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EDITORIAL

The ongoing trends of patient-derived xenograft models in oncology

1 | MAIN TEXT

Patient-derived xenograft (PDX) models have garnered increasing attention since the last decade. These models are typically characterized by the implantation of fresh patient-derived tumor tissues into immunodeficient mice. PDX models are well recognized in academic laboratories, pharmaceutical institutions, and specialized commercial organizations as having the ability to recapitulate genomics, transcriptomics, proteomics, and metabolomics of the parental tumor tissue [1,2]. Recently, these models have been successfully used in preclinical studies to identify potential biomarkers for drug response and resistance, and to measure tumor evolution in response to treatment [3,4]. Favorable outcomes demonstrated using PDX models could be used as ideal models for preclinical research and clinical translation studies.

At present, the concept of co-clinical trial, the simultaneous use of the so-called Avatar models, has attracted growing attention and has been expanded to include PDX models. These Avatar models are generated from patients enrolled in clinical trials and are simultaneously treated with the same anticancer therapies as the patients [5]. Several retrospective studies have shown that responses of PDX models toward certain agents were strongly correlated to the clinical response seen in the patients [6]. Moreover, Avatar models have been involved in 15 clinical trials covering different tumor settings, including prostate cancer, breast cancer, lung cancer, colorectal cancer, sarcoma, head and neck carcinoma, ovarian cancer, and pancreatic cancer (https://ClinicalTrials.gov). Some prospective studies were also performed using PDX models to guide clinical treatment decisions in a small number of patients and demonstrated prolonged survival [7,8]. Stebbing's et al. [8] showed that 20.1% (6/29) of their investigated patients with advanced sarcoma obtained direct clinical benefits from PDX-guided therapy. Bousquet et al. [9] suggested that PDX models could be used to select the most aggressive clones in a primary tumor with similar gene expression characteristics as the corresponding metastatic tumors. Associated drug screen results could provide an optimal therapeutic option to patients suffering from recurrence or metastasis. These data indicated that PDX models have the potential to directly influence clinical decision making.

However, the reliability of the cancer cells within a PDX has been questioned, impeding the potential future applications of these models. The following represent the main problems associated with PDX models: 1) The current PDX is both time-consuming and expensive. It takes 4 to 8 months to generate a complete PDX cohort for *in vivo* drug screening. If the current PDX models are to be employed in a clinical setting, patients with advanced-stage cancer could suffer from tumor progression or even death before the screening results are obtained. 2) Intratumor heterogeneity could influence the growth of PDX tumors. A PDX model is usually established by using only a single piece of tumor tissue. However, this piece of tissue may not be able to represent the whole tumor due to the existence of intratumor heterogeneity. 3) Genomic evolution is another problem of PDX. A study performed by Uri et al. [10] showed that the particular copy number alterations (CNAs) in PDX models were different from those in patients by characterizing the CNA dynamics in 1110 PDX models from 24 cancer types. As a result of genetic drift and selection pressure, genomic evolution has been observed in PDX's tumors and this might affect the results of drug response in some PDX models [10,11]. 4) Human tumor stromal components could not be maintained permanently in PDX models. The stromal components include the extracellular matrix, cancer-associated fibroblasts, endothelial cells, and immune cells. Since the establishment of PDX models, human stromal in tumors are gradually replaced by murine stroma which could probably alter the tumor microenvironment. The interaction between human tumor cells and human stromal could be lost, and anticancer drugs, such as antiangiogenic drugs, acting on human stromal cells

Abbreviations: CNAs, copy number alterations; PDX, patient-derived xenograft; PDX-MI, PDX model minimal information standard

would lose their efficacy. [12]. 5) PDX models lack an immune system. The current PDX models are constructed in immuno-compromised mice lacking an immune system, which brings another challenge to immune-oncology research.

