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Interleukin 10 Reduces the Severity of Acute Necrotizing Pancreatitis in Mice

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Interleukin-10 (IL-10) has recently been identified as a major anti-inflammatory cytokine, and there have been several reports that IL-10 administration reduces severe necrosis in cerulein- or choline deficient (CDE)-induced pancreatitis. We investigated the effect of IL-10 in a mouse model of acute necrotizing pancreatitis induced by ten intraperitoneal infusion of cerulein (50 μg/kg) at hourly intervals and a single intraperitoneal injection of LPS (10 mg/kg) concomitant with the first cerulein injection. The IL-10 treated group was also injected with 10,000 U of IL-10 seven times intraperitoneally every 2 h beginning 1 h before the cerulein infusion. The pancreas was examined for histological changes and analyzed for tissue TNFα mRNA and IL-1β mRNA by RT-PCR. Serum amylase and lipase release peaked at 12 h after the first cerulein injection, but their concentrations at 12 and 24 h were significantly reduced by IL-10. Histologically, acinar cell necrosis and vacuolization were dramatically attenuated at 12 and 24 h in the IL-10 treated group, and induction of tissue TNFα mRNA and IL-1β mRNA in the pancreas was significantly reduced by IL-10. In conclusion, IL-10 is capable of decreasing the severity of experimental acute necrotizing pancreatitis. Inhibition of TNFα and IL-1β production in the pancreas may explain the protective effect of IL-10.

Key words: IL-10, TNFα, IL-1β, pancreatitis, mouse

Introduction

Acute pancreatitis is a common disease and in its severe form is associated with high mortality. Although its progression varies to some extent with the severity of pancreatic destruction, the extrapancreatic manifestations, such as respiratory, cardiovascular, and hepatic dysfunction, contribute most significantly to the mortality from this disease[1]. Several recent studies have reported that the proinflammatory cytokines, tumor necrosis factor (TNF) α and interleukin (IL)-1β are associated with sepsis and distant organ dysfunction, and that these cytokines may play a central role in the progression of pancreatitis and multi-organ failure[2)~4)]. Interleukin-10, however, has recently been identified as a major anti-inflammatory cytokine that inhibits the production of other cytokines by activated macrophages, and there have been several reports that administration of IL-10 reduces the severity of

experimental sepsis and pancreatitis in animal models[5)~9)]. We investigated the effect of IL-10 in a mouse model of necrotizing pancreatitis and sepsis induced by cerulein and LPS.

Materials and Methods

Animals

Male Balb/c mouse weighing 20～24 g were housed at 23 ℃ under a 12 h day/night cycle. Beginning 18 h before the start of the experiments, the animals were deprived of food but given access to water. All experiments were approved by the Animal Use and Care Committee of Tokyo Women's Medical University.

Experimental protocol

Acute pancreatitis was induced by 10 intraperitoneal injections of cerulein (50 μg/kg) at hourly intervals and a single intraperitoneal injection of LPS (10 mg/kg) concomitant with the first cerulein injection. Cerulein and LPS were purchased from Sigma Chemical Co. (St. Louis, MO, U.S.A.).

The animals were divided into three groups. ① A healthy control group (n = 12). ②A IL-10 (+) group (n = 24) intraperitoneally injected with 10,000 U of murine recombinant IL-10 one hour before the first in cerulein injection and every 2 h thereafter until 11 h after the first cerulein injection. IL-10 was a gift from DNAX Reseach Institute (Palo Alto, CA, U.S.A.). ③A IL-10 (－) group (n = 24) intraperitoneally injected with 0.2 ml saline alone one hour before the first cerulein injection and every 2 h thereafter. The procedure is summarized in Fig. 1. Animals were sacrificed by intraperitoneal injection of sodium pentobarbital (50 mg/kg) at 3, 6, 12, or 24 h after the first injection of cerulein.

