Increased expression of inducible nitric oxide synthase (iNOS) in N-nitrosobis(2-oxopropyl)amine-induced hamster pancreatic carcinogenesis and prevention of cancer development by ONO-1714, an iNOS inhibitor

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Abstract

Elevated protein expression of inducible nitric oxide synthase (iNOS) has been observed in human pancreatic cancers and therefore, iNOS may play important roles in pancreatic carcinogenesis. This was examined in the present study, using an experimental model with N-nitrosobis(2-oxopropyl)amine (BOP)-treated hamsters. Reverse transcription-polymerase chain reaction analysis demonstrated iNOS expression in a hamster pancreatic cancer cell line as well as in human pancreatic cancer cell lines. Immunohistochemical analysis revealed increased expression of iNOS protein in atypical hyperplasia and ductal adenocarcinomas of the pancreas in BOP-treated hamsters. In addition, iNOS expression was also observed in macrophages and islet cells in pancreatic tissue surrounding tumors. In order to assess the role of iNOS expression in carcinogenesis in the pancreas, the effects of ONO-1714 [((S, 5S, 6R, 7R)-7-chloro-3-imino-5-methyl-2-azabicyclo[4.1.0]heptane], an iNOS inhibitor, on hamster pancreatic ductal carcinogenesis were investigated. Female Syrian golden hamsters were treated with BOP at 10 mg/kg body wt, four times for 1 week, and 1 week after the last carcinogen treatment, ONO-1714 was administered at doses of 100 and 200 p.p.m. in the diet for 15 weeks. The incidences and multiplicities of atypical hyperplasia and invasive adenocarcinoma and total adenocarcinomas (non-invasive and invasive adenocarcinomas) in the pancreas were significantly lowered by treatment with 200 p.p.m. ONO-1714. Treatment with 100 p.p.m. ONO-1714 also significantly decreased the multiplicities of invasive and total adenocarcinomas. Moreover, treatment with 200 p.p.m. ONO-1714 reduced the number of BOP-induced cholangiocellular tumors. These results suggest that iNOS plays roles in promoting pancreatic carcinogenesis in both early and late stages in hamsters.

Introduction

Pancreatic cancer is steadily increasing in incidence and has a very poor prognosis (1). For development of effective chemotherapeutic and chemopreventive agents, elucidation of causative factors and mechanisms underlying pancreatic carcinogenesis is very important. As with other cancers, chronic inflammation is considered to be one of the risk factors (2). Epidemiological studies have shown that in addition to the environmental factors like cigarette smoking and dietary habits, pancreatitis is very important (3). Causes of pancreatitis are known to include alcohol drinking, smoking, gallstones, hyperlipidemia and stress (4,5).

Abbreviations: BOP, N-nitrosobis(2-oxopropyl)amine; cDNA, complementary DNA; iNOS, inducible nitric oxide synthase; IL, interleukin; NO, nitric oxide; NOS, nitric oxide synthase.

Chronic inflammation is associated with release of many cytokines and activation of nuclear factor κB, resulting in the expression of nuclear factor κB-regulated, inflammatory-related genes, such as inducible nitric oxide synthase (iNOS) (6). The resultant overproduction of nitric oxide (NO) contributes to multistage carcinogenesis by inducing DNA mutations and tissue damage (6). Increased expression of iNOS in human pancreatic cancers has been described (7–9) and expression has been also reported in a rat pancreatitis model (10).

Suppressive effects of iNOS-selective inhibitors, (1S, 5S, 6R, 7R)-7-chloro-3-imino-5-methyl-2-azabicyclo[4.1.0]heptane (ONO-1714) and L-NAME (1-iminoethyl)lysine tetrazole-amide (SC-51), on pancreatitis in rats have been reported (11,12). ONO-1714 is 10-fold more selective for human iNOS than for human endothelial nitric oxide synthase (NOS), very potent in inhibiting plasma NO elevation in lipopolysaccharide-treated mice with a 50% inhibition dose of 0.010 mg/Kg subcutaneously and less toxic with a maximum tolerated dose of 50 mg/kg intravenously in mice (13,14). In addition, ONO-1714 is effective even when orally administered and our previous studies have demonstrated suppressive effects of ONO-1714 on growth of tumors formed in nude mice after subcutaneous injection of the K-ras mutant-transfected cells (15), aberrant crypt focus formation and large tumor development in the colon of rats treated with azoxymethane (16) and on colon cancer development in Min mice treated with dextran sodium sulfate (17). However, to our knowledge, there have hitherto been no reports concerning effects of iNOS inhibitors on pancreatic cancer development.

