MINI REVIEW

Mouse Models for Cancer Immunotherapy Research

Brian Olson, Yadi Li, Yu Lin, Edison T. Liu, and Akash Patnaik

ABSTRACT

Immunotherapy has revolutionized cancer therapy, largely attributed to the success of immune-checkpoint blockade. However, there are subsets of patients across multiple cancers who have not shown robust responses to these agents. A major impediment to progress in the field is the availability of faithful mouse models that recapitulate the complexity of human malignancy and immune contexture within the tumor microenvironment. These models are urgently needed across all malignancies to interrogate and predict antitumor immune responses and therapeutic efficacy in clinical trials. Herein, we seek to review pros and cons of different cancer mouse models, and how they can be used as platforms to predict efficacy and resistance to cancer immunotherapies.

Significance: Although immunotherapy has shown substantial benefit in the treatment of a variety of malignancies, a key hurdle toward the advancement of these therapies is the availability of immunocompetent preclinical mouse models that recapitulate human disease. Here, we review the evolution of preclinical mouse models and their utility as coclinical platforms for mechanistic interrogation of cancer immunotherapies.

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Recent years have seen dramatic advances in our understanding of the interactions between tumor development and the immune system. In parallel with these efforts, there has been a revolution in the development of therapeutics aimed at harnessing the immune system to mount effective antitumor responses. This is most clearly exemplified by the success of immune-checkpoint blockade (ICB) across a variety of malignancies (1). In addition, vaccine, engineered T-cell transfer, and immunomodulatory strategies hold promise for the future of cancer therapy (2). With the increased focus on the development of effective immunotherapies, a critical challenge is the development of immunocompetent mouse models that replicate human disease and can be utilized to coclinically test novel cancer immunotherapies in parallel with early-phase human investigation.

A crucial aspect of any preclinical model system is that it mimics human cancer development—this includes models that faithfully reproduce the genomic heterogeneity of human cancer, as well as develop a milieu that incorporates the multitude of immune and stromal cell populations that make up the complex tumor microenvironment. However, the development of preclinical tumor models to study immunotherapeutics presents a unique set of considerations. First, the industry gold standard for the development of standard cytotoxic cancer therapies is to utilize xenograft models of human cancer cell lines engrafted into immunocompromised mice to evaluate pharmacology, efficacy, and safety profiles of these agents (3). However, the development of immunotherapy requires a model system with a functionally intact immune system. Second, the inherent heterogeneity and adaptability of the immune system likely explains the relative success of immunotherapy, in that it is able to constantly adapt and evolve along with the tumor. However, finding preclinical models that can recapitulate this adaptability in the face of tumor heterogeneity remains a major impediment in the development of cancer immunotherapies. In this review, we discuss the current landscape of preclinical models available for coclinical immunotherapeutic evaluation (Fig. 1) and the pros and cons associated with each model in this context (Table 1).

MURINE TUMOR MODELS

Syngeneic Tumor Cell Lines

Syngeneic tumor models are the oldest and most heavily utilized preclinical models to evaluate anticancer therapeutics. Using inbred strains such as C3H/HeJ, BALB/c, and FVB mice, it is possible to isolate spontaneous, carcinogen-induced, or transgenic tumor cell lines that can be expanded...
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Immune-deficient murine hosts and further propagation collecting tumor tissue from patients and then injecting into immuno-autochthonous tumor cell growth. Patient-derived xenografts involve C, oncogenes or tissue-specific deletion of tumor suppressors, which drives engineered mouse models incorporating tissue-specific expression of B, engineered mouse models incorporating tissue-specific expression of oncogenes or tissue-specific deletion of tumor suppressors, which drives autochthonous tumor cell growth. C, Patient-derived xenograft models involve collecting tumor tissue from patients and then injecting into immuno-deficient murine hosts and further propagation in vivo. Tumor cells can be injected alone or can be injected along with immune reconstitution using autologous immune cells (from peripheral blood, bone marrow, or selected progenitor populations).

