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The Molecular Genetics of Lung Cancer

With 34 Figures, 13 in Colour

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To Paul, Catrin and Duncan

Preface

Lung cancer, the second most common cancer in men and the third most common in women, is one of the most studied and hence probably one of the best understood of the 'non-heritable' human cancers. Familial aggregation of lung cancer is comparatively rare and, as yet, no gene has been described whose mutation is pathognomonic for, or even largely confined to, lung cancer, as found for example in cancers of the colon, kidney or breast. This should not however be taken as implying that genes are not involved in the etiology of lung cancer. Indeed, a considerable number of inherited genetic variants are now thought to confer susceptibility to the disease. An even larger number of genes have been shown to harbour somatic mutations in lung tumour cells or tissue. The role that these somatic mutations play in lung tumorigenesis can increasingly be understood in terms of their ability to promote cellular growth, to interfere with DNA repair, to confer resistance to apoptosis or to induce cellular transformation, tumour growth, invasiveness, angiogenesis, evasion of host immunity and finally, metastasis.

Perhaps the most characteristic feature of lung cancer is however the very strong association, evidenced by a multitude of epidemiological studies, with cigarette smoking. Although the precise underlying biological mechanisms and pathways responsible for this association are not yet understood, it is nevertheless clear that in lung tumorigenesis we are witnessing a highly complex interplay between genes and environment. Unravelling this complexity promises to be a very substantial undertaking. This is reflected in the fact that the molecular genetics of lung cancer is a burgeoning subject with a very large and widely dispersed literature that is difficult to access. This volume is primarily intended to summarize the current state of knowledge regarding the molecular and genetic mechanisms underlying lung cancer, and focuses specifically on the proximal genetic causes (as evidenced by the different types of somatic and germline mutations in a variety of different genes) and consequences (as adduced by mRNA expression and protein profiling) of this condition.

The introductory chapter is intended to provide an overview of the molecular basis of cancer and discusses the different categories of gene known to be involved in tumorigenesis as well as the underlying mechanisms of mutagenesis. Chapter 2 seeks to set the scene, with short sections on the history of lung cancer research, clinical aspects of the disease, disease classification and the major contribution made by both classical cytogenetic and molecular cytogenetic analysis to the identification of the genes involved. In the absence of a familial predisposition to the disease, the molecular genetic analysis of lung cancer (both small cell and non-small

cell) has been largely confined to the study of the tumour cells themselves. Somatic mutations involving some 120 different human genes have so far been characterized in primary lung tumour tissue or in cells derived from lung tumours. Such mutations may be gross and affect entire chromosomal regions or may instead be more subtle and serve to alter the fine structure of specific genes. A growing number of genes have also been shown to be inactivated by promoter methylation ('epimutation') during lung tumorigenesis. Genes compromised by mutation or epimutation include oncogenes and tumour suppressor genes as well as genes encoding proteins that perform functions in DNA repair, telomerase activity, apoptosis, and cell cycle regulation. This topic is reviewed in Chapter 3. Chapter 4 focuses on recent advances in our understanding of signal transduction pathways, apoptosis and cell cycle control mechanisms that are beginning to allow us to account for the emerging mutation data in terms of, for example, either a growth advantage accruing to the cells and/or an escape from apoptosis. The determination of the temporal order in which these lesions occur and the elucidation of the functional consequences of different combinations and permutations of lesions are extremely important. Chapter 4 attempts to address these topics as well as the identification of new prognostic indicators and the potential for early clinical detection.

Without straying into either epidemiology or toxicology, Chapter 5 attempts to review current knowledge about the genetic damage in the lung cells of smokers and smoking lung cancer patients. The cytogenetic, genetic and epigenetic (methylation) changes that have been associated with smoking are discussed, as are reported differences in mutation frequency or lung cell gene expression between smokers and non-smokers. Finally, the ongoing debate and controversy surrounding the potential role of benzo[*a*]pyrene as a mutagen (specifically with respect to the *TP53* gene) is described and discussed in detail.

A variety of inherited variants in genes encoding xenobiotic metabolising enzymes have been described that may influence lung cancer risk by playing a role in determining levels of cellular exposure to potential exogenous mutagens and carcinogens; these are reviewed in Chapter 6. Also covered are inherited variants in genes encoding DNA repair enzymes that can confer inter-individual differences in DNA repair capacity which may, at least in principle, indirectly modulate lung cancer risk.

New approaches to studying the lung tumour cellular phenotype (e.g. cDNA and oligonucleotide microarrays) are explored in Chapter 7. These approaches promise to greatly increase our knowledge of the consequences of mutation at the level of gene expression and are vital not only for obtaining a better understanding of lung cancer pathogenesis, but also for improving existing tumour diagnostics (identification/classificatory system) and for providing the novel prognostic markers and indicators that are a prerequisite for optimal patient management (Chapter 8). Advances in our understanding of the molecular biology of lung cancer have guided the design and application of a variety of new gene therapy approaches that are currently being explored in the search for the next generation of treatments (Chapter 8).

This volume therefore attempts to describe how the new techniques, methods and approaches of molecular genetics have been used in an attempt to unravel the complexities of lung tumorigenesis by analysis at DNA, RNA and protein levels with potentially important implications for diagnosis, prognosis and treatment as

well as providing new insights into how lung tumours arise from precancerous lesions and eventually progress to metastasis. In relation to the prevalence of the disease, research into lung cancer has historically been under-subscribed and poorly resourced by comparison with the common 'heritable cancers'. It is hoped that by stimulating interest in lung cancer research, this volume will help to reverse this trend.

Cardiff, July 2004 David N. Cooper

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Table of Contents