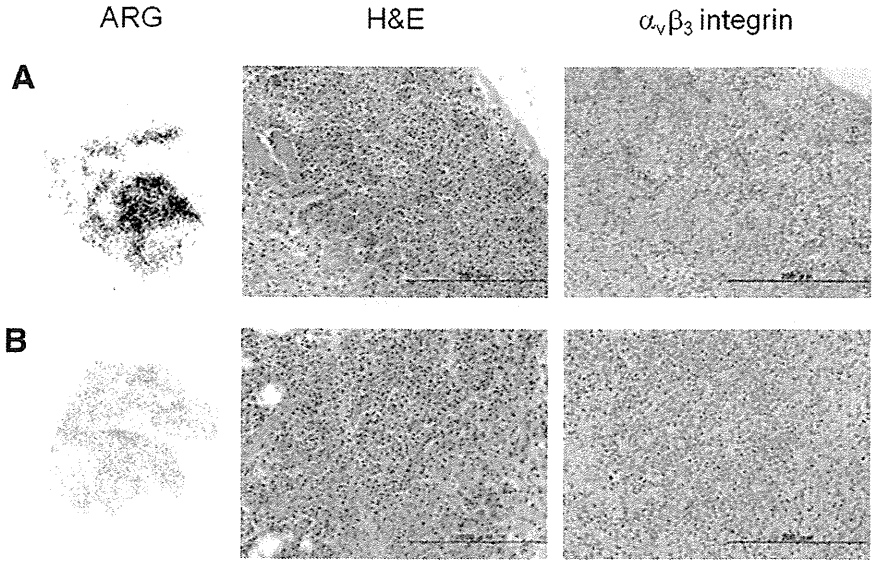

FIGURE 4. Ex vivo autoradiography [A, ^{18}F-FDG; B, ^{111}In-DOTA-c(RGDfK)] and histopathologic analysis of inflammation induced by turpentine oil in mouse model. Sections of inflammatory regions were stained with hematoxylin–eosin (H&E) and anti-$\alpha_v\beta_3$-integrin antibody.

model (Fig. 4 and Fig. 5). In this model, acute inflammation was characterized by focal neutrophil infiltration (Fig. 4). Although ^{18}F-FDG was actively taken up in the inflammatory regions in all cases, ^{111}In-DOTA-c(RGDfK) was not. There was no expression of $\alpha_v\beta_3$-integrin in this inflammatory model. The inflammation-to-muscle ratio for ^{18}F-FDG was much higher than that for ^{111}In-DOTA-c(RGDfK) (8.37 ± 4.37 vs. 1.98 ± 0.60; $P < 0.05$) (Fig. 5).

DISCUSSION

Because $\alpha_v\beta_3$-integrin is often expressed in various kinds of malignant tumors and endothelial cells, tumor imaging with radiolabeled RGD peptides, which are promising agents for $\alpha_v\beta_3$-integrin imaging, has been actively investigated in animal models and cancer patients (*26–29*). Haubner et al. showed that there was a correlation between the tumor uptake of ^{18}F-galacto-c(RGDfK) and the level of $\alpha_v\beta_3$-integrin expression (*27*). We developed ^{111}In-DOTA-c(RGDfK), an ^{111}In-labeled RGD, and demonstrated that this radiopharmaceutical showed high tumor uptake in SKOV-3, a human ovarian carcinoma model, with strong expression of $\alpha_v\beta_3$-integrin (*29*).

Pancreatic cancer, one of the most incurable malignant tumors, can also be imaged with radiolabeled RGD peptides because pancreatic cancer cells express $\alpha_v\beta_3$-integrin (*18*). However, successful cure of pancreatic cancer requires detection in the early stages of carcinogenesis, when the lesions are small. For this purpose, suitable animal models that mimic the clinical situation as closely as possible are ideal tools. The hamster model used in the present study is well established and has been used for numerous studies of pancreatic duct carcinogenesis and its prevention (*20,32,33*). Because this carcinogenesis model appeared to be suitable for evaluation of the usefulness of imaging agents in the early detection of pancreatic cancer, we investigated the possibility of early and accurate detection of this cancer by combining this model and SPECT with ^{111}In-DOTA-c(RGDfK).

In the present study, SPECT with ^{111}In-DOTA-c(RGDfK) clearly demonstrated 66.7% of pancreatic adenocarcinomas in the hamster model. The smallest pancreatic adenocarcinoma detected was 3 mm. This encouraging finding regarding the detection of early pancreatic cancer was validated by the high T/N ratio, as shown by ARG. This good contrast between tumors and normal tissues may be explained by the fact that $\alpha_v\beta_3$-integrin is strongly expressed in adenocarcinoma lesions but not in stroma and normal ductal cells. Our histopathologic examination reconfirmed this finding. The results of the present study demonstrated that our strategy of using $\alpha_v\beta_3$-integrin as a molecular target was entirely appropriate. Especially important was the fact that SPECT yielded no false-positive findings in normal pancreatic tissue.

