Review Article

Evolving trends in pancreatic cancer therapeutic development

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Abstract: Despite advances in translational research, the overall 5-year survival for pancreatic cancer remains dismal and with rising incidence pancreatic cancer is predicted to be the second leading cause of cancer death for many developed countries. Surgical intervention followed by cytotoxic chemotherapy are currently the best options for treatment, but disease recurrence is very common. Efforts to develop new therapeutic agents and delivery systems are necessary to achieve better clinical efficacy with less toxicity. Promising prospects are arising with new preclinical and clinical therapeutic strategies using small molecule targeted therapies, RNAi, stromal therapies, and immunotherapies. With a better understanding of the biology to aid target selection and discovery of biomarkers to aid precision medicine, better opportunities will evolve to shape the therapeutic landscape, enhance patient quality of life and increase overall survival.

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Introduction

Pancreatic cancer has proven to be a challenge for both clinicians and translational researchers. The combination of poor diagnostic tools, nonspecific symptoms, and late presentation in addition to the lack of targeted therapies and large tumor heterogeneity has led to pancreatic cancer's current status as the third leading cause of cancer death behind lung and colon cancer (1,2). By the year 2030, pancreatic cancer is predicted to be the second leading cause of cancer death (3). The prognosis is poor with fewer than 10% of patients alive from the disease after 5 years (1). Despite recent advances in understanding the complex nature of this disease, treatment options remain limited and more recently approved therapeutics have been rendered inefficacious. Surgical resection still provides the best chance of survival but is only possible for a small subset of pancreatic cancer patients (20%), with disease recurrence occurring in most cases. For those presenting with metastatic pancreatic cancer, toxic chemotherapy with dose-limiting side effects is the only option (4).

Pancreatic ductal adenocarcinoma (PDAC) is the most common histological type of pancreatic cancer (about 90%) and is the focus of this review (5). PDAC is an exocrine origin cancer originating in the ductal cells of the pancreas. Pancreatic cancer can also arise from other exocrine cell types like acinar cell carcinoma, pancreatoblastoma, and solid pseudo-papillary neoplasm. Additionally, neuroendocrine tumors can form in islet cells of the pancreas and are classified by the hormones produced. PDAC arises through a temporal progression of genetic mutations, therefore a better understanding of this sequential progression from noninvasive precursor lesions to malignancy may aid in more effective early diagnosis and intervention. Currently, there are three main precursor lesions, pancreatic intraepithelial neoplasms

(PanIN), intraductal papillary mucinous neoplasms (IPMN), and mucinous cystic neoplasms (MCN). With current imaging techniques, PanIN lesions are below the detection limit. IPMNs and MCNs can be detected by radiological examination, but their effective use in diagnosis is still challenging. In addition to being difficult to detect, these lesions have unique biology that may affect therapeutic outcome (6). All three exhibit a multistep progression of morphological and genetic changes that can culminate in malignancy. PanIN lesions are the most well studied and present as a stepwise progression from low-grade PanIN to high-grade PanIN with progression driven by the activation of KRAS (7).

Current therapies

Surgery is still the best treatment option for pancreatic cancer, increasing the 5-year survival rate to about 20%. Unfortunately, only 20% of patients present with surgically resectable tumors. The remaining 80% of patients have either locally advanced or metastatic disease and receive chemotherapy (2). The current standard of care for pancreatic cancer is the nucleoside analog gemcitabine, which extends survival marginally to 6 months compared to 5-fluorouracil (5-FU) (8). For metastatic disease, other common approved chemotherapeutics are nab-paclitaxel in combination with gemcitabine and the four-drug combination FOLFIRINOX (5-FU, leucovorin, irinotecan, and oxaliplatin) (9,10). This regimen is highly toxic, and should only be given to patients with a good performance score (10). Thus far, randomized trials of gemcitabine plus other chemotherapeutic agents have mostly failed to exhibit increased benefit *vs.* gemcitabine alone in the clinic (2). Nab-paclitaxel is a notable exception; with the combination improving overall survival to 8.5 months (9). Despite these improvements, the common development of chemoresistance, either as a result of growth signaling pathways or stromal factors, to gemcitabine still necessitates better therapeutic options (11). Many different treatment modalities have been evaluated over the past decades but with varying levels of success and much room for improvement (*Table 1*).