Figure 1. Preclinical murine models for evaluation of immune-oncology agents. A, Syngeneic tumor models utilize murine tumor cell lines that are grown and expanded in vitro and then injected into immunocompetent hosts (commonly either subcutaneously or orthotopically). B, Genetically engineered mouse models incorporate tissue-specific expression of oncogenes or tissue-specific deletion of tumor suppressors, which drives autochthonous tumor cell growth. C, Patient-derived xenografts involve collecting tumor tissue from patients and then injecting into immuno-deficient murine hosts and further propagation in vivo. Tumor cells can be injected alone or can be injected along with immune reconstitution using autologous immune cells (from peripheral blood, bone marrow, or selected progenitor populations).

models were used in the groundbreaking work by Schreiber and others to identify and characterize the process of immunoeediting (4), using agents such as methylcholanthrene (MCA). Carcinogen-induced models can be interrogated for their impact on tumor development and anticancer immune responses, as well as the evaluation of immunotherapies (5). In contrast to genetically defined cancer models, carcinogen-induced models provide a higher level of genomic instability, resulting in the development of a more “physiologically relevant” tumor microenvironment. However, this complexity also comes with challenges, including issues regarding tumor penetrance and latency, as well as a lack of shared tumor antigens.

Many of these carcinogen-derived tumors were used to generate cancer cell lines, which are commonly utilized to develop syngeneic murine tumor models. One of the central benefits of syngeneic tumor cell lines is their ease of use. Using tumor cell lines that can be rapidly and reproducibly expanded in large numbers prior to implantation into hosts, these syngeneic models can be used for studies that require large group numbers that are difficult to obtain using genetically engineered models or patient-derived xenografts (PDX). Another logistical advantage of using syngeneic tumor models is that they can be genetically manipulated to evaluate specific tumor cell—intrinsic sensitivity or resistance biomarkers of response to immunotherapy. For example, studies evaluating antigen-specific immunization approaches can utilize tumor cells that are engineered to express the target antigen and can be used for in vitro and in vivo analysis of antitumor effector responses. This can be challenging when targeting antigens whose expression is normally restricted to tissues that lack effective preclinical models. Additionally, it is possible to evaluate the relative contribution of various factors that may affect immunotherapeutic efficacy. This is particularly relevant to checkpoint blockade, where checkpoint ligands can be removed or altered to evaluate their contribution to the antitumor response.

Although their ease of use and experimental reproducibility has led syngeneic tumor models to become the most commonly used preclinical model for the evaluation of immunotherapies, these pragmatic benefits also highlight one of the detrimental aspects of this system: namely, that these models lack the genomic and microenvironmental heterogeneity that defines cancer. Tumor heterogeneity results in not just interpatient heterogeneity that makes every patient’s cancer unique, but also intrapatient heterogeneity (6). This is one of the major challenges for the development of effective cancer therapies, and thus an ideal preclinical system to interrogate immunotherapeutics would also effectively model this heterogeneity. However, syngeneic tumor models are largely deficient on both accounts—the cell lines lack mutational patterns that recapitulate human intrapatient genomic heterogeneity and are implanted into a limited number of inbred strains of mice that lack the interpatient heterogeneity. The lack of mutational heterogeneity within the syngeneic xenograft tumors is due in part to the lack of cancer stem cells and other progenitor populations that are present in the tumor microenvironment, which can provide a constant source of tumor mutational evolution (7). In addition, mutational
the implanted tumors develop as a process (4). The immune response during the immunoediting process leads to functional plasticity that helps tumors constantly adapt and evolve. Heterogeneity does not impart the tumor cell–intrinsic characteristics that contribute to genomic instability during the outgrowth of these tumors. Implanted syngeneic tumor cells can certainly behave differently compared to humans (8). Moreover, syngeneic tumor models often have undergone significant selection through adaptation to stringent in vitro or in vivo conditions, which can limit clonal diversity. Although implanted syngeneic tumor cells can certainly behave differently during the outgrowth of these tumors, they often lack the intrinsic characteristics that contribute to genetically heterogeneous tumors. To overcome these challenges, it is possible to inject multiple lineages to result in tumors that are comprised of multiple populations (9); however, this artificial heterogeneity does not impart the tumor cell–intrinsic functional plasticity that helps tumors constantly adapt and evolve to the immune response during the immunoediting process (4).

