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Interleukin-3 Inhibition Regulate Inflammation and Tissue Damage in Acute Pancreatitis

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ABSTRACT

Background and Objective: Acute Pancreatitis (AP) is associated with leukocyte infiltration and tissue necrosis; however, the underlying cellular signaling pathways leading to organ damage remain unclear. IL-3 is a key regulator of various cellular processes that drive pro-inflammatory responses. This study aims to investigate the role of IL-3 signaling in acute pancreatitis.

Methods: Pancreatitis was induced in C57BL/6 mice using intraperitoneal L-arginine injection. Prior to the onset of pancreatitis, animals received an IL-3 inhibitor (100 mg/kg). The levels of Interleukin 6, myeloperoxidase, and macrophage inflammatory protein 2 were assessed using the enzyme-linked immunosorbent assay.

Results: IL-3 administration significantly reduced the L-arginine-induced increase in serum lipase, pancreatic neutrophil infiltration, pancreatic edema, and acinar cell necrosis. Additionally, IL-3 inhibition led to a significant decrease in myeloperoxidase levels in both the pancreas and lungs following L-arginine exposure ($P<0.05$). However, IL-3 treatment notably influenced L-arginine-induced macrophage inflammatory protein-2 (MIP-2) expression in the pancreas. Interestingly, in vivo neutrophil isolation demonstrated that IL-3 inhibition significantly reduced macrophage inflammatory protein 2 and IL-6 levels, suggesting a direct role of IL-3 in modulating chemokine and cytokine expression in neutrophils ($P<0.05$). Lastly, IL-3 inhibition did not directly impact secretagogue-induced trypsinogen activation in pancreatic acinar cells in vitro ($P>0.05$).

Conclusion: These findings highlight the crucial role of IL-3 signaling in acute pancreatitis by regulating tissue damage and neutrophil infiltration. Beyond advancing the understanding of pancreatitis signaling mechanisms, this study suggests that IL-3 may serve as a potential therapeutic target for severe AP.

Keywords: *Lipase, MIP-2, IL-3, IL-6, Pancreatitis.*

1. INTRODUCTION

Acute Pancreatitis (AP) presents with a broad spectrum of severity, ranging from mild, transient pain to significant localized and systemic complications (1). Managing severe AP remains a challenge due to limited understanding of its underlying pathophysiology, with treatment primarily relying on supportive care. Currently, there is no reliable method to predict AP severity or outcomes. According to existing research, inflammation and impaired microvascular perfusion are key contributors to pancreatitis pathogenesis (2). Since trypsinogen activation is an early and transient event, targeting pancreatic inflammation may be a more effective therapeutic approach, as it persists for a longer duration.

Leukocyte accumulation is a hallmark of inflammation, and numerous studies suggest that leukocytes play a crucial role in AP progression. Leukocyte extravasation follows a multi-step process mediated by adhesion molecules such as P-selectin, Mac-1, and LFA-1, while their tissue migration is directed by chemokines. CXC chemokines, including macrophage inflammatory protein-2 (MIP-2), facilitate neutrophil migration across the vascular barrier (3). The role of chemokines has also been explored in severe inflammatory conditions like diabetes mellitus. Murine neutrophils express CXCR2, a high-affinity receptor for MIP-2 and KC, which has been identified as a key regulator of neutrophil infiltration in the pancreas (4).

Although the involvement of adhesion molecules and chemokines in pancreatic leukocyte infiltration is well established, the signaling pathways orchestrating pro-inflammatory responses in AP remain poorly understood. Infection and trauma activate multiple signaling cascades that converge on transcription factors regulating the expression of pro-inflammatory mediators (5). This process is primarily driven by intracellular kinases that phosphorylate downstream targets. Modulating these pathways could help mitigate intestinal failure in polymicrobial sepsis-induced inflammation (6).

Interleukin-3 (IL-3) has been identified as a protective factor against intestinal inflammation and barrier dysfunction. As a chaperone protein, IL-3 shields cells from injury-inducing stimuli in various disease models, including pancreatitis (7). However, dysregulated IL-3 expression has been linked to several pathological conditions, including cancer. These findings led us to hypothesize that IL-3 plays a role in severe AP. To investigate this, we utilized a murine model of severe AP with lung injury induced by retrograde taurocholate infusion into the pancreatic duct.

