

Changes in serum inflammatory factors, adiponectin, intestinal flora and immunity in patients with non-small cell lung cancer

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Abstract. – **OBJECTIVE:** The aim of this study was to explore the changes in the body state of patients with non-small cell lung cancer (NSCLC), including intestinal flora, serum inflammatory factors, immunity and adiponectin.

PATIENTS AND METHODS: A total of 18 NSCLC patients (disease group) and 16 healthy people from the Medical Center (control group) were selected as research objects. The levels of immune molecules immunoglobulin A (IgA), IgG and IgM, and inflammatory factors interleukin-2 (IL-2), C-reactive protein (CRP), tumor necrosis factor- α (TNF- α) and IL-6 were detected via enzyme-linked immunosorbent assay (ELISA). The level of adiponectin was determined using the quantitative kit. In addition, the changes in intestinal flora were analyzed.

RESULTS: The overall survival time of NSCLC patients was significantly affected by IL-2 ($p=0.0026$), CRP ($p=0.03$), TNF- α ($p=0.014$) and IL-6 ($p=0.00018$). It can be seen that these inflammatory factors may play important roles in the progression of NSCLC. The levels of TNF- α ($p=0.037$), IL-2 ($p=0.043$) and CRP ($p=0.000$) in the peripheral blood serum were significantly higher in disease group than control group. Meanwhile, the levels of IgA ($p=0.040$) and IgG ($p=0.000$) in the peripheral blood serum were significantly higher in disease group than control group. However, no significant difference was observed in the level of IgM between the two groups ($p>0.05$). The expression of adiponectin gene (ADIPOQ) could remarkably affect the overall survival rate of NSCLC patients, and patients with high expression of ADIPOQ exerted significantly better prognosis ($p=0.017$). The level of serum adiponectin was evidently higher in control group than that in disease group ($p<0.05$). According to the linear discriminant analysis (LDA) score of the intestinal flo-

ra in both groups, the abundance of some intestinal flora (*Enterobacter* and *Lachnospiraceae*) was markedly higher in disease group than control group ($p<0.05$). However, the abundance of *Bifidobacteria*, *Pediococcus* and *Lactobacillus* was remarkably higher in control group than disease group ($p<0.05$). Correlation analysis indicated that *Lactobacillus* was positively correlated with *Bifidobacteria* ($r=0.44$, $p=0.000$), whereas was negatively correlated with *Enterobacter* ($r=-0.22$, $p=0.024$). Furthermore, *Enterobacter* was negatively associated with *Bifidobacteria* ($r=-0.15$, $p=0.038$) and *Streptococcus* ($r=-0.12$, $p=0.046$).

CONCLUSIONS: Serum inflammatory factors, adiponectin, intestinal flora and immunity may play important roles in the development of NSCLC.

Key Words:

Non-small cell lung cancer (NSCLC), Intestinal flora, Serum inflammatory factors, Adiponectin.

Introduction

Lung cancer has extremely high morbidity and mortality rates in the world, and there are more than one million people diagnosed with lung cancer every year^{1,2}. Non-small cell lung cancer (NSCLC) is dominated over SCLC in total cases, accounting for more than 80%³. NSCLC is characterized by difficult treatment, less sensitivity to chemotherapy, and poor prognosis. It will consume considerable financial and material resources, seriously affecting socioeconomic development⁴. Currently, the cause of NSCLC remains unclear,

which may be related to smoking and exposure to harmful chemicals⁵. The pathogenesis of NSCLC is complex, involving genetic factors, epigenetic regulation and immune-inflammatory level in the body⁶. Therefore, searching for molecules specifically changed during the development of NSCLC will be helpful to clarify the pathogenesis of the disease and to develop new treatment strategies⁷.

In recent years, it has been proved that intestinal flora can affect the progression of a variety of diseases, including respiratory infection in children⁸ and systemic lupus erythematosus⁹. Intestinal flora probably regulates the homeostasis and promotes the metabolic level to affect the development of diseases¹⁰. Intestinal flora has also been considered to play an important role in NSCLC development. In the present study, therefore, the changes in intestinal flora were compared between 18 NSCLC patients and 16 healthy people. The levels of serum immune molecules immunoglobulin A (IgA), IgG and IgM, and inflammatory factors interleukin-2 (IL-2), C-reactive protein (CRP), tumor necrosis factor- α (TNF- α) and IL-6 were determined as well. Meanwhile, the changes in adiponectin were also compared. Our study aimed to explore the changes in the body state of NSCLC patients, and to help discover new treatment methods in clinic.