The Syrian golden hamster provides a unique model animal for the development of ductal pancreatic cancer. With subcutaneous injections of N-nitrosobis(2-oxopropyl)amine (BOP) (18), lesions having close similarities to the major form of pancreatic cancer in humans are induced. Point mutations in codon 12 of the K-ras gene are frequently observed (19), and expression of the fragile hisidine triad gene, a tumor suppression gene, is generally abnormal in pancreatic cancers of hamsters (20), as in human tumors (21,22). Upregulation of cyclooxygenase-2 has been also observed in both BOP-induced pancreatic neoplastic lesions in hamsters and in human lesions (23), although there has been no report of iNOS expression in hamster pancreatic cancer. Therefore in the present study, we examined expression of iNOS in hamster pancreatic ductal cancer and investigated suppressive effects of ONO-1714, an iNOS-selective inhibitor, on hamster pancreatic ductal carcinogenesis induced by BOP.

Materials and methods

Chemicals

(1S, 5S, 6R, 7R)-7-chloro-3-imino-5-methyl-2-azabicyclo[4.1.0]heptane (ONO-1714) was chemically synthesized at Ono Pharmaceutical Co. Ltd (Osaka, Japan), BOP was obtained from Nacalai Tesque (Kyoto, Japan).

Cell culture

A hamster pancreatic cancer cell line, HaP-T1 (24), was obtained from RIKEN Cell Bank (Saitama, Japan) and a hamster pancreatic β-cell cell line, HFT-T15, from Dainippon Pharmaceutical Co., Ltd (Osaka, Japan). Human pancreatic cancer cell lines, Capan-2, HPAF-II, HPAC, HS-776T, MiaPaca-2 and Panc-1, were obtained from Summit Pharmaceutical International Co., LTD (Tokyo, Japan) and BxPC-3 from RIKEN Cell Bank. A human pancreatic normal ductal cell line, HPDE-6 (25), was kindly provided by Dr Ming-Sound Tsao (University Health Network, Toronto, Ontario, Canada). The cells were maintained in RPMI-1640 (Iwaki, Japan), supplemented with 5% fetal bovine serum (HyClone Laboratories, Logan, UT) and 100 units/ml penicillin-streptomycin (GIBCO/Invitrogen Corp., Carlsbad, CA) at 37°C in 5% CO₂. To induce iNOS expression, cells were treated with 10 ng/ml of mouse or human interleukin (IL)-1β (Sigma Chemical Co., St Louis, MO) for 6 h.
Animals
Five-week-old female Syrian golden hamsters weighing ~80 g were obtained from Japan SLC (Shizuoka, Japan) and acclimated to laboratory conditions for a week. They were housed two or three per plastic cage, with sterilized soft-wood chips as bedding, in an air-conditioned animal room, on a 12 h light–dark cycle. Powdered CE-2 (CLEA Japan, Shizuoka, Japan) was used as a standard basal diet. Body weights were measured on a weekly basis and food consumption twice a week. Food and water were made available ad libitum.

Reverse transcription–polymerase chain reaction analysis
Total RNA was extracted from culture cell samples using ISOGEN (Wako Pure Chemical Industries, Ltd, Osaka, Japan). After RNA purification, aliquots of total RNA (2 μg) were subjected to the reverse transcription reaction with oligo-dT or 9mer random primers in a final volume of 20 μl using an Omniscript Reverse Transcription Kit (Qiagen GmbH, Heilden, Germany). Polymerase chain reaction amplification was performed in a final volume of 10 μl with aliquots of complementary DNA (cDNA) (25 ng) and Taq DNA polymerase (Bio-Rad Laboratories, Hercules, CA) using a PTC-200 Peltier thermal cycler (MJ Research, Waltham, MA). The primers used were selected from the common sequences among hamster, mouse, rat and human cDNA sequences of β-actin (26) and the common sequences between hamster and human cDNA of iNOS (accession numbers,AY297461 and D26525)—5′-primer: ACGAGGCCCAGACCGAGA, 3′-primer: TGGCTGGGTGTAGAAGGTCT (product size, 228 bp) for β-actin and 5′-primer: TTCCCCCACCAGGATGATGOG, 3′-primer: GTACCAGCATTGAAGGGCC (product size, 382 bp) for iNOS. The cycling conditions were as follows: 95°C for 3 min, 26 cycles (for β-actin) or 35 cycles (for iNOS) of 94°C for 15 s, 60°C for 25 s and 72°C for 30 s and a 10 min cycle at 72°C. Products were analyzed by 2% agarose gel electrophoresis with ethidium bromide staining.

