Fibroblast Growth Factor (FGF) Signaling Protects Against Acute Pancreatitis-Induced Damage by Modulating Inflammatory Responses

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

AEFG 1   Hai-Jian Tu
BCD 2   Cheng-Fei Zhao
ADF 3   Zhi-wei Chen
BCD 4   Wei Lin
BCD 5   Yu-Cai Jiang

1 Medical Laboratory, Affiliated Hospital of Putian University, Putian, Fujian, P.R. China
2 School of Pharmacy and Medical Technology, Putian University, Putian, Fujian, P.R. China
3 Departmen of Pathology, Affiliated Hospital of Putian University, Putian, Fujian, P.R. China
4 Department of General Surgery, Affiliated Hospital of Putian University, Putian, Fujian, P.R. China
5 Department of Pharmacy, 95th Hospital of Chinese People's Liberation Army, Putian, Fujian, P.R. China

Corresponding Author: Hai-Jian, Tu, e-mail: tuhaijian123456@163.com
Source of support: Science and Technology Plan Projects of Putian City (2018s3001)

Background: Acute pancreatitis (AP) is a symptom of sudden pancreas inflammation, which causes patients severe suffering. In general, fibroblast growth factor (FGF) levels are increased and amylase and lipase activities are elevated during AP pathogenesis, but protein concentration are low. However, the mechanism through which FGF signaling regulates AP pathogenesis remains elusive.

Material/Methods: The concentrations of PGE2, TNF-α, sCRP, FGF1, and FGF2 in the serum samples of the AP group and healthy control group were detected by enzyme-linked immunosorbent assay. In addition, IκBα and p-IκBα levels were analyzed in the serum samples. Subsequently, the AP rat model was established, and FGF1, FGF2, anti-FGF1, and anti-FGF2 antibodies and Bay11-7082 were injected into AP rats. TNF-α, PAI-1 JNK, p-JNK, IκBα, and p-IκBα levels were also examined.

Results: Results showed that levels of PGE2, TNF-α, sCRP, p-IκBα, FGF1, and FGF2, as well as amylase and lipase activity were increased in patients with AP compared with those in healthy people. In addition, protein concentrations were lower in patients with AP than in the healthy group. Activation of FGF signaling by injecting FGF1 or FGF2 also inhibited AP-induced inflammation response in the pancreas and increased amylase and lipase activities, as well as protein concentration. However, the injection of FGF1 and FGF2 antibodies accelerated AP-mediated inflammation responses in the serum. In addition, Bay11-7082 injection inhibited AP activation of inflammation response and amylase and lipase activities. Protein concentration were also increased in AP rats.

Conclusions: FGF signaling protects against AP-mediated damage by inhibition of AP-activating inflammatory responses.

MeSH Keywords: Fibroblast Growth Factor 1 • Fibroblast Growth Factor 2 • Pancreatitis, Acute Necrotizing

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/920684
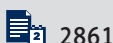
📄 2861   ▦ 3   📊 6   📖 43

Background

Acute pancreatitis (AP) is an acute inflammatory disease with extreme epigastralgia, causing injury to pancreatic cells (especially exocrine cells) due to various causes, such as gallstones, alcohol abuse, metabolic disorders, drugs, and abdominal damage. Among these factors, the main causes of AP are gallstones and alcohol, accounting for 60–80% of all AP cases [1]. AP has been increasing worldwide in recent decades [2–4]. The regulation and ideal treatment of this disease are still unknown.

Patients with AP have a pancreas with varying degrees of fibrosis, acinar cell regeneration, and formation of tubular complexes [5–9]. Past studies have shown that fibroblast growth factor-1 (FGF1), fibroblast growth factor-2 (FGF2), hepatocyte growth factor, transforming growth factor-α [9], insulin-like growth factor-1 [10,11], transforming growth factor-β (TGF-β), and epidermal growth factor levels in the edematous AP rat model were higher in AP rats compared with healthy controls [12–14]. Therefore, these factors are necessary for angiogenesis, mitogenesis, chemotaxis, progression, and sustainability of the enhanced malignant growth [15–19]. Clinical studies demonstrated that growth factors increase the expression in patients with acute necrotizing pancreatitis. Studies using the caerulein-induced rat model found that, some growth factors, such as PDGF-A, FGF2, VEGF, and TGF-β, influence AP and attenuate pancreatic damage and accelerated recovery [20–25]. These studies suggested that growth factors can control and restrict pancreatic damage and stimulate pancreatic regeneration.

Inflammatory responses are known to be associated with damage caused by AP [26–29]. An injured pancreas can activate inflammatory cells in the pancreas to secrete inflammatory mediators (cytokines) [30]. Local inflammation of the pancreas is the body's initial physiological protective response, which is usually strictly controlled at the site of injury. Inflammatory mediators or cytokines induce inflammation through "trigger-like action", making a variety of inflammatory mediators work together to produce a cascade of inflammation amplification effect to spread the inflammation of the pancreas. When the inflammatory response of the pancreas is increased, systemic inflammatory response syndrome (SIRS) and multiple organ failure syndrome (MODS) were induced, leading to death [31].

The FGF family consists of a group of homologous growth-promoting polypeptides that increase proliferation, angiogenesis, and progression of lung, prostate, and colon cancer [32–35]. FGF1, also known as basic FGF receptor 1, elicits cellular responses when bound to a particular FGF by activating signaling pathways that include the phospholipase C/PI3K/AKT, Ras subfamily/ERK, and protein kinase C pathways. Additionally, FGF1 stimulates the activation of Sprouty proteins (SPRY1-4) interacting with GRB2, SOS1, c-Raf, and epidermal growth factor

receptor. These interactions act as negative feedback loops to restrict the magnitude of cellular activation [36]. FGF2 contains intracellular tyrosine kinase domains that bind with transmembrane receptors. This factor promotes angiogenesis and stimulates endothelial cell migration [37–40]. FGF21 can regulate foam cell formation and inflammatory response in Ox-LDL-induced THP-1 macrophages [41]. In addition, S100B regulates inflammatory response during osteoarthritis via FGF1 signaling [42], suggesting that FGF signaling can modulate inflammatory responses. FGF mRNA has been reported to be overexpressed in AP. However, whether FGF signaling modulates inflammatory response to regulate AP pathogenesis is unclear.

This study evaluated the total protein contents, amylase activity, inflammatory response protein levels, and FGF levels in sera of healthy subjects and AP patients. The function of FGF signaling in AP pathogenesis was also analyzed via generation of the AP rat model with injections of FGF1, FGF2, and Bay11-7082, and FGF1 and FGF2 antibodies. In the AP rats, the protein contents, amylase activity, and inflammatory response protein levels were examined. This study revealed that FGF signaling protects from AP-induced damages, and these results will provide useful information for AP therapy.

