From Mice to Men and Back: An Assessment of Preclinical Model Systems for the Study of Lung Cancers

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ABSTRACT

Introduction: Studies of preclinical models are essential for determining the biology of lung cancers and testing new and novel therapeutic approaches. We review the commonly used preclinical models for lung cancers and evaluate their strengths and weaknesses.

Methods: We searched the MEDLINE database via PubMed using combinations of the following medical subject headings: lung cancer; animal models, mice; cell line, tumor; cell culture, mice; transgenic, mice; SCID, transplantation; heterologous; and genetic engineering. We reviewed the relevant published articles.

Results: Multiple examples of the three major preclinical models—tumor cell lines, patient-derived xenografts, and genetically engineered mouse models—exist and have been used by investigators worldwide, with more than 15,000 relevant publications. Each model has its strengths and actual or potential weaknesses. In addition, newer forms of these models have been proposed or are in use as potential improvements over the conventional models.

Conclusions: A large number and variety of models have been developed and extensively used for the study of all major types of lung cancer. While they remain the cornerstone of preclinical studies, each model has its individual strengths and weaknesses. These must be carefully evaluated and applied to the proposed studies to obtain the maximum usefulness from the models.

Keywords: Cell lines; Genetically engineered mouse models; Lung cancer; Patient-derived xenografts; Cell lines; Preclinical models; Neuroendocrine carcinomas; Non–small cell lung cancer; Small cell lung cancer

Introduction

Preclinical models for cancers, including lung cancer, are crucial for understanding biology and for the development and testing of conventional and novel therapeutic agents. Comprehensive reviews of all of the three basic methods that form the pillars of preclinical models have been recently published: cell cultures, patient-derived xenografts (PDXs), and genetically engineered mouse models (GEMMs). However, to the best of our knowledge, no comprehensive review of the entire subject has been published, although murine models were well covered in a recent review.[1] Our aim was to provide such a review of preclinical models for lung cancers. In addition, we discuss some recent novel approaches to potentially improve the basic models.

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There is no perfect model—and there may never be—and we therefore discuss the advantages and disadvantages of each model. Because this review encompasses multiple models, we cannot cover each model in as much detail as do reviews of individual models. However, by giving an overall review of the major models, a clearer picture of the field and the interrelationships and uses of the different models can be obtained.

Because small cell lung cancer (SCLC) tumors are seldom resected, only sparse diagnostic materials are occasionally available for the study of biology and for the development and testing of innovative therapeutic approaches. In vitro models to study this "recalcitrant disease" are therefore of crucial importance for this type of lung cancer.

The use of these models was first explored 30 to 40 years ago. Recently, new approaches have been proposed or implemented that may alter and improve our approach to the study of such models, and these are summarized at the end of this review. The major strengths and limitations of these three basic preclinical model systems are summarized below. The current models, especially for GEMMs, represent major improvements and innovations over the earlier systems. We focus on the more recent models and also discuss newer concepts that may improve or alter our present models. We do not discuss the sparsely studied syngeneic and spontaneous mouse models. The three models allow for experimental tests of various therapeutic approaches and the role(s) of various genetic and epigenetic changes in lung cancer pathogenesis and biology and the study of tumor heterogeneity and stem cells.

Methods

We searched the MEDLINE database via PubMed using combinations of the medical subject headings (MeSH) terms as described in Table 1. In this review, we focus on and frequently cite review articles because they give a broad overview of their respective topics and reduce the number of cited references.

Table 1. Citations to Preclinical Models for Lung Cancer

MeSH Terms Used for MEDLINE Search	No. of Citations
Cell line, tumor and human	11,705
Mice, SCID or mice nude	3223
Animals and models, genetic	923
Totals	15,851

A MEDLINE search was conducted via PubMed on September 16, 2015 using the MeSH term lung neoplasms and the other MeSH terms as indicated.

Results

A recent (September 18, 2015) search of the MEDLINE database using the major MeSH terms carcinoma, pulmonary, and other terms as indicated in Table 1 yielded more than 15,800 citations, with the majority of them referring to lung cancer tumor cell lines. However, the other two major models were also well represented. All of the three "pillars" of the preclinical models for lung cancer are well used and cited.

Tumor Cell Lines

However, the relevance of cancer cell lines has remained controversial for many reasons beyond the scope of this article. Three recent articles have addressed these issues and indicated that carefully characterized cell lines are highly relevant for many but not all studies, and must be evaluated for the specific purpose for which they were used.[2–4] The pros and cons of cell lines are discussed in Table 2. Some of the same statements apply to all of the in vitro models. Of interest, a recent study found that newly established ovarian

Table 2. Strengths and Limitations of Cell Lines for the Study of Lung Cancer

Strengths	Limitations
Maintain cytological appearances and differentiated cell properties	May represent oligoclonal selection and demonstrate genetic drift on prolonged passage
Retain driver oncogenes	Lack of stroma and vasculature may limit use for immunotherapy or vasculature targeting
Useful for in vitro experimentation, drug screening, and testing of targeted gene therapies	More controversial for testing conventional therapies
Relatively inexpensive, technically simple and availability for widespread distribution	Nonmalignant counterpart for peripheral airway adenocarcinomas or SCLC (cultured pulmonary NE cells) not available.
Maintain cytological appearances and differentiated cell properties	Most cell lines are grown as two-dimensional cultures; ability to transfer to a three-dimensional model may ability to differentiate and relevance of drug testing
Can be cryopreserved at early passage before the development of secondary genetic changes	
Immortalized respiratory epithelial cells available for use as nonmalignant counterparts	

NE, neuroendocrine; SCLC, small cell lung cancer.