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Interleukin-3 inhibition alleviates inflammation and tissue damage in severe acute pancreatitis

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Abstract

Background and objective: Acute Pancreatitis (AP) is linked with leukocyte infiltration and tissue necrosis, however the cellular signaling pathways in pancreas which is leading to organ destruction remain unknown. IL-3 is a powerful controller of different cellular processes that promote pro-inflammatory activities. In this study, we investigated IL-3 signaling role of in acute pancreatitis.

Methods: In C57BL/6 mice, pancreatitis was triggered by L-arginine injection (i.p.). Prior to development of pancreatitis, animals were given an IL-3 inhibitor (100 mg/kg). IL-6, MPO, and MIP-2 levels were measured by ELISA.

Results: The administration of IL-3 significantly reduced the rise in L-arginine in serum amylase, pancreatic neutrophil infiltration, pancreatic edema formation, an acinar cell necrosis. Furthermore, in response to L-arginine challenge, inhibition of IL-3 caused a decrement in the MPO levels in both pancreas and lung (P <0.05). However, IL-3 therapy had a significant impact on L-arginine, provoked macrophage inflammatory protein-2 (MIP-2) induction in the pancreas. Interestingly, in vivo isolation of neutrophils revealed that inhibition of IL-3 significantly reduced MIP-2 and IL-6 pointing to a direct function for IL-3 in regulating chemokine and cytokine expression in neutrophils (P <0.05). Finally, trypsinogen activation induced by secretagogue in acinar calls of pancreas in vitro, was not directly affected by the inhibition of IL-3 (P >0.05).

Conclusion: These findings show that IL-3 signaling has an essential role in acute pancreatitis by controlling tissue injury and neutrophil infiltration thus, in addition to clarifying pancreatitis signaling processes, our findings also raise the possibility that IL-3 can represent a new target in the treatment of severe AP.

Keywords: Amylase; MIP-2; IL-3; IL-6; Pancreatitis.

Introduction

(AP) can manifest with a variety of illness severity, from mild, transient pain to localized and systemic consequences.(1) Clinical care of patients having severe AP presents an important challenge to clinicians because to the inadequate information regarding the underlying pathophysiology, which is usually addressed by supportive therapies. Till now there is no reliable way to gauge the outcome and severity of AP. According to the literature, inflammation, and reduced microvascular perfusion are all key factors in the pathophysiology of pancreatitis.(2) Knowing that trypsinogen activation may be an early and temporary event, inflammation in the pancreas may be a more sensible target for therapy because it lasts longer.(3,4)

Leukocyte accumulation is a sign of inflammation, and several studies have

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indicated that leukocytes play a significant role in the development of AP[3]. Leukocyte extravasation is a multi-step, sequential process mediated by distinct adhesion molecules like P-selectin, Mac-1, and LFA-1.[5] Leukocyte tissue navigation is controlled by released chemokines.[6] CXC chemokines promote neutrophil extravascular migration, like macrophage inflammatory protein-2 (MIP-2).[7] Also the role of chemokines has been studied in severe inflammation such diabetes mellitus.[8] Murine neutrophils have a high affinity receptor for MIP-2 and KC called CXCR2.[9]

And it has been demonstrated that CXCR2 is essential in sustaining neutrophil infiltration in the pancreas.[10] However. it is well understood that certain adhesion molecules and chemoattractant play a part in leukocyte infiltration in the pancreas, our knowledge of the signaling pathways that coordinate pro-inflammatory responses in AP is still restricted. Infection and trauma trigger multiple signaling cascades that converge on specific transcription factors that regulate gene expression of pro-inflammatory chemicals. This signal transmission is mainly controlled by intracellular kinases phosphorylating down-stream targets. It may be possible to ameliorate intestinal failure in polymicrobial sepsis inflammation.[11]

By targeting IL-3, which defends against intestinal inflammation and leakage. Interleukin-3 (Il-3) are one of the chaperone proteins that defend live cells in opposition to injury-inducing stimuli in a number of disease models, including pancreatitis. However, it has been discovered that numerous disease states, including cancer, exhibit dysregulated expression of IL-3.[12] These factors led us to the hypothesis that IL-3 contribute to severe AP. We applied a mouse model of severe AP with lung damage based on retrograde taurocholate infusion in the pancreatic duct.