Material and Methods

Patients

Twenty patients, including 10 males and 10 females aged 38–55 years (χ±SD: 45.3±3.34), diagnosed with AP within 2 days after admission at the Affiliated Hospital of Putian University from March 2016 to April 2018 were enrolled in the study. The diagnostic criteria were in accordance with the Guidelines for the Diagnosis and Treatment of Acute Pancreatitis (2014 edition). Additionally, 20 healthy volunteers without a history of pancreatic diseases were recruited and served as a control group, including 10 males and 10 females, ages 38–60 years (χ±SD: 47.2±4.28). The 2 groups had no significant differences in age or sex ratio (P>0.05). The protocol was approved by our hospital Ethics Committee after discussion, and all the patients signed informed consents before they were enrolled.

Enzyme-linked immunosorbent assay

Blood samples were taken within 24 h and 48 h after onset. Next, 2–3 ml peripheral blood was taken from each individual and centrifuged for 5 min at 2500 rpm at 4°C. The supernatant (serum) was moved to a new tube and kept at −20°C. The serum concentrations of PGE2, TNF-α, sCRP, FGF1, and FGF2 were quantified using an ELISA kit (Shanghai Bio-tech Co., Shanghai, China) according to the manufacturer's instruction. The serum concentrations of PGE2, TNF-α, sCRP, FGF1, and

FGF2 were calculated on the basis of their standard curves. All experiments were repeated in triplicate.

Establishment of the AP rat model

A total of 64 SPF-grade SD male rats, weighing approximately 200 g, were used to establish the AP model [43]. The rat model of acute pancreatitis was constructed in 56 rats and 8 controls. In addition to the normal death and the failure of the experimental operation, the subsequent experimental groups were ensured to reach 8 in each group, so that the experiment could proceed normally. Therefore, 64 rats were used. Rats were randomly assigned to the AP, AP+FGF1, AP+FGF2, AP+FGF1 Ab, AP+FGF2 Ab, AP+Bay11-7082, and normal groups, with 8 rats in each group. The rats fasted for 12 h before surgery and were anesthetized by intramuscular injection of ketamine (0.2 ml/kg) and an intravenous injection of 1.5% pentobarbital sodium (1.5 ml/kg, Beijing Chemical Reagent Company, China). Rats were injected with 0.5% metronidazole (50 ml) and cefotaxime sodium (0.5 g) as infection prophylaxis 0.5 h before the operation. After an upper abdominal midline incision was made, the wall of the descending duodenum was incised and cannulated using a central venous catheter through the ampulla of Vater into the main pancreatic duct. The catheter was fixed on the duodenal wall and the skin. At 24 h after model establishment, AP was induced by retrograde injection of 5% taurocholate acid sodium (0.5 ml/kg; Sigma, USA) injected into the central venous catheter of rats in the AP group. The rats in the control group received the same surgical procedure and cannulation, without any infusion. During the recovery and experimental periods, the rat amylase activity, lipase activity, and protein concentration were intravenously injected with total parenteral nutrition without any feeding. After AP induction, FGF1 (100 ng/ml), FGF2 (100 ng/ml), anti-FGF1(100 ng/ml), and anti-FGF2 (100 ng/ml) antibodies or Bay11-7082 (1 μM) were injected into the rats. Pancreas and peripheral blood were collected after 24 h.

Measurement of identification indexes related to acute pancreatitis

We used an automatic biochemical analyzer (Hitachi 7600, Hitachi, Tokyo, Japan) to assess amylase activity, lipase activity, and protein concentration in sera from the patients and rats. We assessed serum amylase and lipase activities by iodine-amylum colorimetry and results are expressed in U/l. All experiments were repeated in triplicate.

Western blot analysis

We lysed 100 mg pancreas tissues using radioimmunoprecipitation assay buffer with 1% PMSF on ice. The total protein concentration was determined using a Bradford protein kit (Bio-Rad, Richmond, CA, USA). The proteins were separated on 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis and electrotransferred onto Immobilon-P Transfer Membranes (Millipore Japan, Tokyo, Japan). The membranes were probed with primary antibodies for 2 h at room temperature. The primary antibodies used were anti-Phospho-SAPK/JNK (Thr183/Tyr185) antibody (1: 1000, Cell Signaling Technology, 4668), anti-SAPK/JNK (1: 1000, Cell Signaling Technology, 9252), anti-p-IκBα antibody (1: 500, Santa Cruz Biotechnology), anti-IκBα antibody (1: 5000, Cell Signaling Technology), anti-PAI-1 antibody (1: 1000, Abcam, ab66705), and anti-TNF-a antibody (1: 1000, Abcam, ab1793). The membranes were incubated for 1 h with secondary antibody at room temperature (1: 2000, Cell Signaling Technology). Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) (1: 2500, Abcam, ab9485) was used as an internal control. Antigen–antibody complexes were then visualized using an electrochemiluminescence kit (GE Healthcare). The protein levels were normalized against those of GAPDH by using Image J software (National Institute of Health, Bethesda, MD, USA). All experiments were repeated in triplicate.

Statistical analysis

The data were analyzed by SPSS17.0 software and the results are expressed as mean±standard deviation (χ±SD). Comparison of data was performed using the t test. Correlation between 2 variables was analyzed using linear correlation method, which showed significant differences between the 2 groups (* $P<0.05$, ** $P<0.01$, and *** $P<0.001$).

Results

Comparison of PGE2, TNF-α, and sCRP concentrations in the sera of patients with AP and healthy people

ELISA was performed to analyze the inflammatory response in AP patients and healthy people. The results showed that PGE2, TNF-α, and sCRP levels were dramatically higher in patients with AP compared with those in the healthy group (Table 1). p-IκBα and total IκBα levels were also analyzed by Western blot using the serum samples of 3 healthy people and 3 AP patients. The data indicated a higher p-IκBα level in patients with AP than in the healthy group, whereas total IκBα level was not changed after AP disease (Figure 1). FGF level is known to be associated with AP; therefore, FGF1 and FGF2 levels were analyzed. The ELISA data suggested that levels of FGF1 and FGF2 were higher in the patient group than in the healthy group (Table 2).

Amylase activity, lipase activity, and protein concentration in the sera of patients with AP and healthy people

The amylase activity, lipase activity, and protein concentration were the general factors examined next during AP pathogenesis.

