American Journal of Pathology, Vol. 149, No. 2, August 1996

Expression of Peptidyl-Glycine α-Amidating Mono-Oxygenase (PAM) Enzymes in Morphological Abnormalities Adjacent to Pulmonary Tumors

Alfredo Martínez,* Anthony M. Treston,* Laura Saldise,† Luis M. Montuenga,† and R. Ilona Linnoila*

From the Biomarkers and Prevention Research Branch, Division of Clinical Sciences, National Cancer Institute, National Institutes of Health, Maryland, and the Department of Histology and Pathology,† University of Navarra, Pamplona, Spain*

Carboxyl-terminal amidated peptide hormones are known to be autocrine growth factors for lung tumors and tumor cell lines. Expression of the enzymes necessary for the biosynthesis of active amidated peptide hormones is therefore necessary for autocrine growth stimulation in lung tumors and possibly in the early proliferative stages of lung carcinogenesis. The peptidyl amidating enzymes have previously been identified in cell lines of all histological types of lung cancer and in lung tumors by immunohistochemistry and in situ hybridization. In this study we analyzed the expression of the peptidyl amidating enzymes in histological abnormalities found in the proximity of pulmonary tumors from a series of 59 patients. Most of the lesions in both the proximal airways (basal cell hyperplasia, carcinoma in situ, and some squamous metaplasia) and the alveoli (type II cell hyperplasia, bronchiolization of the alveoli, atypical alveolar hyperplasia, and isolated atypias) had a high proportion of cells strongly positive for the peptidyl amidating enzymes. The intense expression of peptidyl amidating enzymes in type II cell hyperplasia and atypical alveolar cells, together with the high frequency of these abnormalities in the alveoli, which is an area that does not express these enzymes in normal lung, points to the involvement of peptide hormones in the growth biology of pulmonary tumors. These findings suggest that peptide hormone stimulation of mitogenesis is an early event in tumor progression and merits additional investigation as a target for early detection and chemo-intervention of lung carcinogenesis. (Am J Pathol 1996, 149:707–716)

Lung cancer is the most frequent cause of cancer death of both males and females in the United States, accounting for one in three cancer deaths.[1] In the last 30 years, survival of this disease has improved only minimally to 14% at 5 years after diagnosis.[1] To improve survival outcome, it is important to identify lung cancer before dissemination from the bronchopulmonary epithelium.[2]

With cigarette smoking and other environmental insults, the entire respiratory tract is exposed to carcinogens and pro-carcinogens and is at risk for cancer development. Continuous exposure results in cumulative mutations, and the risk of cancer development is related to the extent of genetic damage, which eventually lead to morphological changes. This phenomenon has been called field cancerization.[3] As a consequence, a variety of epithelial changes representing all stages of progression from normal cells to frank tumor can be observed throughout the respiratory tract of both smokers and lung cancer patients.[3–5] Typically, these lesions may proceed to cancer independently from each other.[6] Saccomanno et al[7] have demon-

Supported by grants from the Spanish Government: PF93–16525626 (Ministerio de Educacion y Ciencia) and DGICYT PB93–0711 (Direccion General de Investigacion Científica y Técnica).

Accepted for publication April 18, 1996.

Address reprint requests to Dr. Alfredo Martínez, BPRB, DCS, National Cancer Institute, 9610 Medical Center Drive, Room 300, Rockville, MD 20850-3300.

A. Martinez and A. M. Treston contributed equally to this paper, and are designated as co-first authors.