Biomere

COMMUNITY BLOG

MOUSE MODELS OF CANCER: WHICH ONE IS RIGHT FOR YOU?

Animal models have been the cornerstone of cancer drug development for decades and different types of tumor mouse models have been used extensively to study cancer biology and evaluate single and combination therapies. However, mouse models of cancer have also been widely acknowledged to have limited translational value and in many cases, do not accurately recapitulate tumor biology. This is especially true in the space of immuno-oncology where there are fundamental differences between the mouse and human immune systems. It is important to note that both simple and complex mouse models have a role in oncology drug development and the selection of the model is dependent on the scientific question that is being answered. For example, mice bearing subcutaneous tumors are useful for screening multiple drug assets for efficacy using simple endpoints such as tumor killing[1]. Once promising assets are identified, more complex models are needed to understand the drug mechanism of action and off target effects.

There are several types of more complex mouse models that can be broadly segmented as transplanted models, carcinogen induced models and genetically modified models. In the past several years, there has been an increased focus on transplanting patient tumors into mouse models. Patient derived Xenografts or PDX models have become the mainstay of oncology drug development primarily due to the availability of patient tumors via biopsy and surgical excisions. The patient tumors can be implanted into animals that have compromised immune systems so that the mouse model does not reject the human tumor – while this model is useful to study tumor growth and development in an *in vivo* setting, it is not useful to evaluate therapies that target immune cells such as checkpoint inhibitors. Several research model providers have developed humanized mice where components of the human immune system are introduced into immune-compromised mice such as the NSG or NCG models. Human PBMCs (peripheral blood mononuclear cells) isolated from human donors can be injected into the mice to mimic the human *in vivo* immune response to a xenografted tumor. One such model was reported where colorectal cancer xenografts were implanted into NSG mice that had been injected with human PBMCs[2] and the effect of a combination of nivolumab (anti-PD1 therapy) and regorafenib (a multi-kinase inhibitor) was evaluated[2]. Interestingly, the model was most predictive in an autologous setting where the tumor tissues and PBMCs were from the same patient as the allogeneic model showed nonspecific graft-vs-host issues[2]. These results suggest that humanized models have a limited role in evaluating response to anticancer therapies and there is an unmet need for robust allogeneic humanized mouse models. Another type of transplant-based mouse model are syngeneic, where the mice with an intact immune system are injected with mouse tumor cells derived from mice with the same genetic background. Essentially, syngeneic models are mouse focused where a mouse tumor is evaluated in the context of a mouse immune system. While this model can be a useful proxy for the human state in some situations. Syngeneic models are reliable and cost-effective and can be used for short-lived efficacy studies. However, there are limited number of syngeneic cell lines and models and in many cases, limited translation to human disease.

Genetically modified mouse models (GEMMs) have been developed for decades and the first reported GEMM was in the 1980s[3]. The development of GEMMs has expanded rapidly as more advanced gene editing methods have been developed such as Cre-loxP, CRISPR-Cas9, RNA interference etc[3]. As gene editing methods have become more precise with less off-target effects, GEMMs have become more advanced and recapitulate several hallmarks of the disease state. However, developing GEMMs is an expensive and time-consuming exercise and in many cases, requires detailed knowledge of disease drivers. The genetic engineering required to build a relevant GEMM can be complicated with no guarantee of success. However, once a GEMM is successfully developed, it can be used to study disease development and progression, identify biomarkers for diagnostic use and prognostic monitoring and can be used to evaluate anticancer therapies. SEMMs or somatically engineered mouse models are another type of engineered model where somatic cells in the organ of interest are genetically engineered to express oncogenes or tumor suppressors[4].

While there are several types of mouse models of cancer available, selecting the best model is not easy and requires a deep understanding of disease biology[4]. Multiple types of models may be used in a specific anticancer therapy development program that is dependent on the stage of drug development and the scientific questions that are being asked.

References:

1 https://www.nature.com/articles/s41416-019-0495-5
2 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9532947
3 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5286388
4 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8288236