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A Comprehensive Review of the Many Models Used In Lung Cancer Research

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ABSTRACT:
Animal models referred to the animal experimental object and narrated material that can simulate the human body set up in medicinal research. As the second-largest disease in terms of morbidity and mortality after cardiovascular disease, cancer has forever been the subject of human attention all around the world, which composed it a research hotspot in the medicinal field. The continuation of the pace of model lung cancer in mice has led but also to new intends of comprehending the molecular pathways governing human lung tumor, but it had also established a colossal reservoir of a chosen instrument to testing treatments against this malignancy. Most sophisticated somatic animal models for non-small cell lung cancer, limited cell lung cancer, and lung squamous cell carcinoma have been created that intimately emulate human lung cancer. In this paper, some animal models and the applications betterment of animal models in tumor research are consistently reviewed.

KEYWORDS: Lung cancer, animal model, Zebrafish Model, Xenograft Models, Orthotopic models, Humanized mice.

I. INTRODUCTION:

With the efficient controlling of severe communicable diseases and the extension of human life expectancy, cancer had now become part of the important disease that gravely hazards human health. Act by 2015 estimating by the world health organization (WHO), cancer it's the first or 2nd main bring on of death. The development and research of new diagnostic methodologies and innovative treatment instruments are critical for decreasing the worldwide incidence of cancer. The animal experiment is a key bridge between cell experiment and clinical experiment. In certain conditions, the occurrence and development the animal disease are analogous to that of human beings, and animals have lookalike anatomy, physiology, and heredity to human beings . Therefore, animal models are frequently used to examine human diseases. With the constant development the precision medication and customized medicine, investigators looking for standardized and customized tumor models that are more lookalike to human tumors. animal models referred to the animal experimental object and narrated material that can simulate the human body set up in medicinal research. At the same time, ever more animal models have been designed and used in cancer research.

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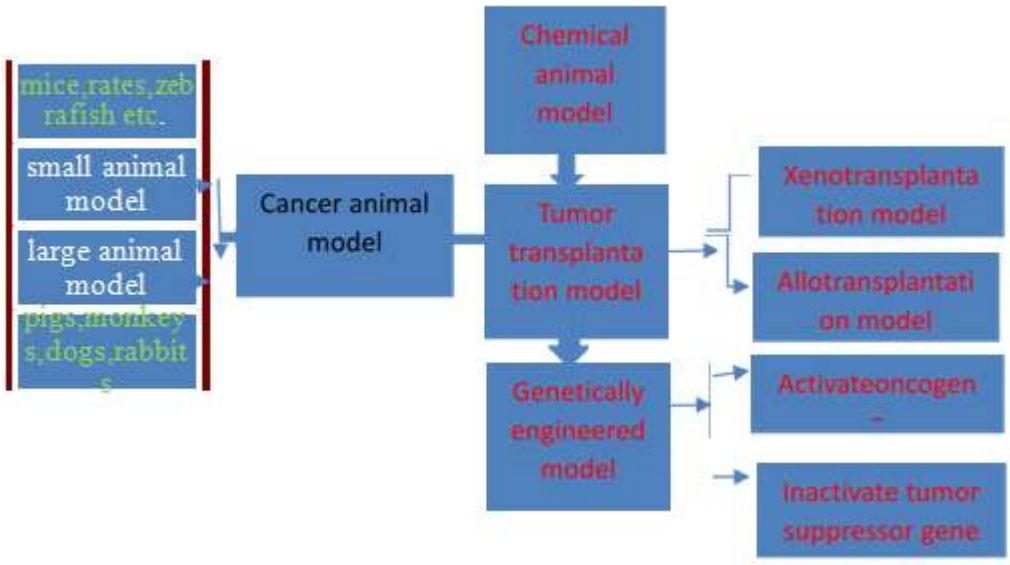

Two frequently used classifications mean cancer animal models. The dashed red box is representing the classifications according to various modeling methods. Howsoever classifications did according to divergent species. The green box denotes the species of animal included in the present classification.

