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Ovarian and cervical cancer patient derived xenografts: The past, present, and future

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HIGHLIGHTS

- PDX models show genetic and molecular patterns similar to patient tumors when cell lines do not.
- PDX models can be used to personalize treatments for women with gynecologic malignancies.
- Collaborative research can expand the use or role and improve the reliability of results in studies using PDX models.

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ABSTRACT

Preclinical research in gynecologic malignancies has largely relied upon cloned cancer-derived cell lines and tumor xenografts derived from these cell lines. Unfortunately, the use of cell lines for translational research has disadvantages because genetic and phenotypic alterations from serial passaging have resulted in expression profiles that are different from the original patient tumors. The patient-derived xenograft (PDX) model derived from human tumor not previously cultured has shown better representation of the heterogeneity of gynecologic malignancies and the human tumor microenvironment with preservation of cytogenetics, cellular complexity, and vascular and stromal tumor architecture. Studies have shown promise with these models to analyze tumor development and adaptation, test drug efficacy, and predict clinical outcomes. Their ultimate value may be seen with preclinical drug screening including novel targeted therapies, biomarker identification, and the development of individualized treatment plans. This article reviews PDX model development, current studies testing chemotherapeutics and targeted therapies, and limitations of the PDX model in gynecologic malignancies.

Contents

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1. Introduction

Gynecologic malignancies are heterogeneous diseases with histopathology and cellular heterogeneity that differ from patient to patient. Current treatment for most gynecologic malignancies involves surgical resection and/or cytotoxic chemotherapies. Five-year overall survival for women with ovarian and cervical cancers is almost 45% and 70%, respectively [1]. Technological advances in genetic testing and biomarker detection have shifted treatment of numerous malignancies to a more personalized approach with therapies targeting molecular alterations in an individual`s tumor. There is recent evidence suggesting that this approach may improve overall survival [2]. Success using these targeted therapies has been limited by multiple factors. A major limitation is that preclinical models of gynecologic malignancies may not accurately reflect tumor cytogenetics and heterogeneity.

Our knowledge of gynecologic cancer biology is largely based on in vitro experiments using established cell lines. For ovarian cancer, cell lines have been generated using cancer cells isolated from patient ascites or pleural fluid, but it can be more difficult to generate an in vivo model using these same cells [3]. Many have called this model into question because cell culture lacks the mixture of epithelial, stromal, immune, and endothelial cells present in human tumors [4]. The human tumor heterogeneity creates a complex microenvironment that enables cellular growth, the development of cancer resistance, and metastasis [4,5]. Cell lines cultured from patient samples collected decades ago are still used in laboratories across the country, yet commonly used cell lines have shown genetic and phenotypic modifications resulting in expression profiles that are different from patient samples [6]. In vitro cell culture lacks the stroma and mesenchymal elements present in human tumors to generate the paracrine production and signaling pathways necessary to support tumor proliferation and metastasis formation [7–9]. Continuous cellular subculturing and passaging with the use of enzyme treatment used for in vitro cell maintenance may be selecting a genetically and phenotypically uniform cancer cell subclone that flourishes in the plastic dish of the laboratory setting yet lacks the heterogeneous microenvironment seen in human tumors [10].

Due to the lack of heterogeneity of in vitro cell culture, alternative models more closely resembling human tumors have been investigated. Researchers created xenograft models in mice using cells implanted from those established cell lines. These conventional xenografts are widely used among researchers and often made with human-derived cell lines, but their functional utility has been questioned [11]. The accuracy with which conventional xenografts reflect the human population has been questioned as these models lack the donor tumor heterogeneity and tumor microenvironment [12]. In an effort to create a better preclinical model of human tumors, patient derived xenograft (PDX) models were developed and their utility is still being evaluated. It remains unclear if PDX models are superior to conventional xenografts when analyzing tumor development and adaptation, testing drug efficacy, or predicting clinical outcomes as few studies have been done comparing the two models head-to-head in gynecologic malignancies. Currently, research continues to support the use of human PDX xenografts established from cell lines, particularly as a panel of xenografts rather than a single xenograft, as they have been found to reliably predict clinical efficacy [13,14].

