

Clinical and Biological Relevance of Recently Defined Categories of Pulmonary Neoplasia

Edward Gabrielson

1. Introduction

The clinical management of lung neoplasia now involves considerations of several diagnostic categories that were not in common use only a few years ago. In particular, there is now an increased recognition of neuroendocrine differentiation in lung cancer, including acknowledgment of large-cell neuroendocrine cancer as a distinct class of lung cancer. In addition, there is growing awareness of various form of early neoplasia in the lung, particularly *in situ* squamous cell proliferations and atypical adenomatous proliferations. With an emphasis on implications for clinical management, this review will discuss the biology of these important categories of lung neoplasia and compare them to other commonly recognized forms of lung tumors.

2. Neuroendocrine Differentiation and Classification of Lung Neoplasia

Other than the distinction between benign and malignant, the distinction between small cell cancer (SCLC) and non-small cell cancer (NSCLC) is perhaps considered to be the most important diagnostic decision made by the pathologist in the evaluation of lung neoplasms. SCLC is well-recognized to be highly aggressive and, because it is most often widely disseminated by the time a diagnosis is made, it is usually treated by chemotherapy rather than surgery.

SCLC is well-recognized as a highly malignant form of lung cancer, with neuroendocrine differentiation among its distinguishing characteristics. Carcinoid tumors, with an even greater degree of neuroendocrine differentia-

tion, typically have a low malignant potential and thus represent the other end of the clinical spectrum of lung tumors. These two types of neoplasia, which are clinically diverse, are frequently thought to represent different ends of a single biological class of tumors, based on the neuroendocrine differentiation common to these types of neoplasms. However, as discussed below, there is significant evidence to suggest that SCLC and carcinoid tumors are fundamentally different disease processes. In addition to these common forms of pulmonary neoplasia, a class of tumors known as large cell neuroendocrine carcinoma has been recently recognized. The accurate classification of lung tumors with neuroendocrine differentiation is thus more complex than previously recognized.

2.1. Small Cell Lung Cancer

Small cell lung cancers are distinctive tumors, with a characteristic cellular morphology that includes scant cytoplasm (thus resulting in an overall relatively small size of the cells), finely granular chromatin, absent or conspicuous nucleoli, and frequent mitoses (*see Fig. 1*). In actuality, the nuclear morphology, chromatin distribution, and high mitotic rate are more important than cell size in establishing the diagnosis, and variants of SCLC, all with similarly poor prognosis, are recognized (*1*). Although small cell lung cancers usually have only vague semblance to the usual neuroendocrine architecture in terms of nesting of cells and vacularity, electron microscopy has demonstrated that many SCLCs have dense-core granules typical of neuroendocrine cells. Dense-core granules in SCLC are occasionally situated in cell processes that resemble dendrites (*2*) but are generally few and small (100 to 13 nm). Moreover, approximately one-third of SCLCs do not have dense core granules, and cytoplasmic structures of other differentiation pathways, such as glandular structures or cytokeratin bundles, are also occasionally seen (*3*). Immunohistochemical studies of small cell lung cancer have confirmed the expression of markers of neuroendocrine differentiation but, again, these markers are not expressed in about 20% of small cell lung cancers (*4*). Furthermore, epithelial (cytokeratin) markers are expressed at variable levels (*5*), suggesting that many small cell cancers share differentiation phenotypes with non-small cell cancers. Thus, when classifying SCLC on the basis of neuroendocrine differentiation, it must be remembered that the association between small cell lung cancer and neuroendocrine differentiation is not absolute. Importantly, the diagnosis of SCLC is established by the characteristic microscopic morphology, and not by immunohistochemical or ultrastructural demonstration of neuroendocrine differentiation.

