PROGNOSTIC SIGNIFICANCE OF ONCOGENES AND ONCO-SUPPRESSOR GENES IN LUNG CANCER.

DA SPANDIDOS[1,2], M CHATZIPANAYOTOU [1,2] AND V ZOUMPOURLIS[1]

1. Institute of Biological Research and Biotechnology, National Hellenic Research Foundation, Athens.
2. Medical School, University of Crete, Heraklion, Greece.

Prognosis in lung cancer, one of the commonest cancers in the developed world, is poor, with less than 13% of all lung cancer patients surviving more than 5 years after diagnosis. With such an elevated mortality rate, it is important to elucidate the genetic changes involved in the pathogenesis of lung cancer.
The process of carcinogenesis can be divided into the three stages of initiation, promotion and progression based on evidence mainly from experimental models. Such processes have been studied indirectly in humans by measurements of age-dependent cancer incidence. The development of cancer requires multiple genetic alterations, each assumed to consist of the activation of an oncogene or the inactivation of a tumor-suppressor gene that is able to disrupt strictly controlled cellular processes such as differentiation and growth (1,2).
Lung cancer, although second to prostate cancer in terms of frequency, is clearly the number one cause of cancer deaths among both males and females. Lung tumors are carcinomas originating from the respiratory epithelium and are classified on the basis of histological type. The two main types are small cell lung cancer (SCLC) with few subtypes and non-small cell lung cancer (NSCLC) with a large number of subtypes. SCLC most probably arises from pulmonary neuroendocrine (NE) cells and accounts for about 25% of all lung tumors. It is an extremely aggressive neoplasm, is frequently associated with distant metastases and has the poorest prognosis of all lung tumors. NSCLC usually lacks the neuroendocrine features that characterise the SCLC tumors and is classified according to its cell of origin. The NSCLCs include: squamous cell carcinomas which may originate from a metastatic squamous epithelium; adenocarcinomas which arise in the major bronchi; and large cell carcinomas which are predominantly undifferentiated tumors some of which may represent their basal or stem cell origin. NSCLC is treated primarily with surgery and radiotherapy while SCLC with chemotherapy (3).
The conversion of normal lung stem cells to malignant ones involves a series of changes in different sets of genes (oncogenes and onco-suppressor genes). Such a series of events has been demonstrated in colorectal carcinoma by Fearon and Vogelstein (4).
Although in lung cancer the sequential events are not yet established, data from different laboratories have focused on the chromosomes, oncogenes and onco-suppressor genes.
Several studies have shown alterations in chromosomes 1, 3, 6, 7, 8, 11, 13, 15, 17 and 19 by RFLP analysis. The most frequent changes are deletions in the region

p21.3 of chromosome 3 in both NSCLC and SCLC. This region is believed to encode a yet unknown onco-suppressor gene (5,6).

Type I growth factor receptors. This group of molecules include three transmembrane glycoprotein (c-*erb*B-1, c-*erb*B-2 and c-*erb*B-3) related sequences and intrinsic tyrosine kinase activity. It has been shown that c-*erb*B-1 and c-*erb*B-2 are commonly overexpressed in NSCLC. Overexpression of c-*erb*B-1 (EGF-r) is frequently a result of c-*erb*B-1 gene amplification (7-9).

ras gene family. Members of the *ras* family of proto-oncogenes, comprised of K-*ras*, H-*ras* and N-*ras*, are inner plasma membrane associated GTPases that bind GTP cleaving it to GDP. They are involved in signal transduction. Activated *ras* oncogenes, by point mutations in codons 12, 13 and 61 have frequently been detected in NSCLC. There is evidence linking mutations in each member of the *ras* family with poor prognosis. K-*ras* is mutated in 30% of adenocarcinomas and there is a correlation with smoking history with about 30% of smokers compared with 2% of non-smokers having G-T transversions at codon 12. This type of mutation is consistent with exposure of the lung to carcinogens in tobacco smoke such as benzo[a]pyrene (10,11).

myc. The *myc* gene family encodes at least three proteins c-MYC, N-MYC and L-MYC of MW 62-68 kDa. Gene amplification and overexpession of the *myc* family has been shown to be an important feature of SCLC. It has been postulated that *myc* amplification occurs more frequently in patients who have undergone chemotherapy. Amplification of the c-*myc* gene is found in about 10% and increased expression in about 50% of NSCLCs of all types (12-14).

c-raf-1. The c-*raf* proto-oncogene located in chromosome 3p14-25 encodes a serine/threonine specific protein kinase, p74 which is located on the inner plasma membrane. Molecular analyses have shown 45% loss of heterozygocity in SCLCs (1).

c-fos, c-jun. c-*fos* and c-*jun* oncogenes form a complex, AP-1, which acts as a transcriptional factor. Recent reports show an increased AP-1 activity in NSCLC. As there is evidence that AP-1 may be involved in signal transduction, elevated levels may be oncogenic.

c-myb. This proto-oncogene is located on chromosome 6q24 and encodes a nuclear transactivator. Recent studies in NSCLC show that aberrant c-*myb* expression, either deletions or defect RNA transcription, may play a role in lung carcinogenesis (1).

p53. The p53 is located in the 17q13 chromosome and encodes a 393bp protein which structurally resembles a transcriptional activator factor. p53 functions as a negative regulator of cell growth and may play an important role in genomic stability and DNA repair. Loss of wild type p53 functions either by mutation, complex formation with viral products or cellular negative regulator(s) such as the *mdm2* gene product, or alteration in subcellular localisation removes an important tumor suppressor mechanism and promotes tumorigenesis.

Mutations in p53 are the commonest genetic changes detected in several different types of cancers and are a common feature of NSCLCs. The frequency varies with

the type of pulmonary cancer with about 67% of 5q CLCs and 37% of adenocarcinomas. p53 mutations carrying G:C-->T:A transversions are found in about 50% of NSCLCs. This type of mutation may be caused by benzo[a]pyrene a potent mutagen found in tobacco known to cause transversions of this kind. Mutations of the p53 are present in over 75% of the SCLC cases. p53 alterations have been observed in primary tumors as well as in metastases suggesting its early role in the pathogenesis of SCLC (15-17).

RB. The Rb-1 protein product, pRB, is a DNA binding protein of 110 kDa that is thought to be related to events crucial to cell division. The cloning and characterisation of the Rb1 gene showed that the loss of the gene or its protein product by homozygous deletion or mutation was the event that resulted during development.

There is evidence that the survivors of hereditary retinoblastoma are at higher risk for developing lung tumors and to develop them at an earlier age than the general population. Relatives of retinoblastoma patients who are carriers of an RB-1 mutation have a 15-fold increased risk of lung cancer compared to the general population (18).

Regadless of the tissue or origin, the development of a cancer cell from a normal cell involves a series of genetic changes that contribute to a loss of normal growth control mechanisms. For lung cancer these events are still poorly understood. Significant progress has been made recently in determining the status of oncogenes such as p53 whose role is considered to be important in the multistep process of carcinogenesis.

It is obvious that further detailed studies are required in order to correlate mutations with factors such as diagnosis, clinical parameters, genetic predisposition and prognosis.

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