Immune Response of Regional Lymph Nodes in Patients with Lung Cancer

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To clarify immune response of regional lymph nodes in 30 patients with lung cancer, the T cell population, phytohemagglutinin (PHA) and Concanavalin A (ConA) stimulation and the T cell subpopulation bearing Ig-G Fc receptors (Tg cells) were tested concerning the clinical stage, histology and the lymph nodes locations.

The T cell population, and PHA and ConA response rates in regional lymph nodes of stage I patients were grossly the same as those of benign lung diseases, but were statistically higher than those of stage III patients (p<0.025, p<0.005).

Among the three histological types of lung cancer, regional lymph nodes of adenocarcinoma had the greatest T cell populations, and PHA and ConA responses.

Concerning the location of lymph nodes, the closer the lymph nodes was to the tumor, the greater was its T cell population, and vice versa. However there was no difference in PHA and ConA responses.

All lung cancer patients revealed a significant increase of Tg cells in regional lymph nodes and in their peripheral blood lymphocytes compared with peripheral blood lymphocytes in normal subjects (p<0.005).

(Key Words: T Cell Population, Mitogen Response, T Cell Bearing Ig-G Fc Receptor.)

INTRODUCTION

With the progress made in tumor immunology, the immune response of regional lymph nodes in malignancies has become clearer, and the complete extirpation of those lymph nodes has come to be of doubtful significance from an immunological standpoint (1, 13, 15).

The purpose of this paper is to measure immune response of regional lymph nodes in lung cancer patients by studying the T cell population, PHA and ConA stimulation, and the Tg cell population with respect to the clinical stage, histology and location of the lymph nodes.

MATERIALS AND METHODS

Thirty patients with lung cancer who underwent surgical resection were studied. The stage and histology were confirmed from the resected specimens. There were nine stage I patients, 21 stage III patients, 17 squamous cell carcinomas, 10 adenocarcinomas, two undifferentiated carcinomas and one mucoepidermoid carcinoma. Extirpated regional lymph nodes were classified into three groups according to the location,

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i.e. group 1: intrapulmonary and hilar lymph nodes, group 2: subcarinal lymph nodes, and group 3: mediastinal lymph nodes (Fig. 1) (12). In addition, those taken from six patients with benign lung diseases were studied as control samples.

Fig. 1 Sites of regional lymph nodes

The T cell population was calculated by measuring E rosette forming cells. PHA and ConA stimulations were studied at a concentration of 20 μg/ml and 5 μg/ml respectively with a lymphocyte concentration of 5 × 10^5/ml. The lymphocytes were cultured for 3 days with the addition of 1 μCi of 3H-thymidine after 48 hours of incubation. The response rate was calculated by the ratio of counts per minute of regional lymph nodes cells to those of peripheral blood lymphocytes of normal subjects. Tg cells were examined by the double rosette method employing chicken erythrocytes as indicators (17).

RESULTS

The mean T cell populations of regional lymph nodes were 52 ± 13% in stage I, 43 ± 11% in stage III, 39 ± 8% in metastatic lymph nodes and 53 ± 8% in lymph nodes of benign lung diseases. A marked decrease in the mean T cell population was observed with advances in the stage, and statistical differences were found between those of stage I and stage III, and stage I and metastatic lymph nodes with respective p values of 0.025 and 0.01. However, the T cell populations of stage I did not differ much from those observed in benign lung diseases (Fig. 2).

Among the three histological types of lung cancer, regional lymph nodes of adenocarcinoma showed the highest T cell population, i.e., 52 ± 12% in adenocarcinomas, 42 ± 10% in squamous cell carcinomas and
44 ± 6 % in undifferenciated carcinomas, and there was a statistical difference between those of adenocarcinomas and squamous cell carcinomas with a p value of 0.005 (Fig. 3).

Concerning the location of the lymph nodes, the mean T cell population was 50 ± 14% in group 1, 46 ± 12% in group 2 and 41 ± 10% in group 3. It was observed that the closer the lymph nodes were to the tumor, the greater the T cell population, and vice versa. The T cell population of peripheral blood lymphocytes in lung cancer patients was found to be 63 ± 20%, which was greater than those of the regional lymph nodes (Fig. 4).

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**Fig. 2**  T cell percentage of regional lymph nodes