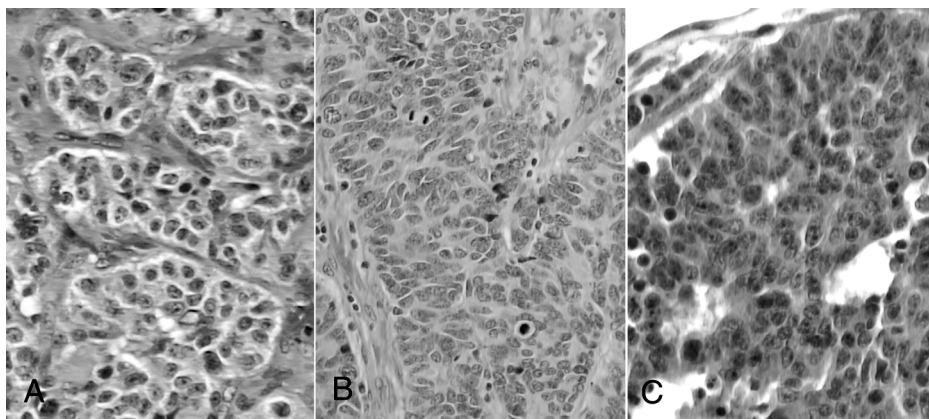


Fig. 1. Representative histology of pulmonary carcinoid (A), small cell lung cancer (B), and large cell neuroendocrine cancer (C). Note the “organoid architecture,” lack of nuclear atypia, and low mitotic rate that distinguish carcinoid from the highly malignant forms of lung cancer. Small cell lung cancer has fewer and smaller nucleoli, as well as generally smaller cells, than the large cell neuroendocrine cancer. Other distinguishing characteristics are discussed in the text and references.

2.2. Pulmonary Carcinoid Tumors

Another common class of lung neoplasms with neuroendocrine differentiation is that of pulmonary carcinoid tumors, which are relatively uncommon (about 8% of all lung tumors) but distinctive neoplasms (6). Although these tumors have been previously classified as bronchial adenomas, they are now considered to be neoplasms of variable malignant potential. Most carcinoid tumors (typical carcinoids) are relatively well-circumscribed and have an “organoid” microscopic appearance similar to carcinoid tumors of other organs (see Fig. 1). Consistent with their nonaggressive nature, mitoses are infrequent and lymphatic or vascular invasion are rare in tumors classified as “typical carcinoid” (6).

A subset of pulmonary carcinoid tumors does have morphological and clinical features consistent with a relatively aggressive clinical biology (7). These tumors, termed atypical carcinoids, have increased numbers of mitoses compared to typical carcinoids and frequently manifest other morphological characteristics of malignancy, such as necrosis, lymphatic invasion, and vascular invasion. The prognosis of atypical carcinoid is intermediate between that of typical carcinoid and small cell lung cancer, and is related to the morphological characteristics of malignancy (8,9). These neoplasms are

generally treated by aggressive surgery, including lymph-node dissection (10), and benefits of chemotherapy for treatment are still uncertain.

For many years, typical carcinoids and atypical carcinoids have been considered to represent the benign and intermediate levels of the spectrum of neuroendocrine lung tumors (respectively), with SCLC representing the malignant end of the spectrum of this group of tumors. A common progenitor cell, the Kulchitsky cell (11), has been proposed for all of these forms of neoplasia although, as discussed below, there is substantial evidence to suggest that SCLC and pulmonary carcinoid are fundamentally different classes of neoplasia.

Interestingly, carcinoid tumors typically show a much higher degree of neuroendocrine differentiation than small cell cancers. Electron microscopy almost invariably demonstrates numerous dense-core granules and immunohistochemical markers of neuroendocrine differentiation typically stain these neoplasms with high intensity. These findings argue against a direct link between the extent of neuroendocrine differentiation and aggressive clinical biology.

2.3. Large Cell Neuroendocrine Cancer and Neuroendocrine Features in NSCLC

Neuroendocrine differentiation in pulmonary neoplasms extends beyond SCLC and carcinoid tumors. Recognizing that all non-small cell lung cancers with neuroendocrine differentiation cannot be neatly classified as atypical carcinoids or as SCLC, Travis and colleagues proposed large-cell neuroendocrine cancer (LCNEC) as a new category of lung cancer (12). This category of lung cancer is defined by light microscopic evidence of neuroendocrine differentiation (e.g., organoid, palisading, trabecular or rosette-like growth patterns), large cell size, prominent nucleoli, high mitotic rate, coagulative necrosis, and neuroendocrine differentiation by electron microscopy or immunohistochemistry (*see Fig. 1*).

LCNEC occurs most frequently in the seventh decade of life and, similar to SCLC, occurs almost exclusively in smokers (13). More than half of LCNEC patient present with at least stage II disease and 5- and 10-yr survival rates for this cancer are only 27% and 9%, respectively (8). Thus, survival for this cancer is significantly worse than for atypical carcinoid and is not significantly different than that of SCLC of comparable stage. Because this category of lung cancer is relatively rare and only recently recognized, there is insufficient data to determine whether LCNEC has a response to chemotherapy comparable to SCLC.