HISTORY OF TUMOR MODEL

The origin of our failure to spot drugs that have increased clinical activity is multifactorial and includes, but isn't limited to, differences in the efficacy of the medicine in mice versus humans. Toxicity issues also are a standard source of drug failure and are related to the utilization of models selected for simple modeling and a high incidence of positive responses. Many commonly used solid tumor models are biased toward false-positive results because they're selected supported simple use, sensitivity to therapeutics, rapid climb, and other attributes that facilitate studies, but not clinical correlations. These deficiencies are often reduced by strict attention to proper design and conduct of efficacy studies, also because the incorporation of a rational design supported an understanding of tumor biology, variant selection, and surrogate endpoints and therefore the integration of testing strategies that reflect clinical tumor biology. The history of animal models within the development of cancer drugs has been previously discussed. however, few of those reviews have incorporated recommendations for future approaches.

Lung cancer	Xenograft model	BPIQ-induced anti-lung cancer is involved in mitochondrial apoptosis. BPIQ could be a promising anti-lung cancer drug for further applications
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Lung cancer	Xenograft model	DFIQ exerts anticancer potential in vivo and in vitro and can induce apoptosis. DFIQ-induced apoptosis is associated with lysosome accumulation and the induction of the expression of apoptosis factors, such as Bax, Bad, and tBid.
Lung cancer	Xenograft model and Transgenic	Bevacizumab, endostar and apatinib demonstrated remarkable angiogenesis and tumor inhibition effect

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	model	in the zebrafish model, within the nonlethal dose range. Endostar and bevacizumab showed competitive anti-tumor efficacy
ung cancer	mouse	PG545 was highly effective in PDX that did not respond to conventional chemotherapy (cisplatin), while other PDX tumors responded well to cisplatin and to a lower extent to PG545.
Lung cancer	rat	The severely immunodeficient SD-RG rats support fast growth of PDX compared with mice, thus holding great potential to serve as a new model for oncology research.

1.MOUSE MODELS

The use of mouse models for spontaneous or chemically induced lung tumors features a long history. While susceptibility and incidence of spontaneous lung tumors vary between well-established mouse-inbred strains, all their molecular pathologies share many similarities with human carcinoma. Mouse lung tumor development shows initial hyperplastic foci in bronchioles and alveoli, which then become benign adenomas and eventually adenocarcinomas . The very reproducible tumor latency depends on strain susceptibility and/or application of carcinogen-induction protocols. The most potent carcinogens are the cigarette smoke carcinogens, like polycyclic aromatic hydrocarbons, tobacco-specific nitrosamine, and benzo[a]pyrene (B[a]P). However, cigarette smoke itself is sufficient to induce reproducibly lung tumours in A/J mice after a 5-month exposure period followed by an important 4-month recovery period. Exposure of B6C3F1 female mice to lifetime (30 months) cigarette smoke resulted in 48% benign and malignant lung tumors through distinct (epi)genetic pathways. Therefore, there are clear differences between (spontaneous) murine and human lung tumors. it's been especially hard to duplicate the well-characterized pre-malignant lesions in human airway epithelium . Differences in susceptibility to carcinoma development between various mice strains remain, however, very intriguing. Most susceptible strains, like A/J and BALB/C, do have a polymorphism in intron 2 of Kras and a CDKN2a polymorphism was found in BALB/C, influencing their sensitivity to carcinoma.

The development and research of the latest diagnostic methods and innovative treatment tools are essential to scale back the worldwide incidence of cancer. The animal experiment is a crucial bridge between cell experiments and clinical experiments. Under certain conditions, the occurrence and development of animal diseases are almost like that of the citizenry, and animals have similar anatomy, physiology, and heredity to the citizenry. Therefore, animal models are often wont to study human diseases. In cancer research, the utilization of animal models can help us understand the genetic basis of cancer and therefore the role of specific genes and gene mutations within the occurrence and development of cancer, which also facilitates the event and testing of antineoplastic drugs.18 With the continual development of precision medicine and personalized medicine, researchers are trying to find standardized and personalized tumor models that are more almost like human tumors. There are many animal types and construction methods wont to construct cancer animal models, and therefore the progress of every animal model in tumor research has its characteristics, which can be described below.