Assays

Serum amylase levels were measured by an enzymatic assay using a 2-chloro-4-nitrophenyl-β-D-maltopentaoside according to the manufacturer's instructions (Daiichi Pure Chemical Co., Ltd., Tokyo Japan). Serum lipase levels were measured by an turbidimetric assay according to the manufacturer's instructions (Daiichi Pure Chemical Co., Ltd.).

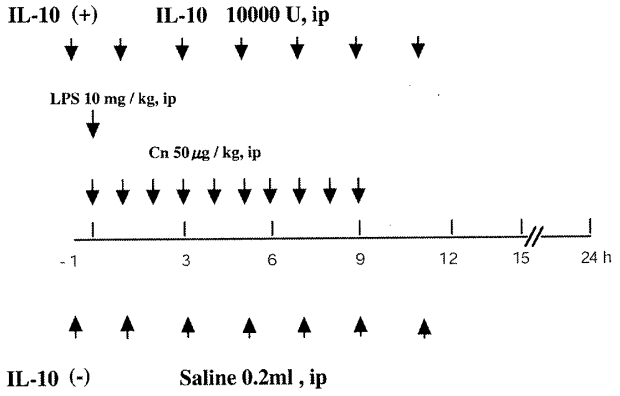

Fig. 1 Experimental protocol

Histological assessment of pancreas and lung

Specimens of pancreas and lung were fixed with 10% buffered formalin, dehydrated in an ethanol series, and embedded in paraffin. They were then cut into sections 3-μm thick and stained with hematoxylin and eosin.

Pancreatic sections were graded in a blinded manner for extent and severity of interstitial edema, acinar cell necrosis, vacuolization, and inflammatory cell infiltration according to Neaderau et al[10)].

Interstitial edema was graded on the following scale: 0 ; absent, 1; diffuse expansion of interlobular septa, 2; 1 + diffuse expansion of interlobular septa, 3; 2 + diffuse expansion of interlobular septa, 4; 3 + diffuse expansion of interlobular septa. Acinar cell necrosis and vacuolization were graded according to the approximate percentage of cells involved: 0 ; 0%, 1 ; ＜5%, 2 ; 5～＜25%, 3 ; 25～＜50%, 4 ; ≧50%.

Inflammatory cell infiltration was graded on the following scale: 0 ; absent, 1; minimal, 2; mild, 3; moderate, 4; severe.

Lung sections were graded in a blinded manner for extent and severity of edema and inflam-

Table 1 Primers used for RT-PCR

TNF α	sense	5′-ATGAGCACAGAAAGCATGATC-3′
	anti-sense	5′-TACAGGCTTGTCACTCGAATT-3′
IL-1 β	sense	5′-CAGGATGAGGACATGAGCACC-3′
	anti-sense	5′-CTCTGCAGACTCAAACTCCAC-3′
β actin	sense	5′-TGTGATGGTGGGAATGGGTCA-3′
	anti-sense	5′-TTTGATGTCACGCACGATTTC-3′

matory cell infiltration according to Osman et al[11]. Edema was graded on the following scale: 0 ; absent, 1; slight edema of the alveolar walls, 2; moderate edematous thickening of alveolar walls with occasional alveoli containing coagulated edema fluid, 3; extensive occurrence of alveolar and interstitial edema.

Inflammatory cell infiltration was graded on the following scale: 0 ; absent, 1; slight focal inflammation, 2; moderate granulocytic margination of necrosis, 3; widespread and pronounced granulocytic margination of necrosis.

Polymerase chain reaction analysis of TNFα mRNA and IL-1β mRNA expression

Total RNA was isolated from the pancreas and lung with an RNA purification kit (ISOGEN: Nippon Gene Inc, Toyama, Japan) and quantified by measuring the absorbance at 260 nm. The integrity of the isolated RNA was verified by the pancreas of equimolar 18S and 28S ribosomal RNA bands following denaturing electrophoresis. A 1 μl/μg amount of total RNA was reverse transcribed into complementry DNA with a commercial RT kit (Advantage TMRT-for-PCR: CLONTECH, Palo Alto, CA, U.S.A.).