1.1. The PDX model

The PDX model is created by immediately transplanting surgically resected patient tumors into immunocompromised mice in an effort to maintain similar cytogenetics and tumor heterogeneity to the donor tumors. Some of the early PDX studies were successful in establishing tumor models using melanoma, breast, pancreatic, lung, colorectal, and brain cancers [15]. Advances in the understanding of cellular invasion, angiogenesis, chemoresponsiveness, and biomarker identification have been evaluated with these PDX models [16–18]. PDX tumors have shown preservation of cytogenetics, cellular complexity, and glandular, vascular, and stromal architecture when compared to their human counterparts [19–21]. Similar copy number alterations and gene expression profiles with the lack of interspecies chromosomal hybridization suggests genetic stability between PDX and patient tumors [20–22]. Analysis of The Cancer Genome Atlas identified many genes that are commonly gained or lost in ovarian cancer, and Weroha et al. found similar genetic gains and losses in 41 different xenograft tumors [23]. In general, PDX tumors are grown in an environment that more closely resembles the source tumor since tumor cells are exposed to oxygen, nutrients, and hormones in a similar manner as human tumors [10]. After establishing PDX models in non-gynecologic malignancies, researchers have now successfully developed ovarian and cervical cancer PDX models that have demonstrated similar genetic and molecular patterns as patient tumors [22–25].

Engraftment rates appear to vary depending on the cancer type. Ovarian cancer has one of the higher engraftment rates ranging from 65–100% while cervical cancer engraftment is lower at 48% [10,23,24,26,27]. Orthotopic and nonorthotopic implantation sites have been compared as this has been shown to affect engraftment rates [27]. Nonorthotopic sites in the subcutaneous flank, mammary fat pad, and sub-renal capsule may lack the same microenvironment seen in the orthotopic sites within the ovary or peritoneum, but engraftment rates are still quite high [24,27]. Both orthotopic and nonorthotopic ovarian PDX models have demonstrated similar histology, genetic and molecular expression profiles, and overall tumor phenotype when compared to the original tumor [24,26]. Tumor growth, metastatic patterns, and development of ascites similar to that in humans have also been demonstrated in orthotopic ovarian cancer PDX models [28]. It is important to note that despite the replacement of human stroma with murine stroma in these PDX tumors, the ovarian tumor histology and oncogene expression are preserved when serially transplanted for at least six generations [24]. Evaluation by gynecologic pathologists confirmed similar histology between the patient and PDX tumors for six generations including identification of mixed epithelial histology seen in several patient tumors present in the corresponding PDX tumor [24]. Dobbin et al. also found similar cancer drug target gene expression in the patient and PDX tumors on qPCR analysis [24]. In addition to ovarian PDX tumors, orthotopic cervical cancer PDX models have demonstrated similar metastatic, histologic, and stromal patterns as well as similar gene expression when compared to their donor patient tumors even after tumor was passaged for five generations [25].

Even though orthotopic models may have a tumor microenvironment that more closely resemble human tumors, orthotopic models tend to have lower engraftment rates and more difficulty monitoring tumor growth than subcutaneous models. In the case of ovarian cancer models, mice may develop large volumes of ascites that compromise survival even before tumor growth is detected. After extensive genotypic and phenotypic comparison, orthotopic and nonorthotopic models appear to be equivalent but many researchers utilize nonorthotopic PDX models because of technically simpler implantation that is less time consuming and easier monitoring of tumor growth [23,29]. These models are used to establish drug efficacy, identify biomarkers, and to develop personalized medicine strategies that include targeted therapies.

1.2. Cytotoxic chemotherapy in the ovarian PDX model

Several cytotoxic chemotherapeutic agents used in ovarian cancer have been tested in PDX models to evaluate drug efficacy and establish mechanisms of action (Table 1). In 2001, Ghamande et al. established serous ovarian carcinoma PDX models in severe combined immunedeficient (SCID) mice demonstrating tumor growth inhibition of both subcutaneous and intraperitoneal tumors treated with cisplatin and paclitaxel [30]. Ovarian serous, mucinous, clear cell, undifferentiated, and carcinosarcoma tumors were implanted subcutaneously into