Another challenge associated with syngeneic models is that the implanted tumors develop as de novo poorly differentiated malignancies and do not undergo the natural steps of tumor evolution that can be observed with genetically engineered models, which include premalignant transformation, tumor development, and progression (10). This results in abbreviated tumor growth in most syngeneic tumor models, resulting in tumor outgrowth over the span of weeks. In contrast, there is usually a latency period prior to development and amplification of antitumor immune responses elicited by immunotherapy (as opposed to cytotoxic agents), so clinical benefit is often observed as increases in overall survival compared with objective clinical responses (11). Therefore, the rapid kinetics for tumor growth in syngeneic models often provides an inadequate time window to evaluate immunotherapy efficacy. In addition, it does not permit the evaluation of immunotherapeutics in earlier stages of disease, which have been suggested as a potentially optimal time point to initiate immunotherapeutic interventions in certain cancers to maximize clinical benefit (12).

A pivotal consideration for preclinical models evaluating immunotherapies is the role of the tumor microenvironment in the generation of antitumor responses. The various populations that come together to form a malignant lesion—not just the tumor cells, but also the surrounding stroma, vasculature, and immune populations themselves—are all critical components in determining whether immune-based therapies will be able to successfully infiltrate and eliminate tumor cells. However, most syngeneic tumor models utilize subcutaneous implantation, which (although convenient for measuring tumor shrinkage) lacks the complex architecture that is associated with de novo tumor growth. Although orthotopic injections have attempted to circumvent this limitation, this can be technically demanding depending on the tumor site and also relies on injecting cancer cell lines that are already poorly differentiated into a healthy organ. As a result, although the tumor may grow at the organ site, the lack of autochthonous disease does not allow for the natural development of the complex tumor microenvironment. Additionally, the process of injecting syngeneic tumor cells itself can promote inflammatory immune responses, which can vary depending on the site of injection, further confounding the interpretation of immunotherapeutic efficacy (13). As a result, the identification of reliable autochthonous genetically engineered mouse models (GEMM) for tumor development and therapeutic evaluation has been a focus of intense research over the past two decades.

### Table 1. Preclinical models for cancer immunotherapy

<table>
<thead>
<tr>
<th>Model</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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<tbody>
<tr>
<td>Syngeneic tumor cells</td>
<td>• Reproducible and rapid growth</td>
<td>• Lack of native tumor microenvironment</td>
</tr>
<tr>
<td></td>
<td>• Easily manipulated</td>
<td>• Variability of phenotype depending on the site of engraftment</td>
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<tr>
<td></td>
<td>• No host breeding requirements</td>
<td>• Relatively few transplantable cell lines</td>
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<tr>
<td></td>
<td></td>
<td>• Lack of heterogeneity</td>
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<tr>
<td></td>
<td></td>
<td>• Relatively few host strains</td>
</tr>
<tr>
<td>Genetically engineered</td>
<td>• Autochthonous growth provides native microenvironment</td>
<td>• Breeding challenges</td>
</tr>
<tr>
<td></td>
<td>• Tumor development driven by relevant genetic alterations</td>
<td>• Variability in penetrance and latency</td>
</tr>
<tr>
<td></td>
<td>• Can incorporate genomic instability</td>
<td>• Low immunogenicity due to defined perturbations</td>
</tr>
<tr>
<td>Patient-derived xenograft</td>
<td>• Reproduces complexity of human disease (genomic heterogeneity, cell types)</td>
<td>• Conducted in immune-deficient host (relies on human immune cells transferred in xenograft)</td>
</tr>
<tr>
<td></td>
<td>• Does not require immune reconstitution</td>
<td>• Murine stroma</td>
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<tr>
<td></td>
<td></td>
<td>• Low implantation rate</td>
</tr>
<tr>
<td>Humanized patient-derived xenograft</td>
<td>• Reproduces complexity of human disease and immune system</td>
<td>• Requires autologous immune reconstitution</td>
</tr>
<tr>
<td></td>
<td>• Can utilize engineered hosts to increase immune reconstitution</td>
<td>• Low rates and duration of immune reconstitution</td>
</tr>
</tbody>
</table>

