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Original Article

Effect of TSLP on the function of platelets and IL-25 in chronic obstructive pulmonary disease

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Abstract: Objective: To investigate the effect of thymic stromal lymphopoietin (TSLP) on the function of platelets and IL-25 in patients with chronic obstructive pulmonary disease (COPD) and its monitoring value. Methods: 126 patients with COPD and 119 healthy subjects were selected for retrospective analysis. TSLP and IL-25 levels in the serum were measured using enzyme-linked immunosorbent assay (ELISA). The platelet level was detected using the automatic blood cell analyzer, while platelet aggregation ability was detected using the platelet aggregation analyzer. The correlation between TSLP and the partial pressure of oxygen (PaO_2) and partial pressure of carbon dioxide ($PaCO_2$) was analyzed. Results: The TSLP in the COPD group was significantly higher than that in the control group (P<0.001). IL-25, platelet count, and platelet aggregation rate in the high-TSLP group were significantly higher than those in the low-TSLP group (P<0.001). The PaO_2 in the high-TSLP group was significantly lower than that in the low-TSLP group (P<0.001), while the $PaCO_2$ in the high-TSLP group was significantly higher than that in the low-TSLP group (P<0.001). Linear correlation analysis showed that TSLP was negatively correlated with PaO_2 (r=-0.880, P<0.001) but positively correlated with $PaCO_2$ (r=0.878, P<0.001). Conclusion: The expression of TSLP can be used as an effective indicator for monitoring the severity of COPD in patients, and is considered as a potential target for the treatment of COPD.

Keywords: TSLP, platelets, IL-25, chronic obstructive pulmonary disease

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease characterized by persistent airflow limitation. It is a common disease in the respiratory system. The majority of patients affected by the disease are mainly middle-aged and older men [1].

According to statistics, in 2016, the number of new patients with COPD in the world exceeded 5 million, which is about 10 times higher than the number of patients ten years ago [2]. More statistical reports show that about 8.2% of people over the age of 40 will have COPD [3]. Additionally, the mortality rate of COPD is extremely high, and it is now one of the top five diseases that endanger human life [4]. According to statistics, the five-year survival rate of patients with COPD is only 28.4% [5]. Several studies report that COPD is expected to have the third highest mortality rate, after gastric and lung cancer, in 2030 [6]. COPD mainly manifests as cough, expectoration, and dyspnea. Damage to the lungs can also cause inflammation of surrounding organs and accelerate the deterioration of the disease [7]. The pathogenesis of COPD has not yet been clarified, but it is believed that smoking is the leading cause of COPD [8]. Through advancements in research, several studies have shown that infection, air, protease-antiprotease imbalance, and oxidative stress may cause COPD [9-11]. Efforts have been made to effectively improve the diagnosis and treatment of COPD, but no significant breakthrough has been made yet. In clinical practice, COPD is classified as an incurable chronic disease similar to diabetes and hypertension. To reduce the effects of the disease on patients, it is necessary to take large quantities of medication for a long time [12, 13].

In recent years, research has focused on targeted therapy for COPD. This led to the discov-

Table 1. Comparison of clinical data between the COPD and control groups [n (%)]

	COPD group (n=124)	Control group (n=119)	X^2 or t	P
Age	52.84±8.84	53.67±9.16	0.719	0.473
Body weight (KG)	66.13±12.34	64.81±13.47	0.426	0.797
Body temperature (°C)	36.28±0.84	36.12±0.70	1.610	0.109
Sex			0.065	0.799
Male	107 (86.29)	104 (87.39)		
Female	17 (13.71)	15 (12.61)		
Living Environment			0.699	0.403
Town	77 (62.10)	80 (67.23)		
Rural	47 (37.90)	39 (32.77)		
Smoking			0.934	0.334
Yes	114 (91.94)	105 (88.24)		
No	10 (8.06)	14 (11.76)		
Sports habit			0.266	0.606
Yes	24 (19.35)	20 (16.81)		
No	100 (80.65)	99 (83.19)		