The complementry DNA (cDNA) obtained was used as a template, and the pancreatic and pulmonary cDNA were amplified by the polymerase chain reaction (PCR) using a commercial PCR kit (Gene Taq, Nippon Gene Inc). Thirty-five PCR cycles were performed for TNFα and IL-1β (each cycle consisted of after 94 ℃, for 30 sec, 60 ℃ for 30 sec, 72 ℃ for 1 min) in a reaction mixture containing mouse-specific cDNA primers (Continental Laboratory Products, CA, U.S.A.) for individual cytokines (Table 1). Thirty cycles of PCR for β actin (internal standard) were performed. An aliquot of the reaction product (10 μl) was subjected to electrophoresis on 2% agarose gel, after staining with ethidium bromide, the bands were visualized under ultraviolet light.

Statistical analysis

Results are shown as means ± standard error of the mean (SEM) . The pancreatic enzyme data were assessed by the unpaired Student's *t*-test. The histological findings in the pancreas and lung are expressed as the ranges of the scores and means ± SEM, and they were compared by means of a nonparametric test. A p value of < 0.05 was considered statistically significant.

Results

Serum amylase levels

The changes in serum amylase levels are shown in Fig. 2. Serum amylase release peaked 12 h after the first cerulein injection in both the IL-10 (−) group and the IL-10 (+) group. Similar increases in amylase concentrations were subsequently observed in both groups, but the peak values were significantly higher in the IL-10 (−) groups than in the IL-10 (+) groups at 12 h [IL-10 (−) group, 48,400 ± 6,960 vs IL-10 (+) group, 37,600 ± 3,730; $p<0.05$] and at 24 h [IL-10 (−) group, 24,000 ± 3,400 vs IL-10 (+) group, 12,000 ± 1,100; $p<0.05$].

Serum lipase levels

The changes in serum lipase levels are shown in Fig. 3. Serum lipase release peaked 12 h after the first cerulein injection in both the IL-10 (−)

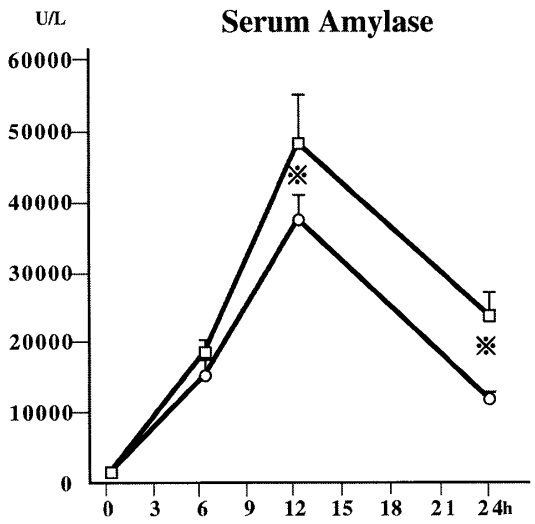

Fig. 2 Serum amylase levels after induction of pancreatitis in the IL-10 (−) and IL-10 (+) groups
Significant differences were observed at 12 and 24 h.
□: IL-10 (−), ○: IL-10 (+), ※: $p<0.05$.

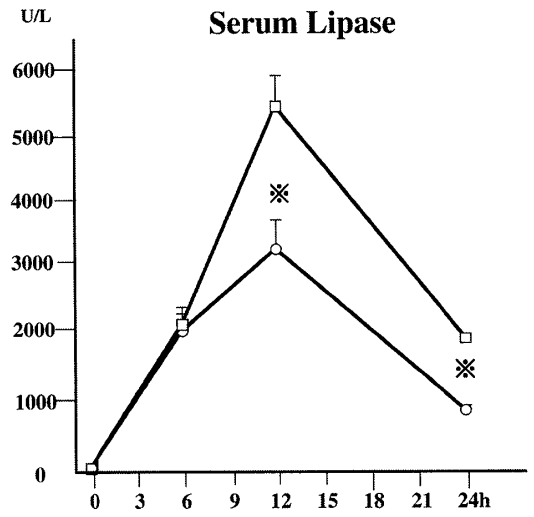

Fig. 3 Serum lipase levels after induction of pancreatitis in IL-10 (−) and IL-10 (+) groups
Significant differences were observed at 12 and 24 h.
□: IL-10 (−), ○: IL-10 (+), ※: $p<0.05$.

