The Expression and Significance of CD4+ T Lymphocyte in the Peripheral Blood of Patients with Asthma

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Abstract

Objective: To detect the CD4+ T lymphocyte proportion in the peripheral blood of the patients with bronchial asthma at different stages by flow cytometry.

Methods: 53 patients with asthma were recruited and divided into three groups: the acute exacerbation group of 28 cases, the mild remission group of 20 cases and the moderate to severe remission group of 5 cases. At the same time, the normal controlled group of 16 cases was set up as contrast. The proportion of Th1, Th2, Th17 and Treg in the peripheral blood of the patients with asthma and normal controlled cases were detected by flow cytometry respectively. Lung function tests were simultaneously performed in the patients with asthma groups and normal controlled group. High-resolution CT was taken in the remission and the normal group, then the ratio of 2 airway wall thickness to outer diameter (2T/D), the ratio of wall area to total airway area (WA%), lung densities in both the inspiratory and expiratory phases and the two phase difference were measured in everyone who took the HRCT.

Results: The acute group had a much lower Th1 and Treg proportion than the mild remission group and the normal group (P<0.05), and the remission group also had a lower proportion than the normal controlled group (P<0.05), but the Th1 and Treg proportion difference was not statistically significant between the two remission groups; The proportion of Th2 and Th17 in peripheral blood in acute group was higher than that in the mild remission group and the normal group (P<0.05), and that in the two remission group was also higher than that in the normal group (P<0.05), the proportion of Th2 in the acute group was higher than that in the moderate-severe remission group, but Th17 was not statistically significant between the two groups, the proportion of Th17 in the moderate-severe remission group was higher than that in the mild remission group, but Th2 was not different between the two groups; The ratio of Th1, Th2 and the ratio of Th17, Treg was obviously significant between the acute group, the mild remission group and the normal group (P<0.01), the ratio of Th17 and Treg between any two groups was statistically significant (all P<0.05), whereas the ratio of Th1 and Th2 was not significant between the mild remission group and the moderate to severe remission group, but it was also significant among the other two groups; 2T/D, WA%, inspiratory phase CT values and the different CT values between inspiratory phase and expiratory phase were statistically significant among the two remission and the normal groups (P<0.05), but inspiratory phase CT value in the three groups showed no significant difference.

Conclusions: There were CD4+ T lymphocyte immunological function disorders in peripheral blood of patients with acute exacerbation and remission of asthma, of which Th2 and Th17 had an enhanced immune response phenomenon, with an obviously enhanced expression for Th17 cells in moderate-severe remission asthma patients. However, Th1 and Treg cells with a protective effect had a lower functioning. Therefore there existed not only Th1/Th2 imbalance but also Th17/Treg imbalance in peripheral blood of asthma; airway wall thickness pathological changing phenomenon and gas retention phenomenon existed in asthmatic patients too; the diffusion capacity of patients with bronchial asthma and the normal controlled group did not be obviously different.

Keywords: Bronchial asthma; CD4+ T lymphocyte; Flow cytometry; HRCT; Lung function

Introduction

Bronchial asthma is a chronic inflammatory disorder of the airways which are involved with eosinophils cells (EOS), neutrophils, mast cells, T lymphocytes, airway epithelial cells, other cells and cytokines. Airway inflammation of asthma is an inflammatory response with EOS and Th2 cytokine predominantly high expressed. Experimental and clinical studies have confirmed that Th1/Th2 imbalance is involved in airway inflammation response. However, for some refractory asthma patients and early asthma patients who have the significant airway structural changes, Th1/Th2 imbalance cannot fully explain the clinical characteristics and phenotype. Especially in some non-EOS based refractory asthma patients, the phenotype of airway inflammation is neutrophils or smooth muscle cell proliferation based less inflammatory cells of which Th17 cells play an important role. Th17 cells are a new type of CD4+ T lymphocytes discovered recently, both experimental and clinical studies found that Th17 cells and airway neutrophilic inflammation mediated by Th17 cells are closely related to asthma severity [1]. In recent years, some researchers have suggested that Th17/Treg imbalance plays a key role in the occurrence and development of asthma, particularly in patients with refractory or special inflammation phenotype [2-6]. This study detected the expression of Th1, Th2, Th17, Treg of asthma patients in the acute, paracmastic phase and the normal group respectively, and moreover, explored the changes of lung function

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and airway wall structure by high-resolution CT. This study aims to
clarify that how Th1/Th2 imbalance and Th17/Treg imbalance play a
role in the pathogenesis of asthma patients, especially in the patients
with airway structural changes, and also aims to tell the phenotypic
characteristics of Th1, Th2, Th17 and Treg in the peripheral blood of
different types of asthma patients.