Therapeutic potential of commonly mutated genes

The majority of pancreatic cancer cases are sporadic with only 10% familial cases presented. Targeting the products of the four most commonly mutated genes in pancreatic cancer has been a pharmacological challenge. The most common genetic mutations are activating mutations in the oncogene *KRAS*, and inactivating mutations in the tumor suppressors *CDKN2A*, *TP53*, and *SMAD4* (12). The products of these genes are involved in large binding complexes and disrupting these protein-protein interactions with small molecules has been difficult to achieve clinical efficacy (13).

Kirsten rat sarcoma (KRAS) is mutated in more than 90% of PDAC cases (14). The most common KRAS mutation in PDAC is at the G12 residue to G12D (41%), G12V (34%), or G12R (16%). These mutations stabilize the GTP-bound active state, leading to persistent KRAS signaling through various effector proteins such as PI3K and RAF kinases. Constitutive KRAS signaling leads to increased cell proliferation, increased motility and invasion, and alteration of cell metabolism to sustain tumor growth (15). The importance of Ras signaling in a variety of cancer types has led to a new NCI effort to target RAS cancers by combining academic and industrial efforts in the Ras Initiative at the Frederick National Laboratory for Cancer Research (FNLCR) (https://www.cancer.gov/research/key-initiatives/ras). Recent years have shown increased efficacy of RAS inhibitors for other cancer types and some of these approaches have potential clinical benefit for pancreatic cancer patients. For example, Welsch *et al.* developed a pan-RAS inhibitor that has a low therapeutic index for PDAC but shows preclinical efficacy in breast cancer mouse models (16). Also, KRAS G12C allele-specific inhibitors have shown promise in preclinical research. Ostrem *et al.* (17) developed the first covalent inhibitor against G12C KRAS, and recently Amgen is currently recruiting for a phase 1 clinical trial for the small molecule inhibitor AMG 510 for G12C mutant solid tumors (NCT03600883). The G12C mutation is rare in pancreatic cancer cases (1%), however further investigations into allele-specific KRAS inhibitors open the possibility of a KRAS G12D inhibitor in the future (15). Another approach to target KRAS is by disrupting interactions between KRAS and KRAS effector proteins. The Reddy group developed a small molecule Ras-mimetic, rigosertib, to disrupt RAS binding interactions with its effector proteins, blocking the RAS-RAF-MEK signaling pathway. *In vitro* studies demonstrate that rigosertib treatment suppresses pancreatic cancer lesion development compared to the control, but in the clinical trial, the combination of rigosertib with gemcitabine did not show improvement compared to gemcitabine treatment alone in pancreatic cancer patients