2.Zebrafish Model

The zebrafish cancer model may be a vertebrate model rising in recent years, and it's one among the foremost promising models at the present. The genomes of zebrafish are homologous and conservative to humans, which provides an honest basis for the study of the event of varied cancers. Compared with the foremost commonly used mouse models, the zebrafish model has some unique advantages in cancer research: (1) small size, low cost, and fast reproduction; (2) transparent embryos, it's convenient to watch and track the proliferation, spread, and metastasis of cancer cells in real-time; (3) transgenic zebrafish. and immunodeficient zebrafish can remain transparent after adulthood. (3) because zebrafish is fertilized in vitro, the gene operation is comparatively easy, and therefore the transgenic animal model are often established quickly. At present, a spread of zebrafish cancer models are established using transgenic, genome editing, xenotransplantation, drug-induced toxic damage than on.

3.Patient-Derived Tumor Xenograft (PDX) Model:

International Journal of Pharmaceutical Research and Applications
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The normal xenotransplantation model is to determine a stable cell line by screening human tumor cells in vitro, subculturing them, then injecting them into immunodeficient mice to determine model. This model is named the cell line-derived xenograft (CDX) model, which has the benefits of easy to get tumor cell lines and straightforward to repeat experiments. However, with the continual passage of tumor cells to adapt to the external Petri dish environment, the tumor microenvironment has changed, leading to the formation of tumors in mice that cannot accurately reflect the characteristics of the first tumor. PDX model may be a tumor model established by transplanting fresh tumor tissue from patients into animals by surgery. at the present, the animals used are mainly immunodeficient mice. With the exploration of researchers, zebrafish and other animals provide a replacement tool for the establishment of PDX models. Compared with the CDX model, the foremost important advantage of the PDX model is that it completely retains the tumor microenvironment, avoids the effect of repeated passage on tumor heterogeneity, and may better simulate the tumor growth process in patients.

4. Xenograft Models:

For the aim of this review, murine models are often divided into the subsequent groups: xenograft, transgenic, syngeneic, and spontaneous model systems. Xenograft models require the injection of human cancer cells into immunocompromised mice, either subcutaneously, orthotopically, or systemically. Immunocompromised mice like athymic nude and severe-compromised immunodeficient (SCID) mice are frequently utilized as implanted human cells are likely to be rejected by the host system in an immunocompetent system. Once implanted, cells require a growth period of 1 to eight weeks counting on cell type and therefore the number of cells injected. Xenograft models are primarily wont to examine tumor response to therapy in vivo before translation into clinical trials. Cell lines and current xenograft models for the study of carcinoma are summarized in Table 1.

Table 1

CELL LINE	Description	histology	mutation	Animal model	Tumors
DMS-273	SCLC	SCLC	P53 mutation	Female BALB -C nude mice	14 days
DMS-114	SCLCS	SCLC	P53 Mutation		
NCI-H526	SCLCS	CLC	P53 Mutation	Female athymic nu/nu mice	20 days
NCI-H82	SCLC	SCLC	P53 Mutation		25 DAYS
DMS 53	SCLC	SCLC	P53 Mutation	Female BAL B/C nude mice female nude athymic	4-8weeks
NCI H-69	SCLC	SCLC	P53 mutation	Female athymic nu/nu mice Hind flank	15 days-4 weeks

Both the typical number of tumors that engraft (tumor take) and therefore the average time to palpable tumors are hooked into the number of cells implanted, growth characteristics of every cell-line like doubling time, cell-size, density, morphology, and therefore the use of growth factors like matrigel. Models for SCLC are generally limited, however, the NCI-H69 and DMS-53 cell lines are the foremost widely used for xenograft studies but are often problematic as they characteristically grow in suspension, leading to difficulty in obtaining an accurate cell count before implantation. These characteristics may contribute to a highly variable tumor take and growth rates of those models. additionally, to traditional xenograft models, ex vivo models are often utilized in which tumors are surgically far away from patients and tumor cells are grafted into the immunocompromised murine system either subcutaneously or orthotopically. As a result, therapy regimens for every patient were tailored

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consistent with observed tumor response within the xenograft models.