Patients and Methods

Patients

The asthma group: The asthma patients were selected from
respiratory Department of the First Hospital of Shanxi Medical
University, in line with “bronchial asthma prevention and treatment
These patients were older than 18 years old, they did not smoke and did
not have other chronic respiratory disorders and other diseases which
affected the airway structure. Patients with chronic inflammatory
diseases should also be ruled out. Selected patients were divided into
acute stage (n=28) and remission stage, the remission group was divided
into mild remission (n=20) and moderate to severe remission (n=5)
groups by symptom assessment and pulmonary function test results.

The normal contrast group: The patients of this group were healthy
by physical examination. All of them didn't have a history of allergic
disease and family history, and they didn't take drugs such as hormones
and immunomodulatory drugs in the past three months (n=16).

The four groups above have no significant differences in age
distribution, gender ratio and disease history.

Laboratory equipment and reagents: 1), Equipment Flow
cytometry (U.S. BD Biosciences), 64-slice spiral CT (GE's), ME511L
PACS system (Japan TOTOKU Company), Vmax229 pulmonary
function analyzer (U.S. Sen Disi company), auto trim levels centrifuge,
-70°C refrigerator (Japan SANYO).

Reagents

U.S.BD Biosciences LEUKO ACTIVE CKTL CD4 monoclonal
antibody (FITC-labeled), CD25 mAb (PerCP-Cy5.5 mark) CYTOFIX/CYTOPERM BUF KIT, HUMAN FOXP3 BUF SET IL-4 antibody (PE
marker), IFN-r antibody (PerCP-Cy5.5 marker), IL-17 antibody (Alexa
Fluor 647 labeled), Foxp3 antibodies (PE labeled) corresponding to
the various antibody isotype control; lymphocyte separation medium,
RPMI-1640 complete medium, PBS solution.

Methods

Analysis of the CD4+T lymphocyte subpopulations by flow
cytometry

• Cell preparation and activation: Fasting peripheral blood of
5 mL was collected in sterile heparinized blood collection tube. PBS
solution was diluted with an equal proportion, then the blood and PBS
solution were mixed; 3 mL lymphocyte separation medium was added
to a new 15 mL centrifuge tube, the diluted whole blood was added
slowly to the liquid surface of the lymphocyte separation medium,
centrifuged 2000 rpm for 20 minutes; The white lymphocyte layer was
suctioned to another centrifuge tube, then 5 mL PBS liquid was added,
centrifuged at 1000 rpm for 5 minutes, the supernatant was discarded;
Then 5 mL RPMI-1640 complete medium was added to resuspend
the cells, 1500 rpm for 5 minutes, the supernatant was throwed away.
Then the cells were re-suspended with RPMI complete medium and the
cell concentration was adjusted to 1×10^7/mL, the cell suspension was
transferred to a sterile 12-well plates, a cell stimulating agent (including
PMA and ionomycin, monensin) 2 ul/mL was added into it, mixed.
12-well plates were trained at 5% CO2, 37°C incubator for 4-6 hours,
to the time after the cultured cells were harvested, centrifuged at 1000
rpm for 5 minutes, the supernatant was removed, then the cells were
suspended with 2 mL PBS, centrifuged 1500 rpm for 5 minutes,
and the supernatant was discarded.

• Cell surface staining: 2×10^6 cells were put into per tube, then 20
ul. CD4 labeled antibody was added into each tube, then 5 ul. CD25
labeled antibody was added into the Treg tube, reacting in the dark
at room temperature for 20 minutes; then 2 mL PBS liquid were added
to each tube, 1000 rpm centrifuged for 5 minutes, the supernatant
was throwed away.

