Full Paper Bioscience of Microbiota, Food and Health Vol. 37 (1), 1–8, 2018

An immune-modulating formula comprising whey peptides and fermented milk improves inflammation-related remote organ injuries in diet-induced acute pancreatitis in mice

Kentaro NAKAMURA[1]*, Kazuhiko FUKATSU[2], Akina SASAYAMA[1] and Taketo YAMAJI[1]

[1]*Nutrition Research Department, Food Science & Technology Research Laboratories, Meiji Co., Ltd., 1-29-1 Nanakuni, Hachiouji, Tokyo 192-0919, Japan*

[2]*Surgical Center, The University of Tokyo, Tokyo, Japan*

Received May 31, 2017; Accepted July 30, 2017; Published online in J-STAGE August 25, 2017

It has been demonstrated that an immune-modulating enteral formula enriched with whey peptides and fermented milk (IMF) had anti-inflammatory effects in some experimental models when it was administered before the induction of inflammation. Here, we investigated the anti-inflammatory effects of the IMF administration after the onset of systemic inflammation and investigated whether the IMF could improve the remote organ injuries in an acute pancreatitis (AP) model. Mice were fasted for 12 hours and then fed a choline-deficient and ethionine-supplemented diet (CDE diet) for 24 hours to induce pancreatitis. In experiment 1, the diet was replaced with a control enteral formula, and mice were sacrificed at 24-hour intervals for 96 hours. In experiment 2, mice were randomized into control and IMF groups and received the control formula or the IMF respectively for 72 hr or 96 hr. In experiment 1, pancreatitis was induced by the CDE diet, and inflammatory mediators were elevated for several days. Remote organ injuries such as splenomegaly, hepatomegaly, and elevation of the hepatic enzymes developed. A significant strong positive correlation was observed between plasma MCP-1 and hepatic enzymes. In experiment 2, the IMF significantly improved splenomegaly, hepatomegaly, and the elevation of hepatic enzymes. Plasma MCP-1 levels were significantly lower in the IMF group than in the control group. Nutrition management with the IMF may be useful for alleviating remote organ injuries after AP.

Key words: immune-modulating formula, acute pancreatitis, inflammation, remote organ injury

INTRODUCTION

It is well known that inflammation is an essential process in protecting the host against foreign invasion. However, uncontrolled and excessive production of pro-inflammatory cytokines occurs in a variety of clinical conditions, and this is called systemic inflammatory response syndrome (SIRS) [1, 2]. SIRS leads to multiple organ failure (MOF) that increases the risk of impaired functions and mortality in intensive care unit (ICU) patients. Acute pancreatitis is a potentially lethal disease with a wide variation of clinical features and severity [3]. Most patients have a mild form of the disease and recover, but some patients develop severe acute pancreatitis (SAP) with a poor prognosis and high mortality. The high mortality rate of SAP often comes from MOF, which is related to SIRS. Inflammatory cytokines, which are released during the early stage of SAP, have been shown to be mediators of the associated pathogenesis of SAP [4–8]. Therefore, control of inflammation has been thought to improve clinical manifestations.

Nutritional support, especially enteral nutrition, can have a significant beneficial impact on the treatment of SAP. Enteral nutrition in severe acute pancreatitis has been demonstrated to reduce mortality rate, systemic infection, and MOF compared with parenteral nutrition [3]. Recent clinical guidelines also recommend enteral nutrition rather than parenteral nutrition or no nutrition to patients with predicted SAP [9, 10]. Various formulations for enteral nutrition have also been tried to improve the outcome of SAP, such as enteral formulas supplemented with probiotics, prebiotics, and synbiotics. However, these forms of supplementation have been reported not to improve the clinical outcomes of SAP [11, 12]. An immune-modulating formula (IMF), which is an enteral formula enriched with anti-inflammatory nutrients, has emerged, and some promising facts have been reported [13]. Recently, an IMF enriched with whey-hydrolyzed peptides, fermented milk, isomaltulose, ω-3 polyunsaturated fatty acids, and antioxidant molecules (vitamin A, C, and E and zinc and selenium) was developed. This formula has been demonstrated to suppress systemic inflammation and improve survival in a murine gut ischemia-reperfusion model and experimental hepatitis model [14, 15]. The IMF was administered before the induction of inflammation in previous

*Corresponding author. Kentaro Nakamura (E-mail: kentarou.nakamura@meiji.com)

Table 1. Diet composition (per 100 kcal)

