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REVIEW ARTICLE

Advantages and limitations in the establishment and utilization of patient-derived xenografts in gastric cancer

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Abstract

Owing to the high genetic heterogeneity of tumors, small number of therapeutic strategies available, and frequent presentation of drug resistance, the prognosis for patients with advanced gastric cancer (AGC) are unsatisfactory. The utility of traditional cancer cell lines in translational research is limited by their poor correspondence to the genomic alterations and expression profiles that occur in actual patient tumors. In the last decade, increasing attention has been given to patient-derived tumor xenografts (PDTXs), which can faithfully recapitulate the histopathology, molecular characteristics, and therapeutic responses of the patient's tumor. However, the widespread development and utilization of PDTXs is restricted by factors such as the timeframe of establishment, lymphoma transformation during passaging, the immunodeficient microenvironment, and pharmacokinetic differences between mice and humans. In this review, we summarize the establishment and characterization of PDTX models for gastric cancer (GC). We then weigh the advantages and limitations of PDTXs when used to evaluate novel compounds, identify effective biomarkers, demonstrate resistance mechanisms, and predict clinical outcomes.

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In China, gastric cancer (GC) is the third leading cause of cancer-related deaths [1], and about 70% of patients with gastric cancer are diagnosed at an advanced stage [2]. For many years, fluorouracil-based combination chemotherapy has been the main treatment for advanced gastric cancer (AGC), with a clinical response rate of 40% and median survival duration being 10–14 months [3]. Despite the survival benefits that have been achieved by anti-cancer drugs (e.g., trastuzumab [4], ramucirumab [5], and apatinib [6]) that have specific targets, the prognosis for a patient with AGC is still grave, due to the limited molecular targets available and inevitable drug resistance. Therefore, exploring new therapeutic targets is an urgent goal in the development of improved treatments for GC. In preclinical studies, many targeted therapies (using drugs with specific targets) have shown excellent anti-tumor activity, but in most clinical trials, they have resulted in failure [7].

It is well known that suitable preclinical animal models are essential for subsequent clinical trials of human medical treatments. Traditionally, *in vitro* cell lines and *in vivo* animal models derived from cancer cell lines have been the most commonly used tools in predicting the clinical outcomes of novel drugs. Nevertheless, owing to the lack of tumor heterogeneity, differences in microenvironments, and accumulation of genetic aberrations during passaging, cell line-based models have limitations for predicting therapeutic efficacies [8]. In recent years, patient-derived tumor xenograft (PDTX) models have emerged as favorable preclinical models, because they are highly consistent with a patient's own physiological system in terms of biological characteristics and drug response [9–10]. In this review, we summarize the establishment and application of PDTX models for GC

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and elaborate on their benefits and limitations.

Establishment of the PDTX model

PDTX models are established by transplanting freshly resected tumors from human patients into immunodeficient mice. This enables the PDTX animal to preserve the histological morphology, architecture, and molecular features of the patient's original tumor tissues [11]. Increasing numbers of PDTXs have been successfully established for patients with melanoma, lung cancer, breast cancer, pancreatic cancer, and colorectal cancer [12–13]; these PDTXs accurately recapitulate the histopathological features, genomic alterations, and expression profiles of the patients' primary tumors [9, 14–15]. The establishment of PDTX models for GC patients has been reported in several studies [9, 16–28] (Table 1). In these studies, the PDTX was mainly derived from surgical tumor samples taken at an early stage. The stable engraftment rate varied from 5% to 100%, and was associated with the patients' gender [25], histological type [16, 28], procedure times [28], tumor sites [27] [metastatic tissue, 65% (51/79) vs. primary tissue, 27% (10/37), $P < 0.001$], and chemotherapy status [26] [prior to chemotherapy, 52.1% (37/71) vs. after chemotherapy, 21.9% (25/114), $P < 0.001$]. As has been shown for PDTXs of melanoma, the degrees of immunosuppression achieved in recipient mice can differ amongst multiple mouse strains, and this is a critically important factor for successful xenograft establishment [29]. In PDTXs of GC, mice displaying greater immunodeficiency appear to demonstrate a higher transplantation success rate [25, 28] [nude mice, 14/83 (16.9%) vs. non-obese diabetic/severe combined immunodeficiency (NOD/SCID) mice, 32/119 (26.9%); nude mice, 8% (6/75) vs. NOD/Shi-scid/IL-2Rγnull (NOG) mice 10.5% (9/86)]. Recently, Chijiwa *et al* subcutaneously inoculated 116 surgically removed tumor tissues into NOG mice and established 61 PDTXs [27]. High transplantation rates were observed for tumors of the respiratory (67%), gastrointestinal (58%), and urological (57%) systems [27].

