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A Review of Progress in the Construction and Application of Human-Derived Xenograft Models for Bladder Cancer

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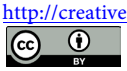

Abstract

The patient-derived xenografts (PDX) model is an animal model established by transplanting primary tumors or fresh tumor tissues of patient origin directly into immunodeficient mice, which preserves the heterogeneity and survival microenvironment of the primary tumor and is widely used in preclinical and precision medicine research of tumors. This article reviews the construction of the PDX model of human bladder cancer and the progress of the application of the PDX model in bladder cancer.

Keywords

Bladder Cancer, PDX Model, Tumor Transplantation, Preclinical Study

1. Introduction

Bladder cancer refers to malignant tumors that occur on the bladder mucosa, more than 90% are uroepithelial carcinomas, and the rest are adenocarcinomas, squamous carcinomas, small cell carcinomas, *et al.* Bladder cancer can occur at any age and its incidence increases with age [1], more men than women suffer from it, and smoking is one of its most important risk factors [2], and more than 430,000 people worldwide are diagnosed with bladder cancer each year [3]. The depth of infiltration is one of the most valuable indicators to determine the prognosis of bladder cancer, which can be divided into non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC), of which about 75% are non-muscle-invasive [4]. Local surgical resection and adjuvant intravesical immunotherapy or chemotherapy can have a good treatment effect, however, 10% - 20% of NMIBC will recur and some will progress to MIBC [5]. For patients with MIBC, treatment consists of radical cystectomy and cisplatin-containing

chemotherapy regimens [6], but about half of these patients develop advanced disease [7]. Advanced bladder cancer is usually treated with nonspecific chemotherapy, such as the combination of cisplatin and gemcitabine [8], but the side effects of chemotherapy often cause greater suffering to patients. The overall efficiency of treatment for bladder cancer patients is low and the prognosis is poor; therefore, finding reliable tumor prediction models is crucial for individualized and precise treatment of bladder cancer and the screening of new drugs.

Currently used in bladder cancer tumor models are genetically-engineered mouse models (GEMM), cell line-derived xenografts (CDX) models and patient-derived xenografts (patient-derived xenografts, PDX) model, *et al.* [9] [10] [11]. Among them, the GEMM model cannot be used for accurate screening of clinical drugs for individualized therapy because its molecular phenotype and genetic characteristics are not very similar to those of human malignant tumors [12] [13]. The CDX model, although widely used, differs significantly from human-derived tumors in terms of biological properties because most of the cell lines used are purified artificially or cultured for multiple generations [11]. The PDX model is an animal model established by transplanting primary tumors or fresh tumor tissues of patient origin directly into immunodeficient mice, and compared with other animal models, PDX model can preserve the heterogeneity and microenvironment of the primary tumor to a high degree even with successive passaged expansion [14] [15], and the primary tumor is highly consistent in terms of genomic performance [16], which better simulates the growth of the primary tumor in patients. In recent years, PDX model has become a powerful tool for new drug development, drug effectiveness research, individualized drug screening and clinical prognosis prediction [17]. In this paper, we mainly review the construction of the PDX model of human bladder cancer and the progress of the application of the PDX model in bladder cancer.

2. Construction of PDX Model for Bladder Cancer

2.1. Selection of Transplanted Mice

PDX model is a xenograft model, and in order to avoid immune rejection between different species, immunodeficient mice are mostly used for the construction. The commonly used immunodeficient mice are Nude mice, severe combined immunodeficiency (SCID) mice, non-obese diabetic/severe combined immunodeficiency (NOD/SCID) mice, and NOD/SCID/interleukin [IL]2γ-receptor deficient (NSG) mice *et al.*

1) Nude mice: no coat, lack of mature T cells, normal but functionally imperfect B cells, low NK cell carcinoma in young age, which will gradually recover in adulthood [18]. 4 - 6 weeks old BALB/c nude mice can be selected for transplantation to reduce the increased immune rejection in adulthood. The greatest advantage of Nude mice is that they have no coat to facilitate the observation of subcutaneous graft size; however, they retain some humoral and non-specific

immunity, which makes them not yet the best choice for constructing PDX models.

2) SCID mice: have a coat, lack of T and B cells, and the presence of intrinsic immunity and NK cells [19]. Higher immunodeficiency results in higher xenograft success rate than BALB/c nude mice; however, they have leakage phenomenon [20], there is a possibility of regeneration of T and B cells in vivo with the increase of mouse age.

3) NOD/SCID mice: have a coat, lack T and B cells, and have low intrinsic immunity and NK cell activity [21]. The highly defective immune function allows a higher xenograft success rate than SCID mice [22], and is one of the more ideal xenograft model animals; however, their short lifespan and high incidence of lymphoma make them unsuitable for experimental studies with longer cycles [23].

