Pharmacology & Therapeutics 142 (2014) 351–361

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: B. Teicher

Fit-for purpose use of mouse models to improve predictivity of cancer therapeutics evaluation

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ARTICLE INFO

Available online 8 January 2014

Keywords:
Tumor models
Mouse
Cancer therapeutics
Predictivity
Preclinical
Drug evaluation

ABSTRACT

Preclinical animal models are useful tools to better understand tumor initiation and progression and to predict the activity of an anticancer agent in the clinic. Ideally, these models should recapitulate the biological characteristics of the tumor and of the related tumor microenvironment (e.g. vasculature, immune cells) in patients. Even if several examples of translational success have been reported it is a matter of fact that clinical trials in oncology often fail to meet their primary endpoints despite encouraging preclinical data. For this reason, there is an increasing need of improved and more predictive models.

This review aims to give an overview on existing mouse models for preclinical evaluation of cancer therapeutics and their applicability. Different types of mouse models commonly used for the evaluation of cancer therapeutics are described and considerations for a "fit-for purpose" application of these models for the evaluation of different cancer therapeutics dependent on their mode of action are outlined. Furthermore, considerations for study design and data interpretation to translatability of findings into the clinics are given.

Conclusion: Detailed knowledge of the molecular/biological properties of the respective model, diligent experimental setup, and awareness of its limitations are indispensable prerequisites for the successful translational use of animal models.

Contents

Abbreviations: SCID, severe combined immunodeficiency; NOD, non-obese diabetes; MHC, major histocompatibility complex; NK cell, natural killer cell; Th1 or 2, t helper cell type 1 or 2; AOM, azoxymethane; DSS, dextran sodium sulfate; MNNG, N-methyl-N-nitro-N-nitrosoguanidine; GEMM, genetically engineered mouse model; ADCC, antibody dependent cellular cytotoxicity; EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; PI3K, phosphoinositide 3-kinase; MDM2, mouse double minute 2 homolog; PK, pharmacokinetic; FAP, fibroblast associated protein; HGF, hepatocyte growth factor; ALL, acute lymphatic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; CLL, chronic lymphocytic leukemia; CTLA-4, cytotoxic T lymphocyte antigen-4; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand 1; RECIST, response evaluation criteria in solid tumors; LD, longest diameter; CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease; PFS, progression-free survival; DFS, disease-free survival; OS, overall survival; pCR, pathological complete response; TGI, tumor growth inhibition; NSCLC, non-small-cell lung carcinoma; SEM, standard error of the mean; Cy5, cyanin-5.

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0163-7258/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pharmthera.2014.01.001

1. Introduction

Cancer is a major health problem worldwide and one of the leading causes of death accounting for 7.6 million deaths (around 13% of all deaths) per year. Moreover, worldwide mortality rates from cancer are projected to continue rising, with an estimated 13.1 million deaths in 2030 (Ferlay et al., 2013). Therefore novel and superior approaches for early diagnosis and treatment of cancer are highly warranted and in the past decades large amounts of public and industry resources have been invested into identification of novel approaches to fight cancer.

Despite the huge effort, clinical success rate from first-in-man to registration for novel cancer therapeutics is at a discouraging rate of 5% (Kola & Landis, 2004). Therefore while significant progress in therapeutic options has been made for selected cancer types such as breast cancer and Non-Hodgkin's Lymphoma (NHL), efficacious treatment options remain poor for a large number of patients with other types of cancer such as for example pancreatic and lung cancer. Consequently, the 5-year relative survival rates have improved for female breast cancer patients from 63% in the early 1960s to 90% today, and for NHL from 47% in 1975 to 70% (ASCO, 2012). In contrast, 5-year survival rates remain low at 16% and 6% for lung and pancreatic cancer patients, respectively (ASCO, 2012).

As virtually all novel cancer therapeutics undergo extensive preclinical evaluation prior to entry into clinical trials the overwhelming clinical attrition rate of 95% indicates a strong discrepancy between preclinical efficacy and clinical response. This review has the aim to give an overview on existing mouse models for preclinical evaluation of cancer therapeutics and their applicability. It is clear that all mouse models have a "model" character with several intrinsic limitations. However, we believe that a "fit for purpose use" of preclinical cancer models, selecting models closely representing the tissue in focus and the drug target, combined with suitable study design and interpretation of results may be a way to improve predictivity of preclinical cancer therapeutics evaluation.

We first describe different types of mouse models commonly used for the evaluation of cancer therapeutics, followed by a section outlining the application of these models for the evaluation of different cancer therapeutics dependent on their mode of action. Considerations for study design and data interpretation to translatability of findings into the clinics are given in the final section.