Immunohistochemistry
Paraffin sections from formalin-fixed tissues of hamster normal pancreas and pancreatic tumors obtained in our previous study (26) were used for immunohistochemical analyses with the avidin–biotin complex immunoperoxidase technique as described previously (27). As the primary antibody, monoclonal mouse anti-iNOS IgG (BD Biosciences Pharmingen, San Diego, CA #610328) was applied at 50% dilution. As the secondary antibody, biotinylated anti-mouse IgG raised in a horse, affinity purified and absorbed with rat serum (Vector Laboratories, Burlingame, CA) was employed at 200× dilution. Staining was performed using avidin–biotin reagents (Vectastain ABC reagents; Vector Laboratories). The sections were counterstained with hematoxylin. As a negative control, duplicate sections were immunostained without exposure to the primary antibody.

Study on the effects of ONO-1714, an iNOS inhibitor, on BOP-induced pancreatic carcinogenesis in hamsters
A total of 126 hamsters at 6 weeks of age were injected subcutaneously with BOP (four times; on days 1, 3, 5 and 7) at a dose of 10 mg/kg body wt, whereas 18 hamsters received saline as vehicle controls. One week after the last BOP treatment, one-third of each group was given basal diet, diet containing 100 p.p.m. or 200 p.p.m. of ONO-1714 for 15 weeks. The doses were based on our previous study in mice (15,17) and rats (16) and a preliminary study in hamster (18). In the saline group, one-third of each group was given basal diet, diet containing 100 p.p.m. or 200 p.p.m. of ONO-1714 for 15 weeks. The doses were based on our previous study in mice (15,17) and rats (16) and a preliminary study in hamster (18).

Expression of iNOS messenger RNA in human and hamster pancreatic cancer cell lines
Expression of iNOS messenger RNA in human and hamster pancreatic cancer cell lines was examined by reverse transcription–polymerase chain reaction. As shown in Figure 1, iNOS was constitutively expressed in five of seven human pancreatic cancer cell lines, BxPC-3, Capan-2, HPAF-II, HPAC, HS-766T, MiaPaca-2 and Panc-1. On treatment with IL-1β, expression of iNOS in the other two cancer cell lines, Capan-2 and HPAC, and a human pancreatic normal ductal cell line, HPDE-6, was induced, and the expression in HPAF-II and HS-766T was enhanced. Expression of iNOS was also constitutively observed in a hamster pancreatic cancer cell line, HaP-T1, and a hamster β-cell line cell line, HIT-T15, and in both cases was markedly enhanced by treatment with IL-1β.

Table I. Expression of iNOS and β-actin mRNA in human and hamster pancreatic cancer cell lines

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>iNOS</th>
<th>β-actin</th>
</tr>
</thead>
<tbody>
<tr>
<td>BxPC-3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Capan-2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>HPAF-II</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>HPAC</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>HS-766T</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>MiaPaca-2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Panc-1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>HPDE-6</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Effects of ONO-1714 on pancreatic tumor development in BOP-treated hamsters
To examine the role of iNOS on pancreatic carcinogenesis, hamsters were treated with a pancreatic carcinogen, BOP, then were fed a diet containing the iNOS inhibitor, ONO-1714, at doses of 100 or 200 p.p.m. for 15 weeks. The final body weights (g) and average food intake of hamsters are shown in Table I. The body weights and average food intake in the BOP + basal diet group were lower than those in the saline + basal diet group (P < 0.05), and the average body weight in the saline + 200 p.p.m. ONO-1714 group was 13% lower.
than in the BOP + basal diet group ($P < 0.01$). However, in the BOP-treated groups, no significant differences were observed after treatment with ONO-1714.

