Preclinical models of pancreatic ductal adenocarcinoma

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Abstract: Unlike many other cancers, pancreatic ductal adenocarcinoma (PDAC) has seen only incremental improvement in mortality despite significant advances in our understanding of the underlying biology. A primary obstacle to progress has been our inability to properly model PDAC in a preclinical setting. PDAC is difficult to study because of its genetic heterogeneity, intricate stromal microenvironment, and complex interplay with our immune system. Finding a model that properly accounts for all these criteria remains difficult. This review summarizes the five primary models currently in use: human PDAC cell line, cell line xenograft, patient derived xenograft, genetically engineered mouse model (GEMM), and organoids. We delve into the advantages of disadvantages of each model, while discussing how each model has been or could be used in the preclinical setting.

Keywords: Pancreatic ductal adenocarcinoma (PDAC); preclinical model; organoids

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) accounts for upwards of 90% of all pancreatic malignancies (1) and presents a substantial health problem, with an estimated 367,000 new cases diagnosed worldwide in 2015 and an associated 359,000 deaths in the same year (2). PDAC is currently the fourth highest cause of cancer death in developed countries and its five year survival is less than 5% while average survival is only 6–9 months after diagnosis (3-5), If outcomes are not improved, the disease is predicted to be the second leading cause of cancer-related mortality within the next decade, likely due to an aging population (6).

This bleak outlook for PDAC is predicated on several factors. The disease has an early and insidious dissemination, which is often due to non-specific or non-existent symptoms, a lack of sensitive and specific tumor markers, and difficulties in imaging early-stage tumors (7,8). The aggressive nature of PDAC leads to rapid invasion of local

structures and early metastases, which leaves only 15–20% of patients as candidates for curative surgical resection (5). Even with surgical resection, PDAC 5-year survival only improves to 15–20% (9). PDAC is characterized by a remarkable resistance (or tolerance) to most conventional treatment options, including chemotherapy, radiotherapy and molecularly targeted therapy (10). PDAC harbors extensive genetic and epigenetic heterogeneity, not only among tumors from different individuals, but also within a single tumor and across metastatic sites from the same individual (11). Finally, PDAC has a complex and dense tumor microenvironment that is difficult to assemble and study, while also posing a significant barrier to treatment administration (12,13).

Significant advances in our understanding of PDAC have been made. Activating mutations in the *KRAS* oncogene appears to be the initiating event in the vast majority of PDAC. Studies have shown that activating KRAS mutations are uniquely sufficient to initiate premalignant lesions, termed pancreatic intraepithelial neoplasia (PanIN), in the exocrine pancreas (14). PanIN can progress to locally invasive and metastatic pancreatic cancer by way of stepwise mutations in tumor suppressor genes (15). Genetic alterations affecting *CDKN2A*, *TP53* and *SMAD4* cooperate with oncogenic *KRAS* to accelerate the progression of PDAC (16,17). Genome wide studies of PDAC have identified additional mutations and pathways that are crucial to the progression of PDAC (18,19). Other studies have demonstrated the importance of chromosomal alterations, ubiquitin proteases and transcription factor alterations that work in concert with KRAS mutations to drive PDAC forward (19-22). While our molecular knowledge of PDAC has rapidly progressed, the translation of this knowledge into relevant therapies has moved rather slowly.

Effective models of PDAC are absolutely critical to improving patient outcomes. Preclinical models provide a bridge to the clinic, a tool for developing strategies for early disease detection and are a requisite part of the drug development pipeline. However, these goals have remained frustratingly elusive, presumably due to our limited ability to reproduce critical in vivo features of the disease. Notably, our preclinical models struggle to reproduce the stromal microenvironment and the tumor interaction with the immune system. PDAC is characterized by a prominent fibrotic reaction with only small nests of adenocarcinoma cells; a number of studies provide compelling evidence that the stromal reaction plays a critical role in PDAC progression (23-25). The extensive fibrosis creates an environment characterized by severe hypoxia and nutrient deprivation (26,27). PDAC cells are adapted to survive in these conditions through various mechanisms, mainly driven by hypoxia-inducible transcription factor 1α (HIF1 α) and oncogenic KRAS (28,29). The hypoxia and nutrient deprivation creates a climate conducive to further mutations and leads to PDAC's characteristic heterogeneity (11,30). The excessive fibrosis also creates deficient vasculature, which makes drug delivery difficult (13,31,32). This makes treating PDAC more intricate because therapies have to target not only the cancer cells themselves but also the stroma (33). Highlighting the complexity of the stromal role in PDAC, several studies in murine PDAC models have shown that completely ablating the stroma paradoxically led to more aggressive tumor types and decreased overall survival, suggesting a protective role of stroma (34,35).