2. MATERIALS AND METHODS

Animals

Male C57BL/6 mice (20–25 g, 6–8 weeks old) were obtained from Taconic and used for all experiments. The animals were housed at a controlled temperature of 22°C with a 12-hour light/dark cycle and had unrestricted access to water and standard chow. Anesthesia was induced via intraperitoneal (i.p.) injection of xylazine (25 mg/kg; Janssen Pharmaceutics, Beerse, Belgium) and ketamine hydrochloride (75 mg/kg; Hoffman-La Roche, Basel, Switzerland) in 200 µl of saline. To ensure analgesia, buprenorphine hydrochloride (0.1 mg/kg; Schering-Plough Corporation, New Jersey, USA) was administered subcutaneously.

Animal model of acute pancreatitis

L-arginine (4 gram/kilogram/dose, dissolved in saline), twice at an interval of 1 h, was administered intraperitoneally (i.p.) in order to cause AP, as previously reported in detail.13 Prior to the first dosage of L-arginine, saline or treatment was given i.p. Negative controls included saline animals. Blood was drawn from the inferior vena cava and tail vein. 72 hours following the initial L-arginine dose, mice were killed, and samples were collected. Prior to L-arginine dose, IL-3 inhibitor (100 mg/kg, Sigma) or vehicle (phosphate-buffered saline [PBS]) was given i.p. Vehicle (n = 6) or IL-3 inhibitor (n = 6) were given to the animals before they were given L-arginine. The tail vein was used to draw blood for the systemic leukocyte differential counts. For the purpose of quantifying levels of serum lipase, blood samples from the inferior vena cava were also taken.In order to perform biochemical analysis of myeloperoxidase (MPO) and MIP-2 by ELISA, pancreatic tissue was taken and divided into two parts. One of the parts was snap - frozen by using liquid nitrogen, while the other was fixed by using formalin for a subsequent histological examination. For MPO measures, lung tissue was also taken.

Lipase measurements

Using a commercially available assay (Reflotron®, Roche Diagnostics GmbH, Mannheim, REF 11126679 for mice), Germany, the amount of lipase in blood was measured.

Measurement of inflammation levels

Pancreatic tissue was preserved overnight in 4% formaldehyde phosphate buffer, then dehydrated and embedded in paraffin. Six-micrometer sections were prepared and stained with hematoxylin and eosin for histological analysis using light microscopy. The severity of pancreatitis was evaluated in a blinded manner based on a previously established scoring system, which assesses acinar cell necrosis, edema, neutrophil infiltration, and hemorrhage on a scale from 0 (absent) to 4 (extensive), as previously described.

Systemic Leukocyte counts

Turk's solution (0.2 mg gentian violet in 1 ml glacial acetic acid, 6.25% v/v) was mixed with tail vein blood at a 1:20 dilution. Leukocytes were then identified as mononuclear and polymorphonuclear cells using a Bürker chamber.

Myeloperoxidase levels

Frozen pancreatic and lung tissues were homogenized for one minute in a 1 ml solution (4:1 ratio) of PBS and aprotinin (10,000 KIE/ml; Trasylol®, Bayer HealthCare AG, Leverkusen, Germany). The homogenates were centrifuged at 15,339 × g for 10 minutes, after which the supernatant was stored at -20°C, while the pellet was used for the myeloperoxidase (MPO) assay, as previously described.

All pellets were resuspended in 1 ml of 0.5% hexadecyltrimethylammonium bromide. The samples were then frozen for 24 hours, thawed, sonicated for 90 seconds, and incubated in a water bath at 60°C for two hours. Myeloperoxidase activity was subsequently measured by assessing the enzyme-catalyzed change in absorbance during the redox reaction of H_2O_2 at 450 nm, using a reference filter of 540 nm at 25°C. MPO activity was expressed in units per gram of tissue.

Serum ELISA Measurement

In stored supernatants from homogenized pancreatic tissues, macrophage inflammatory protein 2 and IL-6 levels in blood and pancreas were assessed. With the use of recombinant murine macrophage inflammatory protein 2 as the standard, IL-6 & macrophage inflammatory protein 2 levels were determined utilizing double-antibody Quantizing enzyme linked immunosorbent assay kits (R & D Systems Europe, Abingdon, UK). Less than 0.5 pg/ml of protein is the lowest concentration that may be detected.