Heterogeneity requires clonal evolution of differentiated cancer cells, which can be challenging with many syngeneic murine models given their overall lower levels of genomic instability compared with humans (8). Moreover, syngeneic tumor models often have undergone significant selection through adaptation to stringent in vitro or in vivo conditions, the effect of which is to limit clonal diversity. Although implanted syngeneic tumor cells can certainly behave differently during the outgrowth of these tumors, they often lack the intrinsic characteristics that contribute to genetically heterogeneous tumors. To overcome these challenges, it is possible to inject multiple lineages to result in tumors that are comprised of multiple populations (9); however, this artificial heterogeneity does not impart the tumor cell–intrinsic functional plasticity that helps tumors constantly adapt and evolve to the immune response during the immunoediting process (4).
Genetically Engineered Mouse Models

Over the last two decades, there has been a remarkable growth in our understanding of the genetic basis for cancer, followed by the development of genetic engineering techniques. These advances have led to the invention of mouse models with incorporation of specific genomic alterations to provide autochthonous tumor development in a tissue-specific manner. These models predominantly utilize either tissue-specific promoters to drive either expression of an oncogene (either viral oncogenes such as the SV40 large T antigen, ref. 10; or oncogenes relevant to tumor formation, such as Kras and MYC such as the SV40 large T antigen, ref. 10; or BRAF relevant to tumor formation, such as the SV40 large T antigen, ref. 14, or BRAFV600E in melanoma, ref. 15) or tissue-specific expression of recombinase enzymes to drive deletion of tumor suppressors (such as PTEN and TP53 in prostate cancer, ref. 16; or APC in colon cancer, ref. 17). Using these genomic alterations, it is possible to not only drive autochthonous invasive cancer development but also develop precancerous lesions such as prostatic intraepithelial neoplasia in prostate cancer models (18) or pancreatic intraepithelial neoplasia (PanIN) in pancreatic cancer models (19). This extended period of tumor development and progression allows for longer windows for immunotherapeutic intervention, which are often needed to generate an effective antitumor immune response and to model immune-related adverse events (irAE; ref. 20).

As genetically engineered models drive neoplastic transformation of normal cells at the relevant organ site to drive tumor growth, this gradual development and progression of cancer allows for the autochthonous development of a complex tumor microenvironment. This is a critical advantage of GEMMs, relative to syngeneic tumor models, that makes them particularly relevant for evaluating immunotherapeutic modalities. The de novo tumor microenvironments that develop in the context of GEMMs contain native immunosuppressive stroma and vasculature, both critical variables that determine the magnitude and composition of immune cell infiltration. Additionally, it is possible to utilize models where the alteration driving tumor growth is relevant to the tumor immune microenvironment and ultimately can affect the efficacy of immunotherapy. For example, loss of PTEN in melanoma has been shown to associate with an immunosuppressive tumor microenvironment (21), and, using models in which tumor development is driven by PTEN loss, it is possible to evaluate therapeutic modalities that make these tumors more susceptible to immunotherapeutic intervention (21).

In contrast to human disease, which most often arises from the gradual accumulation of mutations in a small fraction of cells within the organ of origin that ultimately lead to transformation, GEMMs that utilize tissue-specific promoters drive oncogenesis in all cells of that lineage. In addition, by overexpression or deletion of a select number of genes, the tumor mutational burden in genetically engineered models may not replicate that seen in the corresponding human disease (22, 23). This is critical when evaluating immunotherapies, as increased mutational burden (and subsequent neoepitope generation) is an important consideration when evaluating the efficacy of ICB (24). However, by targeting genes associated with mismatch repair and genomic stability (such as MLH1, ref. 25; BRCA1/2, ref. 26; APC, ref. 17; and MiTERT, ref. 27), it is possible to not only promote tumorigenesis but also drive the accumulation of additional mutations. This increased mutational rate promotes generation of neoantigens that can be recognized by CD8+ T cells (28) and facilitates immunediting (4, 29). In addition, the increased genomic instability can facilitate coevolution of the antitumor immune response along with tumor escape mechanisms, which may ultimately lead to immunotherapy resistance.