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**Fig. 3**  T cell percentage of regional lymph nodes
Responses to PHA and ConA stimulation were $87 \pm 46\%$ and $106 \pm 39\%$ in stage I, $50 \pm 30\%$ and $69 \pm 30\%$ in stage III, $36 \pm 30\%$ and $57 \pm 30\%$ in metastatic lymph nodes and $84 \pm 22\%$ and $123 \pm 24\%$ in those of benign lung diseases respectively. As in the case of the T cell population, there was also a prominent decrease with the progress of the disease, and statistical differences were observed between stage I and stage III, and stage I and metastatic lymph nodes with a p value of 0.005. The response rate of regional lymph nodes in stage I was grossly the same as that of benign lung diseases. In a small number of cases in which preoperative radiotherapy or long-term chemotherapy were applied, regional lymph nodes showed lower response rates than those of metastatic lymph nodes (Fig. 5).
Fig. 6 shows the relationship between T cell percentage and PHA response with respect to the stage. Each rectangle is formed from the mean T cell percentage and the mean PHA response ± 1 standard deviation. As mentioned above, quantitative and functional ratios of T cells declined with advances of the stage and those in stage III lymph nodes did not differ much from those observed in metastatic lymph nodes. On the contrary, regional lymph nodes in stage I patients showed higher levels of T cell function despite lower levels of T cell population in contrast to the peripheral blood lymphocytes in lung cancer. These results suggest that local immune response is stronger than systemic immune response. The same relationship between T cell percentage and ConA response was observed (Fig. 7).

![Fig. 6](image)

**Fig. 6** Relationship of T cell percentage and PHA response of regional lymph nodes cells and peripheral blood lymphocytes in patients

![Fig. 7](image)

**Fig. 7** Relationship of T cell percentage and ConA response of regional lymph node cells and peripheral blood lymphocytes in patients
The relation between mitogen response and histological type showed that adenocarcinomas had a stronger response than the other two types. Especially in ConA stimulation, there was a statistical difference between adenocarcinomas and squamous cell carcinomas (fig. 8).

T cells are classified into several subsets according to their functions. T cells bearing the Fc portion of the IgG molecule are thought to be suppressor T cells. The proportion of Tg cells in regional lymph nodes increased prominently in all stages of lung cancer, and were $3.6 \pm 1.5\%$ in stage I, $3.5 \pm 1.7\%$ in stage III and $3.6 \pm 0.5\%$ in metastatic lymph nodes. These values are statistically higher than the value of $1.5 \pm 1.1\%$ in peripheral blood lymphocytes of normal subjects (Fig. 9).

**Fig. 8** Response of regional lymph nodes to PHA and ConA stimulation

**Fig. 9** IgG-FcR$^+$ T cell percentage of regional lymph nodes
PBLs of patients $>$ PBLs of normal subjects ($p<0.005$)
PLNCS of patients $>$ PBLs of normal subjects ($p<0.005$)
DISCUSSION

It has been mentioned that the regional lymph nodes in malignancies have immune responses (4, 6, 8, 9). Crile (3) reported that conservative operations and radical operations gave the same survival rates at ten and fifteen years in stage I and stage II mammmocarcinomas. Ota (14) and Yasumoto (18) thought that regional lymph nodes might contribute to the defense mechanism against cancer cells by the cytotoxic activity of the lymphocytes in the regional lymph nodes on bronchogenic carcinoma cell lines, and they stated that it might not be advisable to extirpate widely mediastinal lymph nodes uniformly in lung cancer patients.

In this article we examined the immune response of regional lymph nodes in lung cancer patients who underwent surgical resection and added some consideration concerning the extirpation of regional lymph nodes from an immunological standpoint.

T cell population, and PHA and ConA response rates in regional lymph nodes cells of stage I patients were grossly the same as those in benign lung diseases, but were statistically higher than those of stage III patients which did not differ much from those observed in metastatic lymph nodes. These results suggest that, if regional lymph nodes are considered to be the first barrier to the malignancy, regional lymph nodes of stage I patients show sufficient immune response and it may have physiological and clinical significance to leave those lymph nodes at the time of extirpation. However, it may be of little significance to leave regional lymph nodes in stage III patients. To evaluate this significance it will be necessary to observe long-term clinical courses and compare prognosis between those with complete extirpation and those without extirpation.

Among the three histological types of lung cancer, adenocarcinomas showed the greatest T cell population and PHA and ConA responses, and therefore they might provide a stronger immunological irritation to the regional lymph nodes than the other two histological types. This may also be related to the tendency of early metastasis of adenocarcinomas to the regional lymph nodes.

Concerning the location of lymph nodes, the closer the lymph nodes were to the tumor, the greater their T cell population and vice versa. This may reflect immune response according to the strength of tumor irritation of the regional lymph nodes.

Tg cells are thought to have a suppressor function. Cantor (2) in his study of T cells in mice, differentiated among helper cells, suppressor cells and killer cells according to Ly antigens, which are an autologous antigen of mice. Among human T cells it is impossible to discriminate T cells according to their functions using autologous antigen at present, but various studies have been performed to differentiate T cells using Fc receptors (5, 10, 11). In our study there was a statistically increased population of Tg cells in regional lymph nodes and peripheral blood lymphocytes in lung cancer patients than in peripheral blood lymphocytes of normal subjects. This results agreed with the reports of Imai (7) and Shimpo (16) who stated that peripheral blood lymphocytes of various malignancies showed
higher populations of Tg cells than those of normal subjects. Whether Tg cells and suppressor cells are identical remains uncertain, but we think further evaluations are necessary concerning this problem.

REFERENCES