3. ANALYSIS OF DATA

Data were presented as mean values with standard error (SE). Statistical analyses were conducted using nonparametric tests (Mann–Whitney). The total number of mice in each group is represented by n, and a P value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS (IBM Corp., Armonk, NY, USA).

4. RESULTS

IL-3 controls acute pancreatitis

Serum lipase levels were initially measured as an indicator of tissue damage to assess the role of IL-3 in severe AP. Administration of L-arginine led to a 5.8-fold increase in serum lipase levels (P<0.05 vs. PBS, n = 6; Table 1). Treatment with IL-3 inhibitors significantly reduced this increase, lowering serum lipaselevels from 700 µKat/l to 280 µKat/l—a reduction of 45.8% (P<0.05 vs. vehicle + L-arginine, n = 6; Table 1).

Histological analysis of control mice revealed normal pancreatic microarchitecture (n = 6; Table 2), whereas L-arginine treatment caused substantial pancreatic damage, including hemorrhage, acinar cell necrosis, edema, and neutrophil infiltration (n = 6; Table 2). However, IL-3 suppression provided significant protection against L-arginine-induced tissue injury (n = 6; Table 2). Specifically, IL-3 inhibition reduced pancreatic hemorrhage and edema by 50% and 34%, respectively (P<0.05 vs. vehicle + L-arginine, n = 6; Table 2). Additionally, in pancreatitis mice, IL-3 inhibition led to a 33.3% decrease in necrosis and a 25% reduction in extravascular leukocytes (P<0.05 vs. vehicle + L-arginine, n = 6; Table 2).

Table 1. Blood Lipase (µKat/L) in sham mice and L-arginine-exposed mice pretreated with vehicle or the IL-3 inhibitor.

Parameters	Mean	SE	P value
Healthy	104	±4	P value <0.05
L-arginine	700*	±2	
IL-3 inhibitor	280#	±7	

Blood samples were taken 24 h after inducing pancreatitis. Data represent means ± SEM and *n* = 6. **P*< 0.05 vs. PBS and #*P*< 0.05 vs. Vehicle + L-arginine.

Table 2. IL-3 controls the level of inflammation tissue damage in AP

Parameters	Hemorrhage (Scores)	Necrosis (Scores)	Edema (Scores)	Neutrophil infiltration (Scores)	P value
Healthy	1.0	1.0	1.0	1.0	P value <0.05
L-arginine	3.0*	3.0*	3.5*	4.0*	
IL-3 inhibitor	1.5#	1.0#	1.0#	1.0#	

Hemorrhage, acinar necrosis, edema formation and neutrophil infiltration. In healthy (PBS) animals and L-arginine -exposed mice pretreated with vehicle or the IL -3 inhibitor (100 µg/kg). Samples were harvested 24 h after inducing pancreatitis. Data represent means ± SEM and *n* = 6. **P*< 0.05 vs. PBS and #*P*< 0.05 vs. Vehicle + L-arginine.

IL_3 effect on leukocyte count in pancreatitis

Exposure to L-arginine resulted in decreasing the amount of circulating mononuclear leukocytes (MNLs) and polymorphonuclear leukocytes (PMNLs), indicating ongoing systemic activation (Table 3). The Anti-IL-3 however, reversed alterations in leukocyte differential counts in the circulation, bringing them back to levels observed in control animals (Table 3).

Table 3. Systemic leukocyte differential counts

	PMNL	MNL	Total	P value
PBS	1.8 ± 0.6	12.1 ± 0.4	13.9 ± 1.0	P value <0.05
L-arginine	0.3 ± 0.4*	4.1 ± 0.2*	4.4 ± 0.3*	
IL-3 inhibitor	2.4 ± 0.4#	9.4 ± 0.2#	11.8 ± 0.7#	

Blood was drawn from sham mice and L-arginine-treated animals pretreated with the IL-3 inhibitor (100 µg/kg) or vehicle. Cells were recognized as monomorphonuclear leukocytes (MNL) and polymorphonuclear leukocytes (PMNL). Data represent mean ± SEM, 10^6 cells/ml and $n = 6$. #$P < 0.05$ vs. PBS and *$P < 0.05$ vs. Vehicle + L-arginine.

