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Harnessing genetically engineered mouse models for preclinical testing

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Abstract

Recent studies cast doubt on the value of traditionally used models as tools for testing therapies for human cancer. Although the standard practice of xenografting tumors into immunocompromised mice generates reproducible tumors, drug testing in these models has low predictive power when compared to the clinical responses in Phase II trials. The use of tumor-bearing genetically engineered mouse models holds promise for improving preclinical testing. These models recapitulate specific molecular pathways in tumor initiation or progression and provide a biological system in which to study the disease process for assessing efficacy of new therapies and proof-of-principle for testing molecularly targeted drugs. In this review, we discuss the advantages and limitations of genetically engineered mice and plausible solutions for adapting these valuable tumors for wider use in preclinical testing by transplantation into naïve recipients. We also provide examples of comparative molecular analysis of mammary tumors from MMTV-Polyoma Middle-T antigen and MMTV-wnt1 models as tools for finding clinical correlates, validating existing models and guiding the development of new genetically engineered mouse models for cancer.

Keywords: Gene expression; Breast cancer; Microarray; MMTV-PyMT; MMTV-wnt1; Transgenics; Transplantation; Xenografts

1. Introduction

Although great progress has been made in understanding mechanisms of tumorigenesis resulting in development of many anticancer drugs, most drugs that show preclinical efficacy fail to predict clinical response [1]. Even among cancer drugs that pass Phase I testing, only 1 in 10 is ultimately approved much to the distress of patients, pharmaceutical companies, and the scientific community. Most drugs fail Phase II clinical trials largely because of inappropriate guidance from preclinical studies. Among many reasons why preclinical studies fail to correlate with clinical efficacy are differences in drug metabolism, pharmacokinetics and pharmacodynamics, many of which are not addressed in most drug studies in mice [2,3]. In addition, molecularly targeted drugs may fail to reach appropriate targets, and the widespread use of immunocompromised mice for preclinical testing makes it difficult to predict the role of the host in response to therapies.

Drug screening relied almost entirely on syngeneic mouse tumors until 1980 [2,4]. These studies led to identification of many currently used chemotherapeutic agents, such as alkylating and other DNA-damaging agents [5,6]. Availability of immunocompromised mice was followed by rapid adaptation of these models for screening many anticancer agents using human tumors and cell lines. Recent reviews on the outcome of these screens revealed large variability between responses in mice and humans, and a low predictive power to the

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outcome of Phase II clinical trials [7,8]. A somewhat better predictive value was achieved when tumors were transplanted directly from patients into mice [9].

It has been proposed that genetically engineered mouse (GEM) models of cancer would improve anticancer drug development. When first introduced, GEM were characterized by development of hematopoietic malignancies and tumors at multiple anatomic sites [10,11]. These models provided limited opportunity for preclinical assessment of novel therapeutics. Over the last 30 years, transgenic technology has evolved to allow manipulation of the mouse genome to constitutively or conditionally alter expression of specific genes leading to cancer. These models have contributed significantly to the understanding of the molecular pathways responsible for initiation and progression of human cancer, and highlighted the importance of specific oncogenes and tumor suppressor genes in carcinogenesis. Extensive discussion of the characteristics of constitutive, tissue specific, and inducible GEM models is outside the scope of this review and has been summarized recently [2,4,10]. Although GEM models may improve preclinical testing, so far, they have not been used in development of any FDA approved anticancer agents. Only few of these models have been examined for similarities in response to standard cytototoxic agents with response in an average patient [12]. Systematic analysis and side-by-side comparison of drug efficacy in tumors driven by common molecular pathways using xenografts and GEM with clinical outcome is urgently needed. In addition, two critical issues have not been appropriately addressed and must be considered when choosing GEM models drug development: (1) the molecular alteration that drives tumorigenesis in the animal model should have a specific correlate in human disease, and (2) the clinical trial must include a study to demonstrate that the drug reaches the intended target molecule or pathway.

2. Limitations in using GEM for drug development

In spite of their contributions to cancer biology, there are few examples of the use of GEM in preclinical testing because of significant obstacles which prevent widespread use. These include the spontaneous and multifocal nature of tumor development, variable penetrance resulting in lack of synchrony in tumor development, and complicated breeding schemes. These issues have not been systematically addressed.

A major obstacle in using GEM for screening drugs is difficulty in simultaneously obtaining sufficient numbers of animals at the same stage of tumor development. Variability in time of progression to the predetermined tumor size required for drug testing can be measured in weeks-to-months, and results in significant differences in age of animals and tumor stage at any given time in the same mouse colony. Although these differences may recapitulate development and progression of human disease, they make it nearly impossible to translate preclinical results into the design of correlative clinical trials. Furthermore, to be useful for preclinical testing, mouse models should be cost-effective and generate tumors in a relatively short period of time. Only few GEM models, such as the Murine Mammary Tumor Virus-driven Polyoma Middle-T antigen (MMTV-PyMT) and the RIP-TAG model of pancreatic cancer, develop tumors over a narrow time span from birth (2–3 months) [13,14], with relatively uniform appearance, histology and molecular markers [15,16].

To have an impact on overall survival of patients with cancer, better mouse models of metastatic disease are desperately needed and GEM that develop metastasis are very valuable for these studies [17]. Notably, the contribution of genetic polymorphism in metastatic susceptibility was demonstrated by differences in the frequency of metastasis in different MMTV-PyMT mouse strains [18]. Thus, GEM models permit investigation of important determinants of metastasis that are not possible to address using cultured cells or xenografts. Yet, the multifocal nature of the tumors arising in GEM limits their use because it is not possible to establish the source of metastatic disease and thus interpret therapeutic efficacy.

3. Adapting GEM for preclinical testing

An alternative modality for generating a large cohort of mice bearing synchronous genetically driven tumors is transplantation. A recent study showed that subcutaneous transplantation of mammary tissue from young MMTV-PyMT mice into syngeneic naïve recipients generates tumors but requires multiple passages *in vivo*, and few of these lines develop metastasis [19]. A similar approach has been used in allografting prostate cancer tumor fragments from 12T10 transgenic mice [20]. However, generating multiple small similar-sized fragments limits the number of secondary recipients and introduces variability due to regional heterogeneity within the tumor and the number of implanted tumor cells.

Cell suspensions have been used in studying mouse and human hematopoietic tumors and characterizing the stem cell compartment [9,21,22], but are less commonly used for transplantation of solid tumors. The Developmental Therapeutics Program at NCI has used cell suspensions for drug screening in human and murine