Patients and Methods

General Data

The selection of patients was based on the guideline proposed by the Union for International Cancer Control (UICC). A total of 18 NSCLC patients (disease group) in our hospital and 16 healthy people from the Medical Center (control group) were selected as research objects. General data (name, gender, age, height and weight) and clinical data (disease history, family history, smoking and drinking history and drug allergy history) were collected in both groups. The mean age was (57.42 \pm 3.35) years old in disease group and (56.11 \pm 4.85) years old in control group, respectively. There were no statistically significant differences in such general data as gender and age distribution between the two groups ($p>0.05$). This investigation was approved by the Ethics Committee of Linyi Central Hospital.

Inclusion criteria for NSCLC patients in disease group were as follows: (1) patients with a history of smoking or exposure to harmful chemicals, (2) those with such clinical symptoms as

chest distress, cough or blood-stained sputum, (3) those with lung tumor shown in chest X-ray examination, or (4) those pathologically diagnosed with NSCLC.

Specimen Collection

5 mL of peripheral blood was first collected by nurses into pro-coagulation tubes, followed by centrifugation at 3000 rpm for 10 min within 30 min. The supernatant was then carefully transferred from pro-coagulation tubes into new 1.5 mL centrifuge tubes and stored at -20°C for later use.

Determination of Levels of Serum Immune and Inflammatory Factors

The levels of serum immune molecules IgA, IgG and IgM, and inflammatory factors IL-2, CRP, TNF- α and IL-6 were determined according to the instructions of enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN, USA). The supernatant of peripheral blood frozen was detected, with 3 replicates in each group. Optical density (OD) value at 550 nm was measured using a micro-plate reader (Bio-Rad, Hercules, CA, USA), and converted into the actual concentration of IgA, IgG, IgM, IL-2, CRP, TNF- α and IL-6. The mean sensitivity of the test was <0.42 pg/mL, and the inter-assay coefficient of variation was 6.3%.

Quantitative Detection of Adiponectin

The level of serum adiponectin was detected in both groups using the quantitative detection kit (Mercodia, Winston Salem NC, USA). Briefly, the serum was diluted with buffer, added into the sample well and shaken on a plate oscillator. After incubation and washing, the serum was added with enzyme conjugate solution, 3,3',5,5'-Tetramethylbenzidine, 4,4'-Bi-2,6-xylylidine (TMB) substrate and stop buffer. OD value at 450 nm was measured by a micro-plate within 30 min and converted into the content of adiponectin.

Detection of Intestinal Flora

Fresh, mid-posterior-segment and internal fecal samples (1 g each) were first collected from each object, and immediately frozen in a refrigerator at -80°C. Subsequently, the samples were sent to TinyGene for analysis of intestinal flora. DNA was extracted from samples, and PCR-DGGE was performed. Microbial diversity was finally analyzed, so as to determine the distribution of intestinal flora.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 22.0 software (IBM, Armonk, NY, USA) was used for statistical analysis. Measurement data were expressed as mean \pm standard deviation ($\bar{x} \pm s$). The *t*-test was used for intergroup comparison, and Pearson's correlation analysis was conducted. Survival analysis was performed using the Kaplan-Meier plotter method. $p < 0.05$ was considered statistically significant.

Results

Inflammatory Factors Affected Survival Prognosis of NSCLC Patients

To find the inflammatory indexes that affected NSCLC patients, the inflammatory molecules significantly related to the survival and prognosis were screened, including IL-2, CRP, TNF- α and IL-6. It was found that the overall survival time of NSCLC patients could be significantly affected by IL-2 ($p=0.0026$), CRP ($p=0.03$), TNF- α ($p=0.014$) and IL-6 ($p=0.00018$) (Figure 1). Therefore, it can be seen that these inflammatory factors may play important roles in the progression of NSCLC.

Changes in Levels of Inflammatory Factors in Both Groups

As shown in Table I, the levels of TNF- α ($p=0.037$), IL-2 ($p=0.043$) and CRP ($p=0.000$) in the peripheral blood serum were significantly higher in disease group than control group.

Changes in Levels of Immune Indexes in Both Groups

As shown in Table II, the levels of IgA ($p=0.040$) and IgG ($p=0.000$) in the peripheral blood serum were obviously higher in disease group than control group. However, no significant difference was observed in the level of IgM between the two groups ($p > 0.05$).

