

Original Article

Circulating levels of molecules associated with JAK2/STAT3 signaling pathway in patients with acute pancreatitis

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Abstract: The JAK2/STAT3 pathway was activated in cerulein-induced AP rats' pancreatic acinar cells. However, the role of JAK2/STAT3 signaling pathway in humans with acute pancreatitis (AP) is yet unknown. Thus, the differences and correlation of molecules associated with JAK2/STAT3 signaling pathway including serum free fatty acid (FFA), leptin, p-JAK2, and p-STAT3 were investigated to elucidate its underlying pathogenesis. 34 adult patients with AP were enrolled. 10 volunteers formed the control group. The serum levels of leptin, p-JAK2, and p-STAT3 were measured upon hospitalization by ELISA and FFA using microcolorimetry. The differences in serum FFA, leptin, p-JAK2, and p-STAT3 concentration were analyzed. According to scores of the modified CT severity index (MCTSI), 18 were mild AP and 16 severe. The differences of serum FFA, leptin, p-JAK2, and p-STAT3 concentrations in the subgroups with MCTSI scores < 4 and ≥ 4 were compared. The factors affecting serum p-STAT3 levels were also evaluated. The levels of leptin, FFA, p-JAK2, and p-STAT3, was significantly increased in AP group than the controls ($P < 0.05$). No differences in serum FFA, leptin, p-JAK2, and p-STAT3 were observed. Univariate analysis showed that FFA and p-JAK2 levels were significantly associated with that of p-STAT3. Multivariate analysis revealed FFA and p-JAK2 as independent correlation factors for p-STAT3 ($R^2 = 0.644$, $P < 0.0001$). These data showed that the circulating molecules associated with JAK2/STAT3 signaling pathway including FFA, leptin, p-JAK2, and p-STAT3 increased in AP patients without any correlation with its severity. The level of p-STAT3 was independently correlated with the increase of p-JAK2 and FFA.

Keywords: Acute pancreatitis, JAK2/STAT3 signal pathway, interleukin-6, free fatty acid, leptin

Introduction

Acute pancreatitis (AP) is a common, noninfectious inflammation of the pancreas, and the etiology of AP includes biliary, hyperlipidemia, and alcohol abuse. Although different causes exhibit diverse pathogenesis, the inflammatory disorder is common in AP patients, causing local tissue destruction and distant organ damage [1]. The Janus kinase (JAK)-signal transducers and activators of transcription (STAT) signaling pathway are involved in immune response, inflammatory reaction, fat metabolism, and other processes [2]. The abnormal activation of the JAK-STAT pathway may induce a variety of inflammatory diseases [3]. The animal studies have demonstrated that the JAK2/STAT3 pathway was activated in cerulein-induced AP rats'

pancreatic acinar cells [4, 5]. In a previous study [6], we found that JAK2/STAT3 signaling pathway was activated by high-dose linoleic acid in pancreatic exocrine cells and the expression of IL-6, TNF- α , and FAS, which are downstream proteins of the JAK2/STAT3 pathway, was increased. However, whether the JAK2/STAT3 pathway is activated in humans with AP is yet ill-understood.

Free fatty acid (FFA), produced by the hydrolysis of triglyceridemia (TG), is toxic to tissues and organs. Upon interaction with albumin, FFA converts into nontoxic and can be transported. Regardless of etiology, the elevated serum TG levels are positively and independently correlated with persistent organ failure in AP patients [7]. Excessive levels of serum TG produce

Table 1. Characteristics of the examined groups

	Controls (n = 10)	AP patients (n = 34)	P-value
Gender			0.895 ^b
Male	5	16	
Female	5	18	
Age	50.50±17.36	50.32±16.58	0.977 ^a
BMI (kg/m ²)	20.4±8.90	23.5±9.32	0.378 ^b

^at-test; ^bChi-square test.

