(Rb) has been mapped to chromosome 13q 14. In studies of SCLC cell lines chromosome 13 was absent of hypodiploid in 17/21 specimens evaluated.

Further studies using the Rb complementary DNA probe revealed structural abnormalities within the Rb gene in 1/8 primary SCLC tumors, 4/22 SCLC cell lines, and 1/4 pulmonary carcinoids. In contrast, no abnormalities were detected in other cell types of lung cancer. Further, Rb mRNA expression was absent in 60% of SCLC cell lines in contrast to 10% NSCLC cell lines. These findings suggest an important role for the Rb gene in the pathogenesis of SCLC, but not of NSCLC. These observations, in addition to reports that abnormalities in the Rb gene can be found in some osteosarcomas and other mesenchymal tumors, suggest that this gene may be important in the biology of a wide range of common tumors.

References

Monoclonal Antibodies in Lung Cancer*
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The invention of the monoclonal antibody technique by Kohler and Milstein in 1975 has had great impact on the study of human lung cancer. During the past 8 years, a growing number of reports describing monoclonal antibodies to structures of human lung tumors have been published. Most of the work was done with the aim to study the biology of lung tumors and to identify structures which might be useful for diagnosis or therapy. This review will focus mainly on antibodies to surface membrane antigens. The identification and characterization of cell surface antigens is important in two ways: (1) cell surface antigens allow separation of subpopulations of viable cells for biologic studies and (2) they are the obvious targets for investigations aiming to develop tumor-specific therapy.

To generate antibodies against previously unknown membrane antigens, whole cells or membrane extracts of cell lines or tumor tissues are used. Virtually all antibodies to lung tumor cells have been selected by phenotypic criteria based on the differential binding between tumors of various lineage or between tumor and normal cells. It is thus obvious that the biologic or functional significance of the antigens so identified remains largely unknown. An exception is a recently described glycoprotein antigen heterogeneously expressed in squamous cell carcinomas, which was found to be associated with clonogenic cells and cells able to form tumors in nude mice.1

Reports on antibodies from different laboratories vary widely on methods and material used for the characterization of antibody and antigen. This renders the analysis of publications difficult at times. An important first step for a direct and comparative analysis has recently been made for antibodies to small cell lung cancer antigens.1 For antibodies to other lung tumors a preliminary grouping has to rely on the tissue reactivity reported. Most antibodies generated to lung tumors have been found to identify antigens present on a wide range of epithelial tumors and normal epithelial

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cells. A smaller number of antibodies appear to identify antigens of a certain lineage relationship. The space limitation will only allow the mention of some examples. Several reports describe antibodies of preferential reactivity with non-small cell carcinoma but not small cell carcinoma. A similar pattern of reactivity can also be seen with antibodies to blood group antigens of the Lewis or NM system. Of many antibodies to squamous cell carcinoma, very few, if any, suggest there might be an antigen with differential expression on squamous cell carcinoma, but not on adenocarcinoma of the lung. In contrast, there are indications that antigens exist, which are selectively expressed in adenocarcinoma, but not in squamous cell carcinoma. Recently, we reported on an antibody to a mesothelial membrane antigen, which allows positive discrimination between mesothelioma and adenocarcinoma, a differential which can pose difficulties for the pathologist. Virtually all of the antibodies to non-small cell lung tumors also stain normal counterpart tissue, such as bronchus, alveolar lining cells, or normal mesothelial cells. This, however, does not exclude a differential expression between tumor and normal tissues, since variations in antigen density may not be visible when a method with a low threshold of detection such as immunoperoxidase staining is used.

Based on reports of tissue staining, at least 4 groups of antibodies to small cell lung carcinoma can be discerned. Many antibodies react with a broad range of normal epithelial tissues and tumors and thus identify epithelial antigens. Other antibodies react with normal tissues and tumors of neural and neuroendocrine differentiation, but not with non-small cell carcinoma, and thus may be termed to recognize neuroendocrine antigens. Such antibodies might be useful in biologic studies of differentiation processes and lineage interrelationships of human lung tumors and in the clinic as adjuncts to conventional morphologic diagnosis. Antibodies generated against macrophages and natural killer cells were later found to also react with small cell carcinoma, indicating that there are antigens which are shared between WBCs and small cell carcinoma. Some antibodies raised against small cell lung carcinoma have been found to recognize antigens expressed on tumor cell membranes, but not on normal tissues, and thus have been termed to recognize tumor-associated antigens. These include antibodies LAM8 and SWA20, which both identify membrane antigens strongly or moderately expressed on 45% of small cell carcinomas but not on non-small cell carcinomas or normal tissues.

Most of the epithelial type antibodies to small cell lung carcinoma reported earlier were found to identify glycolipids and many were directed against the sugar sequence lacto-N-fucopentaoase III. In contrast, the neuroendocrine antigens and the tumor-associated antigens on small cell lung carcinoma were identified to be glycoprotein antigens. The latter have been shown to be complex sialoglycoproteins with molecular weights at 180 and 100 KDa on immunoblots.

Monoclonal antibodies against antigens with differential expression in tumor cells and hematopoetic cells have been used by us and others to detect bone marrow metastasis of small cell carcinoma that escaped detection by conventional morphology. Although the detection of antigen positive cells is not an absolute proof for metastatic disease, the presence of occult small cell carcinoma in bone marrow has since also been supported by direct culture methods. It remains to be determined whether the presence of micro-metastatic deposits is of prognostic importance or whether it might serve as a marker for the effect of chemotherapy on micrometastatic disease. We and others have shown that several log of tumor cells can be removed from contaminated marrow with monoclonal antibody techniques. The clinical application of purging bone marrow, however, will depend on whether high-dose chemotherapy with autologous marrow rescue will have an impact on the prognosis of small cell carcinoma.

Membrane antigens which are shed in sufficient quantities from tumor cells might serve as serum markers. Several antibodies reacting with such antigens have been reported. These include antibodies against squamous cell carcinoma, adenocarcinoma and small cell carcinoma. Although many of these antibodies are unlikely to be highly specific for a given type of tumor but rather identify epithelial markers or blood group-related antigens, some antibodies alone or in combination could prove to be useful in serum monitoring of lung cancer.

The therapeutic use of antibodies to lung tumor antigens is beginning to be explored. Studies in xenograft models of small cell carcinoma have shown that with certain antibodies such as SWA11 selective tumor uptake sufficient for radioimmunotherapy of established tumors is possible. In the near future a growing number of clinical studies will investigate the tolerance and effectiveness of different antibody-conjugates targeted against membrane antigens of lung tumors. In addition, alternative therapeutic approaches are focusing on antibodies directed against growth factors such as bendorsin or the use of tumor-specific vaccination with anti-idiotypic antibodies mimicking tumor-associated antigens. While intensive preclinical investigations on therapeutic uses of antibodies to lung tumors will have to continue, the time has now come also to test their use in carefully controlled clinical trials.

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Lung Cancer and Autocrine Growth Factors

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From recent progress in cancer research, the hypothesis has been proposed that cancer cells have the ability to produce growth factors and to stimulate tumorigenesis by responding to these factors. This mechanism is now known as the autocrine growth mechanism of cancer cells, and factors responsible for this mechanism are called autocrine growth factors.1 We have recently examined biologic and clinical implications of possible autocrine growth factors for lung cancers. Here, we review our observations indicating...