Distinguishing LCNEC from atypical carcinoid is important from the standpoint of prognosis and, as discussed below, from the standpoint of

studying the biology of these different forms of neoplasia. Yet, the diagnosis of these tumors can be difficult, even in the hands of pathologists with expertise in pulmonary neoplasia (14).

Finally, a discussion of neuroendocrine differentiation in lung tumors should acknowledge that a significant percentage of non-small cell lung cancers have subtle characteristics of neuroendocrine differentiation, but not of a sufficient extent to warrant a diagnosis of SCLC or NLNEC. For example, one study reported that 12 % of non-small cell lung cancers stained immunohistochemically for two or more markers of a neuroendocrine panel (neuron-specific enolase (NSE), chromogranin A, Leu-7, gastrin-releasing peptide) (15). These tumors were not found to have any difference in clinical outcome, however, suggesting that neuroendocrine features in NSCLC may not be clinically significant.

2.4. Neuroendocrine Differentiation in Classification of Pulmonary Neoplasia

Although pulmonary carcinoid tumors are often considered to be a part of the same spectrum of lung neoplasms as SCLC and LCNEC by virtue of neuroendocrine differentiation, there is significant molecular evidence that pulmonary carcinoid tumors are distantly related to these more aggressive forms of lung cancer. For example, while carcinoid tumors, SCLC, and LCNEC share a number of loci where loss of heterozygosity (LOH) is common, the patterns of p53 mutations are different between atypical carcinoids and SCLC or LCNEC (16). Additional molecular evidence to separate carcinoid tumors from high-grade neuroendocrine cancers comes from analysis of the *MEN1* (multiple endocrine neoplasia type 1) gene, which is frequently mutated in typical and atypical carcinoid tumors (17). In a study of small cell cancer, no mutations of this gene were found in any of the 45 SCLC samples (primary tumors and cell lines) analyzed and mutation of the gene was found in only 1 of 13 LCNEC samples studied (18). Although it is possible that mutation of this gene represents a link between LCNEC and carcinoid, the possible misclassification of this single sample also remains a possibility. Finally, cDNA array studies have found little similarity in overall gene-expression patterns between carcinoid tumors and SCLC (19).

More compelling evidence to classify carcinoids as distinct from SCLC or NCNEC, as opposed to a part of a continuous spectrum of neuroendocrine tumors, comes from clinical data. Notably, there is no evidence that tobacco smoking is a significant cause of pulmonary carcinoid (13), although tobacco is clearly implicated as a cause of most cases of SCLC and NCNEC. Furthermore, clinical progression from typical carcinoid to high-grade neuroendocrine cancer (SCLC or LCNEC) has not been documented. Thus, while typical carcinoid,

atypical carcinoid, LCNEC, and SCLC all share properties of neuroendocrine differentiation, there are substantial biological differences that separate the carcinoid tumors from high-grade neuroendocrine cancers.

Thus, many aspects of possible developmental relationships among SCLC, LCNEC, and carcinoid tumors are still unknown. It appears that there are fundamental and important differences between SCLC and carcinoid tumors on biological and molecular levels, yet these tumors still share the distinctive neuroendocrine properties. A common molecular link on this level may be expression at high levels of the human achaete-scute homolog-1 (HASH) gene, a basic helix-loop-helix transcription factor, in both SCLC and carcinoid tumors (20). While expression of this transcription factor may be a common link between various forms of lung neoplasms with neuroendocrine differentiation, there is also clearly differential regulation of other molecular pathways in these various forms of lung tumors, which define the extent to which different tumors are malignant.

3. Early Neoplasia in the Lung

Another important area of pulmonary neoplasia that will be discussed in this chapter is that of early neoplasia in the lung. Currently, there is a great deal of interest in understanding the development of cancer and developing therapeutic interventions to halt or reverse the progression of lung cancer. As early forms of neoplasia are being recognized more frequently in patients, there is a need to have a sufficient understanding of the biology of these lesions to make reasonable treatment decisions.

It is probably appropriate to first note that in light of the evidence discussed above, there is no rationale for considering pulmonary carcinoid tumors, or the related “carcinoid tumorlets” to be precursors to SCLC or LCNEC. The precursor lesion for these tumors remains elusive and, because of the rapid growth rate usually seen in these highly malignant forms of cancer, may be difficult to find in analysis of lung cancer tissue.