Table 1. Comparison results for concentrations of PGE2, TNF-α, and sCRP in the serum of 2 groups (χ±SD).

Group	No. of people tested	PGE2 (pg/l)		TNF-α (pg/ml)		sCRP (ng/l)	
Time (h)		24	48	24	48	24	48
The patients	20	2.08±0.27**	1.18±0.12**	65.11±20.42**	48.31±13.56**	4.13±0.35**	2.53±0.32**
Healthy control	20	0.23±0.13	0.29±0.12	35.78±10.17	36.09±11.21	1.45±0.79	1.58±0.41
P		P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001

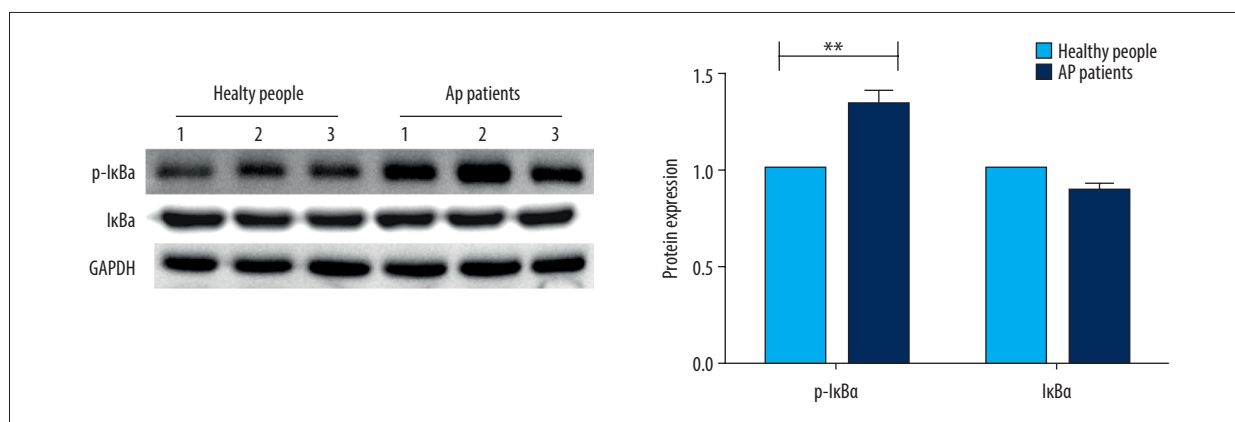T value: Similarity between 2 groups; 24- and 48-hour blood samples were tested.

Figure 1. Effects of AP and FGF on p-IκBα and IκBα levels. The p-IκBα and IκBα levels were analyzed by Western blot analysis using the serum of healthy people and patients with AP. GAPDH was used as an internal control. The 1,2,3 represents the random person number of the samples. The experiments were repeated 3 times. The significant differences between the healthy people and AP patient groups were analyzed (** P<0.01).

Table 2. Comparison of results for concentrations of FGF1 and FGF2 in the serum of 2 groups (χ±SD).

Group	No. of people tested	FGF1 (ng/ml)		FGF2 (ng/ml)	
Time (h)		24	48	24	48
The patients	20	2.24±0.12*	2.64±0.45*	17.31±0.78*	3.43±0.56*
Healthy control	20	1.34±0.32	1.52±0.15	10.12±0.32	1.98±0.21
P		P<0.01	P<0.01	P<0.01	P<0.01

T value: Similarity between 2 groups; 24 - and 48-hour blood samples were tested.

To examine these 3 factors, blood samples were collected from 20 patients with AP and 20 healthy people. The amylase and lipase activities are significantly higher in patients with AP than in the healthy group, and the protein concentration was significantly lower. These results indicated that basal PF and enzyme secretions were activated during the early stage of AP (Table 3).

FGF1 and FGF2 injection reduced inflammation response and increased amylase and lipase activities

In patients with AP, inflammation response was activated, which was assessed by detecting the PGE2, TNF-α, and sCRP concentrations in the serum samples. FGF1 and FGF2 levels and amylase and lipase activities were increased, but protein concentration was decreased. However, whether FGF signaling and inflammation response are connected remains unknown. To analyze the relationship between FGF signaling and inflammation response, the AP rat model was generated by injection of sodium taurocholate. After the AP model was established, the rat pancreas was extracted for experiments. Western blot analysis showed that the levels of p-JNK, p-IκBα, TNF-α, and PAI-1 were all higher in the AP rat pancreases compared with those in normal rats, but total JNK (t-JNK) and IκBα levels were not changed by AP (Figure 2). To investigate the FGF function, FGF1 or FGF2 was injected into AP rats. Western blot results

Table 3. Comparison results for amylase activity, lipase activity, and protein concentration in the serum of 2 groups (χ±SD).

Group	No. of people tested	Amylase (U/l)		Lipase (U/l)		Protein concentration (g/l)	
Time (h)		24	48	24	48	24	48
The patients	20	267.12±160.24**	210.23±55.47*	513.65±139.67**	125.45±58.28*	34.13±4.64**	45.12±10.12*
Healthy control	20	68.46±22.15	70.43±20.56	90.32±19.26	89.62±18.53	55.56±12.28	54.89±11.32
P		P<0.001	P<0.01	P<0.001	P<0.01	P<0.001	P<0.01