Pancreatic lesions were histopathologically diagnosed as atypical hyperplasia, non-invasive adenocarcinomas and invasive adenocarcinomas. Incidence and multiplicity data are summarized in Table II. The incidence of atypical hyperplasia and adenocarcinomas induced by BOP was lower in the group treated with 200 p.p.m. ONO-1714 than in the control group (21 versus 52% at $P < 0.005$ and 45 versus 69% at $P < 0.05$, respectively). Remarkably, the incidence of invasive adenocarcinomas was significantly lower in the 200 p.p.m. ONO-1714 group than in the control group (12 versus 45% at $P < 0.001$). Multiplicities of total adenocarcinomas were significantly decreased by treatment with 100 p.p.m. (0.76 ± 0.82, $P < 0.05$) and 200 p.p.m. ONO-1714 (0.60 ± 0.77, $P < 0.01$) compared with the control value (1.19 ± 1.10). It was notable that the multiplicities of invasive adenocarcinomas in the 100 p.p.m. and 200 p.p.m. ONO-1714 groups were only one-half (0.36 ± 0.62, $P < 0.05$) and one-fifth (0.14 ± 0.42, $P < 0.01$) of the control value (0.74 ± 1.01), respectively. On the other hand, the multiplicities of non-invasive adenocarcinomas did not significantly differ among the three groups. Figure 3 shows the size distribution of pancreatic adenocarcinomas. The numbers of carcinomas <3, 3–5 and ≥5 mm in diameter in the BOP + 100 p.p.m. ONO-1714 group were 55, 56 and 86% of the BOP + basal diet values, respectively, suggesting that treatment with 100 p.p.m. ONO-1714 tended to suppress the development of carcinomas <5 mm in diameter, but not the larger lesions. On the other hand, those in the BOP + 200 p.p.m. ONO-1714 group were 75, 38 and 29% of the control group, respectively, indicating that treatment with 200 p.p.m. ONO-1714 tended to suppress the development of carcinoma >3 mm in diameter and significantly reduced the development of carcinoma >5 mm in diameter ($P < 0.05$).

In addition to pancreatic ductal tumors, tumors of the bile duct, liver, lungs and kidneys have been reported to be induced by BOP in hamsters (18). In the present study, hepatocellular and cholangiocellular tumors were observed in the BOP-treated group at incidences of 12 and 50%, respectively (Table III). The cholangiocellular tumors developed in both intra- and extrahepatic bile ducts. The incidences of hepatocellular and cholangiocellular tumors were not significantly changed by ONO-1714 administration, but the multiplicity of cholangiocellular tumors was significantly decreased by 200 p.p.m. ONO-1714 treatment compared with the controls (0.38 ± 0.66 versus 1.14 ± 1.57 at $P < 0.005$) (Table III). In contrast, the incidences and multiplicities of lung tumors were statistically increased by 100 p.p.m. ONO-1714 [33/42 (79%) at $P < 0.05$ and 1.60 ± 1.29 at $P < 0.05$, respectively] and slightly but not significantly by 200 p.p.m. ONO-1714 [26/42 (62%) and 1.26 ± 1.33, respectively] compared with the control group [21/42 (50%) and 0.98 ± 1.42, respectively]. A renal mesenchymal tumor and a hemangioma were observed in the BOP + basal diet group, an angiosarcoma in the BOP + 100 p.p.m. ONO-1714 group and a nephroblastoma in the BOP + 200 p.p.m. ONO-1714 group, but their incidences were not significant. Tumors in the pancreatic duct, bile duct, liver, lungs and kidneys were not observed in the saline vehicle ($n = 15$) or 100 p.p.m. and 200 p.p.m. ONO-1714 group hamsters without the BOP treatment ($n = 15$, each).