Table 2 Serum TNF α level

Time after pancreatitis induction	IL-10 (+) n=5	IL-10 (−) n=5	Statistical significance
6 h	0 ± 0.0	0 ± 0.0	N.S.
12 h	0 ± 0.0	7 ± 3.4 (1 ~ 19)	$p < 0.05$

Data are expressed as means ± SEM.

group and the IL-10 (+) group. At 12 h after the first cerulein injection, similar increases in lipase concentrations were observed in the IL-10 (−) animals and IL-10 (+) animals, but the peak values in the IL-10 (−) groups were significantly higher than in the IL-10 (+) groups at 12 h [IL-10 (−) group, 5,320 ± 800 vs IL-10 (+) group, 3,650 ± 305; $p<0.05$] and at 24 h [IL-10 (−) group, 860 ± 438 vs IL-10 (+) group, 584 ± 59; $p<0.05$].

Serum TNFα level

Table 2 shows the serum TNFα level in each group of animals at 6 and 12 h after the first cerulein injection. Twelve hours after the first cerulein injection, the serum TNFα concentrations tended to decrease in the IL-10 (+) group.

Histological assessment of the pancreas

Table 3 shows the histological findings in the pancreas in each group of animals at 6, 12, and 24 h after the first cerulein injection. Acinar cell necrosis and vacuolization at 6 and 12 h were significantly less severe in the IL-10 (+) group than in the IL-10 (−) group, and by 24 h acinar cell necrosis, vacuolization, and inflammatory cell infiltration were dramatically attenuated in the IL-10 (+) animals. The histological appearance of the pancreas at 12 and 24 h in each group of animals is shown in Fig. 4.

Histological assessment of the lung

Table 4 shows the histological appearance of lung in each group of animals at 6, 12, and 24 h.

Table 3 Histological findings in the pancreas

Time after pancreatitis induction	IL-10 (−)	IL-10 (+)	Statistical significance
6 h			
Edema	2.5 ± 0.2 (2 ~ 3)	2.0 ± 0.2 (1 ~ 3)	
Cell infiltration	1.8 ± 0.2 (1 ~ 3)	1.2 ± 0.2 (1 ~ 2)	
Vacuolization	2.4 ± 0.2 (2 ~ 3)	1.4 ± 0.2 (1 ~ 2)	$p < 0.05$
Necrosis	2.0 ± 0.2 (1 ~ 3)	1.0 ± 0.2 (0 ~ 2)	$p < 0.01$
12 h			
Edema	2.8 ± 0.2 (2 ~ 3)	2.4 ± 0.2 (2 ~ 3)	
Cell infiltration	2.4 ± 0.2 (1 ~ 3)	1.8 ± 0.2 (1 ~ 3)	
Vacuolization	2.8 ± 0.2 (2 ~ 3)	1.6 ± 0.2 (1 ~ 2)	$p < 0.05$
Necrosis	2.6 ± 0.2 (2 ~ 3)	1.2 ± 0.2 (1 ~ 2)	$p < 0.01$
24 h			
Edema	3.0 ± 0.2 (2 ~ 4)	2.6 ± 0.2 (2 ~ 3)	
Cell infiltration	2.8 ± 0.2 (2 ~ 4)	2.0 ± 0.2 (1 ~ 3)	$p < 0.05$
Vacuolization	2.8 ± 0.2 (2 ~ 4)	1.4 ± 0.2 (1 ~ 3)	$p < 0.05$
Necrosis	3.4 ± 0.2 (2 ~ 4)	1.8 ± 0.2 (1 ~ 3)	$p < 0.01$

Data are expressed as means ± SEM.