Methods

Study Design

A descriptive, original and experimental study was conducted recruiting animal experiment conducted on 18 male mice divided in to three groups. This study conducted in Hawler Medical University - College of Pharmacy animal house. The study was carried out from June 2, 2023, to December 27, 2023. Sample type was blood and tissue selected. Inclusion criteria only 6–8 weeks male mice, Exclusion criteria Female and mice were aged more than 8 weeks or less than 6 weeks.

Animals

Taconic-purchased C57BL/6 male mice, weighing 20–25 g (6–8 weeks), were used in all investigations. The animals were kept in a temperature of 22°C with a 12 h light/ dark cycle fed water and standard chow ad libitum. Based on the animal welfare standards legislation, and the Regional Animal Experimentation Ethical Committee has been given its approval REF No. (HMU-EC-Ph 07042023-213). Mice were anesthetized by administering 25 mg/kg of xylazine (Janssen Pharmaceutics, Beerse, Belgium) and 75 mg/kg of ketamine hydrochloride (Hoffman-La Roche, Basel, Switzerland) intraperitoneally (i.p.) in 200 µl of saline. Buprenorphine hydrochloride 0.1 mg/kg (Schering-Plough Corporation, New Jersey, USA) was subcutaneously injected to provide analgesia (Schering-Plough Corporation, New Jersey, USA).

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.

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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 amylase, 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. This study assessed whether Anti-IL3 improves AP by carefully defining variables, outcomes, and diagnostic criteria, this research insures valid and reliable conclusions.

Amylase measurements

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

After application to the test strip, the sample flows into the reaction zone, where, in the case of blood samples, the separation of the erythrocytes from the plasma occurs. The salivary gland a-amylase is inhibited by 2 monoclonal antibodies. The pancreatic a-amylase cleaves the substrate indolyl-a, D-maltoheptaoside; the a-glucosidase contained in the test leads to the production of indoxyl and glucose. The released indoxyl is coupled with 2-methoxy-4-morpholinophenyldiazoniumtetrachloroz-inkate to give a purple dye. The amount of dye formed per unit of time is directly proportional to the a-amylase activity:

indolyl-a, D-maltoheptaoside pancreatic a-amylase indoxyl + glucose a-glucosidase indoxyl + 2-methoxy-4-morpholino- → purple dye phenyldiazoniumtetrachlorozincate.

The enzyme activity is measured kinetically at a wavelength of 567 nm and 37 °C, and is displayed after about 175 seconds in U/L or ukat/L.

Tissue preparation

Tissue being preserved in 4% formaldehyde phosphate buffer for a whole night, pancreas samples were dried and paraffin embedded. Light microscopy was used to analyze six micrometer sections that had been stained with hematoxylin and eosin. Pancreatitis severity was assessed in a blinded way through the use of a previously developed scoring system including acinar cell necrosis, oedema, neutrophil infiltrate and hemorrhage on a 0 (absent) to four (extensive) scale as formerly explained in detail and sample was determined according to previous study.[14]

Systemic Leukocyte counts

Turks' solution (0.2 mg gentian violet in 1 ml glacial acetic acid, 6.25% v/v) and tail vein blood were mixed in a 1:20 dilution. In a Burker chamber, leucocytes were recognized as monomorphonuclear and polymorphonuclear cells.

MPO activity

For one minute, the frozen pancreatic and lung tissues were homogenized using a 1 ml combination (4:1) of PBS and aprotinin 10,000 KIE ml-1 (Trasylol®, Bayer HealthCare AG, Leverkusen, Germany). The homogenate samples were centrifuged (15339 g, 10 min), and the supernatant was kept at - 20 °C, and the pellet was utilized for the MPO test as formerly explained.[15] All pellets were mixed with 1 ml of 0.5% hexadecyltrimethylammonium bromide. The sample was then defrosted for 24 hours, thawed, sonicated for 90 seconds, and placed in a water bath at 60°C for two hours, after which the MPO activity of the supernatant was measured. The MPO-catalyzed change in absorbance in the redox reaction of H_2O_2 (450 nm, with a reference filter of 540 nm, 25°C) was used to spectrophotometrically measure the enzyme activity. MPO units per g of tissue are used to express values.

