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Patient Derived Tumor Xenografts: transforming clinical samples into mouse models

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Introduction

Despite new insight into the pathogenesis and development of cancer, most novel therapies fail upon reaching Phase III clinical trials. This occurs even though millions of dollars are spent on target validation and drug optimization in preclinical models. When evaluating our approach to target discovery, we should consider if our current, powerful genomic technologies are being used on model systems that have poor clinical predictive power.

Monocellular layers of tumors cultivated in vitro and mouse xenografts derived from those cells, have been the standard toolkit for cancer biologists for decades. Yet, data suggest that the behavior of these lines has diverged substantially from the actual tumors from which they were derived. Patterns of gene expression are reduced in complexity in cell culture models, suggesting that heterogeneity is lost once a tumor is removed from a patient and cultured in the laboratory (1). The selective pressure of cell culture allows the least differentiated cells to thrive, resulting in distinct and irreversible losses of important biological properties (1). Mouse xenografts of human tumor cell lines have had variable, and often poor, predictive power in the translation of cancer therapeutics into clinical settings (2). In recent years, mouse xenografts that have been selected and properly characterized have shown utility for predicting responsiveness to targeted agents (3). However, these models fail to reproduce the tumor microenvironment and tumor cell interactions with the innate immune system, both of which are integral to tumor development, proliferation, and metastasis (1). Genetically engineered mouse models provide an alternate model that includes a fully functioning immune system, though they do not encompass a human origin.

The clinic as a source

The imperative for better, more clinically predictive models of human cancer is obvious. “Tumor graft models” (also known as Patient-Derived Xenografts or PDXs) are based on the transfer of primary tumors directly from the patient into an immunodeficient mouse. To accomplish this, patient tumors must be obtained fresh from surgery, at which point they are mechanically or chemically digested, with a small portion saved as a primary stock, and established in a NOD-SCID mouse. This breed of mouse lacks Natural Killer cells and is considered more immunodeficient than a nude mouse. PDX models are maintained by passaging cells directly from mouse to mouse once the tumor burden becomes too high. Tumors can be engrafted heterotopically or orthotopically. Heterotopic PDX models involve implanting tumors into the subcutaneous flank of a mouse. This method allows for easier

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cell transfer and precise monitoring of tumor growth and location (4) Orthotopic models are more technically challenging and time consuming. This method involves direct implantation to the mouse organ of choice. In some cases, additional imaging studies may be needed to verify location of tumor grafts after implantation. Orthotopic transplants are considered to more accurately mimic the human tumors from which they are derived than heterotopic transplants when comparing histology and gene expression profiles from mice to patients (5). This is likely due to the effects of the tumor microenvironment. Seemingly small procedural differences such as injection of breast tumors into thoracic instead of abdominal mammary gland can affect PDX success rate and behavior. (6). Colon cancer cells can exhibit differential sensitivity to chemotherapy depending on the anatomical location of grafts in nude mice (7) Despite the technical difficulties of creating orthotopic models, direct comparisons of both engraftment models show that orthotopic models are also able to better predict a patient's response to chemotherapy (7), (8). In fact, PDX responses to chemotherapy resemble the response rates (9), (10), (11) of monotherapy in clinical trials (5).

PDX models may be superior to traditional cell line - xenograft models of cancer because they maintain more similarities to the parental tumors. Detailed examination of PDX mice indicate that histology (12) (13) and gene expression profiles are retained (14), along with SNPs (15) and copy number variants (1),(13),(16), (17). To date, there have been no proteomic studies or examinations of DNA methylation patterns. Although miRNA expression has not been thoroughly characterized in most PDX models, one study indicated 17% of miRNAs were differentially expressed between primary lung tumors and grafts. Differences in miRNA expression patterns were not seen to increase with extended passage in this study (18). While most PDX models in use have not been extensively genetically profiled, published studies do indicate that genetic alterations are more prevalent in the engrafted tumors compared with their parental cancers (19), (20). As expected, less differentiated tumors seem to be more labile, unstable and prone to changes (13), (18). Because of this, a single recipient animal usually fails to capture the inherent variability of each cancer, and so multiple engraftments are needed to preserve tumor heterogeneity, even for a single donor tumor (21). Initial engraftment is the moment at which the most genetic variation arises (14). Genes associated with stromal gene ontology annotations are most altered, most likely due to loss of the human stromal compartment and interactions with the mouse stromal microenvironment (14), (17) (19). Subsequent genetic changes occurring with each passage to a new mouse host are thought to represent genomic rearrangements intrinsic to tumor progression. Most authors advocate using PDX models with a low passage number (<10) to preserve the genetic integrity of the parental tumor (22). The impact and degree of genetic alterations that occur with each tumor passage remains unclear. Published reports of PDX models differ in whether significant molecular subtype classification changes occurring over time between the parental tumor and its PDX derivative (14), (17), (20).

Why are PDX mice not the standard for modeling human cancer?

