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Patient Derived Xenografts (PDX) for personalized treatment of pancreatic cancer: emerging allies in the war on a devastating cancer?

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ABSTRACT

The prognosis of pancreatic ductal adenocarcinoma (PDAC), the eighth most lethal cancer for men and ninth for women worldwide, remains dismal. The increasing rates of deaths by PDAC indicate that the overall management of the disease in 21st century is still insufficient. Thus it is obvious that there is an unmet need to improve management of PDAC by finding new biomarkers to screen high risk patients, confirm diagnosis, and predict response to treatment as well more efficacious and safer treatments. Patient Derived Xenografts (PDX) have been developed as a new promising tool in an effort to mirror genetics, tumor heterogeneity and cancer microenvironment of the primary tumor. Herein we aim to give an updated overview of the current status and the perspectives of PDX in the search for the identification of novel biomarkers and improved therapeutic outcomes for PDAC but also their use as a valuable tool towards individualized treatments to improve the outcome of the disease. Furthermore, we critically review the applications, advantages, limitations, and perspectives of PDX in the research towards an improved management of PDAC.

Significance: This review provides a comprehensive overview of the current status and the potential role as well as the challenges of PDX in the road to fight one of the most lethal cancers in the developed countries, pancreatic ductal adenocarcinoma.

1. Introduction

Pancreatic cancer is the eighth most common cause of cancer death for men and ninth for women worldwide [1] with an incidence of approximately 1–10/100.000 men and women per year. Pancreatic ductal adenocarcinoma (PDAC) represents 85% of all cases of pancreatic cancer [2]. Smoking cessation, diabetes mellitus, obesity along with genetic predisposition are certain risk factors incriminated for the development of PDAC [3–6]. Despite the constant efforts to develop novel diagnostic tools and treatment approaches, it is projected that PDAC will rise to second most common cause of cancer death by 2030 [7].

Transcriptional profiling of pancreatic tumor tissues revealed the existence of three subtypes of PDAC termed classical, quasimesenchymal (QM-PDA) and exocrine-like with therapeutic response differences between them [8]. However, screening a large panel of pancreatic cell lines, researchers identify the existence only of classical and QM-PDA subtypes suggesting an inadequately representation of the PDAC heterogeneity by the currently used PDAC cell lines [9].

Human cancer cell lines and animal cancer models derived from these cell lines (xenografts) are widely used in translational research. Among other pitfalls, they show limited potential to mirror the actual tumor microenvironment, intratumoral clonal heterogeneity and human stromal properties [10], parameters that greatly affect tumor invasion [11], tumor migration [12], recurrence [13] and drug resistance [14]. As an alternative, Patient Derived Xenografts (PDX) developed by the engraftment of patients' excised tumors directly into immune-deficient animal models have been developed as novel preclinical tools that could achieve greater resemblance to human cancer genetics, tumor heterogeneity and microenvironment [15,16]. As the number of studies assessing the feasibility of PDX increases, it is necessary to examine whether these preclinical models are more reliable and efficient compared to traditional methods. Thus, the purpose of this

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review is to summarize and discuss the existing evidence regarding the use of PDX as preclinical models in basic and translational research as well as a potential clinical tool in the context of personalized medicine in PDAC.

2. A short introduction to the methodology for the development of PDX

The establishment of Patient Derived Xenografts (PDX) in mice from human tumors, either primary or metastatic, is extensively described in the literature [15,17,18]. Although some groups have developed specific methodological approaches, the basic methodology is common. Briefly, fresh tissue pieces of primary or metastatic solid tumors are collected by surgery or biopsy procedures [19,20]. Tumors are implanted into mice as small tumor pieces [21] or single-cell suspensions, either alone or mixed with Matrigel® [17,22], human fibroblasts [23] or mesenchymal stem cells [24].

A variety of immunocompromised mouse strains, carrying different degrees of immunosuppression, have been used for the engraftment of patients' excised tumors. The preferred mouse strains for many groups though are the more severely immunosuppressed strains, such as the NOD/SCID (NOD.CB17-*Prkdc*^{scid}/J) or NOD/SCID/IL2g-receptor null (NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl}/SzJ or more commonly known as NSG) mice that are better suited for PDX generation due to higher engraftment rates [25].