	CF	IMF
Proteins (g)	4.0	5.0
Protein (% kcal)	16	20
Protein sources	Milk protein, sodium caseinate	Whey-hydrolyzed peptides, fermented milk
Carbohydrates (g)	15.5	14.5
Carbohydrates (% kcal)	59	55
CHO sources	Dextrin	Dextrin, isomaltulose
Lipids (g)	2.8	2.8
Lipids (% kcal)	25	25
Lipid sources	LCT	LCT, MCT, EPA, DHA
Others	Vitamin mix, mineral mix	Vitamin mix, mineral mix

CF: control enteral formula; IMF: immune modulating formula; LCT: long chain triglycerides; MCT: medium chain triglycerides; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid.

studies, while the IMF sometimes could only be administered after the onset of systemic inflammation for ICU patients.

The present study was aimed to investigate the anti-inflammatory effects of IMF administration after the onset of systemic inflammation and to investigate whether the IMF could improve inflammation-related remote organ injuries. Thus, we confirmed that sustained inflammation and subsequent remote organ injuries such as liver and spleen injuries occurred in a diet-induced acute pancreatitis model and then investigated whether administration of the IMF after the onset of systemic inflammation could improve these complications in this model.

MATERIALS AND METHODS

Animals

Three-week-old male C57BL/6 mice were purchased from Japan SLC (Hamamatsu, Japan). The mice were housed in plastic cages under controlled temperature and humidity with a 12-h light/dark cycle and fed commercial chow with water *ad libitum* for 1 week. The experiments reported herein conformed to the guidelines for the care and use of laboratory animals of Meiji Co., Ltd. (Kanagawa, Japan).

Formulas

We used MEIN® (Meiji Co., Ltd.) as the IMF; it is an enteral formula enriched with nutrients with anti-inflammatory properties and has been demonstrated to have anti-inflammatory effects in some experimental models [14, 15]. We used the standard enteral formula MEIBALANCE® (Meiji Co., Ltd.) as the control formula; it contained the minimum nutrition needed to survive and is popularly used for tube-feeding patients clinically. We have used MEIBALANCE as the control diet in a previous study [15]. The diet compositions are listed in Table 1. The control formula and the IMF were purchased from Meiji Co., Ltd., in liquid form. The control formula and the IMF were already sterilized when purchased, so the lactic acid bacteria contained in the fermented milk were heat killed. These diets were lyophilized and then vacuum-packed and refrigerated with an oxygen absorber and desiccants until administration to avoid rotting and oxidation.

Diet-induced severe acute pancreatitis

To induce severe acute pancreatitis in mice, we used a choline-deficient diet supplemented with 0.5% ethionine (CDE diet). The choline-deficient diet and ethionine were purchased from Dyets, Inc. (Bethlehem, PA, USA), and Sigma-Aldrich (St Louis, MO, USA). Mice were fasted overnight for 12 hr after acclimation (−24 hr). These mice were then fed the CDE diet in powder form *ad libitum* for 24 hr (0 hr). After feeding with the CDE diet, the CDE diet was replaced with the control enteral formula or the IMF. The mice were euthanized to collect their tissues and blood from the abdominal vena cava.

Experiment 1 (time course study)

Mice were randomized into five groups and fasted overnight for 12 hr (−24 hr; n=6) and then fed the CDE diet for 24 hr (0 hr; n=6) (Fig. 1). After feeding with the CDE diet, the CDE diet was replaced with the control enteral formula for 24 hr, 48 hr, 72 hr, or 96 hr (n=8, 8, 10, and 9, respectively). Organ weights and plasma amylase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), and monocyte chemoattractant protein-1 (MCP-1) were measured at each time point.

Experiment 2 (effects of the immune-modulating formula)

Mice were fasted for 12 hr (−24 hr; n=9) and then fed the CDE diet. These mice were randomized into control (n=18) and IMF (n=18) groups (Fig. 1). The control or IMF mice received the control enteral diet (MEIBALANCE) or the IMF (MEIN) *ad libitum* for 72 hr or 96 hr. Mice were excluded if their food intake was less than half that during feeding with the CDE diet. Organ weights and plasma amylase, AST, ALT, IL-6, TNF-α, and MCP-1 were measured at each time point.

