LUNG CANCER

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LUNG CANCER

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Preface

Lung cancer is a challenge for both the clinician and the scientist. Despite intensive antismoking campaigns, the incidence of lung cancer continues to increase both in the United States and in many other countries. Unfortunately, little progress has been made in early detection or the treatment of advanced disease, and consequently there has been little change in survival rates over the past 15 years. Recently, new observations in the basic and clinical sciences have increased our understanding of lung cancer at the molecular level. These advances offer promise for improved prevention and therapy strategies. This book is an attempt to summarize this information in both clinical and basic science.

The first section of the book discusses the biology of lung cancer. Genetic factors appear to contribute to the development of lung cancer. Understanding of the carcinogenesis process at the molecular level may translate into new prevention and therapy strategies. The section on surgery describes advances in selecting patients for resection and accurately predicting survival by staging. Operations which preserve functioning lung are important in this patient group, and the results of these procedures are described. Radiation therapy is an important primary therapy modality for many lung cancer patients. This section includes studies of altered fractionation and chemoradiation, which have improved the results of radiation therapy. New chemotherapeutic agents and agents which reduce the morbidity from chemotherapy are described in the next section. The final section includes new strategies for prevention, early detection, and therapy.

Our goal is to provide a succinct and readable summary of recent research in lung cancer, so that practicing physicians can determine how these findings will influence the management of their patients. The breadth of specialties represented in this book emphasizes the importance of multidisciplinary care of the lung cancer patient.

Jack A. Roth
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Waun Ki Hong

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I

BIOLOGY OF LUNG CANCER

1

Genetic predisposition to lung cancer

PETER G. SHIELDS & CURTIS C. HARRIS

Lung cancer is a significant cause of worldwide morbidity and mortality. In the United States, the incidence is second only to prostate cancer in males, and colorectal and breast cancer in females [1]. It is the leading cause of cancer death due to its refractoriness to treatment. Thus, methods in lung cancer prevention are a high priority. Tobacco continues to be the major cause of lung cancer; reduction in consumption would lead to significant risk reduction [2]. The relative risk for lung cancer in current smokers compared to those who have never smoked is 22.4, and the smoking attributable mortality, in 1991, is 143 000 deaths [3]. The risk of lung cancer from passive exposure also has been well documented [4,5] and its role as an occupational hazard has recently been highlighted [6]. Other carcinogenic exposures, which are primarily occupational, can lead to lung cancer, including asbestos, radon, arsenic, chromium, nickel, and polycyclic aromatic hydrocarbons [7]. The relationship of these agents, including tobacco, to an individual's lung cancer risk on a genetic basis, is now being explored.

Evidence that lung cancer risk has a multifactorial basis, including inherited predispositions, can be inferred from both epidemiologic studies, laboratory studies, and the integration of the two through molecular epidemiologic methods. The risk of lung cancer is higher in those who are related to persons with lung cancer [8], and also parallels the risk of other tobacco-related diseases such as chronic bronchitis [9]. On a molecular level, as will be described in this chapter, inherited predisposition to lung cancer involves the capacity for carcinogen metabolic activation, DNA structure, germline mutations coding for dysfunctional genes, or capacity to repair DNA damage. The determination of lung cancer risk in an individual might directly or indirectly assess these factors by determining carcinogen–DNA adduct levels that reflect a biologically effective dose of a carcinogen, somatic mutations, or gross cytogenetic abnormalities.

MULTISTAGE CARCINOGENESIS

Carcinogenesis is a multistage process of normal growth, differentiation, and development gone awry. It is driven by spontaneous and carcinogen-induced genetic and epigenetic events. Figure 1.1 presents a simplified scheme

for cancer formation. The direct effects of carcinogenic agents upon DNA result in mutations and altered gene expression. These genetic effects, together with additional carcinogen exposure, are then involved in tumor promotion, whereby cells have selective reproductive and clonal expansion capabilities mediated through altered growth, resistance to cytotoxicity, and dysregulation of terminal differentiation [10]. Abnormal signal transduction has been also noted as a contributory mechanism [11]. Progressive phenotypic changes and genomic instability occur (aneuploidy, mutations, and gene amplification) [12,13]. These genetic changes enhance the probability of "initiated" cells transforming into a malignancy, the odds of which are increased during repeated rounds of cell replication [14]. Angiogenesis then allows for a tumor to grow beyond 1 or 2 mm in size [15]. Ultimately, tumor cells can disseminate through blood vessels, invading distant tissues and establishing metastatic colonies [16].