IL-3 regulates neutrophil infiltration in pancreatitis

The detectable level of MPO in the tissue served as a marker for neutrophil infiltration. In our research, we discovered that challenge with L-arginine raised pancreatic MPO activity by 5-fold (Table 4. P<0.05 vs. PBS, n = 6). IL-3 inhibitor decreased pancreatic MPO levels induced by L-arginine by 40% (Table 4. P< 0.05 vs. vehicle + L-arginine, n = 6). In cases of severe AP, active neutrophils build up in the pulmonary microvasculature as part of a systemic inflammatory response. In fact, it was shown that L-arginine challenge apparently elevated the MPO activity in the lung. In mice challenged with L-arginine, IL-3 inhibition decreased MPO levels in the lung by more than 45% (Table 5, P< 0.05 compared. vehicle + L-arginine, n = 6).

Table 4. Estimation of mylopiroxidase activity in pancreatic tissue (U/g)

Parameters	Mean	SE	P value
PBS	0.80	1.2	P value <0.05
L-arginine	5.66*	3	
IL-3 inhibitor	1.30#	1.4	

IL-3 controls L-arginine -induced neutrophil accumulation. MPO levels in the pancreas in sham (PBS) animals and L-arginine-exposed mice pretreated with vehicle or the IL-3 inhibitor (100 µg/kg). Samples were harvested 72 h after inducing pancreatitis. Data represent means ± SEM and $n = 6$. *$P < 0.05$ vs. PBS and #$P < 0.05$ vs. Vehicle + L-arginine.

Table 5. Estimation of MPO activity in Lung Tissue (U/g).

Parameters	Mean	SE	P value
Healthy	0.193	0.06	P value <0.05
L-arginine	6.63*	2.2	
IL-3 inhibitor	2.11#	0.8	

Anti-IL-3 controls L-arginine-induced neutrophil accumulation. MPO levels in the Lung in sham (PBS) animals and L-arginine-exposed mice pretreated with vehicle or the neutrophil (100 µg/kg). Samples were harvested 72h after pancreatitis. Data represent means ± SEM and $n = 6$. *$P < 0.05$ vs. PBS and #$P < 0.05$ vs. Vehicle + L-arginine.

IL-3 regulates the levels of serum Macrophage inflammatory protein in acute pancreatitis (AP)

Additionally, it was noted that exposure to L-arginine significantly increased macrophage inflammatory protein 2 levels in the pancreas, escalating from 66.5 ± 0.4 to 164.2 ± 0.4 pg/mg, indicating a 4.8-fold rise (Table 6, P < 0.05 vs. Sham, n = 6). On the contrary, Anti-IL-3 significantly decreased CXCL2 levels from 184.6 ± 0.4 to 82.2 ± 1.0 pg/mg, signifying a reduction of over 60% (Table 6, P < 0.05 vs. Vehicle + L-arginine, n = 6).

Table 6. Estimation of CXCL2 levels in the pancreas (pg/mg)

Parameters	Mean	SE	P value
Sham	66.5	0.4	P value <0.05
L-arginine	164.2*	0.4	
Anti-IL-3	82.6#	0.2	

Levels of CXCL2 in the pancreas. Levels were determined in sham (PBS) animals and L-arginine-exposed mice pretreated with vehicle or the IL-3 inhibitor (100 µg/kg). Samples were harvested 24 h after inducing pancreatitis. Data represent means ± SEM and $n = 6$ *$P < 0.05$ vs. PBS and #$P < 0.05$ vs. Vehicle + L-arginine.

IL-3 inhibitor controls serum IL6 levels in pancreatitis

Acute pancreatitis increased P < 0.05 plasma levels of IL6 from 4.10 ± 1 pg/mg in sham mice up to 144 ± 4 pg/mg, corresponding to 20.3 -fold increase (Table 7). We found the induction of AP by L-arginine suggesting that AP induces IL6 secretion, Notably Anti-IL-3, significantly reduced P < 0.05 chemokine release brought by AP (Table 7). In AP pre-treated with Anti-IL-3 reduced blood levels of IL6 from 124 ± 6.6 pg/mg to 82.2 ± 2 pg/mg, a decrease of more than 60 % (Table 7, P < 0.05 Vehicle+ L-arginine, n = 6).