Edema and inflammatory cell infiltration at 6 and 12 h were significantly less severe in the IL-10 (+) group than in the IL-10 (−) group, and at 24 h edema had decreased slightly in the IL-10 (+) animals. The histological appearance of the lung at 12 h in each group of animals is shown in Fig. 5.

Pancreatic tissue TNFα mRNA and IL-1β mRNA

Pancreatic tissue TNFα mRNA and IL-1β mRNA were detectable at 3 h in both groups. The IL-10 (+) group showed significant attenuation of the increase of TNFα and IL-1β mRNA at all time points investigated Fig. 6. All of the mice in the IL-10 (+) group survived the experiment, but, about 5% of the mice in the IL-10 (−) group died from 12 h onwards.

Discussion

Oxygen-derived free radicals[12] cholecystokinin[13], impaired pancreatic blood flow[14], nitric oxide[15], and cytokine have been considered progression factors of severe acute pancreatitis, but, the pathogenesis of pancreatitis is not very clear. We investigated the effect of IL-10 in a mouse model of necrotizing pancreatitis induced by cerulein and LPS, and the results of our study can be summarized as follows.

Serum amylase and lipase release peaked at 12 h after the first cerulein injection, and both the amylase and lipase concentrations at 12 and 24 h were significantly reduced by IL-10 treatment. Histologically, acinar cell necrosis and vacuolization in the pancreas were dramatically attenuated at 6, 12 and 24 h in the IL-10 treated animals.

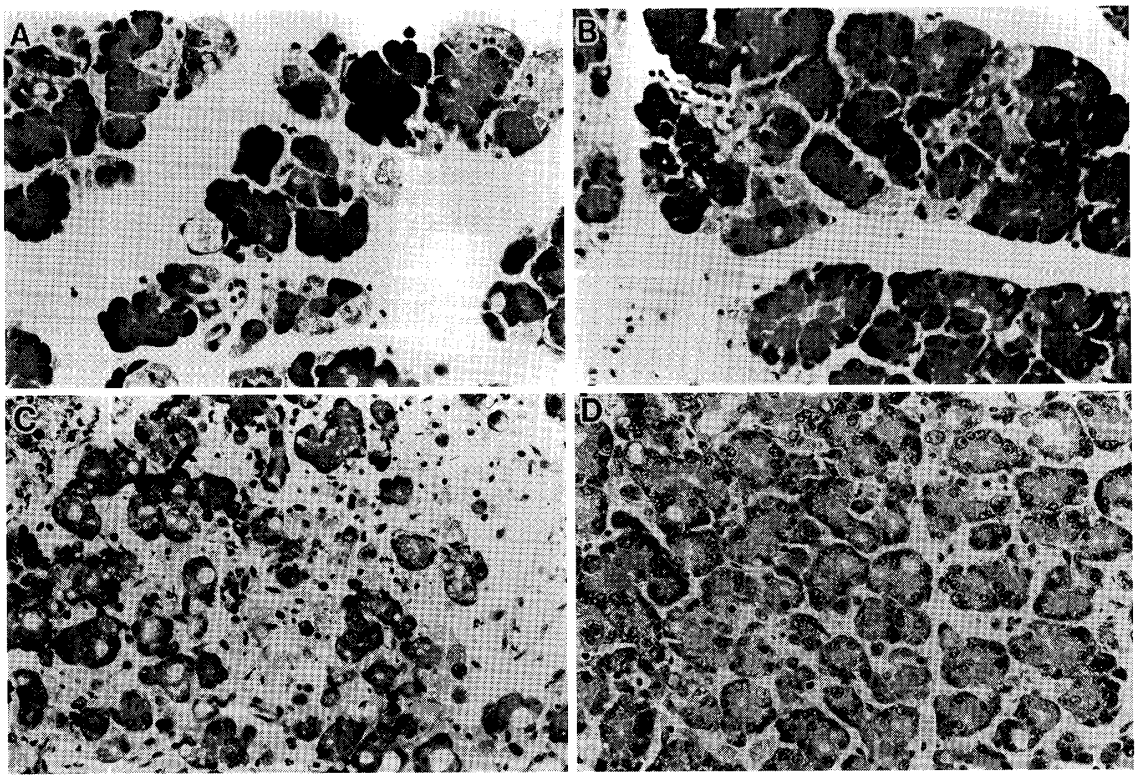

Fig. 4 Histological changes in the pancreas 12 h and 24 h after the first injection of cerulein

Acinar cell necrosis and vacuolization were dramatically attenuated at both 12 and 24 h in the IL-10-treated animals.