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MIP-2 and IL-6 levels measurement by ELISA

In stored supernatants from homogenized pancreatic tissues, MIP-2 and IL-6 levels in blood and pancreas were assessed. With the use of recombinant murine MIP-2 as the standard, IL-6 &MIP-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.

Trypsinogen activation in isolated acinar cells

As previously mentioned, collagenase digestion and mild shearing were utilized to prepare pancreatic acini cells.[16] The cells were subjected to a 150 µm cell strainer (Partec, England) after being immersed in HEPES-Ringer buffer (pH 7.4) that had been saturated with oxygen. Single-cell acinar cells (1 × 10^7 cells/well) were treated for 30 minutes with either vehicle or radicicol (200 µM) before being stimulated in duplicate with 100 nm cerulein (37°C, 30 min).

Following the removal of the buffer solution, the cells were rinsed two times with buffer (pH 6.5) containing 5 mM 3-(morpholino) propane sulphonic acid (MOPS), 250 mM sucrose, and 1 mM MgSO4. Using a potter Elvejham-style glass homogenizer, the cells were then homogenized in cold (4°C), MOPS buffer. Following a centrifugation (56×g, 5 min) of the resultant homogenate, the supernatant was employed for an experiment. Boc-Glu-Ala-Arg-MCA was used as the substrate for the fluorometric measurement of trypsin activity that was previously discussed[17, p. 199]. Assay buffer (50 mM Tris, 150 mM NaCl, 1 mM CaCl2, and 0.1% BSA, pH 8.0) was added to a cuvette containing the acinar cell homogenate for this purpose. Substrate was used to start the reaction, and the fluorescence emitted at 440 nm was observed in the reaction to stimulation at 380 nm. A standard curve produced by measuring pure trypsin was used to quantify the trypsin levels (pg/ml). Trypan blue dye exclusion showed that the pancreatic acinar cells had a viability of greater than 95%.

Analysis of data

The data is shown as mean values ± SEM. Non-parametrical tests (Mann-Whitney) were used for statistical assessments, represents the number of animals, and P <0.05 was regarded as significant. Statistical analysis was performed by use of SPSS (IBM Corp., Armonk, N.Y., USA).

Results

IL-3 controls tissue damage in pancreatitis

Serum amylase levels were initially assessed as a marker of tissue damage to investigate the involvement of IL-3 in severe AP. We found that administering L-arginine caused a 5.8-fold rise in serum amylase levels (Table 1, P <0.05 vs. Sham, n = 6). The serum amylase levels caused by L-arginine dropped as a result of treatment with the IL-3 inhibitors from 728 µKat/l to 261 µKat/l, or a reduction of 35.8% (Table. 1, P <0.05 vs. vehicle + L-arginine, n = 6). The pancreatic microarchitecture of control mice was normal, according to an analysis of tissue morphology (Table 2, n = 6), but L-arginine significantly damaged the pancreatic tissue structure, causing hemorrhage, acinar cell necrosis, edema formation, and neutrophil accumulation (Table 2, n = 6). We discovered that suppressing of IL -3 protected against L-arginine-provoked tissue destruction (Table 2, n = 6).

For instance, it was shown that the administration of IL-3 decreased the pancreatic hemorrhage and edema caused by L-arginine by 50% and 28.5%, respectively (Table 2 a and c, P <0.05 vs. vehicle + L-arginine, n = 6). Furthermore, in pancreatitis mice, IL-3 reduced the number of necrosis and extravascular leukocytes by33.3%, and 25% (Table 2 b and d, P <0.05 vs. vehicle + L-arginine, n = 6).

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Anti-IL_3 effect on leukocyte differential count in AP

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

Parameters	Mean	SE	*P* value
Sham	124	±2	<0.05
L-arginine	728*	±4	
Anti-IL_3	261#	±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 regulates tissue damage in AP

Parameters	Hemorrhage (Scores)	Acinarcell necrosis (Scores)	Edema formation (Scores)	Neutrophil infiltration (Scores)	*P* value
Sham	1.0	1.0	1.0	1.0	<0.05
L-arginine	3.0*	3.0*	3.5*	4.0*	
Anti-IL-3	1.5#	1.0#	1.0#	1.0#	

Hemorrhage, acinar necrosis, edema formation and neutrophil infiltration. 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.