4) NSG mice: have a coat, lack T, B, and NK cells, and have low intrinsic immunity [24]. The highest degree of immunodeficiency [25] [26], and therefore little immune rejection of human-derived tumor tissue, makes them one of the most ideal immunodeficient mice for constructing PDX models.

Although there are many immune-deficient mouse strains to choose from, each with its own advantages and disadvantages, researchers need to select the immunodeficient mouse species that best meets their experimental needs based on a variety of factors such as the time required for the study, cost, and success rate.

2.2. Pre-Transplant Preparation

Surgically obtained active tumor tissue blocks were collected in centrifuge tubes as soon as possible and transported to the laboratory for transplantation within two hours under aseptic and low temperature conditions [27]. The tumor tissue was stained with trypan blue dye under sterile conditions to detect the activity of the tumor tissue, and the tumor tissue with high activity was selected for the next step, tumor tissues with a high degree of activity after staining were sterilized by iodine vapour immersion, and necrotic or abnormal characterized tissues, such as inflammatory parts, white soft or liquefied parts, were excluded [28]. Trim the treated tumor tissue into 2 × 2 × 2 mm size and inoculate on ice [29], and inoculated with cannula needle adsorption for transplantation. The treated tumor tissue is usually infiltrated with stromal gel to improve the graft success and growth rate [30].

2.3. Selection of Transplantation Site

The selection of a suitable transplantation site is one of the important factors for the successful construction of PDX model. Currently, the common transplantation sites include subcutaneous transplantation, renal peritoneal transplantation and in situ transplantation.

1) Subcutaneous transplantation: human-derived tumor tissue is transplanted

into the subcutis of mice, and the transplantation site is often chosen from the scapular region or inguinal region of mice with relatively abundant blood supply. It is one of the most commonly used methods to construct PDX models because it is simple [31], easy to use, less traumatic to mice, and can visually reflect the growth of transplanted tumors; however, the characteristics of transplanted tumors may differ from those of primary tumors because of the lack of microenvironment of primary tumors under the skin of mice [32], and subcutaneous transplanted tumors rarely metastasize and spread, which is not conducive to the experimental study of aggressive tumors [33].

2) Renal peritoneal transplantation: transplantation of human tumor tissue under the renal capsule in mice. Because of the rich blood supply in the peritoneum, the transplanted tumor can receive more nutrient supply and also retain the molecular characteristics of the tumor, and the tumorigenic rate is higher than that of subcutaneous transplantation; however, its operation is complicated and difficult, and it is traumatic to mice increasing the risk of infection and requires imaging techniques to observe the growth of tumor [34], which limits its application in the PDX model.

3) In situ transplantation: transplantation of human-derived tumor tissue into the corresponding mouse organ of its origin. Compared with the first two transplantation methods, in situ transplantation is the closest to the primary tumor growth microenvironment and heterogeneity, and can better reproduce the growth and metastasis characteristics of the primary tumor, and its tumorigenic rate is significantly higher than that of subcutaneous transplantation [35]; however, in situ transplantation is no less difficult to operate than renal peritumor transplantation, and observation of tumor growth also requires the use of imaging techniques, which brings disadvantages to in situ transplantation.

In conclusion, investigators need to consider various factors to select the appropriate transplantation site for constructing PDX models, to maximize the success rate of modeling and to preserve the characteristics of the primary tumor itself.

3. Application of PDX Model in Bladder Cancer

3.1. Application of PDX Model in the Pathogenesis and Signaling Pathway of Bladder Cancer

Many researchers have explored the pathogenesis of bladder cancer by constructing PDX models, and some of the conduction pathway studies can also provide new directions for targeted treatment of bladder cancer.

3.1.1. Application of PDX Model in the Pathogenesis of Bladder Cancer

It is very urgent to clarify the mechanism of occurrence and development of bladder cancer. Because the PDX model is highly consistent with primary tumors in terms of genomic expression [16], many researchers have explored the mechanism of occurrence and development of bladder cancer by constructing a PDX model of bladder cancer, which provides a certain reference for the explo-

ration of the pathogenesis of bladder cancer.