A: IL-10 (−) at 12 h, B: IL-10 (+) at 12 h, C: IL-10 (−) at 24 h, D: IL-10 (+) at 24 h.

Hematoxylin-eosin stain; original magnification × 100.

Table 4 Histological findings in the lung

Time after pancreatitis induction	IL-10 (−)	IL-10 (+)	Statistical significance
6 h			
Edema	1.3 ± 0.2 (1 ~ 2)	0.7 ± 0.2 (0 ~ 1)	$p < 0.05$
Cell infiltration	1.7 ± 0.2 (1 ~ 2)	0.7 ± 0.2 (0 ~ 1)	$p < 0.05$
12 h			
Edema	1.8 ± 0.2 (1 ~ 2)	1.0 ± 0.2 (0 ~ 2)	$p < 0.05$
Cell infiltration	2.0 ± 0.2 (1 ~ 3)	1.3 ± 0.2 (1 ~ 2)	$p < 0.05$
24 h			
Edema	2.4 ± 0.2 (2 ~ 3)	1.7 ± 0.2 (1 ~ 2)	$p < 0.05$
Cell infiltration	2.5 ± 0.2 (2 ~ 3)	2.0 ± 0.2 (1 ~ 3)	

Data are expressed as means ± SEM.

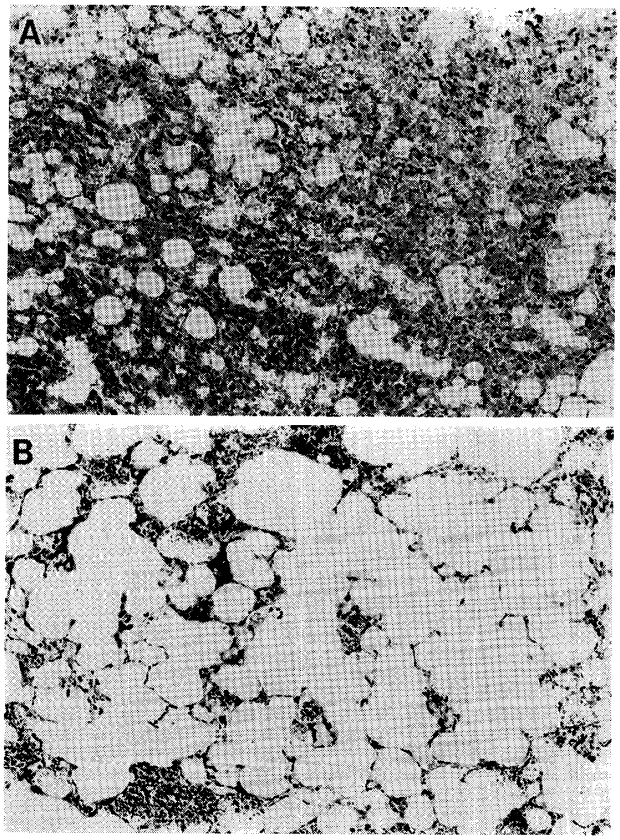

Fig. 5 Histological changes in the lung 12 h after the first injection of cerulein
The edema was dramatically attenuated in the IL-10-treated animals.
A: IL-10 (−) animal at 12 h, B: IL-10 (+) animal at 12 h.
Hematoxylin-eosin stain; original magnification × 100.