### Table I. Final body weights of the hamsters and average food intake

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of animals</th>
<th>Final body weight (g)</th>
<th>Food intake $^a$ (g/hamster/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOP + basal diet</td>
<td>42</td>
<td>199 ± 21$^{b,c}$</td>
<td>10.8 ± 0.4$^c$</td>
</tr>
<tr>
<td>BOP + 100 p.p.m. ONO-1714</td>
<td>42</td>
<td>200 ± 17</td>
<td>11.0 ± 0.6</td>
</tr>
<tr>
<td>BOP + 200 p.p.m. ONO-1714</td>
<td>42</td>
<td>193 ± 19</td>
<td>10.5 ± 0.5</td>
</tr>
<tr>
<td>Saline + basal diet</td>
<td>6</td>
<td>219 ± 18</td>
<td>11.7 ± 1.0</td>
</tr>
<tr>
<td>Saline + 100 p.p.m. ONO-1714</td>
<td>6</td>
<td>194 ± 22</td>
<td>10.8 ± 0.1</td>
</tr>
<tr>
<td>Saline + 200 p.p.m. ONO-1714</td>
<td>6</td>
<td>190 ± 13$^d$</td>
<td>10.1 ± 0.1</td>
</tr>
</tbody>
</table>

$^a$Total food intake of each animal cage for 15 weeks was divided by animal number in each cage and the total period (days).

$^b$Data are mean ± SD.

$^c$Significantly different from the saline + basal diet group at $P < 0.05$.

$^d$Significantly different from the saline + basal diet group at $P < 0.01$.
Discussion

The present study demonstrated that iNOS is expressed in pancreatic cancer cells and that the iNOS inhibitor, ONO-1714, can effectively suppress the development of atypical hyperplasia and cancer, especially invasive cancers, in the hamster pancreas after treatment with BOP. The results indicated that iNOS plays important roles in the development of preneoplastic lesions at an early stage of pancreatic carcinogenesis and also in cancer invasion and expansion in later stages.

In our previous study of colon carcinogenesis, ONO-1714 suppressed the development of rat colon tumors >3 mm in diameter (16), in line with the present findings. It has been reported that angiogenesis is necessary to supply oxygen and nutrients to solid tumors >1–2 mm³ in size (28). NO enhances vascular permeability, partly through activation of matrix metalloproteinases (29), suggesting that suppression of the development of large tumors in ONO-1714-treated groups may be associated with inhibition of angiogenesis by the iNOS inhibitor.

Expression of iNOS has been detected in more than half of human pancreatic cancers (7–9). Here, iNOS expression was observed in most of the hamster pancreatic cancers and atypical hyperplasia. In the BOP-induced pancreatic ductal carcinogenesis model in hamsters, G to A transitions at the second base of the codon 12 of the K-ras gene have been shown to be quite frequent in pancreatic cancers and even in preneoplastic lesions at lower frequency (30). Our previous study revealed that iNOS expression can be markedly elevated by transfection of K-ras mutant cDNA into IEC-6 rat intestinal epithelial cells in the presence of IL-1β or lipopolysaccharide through the activation of promoters on nuclear factor κB, C/EBP and CRE-like sites and that growth of tumors formed in nude mice by subcutaneous injection of the K-ras mutant-transfected cells can be suppressed by feeding diets containing NO inhibitors (15). It is feasible that iNOS expression in pancreatic cancers could also be associated with K-ras activation. Indeed, human pancreatic cancers frequently harbor K-ras mutations (21,31–33) and other cancers with frequent K-ras mutations, such as colon (32,33), lung (33) and intrahepatic bile duct carcinomas (34), also show increased iNOS expression (35–37). Thus, NO produced by iNOS may be generally involved in tumor development by activated K-ras, and iNOS-selective inhibitors should be considered as possible candidates for the prevention of all cancers featuring K-ras activation.

K-ras mutations are observed from early stages of carcinogenesis in the pancreas, colon, lungs (30,33) and intrahepatic bile ducts (38). Our previous studies in the azoxymethane-induced rat colon carcinogenesis model showed frequent K-ras-activating mutations in hyperplastic aberrant crypt foci (39) and suppression of aberrant crypt focus development by the iNOS inhibitor ONO-1714 (16). The present study also showed iNOS expression in precancerous lesions and suppression of the development of atypical hyperplasia in the pancreas of hamsters by an iNOS inhibitor. It can thus be concluded that K-ras-enhanced iNOS expression may contribute to the development of early precancerous lesions.