Table 1 Summary of clinical trials in patients with pancreatic cancer

Type of therapy	Molecule	Phase	n	Population	Main result	Trial
Traditional Chemotherapy	Gemcitabine		126	Advanced pancreatic cancer	23% clinical benefit; OS: 5.6 mo	Burris *et al.*
	FOLFIRINOX	II/III	342	Metastatic pancreatic cancer	OS: 11 mo; PFS: 6.4 mo	Conroy *et al.*
	Nab-paclitaxel and Gemcitabine	III	861	Advanced pancreatic cancer	PFS:5.5 mo; OS: 8.5 mo	Von Hoff *et al.*
Platinum-based chemotherapy	PAXG	I/II	137	Stage III/IV pancreatic cancer	PFS at 6 months: 74%	Reni *et al.*
	Cisplatin + AG	Ib/II	25	Untreated metastatic PDA	CR: 2%; OS: 16.4 mo	Jameson *et al.*
SMI	Rigosertib + gemcitabine	II/III	106	Metastatic pancreatic cancer	No benefit over monotherapy	O'Neil *et al.*
	Ruxolitinib + capecitabine	III	321	Metastatic pancreatic cancer patients high CRP levels	No survival benefit	Hurwitz *et al.*
	Ibrutinib	II/III	320	Metastatic pancreatic cancer	No survival benefit	Tempero *et al.*
PARP	Olaparib + ICM	I	66	Advanced pancreatic cancer	No survival benefit	Yarchoan *et al.*
	Olaparib	III	154	Metastatic pancreatic cancer with BRCA 1/2 mutation	PFS: 7.4 months	Golan *et al.*
	Rucaparib	I	19	Advanced pancreatic cancer	ORR: 16%	Shroff *et al.*
Biological	LODER	I/IIa	15	LAPC	OS: 15.2 months	Golan *et al.*
	PEGPH2O + AG	II	279	Stage IV untreated PDA	OS: 9.2 months in HA-high tumors	Hingorani *et al.*

OS, overall survival; PAXG, cisplatin, capecitabine, gemcitabine, and nab-paclitaxel; PFS, progression-free survival; AG, nab-paclitaxel and gemcitabine; PDA, pancreatic ductal adenocarcinoma; CR, complete response; LAPC, locally advanced pancreatic cancer; ICM, irinotecan, cisplatin, and mitomycin; ORR, objective response rate; HA, hyaluronic acid; CRP, C reactive protein; mo, months.

(18,19). Recently, an RNAi approach to target KRAS led to overall survival of about 18 months in locally advanced disease in phase I/IIa studies and is currently recruiting for stage IIb studies. To prevent KRAS translation, patients are given tumoral implantation of LODER (LOcal Drug EluteR) containing siRNA for KRASG12D. Administration of oligonucleotides has many challenges including delivery and maintaining activity but using LODER *in vivo* leads to prolonged regional drug release and effective delivery and protection of the siRNA. This study is promising with a good safety profile and a prolonged clinical benefit compared to gemcitabine (20).

The cyclin-dependent kinase inhibitor 2A (*CDKN2A*) gene encodes for p16/Ink4a and p14/Arf which inhibit cyclin-dependent kinase 4/6 (CDK4/6) and activate p53 respectively. Inactivation of this tumor suppressor leads to hyperactivation of CDK4/6 and increased proliferation (21,22). Attempts have been made to restore *CDKN2A* function via pharmacological inhibition of CDK4/6 using inhibitors like palbociclib. In the context of monotherapy, CDK inhibitor treatment usually results in resistance, but preclinical studies support the combination of CDK inhibitors with platinum-based chemotherapeutic agents like cisplatin (23). Currently, a clinical trial for palbociclib with cisplatin or carboplatin is recruiting for metastatic pancreatic cancer (NCT02897375) (24). Preclinical studies in patient-derived mouse xenograft models of PDAC demonstrate retinoblastoma protein (RB) high subtype-specific activity of CDK inhibitors, suggesting RB stratification of patients may lead to better clinical efficacy of CDK inhibitors (25).

P53 is a tumor suppressor normally functioning in regulating DNA repair, senescence, and apoptosis and commonly mutated in multiple cancer types (26,27). In pancreatic cancer patients, p53 accumulation is correlated with worse overall survival, and mutated p53 has been shown to decrease the success of chemotherapy (28). Gemcitabine induced apoptosis is dependent on p53 signaling. Mutation of p53 leads to gemcitabine chemoresistance, but this can be reversed by reactivating p53 using small molecules (CP-

31398 and RITA) (29). Small molecules that reactivate p53 have been shown to induce cell death and are being investigated for clinical activity in hematological cancers. APR-246 is the first small molecule targeting p53 to enter clinical trials. This p53 reactivating molecule demonstrates a good safety profile in a phase 1 trial for refractory hematological cancer (NCT00900614) and is currently being tested in combination with various chemotherapeutics for hematological cancers, ovarian cancer, and esophageal cancer (30). The possible success of p53 reactivating molecules in solid tumors will be especially interesting as chemosensitizing agents to gemcitabine. In addition, targeting murine double minute 2 (MDM2), an E3 ubiquitin-protein ligase that mediates the degradation of p53, has been extensively explored as an alternative strategy to target the p53 pathway (31-33).

