

# The Role of IL-6 in Macrophage-Mediated Fibrosis in Alcoholic Chronic Pancreatitis

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**Abstract:** Alcoholic chronic pancreatitis has become one of the important factors that threaten the safety of human life and endanger human tissue cells for the occurrence and spread of metabolic syndrome diseases. Therefore, this article is studying the role of IL-6 in the disease, with the purpose of improving the level of medical treatment through the study of interleukins. This article mainly adopted the experimental method and the control method to test and analyze the signal pathway of IL-6 in stimulating the differentiation of macrophages, and then draw relevant conclusions, and found that it has a catalytic effect in macrophage-mediated fibrosis. Experiments show that the STAT3 in the experiment is greater than 0.5, and the STAT3 signal pathway is positively correlated with the IL-6 concentration.

**Keywords:** IL-6, alcoholic chronic pancreatitis, macrophages, fibrosis

## 1. Introduction

Alcoholic pancreatitis is a disease of immune regulation, and its pathogenesis is closely related to the secretion of gastrointestinal enzymes in traditional Chinese medicine and lymph node metastasis in the spleen. It is mainly manifested by the loss of gastrointestinal microbes, causing various tissue damages. Alcoholic chronic pancreatitis is a gastrointestinal disease. Therefore, this article uses the role of interleukin 6 in macrophage-mediated fibrosis to speed up the determination of treatment options and the improvement of treatment methods.

Many scholars have been studied on macrophages mediated by alcoholic chronic pancreatitis. Zhang Weijie said that interleukin 6 (IL-6) has pleiotropic and multifunctional properties in the immune system [1]. Zhao Fangzhe explored the link between macrophages and interleukin-6 and IPF. The results show that macrophages can induce fibroblast migration and activation [2]. Zhuoyue discussed the role of IL-6, IL-10 combined with acute pancreatitis severity bedside index score in the prognosis assessment of severe acute pancreatitis [3]. This article studied the role of IL-6 in macrophage-mediated fibrosis in alcoholic chronic pancreatitis.

This article first understands alcoholic chronic pancreatitis, macrophages, IL-6 and fibrosis. Then, we conducted experiments on the role of IL-6 in macrophage-mediated fibrosis in alcoholic chronic pancreatitis. Finally, the data results are drawn and analyzed, and the conclusions are summarized.

## 2. The role of IL-6 in macrophage-mediated fibrosis in alcoholic chronic pancreatitis

### 2.1 Alcoholic chronic pancreatitis

Pancreatitis is inflammation caused by the activation of pancreatin. The incidence of alcoholic pancreatitis ranks first in Europe and America. In my country, its incidence rate is also on the rise compared to ten years ago. Patients with chronic pancreatitis often experience exocrine dysfunction such as loss of appetite, malnutrition, vitamin deficiency, and diarrhea. The treatment of pancreatitis mainly includes inhibition of pancreatic enzyme secretion, nutritional support, antibiotics and targeted therapy. It is related to the surgical treatment of pancreatic abscess, pancreatic necrosis, infection and other complications. In the gastrointestinal tract, the main source of alcoholic secretion is the salivary glands, and factors such as low amylase activity and slow fibrotic proliferation make it relatively high in combination with the liver [4-5]. Etiology and treatment: Studies have shown that one-third of patients have had at least one recurrence of pancreatitis within a few years of the initial diagnosis of the

disease without alcohol abstinence, but no recurrence has been observed in patients who abstained from alcohol[6-7].The prognosis of alcoholic pancreatitis has the following characteristics: (1) Mild relapse. In a recent survey, one-fifth of patients with alcoholic pancreatitis will relapse after a few years, and only one-tenth of patients with biliary pancreatitis will relapse [8-9]. (2) The development direction is chronic pancreatitis. Studies have shown that acute alcoholic pancreatitis is more likely to develop into chronic pancreatitis than biliary pancreatitis. (3) There are many complications and high mortality. Studies have shown that the mortality rate of patients with alcoholic pancreatitis is 31.7%. Alcoholic pancreatitis is characterized by inflammation and necrosis of the pancreas associated with harmful consumption, and is often accompanied by fibrosis and dysfunction. The onset and progression of the disease can be fast or slow. Chronic pancreatitis usually manifests as repeated or persistent abdominal pain, anorexia, and weight loss. It may also show signs of impaired pancreatic function [10-11].

Alcoholic pancreatitis can only be diagnosed when a patient with pancreatitis has a history of severe alcoholism. Occasionally drinking a small amount of alcohol does not determine that alcohol is the cause of pancreatitis. Generally do not drink alcohol, only drinking before the onset of pancreatitis will not cause pancreatitis, at best it is just a trigger[12].