Preclinical models also struggle to fully recapitulate PDAC because of the intricate interaction between the fibrotic stroma and our immune system. Despite immune cell infiltration in PDAC, the immune system does not actively target the cancer as aggressively as would be expected, which suggests an immunosuppressive phenotype, even at the earliest stages of the disease (36,37). A growing body of evidence suggests that CD4⁺ regulatory T cells in the stroma play a crucial part in warding off the host immune response. This feature is clinically important because factors that mediate the suppression of active antitumor immunity, such as the ligand for programmed cell death protein 1 (PD-L1) expressed on cancer cells, form the basis of the current generation of immunotherapeutic approaches that have been studied in PDAC (38).

This divide between preclinical model responses to therapeutic agents and responses in the clinic has remained quite wide (13). Historically, preclinical testing has mostly occurred in vitro, in 2 dimensional (2D) cell culture assays, or in vivo, in either xenografts or animal models, including genetically engineered mouse models (GEMMs). More recently, hybrid systems where progenitor cells are cultured in 3D, called organoids, have emerged, combining the simplicity and controllability of in vitro culture with the possibility to reconstitute niches more similar to PDAC. Since pancreatic cells are epithelial cells that thrive in contact with other epithelial cells, this 3D architecture allows for these interactions to occur and provides the proper conditions to enable their polarization. In this review, we evaluate the advantages and disadvantages of our current preclinical models and discuss how these findings can be applied to translational studies for our patient's benefit.

Human PDAC cell line

The first human PDAC cell line was established in 1963 (39) and since then many PDAC cell lines have been established and characterized via their unique molecular alterations and phenotypes (40). Studying cell lines provides several very practical advantages for studying PDAC. They are homogenous, easy to propagate and can grow indefinitely. These features allow for low-cost, easily replicable models that can screen essential genes, develop prognostic classifiers, predictive biomarkers and the development of novel anti-cancer drug targets (40).

While cell lines provide easy and rapidly replicable models of PDAC, these same features render them a less than optimal replication of *in vivo* PDAC. First, there are only a handful of well-defined cell lines currently available; therefore they do not represent the heterogeneous nature

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of PDAC (40-42). Indeed, expression profile studies of PDAC cell lines show significant differences between those seen in patient tumors or xenografts (43). Second, these cell lines select for mutations and phenotypes that advantage growth in a monolayer but are unlikely to be favored in vivo (44). The monolayer selection process advantages cancers that yield continuous cell lines, which tend to be the most aggressive, high stage and poorly differentiated tumors, leading to an underrepresentation of slow growing variants (42). The selection of aggressive clones means that these cell lines have already acquired the changes needed for the cells to grow as metastatic deposits in distant sites, rendering them inadequate to study cancer progression (45). At best, individual cancer cell lines provide a snapshot of the tumor at the time the biopsy was taken. This leads to therapies that only target the most aggressive clones, while sparing the majority of the tumor actually present in human PDAC (45). Thirdly, since these cell lines grow as monolayers, they lack the essential tumor microenvironment that leads to structural organization and functional differentiation of the tumor (46). Finally, the lack of an immune system ensures that mutations necessary for warding off the host immune system are significantly underrepresented.

All of these faults inherent in PDAC cell lines render them relevant only as a proof-of-principle preclinical model, making other models crucial for translating this information into possible therapies. Despite these many faults, the ability to grow and manipulate cell lines has allowed our group and others to leverage these characteristics to identify and study biomarkers for early disease detection. For example, cell lines can be grown in stable isotope labeled essential amino acids, a method termed stable isotope labeling by amino acids in cell culture (SILAC). In this way, the entire cellular proteome can be stably labeled for comparative proteomics. Our group has deeply explored this approach to interrogate human serum samples for disease specific protein biomarkers (47-51).