• Cells fixed and rupture

1. Th1, Th2, Th17, 500 ul. 4°C for precooling fixative (Fixation)
was added to the corresponding test tube, mixing, reacting in the dark
at room temperature for 20 minutes, after adding 2 mL1×Perm/Wash
solution, 1500 rpm centrifuged for 5 minutes, the supernatant was added
broken film formers 2 mL 1×(Perm/Wash solution) to resuspend cells,
icubated in the dark place at room temperature after 15 minutes, 1500
rpm centrifuged for 5 minutes, the supernatant was throwed away.

2. Treg 2 mL 1×Human Foxp3 Buffer A was added to the test
tube, mixed, incubated in the dark at room temperature for 10
minutes, centrifuged at 1000 rpm for 5 minutes, the supernatant
was throwed away, and then 2 mL PBS lotion was added, mixed, 1000 rpm
centrifuged for 5 minutes, the supernatant was throwed away, and then
0.5 mL 1×Human of Foxp3 Buffer C was added to each tube, mixed
uniformly, incubated in the dark at room temperature for 20 minutes,
2 mL PBS washings was added to each tube, 1000 rpm centrifuged for 5
minutes, the supernatant was discard.

3. Intracellular staining: 5 ul. IFN-γ antibody, 5 ul. IL-4 antibody,
20 ul. IL-17 antibody and 20 ul. Foxp3 antibody were added to each
tube of Th1, Th2, Th17 and Treg respectively. The corresponding isotype
control antibody were also added to isotype control tubes, mixed in the
dark at room temperature for 30 minutes, added 2 mL PBS washings
were added, centrifuged at 1000 rpm for 5 minutes, 150 ul. Buffer was added
to the supernatant to resuspend cells.

4. Acquisition and analysis by flow cytometry

High-resolution CT scan: The remission asthma patients and the
healthy group were took the chest HRCT inspection. The images
were viewed at the end of expiratory breath holding and inspiration
breath holding respectively, thickness 0.625 mm, layer interval of 1
mm continuous scanning. Scan condition was 200 mA, 140 kV, matrix
512×512 bone algorithm reconstruction. Measurements were conducted
by two experienced thoracic radiologists who didn't know the patients'
disease working independently in PACS system on a window width
of 1500 Hu, window level of-450 Hu. Five sections were obtained: top
of the aortic arch, main carina, 1 cm below the main carina, level of
the pulmonary veins, and 2 cm above the right hemidiaphragm. The
bronchus of more than 1 mm in diameter clearly seen in cross section
was measured at the above level. The imagines were viewed on a work
station using a magnification of an uniform ratio, and measurements of
overall (D) and internal (L) diameter of the bronchi were made using
electronic calipers, with wall thickness (T) being derived from these
measurements(T=(D-L)/2). Airway wall thickness ratio of the outer
diameter of the airway 2 times T/D, accounting for the percentage
of the total cross-sectional area of the airway wall area WA% [WA%=]=π

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While the Kruskal-Wallis (H test) was adopted for unequal variances, and the pairwise comparisons used the Wilcoxon test (α <0.05 level). The description of the experimental results were shown in figures 1-4.

The above results can be seen in tables 1 and 2; Flow cytometry results shown in figures 1-4.

The results of HRCT: Table 3 is the HRCT results, as shown in this table, the airway wall thickness and 2 times of airway lumen diameter ratio (27/D) of the moderate-severe remission period group (0.414 ± 0.03) and the mild remission group (0.403 ± 0.01) were higher than that of the healthy group (0.352 ± 0.01) (P<0.05), there was no statistical significance between the moderate-severe remission period group and the mild remission group.

The expression of Th1/Th2, Th17/Treg of the acute exacerbation, the mild and the moderate-severe remission was statistically significant (all P<0.05); but the expression of Th1/Th2 in mild group and the moderate-severe remission group was no statistically significant.