## **2.2 Macrophages**

Macrophages are phagocytic cells called white blood cells. They are immune cells that can phagocytose pathogens and bacteria. Macrophages are derived from mononuclear organisms and have many functions. They play a great role in the body's own resistance to diseases. The acquisition of macrophages is relatively simple, can be purified and cultured, or used as a primary culture.

Macrophage is a kind of asexual immune system. Its activity is very similar to that of anti-tumor genes. It has a killing effect on cancer tissues. It has also been widely studied in the field of cancer. Macrophages are a kind of enzymes that can activate tissues. Its activity and mechanism of action are mainly reflected in the inhibition of alcoholic secretion. It is a kind of special tissue that can be formed in the intestinal tract and has a corresponding effect on the body by influencing its metabolic pathway to achieve the purpose of preventing and treating diseases.

Macrophages, also called histiocytes, differentiate from monocytes in the blood after leaving the blood vessel. After monocytes invade connective tissues, their size increases, endoplasmic reticulum and mitochondria proliferate, lysosomes increase, and phagocytosis is enhanced. The lifespan of macrophages depends on the tissues and organs where they are found, and they can usually survive for months or longer.

Different functional states of macrophages have different shapes and changes. Macrophages can adhere to glass and plastic surfaces during in vitro culture, and their non-specific cytoplasmic lipase is positive. Macrophages are old wastes that look like protozoan cells, can swallow large foreign bodies, and are rejected by cells and red blood cells at the end of their lives.

Macrophages are not only found in the blood, but also distributed throughout the body. The single-cell defense system is very simple. Macrophages swallow the foreign body and then excrete it as waste. However, if the body is constantly threatened by viruses and foreign proteins, this defense system cannot survive. As organisms evolved into vertebrates, a new defense system was formed. For small foreign objects like viruses, adhesion attacks are more effective. As a result, lymphocytes appeared, which gave up the phagocytic ability of macrophages, and mainly produced antibodies to entangle the enemy, further improving the phagocytic ability of macrophages.

## **2.3 IL-6**

Interleukins can transmit information, activate and regulate immune cells, and play an important role in inflammation.

Interleukin-6 can react with different types of cells, can be activated and synthesized by activated cells, and act on macrophages, liver cells, dormant T lymphocytes, activated B lymphocytes and plasma cells. IL-6 is one of the important mediators of early inflammation. In the acute phase, it stimulates the proliferation of activated T cells and B cells, secretes antibodies and stimulates liver cells to synthesize proteins. It reaches a peak several hours after the bacterial infection enters the body, and when the infection is severe, it increases sharply. IL-6 is a lymphokine produced by activated T cells and fibroblasts. It can transform the precursors of B lymphocytes into antibody-producing cells; combined with colony stimulating factors, it can promote the growth and differentiation of primary

bone marrow cells and improve the lysis function of natural killer cells.

Interleukin-6 is pleiotropic and can affect a variety of physiological functions. IL-6 is an effective activator of STAT3 signaling pathway. The activated P-STAT3 signal protein can quickly transfer to the nucleus. A large number of studies have shown that the activation of STAT3 by IL-6 plays a very important role in tumor progression.

### 2.4 Fibrosis

Fibrosis can occur in various organs. The main pathological change is the increase of fibrous connective tissue in the organ. Sustained development will lead to structural damage, loss of function, and even serious harm to health and life.

Fibrosis is the normal process of body tissue repair after acute inflammation in the body. However, in the process of chronic inflammation, fibrosis will destroy normal tissue structure and cause irreversible tissue damage to tissue function.

Anything that can damage tissue cells can cause tissue cell destruction, necrosis, and inflammation. If the damage is severe or repeated damage exceeds the regenerative capacity of parenchymal cells, the interstitial connective tissue will accumulate in a large amount to protect the defective tissue. Therefore, fibrosis is an essential repair response in order to maintain the relative integrity of tissues and organs after tissue injury. Although it repaired proliferative fibrous connective tissue defects, it lacked the cell structure and function of the original parenchymal organs. This over-repair response is strong and irrepressible, leading to organ fibrosis and deterioration of organ function.

## 3. IL-6 in the macrophage-mediated fibrosis experiment of alcoholic chronic pancreatitis

### 3.1 Experimental materials

Ana-1 cell line;

Ana-1 is one of the commonly used mouse macrophage cell lines, which can transform to M1 or M2 under certain conditions;

C57BL/6 mice;

A total of 36 C57BL/6 mice were used in this experiment, 5-7 weeks old, weighing 16-24 grams, purchased from the Provincial Center for Disease Control and Prevention. Mice use normal feed and are cultured in an environment with a constant temperature of  $23 \pm 3^\circ \text{C}$ , a humidity of  $50 \pm 5\%$ , and a 12-hour light-dark cycle.