Mothers against decapentaplegic homolog 4 (*SMAD4*, also known as *DPC4*—deleted in pancreatic cancer 4) inactivation is found in half of advanced PDAC patients (34). SMAD4 is involved in the transforming growth factor-beta (TGF-β) signaling pathway. SMAD2/3/4 heterotrimeric complexes translocate into the nucleus and activate or repress transcription when TGF-β binds to its receptors. TGF-β can signal through both a SMAD4 dependent signaling pathway and act as a tumor suppressor and a SMAD4 independent signaling pathway acting as a tumor promoter (34). TGF-β signaling regulates a variety of processes like embryonic development, fibrosis, immune function, and wound healing, but the role of SMAD4 in growth arrest and apoptosis make it a tumor suppressor in PDAC by blocking mitogenic signaling (34). Once SMAD4 is deleted or inactivated, TGF-β downstream tumor suppressor signaling is lost while maintaining the SMAD4 independent tumor promoter signaling through Ras and ERK signaling (35). Due to the duality of TGF-β signaling, thus far inhibiting SMAD4 has not been a promising therapeutic approach, but high throughput screening has led to the discovery of a few lead compounds (36).

Other mutations in DNA repair and chromosomal stability genes, like *BRCA1*, *BRCA2*, *PALB2*, and *ATM*, occur in about 10% of cases but may have utility as steps are made towards precision medicine (12,37). In breast cancer, studies have shown that *BRCA1/2* and *PALB2* mutations lead to better response to platinum-based chemotherapy like cisplatin. This may benefit PDAC patients with *BRCA* mutants as this regimen is more tolerable than the FOLFIRINOX regimen (38). The four-drug regimen, cisplatin, nab-paclitaxel, capecitabine, and gemcitabine (PAXG), shows promising efficacy and safe therapeutic tolerability in stage IV PDAC patients. Compared to the nab-paclitaxel and gemcitabine combination, the PAXG regimen has a progression-free survival of 74% *vs.* 46% at six months. Additionally, the median overall survival was 14.4 months and progression-free survival was 8.3 months (39). This is comparable to an additional study evaluating the efficacy of cisplatin, gemcitabine, and nab-paclitaxel in stage IV pancreatic cancer that resulted in median overall survival of 16.5 months and progression-free survival of 10.1 months (40). Phase III clinical trials are necessary but results from multiple phase II studies suggest promise.

Additionally, these mutations may lead to sensitivity to PARP inhibitors like olaparib, veliparib, and niraparib based on preclinical studies (41). Olaparib was the first to be approved by the FDA for ovarian cancer patients with germline *BRCA* mutations who did not respond to chemotherapy in 2014, with FDA approvals for rucaparib and niraparib following in 2016 and 2017. For pancreatic cancer, there are currently five trials recruiting for studies with olaparib. Of the complete trials, those performed without patient stratification based on BRCA mutation status were less successful; olaparib treatment in combination with a trio of DNA damaging agents, irinotecan, cisplatin, and mitomycin C, resulted in high toxicity with modest efficacy (NCT01296763). From this study, there was one long term survivor with the BRCA2 mutation that experienced partial response for four years and ultimately died from acute myeloid leukemia (42). Recently, the Pancreas Cancer Olaparib Ongoing (POLO) trial has reported increased progression-free survival with olaparib in metastatic pancreatic cancer patients with germline BRCA mutations (NCT02184195). In the POLO study, patients with metastatic pancreatic cancer that did not progress during platinum-based chemotherapy received olaparib. Olaparib treatment did not exhibit a significant adverse-effect profile and extended progression-free survival compared to the placebo (7.4 *vs.* 3.8 months), and two patients in the treatment group had a complete response (43). A recent phase II study investigating rucaparib as a monotherapy in 19 patients with *BRCA1/2* mutants had an overall response rate of 16% (NCT02042378), but a larger phase II trial is currently recruiting to evaluate rucaparib in patients with mutated *BRCA1/2* or *PALB2* (NCT03140670) (44).