To identify and validate PDAC specific biomarkers, we have focused our efforts on studying the secreted proteome of disease specific cells. Beyond adenocarcinoma derived cell lines, we have also looked at tumor microenvironment derived cell lines. Pancreatic stellate cells (PSCs) are one of the major supportive cells of the exocrine pancreas. PSCs become activated in response to pancreatic injury and, more importantly, in PDAC (52,53). Upon activation, PSCs proliferate, lose the ability to store vitamin A, and express α -smooth muscle actin (α -SMA) and collagen I (53,54). It

is in the activated state that PSCs play a major role in the pathogenesis of PDAC. Activated PSCs found in tumor desmoplasia that express α -SMA and collagen I are likely the major producers of the extracellular matrix seen in PDAC (54-59). We have characterized, created and SILAC labeled protein libraries consisting of the secreted proteomes of both PDAC (47) and activated PSC cell lines (60). We have demonstrated that these SILAC labeled proteomes can be used as internal standards for biomarker validation and monitoring using an innovative, multiplexed, mass spectrometry-based assay (48).

Furthermore, PSCs differentiate into tumor associated fibroblasts (TAFs), which a growing body of evidence suggests are the key drivers of stromal proliferation and chemoresistance, especially in PDAC (61). Normally, fibroblasts support healthy tissues via the secretion and remodeling of extracellular matrix. In PDAC, TAFs increase rates of proliferation, secrete proteins that activate survival, and, most importantly, promote chemoresistance (62). TAFs role in chemoresistance makes them a possible pharmacological target, which would promote greater tumor access for chemotherapy drugs by reducing surrounding stroma (63).

Cell line based xenograft

One potential solution to address many of the weaknesses of cell lines is to transplant cell lines into severe combined immunodeficient (SCID) murine models to create a cell line xenograft. These models can be made either subcutaneously or orthotopically (directly into the mouse pancreas). After injection, these xenografts recruit and synthesize their own stroma. Subcutaneous transplantation is favored for drug development by pharmaceutical companies because they are convenient, inexpensive, allow for rapid screening to assess safety and efficacy, and allow for easy assessment of tumor size. They form palpable tumor nodules within 2-6 weeks and are largely free of regulatory constraints. However, this is a less biologically faithful model. Orthotopic transplantation is clearly more reminiscent of human PDAC but this procedure is more costly and it is much more difficult to discern the response to a therapeutic agent without sacrificing the murine model (64). Xenografts have some predictive value and have helped prioritize compound testing, while showing more genetic diversity than cell lines grown as monolayers (65,66).

However, cell line based xenografts have significant weaknesses that limit their ability to predict therapeutic

responses in clinical settings. Since the murine models in xenografts have to be immunocompromised, the tumors can develop without the selective pressure that an immune system normally places on PDAC (67). This makes it impossible to research immunotherapy in xenograft models. Additionally, SCID mice are more predisposed to double strand DNA breaks, giving them greater opportunities for mutations and a less robust response to cytotoxic agents than is seen in humans (68). Further limiting their clinical appeal, xenografts select for the most aggressive cancer clones causing them to grow as homogenous masses with limited stromal infiltration even though PDAC is a majority stromal microenvironment (33). Finally, xenografts are made from a limited number of cell lines and subsequently, fail to represent the great genetic and phenotypic diversity apparent in the human disease.

Some of these limitations can be overcome via CRISPR/ Cas9 technology, which allows for the creation of syngeneic and humanized mice. Syngeneic/allograft transplant models are created by transplanting cancerous cells or solid tumors derived from the same genetic strain. This prevents transplant rejection by the host's immune system so immunocompromising the model becomes unnecessary. This allows these models to be particularly efficacious in studying immunotherapies (69,70). The primary shortcoming of syngeneic mice is that the tumor cells are rodent and therefore do not completely recapitulate human PDAC (71). Humanized mice are immunodeficient mice with IL-2 receptor gamma chain mutations, which allows for the development of human immune systems following engraftment of hematopoietic stem cells (72). These mice are now used as in vivo models to study human hematopoiesis, immunity, regeneration, stem cell function, cancer, and human-specific infectious agents without putting patients at risk (72). However, humanized murine models are still limited since they cannot fully replicate the human immune system. They have limited lymph node development, HLA superfamilies, and inappropriate immune cell trafficking (73).

These deficiencies are readily apparent when studies have assessed the clinical effectiveness of therapies shown to have efficacy in cell line xenografts. An assessment by the NCI of evidence accumulated over several decades showed only moderate predictive value and even less correlation between data obtained from xenografts and clinical efficacy (66). Several prominent examples highlight the shortcomings of cell line xenograft models in clinical drug development. In 2000, Bruns *et al.* (74) found that the EGFR inhibitor cetuximab, in combination with gemcitabine, induced an 85% regression in a cell line xenograft model. However, when tested in phase III clinical trial, this treatment was shown to be ineffective (75). Another study found that the PPAR-gamma agonists thiazolidinediones (TZDs) had antitumor activity in xenografts, which was particularly exciting since TZDs have limited toxicity and are already approved as diabetic therapy by the FDA (76). In phase II clinical trials, TZDs were a clear failure as tumors in all patients rapidly progressed during the trial (77). The literature is littered with numerous other clinical trials that have had similar outcomes (65,78-81).