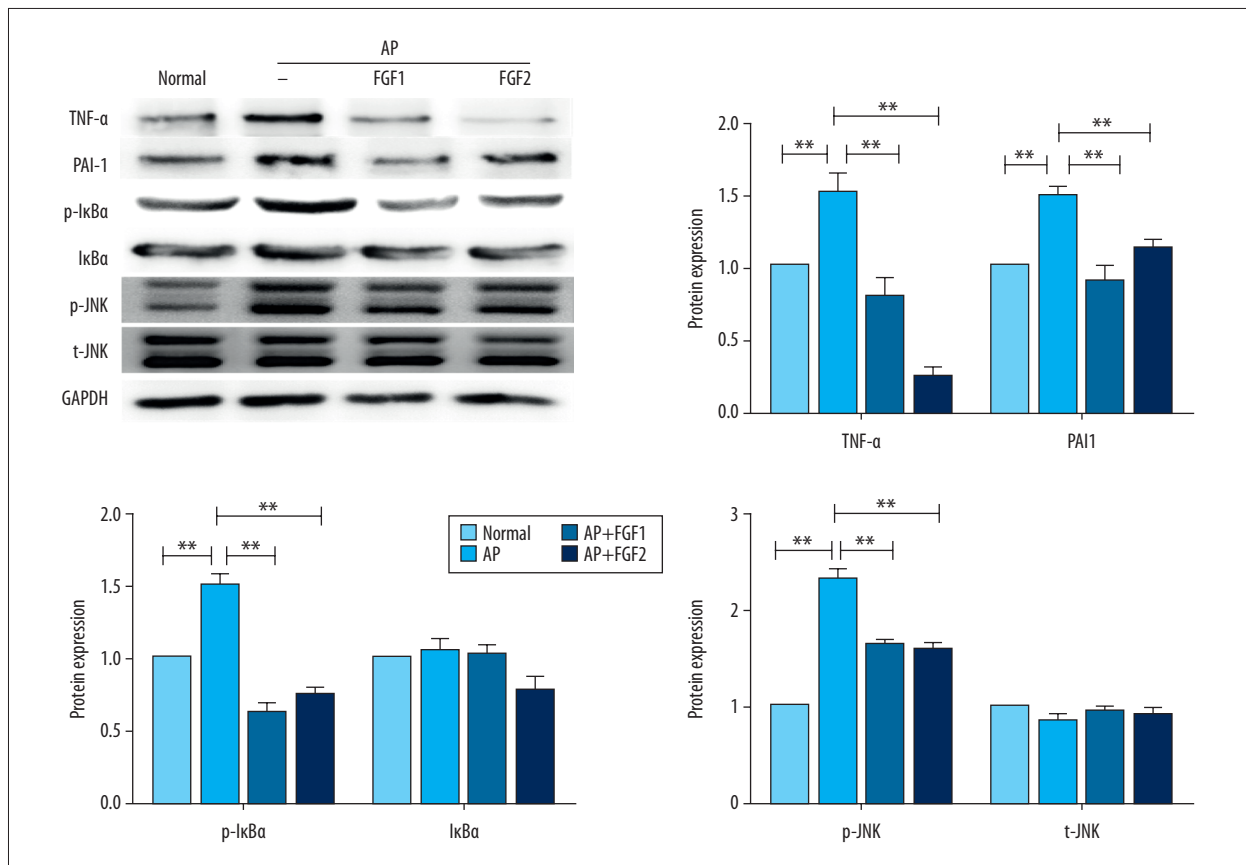T value: Similarity between 2 groups; 24- and 48-hour blood samples were tested.

Figure 2. Effects of AP and FGF on TNF-α, PAI-1, p-IκBα, IκBα, p-JNK, and t-JNK levels. The TNF-α, PAI-1, p-IκBα, IκBα, p-JNK, and t-JNK levels were analyzed by Western blot analysis using the pancreases of normal rats, AP rats, and AP rats injected with FGF1 or FGF2. GAPDH was used as an internal control. The experiments were repeated 3 times. The significant differences between the AP, AP+FGF1/FGF2, and normal groups were analyzed (** P<0.01).

indicated that FGF injection significantly suppressed p-JNK, p-IκBα, TNF-α, and PAI-1 levels in AP rat pancreases, and the levels were similar to those in normal rat (Figure 2). FGF1 or FGF2 antibody was injected into AP rats, and the marker protein levels were monitored. The results showed that the injection of FGF1 or FGF2 antibody inhibited FGF signaling, which increased the levels of p-JNK, p-IκBα, TNF-α, and PAI-1 by AP in rats (Figure 3).

To test whether FGF injection in AP rats also changed amylase and lipase activity and protein concentration, blood samples from normal rats, AP rats, and AP rats injected with FGF1 or FGF2 were collected. Amylase and lipase activities were higher, whereas protein concentrations were lower in the AP rat serum compared with serum from normal rats. However, FGF1 or FGF2 injection inhibited the AP-induced increase of amylase and lipase and AP-mediated reduction of protein contents in the blood serum (Figure 4).
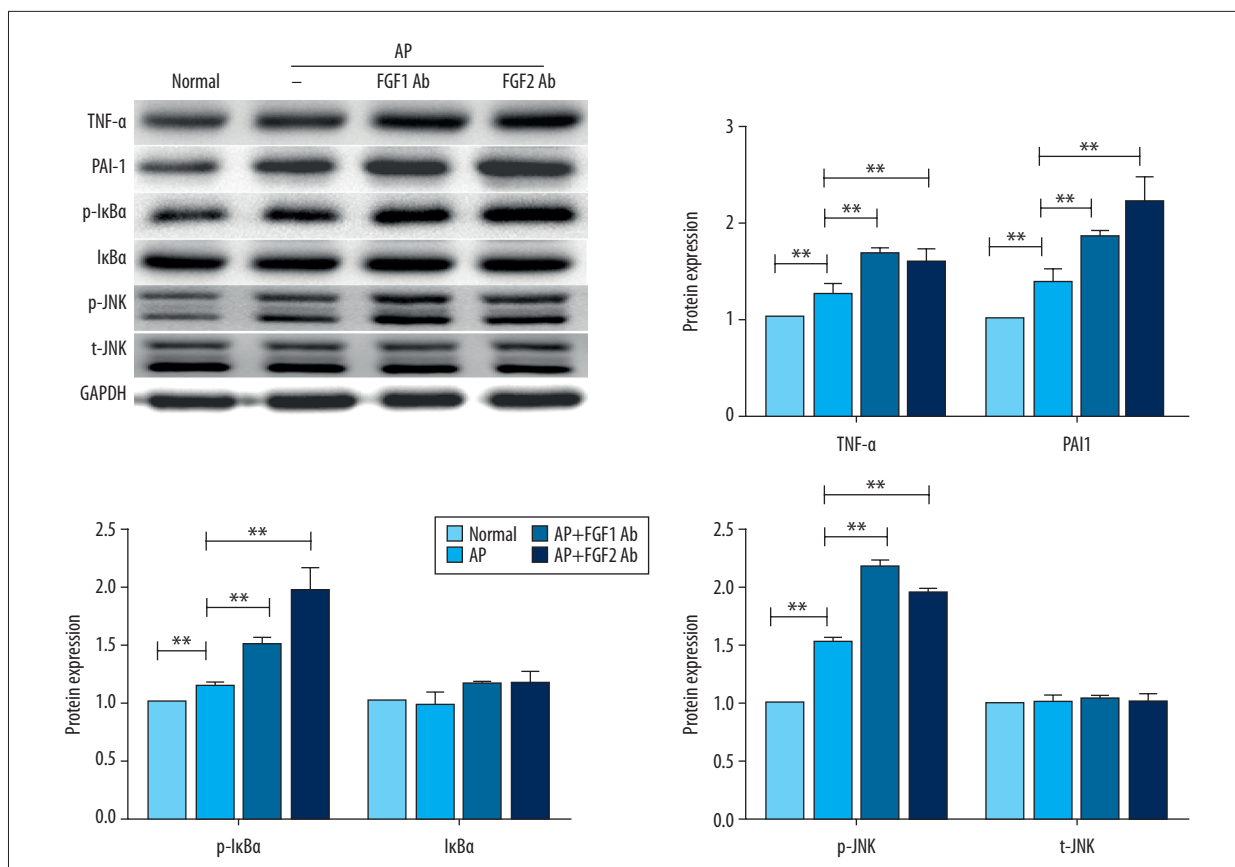
Figure 3. Effects of AP and FGF on TNF-α, PAI-1, p-IκBα, IκBα, p-JNK, and t-JNK levels. The TNF-α, PAI-1, p-IκBα, IκBα, p-JNK, and t-JNK levels were analyzed by Western blot using the pancreases of normal rats, AP rats, and AP rats injected with FGF1 Ab or FGF2 Ab. GAPDH was used as an internal control. The experiments were repeated 3 times. The significant differences between the AP, AP+FGF1 Ab/FGF2 Ab, and normal group were analyzed (** P<0.01).