Development of targeted therapies

Targeted therapies have shown success in other cancer

types, for example, vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) inhibitors for lung and colorectal cancer and PI3K and CKD4/6 inhibitors for breast cancer. However, no clinically significant targeted therapy has been approved for pancreatic cancer (45,46). Erlotinib is the only FDA approved targeted therapy for pancreatic cancer. Although statistically significant, erlotinib only extends lifespan by a few weeks compared to gemcitabine alone leaving an urgent need for new targets and improved therapeutics (47). Many combinations of cytotoxic agents with gemcitabine have been studied in clinical trials, but with little success. The lack of therapeutic success in pancreatic cancer can be attributed to multiple causes, including complex and redundant signaling pathways, poor patient stratification during clinical trials, and eventual drug resistance and disease recurrence. The complex interactions between signaling pathways make single targeted therapy less likely to be effective due to the redundancy and crosstalk between different pathways. This has been a major issue with targeting downstream effectors of KRAS. MAPK kinase inhibitors and PI3K inhibitors have shown little promise, with many failures in clinical trials. The main reason for failure of these approaches is the development of alternative compensating pathways upon monotherapy targeting KRAS or KRAS effector proteins (15). For example, studies have shown that KRAS G12D addiction can be circumvented by activation of YAP1 oncogene in pancreatic cancer (48). Although targeting KRAS itself and its effector molecules has been difficult, studies looking for druggable targets in KRAS dependent tumors have led to a few possibilities, for example, the KRAS associated proteins galectin-3, Son of Sevenless (SOS), and receptor for advanced glycation end-products (RAGE).

Galectin 3, the β-galactoside-specific lectin, has multiple roles and has been implicated in metastasis in a variety of cancers (49). In pancreatic cancer, galectin-3 from cancer cells can activate pancreatic stellate cells (PSCs) in the stroma in a paracrine like mechanism leading to the production of proinflammatory cytokines via NF-kB signaling (50). Additionally, disruption of galectin-3 binding to the cell surface receptor integrin αvβ3 may contribute to KRAS addiction in both pancreatic and lung cancer. KRAS mutant pancreatic tumors in mice show decreased tumor progression upon addition of galectin 3 inhibitor GSC-100 when αvβ3 is expressed (51). Galectin-3 also has been shown to interact with Ras in PDAC cells, and knockdown of galectin-3 led to decreased Ras activity (52). Other galectin-3 inhibitors show anticancer activity in pancreatic cancer models, for example, RN1 and HH1-1. Both RN1 and HH1-1 disrupts the interaction between Gal-3 and EGFR affecting downstream signaling pathways (53,54).

SOS protein is a guanine nucleotide exchange factor converting GDP to GTP. Small molecule inhibitors of SOS1 were the first small molecule RAS binders to regulate RAS activity. SOS inhibitors have been shown to inhibit ERK phosphorylation by binding to the CDC25 domain of SOS, but further studies are needed to evaluate anti-cancer activity in PDAC models (55). RAGE has been shown to maintain KRAS signaling and high levels of NF-kB signaling leading to inflammation. RAGE inhibitors have shown reduced tumor growth in syngeneic mouse models of pancreatic suggesting the feasibility of targeting the KRAS/inflammation feed-forward loop (56).