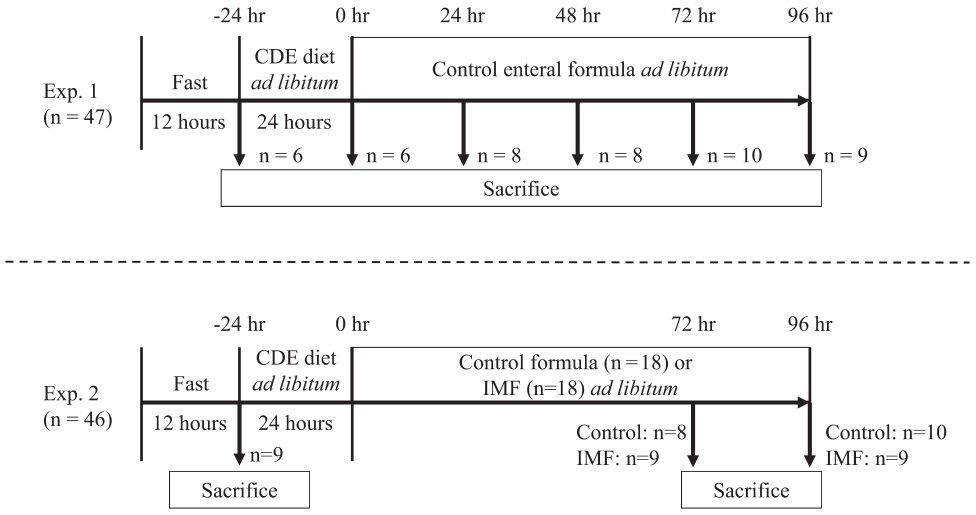

Fig. 1. Experimental protocol. IMF: immune-modulating formula.

Measurement of plasma cytokine, ALT, and AST levels

Plasma cytokine levels were analyzed using a mouse cytometric bead array inflammation kit (BD Biosciences, San Diego, CA, USA) on a FACSCalibur flow cytometer equipped with a 488-nm laser (BD Immunocytometry Systems), according to the manufacturer's protocol. Plasma amylase, ALT, and AST levels were determined enzymatically with an autoanalyzer (Fuji Dri-Chem 3500, Fujifilm, Tokyo, Japan).

Statistical analysis

Data are presented as means ± standard deviations. Differences between the levels at −24 hr and the other time points were assessed using Bartlett's test for variance, followed by Dunnett's test for homoscedastic data or by Steel's test. Comparisons between the control and IMF groups were performed using the Mann-Whitney U-test. The relation between plasma inflammatory cytokine levels and plasma AST or ALT levels was investigated by Pearson's correlation coefficient test. Differences were considered significant at $p<0.05$.

RESULTS

Time course changes in the CDE diet-fed mice

There was no change in dietary intake when intake of the CDE diet was compared with intake of chow in the acclimation period (−24 hr) (Table 2). However, after feeding with the CDE diet, dietary intake was significantly reduced until 48 hr, and it was restored after 72 hr (Table 2).

Pancreatitis was induced by feeding with the CDE diet. Pancreatic weights increased significantly at 0 hr and 24 hr, and they were reduced after 48 hr (Table 3). Plasma amylase increased significantly at 24 hr, and it decreased significantly at 72 and 96 hr (Table 3). Inflammatory mediators such as IL-6, TNF-α, and MCP-1 remained higher until 72 hr (Fig. 2).

Table 2. Body weight change and food intake in experiment 1

Hour	Body weight (g)	Food intake (g)	Diet source
−24 hr	14.6 ± 1.0	2.7 ± 0.4	Chow
0 hr	14.4 ± 0.8	2.9 ± 0.4	CDE diet
24 hr	13.2 ± 0.8 ‡	0.2 ± 0.3 ‡	Control diet
48 hr	13.0 ± 1.2 ‡	1.2 ± 0.9 ‡	
72 hr	13.9 ± 1.5	2.4 ± 0.7	
96 hr	14.7 ± 1.4	2.9 ± 0.4	

Values are means (g) ± standard deviations. ‡$p<0.01$, vs. −24 hr.

Table 3. Pancreas weights and plasma amylase levels in experiment 1

Hour	Pancreas (g)	Amylase (U/l)
–24 hr	0.136 ± 0.025	2,107 ± 510
0 hr	0.170 ± 0.017 ‡	2,193 ± 1,039
24 hr	0.163 ± 0.012 †	10,927 ± 6,946 ‡
48 hr	0.117 ± 0.012	12,445 ± 24,953
72 hr	0.123 ± 0.011	1,561 ± 269
96 hr	0.122 ± 0.019	1,456 ± 255 †

Values are means ± standard deviations. †$p<0.05$, vs. −24 hr. ‡$p<0.01$, vs. −24 hr.