Table 2. Mild subgroup (MCTSI < 4) and severe subgroup (MCTSI ≥ 4) comparison

	Severe subgroup (n = 16)	Mild subgroup (n = 18)	P-value
Age	48.63±16.447	51.83±16.447	0.581 ^a
Etiology			0.567 ^b
Hyperlipidemia	7 (43.7%)	5 (27.8%)	
Biliary	6 (37.5%)	7 (38.9%)	
Others	3 (18.8%)	6 (33.3%)	
WBC	11.29±5.94	9.54±3.26	0.289 ^a
CRP	136.60±116.13	63.9056±50.03	0.031 ^a
LDH	464.50±600.06	268.53±129.32	0.100 ^a
AST	67.76±182.33	66.65±103.74	0.983 ^a
Ranson scores	2.06±1.53	0.94±0.80	0.011 ^a

^at-test; ^bFisher's exact probability test. All those data were measured in the first 12 hours after the patients were admission.

excessive FFA, exceeding the capacity of albumin. As a result, the unconjugated FFA can cause activation of trypsinogen and induce AP [8], which is aggravated by formation of fatty acid ethyl esters [9, 10] and alcohol consumption. Liu et al. [11] showed that Low-dose FFA specifically activated JAK2/STAT3 phosphorylation, thereby causing malignant transformation of hepatocytes both in vitro and in vivo. However, the association of FFA and JAK2/STAT3 signaling pathway in AP has not been extensively studied.

Leptin, a 146-amino-acid peptide hormone, is produced by human adipocytes; it provides information on the availability of fat reserves and regulates fat metabolism [12]. The elevation of serum leptin level in AP has been well documented [13]. Leptin, as a secreted protein, regulates body fat metabolism through JAKs/STATs pathway [14]. Previous studies [15] have confirmed JAK2/STAT3 pathway involvement in the early differentiation of adipose cells and promoting fat formation, whereas the application of AG490 and siRNA silencing gene can

effectively reverse the effect. A recent study also found that leptin activated the JAK2/STAT3 pathways in rat nucleus pulposus cells [16].

Altogether, FFA and leptin have been reportedly correlated with the activation of JAK2/STAT3 signaling pathway. The current study aimed to evaluate the serum levels of FFA, leptin, p-JAK2, and p-STAT3 in patients with AP, their potential relationship with the JAK2/STAT3 pathway and the severity of AP in humans.

Patients and methods

The study protocol was approved by the Ethics Committee of Shanghai General Hospital, Shanghai Jiaotong University. All patients provided informed written consent before the initiation of any treatment. In this retrospective study, patients (n = 34) with AP who were admitted to the Department of Gastroenterology of Shanghai General Hospital, Shanghai Jiaotong University, between August 2015 and April 2016, were included. 10 volunteers formed the control group. Diagnostic criteria for acute pancreatitis

accorded with two or more of the following three criteria: sudden abdominal pain; levels of serum amylase or lipase that were greater than three times the upper limit of normal range; and imaging studies revealing peripancreatic exudation or pancreatic/peripancreatic necrosis [17]. The exclusion criteria were as follows: symptoms appearing after more than 48 h upon admission to the department; acute attack of chronic pancreatitis; and tumors and other causes of pancreatitis.

Peripheral venous blood samples were collected from all analyzed patients for analysis at the time of hospital admission. From these samples, white blood count and biochemical parameters (serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, glutamyl transferase, amylase, electrolytes, glucose, urea, creatinine, lactate dehydrogenase, and CRP), were measured on the day of blood sample collection. For FFA, leptin, p-JAK2, and p-STAT3 measurements, blood samples were withdrawn and serum separated by centrifugation (2000 g for

Table 3. Serum concentrations of leptin, FFA, p-JAK2, and p-STAT3

	Leptin (ng/mL)	FFA (μmol/L)	p-JAK2 (ng/L)	p-STAT3 (ng/L)
AP patients	2.59±3.30	461.33±169.48	445.55±292.19	570.36±386.65
Controls	1.15±1.08	310.26±93.03	102.91±82.95	97.25±80.29
T-value	2.182	3.653	6.058	6.663
P-value	0.035	0.001	P < 0.001	P < 0.001

Table 4. Serum concentrations comparison between mild subgroup (MCTSI < 4) and severe subgroup (MCTSI ≥ 4)

	Leptin (ng/mL)	FFA (μmol/L)	p-JAK2 (ng/L)	p-STAT3 (ng/L)
Severe subgroup	3.42±4.05	421.51±187.37	426.25±279.85	497.15±349.81
Mild subgroup	1.85±2.33	496.71±148.19	462.70±309.78	635.43±415.57
T-value	1.405	1.305	1.042	0.358
P-value	0.170	0.201	0.305	0.723

15 min) and preserved at -80°C until further usage.