### 3.2 Experimental equipment

For the direction of the national experiment in this article, the following equipment has been prepared, and some specific information is shown in Table 1:

Table 1. Information of experimental consumables, instruments and equipment

Equipment	Version	Nation
4 C/ constant refrigerator	DW-86L627	China
-20 C Save the fridge	MDF-U5413	Japan
-80°C ultra-cryopreserved refrigerator	705	America
Cell CO2 incubator	BB15,150L	Germany
Biosafety cabinet	BSC-1000IIA3	China
High-speed and high-capacity centrifuge	5812R	Germany
Full-function enzyme scaler	DG-234	America

### 3.3 Experimental method

In order to study the inhibitory effect and mechanism of IL-6/STAT6 signaling pathway on macrophage-mediated fibrosis in alcoholic chronic pancreatitis, the cell experiment was divided into three parts: (1) For Ana-1 cells with normal IL-6 expression, on the basis of IL-6 stimulation and

activation pathway modeling, the changes in the expression level of related molecules were measured. (2) Lentiviral transfection was used to up-regulate the expression of IL-6 on the surface of Ana-1 cells, and on this basis, experimental grouping and follow-up experiments were carried out. (3) Finally, the cells of each group are collected, and the relevant expression level is measured in real time, data is collected, and analyzed.

The noise of MRI images is a kind of random noise. In order to evaluate the resistance of different fibers to noise, it is often necessary to perform simulation tests.

Different degrees of noise are often added to the system. The specific calculation method is as follows:

DWI amplitude signal noise:

$$S = \sqrt{(X + M_1)^2 + M_2^2} \quad (1)$$

Among them, S represents the amplitude signal, and X is the original signal that is not polluted by noise.

The signal-to-noise ratio SNR is:

$$SNR = \frac{\hat{X}}{\ell_M} = \frac{\sqrt{X^2 - 2\ell_M^2}}{\ell_M} \quad (2)$$

#### 4. Experimental results

##### 4.1 IL-6 anti-fibrosis mechanism

PPAR $\gamma$ , KLF4, SOCS1 and STAT6 are important cytokines that induce the differentiation of macrophages into M2 type on the IL-6 pathway. This article calculates the amount of expression through experiments. The specific situation is shown in Table 2:

Table 2. Relative expression levels of PPAR $\gamma$ , KLF4, SOCS1 and IL-6

	PPAR $\gamma$	KLF4	SOCS1	IL-6
Cori150 ml	1.87	1.42	3.21	0.93
Cori100 ml	2.32	1.59	7.85	0.95
Cori50 ml	2.89	1.84	7.95	0.96
Model	3.87	2.35	13	0.97
Praziquantel	3.76	2	11	0.98
Control	1	1	1	1

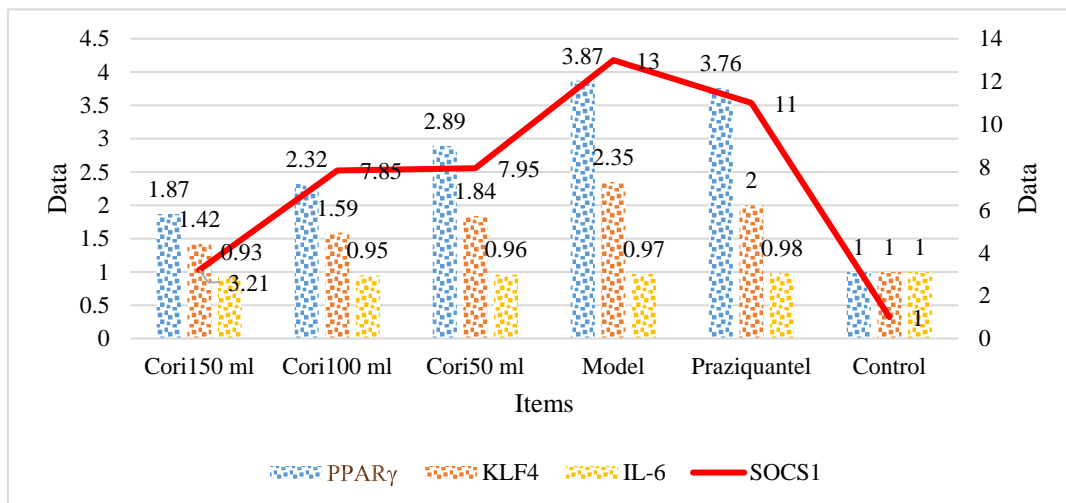


Figure 1. Relative Expression Levels of PPAR $\gamma$ , KLF4, SOCS1 and IL-6

As shown in Figure 1, we can see that the relative expression level of PPAR $\gamma$  maintains a relatively

stable trend in different capacities, and the data of the other three groups also maintain the same trend. Compared with the control group, its expression level did not change significantly. After IL-6 stimulated Ana-1 cells, the levels of PPAR $\gamma$ , KLF4 and SOCS1 in the model group were significantly higher than those in the blank control group.