Remote organ injuries such as splenomegaly, hepatomegaly, and elevation of hepatic enzymes developed. Liver weights increased significantly until 96 hr (Fig. 3A). Though not significantly, spleen weights increased to the same extent as the liver (Fig. 3B). Plasma AST and ALT levels were highest at 0 hr and 24 hr and remained higher until 96 hr (Fig. 3C and 3D). A statistically significant ($p<0.001$) strong positive correlation was observed between plasma MCP-1 levels and plasma AST or ALT levels (Fig. 4A and 4C). Plasma IL-6 levels also significantly correlated, but not strongly, with

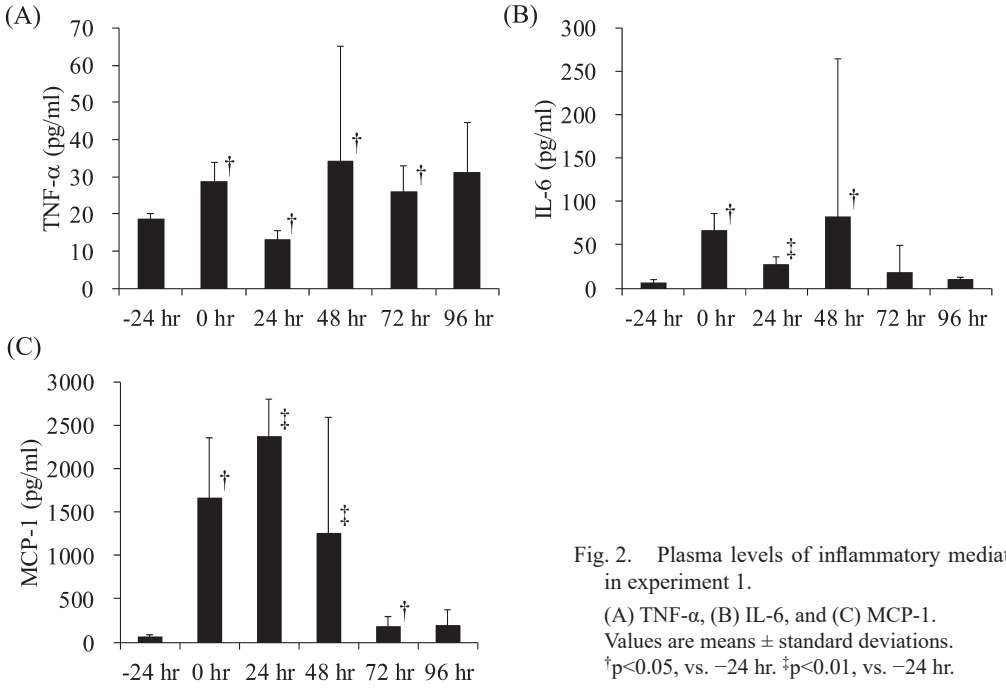

Fig. 2. Plasma levels of inflammatory mediators in experiment 1.
(A) TNF-α, (B) IL-6, and (C) MCP-1.
Values are means ± standard deviations.
†p<0.05, vs. −24 hr. ‡p<0.01, vs. −24 hr.