There are ways to improve the efficacy of xenografts such as a standardized definition of response (82) and a larger available repertoire of cell lines. Overall though, it seems that an improved mouse model which more closely resembles the human disease is needed for effective drug discovery.

Patient-derived tumor xenograft (PDX)

The PDX model was developed to address some of these shortcomings. While similar to cell line xenografts, PDXs are made by transplanting a large piece of a patient's tumor, typically from a surgical resection specimen. One of the main advantages of PDXs is that when these surgical resections are removed, the stroma that surrounds and supports the cancer cells is transplanted as well. This allows PDXs to retain morphological characteristics of the original PDAC specimen as well as metastatic potential from the implantation site (83,84). Furthermore, the murine stroma is integrated into networks of expanding PDAC cells (85). Additionally, PDXs closely mirror responses in human patients to chemotherapeutic agents (86), possibly due to the carried over tumor stroma and replicated murine stroma (83,84,87). In fact, transcriptomic analysis of PDXs can predict the sensitivity to anticancer drugs and the clinical outcome of patients with PDAC (88). PDXs also have consistent biological properties and stable phenotypes across multiple passages (78), allowing for characterization of genetic mutations present in a specific tumor via genome sequencing and gene expression profiling, which may open up the possibility of personalized chemotherapeutic regimens (89). Our group and collaborators have shown that PDXs can be leveraged to generate and test gene expression models of chemotherapy response and resistance (90). Comparing PDXs with differential responses to chemotherapy drugs such as gemcitabine, specific genes

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and pathways can be identified and applied prospectively. In a clinical trial where such a model was applied prospectively to patient derived circulating tumor cells, survival benefit was seen in patients receiving chemotherapy regimens predicted to be effective (90).

Unfortunately, there are several drawbacks to the PDX model. Currently, successful engraftment of resected tumor specimens remains difficult and, ironically, successful engraftment may be a negative predictor of a patient's outcome after surgical resection (91). One way to increase the chances of a successful transplantation is to obtain a large amount of tissue from surgically resected patients but only 15% of PDAC patients are surgical candidates (9), and, even in that small percentage, getting enough tissue is difficult, meaning this will not benefit the majority of patients. Creating PDXs can take up to 6 months and is also prohibitively expensive since it requires generation of secondary and tertiary carriers to effectively test potential agents (92,93). Waiting 6 months is simply untenable for most PDAC patients considering median survival after diagnosis is only 6–9 months (5). Further complicating matters, PDXs, while better than cell line xenografts, may not accurately represent the heterogeneity of PDAC since it has been shown that the more aggressive phenotypes are favored to grow within the murine model (78,91). Evolution occurs with each successive clonal generation, which genetically separates the transplanted tumor from the actual PDAC (94). One study compared the expression of 15 selected genes between primary tumors and PDXs from subcutaneous injections and found that only three genes showed statistically significant co-relations (92). Finally, although PDXs have advantages when compared to cell line xenografts, PDXs still do not fully replicate stromal proliferation of PDAC or the host immune response (95).

Despite their inherent limitations, PDXs have been shown to be useful for PDAC patients that have enough surgical tissue and are projected to live longer than six months (89). PDXs actually have upwards of an 80% predictive value for therapeutic agents in qualifying patients (78). However, until surgical techniques improve, PDXs only have limited utility for PDAC and, hence other preclinical models are necessary.

Genetically engineered mouse model (GEMM)