Effect of Adiponectin Gene (ADIPOQ) on Prognosis of NSCLC

The expression of ADIPOQ could remarkably affect the overall survival rate of NSCLC patients. Patients with higher expression of ADIPOQ exhibited significantly better prognosis, while those with lower expression of ADIPOQ had worse prognosis ($p=0.017$) (Figure 2). The above findings suggest that adiponectin acts as

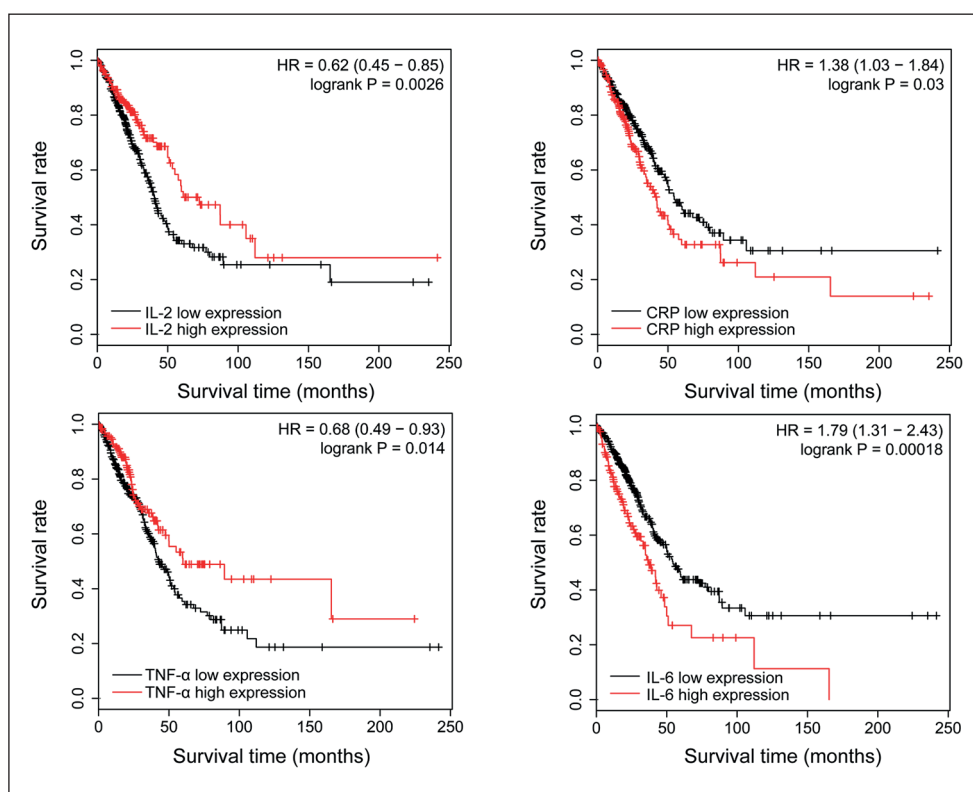


Figure 1. Effects of IL-2, CRP, TNF- α and IL-6 on survival prognosis of NSCLC patients.

Table I. Changes in levels of inflammatory factors in both groups ($\bar{x} \pm s$).

Group	N	TNF- α (ng/L)	IL-2 (ng/L)	CRP (mg/L)	IL-6 (ng/L)
Control group	18	19.67 \pm 2.12	7.54 \pm 0.27	5.32 \pm 2.84	7.42 \pm 1.74
Disease group	16	25.42 \pm 3.21	9.94 \pm 0.84	9.42 \pm 1.84	7.21 \pm 1.36
<i>t</i>		8.42	7.54	13.35	3.03
<i>p</i>		0.037	0.043	0.000	0.421

Table II. Changes in levels of immune indexes in both groups ($\bar{x} \pm s$).

Group	N	IgA (U/mL)	IgG (U/mL)	IgM (U/mL)
Control group	18	94.21 \pm 7.45	83.12 \pm 4.21	123.92 \pm 11.29
Disease group	16	131.46 \pm 8.64	231.23 \pm 13.21	119.84 \pm 10.31
<i>t</i>		7.98	16.43	3.94
<i>p</i>		0.040	0.000	0.273

a tumor suppressor gene in the development of NSCLC, which can delay the progression of the disease.

Changes in Serum Adiponectin Level in Both Groups

The level of serum adiponectin was evidently higher in control group than that in disease group ($p < 0.05$) (Figure 3). It can be inferred that adiponectin is one of the important factors inhibiting NSCLC progression.

Analysis of Intestinal Flora in Both Groups

According to the linear discriminant analysis (LDA) score of the intestinal flora in both groups,

the abundance of some intestinal flora (*Enterobacter* and *Lachnospiraceae*) was markedly higher in disease group than control group ($p < 0.05$). However, the abundance of *Bifidobacteria*, *Pedococcus* and *Lactobacillus* was remarkably higher in control group than disease group ($p < 0.05$) (Figure 4).