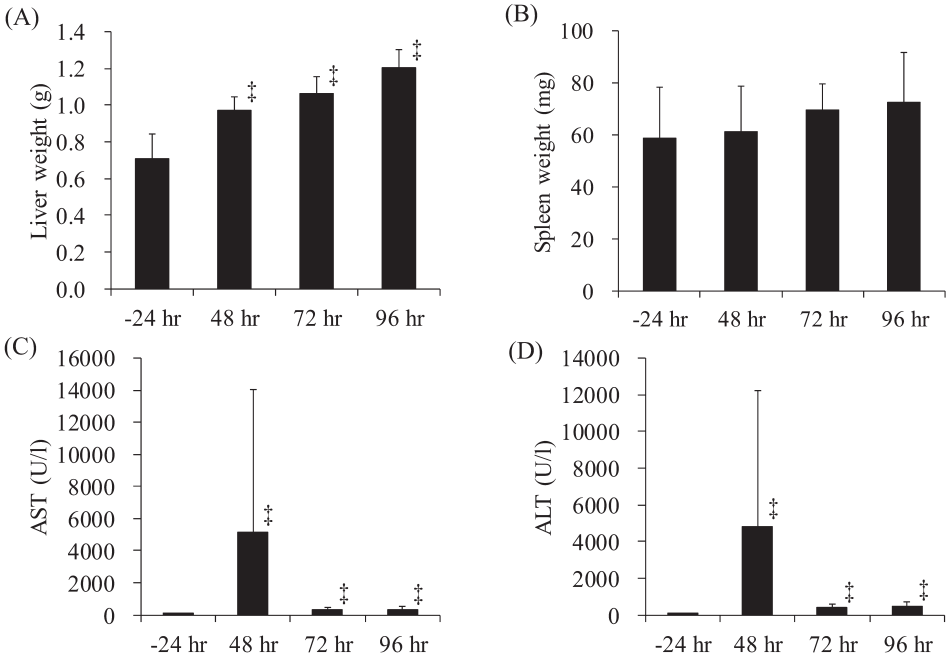

Fig. 3. Incidence of remote organ injury in experiment 1.
(A) Liver and (B) spleen weights and plasma (C) AST and (D) ALT levels.
Values are means ± standard deviations. †p<0.05, vs. −24 hr. ‡p<0.01, vs. −24 hr.

plasma AST and ALT levels. TNF-α did not correlate with these markers.

Effect of the IMF on organ weights

We investigated the beneficial effects of the IMF at 72 hr and 96 hr after feeding with the CDE diet in experiment 2,

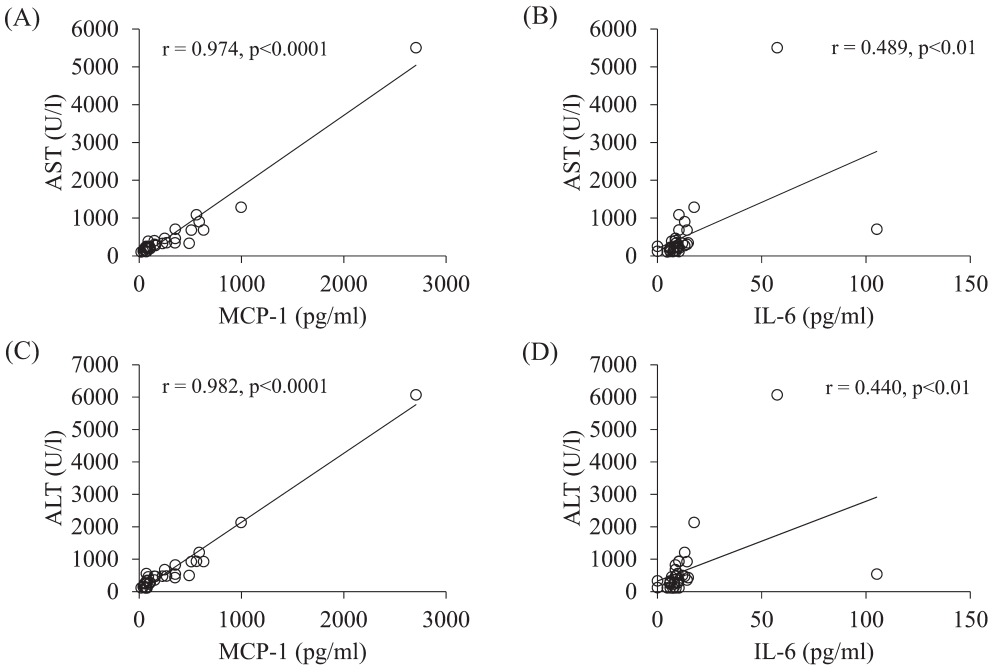

Fig. 4. Correlations between MCP-1 or IL-6 and AST or ALT in experiment 1.

because the level of dietary intake was restored at 72 hr and 96 hr after feeding with the CDE diet in experiment 1. There were no significant differences in body weights and food intake between the control and IMF groups (data not shown). There was also no significant difference in pancreatic weights and plasma amylase levels between the control and IMF groups (Table 4). However, the liver and spleen weights of the IMF group were significantly lower than those of the control mice ($p=0.032$ and 0.046, respectively) at 96 hr (Fig. 5A and 5B).

Table 4. Pancreas weights and plasma amylase levels in experiment 2

Hour	Pancreas (g)		Amylase (U/l)	
	CF	IMF	CF	IMF
−24 hr	0.124 ± 0.024		2,366 ± 954	
72 hr	0.115 ± 0.015	0.114 ± 0.013	1,326 ± 247‡	1,381 ± 371†
96 hr	0.107 ± 0.022	0.113 ± 0.017	1,542 ± 287†	1,566 ± 238†

Values are means ± standard deviations. †$p<0.05$, vs. −24 hr. ‡$p<0.01$, vs. −24 hr.