Inhibition of inflammation response increased amylase and lipase activity and protein concentration in AP rat pancreases

Bay11-7082, an IκBα inhibitor, was injected into the AP model rats. Western blot analysis showed that Bay11-7082 injection significantly reduced the AP-induced p-IκBα, TNF-α, and PAI-1 levels, indicating that Bay11-7082 successfully inhibited the AP-induced inflammation response in rat pancreases (Figure 5). We assessed amylase and lipase activity and protein concentration in normal rats, AP rats, and AP rats injected with Bay11-7082, and found that AP induction significantly increased amylase and lipase activities but reduced protein concentration. In addition, Bay11-7082 injection eliminated the AP-mediated increase in these indicators (Figure 6).

Discussion

The prevalence and mortality rates of AP are increasing. Induction of AP pathogenesis often increases amylase and lipase activities and decreases protein concentration. Previous studies found that a few FGF members, including FGF1 and FGF2, are overexpressed in AP pathogenesis [34]. However, the relationship between FGF signaling and AP damage is unclear. In the present study, 20 patients with AP, including 10 males and 10 females, were selected, and blood samples were analyzed to detect the inflammatory response marker proteins PGE2, TNF-α, sCRP, and IκBα. In parallel, 20 healthy people of similar ages were compared with the patient group. The ELISA and Western blot analysis results clearly indicated that inflammatory response markers were higher in the patients with AP compared with those in the healthy group, regardless of sex. Not surprisingly, FGF1 and FGF2 levels were also significantly higher in the AP patient group than in the healthy group. JNK was also activated by AP, which was observed by the detection of p-IκBα to total IκBα ratio (Figure 1). FGF signaling is known to regulate JNK activity, suggesting that AP can alter FGF signaling. Moreover, amylase and lipase activities were higher and total protein contents were obviously lower in the patient group than in the healthy people. These data suggest that AP pathogenesis increases levels of FGF1 and FGF2 proteins and activates inflammatory responses in humans.
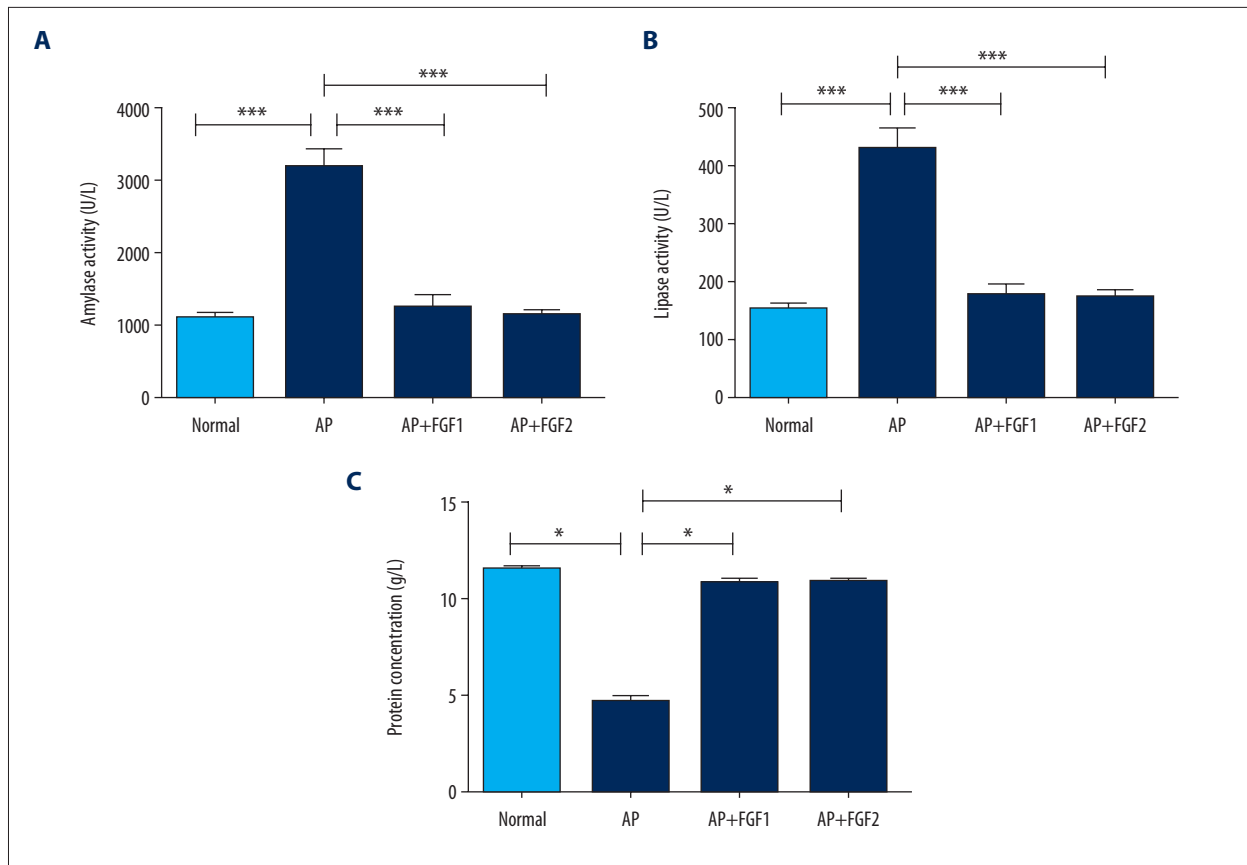
Figure 4. Effects of AP, FGF1, and FGF2 on amylase and lipase activities and protein concentration in the serum. Amylase activity (**A**), lipase activity (**B**), and protein concentration (**C**) were analyzed in the sera of normal rats, AP rats, and AP rats injected with FGF1 or FGF2. The error bar represents±SD (n=8). The significant differences between the AP and AP+FGF1/FGF2, normal group were also analyzed (* P<0.05, *** P<0.001).
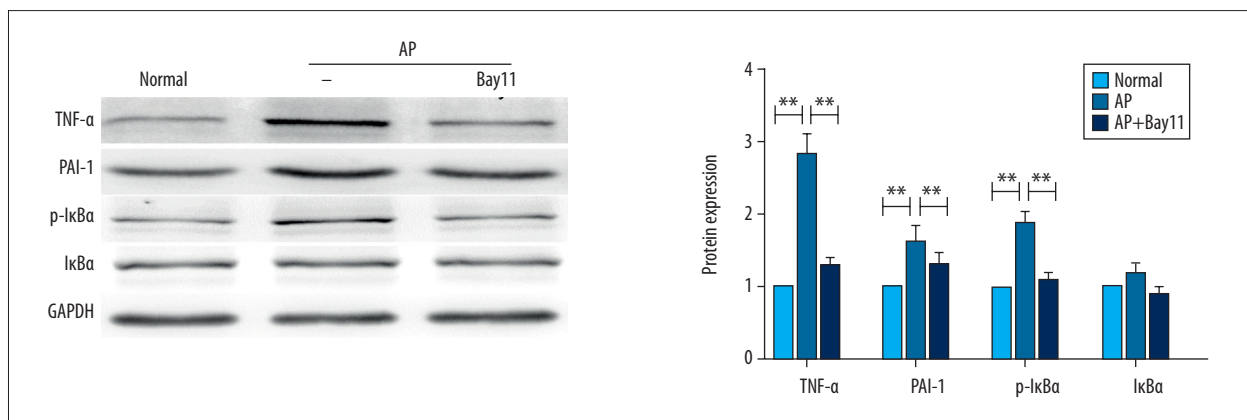