It has been reported that IL-1β induces iNOS expression in pancreatic β-cells (40), and overproduction of NO causes dysfunction and destruction of β-cells (41). In the present study, iNOS expression in pancreatic islets surrounded by cancer-associated inflammation was observed. Epidemiological studies have reported that diabetes mellitus is also a risk factor for pancreatic cancer (3). Therefore, increased expression of iNOS in pancreatic islets may also be involved in pancreatic carcinogenesis and iNOS inhibitors might also be protective against autoimmune diabetes.

In the present study, the iNOS inhibitor ONO-1714 significantly suppressed the development of pancreatic cancer and cholangiocellular tumors, but not of lung tumors. Pancreatic ductal adenocarcinomas and cholangiocellular tumors in BOP-treated hamsters have certain genetic characteristics in common; for example, K-ras-enhanced iNOS expression may contribute to the development of early precancerous lesions.

Table II. Effects of ONO-1714 treatment on the incidences and multiplicities of pancreatic lesions induced by BOP

<table>
<thead>
<tr>
<th>Dose of ONO-1714 in diet</th>
<th>Effective no. of animals</th>
<th>No. of animals with lesions (%)</th>
<th>No. of lesions in the pancreas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Atypical hyperplasia</td>
<td>Ductal adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-invasive</td>
<td>Invasive</td>
</tr>
<tr>
<td>0 p.p.m.</td>
<td>42</td>
<td>22 (52)</td>
<td>15 (36)</td>
</tr>
<tr>
<td>100 p.p.m.</td>
<td>42</td>
<td>24 (57)</td>
<td>13 (31)</td>
</tr>
<tr>
<td>200 p.p.m.</td>
<td>42</td>
<td>9 (21)**</td>
<td>15 (36)</td>
</tr>
</tbody>
</table>

*Hamsters were fed a basal diet or a diet containing ONO-1714, an iNOS inhibitor, for 15 weeks.
**The total represents animals with non-invasive and/or invasive carcinomas.
Percentages in parentheses.
Data are mean ± SD values.
Significantly different from the control group at *P < 0.05, **P < 0.005 and ***P < 0.001.
lungs. It has been reported that several NOS inhibitors are chemopreventive in the rat tracheal epithelial cell transformation system (43). Reduction in lung tumor development in iNOS(−/−) mice has also been reported (44), suggesting that iNOS expression is associated with lung tumorigenesis. However, endothelial NOS and neuronal NOS are also expressed in lung tumors and high total expression levels of the three NOS types have been suggested to be a favorable prognostic sign (45). Thus, it appears that data on roles of NO in lung tumorigenesis are contradictory and the promotive effect of iNOS is not yet conclusive. Interestingly, other chemopreventive agents reported, such as 4-phenylbutyl isothiocyanate (46), phenethyl isothiocyanate (47) and a cyclooxygenase inhibitor, nimesulide (48) suppressed pancreatic cancers and lung tumors, but enhanced (46) or did not affect (47,48) liver tumorigenesis in BOP-treated hamsters. Thus, it can be presumed that the inhibitory mechanisms of these agents on pancreatic cancer may be different from that of ONO-1714. Our previous study on the prevention of hamster pancreatic carcinogenesis by a peroxisome proliferator-activated receptor γ ligand, pioglitazone, also showed significant suppression of the development of pancreatic ductal adenocarcinomas and cholangiocellular tumors, but not of lung adenomas (26). It is known that peroxisome proliferator-activated receptor γ activation inhibits cytokine-mediated iNOS expression (49,50), indicating that inhibitory mechanisms of ONO-1714 and pioglitazone on hamster pancreatic carcinogenesis could be shared, at least in part.

In conclusion, the present study demonstrated probable involvement of iNOS expression in hamster pancreatic ductal carcinogenesis, and suppression of development of pancreatic atypical hyperplasia and invasive adenocarcinomas by treatment with an iNOS inhibitor. Thus, it is proposed that iNOS inhibitors might be promising chemopreventive agents against pancreatic cancer.

Funding

Acknowledgements
We thank Ms Ayami Etoh and Mr Naoaki Uchiya for expert technical assistance. T.Kitahashi was the awardee of Research Resident Fellowship from the Foundation for Promotion of Cancer Research (Japan) for the Third-Term Comprehensive 10 Year Strategy for Cancer Control during the performance of this study.

Conflict of Interest Statement: None declared.

References

Received April 9, 2008; revised June 5, 2008; accepted June 9, 2008