Increasing evidence has shown that the histopathological characteristics of PDTX models are highly consistent with their corresponding primary tumors, and these characteristics are stable over subsequent passages [26, 28]. Recently, a genomic landscape analysis of datasets derived from The Cancer Genome Atlas (TCGA), the Cancer Cell Line Encyclopedia (CCLE), and the Novartis Institutes for Biomedical Research Patient-Derived Tumor Xenograft Encyclopedia (NIBR PDXE) has revealed highly consistent mutation rates between PDTX cells and patient tumor cells [9]; this correspondence has also been specifically verified for GC [26, 28]. In general, PDTX models have retained the genetic expression profiles of their counterpart tumors, nevertheless, genes

Table 1 Summary of patient-derived xenografts of gastric cancer

Study	Year	Mouse strain	Engraftment stable rates	Latency period (day)	Tissue source	HER2 positive	Lymphoma transformation	Correlation with engraftment	PDX concordance with primary tissue
Nakatani [16]	1979	Nude mice	15/33 (45.5%)	NR	Surgery	NR	NR	Histologic type	Histological features
Yoshiyuki [17]	1990	Nude mice	8/32 (25%)	NR	Surgery	NR	NR	NR	NR
El-Rifai [18]	1998	Nude mice	8/NR	NR	Surgery	NR	NR	NR	Genomic features
Milne [19]	2007	Nude mice	3/60 (5.0%)	NR	NR	NR	NR	NR	Histological and genomic features
Jin [20]	2011	Nude mice	1/1 (100%)	NR	Surgery	NR	NR	NR	Histological features
Han [21]	2012	Nude mice	107/114 (94%)*	NR	Surgery	NR	NR	NR	Histological features
Zhang [22]	2013	NOD/SCID	20/NR	NR	Surgery	NR	NR	NR	NR
Chen [23]	2015	NOD/SCID	5/5 (100%)	NR	Surgery	80% (4/5)	NR	NR	Histological features
Huynh [24]	2015	NOD/SCID	8/NR	NR	NR	NR	NR	NR	NR
Zhang [25]	2015	Nude and SCID	49/207 (23.7%)	NR	Surgery	22% (7/32)	NR	Gender and histologic type	Histological and genomic features
Zhu [26]	2015	NOD/SCID	63/185 (34.1%)	65 (11–160)	Biopsies	21.6% (40/185)	1/63 (1.6%)	Chemotherapy status	Histological and genomic features, Chemosensitivity
Gao [9]	2015	NR	215/NR	NR	NR	NR	NR	NR	Genomic features and drug response
Chijiwa [27]	2015	NOG	3/10 (30%)	NR	Surgery	NR	8/61 (13.1%)	NR	Histological and genomic features
Choi [28]	2016	Nude and NOG	15/62 (24.2%)	94 (44–160)	Surgery	NR	5/15 (33.3%)	Histologic type and procedure times	Histological and genomic features

Note: *, 107/114 xenografts derived from 20 patients were established. NOD/SCID, Non-obese diabetic/Severe combined immunodeficiency; NOG, NOD/Shi-scid/IL-2Rγnull; NR, not reported

encoding cell adhesion molecules and immune system regulators have been downregulated [30–31]. This outcome is due to the PDTX being infiltrated with murine stromal components instead of human stromal elements [32].

Overall, the pathological, genomic, and transcriptomic features of PDTXs have been highly consistent with those of the human primary tumors from which they originated. Furthermore, PDTXs remain stable during passaging, which leads to better correspondence between xenografts and original patient tumors in terms of their respective responses to therapeutic chemotherapy [26, 33] and to targeted therapies [9, 23].

Preclinical and clinical utilization

Potential therapeutic targets and the exploration of biomarker efficacy

Traditionally, cancer cell lines were widely used in the process of screening for drug sensitivity [34–35]. Numerous efforts have been made to identify potential therapeutic targets. For example, a single study generated an entire pharmacogenomic landscape of likely functional processes and pathways that interact in cancers, based on integrated analyses of the genomic profiles of 11 289 tumors and 1001 cell lines [36]. A PDTX-based evaluation of those novel targets and compounds has been urgently needed.

In a feasibility study of PDTX clinical trials (PCTs), Gao *et al* [9] evaluated the responses of 62 single or combination therapies on 277 PDTXs. This PCT demonstrated that two pan-PI3K inhibitors (BKM120 and CLR457) and two combination treatments [(LEE011 + everolimus) and (LCL161 + paclitaxel)] had high response rates and increased progression-free survival (PFS); these results had strong implications for future clinical treatments. Other potential therapeutic strategies, such as using the antitumor activity of cetuximab against GC caused by EGFR dysregulation [22], using volitinib against GC caused by c-Met amplification [37], and using BEZ235 [38] and anti-HER3 antibodies in combination with trastuzumab [39] to treat epidermal growth factor receptor 2 (HER2)-positive GC, have been reported. Furthermore, the multikinase inhibitor regorafenib was found to reduce tumor angiogenesis and proliferation, induce apoptosis in xenografts of GC [24], and have antitumor activity consistent with the findings of the so-called "INTEGRATE" large-scale collaborative study [40].