Correlation Analysis of Intestinal Flora in Both Groups

Correlation analysis indicated that *Lactobacillus* was positively correlated with *Bifidobacteria* ($r = 0.44, p = 0.000$), whereas was negatively correlated with *Enterobacter* ($r = -0.22, p = 0.024$). In addition, *Enterobacter* was negatively associated with *Bifidobacteria* ($r = -0.15, p = 0.038$) and *Streptococcus* ($r = -0.12, p = 0.046$) (Figure 5).

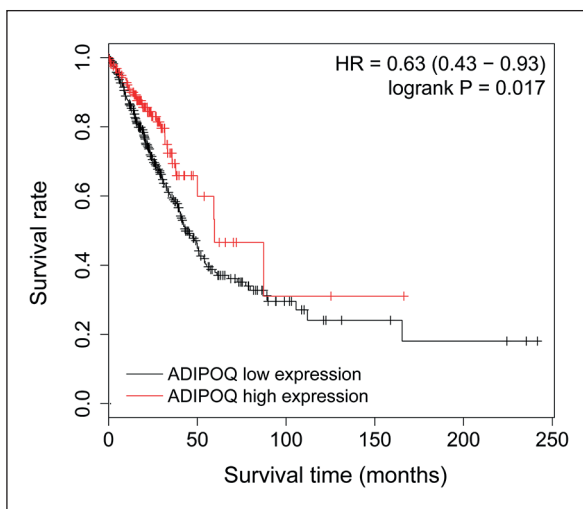


Figure 2. Effect of ADIPOQ expression on prognosis of NSCLC patients.

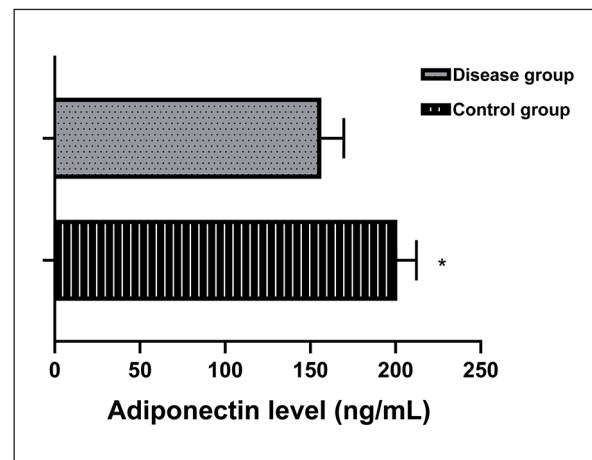


Figure 3. Changes in adiponectin level in both groups (* $p < 0.05$ vs. disease group).

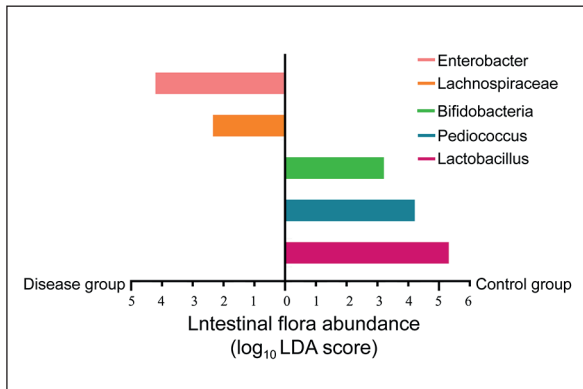


Figure 4. Comparison of LDA score of intestinal flora between the two groups.

Discussion

NSCLC is a pathological type of lung cancer with poor prognosis, which seriously affects the effect of chemotherapy¹¹. About three-quarters of NSCLC patients have already been in the mid-late stage when diagnosed, leading to a lower 5-year survival rate¹². Discovering specific changes during the onset of NSCLC may be helpful for early diagnosis and monitoring of the disease. Current studies have shown that the pathogenesis of NSCLC is related to smoking, long-term exposure to benzene and other harmful chemicals, and exposure to radioactive substances¹³. Due to long-term and chronic exposure to harmful substances, the mutations of genetic materials

occur in NSCLC patients. This may activate proto-oncogenes, inhibit tumor suppressor genes, up-regulate expressions of cancer-related proteins, and ultimately promote cell canceration¹⁴. During this process, activated cancer-promoting genes play important roles. They can cause great changes in the inflammatory level, immune state and metabolic process in patients, thereby resulting in cancer progression¹⁵. Therefore, exploring the changes in the levels of various substances in NSCLC patients is of great significance for finding targeted therapeutic strategies.