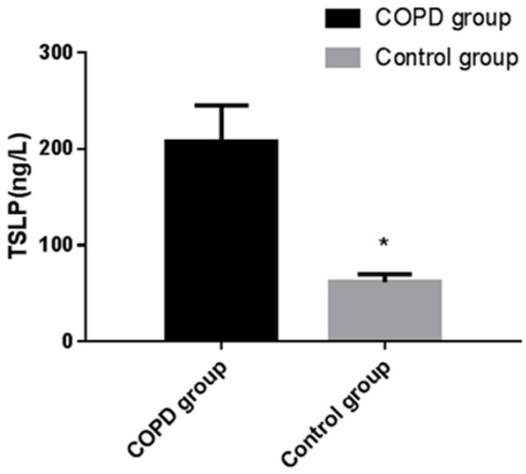

Figure 1. Expression levels of TSLP in the COPD and control groups. The TSLP in the COPD group was significantly higher than that in the control group. *represents P<0.001 when compared with the TSLP level in the COPD group.

ery of thymic stromal lymphopoietin (TSLP), an interleukin-7 (IL-7)-like cytokine. Its role in activating various cells (such as monocytes and T cells) has been shown to contribute to the development of various lung diseases and tumors [14-16].

At present, the role of TSLP is not clear. This study investigated the expression of TSLP and its effects on IL-25 and platelet function in patients with COPD. The aim of the study was to find a potential target for future treatment of COPD.

Materials and methods

General information

From February 2016 to March 2017, One hundred twenty-six patients with COPD who were admitted to our hospital and 119 healthy subjects (a total of 243 participants) were selected for retrospective analysis. 124 patients with COPD were assigned to the COPD group while 119 healthy subjects were assigned to the control group. The experiment was approved by the Ethics Committee of Quzhou People's Hospital, and all the above participants signed an informed consent form.

Inclusion and exclusion criteria

Inclusion criteria: Only patients who were diagnosed with COPD according to the 2014 COPD diagnosis guideline [17], aged between 30-70 years, and had undergone surgery and treatment with antibiotics were included in the study. Additionally, only complete cases and patients who cooperated with our hospital staff were included. Exclusion criteria: Patients with tumors, long-term use of glucocorticoids, cardiovascular and cerebrovascular diseases, immunological diseases, infectious diseases, pneumonia, organ failures, mental disorders, and physical disabilities were excluded from the study. Additionally, pregnant patients and long-term bedridden patients were excluded.

Methods

Sample collection: Patients in the COPD group were treated with targeted therapy after admission. Using anticoagulation and coagulation tubes, 4 ml of venous blood was taken from each patient. Platelet levels in the anticoagulation tubes were measured by an automatic blood cell analyzer (DxH800 Analyzer, Beckman Coultry Technology, Inc.) while platelet aggregation was measured using a platelet aggregation analyzer (Chrono-log 700 Platelet Aggregation Analyzer, Beckman Coultry Technology, Inc.). The coagulation tube was kept at 20°C for 20

Table 2. Comparison of clinical data between the high TSLP and low TSLP groups [n (%)]

	High TSLP group (n=66)	Low TSLP group (n=58)	X^2 or t	P
Age	53.16±8.25	54.08±7.44	0.649	0.518
Body weight (KG)	64.27±11.54	62.37±12.36	0.885	0.378
Body temperature (°C)	37.38±0.62	37.25±0.74	1.064	0.289
course of disease (d)	8.68±2.16	9.04±2.25	0.908	0.366
Sex			0.301	0.583
Male	58 (87.88)	49 (84.48)		
Female	8 (12.12)	9 (15.52)		
Living Environment			0.133	0.715
Town	40 (60.61)	37 (63.79)		
Rural	26 (39.39)	21 (36.21)		
Smoking			0.764	0.382
Yes	64 (93.94)	52 (89.66)		
No	4 (6.06)	6 (10.34)		
Sports habit			0.653	0.419
Yes	11 (16.67)	13 (22.41)		
No	55 (83.33)	45 (77.59)		

min, centrifuged for 10 min (4000 rpm/min), and the supernatant was divided into two parts.

Pressure of oxygen (PaO_2) and carbon dioxide ($PaCO_2$): Blood gas analyzer (Kangli BG-800 blood gas analyzer, Jinan Zhengrong Medical Instrument Co., Ltd.) was used for partial pressure of oxygen (PaO_2) and partial pressure of carbon dioxide ($PaCO_2$).

ELISA: Enzyme-linked immunosorbent assay (ELISA) was used to detect the serum TSLP and IL-25 (the kit was purchased from R&D systems, USA, 300-62, MAB13992), and the detection process was performed in strict accordance with the manufacturer's instructions.