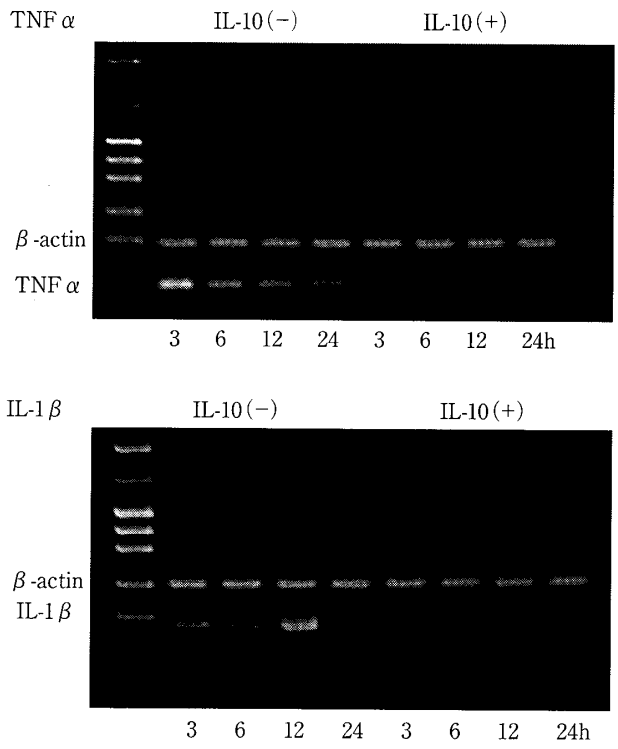

Fig. 6 Expression of TNFα mRNA and IL-1β mRNA in pancreatic tissue 3, 6, 12 and 24 h after the first injection of cerulein
TNFα mRNA and IL-1β mRNA were significantly reduced by IL-10 each time measured.

Edema and inflammatory cell infiltration in the lung were significantly reduced at 6 and 12 h by IL-10. Induction of tissue TNFα mRNA and IL-1β mRNA in the pancreas was significantly reduced by IL-10 at 3, 6, 12 and 24 h after the first cerulein injection.

Several recent studies have reported the possible role of proinflammatory cytokines (TNFα, IL-1β) in mediating the different events involved in acute pancreatitis and its systemic complications, and it is important to compare and contrast the observations in those studies with our own. In a model of severe acute pancreatitis induced by forceful duct injection of bile in rats, Hughes et al[2] showed that administration of anti-TNFα polyclonal antibody before the injection mitigated the severity of the pancreatitis, providing strong evidence that TNFα is a major contributor to morbidity and mortality from acute pancreatitis. Norman et al[3] gave mice intraperitoneal cerulein injections hourly and found that blockade of the proinflammatory cytokine (TNFα and IL-6) cascade at the IL-1 receptor level before or soon after induction of the pancreatitis significantly attenuated the rise in these cytokines and was associated with decreased severity of the pancreatitis and reduced intrinsic pancreatic damage. Denham et al[4] observed decreased severity and mortality from acute pancreatitis induced by a CDE diet (a choline deficient diet supplemented with 0.5 g% ethionine) in transgenic knockout mice deficient in IL-1 type receptors and TNF type 1 re-

ceptors compared with wild type mice. As stated above, TNFα and IL-1β play an important in the progression of pancreatitis and multiorgan failure.

IL-10, on the other hand, is a recently characterized, potent anti-inflammatory mediator that inhibits the production of other cytokines by activated macrophages and reduces the severity of experimental acute pancreatitis. In the recent study, IL-10 treatment reduced the inflammatory response in an animal model of sepsis[5] and intestinal ischemia/reperfusion[16]. In a rat model of acute pancreatitis induced by intravenous cerulein infusion, Rongion et al[6] found that serum amylase, pancreatic edema, vacuolization and inflammation were significantly reduced when IL-10 was administered either before or after the induction of pancreatitis. They reported that the induction of tissue TNFα mRNA, and the TNFα protein level in the pancreas were reduced by IL-10 at 3 and 9 h after induction of the pancreatitis, and van Lathem et al[7] made similar observations. Moreover Kusske et al[8] found that IL-10 decreased inflammation and prevented death in a mouse model of necrotizing pancreatitis induced by a CDE diet. Norman et al[9] showed that induction of tissue TNFα mRNA and IL-1β mRNA in the pancreas, lung, liver, and spleen was significantly reduced by IL-10 in a mouse model produced by intraperitoneal injection of cerulein and feeding a CDE diet. These findings are consistent with our investigation.