The GEMM is a model approach that helps to mitigate many of the shortcomings seen in PDX models. These mice are created by introducing specific gene mutations in oncogenes and/or tumor-suppressor genes that are important in human PDAC, thereby recapitulating PDAC in the mouse. This was first accomplished by introducing activating mutations into KRAS, expressed in a pancreas specific manner, which resulted in ductal lesions reminiscent of PanIN, thought to represent the precancerous lesions which can evolve into PDAC (96). The most robust and well described GEMM is the KPC mouse, which incorporates mutations in the oncogenic KRAS and tumor suppressor Trp53, both driven by a pancreas-specific Cre, the Pdx1-Cre transgene, which is expressed in all cells of the pancreas from an early stage of embryonic development (97). Such autochthonous models recapitulate many of the features of the human disease and have confirmed causative roles for many mutant genes previously identified by human PDAC sequencing efforts. GEMMs have become the standard method to query the effect of a particular genetic mutation on PDAC progression. GEMMs exhibit many of the symptoms that define the human disease, such as pain and cachexia (98,99). GEMMs have been leveraged to study predisposing risk factors suspected in the human disease, such as obesity, a high calorie/high fat diet and chronic pancreatitis, all of which accelerate the development of PDAC in GEMMs (15,100). These similarities have also shown practical applications in drug discovery. For instance, the KPC model has deficient vasculature and dense stroma that decrease the delivery of anti-proliferative agents (13,26,31,32). These properties of the KPC model may explain the resistance to therapeutic agents similar to what is seen in the human disease (13). The advent of GEMMs has led to remarkable strides in our understanding of PDAC pathogenesis and provides an excellent model to investigate novel therapies. This has led to new therapeutic targets such as the autophagy, MEK, PI3K and Notch pathways (101-103). GEMMs have allowed researchers to discover the delicate balance between pro-malignant and restraining properties of the tumor stroma (34,35). Another advantage compared to xenograft models is GEMMs intact immune system, making it a useful tool to study the immune response in PDAC and to test novel immunotherapeutic compounds.

Since GEMMs such as the KPC model recapitulate the development of PDAC, progressing first through PanIN, they represent a promising tool for identifying biomarkers of early disease. Multiple proteomic studies have been performed to date, with several promising candidate biomarkers identified (104,105), although they remain to be successfully validated. With improved proteomic

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techniques and instruments now available, a repeat study of these models is warranted. More recently, glypican-1 expressing exosomes were identified in both PDAC cell lines and GEMMs, with promising results as a candidate biomarker for early detection in human blood (106). Validation of this innovative biomarker is eagerly awaited.

While the development of GEMMs was a pivotal innovation in preclinical PDAC research, significant weaknesses have been identified. GEMMs are expensive and time consuming (20). Attempting to accelerate the development process by introducing multiple genetic alterations at once comes at the cost of making GEMMs a less faithful model for sporadic, non-inherited PDAC. While the extensive stromal component increases the efficacy of preclinical therapeutic trials, the overall lack of neoplastic cellularity makes it difficult to isolate and characterize the malignant cells in murine PDAC (107). Overcoming this problem requires expensive imaging equipment that is not readily available to most labs, which makes them significantly more expensive than cell lines or xenografts. Furthermore, despite having better physiologic overlap with human PDAC than xenografts, there are still significant differences between murine and human malignancies. For instance, p53 and BRCA1 are on the same chromosome in mice, which increases the odds of concomitant deletion (68). Mice also have different telomere properties than humans, which leads to a different progression of mutations not seen in human PDAC (108). These differences between mice and humans are underscored by the failure of a promising hedgehog pathway inhibitor, initially characterized to be effective in the KPC GEMM (13), but a subsequent clinical trial did not confirm these findings. Therefore, investigating other preclinical models that can accurately predict treatment response of the human disease remains a clear and unmet need.

Organoid

As previously discussed, growing cells in two dimensional culture results in vastly different genetic expression compared to those grown in 3D (109-111). The added third dimension exponentially increases the number of cell-to-cell interactions and more closely resembles how cells organize *in vivo*. Recently, the development of innovative organoid approaches has generated great interest. Organoids are 3D structures derived from either pluripotent stem cells, neonatal tissue stem cells or adult-derived stem/ progenitor cells, in which cells spontaneously self-organize into structures that resemble the *in vivo* tissue in terms of

cellular composition and tissue function (112). Normal or malignant pancreatic ductal cells are embedded in Matrigel, which contains critical components of basement membrane, along with growth factor components such as EGF (mitogen), R-spondin-1 (enhances Wnt signalling), Noggin (inhibits BMP signalling), Wnt3a FGF10 (mitogen), nicotinamide, A83-01 (Alk inhibitor) and prostaglandin E_2 (PGE₂, mitogen).

In addition to murine derived organoids, our group has developed an approach to derive organoids from human normal and malignant pancreatic ductal cells (107). Human derived organoids can be established at a high rate from small amounts of tissue, such as a fine needle biopsy. Human derived PDAC organoids possess the mutational complexity found in the human disease, and clonal heterogeneity is maintained even after numerous passages as determined by single cell copy number analysis (personal correspondence). Human and murine derived organoids can be orthotopically transplanted into mice and recapitulate many of the features of the human disease. Unlike xenografts, organoid derived orthotopic tumors form abundant collagen deposition characteristic of PDAC in vivo and in GEMMs (13,107). Normal pancreatic cells, paraneoplastic cells, and neoplastic pancreatic cells are able to grow equally well, which is in contrast to the favored growth of neoplastic cells seen in xenografts and cell lines (113).