Molecular mechanisms of therapy resistance

As the first approved drug targeting epidermal growth factor receptor 2 (HER2), trastuzumab induces antibody-dependent cellular cytotoxicity (ADCC) and blocks HER2-mediated signaling. This results in a response rate of 47.3% when combined with chemotherapy [4]. In contrast, subsequent clinical trials of lapatinib failed to demonstrate survival benefits [41–42]. Overall, the efficacy of these anti-HER2 therapies is limited by intrinsic and acquired drug resistance; this is caused by activation of HER2's downstream pathway, and by up-regulation of HER3 and IGF1R [43].

An ongoing clinical trial determined that up-regulation of HER2, at a high level, occurred in patients who were resistant to trastuzumab but sensitive to afatinib [44]. Pre-trastuzumab and pre-afatinib tissues were obtained to establish PDTXs, conduct protein mass spectrometry, and carry out next-generation sequencing to monitor proteomic and genomic alterations. Mutations of the following genes (resulting in the substitutions indicated) were identified both before and after treatment with trastuzumab: *ERBB3* (V104M), *RUNX1* (r174*), *CARD11* (P567T), *PTPRS* (V276M), and *MAGI2* (L114V). Additionally, the following mutations, as well as other alterations, might contribute to the acquired resistance of trastuzumab: *TP53* (R175H), *MYC* (R83W), *ALK* (L1162Q), and *MLL2* (E622*). Meanwhile, preclinical and clinical results suggested that amplification of EGFR might be associated with afatinib sensitivity in trastuzumab-resistant patients.

A recent study revealed that lapatinib epigenetically induces the upregulation of transcription factor c-Myc, which in turn reduces the sensitivity of breast cancer cells to lapatinib. This negative feedback loop could be suppressed by combining lapatinib with an epigenetic inhibitor [45]. Interestingly, upregulation of c-Myc also has a role in the acquired resistance to c-Met inhibitors that occurs in GC; a combined treatment consisting of c-Myc inhibitors and c-Met blockade was found to exert synergistic antitumor activity in MET-amplified PDTXs [46]. Whether c-Myc functions as a downstream effector in the drug resistance to anti-HER2 therapy that has been observed in GC remains to be explored, using suitable xenografts.

Another important determinant in cancer cell resistance against chemotherapy and other potential target therapies is the activation of the PI3K/AKT pathway. Li *et al* [47] demonstrated that PDTXs containing a pathway-activating mutation of PIK3CA responded to the AKT inhibitor AZD5363. They also showed that the combination of AZD5363 and taxotere could overcome the intrinsic resistance to taxotere observed in a PDTX where the tumor suppressor protein PTEN had been disrupted.

Co-clinical trials and mouse avatars

Tremendous efforts have been made to facilitate the transfer of scientific breakthroughs from one system into another: in this case, from the mouse models (of various human diseases) in which breakthroughs have been

achieved, to the realm of human medical treatment. In an era of precision medicine, the concept of co-clinical trials and the use of "mouse avatars" have come into being, with the aim of integrating mouse-based biomedical techniques into clinical guidance. The "co-clinical trial project" utilizes genetically engineered mouse models (GEMMs) to guide ongoing human clinical trials; the validity of this method was proved by Pandolfi *et al* while researching acute promyelocytic leukemia (APL) [48]. In contrast, the "mouse avatar" technique exploits the capability of PDTX models to faithfully recapitulate the characteristics of a specific patient's tumor, facilitating the evaluation of multiple novel drugs or drug combinations for efficacy against that tumor [49]. Both of these initiatives emphasize the real-time integration and analysis of preclinical and clinical data, which contributes to the stratification of responders, prioritization of drug combinations, demonstration of resistance mechanisms, and exploration of biomarkers. Whereas GEMMs are usually engineered based on the well-defined driver mutations of particular cancers, PDTXs can preserve the accumulated effects of multiple mutations that have not yet been individually cloned and identified.

In 2012, Morelli *et al* [50] conducted a phase I trial that evaluated the efficacy of 22 drugs on xenografts derived from a 29-year-old patient with advanced adenoid cystic carcinoma (ACC). On the basis of the preclinical data, the patient was then given a combination treatment of figitumumab (an anti-IGF1R monoclonal antibody) and PF00299804 (a pan-EGFR inhibitor) for four cycles, followed by figitumumab alone (due to the severe diarrhea related to PF00299804). This resulted in a minor response in the patient's rapidly growing liver lesion [50]. Other studies have demonstrated that mouse avatars can faithfully replicate clinical outcomes in the treatment of small cell lung cancer [51], advanced sarcoma [52], colorectal cancer [53], and HER2-positive, trastuzumab-refractory esophagogastric (EG) cancer [44].