Effect of the IMF on hepatic enzymes and plasma inflammatory mediators

Plasma AST and ALT levels were significantly elevated at 72 hr and 96 hr in both groups. However, the plasma AST and ALT levels of the IMF group were significantly lower than those of the control mice at 72 hr ($p=0.002$ and 0.002 respectively) (Fig. 5C and 5D). Though the plasma MCP-1 levels were also significantly elevated at 72 hr in both groups, the plasma MCP-1 levels were significantly lower in the IMF group than in the control group (Fig. 6C). The plasma TNF-α and IL-6 levels were not significantly elevated at 72 hr and 96 hr in either group (Fig. 6A and 6B). A significant strong positive correlation was found between plasma MCP-1 levels and plasma AST levels in the control group ($r=0.720$, $p<0.005$) but not the IMF groups (Fig. 7).

DISCUSSION

In the present study, we confirmed sustained inflammation in the CDE diet-induced AP model in order to evaluate the beneficial effect of IMF administration after the onset of systemic inflammation. The experimental pancreatitis induced by feeding with the CDE diet has already been established [16]. In this model, acute necrotizing pancreatitis was induced that was accompanied by systemic inflammatory responses and peripancreatic organ injury [17, 18]. However, whereas mice were fed the CDE diet throughout the experiment in most previous studies [16, 19], little has been reported about whether or not systemic inflammation persisted and subsequent remote organ injuries occurred after feeding with the CDE diet ended [4]. The present study showed for the first time that CDE diet-induced pancreatitis led to remote organ injuries such as splenomegaly and hepatomegaly, which were also seen in severe acute pancreatitis in clinical settings. In experiment 1, it was demonstrated that inflammatory mediators such as MCP-1 were elevated for several days after the end of feeding with the CDE diet. Continuing systemic inflammation was expected to lead to development of remote organ injuries. A variety of inflammatory mediators are thought

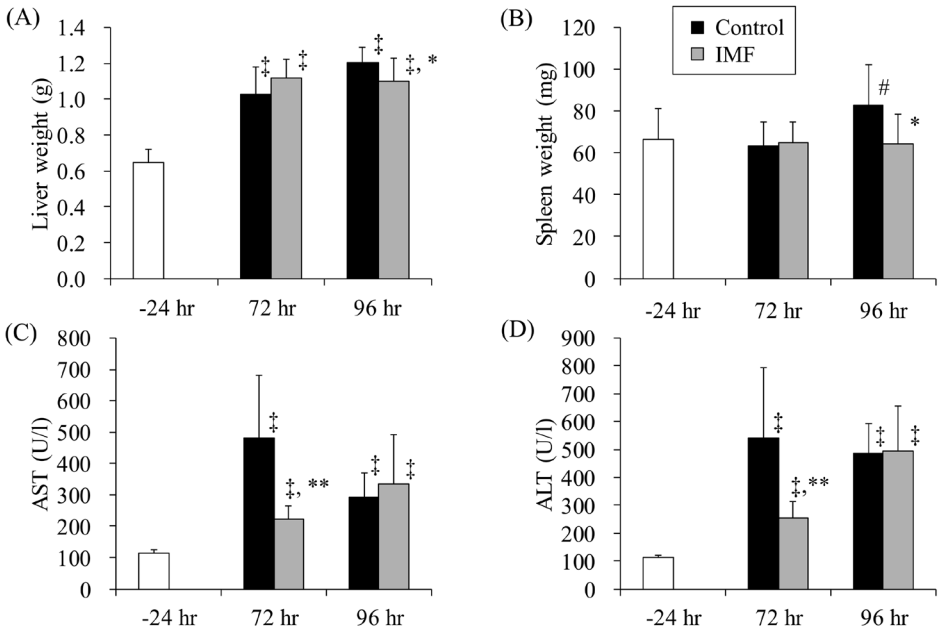

Fig. 5. Incidence of remote organ injuries in experiment 2.

(A) Liver and (B) spleen weights and plasma (C) AST and (D) ALT levels.
Values are means ± standard deviations. #p<0.1, vs. −24 hr. †p<0.05, vs. −24 hr. ‡p<0.01, vs. −24 hr. *p<0.05, vs. control group. **p<0.01, vs. control group.