In view of the above-mentioned drawbacks, several corresponding technical modifications have been proposed. For rapid *in vivo* screening of the most effective therapeutic regimens, miniPDX models have been proposed as a novel alternative. In this model, patient-derived tumor cells are filled into special hollow fiber capsules and are implanted subcutaneously into mice. Subsequently, the response of these tumor cells to a series of drug regimens are evaluated after treatment for 7 days. Drug responses in miniPDX models were found to be consistent with those in the corresponding conventional PDX models [13]. Further, miniPDX models were found to overcome the disadvantages of conventional PDX models such as the long latency period before tumor engraftment and the low engraftment rate. The duration of regimen screening was shortened to only 7 days when miniPDX models were used, which showed great improvement in the waiting time compared to the conventional PDX models (2-4 months). Clinically, these models could aid decision making for first-line therapies. Zhan et al. [14] reported that the chemotherapeutic regimens based on miniPDX-guided selection demonstrated improved outcomes in patients with gallbladder carcinoma. Still, the lack of a tumor microenvironment in miniPDX models hinders the observation of responses towards immunotherapies.

To address the influence of intratumor heterogeneity on treatment decision making, multi-sample implantation could be the key to guarantee a more comprehensive approach. The attempt is to establish multiple PDX models using tissues from different regions of a single tumor and to conduct drug testing on each of these models. This could theoretically cover the genetic and molecular diversity of the corresponding tumor. Besides that, PDX models could also be built with tumor cells derived from liquid biopsies, such as circulating tumor cells, as these are assumed to possess the intratumor heterogeneity of the patient's tumor. However, this approach could still be both time-consuming and skill-demanding due to shortage of available tumor tissue.

Genome evolution was considered inevitable in animal tumor models. Recently, Uri et al. [11] proposed that the risks associated with cancer model evolution could be attenuated by three main strategies, namely tracking and reporting model passages, routinely assessing genetic diversification in the model, and minimizing genomic evolution by avoiding unnecessary passaging. On the contrary, genomic evolution in PDX models can also provide novel avenues for cancer research of tumor evolutionary dynamics.

To better mimic the human tumor microenvironment, human mesenchymal stem cells or tumor-associated stromal cells have been utilized as co-implants into PDX models, where researchers can analyze complex tumor-stroma interactions *in vivo* [15]. However, these stromal elements may only be present in one passage and could be lost when the PDX tumor is to be passaged in new mice unless the human stromal cells were co-injected at every passage. Moreover, it is still uncertain whether human tumor cells could cross-talk with murine cells and "instruct" them to create a microenvironment that favors tumor growth.

In regard to immune reconstruction, humanized PDX models have been constructed followed by the engraftment of human peripheral blood mononuclear cells and hematopoietic stem cells into immunodeficient mice [16]. The humanized PDX models have paved a way for tumor immunology and immunotherapy research. However, the reconstruction of the tumor microenvironment and the immune system can only present in a designated passage when a cohort of PDX mice are used in one experiment. The transfer of human immunocytes into PDX models usually leads to graft-versus-host disease, which does not allow long-term evaluation of the efficacy of immunotherapy [16].

In addition, it is crucial to construct large-scaled PDX platform by multiple institutions. The construction of PDX models is a resource- and labor-intensive project. A large-scaled PDX platform offers advantages to reduce cost, to share rare or particular tumors, and to launch large-scale cancer research projects. Based on the PDX platform, higher immunodeficient mice, such as NOD SCID gamma (NSG), could be used to increase the engraftment rate. Expansion of the source of PDX samples from surgical resection and biopsy to tumor cells from circulating blood, ascites, and pleural effusion makes it possible to construct PDX models with scarce tissues. Besides *in vivo* PDX models, *ex vivo* culture of patients' tumors, such as patient-derived primary cells and organoids, provides additional advantages to rapidly expand primary tumor tissues for large-scale drug screening. It will be highly possible to integrate a patient's own PDX/organoid/ primary cells for discovering effective targets and contributing to tailored treatments.