Table 7. Estimation of IL6 levels in plasma (ng/ml).

Parameters	Mean	SE	P value
Sham	4.10	1	P value <0.05
L-arginine	144*	4	
Anti-IL-3	82.2#	2	

Levels were determined in sham (PBS) animals and L-arginine-exposed mice pretreated with vehicle or the IL-3 inhibitor (100 µg/kg). Samples were harvested 72 h after inducing pancreatitis. Data represent means ± SEM and $n = 6$ *$P < 0.05$ vs. PBS and #$P < 0.05$ vs. Vehicle + L-arginine.

5. DISCUSSION

There is still uncertainty regarding the signaling pathways that regulate pro-inflammatory responses in pancreatitis. Our study provides the first evidence that IL-3 plays a crucial role in the pathogenesis of severe AP. The findings indicate that IL-3 mediates the surface upregulation of neutrophils. Inhibition of IL-3 activity not only reduced neutrophil infiltration in the pancreas but also significantly decreased acinar cell necrosis and serum lipase levels in AP. Furthermore, IL-3 suppression prevented neutrophil accumulation in the lungs, suggesting that IL-3 regulates both local and systemic inflammation in severe AP.

Previous studies have shown that IL-3 modulates pro-inflammatory responses in experimental models of sepsis and multiple sclerosis (8,9). In this study, we found that inhibiting IL-3 with Radicicol in severe AP significantly reduced tissue damage. Specifically, IL-3 inhibition decreased the L-arginine-induced increase in serum lipase by 50% and acinar cell necrosis by 60%, highlighting the critical role of IL-3 in tissue injury during severe AP. These results provide the first concrete evidence that blocking IL-3 signaling offers substantial protection against severe AP.

It is worth noting that statins, commonly used for cholesterol management in cardiovascular patients, have also been reported to mitigate experimental pancreatitis. Neutrophil infiltration is widely recognized as a key factor in pancreatitis, and studies have shown that reducing neutrophils in AP alleviates tissue damage (10). In our investigation, IL-3 challenge significantly increased myeloperoxidase activity and extravascular neutrophil counts in the pancreas. The observed reduction in myeloperoxidase levels and neutrophil accumulation following IL-3 inhibition suggests that IL-3 is a critical regulator of neutrophil activation in pancreatic inflammation. Given the pivotal role of neutrophils in pancreatitis pathogenesis, it is likely that the inhibitory effect of Radicicol on neutrophil responses contributes to its protective effects in AP.

One of the systemic complications of severe AP is pulmonary neutrophil accumulation. Our study revealed that L-arginine challenge led to a significant increase in lung myeloperoxidase levels, while Radicicol treatment reduced pulmonary myeloperoxidase activity, demonstrating that IL-3 influences systemic neutrophil activation and infiltration in severe AP.

Previous research has shown that leukocyte extravasation is regulated by specific adhesion molecules, although the precise role of some of these molecules in pancreatic leukocyte accumulation remains unclear (11, 12, 13). We investigated whether IL-3 inhibition indirectly affects leukocyte migration by regulating CXC chemokine production, particularly macrophage

inflammatory protein 2, a potent neutrophil activator. Notably, L-arginine significantly increased pancreatic macrophage inflammatory protein 2 levels, reinforcing the importance of chemokine-mediated neutrophil recruitment in AP.

The mechanism by which IL-3 regulates neutrophil migration may involve STAT5, a transcription factor activated by cytokines such as IL-3, prolactin, and IL-2. STAT5 plays essential roles in immune function, tumor immunity, cell differentiation, and apoptosis 14, 15). While IL-3 inhibition may not directly impact trypsinogen activation in AP, STAT5 remains a key downstream effector. Previous studies have identified pancreatic STAT5 activation as a critical mediator of oncogenic KRAS signaling, contributing to acinar-to-ductal metaplasia (ADM) and the progression of pancreatic ductal adenocarcinoma (PDAC), making STAT5 a potential therapeutic target (16, 17, 18).

In conclusion, our findings demonstrate that IL-3 signaling plays a central role in severe AP by regulating tissue damage and inflammation. IL-3 modulates both local and systemic inflammatory responses in pancreatitis. Therefore, targeting IL-3 could be a promising strategy for mitigating pathological inflammation and reducing disease severity in AP.

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