3.1. Squamous Cell *In Situ* Proliferations

Squamous carcinoma *in situ* of the bronchial tree, the first form of early neoplasia to be described in the lung, was recognized by Oscar Auerbach and colleagues in an autopsy study of lungs from individuals who had smoked cigarettes (21). Historically, this study was an important link in establishing cigarettes as a cause of lung cancer and it still has relevance today because molecular studies support the role of these *in situ* lesions in the multistage development of invasive lung cancer (22).

In situ squamous cell cancers (and *in situ* dysplastic lesions) do not present with radiographically detectable lesions, but squamous dysplasia or carcinoma

in situ can often be detected during endoscopic examination of bronchi, particularly when fluorescent lighting is used (23). The recognition of *in situ* squamous cell cancers poses some complex patient management dilemmas. Although it is clear that many, and probably most, *in situ* squamous cell cancers will never progress to invasive cancer, it is not possible to predict in which lesions, or even in which individuals, will invasive cancer develop.

Logically, treatment of *in situ* squamous cell lesions should result in a decreased frequency of invasive squamous cell cancer in treated individuals. However, because individuals who have these lesions usually have multiple lesions, it is not feasible to treat *in situ* squamous cell carcinoma of the lung by surgical resection. Moreover, initial chemoprevention attempts for lung cancer have also been unsuccessful in decreasing lung cancer incidence (and possibly even increased lung cancer incidence) (24,25) and thus it is not clear that the chemopreventative agents with favorable activity in the squamous mucosa of the upper aerodigestive tract will help prevent the progression of squamous cell cancer in the lung. However, there remains hope that more specific interventions of lung cancer development will be found, and monitoring these *in situ* squamous lesions is likely to become important in the clinical management of pulmonary neoplasia.

3.2. Early Neoplasia in the Lung: Atypical Adenomatous Lesions

Only relatively recently has a lesion thought to be an early precursor for adenocarcinoma been recognized. In 1988, Miller and colleagues described a finding of discrete foci of atypical bronchioalveolar cells in lungs resected for adenocarcinoma (26). These lesions, known as atypical adenomatous hyperplasia (AAH), can be recognized by routine microscopy as well as molecular studies to have similarities to adenocarcinoma and are thus thought to represent glandular carcinoma *in situ*.

AAH lesions present as 1- to 7-mm nodules with thickened alveolar septae lined by epithelial cells with varying degrees of atypia (see Fig. 2). Unlike most lung adenocarcinomas, there is no disruption of normal lung architecture and no stromal reaction typical of a host response to an invasive cancer. There are commonly (25%) multiple AAH lesions in lungs resected for pulmonary adenocarcinoma, particularly in those lungs of patients who smoke tobacco (26,27). In contrast, AAH has been observed in only 2% of postmortem lungs from patients without lung neoplasms (28).

The link between AAH and adenocarcinoma has been strengthened by molecular studies. In particular, *K-ras* mutations are found at approximately the same frequency in AAH and adenocarcinoma and the predominant type of mutation in both lesions is a G→T transversion at position 1 or 2 of codon 12 (29). Interestingly, however, synchronous AAH and lung adenocarcinoma