Table 3 Systemic leukocyte differential counts

	PMNL	MNL	Total	*P* value
PBS	1.8 ± 0.6	12.1 ± 0.4	13.9 ± 1.0	<0.05
L-arginine	0.3 ± 0.4*	4.1 ± 0.2*	4.4 ± 0.3*	
Anti-IL_3	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.

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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 4.7-fold (Table 4. *P* <0.05 vs. Sham, n = 6). IL-3 inhibitor decreased pancreatic MPO levels induced by L-arginine by 34.6% (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 31.8% (Table 5, *P* <0.05 compared. vehicle + L-arginine, n = 6).

IL-3 regulates the levels of serum CXCL2 in acute pancreatitis (AP)

Additionally, it was noted that exposure to L-arginine significantly increased CXCL2 levels in the pancreas, escalating from 46.5 ± 0.8 to 184.6 ± 0.4 pg/mg, indicating a 3.9-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 92.6 ± 1.0 pg/mg, signifying a reduction of over 50% (Table 6, *P* <0.05 vs. Vehicle + L-arginine, n = 6).

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

Parameters	Mean	SE	*P* value
Sham	1.45	1.12	<0.05
L-arginine	6.86*	1.2	
Anti-IL-3	2.38#	0.8	

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 activityin Lung Tissue (U/g)

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

Anti-IL-3 controls L-arginine-induced neutrophil accumulation. MPO levels in the Lung in sham (PBS) animals and L-arginie-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.

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

Parameters	Mean	SE	*P* value
Sham	46.5	0.8	<0.05
L-arginine	184.6*	0.4	
Anti-IL-3	92.6#	1.0	

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.

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Anti-IL-3 controls plasma IL6 levels in acute pancreatitis (AP)

Acute pancreatitis increased *P* <0.05 plasma levels of IL6 from 6.10 ± 1.4 pg/mg in sham mice up to 124 ± 6.6 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 66.2 ± 2.5 pg/mg, a decrease of more than 53.3 % (Table 7, *P* <0.05 Vehicle+ L-arginine, n = 6).

Trypsinogen activation in acinar cells in vitro

We then questioned whether trypsinogen activation in pancreatic acinar cells might be regulated by IL-3 in vitro. To do this, we separated acinar cells from mouse pancreas and incubated the cells with cerulein. Trypsinogen activation was observed to be more than 1.4-fold higher in cerulein-stimulated cells compared to unstimulated cells (Table 8, *P* <0.05 vs. control, n = 6). Nevertheless, the secretagogue-induced activation of trypsinogen was unaffected by preincubating the acinar cells with radicicol (Table 8, *P* <0.05 vs. vehicle + cerulein, n = 6).

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

Parameters	Mean	SE	*P* value
Sham	6.10	1.4	<0.05
L-arginine	124*	6.6	
Anti-IL-3	66.2#	2.5	

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.

Table 8 Trypsinogen levels in pancreas invitro

Parameters	Mean	SE	*P* value
Negative control	3100	1.5	>0.05
cerulein	4500*	5.4	
Anti-IL-3	3400	7.2	

Acinar cell activation of trypsinogen was measured in negative control cells and in cells exposed to cerulein with PBS or Anti-IL-3 (100 µM). Activation of trypsinogen activation was quantified by measuring enzymatic activity of trypsin fluorometrically by using Boc-Gln-Ala-Arg-MCA as the substrate as described in detail in Materials and Methods. Trypsin levels were calculated using a standard curve generated by assaying purified trypsin. Data represent means ± SEM and *n* = 6. **P* <0.05 vs. negative control.