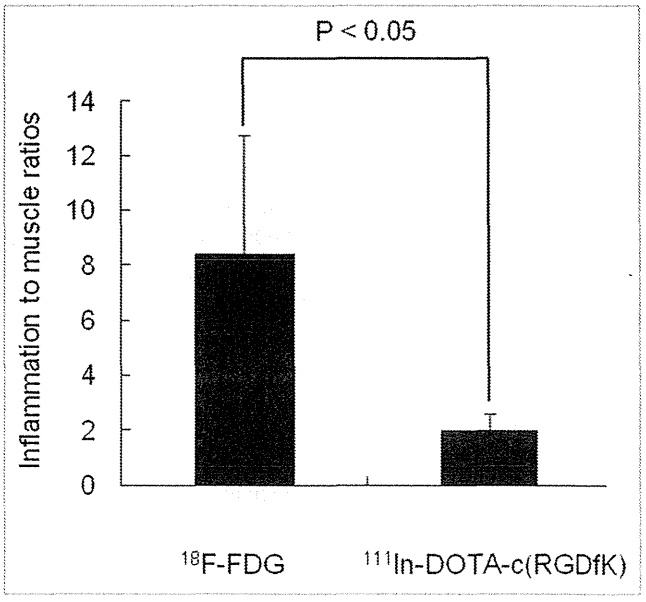

FIGURE 5. Ratios of inflammation to muscle for ^{18}F-FDG and ^{111}In-DOTA-c(RGDfK), as calculated by ARG analysis (n = 4).

ARG analysis demonstrated positive uptake in atypical hyperplasia, but SPECT did not. One reason for this difference could be lesion size. The average size of atypical hyperplasia lesions is 1.0 mm—too small for detection by in vivo SPECT. Another reason could be that the uptake of ^{111}In-DOTA-c(RGDfK) in atypical hyperplasia was relatively lower than that in adenocarcinomas; however, this reason suggests that $\alpha_v\beta_3$-integrin would be a good target for the early detection of pancreatic cancer with radiolabeled RGD peptides because atypical hyperplasia lesions can be regarded as precancerous lesions in terms of carcinogenesis.

In the clinical application of SPECT with ^{111}In-DOTA-c(RGDfK), it is important to clarify the anatomic location of the radionuclide uptake. In the present study, we used a SPECT/CT combination scanner, although this scanner was dedicated to small-animal imaging. Through SPECT/CT fusion imaging, we identified the pancreas on the basis of the location of the kidneys, liver, intestine, and stomach, which are relatively clearly visualized on CT. SPECT/CT combination scanners are becoming popular in clinical practice. Because the performance of clinical CT scanners is better than that of small-animal units with regard to acquisition time, tube voltage, and current × time product (mAs), identification of the pancreas would be easier in clinical practice. Fusion imaging with MRI and scintigraphy is now actively under investigation. Current high-magnetic-field MRI scanners can provide high-resolution anatomic images without contrast agents. Therefore, fusion imaging with MRI and PET or SPECT would overcome the concern about identification of the pancreas (*34*).

^{18}F-FDG PET may have become more popular for the detection of malignant tumors, but ^{18}F-FDG also has a high affinity for inflammatory lesions, resulting in false-positive findings. Because pancreatic masses or swellings are sometimes caused by inflammatory changes, ^{18}F-FDG PET may produce false-positive results. To examine whether SPECT with ^{111}In-DOTA-c(RGDfK) is more useful than ^{18}F-FDG PET in the differentiation of inflammatory lesions, we compared the uptake of ^{111}In-DOTA-c(RGDfK) in inflammatory lesions induced by turpentine in a mouse inflammatory model with the uptake of ^{18}F-FDG. The uptake of ^{111}In-DOTA-c(RGDfK) in inflammatory lesions and the expression of $\alpha_v\beta_3$-integrin were not found, resulting in a significantly lower inflammation-to-muscle ratio for ^{111}In-DOTA-c(RGDfK) than for ^{18}F-FDG. In contrast, ARG indicated high ^{18}F-FDG uptake in inflammatory lesions, in agreement with a previous report (*31*). This profile of $\alpha_v\beta_3$-integrin expression is favorable for distinguishing between tumors and inflammation. In pancreatic lesions, false-positive results for the detection of cancer may be harmful because pancreatic biopsy is somewhat invasive. Therefore, ^{111}In-DOTA-c(RGDfK) may be superior to ^{18}F-FDG for the early and accurate detection of pancreatic cancer.

CONCLUSION

The results of the present study indicated that SPECT with ^{111}In-DOTA-c(RGDfK) is a powerful tool for the diagnosis of pancreatic cancer in the hamster carcinogenesis model, even though a limitation was imposed by the small number of animals evaluated. The specific uptake of ^{111}In-DOTA-c(RGDfK) in tumors and not in inflammatory lesions could decrease the incidence of false-positive findings. Our results will promote the clinical application of ^{111}In-DOTA-c(RGDfK) and other $\alpha_v\beta_3$-integrin imaging agents in the diagnosis of pancreatic cancer.

DISCLOSURE STATEMENT

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