According to the modified CT scoring system (MCTSI) [18], AP patients were divided into mild subgroup (< 4 scores) and severe subgroup (≥ 4 scores). The comparison of the clinical indicators and the levels of serum FFA, leptin, p-JAK2, and p-STAT3 were carried out between the two subgroups.

The total serum leptin level was measured using ELISA (Biolegend, American) in accordance with the test procedure and expressed as ng/mL. The serum concentrations of p-JAK2 and p-STAT3 were measured by ELISA (Meimian, Shanghai, China) according to the manufacturer's recommendations and expressed as ng/L. Any significant cross-reactions or interferences were not seen between human p-JAK2 or p-STAT3 analogs. The level of FFA was measured colorimetrically, according to the instructions on the reagent kit (Neo Scientific, Nanjing, China).

Statistical analysis

The continuous data were expressed as mean ± SE and compared using the independent sample Student's t-test, whereas the categorical variables were expressed as quantities and analyzed using the χ² test or Fisher's exact probability test. The correlations between the two independent parameters with normal distribution were assessed using Pearson's rank correlation test. Multiple stepwise linear regres-

sion analysis was performed to identify the related factors for high levels of p-STAT3. The analyses were conducted with statistical software (SPSS, version 21.0; SPSS Inc.). P-values < 0.05 were considered to indicate statistically significant differences.

Results

During the study period, a total of 34 patients were enrolled that constituted the AP group.

10 volunteers comprised the control group. The mean age of the AP group was 40.3±9.80 years (range, 18-86 years) and 16 patients (47.1%) were males. In our study, no statistically significant differences in gender, age, and body mass index (BMI) were observed between the two groups (Table 1).

According to MCTSI, 18 cases were mild AP and 16 were severe. Any demographic differences were not found between the mild and severe subgroups, except for C-reactive protein (CRP) and Ranson scores. CRP in the severe subgroup (136.60±116.13) was higher than in the mild subgroup (63.9056±50.03) (Table 2).

As seen in Table 3, serum levels of FFA, leptin, p-JAK2, and p-STAT3 were significantly higher in AP group compared to controls (P < 0.05; Table 3). In the AP group, the mean leptin level was 2.59 ng/mL, FFA was 461.33 μmol/L, p-JAK2 was 445.55 ng/L, and p-STAT3 570.36 ng/L. Also, no difference was observed in the two subgroups (Table 4).

As illustrated in Figures 1 and 2, a linear correlation between p-STAT3 and FFA levels (r = 0.345, P = 0.046) and p-JAK2 (r = 0.735, P < 0.0001) was observed in patients with AP. However, there was no significant linear correlation between p-STAT3 levels and leptin levels or BMI in patients with AP. A subsequent stepwise multiple linear regression (including BMI, CRP, FFA, and p-JAK2) analysis identified FFA and p-JAK2 levels as variables that were independently, significantly, and positively associ-