Although GEMMs have several advantages in evaluating immunotherapeutics, these models suffer from some of the same logistical challenges that hamper their use in the evaluation of cytotoxic therapies. First, a central challenge when using GEMMs is with regard to penetration of the tumor phenotype and latency of neoplastic development, which can vary drastically depending on the mechanisms used to induce tumor development. These limitations can be partly overcome via development of GEMMs that target multiple oncogenes or tumor suppressors that can increase penetrance and decrease latency (30). Second, it is necessary to utilize noninvasive imaging modalities, such as ultrasound or magnetic resonance imaging, to monitor tumor development, standardize treatment scheduling, and monitor the kinetics of antitumor immune responses. Third, as with syngeneic models, it is important to consider whether the murine immune target is cross-reactive with the corresponding human target. This includes antigens and surface markers that are present on human immune cells or tumors that are not present on murine cells. Cross-reactivity is particularly relevant with regard to the development of immunotherapeutic vaccines, which recognize antigens within the context of human MHC class I in patients (antigens that are not presented in the context of murine MHC class I). To evaluate these peptide-specific responses, GEMMs that incorporate human MHC class I and MHC class II have been developed that can be used to evaluate peptide-specific T-cell responses that are relevant to human antitumor immune responses (31). Additionally, expression models have been developed that can incorporate expression of target antigens into GEMMs (32), allowing for the rapid development of models that can be used to evaluate antigen-specific immunotherapies. The antigen processing differences between these mouse and human antigen-presenting cells remain, which can affect cross-reactivity with human epitopes, illustrating the underlying challenges that hamper all preclinical models that utilize murine versus human cancer cells. Therefore, an optimal model to evaluate immunotherapies would focus on responses against human tumors in immunocompetent models.

More recently, a large series of congenic C57BL/6J mouse melanoma cell lines were derived from a panel of murine melanoma GEMMs induced by combinations of genetic drivers similar to those found in the human disease (BrafV600E, and deficiencies in Pten, Trp53, Ink4a/Arf, etc.; ref. 33). Called the Yale University Mouse Melanoma (YUMM) syngeneic cell lines, several have been further mutagenized to generate greater somatic mutational loads (34). These panels of genetically defined syngeneic cell lines possess the advantage...
of being derived from the same tissue type, and incorporate
the genetic precision of GEMMs with the ease of use
of transplantable cell lines. With a sufficient number of
these lines, genomic comparisons of the responders against the
nonresponders may uncover genetic mechanisms of resist-
ance to immuno-oncology therapeutics. This would require
a concerted effort to collect and characterize such panels, as
was done for human tumors.

HUMANIZED TUMOR MODELS

PDX Models

Human xenograft models, using human cell lines injected
into immunocompromised hosts such as athymic nude or
severe combined immunodeficiency (SCID) animals, are one
of the oldest models used to evaluate cytotoxic therapies
against cancer. These models have particular relevance for the
development of chimeric antigen receptor (CAR) therapies,
which can utilize either human cell lines or patient-derived
samples to generate xenografts for antitumor efficacy evalua-
tion (35). One of the critical factors that determine the utility
of human xenograft models for other immunotherapeutic
applications is the degree of immunodeficiency of the murine
host. The classic athymic nude mice lack normal thymic devel-
oped and therefore are deficient in T-cell function. However,
because functional innate immune populations such as neu-
rophils and dendritic cells, as well as B cells and natural killer
(NK) cells, remain, many aspects of the immune response,
though perturbed, are present in athymic nude mice. There-
fore, engraftment of human hematopoietic elements and other
primary human cells is quite limited in this model. SCID mice
are deficient in a DNA-dependent protein kinase requirement
for T- and B-cell development, and Rag-deficient mice have
defective Rag1 and Rag2 genes that are also deficient in T- and
B-cell function. The knockout of the IL2rγ chain induces
concurrent deficiencies in IL2, IL4, IL7, IL9, IL15, and IL21
receptor functions and generates mice that lack NK cells. By
combining genetic mutations, the immunodeficiency in the
resultant mice worsens, and with it comes an improvement in
the engraftment of donor human immune cells. Thus, the best
mice for the engraftment of human hematopoietic stem cells
are derived from SCID, Rag1null, or Rag2null mice coupled with
a targeted mutation in the IL2rγ gene (36). The NOD/SCID
IL2rγ chain knockout or “NSG” mouse (NOD.Cg-Prkdcnull
Il2rγtm1Wjl/SzJ), a preclinical model with engineered combined
immunodeficiency, has been among the most frequently used
host for chimeric human–mouse immune reconstitution as
well as other tissue chimeras (37).

