Monoclonal Antibody That Distinguishes Small-Cell Lung Cancer from Non-Small-Cell Lung Cancer

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ABSTRACT

To examine whether a monoclonal antibody, TFS-4, can distinguish small-cell lung cancer from non-small-cell lung cancers, an extensive survey of fresh lung tumors, cancers from other organs, and normal tissue specimens has been carried out. The antibody has been shown to react specifically with small-cell lung cancer (15 of 15) but not with squamous cell carcinoma (0 of 20), adenocarcinoma (0 of 20) of the lung, or large-cell lung cancer (0 of 2). It reacted neither with other malignancies, including colorectal cancer, gastric cancer, and malignant lymphoma, nor with such normal tissues as trachea, lung, liver, pancreas, colon, kidney, spleen, skin, striated muscle, bone marrow, or peripheral blood cells. Interestingly, the antibody cross-reacted with central nervous tissues. The antigenic determinant on small-cell lung cancer and that on human brain were both heat labile and trypsin sensitive, but resisted treatment with neuraminidase, suggesting that they represent similar peptides. TFS-4 may be of clinical use in the diagnosis of small-cell lung cancer, while the antigen may help investigate the nature and origin of small-cell lung cancer.

INTRODUCTION

With the advent of modern therapy of lung cancer, it became apparent that the histological type greatly influences the clinical presentation, response to therapy, and survival. SCLC has a much greater metastatic capacity and responsiveness to treatment than does NSCLC. In SCLC, even early stage cases are seldom cured by surgical resection. On the other hand, the majority of cases respond dramatically to chemotherapy and radiotherapy, and some suitably treated patients with extensive disease survive for long periods (1). Thus, it is essential to know whether the lung cancer is SCLC or NSCLC.

Currently, the distinction is made by light microscopy. However, even expert lung cancer pathologists can disagree on this subtyping of lung cancer (2). Since the development of hybridoma technology has been reported, monoclonal antibodies with high specificity have been used for the differential diagnosis of various diseases (3, 4). We have developed four monoclonal antibodies directed against SCLC (5). One of them has been found to be highly specific for SCLC. The most interesting possibility may be that this monoclonal antibody can distinguish SCLC from NSCLC tumors. To determine the usefulness of the antibody in diagnosis and treatment of SCLC, a large survey of lung tumors and normal tissue specimens has been carried out. In this paper, we describe the specificity of this antibody and the characterization of the antigenic determinant.

MATERIALS AND METHODS

Hybridoma. The production of TFS-4 has been previously reported (5).

RESULTS

Immunohistochemistry. The preliminary examinations revealed that TFS-4 may be of clinical use in the diagnosis of small-cell lung cancer, while the antigen may help investigate the nature and origin of small-cell lung cancer.
malignant cells, while the interstitial tissues were spared. TFS-4 was reactive with none of the conventional squamous cell carcinomas, nor large-cell carcinomas of the lung. In the positive cases the reaction appeared to be confined to cell membranes (Fig. 1).

Reactivity of TFS-4 with cancers from other organs is also shown in Table 1. None of the colorectal cancers, gastric cancers, or lymphomas was reactive with TFS-4. Interestingly, carcinoid tumors and a neuroblastoma showed positive reactions.

In normal tissues, most remarkable staining was demonstrated on central nervous tissues and neuroendocrine cells, including the adrenal gland (medulla and zona glomerulosa), glandular cells of the thyroid gland, Leydig cells of the testis, and stromal cells of the ovary (Table 2). In peripheral nerves, Schwann cells and nerve endings were weakly stained. No reactivity was detected with other tissues including trachea, lung, liver, kidney, colon, pancreas, skin, striated muscle, spleen, bone marrow, or peripheral blood cells. The islet cells of the pancreas, enteroendocrine cells, and Kulchitski cells of the lung were found to be unreactive. An unexpected finding was that the antibody was reactive with cell membranes of cardiac muscles and some smooth muscles (alimentary tract and myometrium of the uterus).