One main advantage of organoids is they allow the comparison of normal pancreatic cells, preneoplastic cells, and PDAC cells due to multiple cultures that are rapidly visible compared to excising specimens from murine models. They provide opportunities to observe and evaluate the disease progression unlike xenografts models that simply repopulate as malignancies in the murine pancreas. Organoids permit more thorough molecular assessment of PDAC via DNA, RNA and protein based assays (113).

Though the organoid model was only recent developed, first described in PDAC in 2015, several studies have already been published demonstrating how organoids can be leveraged to study important biological questions, such as the components of the tumor microenvironment (61), the role of neuronal signaling (114), and the role of redox regulation (115). For instance, organoid cultures have implicated particular subpopulations of TAFs located immediately adjacent to PDAC tissue that produced desmoplastic stroma (61).

Organoids can be grown from surgical resections and fine needle aspirations, which greatly expands the patient

lable 1 K	ey strengths and	weakne	sses of pancreatic aden	ocarcinoma model :	systems		
Model	Ease of growth	Cost	Microenvironment	Immune system F	Heterogeneity	Other strengths	Other weaknesses
Cell line	+++++	¢	I	I	I	Indefinite growth	Genetic homogeneity
						Rapid drug and biomarker screening	Favors more aggressive clones
Cell line	+	\$\$	+	I	I	Useful for testing drug safety/efficacy	Select for aggressive cancers
kenograft							Limited stroma
							Genetic homogeneity
atient	I	\$\$\$	+++++++++++++++++++++++++++++++++++++++	I	‡	Personalized chemotherapy regimen	Select for aggressive PDAC clones
derived cenooraft						Integrates patient and murine stroma	Difficulty with engraftment
						Retains metastatic potential	Only applicable to selected patients
						Mirror patient response to chemotherapy	Long time to grow
						Consistent biological properties	Do not fully replicate stroma
GEMM	I	\$\$\$	+++++	+++++	‡	Interrogate biology of specific gene mutations	Does not fully replicate genetic
						Useful tool for biomarker discovery	complexity of the human disease
Drganoid	++++	\$\$\$	+++++	+	+ + +	Can be orthotopically transplanted into mice	New model, requires further
						Requires small amount of tissue to derive	characterization
GEMM, g	snetically engine	sered m	ouse model.				

pool that can generate models of their PDAC compared to xenograft models. Research is currently being conducted to isolate malignant PDAC cells from patients' blood samples. This would allow the study of the unique mutations and adaptations that cause metastasis which currently remain a mystery. This would also allow for easier sampling of patient tumors without requiring fine needle assays, thus decreasing expensive and invasiveness of sampling. Organoids can also better preserve PDAC cell heterogeneity than other preclinical models by recapitulating stem cells. Possible alterations in plasticity and epigenetics that are only observed in a 3D matrix are now possible to study. Organoids can also create Pan-IN-like structures, which may lead to the development of reliable tumor markers that can detect the cancer before it can enter its rapidly invasive stages. Ultimately, organoids may allow the collection and culturing of enough patient samples to test the responsiveness of an individual patient's cancer's susceptibility to numerous chemotherapeutic and novel agents in a high-throughput fashion, similar to testing bacterial culture susceptibility to particular antibiotics. Validation for such an approach is ongoing (ClinicalTrials.gov Identifier NCT03033927). This model remains early in its characterization and further study is needed to fully understand both strengths and weaknesses of this approach.

Conclusions

We now possess a wide variety of PDAC models for studying disease and therapy, all with model-specific strengths and weaknesses (see Table 1). Choice of model should be made carefully based on purpose of the study and the question that the investigator is attempting to answer. Similarly, while reviewing results of studies utilizing each of these models, the same strengths and weaknesses should be weighed to put these studies in context. New and innovative models continue to be developed which may further move the field forward. Examples include GEMMs with inducible genetic lesions, allowing for genes, such as KRAS to be turned on and off (116), and organoid coculture models which integrate stromal and immune components (61). Expanded use of current models and those in development are likely to lead to greater understanding of disease biology, identification of clinically useful biomarkers of early disease and the development of new and more effective therapies in this challenging disease.

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Footnote

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