Figure 5. Effects of AP and Bay11-7082 on TNF-α, PAI-1, p-IκBα, and IκBα levels. The TNF-α, PAI-1, p-IκBα, and IκBα levels were assessed by Western blot analysis using the pancreases of normal rats, AP rats, and AP rats injected with Bay11-7082. GAPDH was used as an internal control. The experiments were repeated 3 times. The significant differences between the AP, AP+Bay11, and normal group were analyzed (** P<0.01).
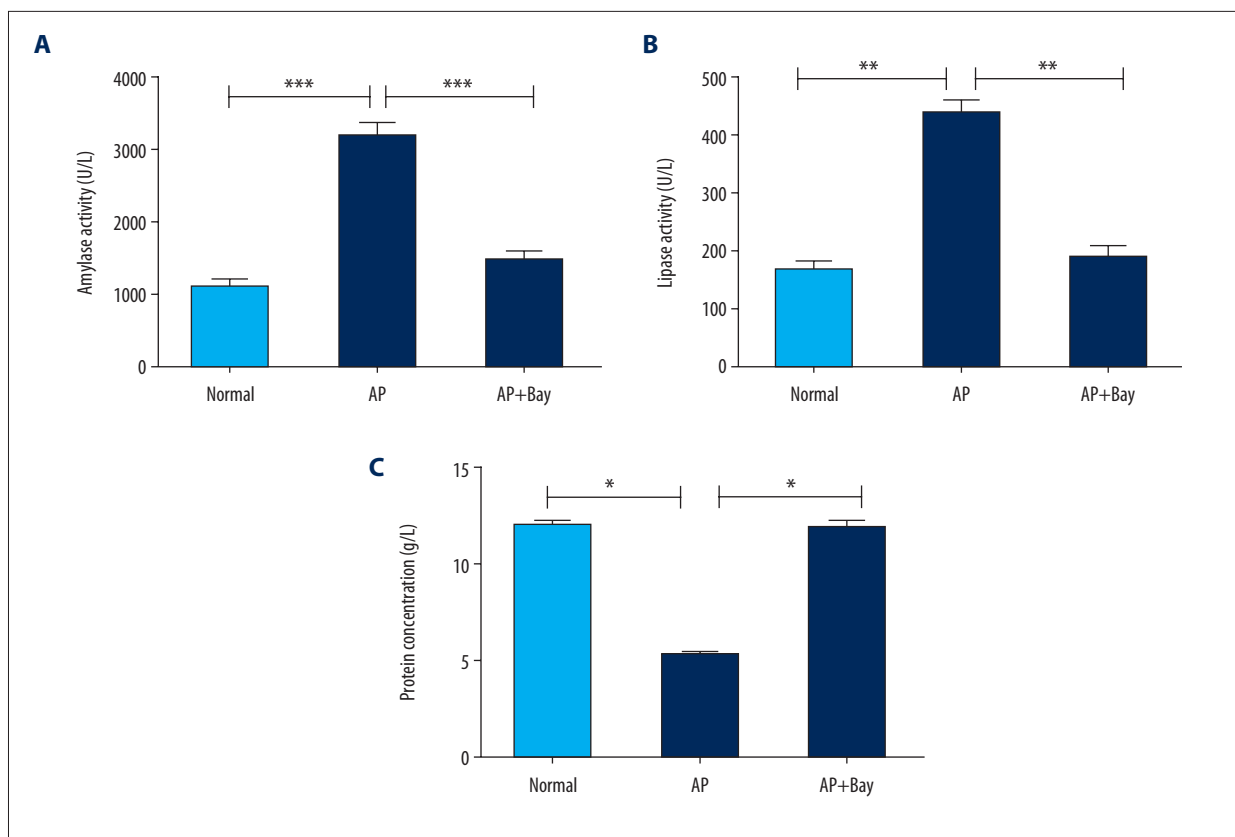
Figure 6. Effects of AP and Bay11-7082 on amylase and lipase activities and protein concentration in the serum. Amylase activity (**A**), lipase activity (**B**), and protein concentration (**C**) were analyzed in the sera of normal rats, AP rats, and AP rats injected with Bay11-7082. The error bar represents±SD (n=8). The significant differences between the AP and AP+Bay11, normal group were analyzed (* $P<0.05$, ** $P<0.01$. *** $P<0.001$).