For the development of PDX, the implantation can be either subcutaneous or in the same organ as the original tumor (orthotopic). Although the subcutaneous PDX models are much easier to develop, more popular and recapitulate the original tumor in great degree developing a microenvironment similar to the original tumor, recent studies show that orthotropic engraftment may result to animal models closer to the clinical image. For example, a recent study reported that in comparison to patients' primary pancreatic tumor the orthotopically implanted tumor had a similar gemcitabine response, unlike the subcutaneous implanted tumors [26]. Additionally, Go et al. recently reported that in a subcutaneous pancreatic cancer xenograft model there was no consistent pattern of metastasis and cancer related muscle wasting, as opposed to the orthotopic model [27]. These differences may be due to the fact that orthotopic implantation gives the advantage that the tumor develops in the same microenvironment and the orthotopic PDX model retains critical aspects of the human disease, such as the desmoplastic microenvironment, consistent metastatic spread, and cancer cachexia [28,29]. In support to the differences related to the site of injection for the development of PDX, Hoover and his colleagues report substantial differences in the biomarker and gene profile of subcutaneous PDX and their orthotopic counterparts [30]. Nevertheless, they report the development of a single PDX and the rest of the work were done on established cell lines. Authors highlight that PEAK1 reduces and MST1R increases > 100-fold in orthotopic as compared to the subcutaneous microenvironment. Similar to those studies, Hiroshima et al. reported that in a case of cervical cancer, the orthotopic model recapitulated more accurately the metastatic potential of the original patient's tumor [31].

After xenograft successfully development, tumors are serially transplanted into multiple mice and this process is repeated until sufficient cohort is achieved for further studies. Tumors from primary xenografts are also used to propagate primary patient derived cell lines. In a recent study Noll et al. compared the original xenografts with the corresponding derived cell lines and showed conservation of histomorphological characteristics and RNA expression profiles [9]. Depending on the cancer type, xenograft engraftment rates exhibit diversity and are related with tumor aggressiveness, histological type, size of tissue implanted, and implantation site [32]. For patients with pancreatic cancer Garrido-Laguna et al. reported that a successful xenograft was generated in 61% of patients and that successful engraftment predicted poor patient survival [26] (see also below). In another study the successful engraftment rate of PDX in pancreatic ductal adenocarcinoma was 55.8% and tumor size was related to successful PDX generation [33]. The studies regarding engraftment method(s) towards the successful development of PDX are too limited and thus additional studies are needed to develop methods to standardize engraftment rates and also to generate models from difficult-to-engraft cancer types especially if these PDX are to be used in the context of personalized medicine.

3. PDX in the preclinical setting

3.1. PDX in the road to discover novel biomarkers for PDAC

Biomarkers have a great role in cancer research and medicine in general, as they can help in many different fields such as diagnosis, prognosis, monitoring of treatment response and estimation of recurrence risk, assess pharmacodynamics, pharmacokinetics and development of drug targets. Diagnosis of pancreatic cancer is very challenging. Patients usually present with non-specific symptoms and at the time of diagnosis 80% of them have already advanced disease [34]. Even results obtained from imaging techniques or from the cytological examination may not be conclusive and often are of ambiguous relevance [35]. Considering the dismal prognosis of PDAC and the fact that there is no approved screening method, there is an urgent need to find new more specific and sensitive biomarkers to screen high risk patients, confirm differential diagnosis and to predict treatment response and progress of the disease. A number of studies report the use of PDX for the development of such more reliable biomarkers for pancreatic cancer (Table 1).

In the context of developing a method for a better prognosis of the disease, a clinical trial using PDX was performed by the group of Hidalgo [26] in 2011. A total of 94 patients with PDAC underwent

Table 1
Summary of studies involving PDX the methods used for gene/protein analyses.

	Biomarkers	Number of PDX	Methods	Outcome
[26]	Engraftment rate	69	Gene expression microarray (Affymetrix U133 Plus 2.0 Genechip), GSEA	Higher engraftment rate = poorer prognosis
[37]	A 16-transcript signature to discriminate c-MYC dependent tumors (MYC-high)	71: - 55 to develop the signature (30 surgically removed, 25 from biopsies) - 16 to validate the findings	Gene expression microarrays (Affymetrix Genechip® Human Gene 2.0 ST Arrays), GSEA, Real Time-qPCR, Western Blotting	Identified highly proliferative PDAC with low degree of differentiation and patients with poor clinical outcome. Identified good responders to JQ1 BET inhibitor.
[38]	Polo Like Kinase 1 (PLK1)	11	Low density microarrays (customized assay) Real Time-qRT-PCR	PLK1 may be a marker to predict gemcitabine resistance.
[39]	WDR5	4	In vivo shRNA screens, GSEA	WDR5 is a crucial regulator of tumor growth in human PDAC.

GSEA: Gene Set Enrichment Analysis; Real Time-qPCR: Real-time quantitative PCR; Real Time-qRT PCR: Real-time quantitative Reverse Transcription PCR; RT-PCR: Reverse Transcription PCR; shRNA: short hairpin RNA.

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