Intestinal flora refers to microorganisms colonized in the ileum, colon, etc., including probiotics (*Lactobacillus* and *Bifidobacteria*) that are able to synthesize essential vitamins in the body¹⁶. At the same time, these microorganisms can affect the intestinal nutrient absorption and synthesis, and trace element intake. Alteration of intestinal flora affects local intestinal homeostasis and systemic homeostasis. Meanwhile, it has been proved to be related to the occurrence and development of a variety of malignant tumors, such as breast cancer¹⁷ and nasopharyngeal carcinoma¹⁸. In NSCLC, inflammatory and immune states may be altered by intestinal flora through affecting local substance absorption and metabolism, thereby affecting its progression. Therefore, discovering the characteristics of intestinal flora in NSCLC patients may help to find the flora promoting or suppressing the development of the disease. Furthermore, this may help to guide the development of probiotic preparations for NSCLC patients. In this study, it was found that the abundance of some intestinal flora (*Enterobacter* and *Lachnospiraceae*) was markedly higher in disease group than that in control group ($p < 0.05$). However, the abundance of *Bifidobacteria*, *Pediococcus* and *Lactobacillus* was markedly higher in control group than disease group ($p < 0.05$). According to the correlation analysis, *Lactobacillus* was positively correlated with *Bifidobacteria* ($r = 0.44$, $p = 0.000$), whereas was negatively correlated with *Enterobacter* ($r = -0.22$, $p = 0.024$). *Enterobacter* was negatively associated with *Bifidobacteria* ($r = -0.15$, $p = 0.038$) and *Streptococcus* ($r = -0.12$, $p = 0.046$). The above results demonstrate that intestinal flora may play important role in the progression of NSCLC.

Inflammatory and immune states are important factors affecting tumor progression. The levels of various inflammatory and immune factors in the body may affect tumor progression via the promotion of immune cell differentiation and the

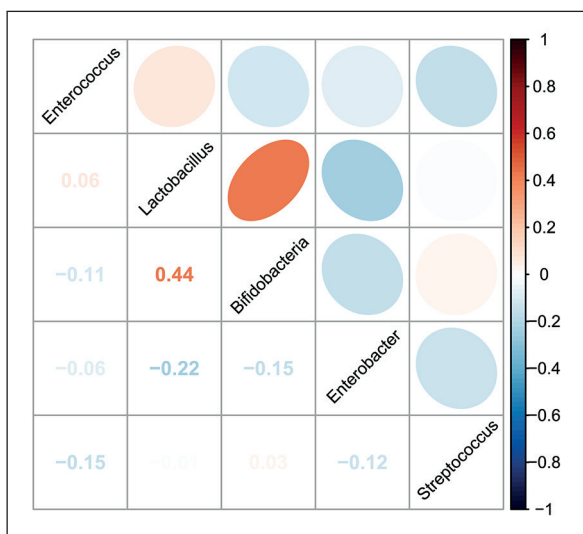


Figure 5. Pearson's correlation analysis of intestinal flora in both groups.

chemotactic effect on cells¹⁹. In this study, the results revealed that the overall survival time of NSCLC patients could be significantly affected by IL-2 ($p=0.0026$), CRP ($p=0.03$), TNF- α ($p=0.014$) and IL-6 ($p=0.00018$). It can be seen that these inflammatory factors may play important roles in NSCLC progression. The levels of TNF- α ($p=0.037$), IL-2 ($p=0.043$) and CRP ($p=0.000$) in the peripheral blood serum were significantly higher in disease group than control group. The levels of IgA ($p=0.040$) and IgG ($p=0.000$) in the peripheral blood serum were markedly higher in disease group than control group. However, no significant difference was observed in the level of IgM between the two groups ($p>0.05$). The above results indicate that inflammatory and immune states are most likely to affect the progression of NSCLC.

Adiponectin, composed of 244 amino acids, is a hormone secreted by adipocytes. It has been found to be associated with metabolic diseases such as diabetes and obesity²⁰. Several reports have also indicated that adiponectin possesses a certain anti-inflammatory effect, which may affect the development of tumors²¹. In this study, the expression of ADIPOQ could remarkably affect the overall survival rate of NSCLC patients. Patients with higher expression of ADIPOQ exhibited significantly better prognosis ($p=0.017$). The level of serum adiponectin was evidently higher in control group than that in disease group ($p<0.05$). These findings prove that adiponectin may exert an anti-tumor effect on NSCLC.

Conclusions

The novelty of this study was that intestinal flora, serum inflammatory factors, immunity and adiponectin are closely associated with NSCLC, which may help to evaluate the condition of NSCLC.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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