Given that ther3e were high levels of FGF1 and FGF2 in the AP patient group, the role of FGF in AP-induced inflammation and enzyme activity changes was further examined in the rat model. AP generation in rats significantly induced inflammation, as examined by the detection of p-IκBα, TNF-α, and PAI-1 levels (Figure 2). However, FGF1 or FGF2 injection in AP rats significantly induced AP, whereas FGF1 and FGF2 antibodies enhanced AP-mediated induction of p-IκBα, TNF-α, and PAI-1 (Figure 3). Moreover, AP induction increased the amylase and lipase activities and reduced the protein concentration in the serum of rats (Figure 4). FGF signaling activation also restored the increase of enzyme activities and decrease of the total protein concentration in AP rats, which suggests that activation of FGF1 and FGF2 signaling protects against AP-induced inflammatory responses and increases the enzyme activities and reduction of total protein concentration. Furthermore, AP activates JNK and increases FGF1 and FGF2 levels (Figures 2, 3). However, high amounts of FGF1 and FGF2 injection suppressed AP-induced JNK activation, suggesting that the over-activation of FGF signaling inhibits JNK activity. Whether the activation of FGF signaling protects against AP-induced damage via inhibition of inflammatory response also remains to be clarified.

Next, the inflammatory response was determined through the application of a specific inhibitor, Bay11-7082, to the AP rat model to assess the inflammatory response function during AP-mediated damage. Bay11-7082 treatment in AP rats significantly inhibited inflammatory response activation during AP pathogenesis and decreased the expression of p-IκBα, TNF-α, and PAI-1, similar to the action of FGF1 and FGF2 (Figure 5). Further examination of amylase and lipase activities and protein contents revealed that Bay11-7082 had a similar function as the FGFs (Figure 6); specifically, it increased enzyme activity and protein contents in the AP rat model. The injection of FGF1 and FGF2 antibodies also promoted the AP-mediated induction of inflammatory response. These data suggest that FGF signaling activation occurs via inhibition of inflammatory response to protect against AP-induced enzyme activity and decrease protein contents.

FGF signaling has diverse functions in tissue development, differentiation, and repair. In many diseases, FGF levels sensitively respond to environmental changes, such as high blood sugar, drugs, and infrared radiation [20,21]. In addition, activation of FGF signaling was shown to greatly repair damage

to tissues or organs. In patients with AP, FGF1 and FGF2 are significantly increased, which can be detected in blood serum, suggesting a protective mechanism in humans to protect against damage from AP by the activation of FGF signaling. FGF signaling activation by the injection of FGF1 or FGF2 significantly reduced the inflammatory response and resulted in normal amylase and lipase activities and protein contents in AP rats. Inflammatory response inhibitor also resulted in a similar effect with FGFs. This finding suggests that FGF signaling-mediated inflammatory response inhibition might be an important way to protect against AP-induced damages. This condition was indirectly analyzed by measuring amylase and lipase activities and protein contents. However, further

histological and biochemical studies are required to determine the mechanisms by which FGF regulates inflammatory signaling to protect against AP-induced damage or even relieve AP generation. Our analyses from the clinical and mechanism perspectives to identify the FGF-inflammatory response pathway are important for AP therapy.

Conclusions

Our analyses show that FGF signaling protects against AP-induced damages via inhibition of AP-activating inflammatory responses.

References:

1. Bank S, Indaram A: Causes of acute and recurrent pancreatitis. Clinical considerations and clues to diagnosis. Gastroenterol Clin North Am, 1999; 28: 571–89

2. Li J, Bu X, Chen X et al: Predictive value of long non-coding RNA intersectin 1-2 for occurrence and in-hospital mortality of severe acute pancreatitis. J Clin Lab Anal, 2019: e23170 [Epub ahead of print]

3. Jacob AO, Stewart P, Jacob O: Early surgical intervention in severe acute pancreatitis: Central Australian experience. ANZ J Surg, 2016; 86(10): 805–10

4. Sun Y, He Y, Wang F et al: Low-methoxyl lemon pectin attenuates inflammatory responses and improves intestinal barrier integrity in caerulein-induced experimental acute pancreatitis. Mol Nutr Food Res, 2017; 61(4)

5. Liao R, Xue L, Qiang Z et al: Release of endogenous hydrogen sulfide in enteric nerve cells suppresses intestinal motility during severe acute pancreatitis. Acta Biochim Biophys Sin (Shanghai), 2019 [Epub ahead of print]

6. Bronowicka-Adamska P, Hutsch T, Gawryś-Kopczyńska M et al: Hydrogen sulfide formation in experimental model of acute pancreatitis. Acta Biochim Pol, 2019; 66(4): 611–18

7. Chen Y, Li W, Xie R et al: Nuclear factor-κB increases intracellular calcium by upregulation of Na+-Ca2+ exchanger 1 in cerulein-induced acute pancreatitis. Pancreas, 2020; 49(1): 111–19

8. Shenoy VK, Beaver KM, Fisher FM et al: Elevated serum fibroblast growth factor 21 in humans with acute pancreatitis. PLoS One, 2016; 11(11): e0164351

9. Kiehne K, Otte JM, Folsch UR, Herzig KH: Growth factors in development and diseases of the exocrine pancreas. Pancreatology, 2001; 1: 15–23

10. Shimbori C, Bellaye PS, Xia J et al: Fibroblast growth factor-1 attenuates TGF-β1-induced lung fibrosis. J Pathol, 2016; 240(2): 197–210

11. Ludwig CU, Menke A, Adler G, Lutz MP: Fibroblasts stimulate acinar cell proliferation through IGF-i during regeneration from acute pancreatitis. Am J Physiol, 1999; 276: G193–98

12. Hançerli Y, Kaplan M, Tanoğlu A et al: Efficacy of tocilizumab treatment in cerulein-induced experimental acute pancreatitis model in rats. Turk J Gastroenterol, 2017; 28(6): 485–91

13. Luo Y, Yang Y, Liu M et al: Oncogenic KRAS reduces expression of FGF21 in acinar cells to promote pancreatic tumorigenesis in mice on a high-fat diet. Gastroenterology, 2019; 157(5): 1413–28

14. He S, Shi D, Han Z et al: Heparinized silk fibroin hydrogels loading FGF1 promote the wound healing in rats with full-thickness skin excision. Biomed Eng Online, 2019; 18(1): 97

15. Li Y, Guo XB, Wang JS et al: Function of fibroblast growth factor 2 in gastric cancer occurrence and prognosis. Mol Med Rep, 2020; 21(2): 575–82