The role of protooncogenes and tumor suppressor genes has become increasingly apparent in the multistage model of carcinogenesis [13]. Protooncogenes are important to the regulatory mechanisms of growth, cell-cycle control, programmed cell death, and terminal differentiation [17]. Activation of protooncogenes enhances the probability of neoplastic transformation, which can either be an early or a late event. Carcinogens can cause mutations in protooncogenes (described below), and they can act as tumor promoters, enhancing the pathologic activities of oncogene protein products. Tumor suppressor genes also play an important role in carcinogenesis [13,17]. These genes code for products that, unlike protooncogenes, enhance neoplastic transformation when their activity is lost. A variety of functions of tumor suppressor genes have been proposed (Table 1.1). These genes are recessively inherited and generally require the loss of both genomic alleles and/or products. However, a dominant negative effect has also been observed, where damage to one allele results in an altered tumor suppressor protein that inhibits the normal protein of the other allele [18]. Loss of suppressor and antimetastasis genes can be an early or a late event, involving several steps, including angiogenesis and metastasis [19].

Table 1.1 Examples of functions of putative tumor suppressor genes. (From [13])

Induce terminal differentiation
Maintain genomic stability
Trigger senescence
Induce programmed cell death
Regulate cell growth
Signal transducers of negative growth factors
Regulators, e.g. PTPaseγ, of tyrosine kinases
Inhibit proteases
Modulate histocompatibility antigens
Regulate angiogenesis
Facilitate cell–cell communication

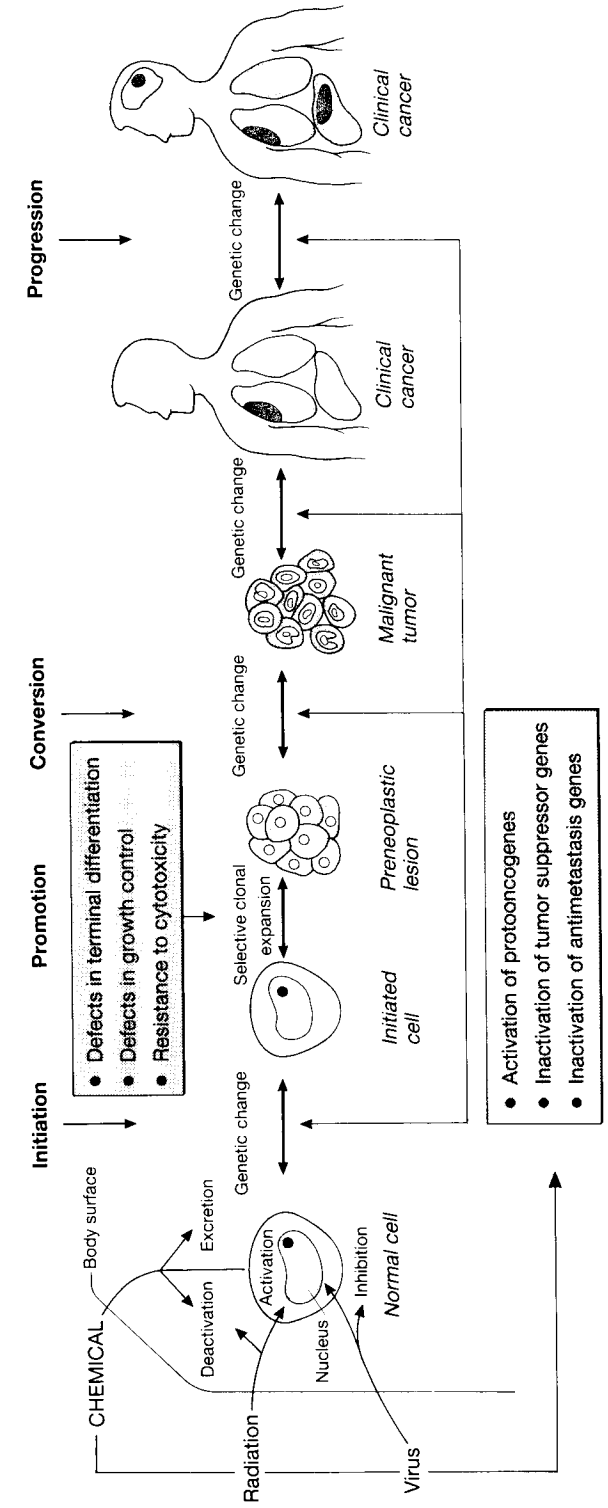

Fig. 1.1 Multistage carcinogenesis.

Tumor suppressor genes can be inactivated by mutagenic and epigenetic mechanisms. For example, the *p53* tumor suppressor gene, located on the short arm of chromosome 17, is the most commonly altered tumor suppressor gene studied so far [20]. Mutations have been commonly found in both small-cell (SCLC) and nonsmall-cell lung cancer (NSCLC) [20]. The *p53* gene normally encodes for a phosphoprotein involved in the control of cell proliferation. Single base substitutions can result in loss of function, or the production of proteins that either interfere with normal function or otherwise directly enhance the probability of neoplastic transformation [21].