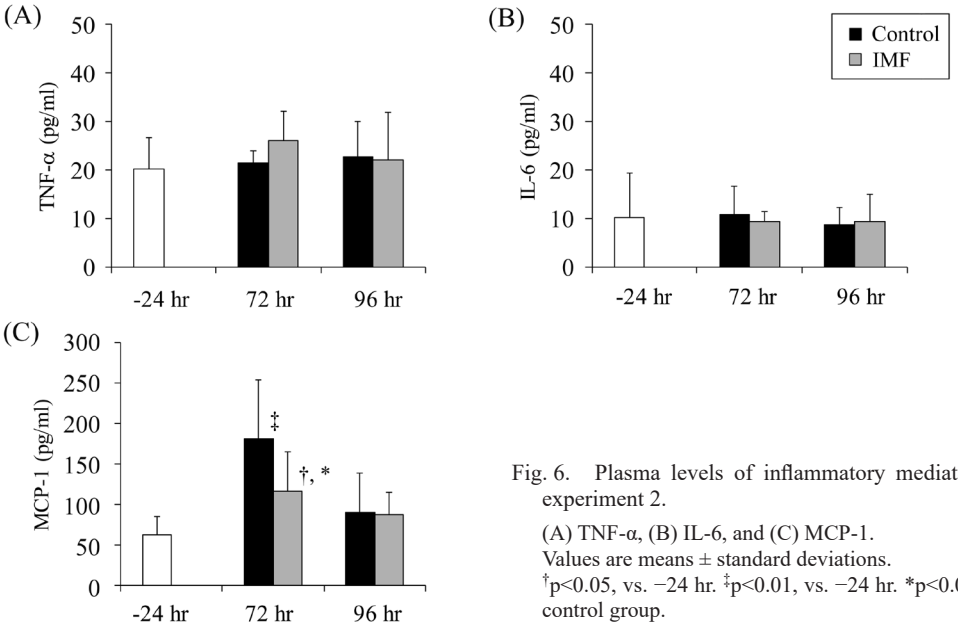

Fig. 6. Plasma levels of inflammatory mediators in experiment 2.

(A) TNF-α, (B) IL-6, and (C) MCP-1.
Values are means ± standard deviations.
†p<0.05, vs. −24 hr. ‡p<0.01, vs. −24 hr. *p<0.05, vs. control group.

to play key roles in the pathogenesis and progression of acute pancreatitis [20], and systemic inflammation has been known as a cause of remote organ injuries in SAP as well as the early predictor of severity in human acute pancreatitis [21, 22]. The present study demonstrated that remote organ injuries, represented as splenomegaly, hepatomegaly, and elevation of hepatic enzymes, developed and were accompanied by acute pancreatitis induced by feeding with the CDE diet. It has been reported that transient splenomegaly was also seen in severe acute pancreatitis in clinical settings and that patients with severe splenomegaly at an early time point had longer hospital stays [23]. Moreover, hepatic enzymes were

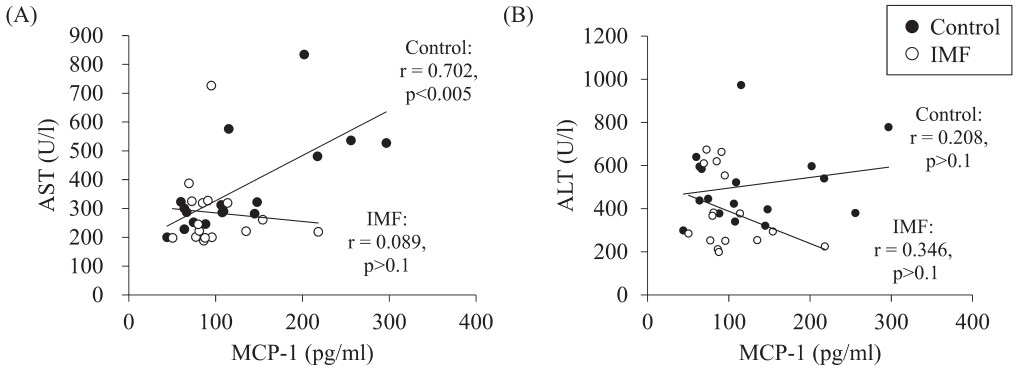

Fig. 7. Correlations between MCP-1 and AST or ALT in experiment 2.

demonstrated to strongly correlate with MCP-1 in the present study. MCP-1 is a family member of the C-C chemokines, and it has been thought to be an important inflammatory mediator in the process of acute pancreatitis and to promote distant organ failure [20, 24]. In clinical settings, serum MCP-1 has been reported to increase in patients with complicated acute pancreatitis, and MCP-1 has been thought to play a pivotal role in the pathological mechanism of complicated pancreatitis [24, 25]. The results of the present study suggest that MCP-1 could be a predictive and prognostic molecular marker for remote organ injuries and severe pancreatitis.