In our opinion, the PDX models improved through the above technical modifications could be termed as PDX 2.0 models. In the foreseeable future, the PDX 2.0 models are expected to play a prominent role in the following aspects. Firstly, PDX 2.0 models are expected to be used in combination with bioinformatics and big data analysis to guide individualized treatment. Next-generation

sequencing technology has been introduced in clinical settings to guide decision-making. However, a study from the Mayo Clinic showed that only a small number of patients with actionable genetic mutations could benefit from genotype-directed therapy [17]. Recently, the integration of PDX models to multi-omics technologies, such as genomics, transcriptomics, proteomics, and metabolomics, has contributed abundantly to the understanding of cancer biology and the discovery of novel targets or biomarkers [18]. It is reasonable to assume that the combination of PDX 2.0 models with omics analysis could be a robust method to indicate individual therapeutic regimens. The tumor samples from one patient could be divided into two parts: one part could be used in omics tests for personalized analysis, while the other could be transplanted into the PDX 2.0 models. The individual omics data could allow clinicians to identify more appropriate treatment options. Further, PDX 2.0 models could be used to test the effectiveness of the identified therapeutic options, and these treatments could be ranked as consideration for administration to the patients. During this process, the PDX 2.0 model should be incorporated into a molecular tumor board platform, composed of a multidisciplinary team of experts in clinical and translational oncology, bioinformatics, and molecular biology.

Secondly, the PDX 2.0 models are expected to be used for identifying therapy-guided molecular subtyping. Complex molecular heterogeneity is one of the main reasons for the failure of targeted therapies. Thus, the identification of specific biomarkers, such as HER2, could help to identify more responsive patients [19]. Recently, the concept of pan-cancer molecular subtype has been proposed to supple the traditional system of cancer classification. This concept will shed light on future therapeutic development strategies for different types of cancer with the same molecular alterations [20]. Hence, more attention should be given to the application of PDX model biobanks containing different types of cancer in identifying therapy-guided molecular subtyping. Several PDX biobanks have been constructed by multiple institutes to share their PDX platforms. The shared live biospecimens and integrated information of therapeutic results with clinical and molecular annotation are well-preserved by the following repositories, i.e. PDX Finder (Europe and USA), NCI PDXNet (USA), EurOPDX (Europe), NCI Patient-Derived Models Repository (PDMR, USA), and Public Repository of Xenografts (ProXe, USA). More national or even international PDX groups are anticipated to conduct comprehensive multidisciplinary studies that involve multiple centers and different cancer types to identify best treatment responses to specific molecular subsets.

To make the PDX models reproducible in different institutions, it is critical to standardize the procedures and the efficacy of evaluation criteria. Recently, some international experts have put up the PDX models Minimal Information Standard (PDX-MI) to define the minimal information in describing the clinical attributes of a patient's tumor, the processes of implantation and passaging of tumors into a host mouse strain, the quality assurance methods, and the use of PDX models in cancer research [21]. Furthermore, PDX platforms should be developed to integrate and converge PDX-relevant resources from multilateral cooperation in a "co-constructed, co-managed, and shared" pattern. Under this pattern, institutions are expected to generate a PDX union to contribute to the construction of large-scale PDX model platform to participate in project operation and management, and to share PDX model resources. Hence, it is necessary to formulate more detailed guidelines and consensuses for quality control. Only when effective and enforceable standard operating procedures are established, then can multiple institutions achieve reliable and reproducible datasets from PDX models.

In short, the current PDX models could be modified in specific ways. Prospectively, the ultimate goal of a PDX model is to be the optimal model that could comprehensively simulate the human body environment. The modified PDX models are expected to combine with big data analysis to guide individualized treatment and be used to identify therapy-guided molecular subtyping. In the predictable future, we believe that the main focus of PDX models will be on how to improve the existing PDX models and their application in clinical settings.

AUTHORSHIP

ZJY, SRY, TWY, and LZX wrote the manuscript. LD and XX revised the work. All authors have read the manuscript and agreed for publication.

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The authors declare no conflict of interest.

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