Carcinogenic agents affect DNA and produce mutational spectra by several molecular mechanisms. Chemical carcinogens generally undergo metabolic activation to electrophilic intermediates that covalently bind to DNA and form adducts. Certain promutagenic adducts can then cause mutations through mispairing or base substitutions during DNA synthesis. The binding of carcinogens to DNA is nonrandom, and sequence specificity has been described [22–24]. Protooncogenes and tumor suppressor genes are important molecular targets of these genetic carcinogens. The *ras* genes are among the best-studied protooncogenes. *Ras* p21 protein products are involved in signal transduction pathways initiated by growth factors and hormones at cell membrane receptors. In several experimental systems, activation is associated with tumor formation [25], angiogenesis [15], and metastasis [19]. Mutations of *ras* protooncogenes have been observed in human cancers, including lung cancer [17,26]. Base substitutions occur nonrandomly at codons 12, 13, and 61 upon exposure to such agents as polycyclic aromatic hydrocarbons (PAH) and radiation, which results in the activation of *ras* protooncogenes in animal models [26–29]. The mutational spectra of tumor suppressor genes also suggest site-specific binding of carcinogens, as well as selective clonal expansion of cells containing certain mutations [30,31]. The spectrum for lung cancer is significantly complex [20], consistent with a multiple-carcinogen tobacco smoke and environmental etiology. Interestingly, the *p53* mutational spectra are similar in SCLC and squamous cell carcinoma; G : C→T : A transversions are common in the latter group of cancers, while G : C→A : T transitions are more common in adenocarcinoma. G to T transversions are most frequently caused by bulky carcinogen–DNA adducts.

Some lung carcinogens, for example, bis(chloromethyl)ether, can damage DNA directly, but most require metabolic activation by cytochrome P450 (CYP) metabolic enzymes having monooxygenase activity [32]. The primary role of cytochrome P450 enzymes is chemical alteration to enhance excretion. During metabolism, however, functional groups can be added or exposed that result in reactive electrophilic intermediates that bind covalently with DNA, forming adducts. Among the best-studied are the epoxidation reactions in the metabolism of polycyclic aromatic hydrocarbons, of which benzo[*a*]pyrene (BP) is one example [33,34]. These compounds are composed of fused benzene rings that are essentially water-insoluble, but are readily absorbed through the lungs and gastrointestinal tract. They are commonly

found as combustion products of fossil fuels (e.g. coal, diesel exhaust) and vegetable matter. Consequently, PAHs occur as environmental pollutants. BP becomes metabolically activated in Phase 1 by forming a reactive diol epoxide (Fig. 1.2). Initially, CYP1A1 and epoxide hydroxylase catalyze the conversion of BP to a dihydrodiol. Then, CYP3A4 converts this product to a diolepoxide (BP-7,8-diol-9,10-epoxide), which is the reactive form. However, along this pathway, intermediates might be removed via conjugation (e.g. glutathione transferase), further oxidation, or reduction. These metabolites can then be excreted in urine or feces.

Independent of carcinogen exposure, human cells are continuously undergoing spontaneous mutations at a low rate [35]. Oxidative damage, polymerase infidelity, chromosomal rearrangements, recombinase infidelity, and telomere reduction are other sources of error. The process of cell and DNA replication can increase the mutation rate [14]. When one considers that the human body contains 10^{14} cells, and that these cells undergo 10^{16} divisions over a person's lifespan, it is quite possible that genomic instability plays an important role in carcinogenesis [13,35].

Oxidative DNA damage following free radical activation is the result of both endogenous and exogenous factors. Endogenously, oxidative damage results from the production of active oxygen species mediated through hydrogen peroxide, superoxide anions (O_2^-), and hydroxyl radicals (OH^-), commonly found in cells associated with inflammation. Lipid peroxidation also can cause oxidative damage. Ionizing radiation, benzo[*a*]pyrene, benzene, cigarette smoke (due to the presence of catechols, quinones, nitrogen oxides, and other agents), and asbestos all cause oxyradical damage. Oxidative DNA damage can be prevented chemically (vitamin E, glutathione, uric acid), or enzymatically (superoxide dismutase, catalase, peroxidase) [36,37].

On a molecular basis, cells also possess the ability to repair DNA damage. Smaller alkyl adducts can be excised, while larger adducts require the excision of several bases. An extensively studied repair enzyme is O^6-alkylguanine-DNA-alkyltransferase. This enzyme repairs damage from alkylating agents such as tobacco-specific nitrosamines and other *N*-nitrosocompounds. It is a suicide protein, in that it transfers the alkyl group to itself and becomes inactivated. Cell cytotoxicity and tumor cell resistance are negatively correlated with the levels of this enzyme [38], and levels vary within organs and among people [39,40]. The enzyme is inhibited by aldehydes [41,42] and alkylating cancer chemotherapeutic agents [43]. Separately, polycyclic aromatic hydrocarbon–DNA adducts can be repaired by a nucleotide excision pathway. A unimodal distribution of repair rates of benzo[*a*]pyrene diol epoxide–DNA adducts has been observed using human lymphocytes *in vitro* [44]. The interindividual variation was found to be substantially greater than the intraindividual variation, which suggests a role for inherited factors.