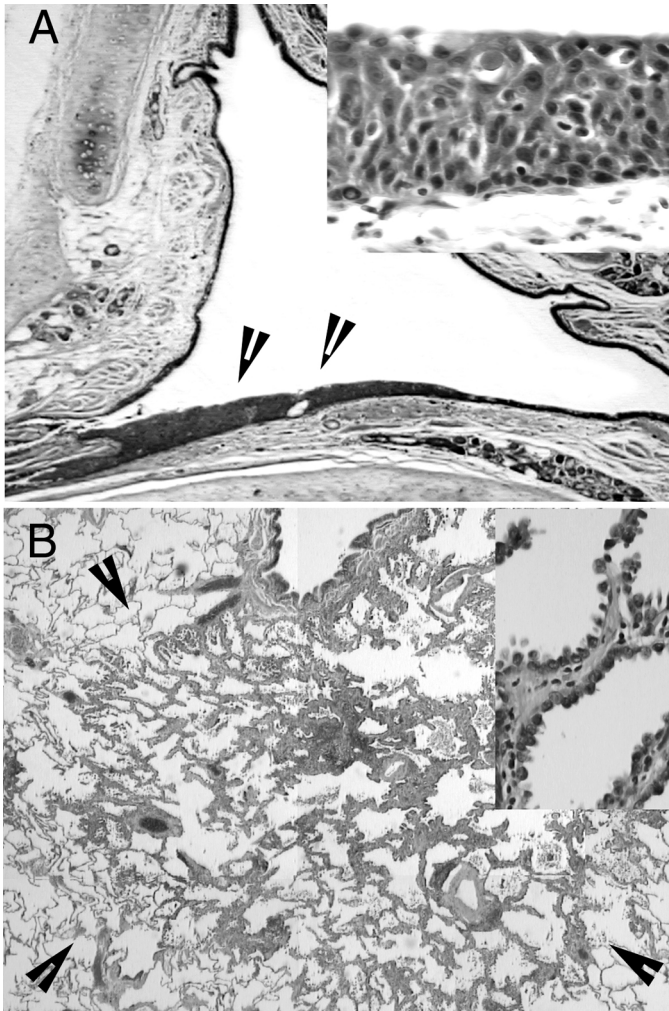


Fig. 2. Early, pre-invasive neoplasia in the lung. Squamous cell carcinoma *in situ* (A, arrows and inset) has lack of cellular maturation, and atypical cells with frequent mitoses, confined to the normal confines of the metaplastic stratified squamous epithelium. Atypical adenomatous hyperplasia (B, arrows and inset) has thickened alveolar septae lined by atypical epithelial cells. The lesion shown has a diameter of 7 mm, considered to be near the upper limits for classifying a lesion as atypical adenomatous hyperplasia as opposed to adenocarcinoma.

lesions often do not share the same *K-ras* base changes, suggesting that independent lesions can be arising simultaneously in subsets of high-risk patients (29). Molecular characteristics that distinguish AAH from adenocarcinoma include lower allelic loss frequencies for chromosomal arms (3p, 9p, and 17p) that are commonly affected in adenocarcinoma (30). In addition, no activation of telomerase activity has been observed in AAH, whereas activation of telomerase is nearly universal in adenocarcinoma (31).

The clinical significance of AAH is still unknown. Because AAH is a multifocal process, it is reasonable to assume that patients with AAH found in a surgical resection specimen have many additional unresected lesions in others portions of their lungs. Yet, the presence of AAH does not appear to unfavorably affect prognosis and may, in fact, be associated with a somewhat better prognosis (32,33). Thus, as for bronchial squamous cell carcinoma *in situ*, AAH does not inexorably progress to invasive cancer.

Because AAH is not as accessible by bronchoscopy as are squamous *in situ* lesions, it is not likely that AAH will be monitored as an intermediate endpoint in lung cancer chemoprevention trials. However, understanding the natural history of these lesions will become increasingly important as small pulmonary lesions are recognized more frequently by high-resolution imaging techniques, such as spiral computerized tomography (CT).

4. Concluding Remarks

The recognition of new classes of pulmonary neoplasia has contributed to our understanding of lung cancer biology, and will hopefully lead to improved clinical management of pulmonary neoplasia. One important area of progress is that of an increased understanding of neuroendocrine differentiation in lung tumors. While it appears that neuroendocrine differentiation itself does not confer an aggressive clinical behavior on a tumor, the NCNEC class of lung cancer does have a distinctively poor prognosis. Recognition of this class of cancers is an important first step in developing effective treatment for patients with this disease.

Additional progress has been made in the recognition of early, pre-invasive neoplasia with squamous or glandular differentiation. Again, our understanding of the biology of *in situ* squamous lesions and AAH is incomplete, compromising our ability to manage patients with these lesions. However, recognizing and monitoring these lesions during chemoprevention trials may help to gauge the effectiveness of various protocols in preventing lung cancer.