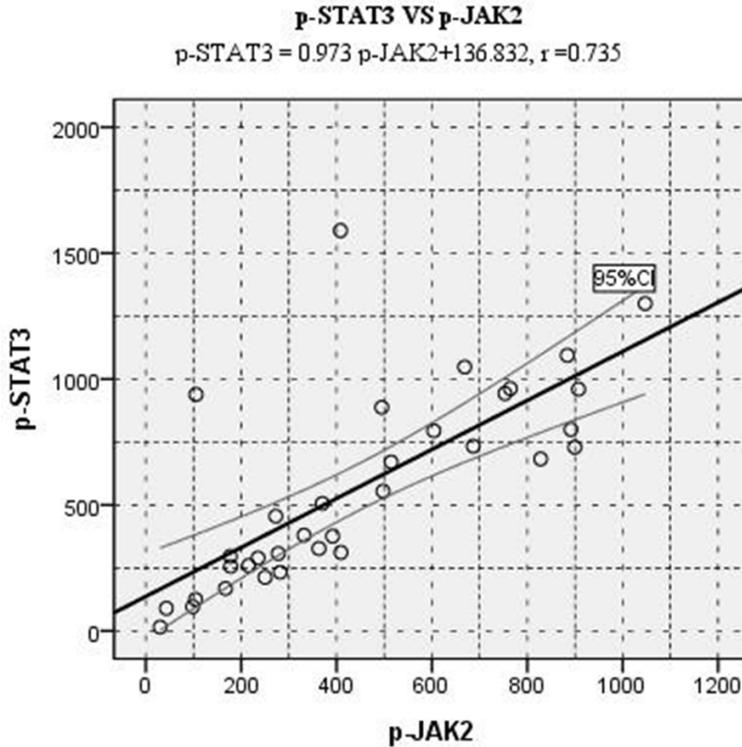


Figure 1. Correlation between P-STAT3 and p-JAK2 levels in patients with AP.

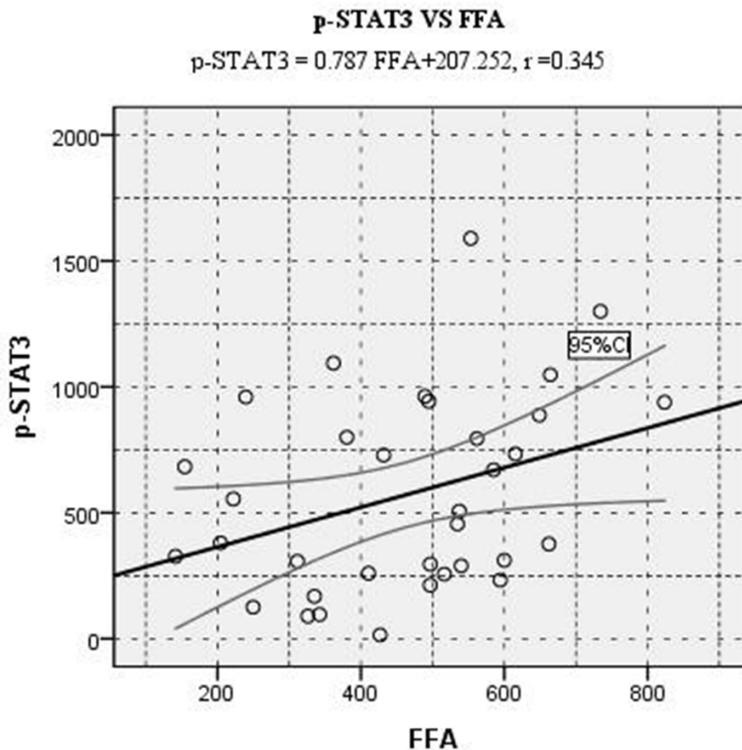


Figure 2. Correlation between P-STAT3 and FFA levels in patients with AP.

ated with the p-STAT3 levels ($R^2 = 0.644, P < 0.0001$).

Discussion

In the present study, we found that serum p-JAK2 and p-STAT3 levels in AP patients were significantly higher than that in the control group, demonstrating that JAK2/STAT3 pathway activation also occurred in AP patients. The changes of related serum molecules exhibited no relationship with the severity of the disease. In addition, the levels of FFA and p-JAK2 were independently and significantly correlated with the concentration of p-STAT3.

The extracellular information, including interferon, growth hormone, interleukin, and other chemical messengers can interact with the membrane receptor and activate the JAK/STAT receptor signaling pathway. The JAK2/STAT3 signaling pathway is induced by their proteins phosphorylation. Subsequently, p-STAT can form dimers, and translocate to the nucleus in pancreatic exocrine cells where it binds to DNA promoters and facilitates gene transcription [19]. In the current study, we observed that serum p-JAK2 and p-STAT3 concentration in AP patients significantly increased, compared to the control group, which indicates that JAK2/STAT3 signaling pathway is activated in AP patients. In AP, in addition to pancreatic tissue, liver, and lung tissue also exhibit the activation of the JAK2/STAT3 pathway [20, 21]. The levels of p-JAK2 and p-STAT3 in serum may be originated in multiple organs.