**4.2 Detection of the signaling pathway of Il-6 to stimulate the differentiation of macrophages**

In the experiment, the signal test was carried out by detecting the expression changes of STAT3 and p-STAT3 protein in the macrophages of each group of the experiment. The specific situation is shown in Table 3:

Table 3. Detection of signaling pathways Il-6 stimulates macrophage differentiation

	STAT3(Experiment)	p-STAT3(Experiment)	STAT3(Control)	p-STAT3(Control)
0	0.75	0.76	0.13	0.12
50	0.80	0.83	0.12	0.15
100	0.90	0.92	0.15	0.17
150	1	1.17	0.16	0.2

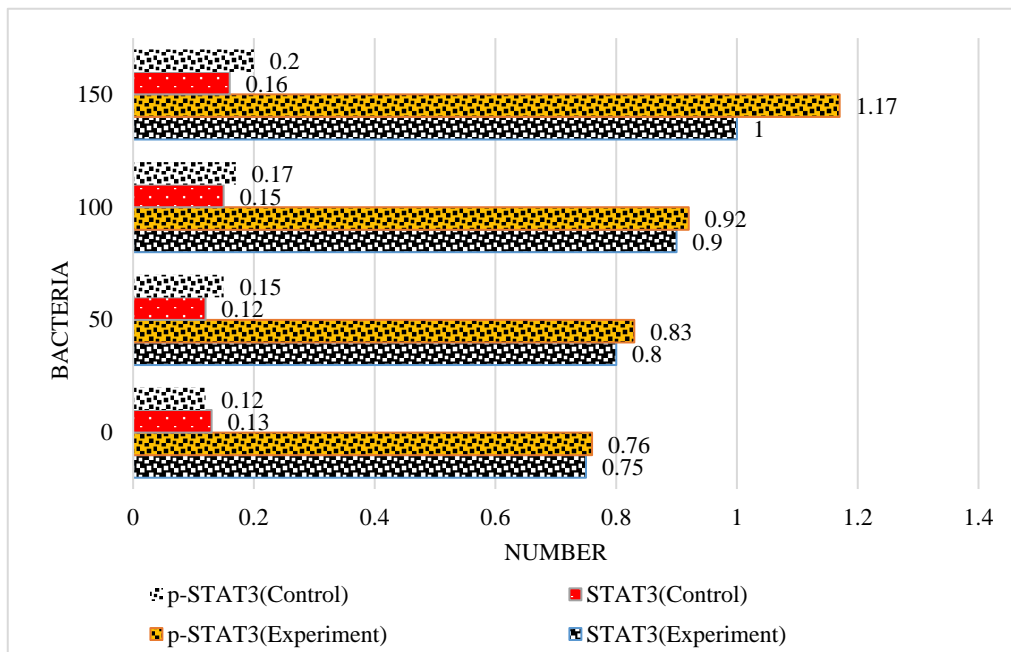


Figure 2. Detection of Signaling Pathways Il-6 Stimulates Macrophage Differentiation

As shown in Figure 2, we can know that there was a large amount of activated p-STAT3 expression in macrophages in the experimental group stimulated by IL-6, and the higher the concentration stimulated by IL-6, the greater the expression of p-STAT3. Only a small amount of p-STAT3 expression is in the control group. In the process of IL-6 inducing the differentiation of macrophages, the STAT3 signaling pathway is activated in the form of p-STAT3, and the degree of activation is positively correlated with the concentration of IL-6.

**5. Conclusion**

IL-6 is a cytokine with multiple biological functions, which can mediate its biological effects through two mechanisms. IL-6 receptor signals control the process of central homeostasis and immune response, such as acute phase response, glucose metabolism, hematopoietic and neuroendocrine system regulation. In colitis, tissue fibrosis, inflammatory arthritis, allergy, infection, inflammation, cardiovascular disease, inflammation-induced tumors, Trans-IL-6 signaling is indicated and can be used for the recruitment and apoptosis of white blood cells and T cells. The function and activation of inflammation play an important role. The fibrosis process is an extremely complex pathological process, involving a variety of signal pathways and cytokine transduction pathways. IL-6 leads to increased

secretion of pro-fibrotic factors and plays an important role in the disease. The role of interleukin 6 studied in this article is still lacking. The experiment is not perfect and needs further improvement.

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