Observation indicators: According to the expression level of TSLP, patients with COPD were divided into a high-TSLP group and a low-TSLP group. Parameters of interest included the clinical information of both COPD and control groups, differential expression of TSLP in both groups, effect of TSLP on IL-25 and platelets, IL-25 and platelet count, aggregation ability, and correlation between TSLP and PaO_2 and $PaCO_2$.

Statistical method: The data were analyzed and processed using the SPSS22.0 statistical software. Data on sex and smoking status in the clinical information of patients were expressed as rates. Comparison between groups was performed using the chi-square test. Data on the expression of TSLP and IL-25 were presented as mean ± standard deviation. The t-test was used for comparison between groups. Correlation was analyzed using linear correlation. Statistical significance was set at $P<0.050$.

Results

General information of the COPD and control groups

These 243 participants comprised 211 males and 32 females, aged 42-64 years, with an average age of 54.27±8.66 years. No significant difference ($P>0.05$) was observed after comparing the age, weight, body temperature, sex, living environment, and smoking and exercise status in the clinical data of the two groups. This demonstrated that the two groups were comparable (**Table 1**).

TSLP is increased in the COPD group

The TSLP in the COPD group was 207.63±37.48 ng/L. This was significantly higher than that in the control group which was 61.83±8.24 ng/L ($P<0.001$) (**Figure 1**).

Clinical data between the high-TSLP and low-TSLP groups has no difference

According to the median expression of TSLP, 66 patients with COPD were assigned to the high-TSLP group (TSLP>207.63 ng/L), and the remaining 58 were assigned to the low-TSLP group (TSLP≤207.63 ng/L). No significant difference ($P>0.050$) was observed after comparing the age, weight, body temperature, sex, living environment, and smoking and exercise status in the clinical data of the high-TSLP and low-TSLP groups. This showed that the two groups were comparable (**Table 2**).

IL-25 expression is higher in the high-TSLP group

IL-25 in the high-TSLP group was 23.66±4.58 pg/mL. This was significantly higher than that

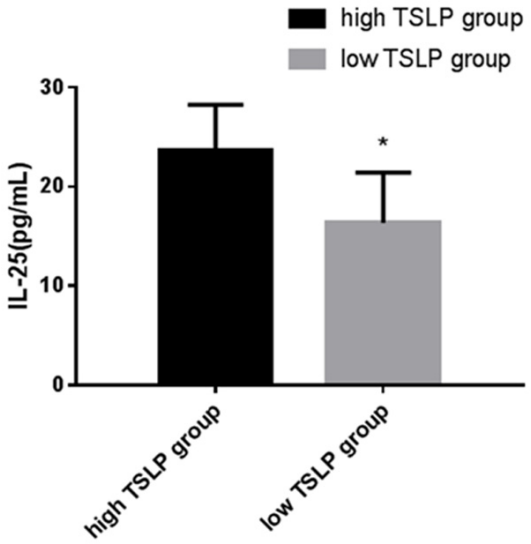

Figure 2. IL-25 expression levels in the high-TSLP and low-TSLP groups. The level of IL-25 was significantly higher in the high-TSLP group than that in the low-TSLP group. *represents P<0.001 for a comparison with the IL-25 level in the high-TSLP group.

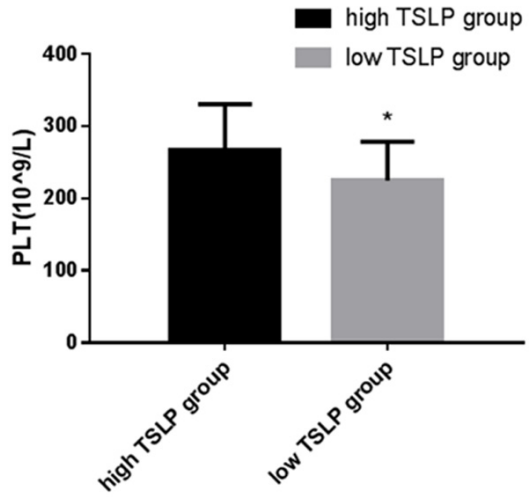

Figure 3. Platelet counts in the high-TSLP and low-TSLP groups. Platelet counts in the high-TSLP group were significantly higher than those in the low-TSLP group. *represents P<0.001 for the platelet count compared with that of the high-TSLP group.

in the low-TSLP group which was 16.34±5.07 pg/mL (P<0.001) (**Figure 2**).