Whereas athymic nude mice were sufficient for engraft-
ment of human cancer cell lines, the NSG mice and their
equivalents are necessary for engraftment of primary human
tumors (38). Using these primary tumor samples, it has been
possible to create PDXs that accurately model the complexity
involved in natural tumor development, including genomic heterogeneity, tumor architecture, and microenvironment
factors that are critical to develop an effective in vivo preclini-
cal tumor model for therapeutic evaluation (although these
tumors are usually injected subcutaneously as opposed to
orthotopically; ref. 39). Given the impact of immunotherapy
across multiple human malignancies, and the limitations of
both syngeneic cell line–based models and GEMMs in
developing tumors that recapitulate the genotypic and phe-
notypic heterogeneity of human cancers, there has been a
growing interest in developing methods of human immune
reconstitution within PDX models in order to construct an
experimental humanized model for evaluation of immuno-
therapy. This experimental system theoretically requires a
match between the reconstructed human hematopoietic sys-
tem and the tumor from the same patient. Although elegant
in principle, there are impediments to the efficient generation
of humanized PDXs. First, a PDX model requires high take
rates for successful propagation of tumors across multiple
mice within a reasonable timeframe. Second, whereas the
PDX models can be generated from a single tumor that is
propagated across multiple mice, the hematopoietic system
cannot, so repeated invasive sampling would be necessary to
develop individual humanized PDX mice. Moreover, patient
survival times and resultant access to hematopoietic blood
cells could be limited, thus lowering the pragmatic feasibility
of this approach.

Recently, it has been shown that NOD/SCID IL2rγ (null;
NSG) mice reconstituted with umbilical cord human CD34+cells
can induce regression of an engrafted human PDX
tumor in response to anti–PD-1 therapeutics (40). The
hematopoietic stem cells were allogeneic to the PDX tumor,
and excellent antitumor responses were observed, taking
advantage of the graft-versus-tumor effect. These responses
were dependent on human hematopoietic engraftment, the
presence of human CD8+ T cells, and the administration
of an anti–PD-1 agent, and were observed regardless of the
degree of HLA matching between the hematopoietic stem
cells and the tumor. Importantly, some donor CD34+ cells
exhibited an excellent response, whereas others were non-
responsive, revealing significant variation in the antitumor
effects of T cells from different donors on the same PDX
tumor. This study suggests that mice harboring human
hematopoietic stem cells and a PDX tumor may have some
use in designing the mechanisms of differential T-cell anti-
tumor activation in human populations (40). However, this
also illustrates a challenge with utilizing allogeneic immune
cells to reconstitute PDX-bearing animals; as these allogeneic
immune cells lack the normal immune surveillance process,
tumor rejection may represent an allogeneic response rather
than recognition of tumor-associated antigens that would
naturally occur outside of an allogeneic system.

In an ideal humanized PDX model system, the hemat-
opoietic stem cells would be autologous to the engrafted
tumor. Reconstitution of a human immune system in an
immunocompromised mouse can also be accomplished by
using peripheral blood mononuclear cells (PBMC) from
adults. Although the ease of collection of PBMCs from
autologous patients allows for their use in autologous
tumor-bearing PDX, challenges arise with regard to the
length of time these cells remain viable after engraftment,
which limits their utility in the evaluation of immuno-
therapies. Moreover, PBMCs generate a robust graft-versus-
host (i.e., human vs. mouse) reaction, which also limits
the window of time for observation (41). Thus, PBMCs,
even from autologous human sources, have a significantly
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limited utility in examining in vivo immune-checkpoint inhibitor action. In contrast, it is possible to generate long-term engraftment using CD34+ cells or other hematopoietic progenitor-rich populations (42). These transferred progenitors can be further modified to incorporate chemokines and other agents that promote long-term engraftment into immunocompromised hosts, as well as other immunomodulating factors that promote the generation of stromal cells and the formation of the tumor microenvironment (42). In addition, the use of autologous tumor-infiltrating lymphocytes to reconstitute PDx-bearing animals has been shown to recapitulate antitumor responses seen in patients (43), although this technology will be limited to malignancies in which sufficient amounts of tumor-infiltrating lymphocytes can be obtained and expanded.

