Preface

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Lung cancer, while not the commonest form of cancer, is the leading cause of cancer deaths in the world and the leading cause of cancer deaths in both men and women in the USA. While the vast majority of cases are due to exposure to tobacco carcinogens, a substantial number occur in never-smokers. Unfortunately, the vast majority of lung cancer patients will die from their disease, and recent advances in diagnosis, pathology, clinical care, and therapeutics have made only a modest dent in mortality rates. However, recent developments in translational medicine, combining our knowledge of the molecular biology of this disease with therapies that target specific molecular changes, have led to expectations that there may be some light at the end of the tunnel. The subject of lung cancer has not previously been reviewed in *Cancer and Metastasis Reviews*. Thus, it is only appropriate that this thematic issue on lung cancer focuses on molecular and translational aspects of this common and dreaded cancer.

Lung cancers may arise from either the central or the peripheral airways. The central airways consist of the bronchi, and their main function is air conduction. The peripheral airways consist of the terminal bronchioles and the alveoli and are involved in gaseous exchange and the production of surfactant. These two airway compartments have very different functions, structure, and carcinogen exposures. Thus, the tumors that arise from them are also different, with most squamous cell and small cell carcinomas arising from the central airways, while most adenocarcinomas arise from the peripheral airways.

It is commonly believed that epithelial tumors develop over a period of decades via a series of sequential and progressive histological and molecular changes resulting in invasive and metastatic cancers. The putative changes in the central and peripheral airways are radically different, with the central airways undergoing a pathway focused on squamous metaplasia and dysplasia, while the putative precursor lesion in the peripheral airways is a proliferation of type 2 alveolar pneumocytes (which produce surfactant) and then to a noninvasive form of adenocarcinoma known as bronchioloalveolar carcinoma. The preinvasive and early cancers of the two airway compartments are discussed in the first two articles by Ishizumi and Noguchi. Ishizumi and coauthors followed a large cohort of heavy smokers having evidence of bronchial dysplasia with sequential endoscopic examinations and biopsies. For the most part, bronchial squamous lesions did not follow the sequential progressive pathway. However, they found that a subset of bronchial preinvasive lesions may be a harbinger of cancer development in both the central and peripheral airways. These findings provide powerful evidence for the field carcinogenesis theory, suggesting that exposure to tobacco smoke carcinogens causes extensive molecular and histologic damage to the entire respiratory tract.

Noguchi discusses adenocarcinomas arising in the peripheral compartment. He discusses the putative stepwise progression of these tumors. Unlike the large central airways, the peripheral airways cannot be sequentially examined endoscopically or by other means. Thus, much of our knowledge of the origins of peripheral adenocarcinomas is educated guesswork based on pathological and clinical observations. Adenocarcinomas are a heterogeneous group of tumors, demonstrating histological and molecular differences. However, as summarized in his article, the major impact of Noguchi's long experience with the natural

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history of peripheral adenocarcinomas is that small noninvasive tumors have 5-year survival rates approaching 100% if adequately removed by surgery. Such survival rates are staggering when compared to the average survival of all non-small cell lung cancers of about 16% in the USA.

The epidermal growth factor receptor (EGFR) gene is the prototype of a family of receptor tyrosine kinases involved in a multitude of important signaling cascades. Deregulation of the family members by mutation, gene copy number alterations, or other means is very frequent in most epithelial cancers. Downstream of the surface located tyrosine kinases lies another gene that plays a crucial role in many cancers, the RAS gene. RAS genes, in particular KRAS, are among the most frequently mutated oncogenes in human cancers. Mutations of both EGFR and KRAS genes play pivotal roles in the origin of peripheral adenocarcinomas. During the last few years, the EGFR gene has received much publicity, because highly specific subgroups of adenocarcinomas respond dramatically to treatment with tyrosine kinase inhibitors that inhibit EGFR signaling. Three interrelated articles discuss pathological, clinical, and therapeutic aspects of the EGFR signaling complex. Yatabe discussed the specific origin of EGFR mutant tumors from the putative stem cells of the peripheral airways, namely, the terminal respiratory unit. Gazdar explains the multiple nodal points of EGFR pathway signaling that offer real or putative sites for targeted therapy and the drugs in current usage. Suda focuses on the KRAS gene and its complex interactions with the EGFR gene.

Our current belief is that only a subset of cancer cells has the ability to divide infinitely. In addition to their stem-like ability to self-renew and differentiate, cancer stem cells are also enriched in cells resistant to conventional radiation therapy and to chemotherapy. The immediate implications of this new tumor growth paradigm not only require a re-evaluation of how tumors are initiated but also on how tumors should be monitored and treated. Lung cancer stem cells have proven difficult to identify, isolate, and characterize, in part because the different compartments of the lung appear to have

different subpopulations of stem cells. Sullivan reviews the state of our present knowledge of lung stem cells and their malignant counterparts.

The advent of whole genome profiling (at the DNA, RNA, and protein levels) has been one of the major driving forces that have changed the cancer genome landscape. However, the generation of gigabytes of data from single samples has resulted in problems for interpretation and for the integration of cross-platform analyses. The ability to link, for instance, gene expression with copy number changes or methylation, greatly enhances the value of any single platform analysis. New approaches to computational biology and data integration are required. This is the theme of the article by Chari.

While the emphasis of most cancer biology studies has been genomic alterations, epigenetic changes that do not alter the basic DNA base pair structure have gradually achieved the recognition that they deserve. Methylation is the best studied and understood epigenetic change, with several hundred putative or known tumor suppressor genes silenced by this mechanism. Heller et al. summarize the large body of literature about methylation in lung cancer.

The final topic of the thematic issue on lung cancer is the emerging role of microRNAs in cancer pathogenesis. As summarized by Du and Pertsimidis, microRNAs are a class of short, 19–25 nucleotide long RNAs that regulate gene expression by binding to sequences in the 3' untranslated region of an expressed mRNA, resulting in either modulation of translation efficiency or degradation of the mRNA. However, this means they can regulate expression of a variety of genes involved in cell proliferation, differentiation, apoptosis, stem cell development, and human disease.

We live in an exciting era of rapid advances in cancer biology. While this thematic issue cannot cover the entire scope of recent advances in lung cancer, our intention is to present some of the recent developments that have the actual or potential ability to alter our basic concepts of lung cancer biology and to have an impact on translational medicine.