Platelet aggregation rate is higher in the high-TSLP group

The platelet count in the high-TSLP group was 267.57±62.87×10^9/L, which was significantly higher than that in the low-TSLP group (224.39±54.21×10^9/L) (P<0.001). The platelet aggregation rate in the high-TSLP group was 36.84±8.57. This was significantly higher than that in the low-TSLP group which was 21.86±6.94 (P<0.001) (**Figures 3** and **4**).

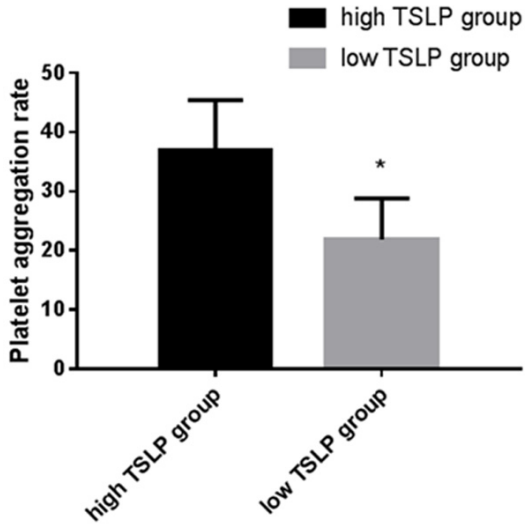

Figure 4. Platelet aggregation rate in the high-TSLP and low-TSLP groups. The platelet aggregation rate in the high-TSLP group was significantly higher than that in the low-TSLP group. *represents a higher platelet aggregation rate than that in the high-TSLP group, P<0.001.

Blood gas indicator PaO_2 is lower while $PaCO_2$ is higher in the high-TSLP group

The PaO_2 in the high-TSLP group was 52.96±6.97 mmHg, which was significantly lower than that in the low-TSLP group (59.84±5.71 mmHg) (P<0.001). The $PaCO_2$ in the high-TSLP group (78.56±8.14 mmHg) was significantly higher than that in the low-TSLP group (72.17±6.39 mmHg) (P<0.001). Linear correlation analysis showed that the TSLP was negatively correlated with PaO_2 (r=-0.880, P<0.001) but was positively correlated with $PaCO_2$ (r=0.878, P<0.001) (**Table 3**, **Figures 5** and **6**).

Discussion

COPD is a common respiratory disease, which is prevalent in middle-aged and elderly people. Recently, the incidence and mortality rates of COPD have been observed to increase every year [18]. Currently, there are limited treatment options for COPD in clinics. Some patients still

Table 3. Comparison of blood gas indices between high TSLP group and low TSLP group

	High TSLP group (n=66)	Low TSLP group (n=58)	t	P
PaO_2 (mmHg)	52.96±6.97	59.84±5.71	5.962	<0.001
$PaCO_2$ (mmHg)	78.56±8.14	72.17±6.39	4.815	<0.001

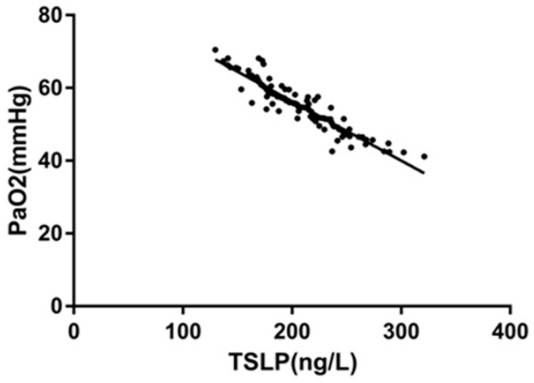

Figure 5. Correlation analysis between TSLP and PaO_2. Linear correlation analysis showed that TSLP was negatively correlated with PaO_2 (r=-0.880, P<0.001).