Given the emerging data that PDX tumors more closely resemble the original clinical cancer than long established cell lines and standard xenografts derived from them, one must ask why these models are not more widely used. There are a number of factors with the potential to hinder the use of PDX mice. Of course, one is cost. Tumor grafts can only be maintained in mice and their passage requires a more specialized skill set than does the simple maintenance of cultured cell lines. Moreover, PDX models can suffer from long latency periods after engraftment and variable engraftment rates. Tumor graft latency, measured as the time between implantation and the development of a progressively growing xenograft tumor can range from two to twelve months (20), (23). Engraftment rates typically vary

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between 23–75% depending on the tumor type. Higher engraftment rates are associated with more clinically aggressive tumors (14). Indeed, patients whose cancers gave higher engraftment rates had poorer overall survival with increased metastatic potential (8). Correlations between poor prognosis and engraftment rate were so marked that it has been suggested to be predictive of disease course (13).

Finally, there is the problem of broad availability and the number of PDX models that have been reported. For example, breast cancer models have been challenging to create because of the multiple possible transplantation sites (interscapular fat pad, mammary fat pad, renal capsule,) and tumor hormone status (24). Newer strategies for building orthotopic models include the additional implantation of human bone marrow-derived mesenchymal stem cells resulting in greater vascularity and maintenance of hormonal status (13).

Tumor-host interactions

Tumor grafts have metastatic patterns very similar to their corresponding original human patients (13). The relationship between a PDX tumor and its mouse host is one that must still be explored in depth. Mice with orthotopic tumor grafts more often develop metastases than from heterotopic models. This may be due to tumor cell intrinsic properties as well as the experimental technique employed (2), (4), (25). Extracellular matrix component genes and stroma related genes are downregulated in the human tumor after engraftment, whilst a compensating overexpression of ECM related genes occurs in the mouse host (20). This interaction can be visualized using transgenic nude mice expressing fluorescent proteins. Human pancreatic tumors initially implanted subcutaneously in an immunodeficient mouse were passaged to a transgenic nude mouse expressing RFP, allowing the tumor to recruit RFP tumor associated fibroblasts and blood vessels (25). Remarkably, peritoneal and liver metastases also harbored this fluorescent encapsulation and the presence of RFP-expressing cells persisted for at least three passages when the tumor was transplanted serially though non-RFP-expressing mice. The tumor was also passaged to other transgenic mice ubiquitously expressing GFP and CFP, and in turn acquired their stroma and corresponding color fluorescence as well. Thus, such models allow more accurate visualization of orthotopic tumors and further analyses of the contribution of the host stroma to metastatic initiation and progression (25).

Technical changes in procedures can affect both engraftment and metastasis rate. A recently published panel of breast cancer grafts showed that metastasis frequencies varied between 38 and 100% depending on the tumor type (13). The authors attributed the high metastatic potential of these models to their lack of *in vitro* manipulation of cells, thus allowing better preservation of tumor initiating cells through direct implantation (13). The metastatic rate of pancreatic tumors after transplantation was dramatically increased by suturing a tumor fragment to the pancreas rather than injecting a cell suspension illustrating how sensitive the behavior of PDX tumors can be to the transplantation protocol (12).

Ex vivo manipulation of PDX models

The ability to manipulate tumor cells ex-vivo is in many ways essential to their utility as cancer models. Although tumor grafts are difficult to manipulate in this way without causing irreversible changes, emerging techniques may provide at least partial solutions. Primary tumors transformed into a cell line and then engrafted into a mouse showed significant changes in gene expression profiles compared with their directly engrafted counterparts. These alterations were not reversed when the tumors were reestablished as secondary xenografts (1). Newer 3-dimensional models of colon, gastric and breast cancer may provide methods to manipulate cells prior to implantation. Colon cancer cells (and many others) have the property of being able to form 3-dimensional spheroids in culture. Colon cancer

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tissue-originated spheroids (CTOS) are made by digesting primary tissues enzymatically and growing under specialized culture conditions (26). This can permit brief in vitro manipulation before engraftment. CTOS cells retain the histology of their parental tumors as well several major oncogene mutations. Interestingly, the authors of this study were not able to form CTOS-derived tumors from single cells and postulated that these spheroids provide a niche for a multicellular unit which helps to retain a minority population of tumor-initiating cells (26). An alternative, known as colospheres, are prepared by mechanically dissociating primary tumors and culturing them in vitro before engraftment into the subrenal capsule of a mouse (27). These units can remain alive for at least 3 weeks on an agarose gel substrate without being dependent on an exogenous basement membrane. Colospheres are more easily formed from advanced stage III and IV cancers than they are from early stage tumors. Colospheres gave rise to pathologically well-differentiated adenocarcinomas in stark contrast to the poorly differentiated carcinomas that arose following a colon cancer cell suspension injection (27). Just as for CTOS, colospheres did not give rise to tumors following single-cell implantation. Moreover, neither procedure permitted the formation of organoids from normal tissue. Tumorigenic spheres have also been formed from gastric adenocarcinoma clinical samples (28).