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The pathogenesis of bronchial asthma is complex, while immune and inflammatory mechanism of CD4⁺ T lymphocyte has reached a consensus. The theory of Th1/Th2 imbalance in the past few decades has been considered to be the core of the pathogenesis of asthma; allergens in patients with asthma can selectively promote Th1 cell proliferation predominant expression of Th2 cells, as a consequence, the Th1/Th2 balance to Th2 conversion [8], which means that Th2 cells have a polarization response. The results of this study confirmed that there existed Th1/Th2 imbalance and the high expression of Th2 cells which have a role of pro-inflammatory in the peripheral blood of asthma patients, and its expression of the acute group was higher in a serious condition, while Th2 expression in acute asthma was also higher than that in moderate-severe remission group, but that in mild group and the moderate-severe remission group was not statistically significant. The expression of Th1 cells which have a role of cell-mediated immunity in the peripheral blood of asthma patients was low, while its expression in the acute phase group was also lower than that in the remission group, but that in the mild group and the moderate-severe remission group was not statistically significant. This result suggested that the expression of Th1, Th2 and Th1/Th2 imbalance in the peripheral blood might be related to the disease severity in patients with bronchial asthma, but the expression of the two values in the mild remission group and the moderate-severe remission group was not statistically significant. However, the treatment effect of the targeted therapy by other animals and clinical studies against the Th1/Th2 imbalance cytokines is not ideal. In recent years, some studies have found that Th1 cells are proinflammatory, and its role of proinflammatory outstrips the anti-inflammatory. In other animal studies, adoptive Th1 cell transfusion has not only failed to reduce the Th2 cell-induced airway hyper responsiveness and inflammation, it can

The results of pulmonary function: Table 4 is the results of pulmonary function, as shown in this table, the FVC/predicted value (%) and FEV₁/predicted value (%) of the healthy group and the mild remission group were higher than that of the acute exacerbation group, while the two values in the mild remission group were also higher than that in the moderate-severe remission group and the healthy group, FEV₁/predicted value (%) in the healthy group was higher than that in the moderate-severe remission group, all P<0.05; FEV₁/FVC (%) was statistically significant among groups other than the acute attack phase group with the mild remission group (P<0.05); the DLCO was not statistically significant among the groups (P=0.061).

Discussion

The pathogenesis of bronchial asthma is complex, while immune and inflammatory mechanism of CD4⁺ T lymphocyte has reached a consensus. The theory of Th1/Th2 imbalance in the past few decades has been considered to be the core of the pathogenesis of asthma; allergens in patients with asthma can selectively promote Th1 cell proliferation predominant expression of Th2 cells, as a consequence, the Th1/Th2 balance to Th2 conversion [8], which means that Th2 cells have a polarization response. The results of this study confirmed that there existed Th1/Th2 imbalance and the high expression of Th2 cells which have a role of pro-inflammatory in the peripheral blood of asthma patients, and its expression of the acute group was higher in a serious condition, while Th2 expression in acute asthma was also higher than that in moderate-severe remission group, but that in mild group and the moderate-severe remission group was not statistically significant. The expression of Th1 cells which have a role of cell-mediated immunity in the peripheral blood of asthma patients was low, while its expression in the acute phase group was also lower than that in the remission group, but that in the mild group and the moderate-severe remission group was not statistically significant. This result suggested that the expression of Th1, Th2 and Th1/Th2 imbalance in the peripheral blood might be related to the disease severity in patients with bronchial asthma, but the expression of the two values in the mild remission group and the moderate-severe remission group was not statistically significant. However, the treatment effect of the targeted therapy by other animals and clinical studies against the Th1/Th2 imbalance cytokines is not ideal. In recent years, some studies have found that Th1 cells are proinflammatory, and its role of proinflammatory outstrips the anti-inflammatory. In other animal studies, adoptive Th1 cell transfusion has not only failed to reduce the Th2 cell-induced airway hyper responsiveness and inflammation, it can

(All P<0.05), there was no statistical significance between the moderate-severe remission period group and the mild remission group; the expiratory CT value of the mild remission group (818.3 ± 11.0 HU) and the moderate-severe remission group (870.8 ± 16.3 HU) was higher than that of the healthy group (777.9 ± 12.1 HU) (P<0.05), while there was no statistical significance between the moderate-severe remission period group and the mild remission group; the inspiratory CT value of the three groups was not statistically significant.

The proportion of Th1 cells in the acute, remission and the healthy group by FACS (from left to right). The expression of Th1 in the healthy was lower than that in the asthma, and its expression in the remission was also lower than that in the acute.

The proportion of Th2 cells in the acute, remission and the healthy group by FACS (from left to right). The expression of Th2 in the healthy was higher than that in the asthma, and its expression in the remission was also higher than that in the acute.
Asthma, which have a role of immunosuppression and immune tolerance was cause serious airway inflammation [9] as well. Therefore, the Th1/Th2 imbalance theory does not fully explain the pathogenesis of asthma.