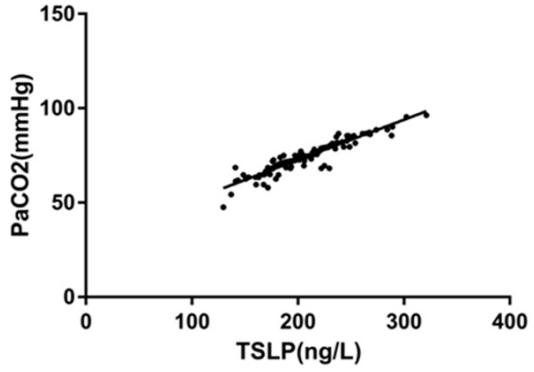

Figure 6. Correlation analysis between TSLP and $PaCO_2$. Linear correlation analysis showed that TSLP was positively correlated with $PaCO_2$ (r=0.878, P<0.001).

experience no fundamental changes in their pathological condition after treatment. Treatments may even worsen the lung function [19]. Some patients have poor autoimmune function, which is more likely to cause various cardiopulmonary complications, threatening the life and health of patients [20]. Therefore, there is an urgent need to find a method for effective treatment of COPD. Research has begun to explore targeted treatments for COPD with attention now being focused on TSLP. As an IL-7-like cytokine, it has some effect on human epithelial, thymic (Th) stromal, and vascular endothelial cells [21]. In recent years, studies have also shown that these cells inhibit and promote both the expression of inflammatory factors and the differentiation of subgroups of Th cells through the TSLP receptor. These cells participate in the development of some forms of inflammation, autoimmune diseases, and tumors [22]. IL-25, a cytokine produced by Th2 cells, enhances Th2 cell-mediated inflammatory response. It promotes airway hyper-responsiveness and eosinophil infiltration in lung tissue [23]. In the pathogenesis of COPD, platelet adhesion and aggregation also play an important role. Platelet membrane surface receptors and platelet agonists can cause molecular structure deformation, which leads to platelet aggregation and release [24]. Currently, the expression of TSLP in patients with COPD is still poorly understood. This study investigated the expression of TSLP and its effects on IL-25 and platelet function in patients with COPD. The aim of the study was to find a potential target for future treatment of COPD.

The results of this study showed that the expression of TSLP in the COPD group was significantly higher than that in the control group, suggesting that TSLP may be involved in the development of COPD. Studies have shown that there is a strong correlation between TSLP and inflammatory infections [25]. Therefore, it is suspected that when the bronchial epithelial barrier is destroyed in patients with COPD, TSLP activates CD4+ T cells, which promotes high expression of TSLP. The level of IL-25 in the high-TSLP group was significantly higher than that in the low-TSLP group, suggesting that TSLP can promote IL-25 expression. TSLP can trigger the abnormal reaction of eosinophils by activating the extracellular signal p38 and causing mitosis in proteases [26]. IL-25 not only induces the release of chemokines from eosinophils, but also delays the apoptosis of eosinophils [27]. In patients with COPD, high expression of TSLP activates eosinophils. Additionally, eosinophils secrete IL-25 thus resulting in a partial inflammatory response in the patient's body via the modulation of L-selectin. This leads to an increase in the proliferation of eosinophils, and promotes the activation of

TSLP and the production of inflammatory cytokines by Th2 cells. The patient's condition is then aggravated through a vicious cycle. The platelet aggregation ability of the high-TSLP group was significantly higher than that of the low-TSLP group, suggesting that TSLP can promote platelet aggregation. This is because TSLP induces the expression of platelet agonists. TSLP promotes platelet activation through receptors and accelerates the secretion of α-particles and dense particles. TSLP rapidly aggregates into platelet membranes, which causes the activation of integrin and leads to the aggregation of a large number of platelets. These platelets are released into the blood, which subsequently block the normal blood flow in the lung tissue, thus aggravating the condition of the patient. The role of TSLP and its effects on platelet function require further investigation. A comparison of the blood gas function between the high-TSLP and low-TSLP groups revealed that the $PaCO_2$ in the high-TSLP group was significantly lower than that in the low-TSLP group, and the $PaCO_2$ in the high-TSLP group was significantly higher than that in the low-TSLP group. Correlation analysis showed that TSLP was positively correlated with $PaCO_2$. This suggests that TSLP can be used as an effective indicator to monitor the severity of COPD in patients.

A limitation of this study is its small sample size. Another limitation is that it is a single-center study. We will conduct a long-term follow-up survey of this study, and further explore the effect of TSLP on IL-25 and platelet function in future studies to improve our experiments.

In summary, TSLP is highly expressed in patients with COPD and can promote the expression of IL-25 and platelet aggregation. TSLP can be used as an effective indicator for monitoring the severity of COPD in patients and is considered as a potential target for the treatment of COPD.

Disclosure of conflict of interest

None.

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