By constructing a PDX model of bladder cancer, the team of Namekawa [36] found that acetaldehyde dehydrogenase 1A1 (ALDH1A1), a marker of tumor stem cells (CSCs), was overexpressed in bladder cancer by assay, while microtubulin *β*3 (TUBB3) was also found to be overexpressed in bladder cancer by gene knockdown. Wang *et al.* [37] transplanted human CD34+ hematopoietic progenitor cells and stem cells into NSG mice to form humanized NSG (HuNSG) mice in order to sustain the human hematopoietic and immune systems, and constructed a PDX model of bladder cancer by HuNSG mice, and found that the PDX model tumors of HuNSG mice could be significantly suppressed by treatment against programmed cell death protein 1 (PD-1). Treatment significantly inhibited. Lee *et al.* [38] established a PDX model of chemotherapy-resistant metastatic MIUBC and applied scRNA-seq technology to compare the tumor microenvironment between the primary tumor and the corresponding PDX model in order to deeply analyze the multiple mechanisms of treatment-refractory tumors. Shi *et al.* [39] used the bladder cancer PDX model *in vivo* experiments, by using protein blotting, biotinylated RNA probe pull-down assays, fluorescent in situ hybridization and immunohistochemistry to assess the potential molecular mechanisms of long-stranded non-coding RNA (lncRNA) LINC01451 in bladder cancer, it was found that LINC01451 was expressed at significantly higher levels in bladder cancer tissues than in normal tissues and promoted bladder cancer proliferation, invasion and metastasis. LINC0145 was shown to be dependent on LIN28A and LIN28B, promoting epithelial mesenchymal transition (EMT) through activation of the TGF-*β*/Smad signaling pathway and subsequently exacerbating bladder cancer progression.

Because of the high genomic heterogeneity between the PDX model and the primary tumor, researchers were able to further explore the pathogenesis of bladder cancer based on this, and their findings also provide some theoretical basis for the development of bladder cancer, which can be further explored along their direction.

3.1.2. Research and Application of PDX Model in Bladder Cancer PD-1/PD-L1 Signaling Pathway

Programmed death ligand 1 (PD-L1), a member of the B7 family of co-stimulatory molecules, is a cell surface glycoprotein that promotes apoptosis by binding to programmed cell death-1 (PD-1), a surface receptor for T and B cells, thereby suppressing host immune function [40]. Because the involvement of T cells is crucial for the assessment of PD-1/PD-L1 signaling in tumorigenesis; however, the role of PD-L1 signaling pathway in the development of NMIBC with different subtypes remains unclear [41], so investigators have developed corresponding humanized animal models.

Blinova *et al.* [40] established six NMBIC PDX models including primary, recurrent gata3-expressing/intracavitary, basal/KRT5/6-expressing and p53 subtypes, and all PDX models were positive for PD-L1 expression, and these

NMIBC were not inhibited by PD-L1 blockers due to different molecular subtypes and tumor suppressors, resulting in tumor growth in all subtypes of bladder cancer, especially p53 NMIBC PDX tolerates anti-PD-L1 therapy. The adverse response of p53 subtype NMIBC to specific anti-PD-L1 therapy may be related to the low expression of CD8+ cells in tumor tissue. Also Blinova *et al.* [42] established 20 models of highly recurrent PD-L1(+) double-negative NMIBC PDX and found that p53 protein expression was an independent factor affecting the survival time of animals treated with anti-PD-L1 in highly recurrent PD-L1(+) double-negative NMIBC PDX mice, and that p53 expression could be considered as a low-grade highly PD-L1-positive GATA3(−)/CR5/6(−) recurrent non-invasive bladder cancer as a prognostic factor for the efficacy of anti-PD-L1 therapy. Pathway studies of PD-1/PD-L1 signaling provide a new direction for exploration of bladder cancer.

These results may have important implications for further clinical research, and assessing PD-L1-related invasiveness and detecting the level of PD-1/PD-L1 pathway signaling molecules will be new directions for further exploration.

3.2. Application of PDX Model in Individualized Precision Treatment and New Drug Development of Bladder Cancer

The PDX model is widely used for individualized precision therapy and the development of new drugs because of its ability to preserve the heterogeneity and microenvironment of the patient's primary tumor and its ability to reproduce the patient's drug sensitivity, among other characteristics. Precisely because of the low overall efficiency and poor prognosis of bladder cancer patients treated, researchers are dedicated to this.