An alternative approach to promote expansion of human immune populations is to make changes to the host, instead of altering the transferred cells. For example, an NSG-SGM3 mouse model was generated by transgenically expressing the human stem cell factor, granulocyte macrophage colony-stimulating factor, and IL3. This model promotes long-term engraftment with expansion of T-cell (CD4+, CD8+, and Tregs), B-cell, and myeloid populations, thus reconstituting an immune system representative of natural complexity (44). Another genetically modified host for immune reconstitution is the MSTRG or MISTRG mouse, which is generated on a Rag2- and Il2γt-deficient background and has been engineered to express macrophage colony-stimulating factor, thrombopoietin, granulocyte/macrophage colony-stimulating factor, either with or without IL3, thus enabling long-term engraftment in both secondary immune tissues and nonhematopoietic organs (45). In addition, NSG mice have been modified to incorporate expression of HLA-A2, an HMC class I haplotype particularly relevant to the development of immunotherapies and the evaluation of antigen-specific T-cell responses. How these modifications will affect antitumor response in reconstituted mice is currently unclear but brings the experimental system closer to the fully humanized state.

FUTURE PERSPECTIVES

Given the recent FDA approvals of cancer immunotherapy across multiple malignancies, the continued development of effective preclinical models to reliably elucidate antitumor mechanism and predict antitumor efficacy in human immunotherapy clinical trials remains an area of critical unmet need. For example, the promising preclinical results observed evaluating IDO inhibitors in combination with ICB in preclinical studies were not recapitulated in phase III melanoma clinical trials. Although current practices largely rely on syngeneic tumor models, the advent of increasingly complex GEMMs that more accurately reflect the autochthonous tumor microenvironment is valuable for predictive evaluation of tumor immunotherapies in the preclinical setting. Furthermore, the continued development of humanized PDx models has the potential of ushering in an era of personalized immunotherapy, i.e., “coclinical” approach, where a patient’s tumor is implanted into humanized immune-reconstituted preclinical models to guide therapeutic decision-making. There are several limitations across syngeneic, GEM, and humanized PDx models, thus posing a challenge for any single model type to recapitulate the heterogeneous antitumor immune responses observed in immuno-oncology clinical trials. However, the continued development of more sophisticated preclinical models will allow us to individualize their selection to most accurately represent the human malignancy being tested and assess responsiveness to immunotherapy. For example, the colorectal MC38 cell line harbors a microsatellite-unstable phenotype (MSI), resulting in a T cell-inflamed tumor microenvironment and robust responses to ICB. On the other hand, the colorectal CT26 cell line harbors a microsatellite-stable (MSS) model, resulting in a non-T cell–inflamed tumor microenvironment and poor responses to ICB. The immunophenotypic characteristics and responsiveness to ICB for MC38 and CT26 lines mirror what is observed in the clinic with patients with MSI and MSS colorectal cancer, respectively (46).

Although the generation of humanized PDx models has focused on reconstituting the patient’s immune system, a critical advance will be to incorporate microbiome analysis into the paradigm of preclinical models. Given that the microbiome within preclinical models can be influenced by several variables, which include the vendor from which animals are procured and housing conditions while on study, it is critical to incorporate these variables when assessing therapeutic responses to immunotherapy. In addition, we anticipate that therapeutic approaches designed to alter the microbiome will become increasingly incorporated into the immunotherapeutic armamentarium (47).

Another critical application of preclinical tumor models that requires further investigation is the modeling of irAEs, as preclinical models do not recapitulate the nature, kinetics, and severity of toxicity observed in patients treated with ICB. As immuno-oncology agents show an unpredictable pattern of irAEs in patients, the discovery of early biomarkers of irAEs and strategies to reverse fatal toxicities, such as myocarditis, are a critical step for the safe development of immuno-oncology combination therapies in the clinic (5). This includes utilizing models that have slower kinetics of tumor regression (allowing for a sufficient timeframe to develop irAEs), incorporating broader measures of toxicity, as well as evaluating these therapies in tumor models more susceptible to autoimmune (such as Treg-depleted model systems; ref. 48). Because irAEs can have diverse manifestations in different tumor histologies, the inclusion of models that accurately reflect irAEs observed in the clinic is of paramount importance (49).

Disclosure of Potential Conflicts of Interest

E.T. Liu is President and CEO of The Jackson Laboratory. No potential conflicts of interest were disclosed by the other authors.

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