We demonstrated for the first time that intake of the IMF after the development of AP improved systemic inflammation and inflammation-related remote organ injuries. Some components in the IMF have been demonstrated to have anti-inflammatory effects and are considered to be responsible for the improvement in splenomegaly, hepatomegaly, and liver injury. Whey-hydrolyzed peptides suppress increases in plasma alanine and aspartate aminotransferase activities as well as TNF-α and IL-6 levels in concanavalin A-induced and D-galactosamine-induced hepatitis models [26]. Whey-hydrolyzed peptides also suppress IL-1β and TNF-α mRNA expression as well as nuclear factor-κB (NF-κB) and Stat 3 activation in the liver and IL-6 mRNA expression in the spleen in a concanavalin A-induced hepatitis model [26]. Another whey-peptide-based enteral formula has also been shown to protect against lipopolysaccharide-induced inflammatory responses [27].

The other components of the IMF, such as fermented milk, ω-3 polyunsaturated fatty acids, antioxidant vitamins, and minerals, were demonstrated to have anti-inflammatory effects. Fermented milk, such as yogurt, and lactic acid bacteria have been reported to have anti-inflammatory effects [28, 29], and they are known to modulate the immune reaction and improve intestinal environment. The gut microflora has been demonstrated to be altered in patients with severe SIRS, and an abnormal gut microflora is thought to affect the systemic inflammatory response after severe insult [30, 31]. We speculate that the fermented milk used here was also involved in the anti-inflammatory effects of the IMF, and further investigation is needed. Omega-3 polyunsaturated fatty acids, particularly eicosapentaenoic acid (EPA), have also been demonstrated to have anti-catabolic effects by reducing the inflammatory state [32]. Antioxidant vitamins and minerals have been shown to attenuate systemic inflammatory responses and to be associated with a reduction in mortality in critically ill patients [33]. Isomaltulose is a low-glycemic disaccharide. It is completely hydrolyzed into glucose and fructose, although slower than sucrose, and absorbed by the small intestine [34, 35]. Isomaltulose has been shown to be less postprandial hyperglycemic and hyperinsulinemic, and it is thought to reduce the burden on pancreatic β-cells [35]. Therefore, it is likely that all of these factors contribute to the improvement of remote organ injuries.

We believe that the IMF also has another benefit for SAP. Whey-hydrolyzed peptides have been shown to hardly have any effect on pancreatic secretion, while intragastric administration of casein or whey protein has been shown to significantly increase pancreatic enzyme secretion [36]. The source of the protein in the IMF was partially replaced with whey-hydrolyzed peptides, so the IMF stimulates pancreatic secretion less than the control formula.

In the present study, the mice ate the respective diets orally, and food intake was *ad libitum*. Further studies in which food is administered via jejunostomy or gastrostomy are required. In practice, patients who cannot ingest normal food orally but still can use the gut as a nutritional route receive an enteral diet via a nasogastric tube, nasoenteric tube, gastrostomy, or jejunostomy. Enteral nutrition in SAP is recommended to be initiated early by infusion through the jejunum to minimize pancreatic stress [9, 10]. Therefore, the contribution of the IMF to SAP outcomes would be revealed more clearly in clinical settings where an adequate volume of the IMF could be administered via gastrostomy or jejunostomy.

In conclusion, nutritional management with the IMF may be useful for alleviating remote organ injuries after severe acute pancreatitis. Although further studies are needed and clinical trials will be necessary to establish the effects in humans, the findings obtained in the present study will provide some insight into new nutritional therapies for severe acute pancreatitis.

ACKNOWLEDGEMENTS

All contributors met the criteria for authorship. KN was involved in the design of the study and in acquisition, analysis, and interpretation of data; KN also drafted the manuscript. KF gave significant advice, provided technical help, and revised the manuscript for this study. AS participated in the design of the study and in acquisition and analysis of data. TY participated in the design of the study and in acquisition and interpretation of data. KN, AS, and TY are employees of Meiji Co., Ltd. The funding source for this study was Meiji Co., Ltd. All authors have read and approved the final version of manuscript.

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