Flow cytometric methods have been employed to select for and manipulate tumor-initiating cells *ex-vivo*. Tumor grafts consisting of distinct cell populations defined by different tumor-initiating capacities and different transcriptional profiles can be formed from single cells, if one first enriches for stem- and progenitor cell markers of human tumor colonic epithelium (29). Thus, a single cell can reproduce the phenotypic repertoire of parental cellular populations from a monoclonal origin, as confirmed by the uniformity of a lentiviral integration site in the diversity of cell types in the graft (29). A similar method has been applied to breast cancer cells where CD44-enriched breast cancer stem cells derived from patient tumors have been orthotopically engrafted into mouse mammary fat pads resulting in tumors which gave rise to spontaneous metastases. These tumors were transduced with a fluorescent reporter facilitating the visualization of as few as ten cells in the mouse and also enabling their retrieval by flow cytometry and subsequent ex-vivo analysis (30). There are as yet no published reports of organoids of other tumor cell lineages although such models are being actively pursued.

Broad utility of PDX models

PDX models offer a powerful tool for studying tumor biology and for evaluating anticancer drugs. The NCI sponsored Pediatric Preclinical Testing Program (PPTP) uses 75 established heterotopic mouse models to fast track anticancer agents from adult Phase I clinical trials into pediatric trials (31). Further testing may also include pharmacokinetic and pharmacodynamic studies, drug combinations and evaluation of orthotopic models (31) (32). This project has resulted in over 50 publications and may be promising for clinical use (21), (32). As with cell lines and their mouse xenograft counterparts, PDX mice also enable the discovery of biomarkers predicting drug sensitivity and resistance (33). These models are being used to develop gene signature patterns that predict tumor response to cytotoxic agents (34). Also, the development of “human-in-mouse” models using normal human tissue engrafted into mice could serve as a control for these drug studies. Unfortunately, investigators have so far been able to form normal “human-in-mouse” models for breast tissues only (35).

PDX models offer the ability to track the initiation and progression of metastasis as well as the fate of circulating tumor cells using in vivo flow cytometry of implanted humor tumors (36). One of many areas that remain underexplored is the co-engraftment, along with the tumor, of normal human peripheral blood or bone marrow cells into NOD-SCID mice,

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resulting in “humanized models.” This reconstitution of the human immune system would allow examination of the role of interactions between xenogeneic human stroma and tumors in progression and metastasis (7). PDX models of human acute lymphoblastic leukemia and acute myeloid leukemia cells have been successfully created, although the murine environment seems to select for subclones resulting in a number of different models (37).

Because PDX mice are derived from human tumors, they offer a route toward personalized medicine for cancer patients. A notable example is a pilot clinical study using pancreatic PDX models to guide treatment for 11 patients with advanced cancers. Seventeen treatment plans were devised with fifteen of these resulting in durable partial remissions (38). This type of modeling is ideal for rare cancers, where no adequate models or validated chemotherapeutic approaches exist. For example, adenoid cystic carcinoma, a salivary gland cancer with only 500 new cases diagnosed per year, has no standard approach available for patients who progress on conventional treatments. Traditionally, patients were enrolled in clinical trials on an empirical basis. A new approach was demonstrated in a patient with this rare cancer: PDX response rates were examined for a panel of chemotherapeutic agents to determine which worked best. One was tested in the patient and resulted in a minor response in a metastatic liver lesion that lasted for 6 months; four other potential treatment options for this patient were also identified (39). While the costs of such an approach presently preclude its large-scale use, these studies do provide an effective proof of principle.

General availability of PDX models

Recent studies of intratumoral heterogeneity suggest that the accuracy of a PDX model depends on the size of the tumor used for engraftment and the need for multiple mouse sublines. The high cost of privately developed models and transfer regulations between academic centers have greatly inhibited the widespread deployment of the PDX methodology. Private companies, such as Oncotest in Germany, and nonprofit research institutions, such as the Jackson Laboratory, have panels of models available for sale with a price tag on the order of several thousands of dollars for each mouse. In France, the Center of Resource for Experimental Models of Cancer (CReMEC) consortium, a mix of hospitals, academic groups, biotech, and pharmaceutical companies, have 54 publically available patient derived colorectal cancer PDX models. All model characteristics and associated clinical, molecular, pharmacological, and histological data are logged in a dedicated database and mice are available from the company Oncodesign (40). The French Ministry of Industry has funded this project for 5.4 million euros (40). Similar collaborations are underway in Europe for bone tumors through the European network to promote research into uncommon cancers in adults and children (EuroBoNeT). It is our opinion that it should be made a priority of the NCI to foster the creation of similar repositories to make PDX models widely available within the community of cancer scientists worldwide.

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