Characteristics of TFS-4 Antigen. To see whether the antigen recognized by TFS-4 on SCLC shares the common features with the antigen on central nervous tissues, an SCLC cell line (NCI-H69), SCLC tumors, and human cerebrum were subjected to treatment with various concentrations of trypsin and neuraminidase, methanol, and heat. As shown in Table 3, TFS-4 antigen(s) on an SCLC cell line, an SCLC tumor sample, and the cerebrum showed similar characteristics, i.e., trypsin sensitive, heat labile, but resistant to neuraminidase and methanol.

Species Specificity of TFS-4. Since TFS-4 seemed to recognize brain-associated antigen, its reactivity with cerebrum from other species was examined. TFS-4 was reactive with cerebrum from chimpanzee and night monkey, but not with that of cow, pig, dog, rabbit, or rat (Table 4).

DISCUSSION

In this paper, we demonstrated that TFS-4 was highly specific for SCLC. The antibody reacted with SCLC but not with NSCLC. With the exception of a neuroblastoma and carcinoid tumors, such cancer cells as carcinomas of the colorectum, stomach, breast, lymphomas, thymomas, leiomyosarcoma, or meningiomas were unreactive with TFS-4. The antibody failed to react with normal lungs, trachea, bronchus, liver, kidneys, colon, breast, skin, spleen, striated muscle, and blood cells. These observations suggest that TFS-4 recognizes an antigen specifically expressed on SCLC but not on NSCLC. Thus, TFS-4 appears to be able to distinguish SCLC from NSCLC tumors.

We have compared the antigenic determinant(s) on SCLC and that on central nervous tissues. Their determinant(s) shared some common properties; that is, it is heat labile, trypsin sensitive, but resists treatment with neuraminidase, suggesting that it is a peptide. The antigen on SCLC has been shown to have a molecular weight of 124,000 on sodium dodecyl sulfate-
polyacrylamide gel electrophoresis under reducing conditions (5). Purification studies of the antigen from human brain revealed the molecular weight of 124,000 under the same conditions (15). These observations suggest that SCLC and human brain share a common antigen on the cell surface. We designated TFS-4 antigen as BASCA. Immunohistochemical studies with normal tissues suggested that BASCA is expressed on cell revealed the molecular weight of 124,000 under the same condi-

tions to primates, and it was not destroyed by exposure to methanol but trypsin. These observations suggest that BASCA is classified as non-small-cell lung cancer. BASCA expressed as non-small-cell lung cancer.

Another monoclonal antibody UJ13A may deserve comment. UJ13A, which was raised against human fetal brain, also reacted with SCLC and showed a similar staining pattern with normal tissues, recognizing central nervous tissues and thyroid gland epithelium. But the antigen is believed to be a glycolipid restricted to primates, and it was not destroyed by exposure to methanol but trypsin. These observations suggest that BASCA is classified as non-small-cell lung cancer.

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Although there have been several reports concerning the monoclonal antibodies for SCLC (5, 7–13), few have been well investigated in terms of reactivity with fresh tumor tissues obtained directly from the patients. The reported results are summarized in Table 5.

HNK-1 was reported to show preferential specificity for SCLC (7, 13). However, a large survey of lung tumors has demonstrated that HNK-1 reacted with more than half of the well-differentiated adenocarcinomas of the lung (8). SM-1 and B10/12 reacted with breast cancers (10, 11). MOC-1 recognized more than half of adenocarcinomas (12). It appears that TFS-4 shows the higher specificity for SCLC among the hitherto reported monoclonal antibodies.

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In conclusion, TFS-4 may be of clinical importance in the differential diagnosis of SCLC from other cancers. BASCA (TFS-4 antigen) may also lead to better understanding of the origin and nature of SCLC cells.

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REFERENCES


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