2. Overview and characteristics of available preclinical models

2.1. Mouse strains commonly used for preclinical tumor models

The discovery of the nude mutation in 1966 on chromosome 11 of athymic mice lacking T-lymphocytes opened the door for the engraftment of human tissues, hematopoietic stem cells or peripheral blood mononuclear cells. The animals' deficient immune system composed mainly of B-cells lacking T-cell support enabled the study of human biological processes in vivo. Subsequently, various genetic modifications were described that led to a higher grade of immunodeficiency, like in SCID (severe combined immunodeficiency) or NOD (non-obese diabetes)/SCID mice. Mice carrying the recessive SCID mutation on chromosome 16 are virtually devoid of T- and B-lymphocyte function despite having a thymus, lymph nodes, splenic follicles, and normal numbers of NK-cells. NOD/SCID mice, however, have an additional mutation causing Beta-2-Microglobulin deficiency. They lack mature lymphocytes, serum immunoglobulin, MHC class 1 expression, and NK-cell activity.

Beige mice are deficient in cytotoxic T-cells, NK-cells, and macrophages. Therefore, the combined immunodeficient SCID/beige mouse variant probably has the weakest immune competence that could be turned against engrafted cells or tissue. Nevertheless, for a high success rate in the creation of humanized mice, additional targeted mutations at the interleukin-2 receptor of NOD/SCID mice were required to allow efficient establishment of human immune cells.

Detailed knowledge of the respective immunodeficient mouse strain regarding the presence and functionality of immune cells is mandatory to select the most appropriate variant for engraftment studies or experiments where an immune response is required. The selection of the most suitable mouse strain is also important for the use of syngeneic tumor models since immunocompetent strains can differ in their predominant immune response type, C57BL/6 and BALB/c mice being prototypical Th1- and Th2-type mouse strains (Watanabe et al., 2004).

2.2. Xenograft models

Xenograft models, usually established by implanting human tumor cell lines subcutaneously into the flank of immunodeficient mice or rats, have long been the standard model for preclinical evaluation of novel cancer therapeutics. In comparison to other in vivo models, xenograft models are easy to handle, produce results relatively quickly and offer high throughput, low variability and good reproducibility.

A large set of well characterized xenograft models, in terms of mutations, signaling pathway activity as well as drug sensitivity/resistance, are available. As the cell lines used for the generation of xenograft models are derived from human tumors the effect of novel therapeutics on a human tumor can be relatively easily studied in an in vivo setting.

However, it is arguable how closely a xenograft model represents a patient tumor situation: Most of the cell lines that are routinely used as xenografts have undergone a high number of in vitro passages and thus differ strongly from the original tumor due to long-term in vitro selection. The cell line origin also implicates a very homogeneous tumor cell population that does not reflect the heterogeneity of human tumors. Furthermore, the fast, subcutaneous growth of xenografts often leads to only limited build-up of tumor stroma and therefore tumor–stroma interactions are difficult to study in standard xenograft models. The subcutaneous location also does not reflect the organ environment of the tumor that may be necessary e.g. for the provision of tissue-specific growth factors. Last but not least, the use of immunodeficient host animals makes it difficult if not impossible to study certain drugs whose mode of action depends on immune effector functions.

Nevertheless, xenograft models are useful for studying targeted drugs or chemotherapeutics that act by direct interaction with the tumor cell. Especially for mechanistic studies where a mode of action hypothesis is investigated or for combination studies that need large numbers of study groups and precise readouts xenograft models are a useful tool.

2.3. Patient-derived models

An alternative to classical xenograft models are patient-derived models. Instead of the transplantation of an established cell line, patient-derived tumor materials (cell suspension or tumor fragments) are transplanted onto immunodeficient animals and then passaged directly from mouse to mouse in vivo. For recent reviews on patient-derived models see Lum et al. (2012) and Tentler et al. (2012).

An advantage of patient-derived models is their direct origin from human tumors without any previous in vitro culture and clonal selection. Thereby the genetic background and heterogeneity of human tumor tissue is preserved in a better way and may retain several characteristics more closely reflecting the patient situation. Another plus of patient-derived models compared to classical cell line based xenograft models is the higher amount of stroma that is initially present within the tumor and may support its growth and tissue homeostasis. During the first passages the stroma is of human origin but is replaced by mouse stroma after several passages (Reyal et al., 2012).

Compared to classical xenografts, patient-derived models are labor intensive (due to in vivo passaging of tumors) and also come with an increased variability and longer timelines. They are less well characterized