References

1. Colby, T. V., and Travis, W. D. (1995) Small cell carcinoma and large cell neuroendocrine carcinoma, in *Atlas of Tumor Pathology, Third Series: Tumors of*

- the Lower Respiratory Tract* (Colby, T. V., K., M. N., and Travis, W. D., eds.), Armed Forces Institute of Pathology, Washington, DC, pp. 235–257.
2. Mackay, B., Ordenez, N. G., Bennington, J. L., and Dugan, C. C. (1989) Ultrastructural and morphometric features of poorly differentiated and undifferentiated lung tumors. *Ultrastruct. Pathol.* **13**, 561–571.
 3. Nomori, H., Shimosato, Y., Kodama, T., Morinaga, S., Nakajima, T., and Watanabe, S. (1986) Subtypes of small cell carcinoma of the lung: morphometric, ultrastructural, and immunohistochemical analyses. *Hum. Pathol.* **17**, 604–613.
 4. Guinee, D. G., Jr., Fishback, N. F., Koss, M. N., Abbondanzo, S. L., and Travis, W. D. (1994) The spectrum of immunohistochemical staining of small-cell lung carcinoma in specimens from transbronchial and open-lung biopsies. *Am. J. Clin. Pathol.* **102**, 406–414.
 5. Tabatowski, K., Vollmer, R. T., Tello, J. W., Iglehart, J. D., Shelburne, J. D., Schlom, J., and Johnston, W. W. (1988) The use of a panel of monoclonal antibodies in ultrastructurally characterized small cell carcinomas of the lung. *Acta Cytol.* **32**, 667–674.
 6. Colby, T. V. and Travis, W. D. (1995) Carcinoid and other neuroendocrine tumors, In *Atlas of Tumor Pathology, Third Series: Tumors of the Lower Respiratory Tract* (Colby, T. V. and Travis, W. D., eds.), Armed Forces Institute of Pathology, Washington, DC, pp. 287–318.
 7. Arrigoni, M. G., Woolner, L. B., and Bernatz, P. E. (1972) Atypical carcinoid tumors of the lung. *J. Thorac. Cardiovasc. Surg.* **64**, 413–421.
 8. Travis, W. D., Rush, W., Flieder, D. B., Falk, R., Fleming, M. V., Gal, A. A., and Koss, M. N. (1998) Survival analysis of 200 pulmonary neuroendocrine tumors with clarification of criteria for atypical carcinoid and its separation from typical carcinoid. *Am. J. Surg. Pathol.* **22**, 934–944.
 9. Beasley, M. B., Thunnissen, F. B., Brambilla, E., Hasleton, P., Steele, R., Hammar, S. P., et al. (2000) Pulmonary atypical carcinoid: predictors of survival in 106 cases. *Hum. Pathol.* **31**, 1255–1265.
 10. Wilkins, E. W., Jr., Grillo, H. C., Moncure, A. C., and Scannell, J. G. (1984) Changing times in surgical management of bronchopulmonary carcinoid tumor. *Ann. Thorac. Surg.* **38**, 339–344.
 11. Cutz, E. (1982) Neuroendocrine cells of the lung. An overview of morphologic characteristics and development. *Exp. Lung Res.* **3**, 185–208.
 12. Travis, W. D., Linnoila, R. I., Tsokos, M. G., Hitchcock, C. L., Cutler, G. B., Jr., Nieman, L., et al. (1991) Neuroendocrine tumors of the lung with proposed criteria for large-cell neuroendocrine carcinoma. An ultrastructural, immunohistochemical, and flow cytometric study of 35 cases. *Am. J. Surg. Pathol.* **15**, 529–553.
 13. Flieder, D. B. and Vazquez, M. F. (2000) Lung tumors with neuroendocrine morphology. A perspective for the new millennium. *Radiol. Clin. North Am.* **38**, 563–577, ix.
 14. Travis, W. D., Gal, A. A., Colby, T. V., Klimstra, D. S., Falk, R., and Koss, M. N. (1998) Reproducibility of neuroendocrine lung tumor classification. *Hum. Pathol.* **29**, 272–279.