In AP, FFA was increased regardless of the etiology [22] and damage to the vascular endothelium and pancreatic acinar cells, producing an ischemic and acidic environment with toxicity [23]. A similar conclusion was achieved in our study. Compared to acute edematous pancreatitis (AEP), higher and sustained elevation of serum FFA levels was found in acute necrotizing pancreatitis (ANP) [24]. FFA values significantly correlated with the clinical course including amylase elevation, lung weight, and arterial oxygen pressure reduction [25]. Our findings showed that the concentration of FFA did not correlate with the severity of AP.

Obesity increases the risk of developing severe AP (SAP) [26] and patients with SAP present higher amounts of fat in the abdominal area [27]. Emerging evidence suggested that the serum leptin level was associated with the severity of pancreatitis positively or conversely. Some studies showed no significant association between serum leptin levels and severity of AP [28, 29]. Despite this characteristic, Panek J et al. [30] demonstrated that the role of leptin was not associated with the severity of acute biliary pancreatitis, which is in agreement with our data.

We also revealed that FFA and p-JAK2 were independently related to the increase in p-STAT3. Furthermore, we speculated that FFA activated the JAK2/STAT3 signaling pathway directly or via IL-6 or both. As a result, serum p-JAK2 and p-STAT3 levels increased. Firstly, STAT3 is the main signaling molecule for IL-6, and the binding of IL-6 to IL-6R α via recruitment of gp130 (IL-6R β) activates JAKs/STATs [31]. The JAK2/STAT3 signaling pathway was activated via IL-6 in hepatocellular carcinoma [32], esophageal squamous cell carcinoma [33] and in fatty liver-associated inflammation [34]. As one of the most accurate predictors of AP severity [35], IL-6 is involved in the whole process of SAP. IL-6/STAT3/CXCL1 (IL-8) cascade promotes acute lung injury (ALI) in AP [20]. Secondly, in low dose FFA exposure, hepatocytes specific genes showed malignant transformation via the IL-6-JAK2/STAT3 pathway, which is the evidence of FFA activating the IL-6-JAK2/STAT3 pathway. In addition, as a result of the lipolytic action on the peripancreatic adipose tissue, FFA levels increase and contribute towards the aggravation of AP [36]. STAT3 was

also seen to act as a downstream signaling pathway in the inflammatory acinar response induced by fat necrosis [36]. Moreover, the plasma FFA can induce high levels of IL-6 in several types of cells and correlate with IL-6 in vivo [37], which might be an underlying mechanism of p-STAT3 increase.

The present study evaluated the severity of the disease with enhanced CT or MRI performed in 5-7 days. The MCTSI score < 4 divided into the mild subgroup, and MCTSI score \geq 4 into the severe subgroup. This study showed no significant differences in p-JAK2 and p-STAT3 between the two subgroups, suggesting that the activation of the JAK2/STAT3 pathway not be the difference in either of the subgroups. However, we cannot exclude the effect of time. The activation of the STAT3 pathway and duration are time-dependent [38]. However, the serum samples for this study were selected at various time-point within 48 h from the onset of symptoms. Therefore, further studies are needed to eliminate the effect of the time factor.

AP is one of the common clinical diseases. At present, the study of the AP pathogenesis is mainly concentrated in the cell and animal experimental stage. However, to the best of our knowledge, this was the first study examining the JAK2/STAT3 signaling pathway in AP patients. Since the sample size of this study was small, the further large sample size is imperative to improve the reliability of the conclusion.

In conclusion, the serum FFA, leptin, p-JAK2, and p-STAT3 levels in AP patients were significantly high in AP patients, but had no relationship with the severity of the disease, demonstrating that JAK2/STAT3 pathway activation also occurred in AP patients. In addition, the levels of FFA and p-JAK2 were independently, significantly related with the concentration of p-STAT3.

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Disclosure of conflict of interest

None.

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