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Discussion

Uncertainty exists regarding the signaling cascades regulating the pro-inflammatory pathways in pancreatitis. Our current work reveals the first evidence that IL-3 performs a significant role in controlling the pathogenesis of severe AP. According to these results the surface upregulation of neutrophils is mediated by IL-3. In addition to reducing neutrophil infiltration in the pancreas, IL-3 activity inhibition significantly reduces acinar cell necrosis and amylase levels in serum in AP. Additionally, we discovered that IL-3 suppression eliminated neutrophil buildup in the lung, indicating that IL-3 regulates local and systemic inflammation in severe AP. In experimental models of sepsis,[16] and multiple sclerosis,[17] IL-3 activity has been shown to regulate pro-inflammatory activities. Herein, we found that IL-3 inhibition with a specific inhibitor of IL-3 (Radicicol) in severe AP led to an apparent reduction of tissue injury. For instance, the treatment of IL-3 reduced the L-arginine -induced rise in serum amylase by 35.8% (Table 1) and the acinar cell necrosis by 33.3% (Table 2 b), indicating that the activity of the IL-3 in severe AP controls an important aspect of the tissue damage. These findings provide the first concrete proof in the literature that blocking the IL-3 signaling pathway offers significant protection against severe AP.

It is noteworthy to mention that statins, which are mostly indicated to control cholesterol levels in patients having cardiovascular problems, have reportedly been shown to lessen experimental pancreatitis.[18] IL-3 it is well accepted that neutrophil infiltration is a key aspect of pancreatitis.[19] For instance, it has often been observed that in AP, neutrophil decline decreases tissue damage.[6] We discovered in the current investigation that in pancreas, IL-3 challenge significantly raised the activity of MPO and the quantity of extravascular neutrophils.

A considerable reduction in MPO levels and extravascular neutrophil counts after IL-3 administration suggests that IL-3 activity is a key controller of neutrophil stimulation in the inflamed pancreas. According to the crucial impact of neutrophils in the pathogenesis of pancreatitis,[19] it is possible to speculate that radicicol's inhibitory impact on neutrophil responses may account for its protective effects in AP. Pulmonary accumulation of neutrophil is one of the systemic consequences of severe AP.[20] We discovered that the L-arginine challenge resulted in a definite rise in lung MPO levels. Interestingly, radicicol reduced pulmonary MPO activity, indicating that IL-3 also controls systemic neutrophil activation and infiltration in severe AP. Numerous investigations have demonstrated that certain adhesion molecules regulate leukocyte extravasation.[21,22] despite the fact that the precise involvement of some adhesion molecules in promoting buildup of leukocyte in the pancreas is mostly unknown. we investigated whether IL-3 inhibitory effects may be indirect and connected to the production of CXC chemokines, including MIP-2, which is a specifically a strong neutrophil activator.[23] Therefore, it was quite interesting to look at MIP-2 production in pancreas in this research. It was discovered that L-arginine caused the pancreas' MIP-2 levels to rise noticeably. The etiology of AP is widely thought to revolve around trypsinogenactivation.[24] Recent research demonstrated that Rho-kinase signaling in acinar cells regulates the stimulation of trypsinogen.[25] Therefore, it was quite interesting to investigate the possibility that IL-3 has a role in trypsin activation. On the other hand, we found that in vitro secretagogoue -induced trypsin activation in isolated acinar cells was unaffected by inhibition of IL-3 activity. In this particular setting, it is noteworthy that IL-3 activity is regulated; still, IL-3 exerts a significant role through decrement of cytokines and chemokines in mice with abdominal sepsis.[12]

The mechanism behind of IL-3 in regulation of neutrophil migration, it might STAT5, because it is activated by various cytokines, including IL-3, prolactin, and IL-2.IL-3 inhibition, might not effect directly on activation of trypsinogen in acute pancreatitis This transcription factor plays key roles in regulating growth and development, immune system function, tumor immunity, and the processes of cell growth, differentiation, and apoptosis.[26] A previous study found that pancreatic STAT5 activation is a crucial downstream effector of oncogenic KRAS signaling, playing an essential role in the initiation of acinar-to-ductal metaplasia (ADM) and the progression of pancreatic ductal adenocarcinoma (PDAC). These findings underscore STAT5 as a potential target for therapeutic intervention.[27]

Conclusion

In conclusion, these results show that in severe AP, IL-3 signaling controls tissue damage. Our findings demonstrate that in case of pancreatitis, IL-3 regulates systemic and local inflammation. Therefore, these findings not solely identify a crucial signaling pathway in AP additionally suggest that targeting IL-3 may be a useful strategy for reducing pathological inflammation in cases of severe AP.

Competing interests

The authors declare that they have no competing interests.

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