15. Linnoila, R. I., Piantadosi, S., and Ruckdeschel, J. C. (1994) Impact of neuroendocrine differentiation in non-small cell lung cancer. The LCSG experience. *Chest* **106**, 367S–371S.
16. Onuki, N., Wistuba, I. I., Travis, W. D., Virmani, A. K., Yashima, K., Brambilla, E., et al. (1999) Genetic changes in the spectrum of neuroendocrine lung tumors. *Cancer* **85**, 600–607.
17. Debelenko, L. V., Brambilla, E., Agarwal, S. K., Swalwell, J. I., Kester, M. B., Lubensky, I. A., et al. (1997) Identification of MEN1 gene mutations in sporadic carcinoid tumors of the lung. *Hum. Mol. Genet.* **6**, 2285–2290.
18. Debelenko, L. V., Swalwell, J. I., Kelley, M. J., Brambilla, E., Manickam, P., Baibakov, G., et al. (2000) MEN1 gene mutation analysis of high-grade neuroendocrine lung carcinoma. *Genes Chromosomes Cancer* **28**, 58–65.
19. Anbazhagan, R., Tihan, T., Bornman, D. M., Johnston, J. C., Saltz, J. H., Weigering, A., et al. (1999) Classification of small cell lung cancer and pulmonary carcinoid by gene expression profiles. *Cancer Res.* **59**, 5119–5122.
20. Ball, D. W., Azzoli, C. G., Baylin, S. B., Chi, D., Dou, S., Donis-Keller, H., et al. (1993) Identification of a human achaete-scute homolog highly expressed in neuroendocrine tumors. *Proc. Natl. Acad. Sci. USA* **90**, 5648–5652.
21. Auerbach, O., Hammond, E. C., and Garfinkel, L. (1979) Changes in bronchial epithelium in relation to cigarette smoking, 1955–1960 vs. 1970–1977. *N. Engl. J. Med.* **300**, 381–385.
22. Wistuba, I. I., Behrens, C., Milchgrub, S., Bryant, D., Hung, J., Minna, J. D., and Gazdar, A. F. (1999) Sequential molecular abnormalities are involved in the multistage development of squamous cell lung carcinoma. *Oncogene* **18**, 643–650.
23. Lam, S., Kennedy, T., Unger, M., Miller, Y. E., Gelmont, D., Rusch, V., et al. (1998) Localization of bronchial intraepithelial neoplastic lesions by fluorescence bronchoscopy. *Chest* **113**, 696–702.
24. The Alpha-Tocopherol, B.-C.C.P.S.G. (1994) The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. *N. Engl. J. Med.* **330**, 1029–1035.
25. Omenn, G. S., Goodman, G. E., Thornquist, M. D., Balmes, J., Cullen, M. R., Glass, A., et al. (1996) Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial. *J. Natl. Cancer Inst.* **88**, 1550–1559.
26. Miller, R. R., Nelems, B., Evans, K. G., Muller, N. L., and Ostrow, D. N. (1988) Glandular neoplasia of the lung. A proposed analogy to colonic tumors. *Cancer* **61**, 1009–1014.
27. Rao, S. K. and Fraire, A. E. (1995) Alveolar cell hyperplasia in association with adenocarcinoma of lung. *Mod. Pathol.* **8**, 165–169.
28. Sterner, D. J., Mori, M., Roggli, V. L., and Fraire, A. E. (1997) Prevalence of pulmonary atypical alveolar cell hyperplasia in an autopsy population: a study of 100 cases. *Mod. Pathol.* **10**, 469–473.

29. Westra, W. H., Baas, I. O., Hruban, R. H., Askin, F. B., Wilson, K., Offerhaus, G. J., and Slebos, R. J. (1996) K-ras oncogene activation in atypical alveolar hyperplasias of the human lung. *Cancer Res.* **56**, 2224–2228.
30. Kitaguchi, S., Takeshima, Y., Nishisaka, T., and Inai, K. (1998) Proliferative activity, p53 expression and loss of heterozygosity on 3p, 9p and 17p in atypical adenomatous hyperplasia of the lung. *Hiroshima J. Med. Sci.* **47**, 17–25.
31. Yashima, K., Litzky, L. A., Kaiser, L., Rogers, T., Lam, S., Wistuba, I. I., et al. (1997) Telomerase expression in respiratory epithelium during the multistage pathogenesis of lung carcinomas. *Cancer Res.* **57**, 2373–2377.
32. Suzuki, K., Nagai, K., Yoshida, J., Yokose, T., Kodama, T., Takahashi, K., et al. (1997) The prognosis of resected lung carcinoma associated with atypical adenomatous hyperplasia: a comparison of the prognosis of well-differentiated adenocarcinoma associated with atypical adenomatous hyperplasia and intrapulmonary metastasis. *Cancer* **79**, 1521–1526.
33. Takigawa, N., Segawa, Y., Nakata, M., Saeki, H., Mandai, K., Kishino, D., et al. (1999) Clinical investigation of atypical adenomatous hyperplasia of the lung. *Lung Cancer* **25**, 115–121.



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