16. Thümmler K, Rom E, Zeis T et al: Polarizing receptor activation dissociates fibroblast growth factor 2 mediated inhibition of myelination from its neuroprotective potential. Acta Neuropathol Commun, 2019; 7(1): 212

17. Schwarz E: Cystine knot growth factors and their functionally versatile proregions. Biol Chem, 2017; 398(12): 1295–308

18. Presta M, Dell'Era P, Mitola S et al: Fibroblast growth factor/fibroblast growth factor receptor system in angiogenesis. Cytokine Growth Factor Rev, 2005; 16: 159–78

19. Thomas-Mudge RJ, Okada-Ban M, Vandenbroucke F et al: Nuclear FGF-2 facilitates cell survival in vitro and during establishment of metastases. Oncogene, 2004; 23: 4771–79

20. Dembiñski A, Warzecha Z, Konturek PC et al: Epidermal growth factor accelerates pancreatic recovery after caerulein-induced pancreatitis. Eur J Pharmacol, 2000; 398: 159–68

21. Tomaszewska R, Dembiñski A, Warzecha Z et al: The influence of epidermal growth factor on the course of ischemia-reperfusion induced pancreatitis in rats. J Physiol Pharmacol, 2002; 53: 183–98

22. Hosokawa M, Tsukada H, Fukuda F et al: Therapeutic effect of basic fibroblast growth factor on experimental pancreatitis in rat. Pancreas, 2000; 20: 373–77

23. Warzecha Z, Dembinski A, Konturek PC et al: Hepatocyte growth factor attenuates pancreatic damage in caerulein-induced pancreatitis in rats. Eur J Pharmacol, 2001; 430: 113–21

24. Dembiñski A, Warzecha Z, Ceranowicz P et al: IGF-1 stimulates production of interleukin-10 and inhibits development of caerulein-induced pancreatitis. Gut, 2002; 51(Suppl. III): A171

25. Warzecha Z, Dembiñski A, Ceranowicz P et al: IGF-1 stimulates production of interleukin-10 and inhibits development of caerulein-induced pancreatitis. J Physiol Pharmacol, 2003; 54: 575–90

26. Staubli SM, Schäfer J, Rosenthal R et al: The role of CRP and Pentraxin 3 in the prediction of systemic inflammatory response syndrome and death in acute pancreatitis. Sci Rep, 2019; 9(1): 18340

27. Sendler M, van den Brandt C, Glaubitz J et al: NLRP3 inflammasome regulates development of systemic inflammatory response and compensatory anti-inflammatory response syndromes in mice with acute pancreatitis. Gastroenterology, 2020; 158(1): 253–69

28. Sternby H, Hartman H, Johansen D et al: IL-6 and CRP are superior in early differentiation between mild and non-mid acute pancreatitis. Pancreatoloy, 2017; 17(4): 550–54

29. Hou C, Zhu X, Shi C et al: Iguratimod (T-614) attenuates severe acute pancreatitis by inhibiting the NLRP3 inflammasome and NF-κB pathway. Biomed Pharmacother, 2019; 119: 109455

30. Al-Hariri MT, Eldin TG, Hashim T et al: Propolis modulates inflammatory mediators and improves histopathology in male rats with L-arginine-induced acute pancreatitis. Sultan Qaboos Univ Med J, 2019; 19(2): e103–7

31. Liu J, Zou G, Yang L et al: Early prediction of persistent organ failure by circulating endothelial progenitor cells in patients with acute pancreatitis. Shock, 2017; 10(5): 251–62

32. Pardo OE, Lesay A, Arcaro A et al: Fibroblast growth factor 2-mediated translational control of IAPs blocks mitochondrial release of Smac/DIABLO and apoptosis in small cell lung cancer cells. Mol Cell Biol, 2003; 23: 7600–10

33. Udayakumar TS, Nagle RB, Bowden GT: Fibroblast growth factor-1 transcriptionally induces membrane type-1 matrix metalloproteinase expression in prostate carcinoma cell line. Prostate, 2004; 58: 66–75

34. Liu B, Fang M, Lu Y et al: Fibroblast growth factor and insulin-like growth factor differentially modulate the apoptosis and g1 arrest induced by anti-epidermal growth factor receptor monoclonal antibody. Oncogene, 2001; 20: 1913–22

e920684-9

Indexed in: [Current Contents/Clinical Medicine]   [SCI Expanded]   [ISI Alerting System]
[ISI Journals Master List]   [Index Medicus/MEDLINE]   [EMBASE/Excerpta Medica]
[Chemical Abstracts/CAS]

35. Brattstrom D, Bergqvist M, Hesselius P et al: Elevated preoperative serum levels of angiogenic cytokines correlate to larger primary tumours and poorer survival in non-small cell lung cancer patients. Lung Cancer, 2002; 37: 57–63

36. Helsten T, Schwaederle M, Kurzrock R: Fibroblast growth factor receptor signaling in hereditary and neoplastic disease: Biologic and clinical implications. Cancer Metastasis Rev, 2015; 34(3): 479–96

37. Jaye M, Schlessinger J, Dionne CA: Fibroblast growth factor receptor tyrosine kinases: Molecular analysis and signal transduction. Biochim Biophys Acta, 1992; 1135: 185–99

38. Winterhoff B, Konecny GE: Targeting fibroblast growth factor pathways in endometrial cancer. Curr Probl Cancer, 2017; 41(1): 37–47

39. Holzhauser S, Lukoseviciute M, Andonova T et al: targeting fibroblast growth factor receptor (FGFR) and phosphoinositide 3-kinase (PI3K) signaling pathways in medulloblastoma cell lines. Anticancer Res, 2020; 40(1): 53–66

40. Winterhoff B, Konecny GE: Targeting fibroblast growth factor pathways in endometrial cancer. Curr Probl Cancer, 2017; 41(1): 37–47

41. Wang N, Li JY, Li S et al: Fibroblast growth factor 21 regulates foam cells formation and inflammatory response in Ox-LDL-induced THP-1 macrophages. Biomed Pharmacother, 2018; 108: 1825–34

42. Zhu L, Weng Z, Shen P et al: S100B regulates inflammatory response during osteoarthritis via fibroblast growth factor receptor 1 signaling. Mol Med Rep, 2018; 18(6): 4855–64

43. Jin Y, Bai Y, Li Q et al: Reduced pancreatic exocrine function and organellar disarray in a canine model of acute pancreatitis. PLoS One, 2016; 11(2): e0148458.