Pan *et al.* [43] established 22 PDX models of bladder cancer using NSG mice that maintained morphological fidelity and whole-exome sequencing revealed 92% - 97% genetic aberrations in these PDX models and patient tumors, including multiple druggable targets. The team of Martin [8] using the PDX model of bladder cancer, found that methionine adenosine transferase 1a (MATA1A) was significantly elevated after 21 days of cisplatin/gemcitabine drug treatment both before and after recurrence by RNA sequencing analysis, suggesting that upregulation of MATA1A is a potential mechanism for the process of bladder cancer from quiescence to chemotherapy drug resistance. Cirone *et al.* [44] showed that clinically relevant doses of PI3K/AKT/MTOR pathway inhibitor PF-04691502, and MEK pathway inhibitor PD-0325901 slowed tumor growth in bladder cancer PDX model through two successfully established bladder cancer PDX models. Zeng *et al.* [45] successfully established three PDX models of bladder cancer and demonstrated for the first time that the PI3K/AKT pathway inhibitor Pictilisib effectively potentiated the antitumor effects of cisplatin and gemcitabine in human bladder cancer *in vitro* and *in vivo*. Their results also show that riboprobe S6 expression is a potential candidate biomarker for assessing Pictilisib response, and the team's preclinical data provide good insight into the treatment of bladder cancer with Pictilisib and chemotherapeutic agents in further clinical

trials. Borgna *et al.* [46] according to knock down antisense non-coding mitochondrial RNAs with targeted antisense oligonucleotide Andes-537S, tumor growth was significantly inhibited in the corresponding bladder cancer PDX model compared to the control group, suggesting that antisense non-coding mitochondrial RNAs may be an effective target for adjuvant treatment of bladder cancer. Kamoun *et al.* [47] validated the expression of Ephrin receptor A2 (EphA2) in Ephrin/Eph receptor intercellular signaling molecules in 177 human bladder cancer samples using immunohistochemistry and found that nanotherapeutic agents (EphA2-ILs-DTXp) with a novel EphA2-targeting antibody-directed nanotherapeutic encapsulating an unstable doxorubicin prodrug were more effective in their established four-group PDX model of EphA2-positive bladder cancer and that the combination of EphA2-ILs-DTXp and gemcitabine resulted in more pronounced tumor growth inhibition than either single agent or the combination of doxorubicin and gemcitabine, supporting the clinical exploration of EphA2-targeted therapy for bladder cancer.

These preclinical studies can be used not only to screen for the most effective molecularly guided targeted therapies, effective first-line chemotherapy and salvage chemotherapy, but also for drug repurposing and secondary resistance mechanisms to guide further personalized treatment and drug development, providing another option for the precision treatment of bladder cancer.

4. Current Problems with the PDX Model

It has become an important research strategy for people to study bladder cancer through the PDX model, and although the PDX model has been widely used, it still has some limitations and challenges: 1) Not all tumors are established as xenografts, which means that the PDX platform is not representative of the patient population. 2) As the PDX model adds value and passes on, the cellular stroma of mice gradually replaces the primary tumor stroma [48]. 3) When transplantation of small amounts of tumor tissue is performed, the primary tumor often loses some of its traits due to genetic drift, which affects the heterogeneity of the primary tumor [49]. 4) Due to the use of immunodeficient mice for modeling, PDX models do not reflect the effect of the immune environment on the primary tumor [50]. 5) Several sites commonly used for PDX model construction such as subcutaneous grafts and renal peritoneal grafts do not most realistically reflect the survival environment of the primary tumor, resulting in corresponding changes in the structure and morphology of the model compared to the primary tumor [51]. 6) PDX modeling is time-consuming, and the tumorigenesis time varies for different pathological staging, usually taking 2 to 8 months, with first-generation models often taking 4 to 5 months, which does not provide timely feedback on the results for rapidly progressing diseases with short patient survival cycles, limiting individualized treatment. 7) PDX modeling is costly and the success rate of modeling varies with different tumor types [51]. 8) There are still few reports on the use of PDX modeling for preclinical drug stu-

dies and related drug sensitivity in bladder cancer, and it does not provide sufficient theoretical basis for the exploration of bladder cancer.

5. Summary and Prospect

This paper reviews the progress of the construction and application of PDX model for bladder cancer. It introduces the selection of transplanted mice required for the construction of PDX model for bladder cancer, the treatment before transplantation, the selection of transplantation sites and some research results made by researchers on bladder cancer disease by using PDX model, including the pathogenesis of bladder cancer, related signaling pathways and individualized precision treatment and new drug development.

Although the PDX model has many shortcomings, it still has advantages over other experimental models in the study of tumor development mechanisms, identification of tumor biomarkers, new drug development and preclinical drug screening for precision medicine. However, it is still more advantageous than other experimental models in studying the mechanism of tumor development, identifying tumor biomarkers, new drug development and preclinical drug screening for precision medicine. It is believed that with the continuous upgrading of PDX model technology, precision medicine and translational medicine will take a new step forward in the future. The MiniPDX model, which can be molded faster [52], and the humanized heterozygous (Hu-PDX) model [53], which provides a more similar growth environment to the human body, have been investigated to compensate for the shortcomings of the existing PDX models. It is believed that with the continuous updating and upgrading of PDX model technology, precision medicine and translational medicine will take a new step forward in the future.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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