Meanwhile, the experiment also suggested there was another imbalance of CD4+ T lymphocytes in the peripheral blood of bronchial asthma, the Th17/Treg imbalance, which means that the expression of Th17 cells which have a role of pro-inflammatory in the peripheral blood of asthma patients was high, and its expression in the acute group was higher than that in the asthma, and its expression in the remission was also lower than that in the acute.

The Th17/Treg imbalance as well. The severity of asthma is closely related to them. At the same time, the study found that the expression of Th17 cells was not statistically significant between the acute attack phase and the moderate-severe remission group, while its expression in the moderate-severe remission group was higher than that in the acute. Therefore, the Th1/Th2 imbalance theory does not fully explain the pathogenesis of asthma.

The results of pulmonary function (τ ± s).

Figure 4: The proportion of Treg cells in the acute, remission and healthy group by FACS (from left to right). The expression of Treg in the healthy was lower than that in the asthma, and its expression in the remission was also lower than that in the acute.
Asthma is a disease characterized by expiratory flow limitation, airflow obstruction and its reversible possibility. Therefore, early assessment of lung function of asthma patients is particularly important, especially to clear whether there is airflow obstruction and its reversible possibility.

CD4+T lymphocytes is a group of plasticity, the relationship among their subsets is intricate. The ratio imbalance among them is an important cause to asthma, and the release of inflammatory cytokines may be the key to break the balance. The studies found that TH17 cells in asthma patients are more closely related to both the severity of the disease and symptom control. They may be the important reasons of refractory asthma, severe asthma and airway remodeling in asthma patients, they provide the biological targeting for the treatment of refractory and severe asthma. At the same time, they provide a new research direction for asthma airway remodeling.

Pulmonary function test is an important function testing means to evaluate respiratory physiology function of patients with asthma. The results of this study showed that FVC% expected value and FEV1% predicted value in the healthy group and the mild remission group were both higher than those in the acute exacerbation group, and those in the mild remission group were also higher than those in the moderate-severe group. FEV1% predicted value in the healthy group was higher than that in the moderate-severe remission group; FEV1/FVC in each two groups other than the acute attack group and the mild remission group was statistically significant; DLCO had no significant difference among the three groups. However, neutrophilic asthma patients have poor response to steroid therapy. A number of studies have shown that TH17 cells are closely related to respiratory neutrophils inflammation [10-11]. Neutrophilic inflammation and severe asthma is positively correlated. The inspiratory CT value was no significant difference among the three groups. These results suggest that there are different degrees of airway wall thickening and gas retention in the asthma patients. Asthma is a disease characterized by expiratory flow limitation, which may be the reason that inspiratory phase CT value among the three groups was not significant difference. Airway wall thickening is related to airway remodeling, so by HRCT measuring airway wall thickness can provide valuable information for the evaluation of airway remodeling in patients with asthma, while it can also provide the basis for early clinical interventions. In this study, the affection factors of acute exacerbation of bronchial asthma patients such as acute airway wall edema, bronchospasm, mucus embolism, airway secretions and other reversible factors affecting the airway wall thickness can lead to overestimate their airway wall thickness disease, so that HRCT was not performed. In addition, the some enrollers had poor compliance, therefore, the experimental results failed to do correlation analysis with the other related measuring.

Bronchial asthma is characterized by chronic airway inflammation and airway remodeling. The results of this study showed that there existed TH1/TH2 and TH17/Treg immunoregulatory imbalance in the peripheral blood of patients with asthma; the study confirmed that the expression of proinflammatory Th2 cells and Th17 cells was high in acute exacerbation, while the expression of Th17 cells in the moderate-severe remission group was also higher than the mild remission group. This study also confirmed there were changes of airway wall thickness, gas retention, changes of lung function (airflow obstruction) in asthma patients. The study further clarifies the differences of CD4+T lymphocyte subsets expression in the peripheral blood in asthma patients, which has important implications for the clinical judgment of asthma staging and clinical classification, it can guide clinical treatment, and especially it will bring the research direction for the biological targeted therapy for refractory asthma and special type of asthma patients.
Bronchial asthma prevention and treatment guidelines (Definition, diagnosis, treatment and management program of bronchial asthma). Chinese Journal of Tuberculosis and Respiratory Diseases 31: 177-185.


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