Endotoxemia is associated with a poor prognosis in acute pancreatitis, and severe gram-negative bacterial infections can lead to the development of necrotizing pancreatitis. LPS, the major constituent of the cell walls of gram-negative bacteria, is among the most potent toxic substances produced by living organisms. Howard et al[17] created a model of lethal endotoxemia model by injecting LPS, and we used cerulein to create a model of pancreatitis administered LPS as a septic challenge. We think that the pancreatitis in our experimental model progressed to necrotizing pancreatitis with sepsis at 12 h after induction of the pancreatitis, because LPS was given in the same dose as in the model of sepsis created by Howard et al and histological examination showed not only edema and cell infiltration but necrosis as well. In a clinical study, Isenmann et al[18] showed that bacterial infection and extent of necrosis were determinants of organ failure in patients with acute necrotizing pancreatitis, and in an experimental study, Mithofer et al[19] found that antibiotic treatment reduced early and late septic pancreatic complications and improved survival from acute necrotizing pancreatitis induced by cerulein plus an intraductal bile acid infusion.

Finally we confirmed that sepsis is an important factor in the progression of acute pancreatitis, and we wish to emphasize that the discovery that IL-10 reduced the severity of pancreatitis with sepsis is an important finding in terms of protection against pancreatitis. Our data showed that histologic findings in the pancreas and lung were improved by IL-10 and induction of tissue TNFαmRNA and IL-1β mRNA in the pancreas was reduced. We therefore, conclude that IL-10 inhibits proinflammatory cytokines (TNFα and IL-1β) and not only mitigates the local inflammatory response in the pancreas but prevents progression to multi-organ failure. Norman et al detected TNFα and IL-1β mRNA and protein in the pancreas early in the course of pancreatitis in a mouse model created by intraperitoneal injection of cerulein and feeding a CDE diet, and they observed a significant delay between cytokine production in the pancreas and distant organs (lung, liver, spleen). These findings suggested that proinflammatory cytokine production in the pancreas occurs before distant organ dysfunction de-

velops and that progression of the pancreatitis is reduced by inhibiting production of these cytokines.

In conclusion, our findings indicate that IL-10 is capable of decreasing the severity of experimental acute necrotizing pancreatitis and inhibition of TNFα and IL-1β synthesis in the pancreas explain the protective effect of IL-10.

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マウス壊死性膵炎モデルにおけるIL-10投与効果の検討

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［目的］Interleukin-10（IL-10）は抗炎症性サイトカインとして知られており，セルレイン（Cn）やコリンデフィシエントを用いた実験膵炎モデルでIL-10を投与することで膵炎が改善するという報告がある．今回我々は，セルレインおよび，リポポリサッカライド(LPS)を用いたマウス壊死性膵炎モデルを作製し，IL-10の投与効果を検討した．

［方法］マウスにLPS 10 mg/kg 1回（Cn初回投与時）腹腔内投与＋Cn 50 μg/kg 1時間毎に計10回腹腔内投与して膵炎を作製し，IL-10 10,000 UをCnおよびLPS初回投与1時間前より2時間毎に計7回投与し，その投与効果を検討した．

［結果］①血清膵酵素上昇はCn初回投与時より12, 24時間後でIL-10投与により抑制された．②膵組織学的にCn初回投与時より12，24時間後でIL-10投与により空胞形成や壊死が軽減した．③分子生物学的にCn初回投与時より3, 6, 12, 24時間後でIL-10投与により膵組織中のTNFα, IL-1β mRNAの発現が抑制された．

［結論］IL-10は実験壊死性膵炎において，TNFα，IL-1βの産生を抑制し，重症化を軽減させると考えられた．