Murine Models of Cancer

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Abstract Cancer is a class of diseases in which a group of cells displays uncontrolled growth and invasion that destroys adjacent tissues, and sometimes send metastasis to other locations in the body. When one is interested in cancer research, mice will be the preferred animal. Murine models of cancer include transplantable models, spontaneous and autochthonous models, human tumor xenografts, orthotopic models, models of metastasis and transgenic tumor models.

Keywords: mice, models, cancer

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1. Introduction

Experimental models of cancer have played an important role in cancer drug discovery for many years. They serve as tools for the elucidation of the molecular basis of neoplastic transformation, the processes involved in tumor progression and metastasis, and the determinants of therapeutic success or failure [1]. Recently, transgenic models have been used to validate and prioritize new strategies for therapeutic intervention [2]. When one is interested in curing human cancer, mice will be the preferred animal to perform cancer research upon. This is attributed to that mice share many common features with humans and develop all the types of cancer that humans develop. They also have the same genes involved in a lot of these cancers [3]. Mice are readily available. Furthermore, human tumors can be implanted in mice. In addition, mice have simpler genetics. Genetically identical mice simplify experiments by minimizing the confusion that arises when testing drugs on mixed populations. In theory, genetically identical mice should all respond the same to a given form of treatment. By adding or deleting genes from mice, scientists learn how that gene's products influence a treatment and thus, obtain valuable clues to the biochemistry of cancer [4].

In vivo cancer models can be considered to fall within two broad classes, transplantable models and in situ models. Transplantable models are the most commonly used for drug evaluation, while in situ models such as cancer-prone transgenic mice provide a rich source of information on cancer etiology [5]. Also, these models are useful in the development and testing of new imaging techniques and contrast agents [2].

2. Transplantable Models

Transplantable leukemia and solid tumor models were developed from spontaneous or induced tumors subsequently adapted to serial in vivo passage in the same animal strain [6]. Transplantable solid tumor models were developed in 1960 by exposure of rodents to chemical carcinogens. This provided a variety of tumor histotypes and tumors with different growth rates within each histotype [2]. Also, solid tumor fragments were implanted into the subcutaneous space, and therapy was assessed by caliper measurement [7]. Advantages of these models include their low cost and reproducibility. Imaging was generally not needed for assessment of tumor response in these easily accessible and observable tumors. In addition, the tumors grow in an immune-competent host, making these models appropriate for the study of immune modulation and vaccine approaches [4].

2.1. Ehrlich Carcinoma

Ehrlich carcinoma is one of the commonest transplantable tumors that appeared firstly as a spontaneous breast cancer in a female mouse, and then Ehrlich and Apolant in 1905 used it as an experimental tumor by transplanting tumor tissues subcutaneously from mouse to mouse. In 1932, Loewenthal and Jahn obtained the liquid form in the peritoneum of the mouse and named it as Ehrlich ascites carcinoma. Then, this tumor was converted to a tumor model which is suitable for qualitative and quantitative cancer researches. After 1948, Ehrlich cells had spread rapidly around the research institutes all over the world [8].

Ehrlich carcinoma is an undifferentiated carcinoma that has high transplantable capability, no regression, rapid proliferation, shorter life span, 100% malignancy and also does not have tumor-specific transplantation antigen. Ehrlich carcinoma has a resemblance with human tumors which are the most sensitive to chemotherapy due to the fact that it is undifferentiated and that it has a rapid growth rate [9] (Kabel et al., 2013).

Tumor virulence increases via repetitive passages, while the proliferating rate of such tumors increases gradually. However, differentiation gradually disappears, while the cells get free growth control mechanisms, and in the end, are converted to the ascites form. Ascites fluid contains 10 million neoplastic cells in 0.1 cc. Ehrlich carcinoma is used as ascites or a solid form. If ascites fluid containing the tumor cells is injected intraperitoneally, the ascites form is obtained, but if it injected subcutaneously, a solid form is obtained [10].

Following the inoculation into the peritoneal cavity of mice, Ehrlich carcinoma cells grow in two phases: a proliferating phase, in which the number of cells increases rapidly, and a plateau phase followed by a resting phase, in which the number of cells stays almost constant [8]. During the transition from the proliferating phase into the plateau phase, morphological and metabolic changes occur, such as: structural deterioration, decreased number of mitochondria, decreased DNA and RNA synthesis, loss of intracellular purine and pyrimidine nucleotides, decreased protein synthesis, decreased glutathione concentration and increased triglycerides, cholesterol esters and free fatty acids [11]. After a given time, the host animal died due to the pressure exerted by the tumor volume and/or the damage that resulted from the tumor [8].

3. Spontaneous and Autochthonous Models

These models include mammary and colon tumors which are induced in animals with a carcinogen. The major advantage of these models is that they may be more relevant to the development of human disease because the tumors reside in the tissue appropriate for the histotype. However, studies against tumors induced in this fashion are difficult because of low tumor incidence, variable and delayed onset of tumor growth and deep tissue location of the tumors. Assessment of tumor burdens is often performed by terminal sacrifice, complicating treatment and data collection. Also, autochthonous model systems require the handling and administration of known potent human carcinogens [12].