5.Orthotopic models:

Provide a reliable representation of the tumor environment as cells are implanted directly into the organ during which the disease originates. the foremost practical orthotopic model involves endobronchial inoculation of the A549 or H460 cell lines into athymic NCr-nu/nu mice. The procedure leads to a post-surgery death rate of but 5 percent. the speed of tumor engraftment is 90 percent and tumor growth is monitored through high-resolution chest roentgenography or bioluminescence via transfection of luciferase-containing constructs . Orthotopic xenograft models provide the very valuable advantage of accurate representation of the tumor microenvironment in evaluating drug therapies. this enables for a reliable prediction of toxicity, and understanding of microenvironment-dependent responses to chosen therapies. hooked into the number of cells implanted, growth characteristics of every cell-line like doubling time, cell size, density, morphology, and therefore the use of growth factors like matrigel. Models for SCLC are generally limited, however, the NCI-H69 and DMS-53 cell lines are the foremost widely used for xenograft studies but are often problematic as they characteristically grow in suspension, leading to difficulty in obtaining an accurate cell count before implantation. These characteristics may contribute to a highly variable tumor take and growth rates of those models. additionally, to traditional xenograft models, ex vivo models are often utilized in which tumors are surgically far away from patients and tumor cells are grafted into the immunocompromised murine system either subcutaneously or orthotopically. As a result, therapy regimens for every patient were tailored consistent with observed tumor response within the xenograft models.

6.Syngeneic Models

Syngeneic murine models entail the injection of immunologically compatible cancer cells into immunocompetent mice. the supply of syngeneic models to review carcinoma is extremely limited. the sole reproducible syngeneic model for carcinoma so far is the Lewis lung carcinoma (LLC) model. LLC may be a cell line established from the lung of a C57BL mouse bearing a tumor resulting from the implantation of primary Lewis lung carcinoma. The cell line is very tumourigenic and is primarily wont to model metastasis also as evaluate the efficacy of chemotherapeutic agents in vivo [36]. for instance, the LLC model was a successful preclinical model for Navelbine evaluation in vivo, before its implementation.

7. Transgenic and Conditional Transgenic Models

Genetically engineered models (GEM) are used to induce spontaneous neoplastic growth via transgenic, conditional, or drug-induced mechanisms. Transgenic mice are created by microinjection of DNA into the pronucleus of zygotes and injection of embryonic stem cells into blastocysts to produce the desired loss or gain of function mutations. Transgenic mouse models for lung cancer may be general, where tumors arise in the lung and in organs other than the lung or specific, where the lung alone is the target of the transgene. The latter models are more useful, as the frequency of the development of lung cancer is often higher and the pathology of the disease is not complicated by tumors at other sites. Transgenic mice are ideal for examining the role of genetic abnormalities in tumor initiation and progression. One of the first viral oncogenes to be targeted to the lung was the Simian virus T antigen (TAg). The tag binds to and inactivates p53 and pRB, both of which have been reported to be mutated or functionally altered in lung cancer . Through the use of the lung-specific promoters Clara cell secretory protein (CCSP), also known as uteroglobin promoter, and alveolar type II surfactant protein C (SP-C), these transgenes resulted in the development of adenocarcinoma in a murine model . The mice developed multifocal bronchioalveolar neoplasias very rapidly and often died before four months of age, making investigation of the early events in carcinogenesis difficult. These models typically resulted in tumor growth in 100 percent of animals but exhibited rapid and aggressive growth which prevented the analysis of early transformation events. Transgenic mice have also been generated through the fusion of oncogenes with lung-cell-specific promoters such as calcitonin gene-related peptide (CGRP), SP-C, or CC10.