Limitations and corresponding solutions

Despite a PDTX model's resemblance to a specific instance of a human disease, several limitations to this method need to be recognized.

The period from model establishment to clinical guidance

Widespread use of mouse avatars to treat GC is limited by the time and cost required to establish stable xenografts. In terms of clinical decision-making timeframes, the period from stable mouse avatar engraftment to preclinical data collection may be too long to be of practical use. Although transplantation procedure optimization (e.g., through the use of support matrix materials and the minimization of *ex vivo* procedure time) and high-throughput screening based on genomic profiles would reduce the time needed to complete the process, many significant improvements must be made before we see the universal application of mouse avatars to the treatment of GC. However, using PDTX models not only to generate treatment recommendations for the individual donor of the specific PDTX, but also to identify novel therapeutic strategies and biomarkers that can be applied to the treatment of future patients experiencing tumors with molecular characteristics similar to those of a given PDTX, is a concept with more significant clinical impact.

Lymphoma transformation during the passaging of PDTX

When the tumor-burden becomes too great for a PDTX mouse, researchers "passage" that tumor into the next generation of PDTX mice. It is noteworthy that lymphoma transformation accounted for 1.6% (1/63) to 33.3% (5/15) of the transplantable GC PDTXs observed during the passaging of tumor tissue. This kind of lymphoma mainly originates from patients who had epithelial tumors and who presented pathological characteristics of B-cell lymphoma [54–55], especially in tissues infected with the Epstein-Barr virus (EBV) [26–28]. This phenomenon has been reported in PDTX models for various primary cancers inoculated into NOD/SCID [56], NSG [57], and NOG [58] strains of mice, but not for those inoculated into nude mice. One possible explanation is that EBV infected the B-cells in donors, then remained latent until implantation into immunocompromised mice; however, natural killer cells in nude mice can interfere with the reactivated EBV, thus resulting in their resistance to lymphoma transformation in PDTXs [57]. The identification and reduction of lymphoma transformation are critical factors to improving the successful engraftment rate of PDTXs. This could be facilitated by: (1) the detection of EBV-infection and inflammatory infiltration of the primary tissues, before inoculation; (2) histopathology diagnosis during passaging; and (3) blockade strategies using rituximab [58].

The immunodeficient microenvironment

The necessity of using immunodeficient hosts in the establishment of PDTXs results in the rapid loss of human stromal elements and human functional immune system elements. This restricts the therapeutic response of the PDTX to immunomodulatory agents. However, the emergence of humanized mice has helped to address this obstacle. Patient-matched immune systems could be reconstructed in the xenograft environment by mobilizing hematopoietic stem and progenitor cells (HSPCs) [59]

or mature circulating peripheral blood mononuclear cell (PBMCs) [32] from the patient. Admittedly, this is a great challenge because inappropriate immune responses against human or murine tissues might be induced [32].

Divergence in pharmacokinetic and metabolic profiles

There are vast differences between the pharmacokinetic and metabolic profiles of the murine system vs the human system. Wong *et al* [60] reported treatment efficacies in humans that were consistent with those in xenografts that had received the same treatment. Instead of employing the maximum tolerated dose (MTD) in mice, which might lead to overestimations of therapeutic responses, dosages were calculated according to the pharmacokinetic parameters of humans. Furthermore, whether certain novel compounds are safe for human should be taken into considerations. Currently, several software packages – including Cloe® PK (Cyprotex), PK-Sim5® (Bayer Technology), and GastroPlus™ (Simulations Plus, Inc.) – allow for the comparison of pharmacokinetic parameters and extrapolation of PDTX model testing results to clinical trials [49].

Conclusions and future prospects

In summary, while PDTX models can closely approximate very specific human pathologies, they are not perfect replications of those pathologies. As interest in and experience with PDTXs has increased over the past decade, databases with clear histopathological and molecular backgrounds have been created, such as the PDX collection of the EurOPDTX Consortium (http://europdx.eu/pdx-collection.html) and the repository of PDX models maintained by the Jackson Laboratory (http://jaxservices.jax.org/invivo/PDTX.html). Those resources significantly facilitate the clarification of tumor biology, evaluation of drug efficacy, demonstration of drug resistance mechanisms, and identification of biomarkers [61]. Ongoing efforts to overcome the limitations of the PDTX method may broaden its application further and strengthen its reliability as a guide for individual patient therapies.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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