4. Human Tumor Xenografts

Xenotransplantation is the transplantation of tissues or organs from one species into a different species. The application of xenotransplantation techniques to the growth of human tumors in experimental animals was a major breakthrough in cancer biology and drug discovery research [5]. They include:

4.1. Subrenal Capsule

This model takes the advantage of the immunologically privileged status of the subrenal capsule (SRC). Human tumor fragments implanted under the SRC are not subjected to immediate rejection. Changes in tumor volume during therapy are determined by invasive measurements with an ocular micrometer. Unfortunately, the SRC xenograft assay is labor intensive and both tumor growth and response to therapy are often highly variable [2].

4.2. Human Tumor Xenografts in Immunodeficient Animals

These animals have genetic immune deficiencies that minimize or prevent the rejection of the grafted tissues from other species. The difficulty in using immune compromised animals is that they are highly susceptible to viral, bacterial and fungal infections that can alter the outcome and reproducibility of experiments. Therefore, immunodeficient animals are maintained in specific pathogen-free environments, which may increase the research costs [5].

Methods of xenograft studies in immunodeficient mice include subcutaneous xenografts and the hollow fiber assay. Subcutaneous xenografts are human tumor xenografts that are injected underneath animal's skin. These models provide a direct assessment of efficacy against a human cancer through simple, non-invasive caliper measurement of tumor size. The accessibility of the tumor is also an advantage for harvesting of tumor tissue. Several studies have suggested that human tumor xenograft models are better predictors of clinical activity of tumors [13]. The disadvantagesof this model include that human cells are placed in a murine environment creating interactions that may not reflect the human disease process. Other disadvantages include occasional tissue ulcerations, loss of metastatic potential and undifferentiation of the tumor. Also, the genomic instability of human cancer requires that considerable care be taken to avoid unintended change of the model over time and multiple passages. Despite these potential shortcomings, human tumor xenograft testing remains the mainstay of in vivo anticancer therapeutics evaluation [2].

The hollow fiber assay utilizes polyvinylidene fluoride hollow fibers inoculated with human tumor cell lines. The fibers are then sealed and implanted into the intraperitoneal cavity or subcutaneous space of an immunodeficient mouse for 3-10 days. After treatment, the fibers are removed and live cells are counted. Advantages of this method are that multiple cell lines can be tested simultaneously in one animal contributing to low cost. Disadvantages are that the technique requires surgery, the tumor cells are unable to interact with the normal stroma and the cells have no opportunity to develop a blood supply. Hence, this assay does not reflect treatment-induced changes in stroma-tumor interactions and vascular effects [14].

5. Orthotopic Models

It involves implantation of a tumor into the organ from which it arouses. A theoretical advantage of this model is that the tumor cells grow in their native in situ environment. Orthotopic models have additional advantages over subcutaneous and hollow fiber systems including retention of differentiated structures within the tumor, vascular growth differences, more realistic tissue pharmacokinetics at the tumor site, and metastatic spread. However, tumor implantation for orthotopic models requires complex surgery. Observation of tumor growth in internal organs requires serial sacrifice of animals, tumor rates of growth can be highly variable and it may be difficult and costly for pharmacodynamic and pathological analysis [5].

6. Models of Metastasis

Several models of metastasis employ direct or systemic injection techniques. The choice of the site or route of injection is based on vascular proximity to the target organ. For example, liver metastases models often rely on intrasplenic injection, lung metastases can be obtained from tail vein injection, and bone metastases from intracardiac injection [2]. However, these models require longer staging periods and generally have poorer reproducibility and organ specificity [15].

7. Transgenic Tumor Models

Transgenic tumor models are created by the introduction of heritable or somatic mutations that are implicated in neoplastic transformation. Target genes can be replaced by new, conditionally expressed, conditionally turned off or mutated genes. An advantage of transgenic models is that the etiology of tumor development closely mimics that in humans. The animals can be treated with therapeutic agents at any stage of tumor development to further elucidate therapeutic efficacy and the mechanism of action [16]. An example of transgenic mouse models with germ line mutations are the TRAMP (transgenic adenocarcinoma of the mouse prostate) model which was created by linking the prostate-specific probasin promoter to a specific antigen. These animals develop variably differentiated tumors that metastasize primarily to the lungs and lymph nodes. This model has been used to study late events in prostate tumorigenesis and mechanisms of angiogenesis [17].

8. Conclusion

Mice is the preferred animal to perform cancer research upon. Murine models of cancer include transplantable models, spontaneous and autochthonous models, human tumor xenografts, orthotopic models, models of metastasis and transgenic tumor models. Each of these models has its advantages and disadvantages.

Competing Interests

The authors have no competing interests.

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