8. Carcinogen-Inducible Models

The silencing effects of shRNAs can be reversible depending on how the transgenic animal is constructed, allowing for temporal disruption of gene expression for exploration of impacts at specific moments during development. p19ARF has recently been validated as a therapeutic target for lung cancer using a quick and scalable method for producing shRNA transgenic mice. Embryonic stem cells (ESCs) have also been used to create multiallelic mouse models quickly. Multiple rounds of disease-associated allele targeting in ESCs, followed by blastocyst injection and implantation,

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result in chimeric animals with tumors growing from engineered cells in a normal milieu. Cross-breeding of chimeric animals can result in mice that are entirely generated from ESCs. This technology was utilized to create two separate lung cancer models to investigate the activation of pathways downstream of certain mutations and to assess the efficacy of therapeutic targeted strategies. Humanized mice, in which a copy of the human gene substitutes the mouse gene, can be used to address the effect of the human gene in transgenic mouse models in specific circumstances. Similar to human patients, mice with the EGFR mutation and treated with the EGFR inhibitor erlotinib had lower levels of markers linked with EGFR expression. This suggests that mouse models could be useful in identifying novel biomarkers.

9.HUMANIZED MICE:

Several animal models, including immunodeficient mice reconstituted with human stem cells or lymphocytes, have been referred to as "humanized mice. Graft-versus-host disease and solid organ transplantation are studied using these humanized mice. Humanized mice are those that have been injected with stem cells and then immunized, or immune-deficient mice that have had T cells from immunized patients/donors injected into them. The effect of immunology on tumor/viral growth can then be studied by challenging them with human tumor xenografts or viruses. The function of interactions between xenogenic human stroma and tumors in tumor growth and metastasis is also studied using humanized mice transplanted with parts of human organs.

10.ORTHOTOPIC TUMOR MODELS:

Clinical data have revealed that tumor response to chemotherapy is influenced by the organ environment. Orthotopic implantation causes fast growth of local tumors as well as distant metastases in various tumor types. There is also a significant, site-specific variance in chemotherapeutic response. The highly metastatic KM12L4a human colon cancer cell line was used to implant colon carcinoma cells into several anatomical regions of nude mice in one investigation. Mice were injected in the subcutis (ectopic location), spleen (experimental liver metastasis), or cecum in this investigation (growth at the orthotopic site). Tumor-bearing mice were given doxorubicin and their responses were then assessed. After two i.v. injections of doxorubicin (10 mg/kg), tumors developed in the s.c. tissue revealed an 80 percent reduction of growth, compared to 40 percent inhibition in intracecal tumours and less than 10% inhibition in liver lesions. Orthotopic tumour models, therefore, appear to be a better model for assessing the form and growth features of clinical disease, as well as being more typical of a primary tumour in terms of tumour location and metastasis.

11.AUTOCHTHONOUS MODEL:

Autochthonous tumors, which include naturally occurring tumors as well as chemical, viral, or physical carcinogen-induced tumors, are thought to better mimic human tumors than transplanted tumors. Orthotopic development, tumor histology free of transplant-induced alterations, and spread via lymphatic and arterial arteries surrounding and inside the initial tumor are all advantages of autochthonous malignancies. Despite their advantages, autochthonous tumor models have not been frequently employed as drug development animal models. The time and frequency of tumor induction, the number of tumors created, and hence the number of animals necessary for a study are all variables in autochthonous tumor models.

II. CONCLUSIONS

Perspectives for the future The development and use of murine lung tumor models has a primary goal of gaining insight into lung cancer biology by dissecting the molecular pathways that are important for lung tumor onset and progression. The causal links between genotypic abnormalities and lung tumor phenotype should emerge as a result of this. Genome-wide expression profiling and comparative genomic hybridization techniques will undoubtedly aid in the identification of genes important for the progression of lung cancer into a full-blown disease. This knowledge can then be used to construct further preclinical intervention experiments, first utilizing inducible siRNA inhibition to prove the importance of specific gene products for tumor maintenance, and then employing small molecule inhibitors to disrupt the same pathway. Given the growing recognition that only therapeutic combinations can prevent long-term tumor growth, the challenge now is to figure out which combinations are the most effective and least hazardous. Although a thorough understanding of the tumor's faulty pathways may lead to the most appealing inhibitor combination, experience has taught us that drug schedule, dose, and order are all important factors in their success.

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They can assist us in gaining a deep understanding of basic lung tumor biology, finding markers for early lung cancer diagnosis, and testing and validating anti-lung cancer medicines. We must now demonstrate that these models can deliver on their promises.

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