Recent clinical trials

PEGPH20 (pegylated hyaluronidase for stromal modulation) is a promising strategy for patients with hyaluronic acid (HA) high pancreatic cancer. The idea behind this therapeutic is to modulate the stroma instead of targeting one specific part of a pathway. PEGPH20 in combination with the standard of care, gemcitabine with nab-paclitaxel, shows efficacy in Phase II trials with an increase in progression-free survival, 9.2 *vs.* 5.3 months, for patients with HA high tumors (NCT01453153) (57). This therapeutic is being investigated in phase III clinical trial (NCT02715804) currently for HA high stage IV pancreatic cancer. Double the patients in the treatment group had thromboembolic events compared to the control, which was a major concern from the phase II trial. After adding enoxaparin prophylaxis to both arms of the study, thromboembolic events were reduced to an insignificant difference. An additional concern is musculoskeletal events. The administration of dexamethasone was shown to reduce the severity of this event (57). Preclinical studies suggest that degradation of HA leads to a decrease in interstitial tumor pressure allowing for chemotherapeutics to distribute throughout the tumor more effectively (58). PEGPH20 breaks down HA crosslinking in the extracellular matrix. Given the success *in vitro* and in clinical trials thus far, hyaluronan may be a necessary component to sustain a protumorigenic microenvironment. Targeting other ECM components may enhance current chemotherapeutics by remodeling the tumor microenvironment.

The use of JAK/STAT pathway inhibitors shows a marginal improvement in overall survival across all patients. JAK/STAT signaling is an important modulator of inflammation and immunity. A subset of patients with above median C-reactive protein (CRP) levels receiving ruxolitinib and capecitabine showed an almost two-fold increase in overall survival (59). This is in agreement with a previous clinical trial (CALGB80303) that investigated the role of inflammation in patients with metastatic pancreatic cancer. The phase III study of gemcitabine and bevacizumab suggested that CRP and albumin levels have prognostic value in pancreatic cancer (60). Phase III studies of the JAK1/JAK2 inhibitor ruxolitinib, unfortunately, did not show improved clinical outcomes for patients with advanced/metastatic pancreatic cancer, even in groups with high CRP (61).

Bruton's tyrosine kinase (BTK) is a non-receptor tyrosine kinase critical for B lymphocyte signaling. BTK also is important for macrophage functioning, acting as a node for innate and adaptive immunity (62). The BTK inhibitor ibrutinib is an anticancer drug primarily used for lymphoma but is currently being tested in the clinic for pancreatic cancer (63). Preclinical studies in mouse models suggest that treatment with ibrutinib may modulate the tumor microenvironment, making it less immune suppressive. BTK along with PI3Kγ regulate immune suppression via B cells and macrophages to mobilize CD8+ cells in pancreatic cancer models. Ibrutinib reprogramming of B cells leads to an increase in CD8+ T cells and suppressed tumor growth (64). Clinical trial results have not been released, but it is believed that ibrutinib acts by converting a Th2 response to a Th1 response, which will be important in the context of immunotherapy and its potential efficacy in pancreatic cancer (63,65). It is important to keep in mind that BTK inhibition via ibrutinib has off-target effects with many other kinases and has been shown to have cytotoxic cancer affects in BTK independent tumors (66).

Transcriptional coactivators and nuclear receptors

Targeting transcriptional coactivators is a viable therapeutic approach currently in the preclinical stage. Through protein-protein interactions, transcriptional coactivators activate oncogenic signaling via multiple effector proteins. Inhibition of transcriptional regulators has shown anti-cancer activity in multiple cancer types (67). Transcriptional coactivators implicated in pancreatic cancer include SRC-3, MTA1, and YAP and exhibit *in vitro* and *in vivo* anti-cancer activity in models of pancreatic cancer upon depletion.

Steroid coactivators act as a signaling hub and canonically signal through nuclear receptors (68). Many nuclear receptors like EGFR, IGF-1R, and MUC1 are implicated in pancreatic cancer disease progression (69). Nuclear receptor functioning is dependent upon coregulator recruitment leading to either enhanced transcription in the presence of coactivators or repressed transcription in the presence of corepressors (70). Coregulators can modify chromatin via changing acetylation and methylation states, performing chromatin remodeling, and recruiting other enzymes to form protein complexes. The Steroid Receptor Coactivator family includes SRC-1, SRC-2, and SRC-3 and has been shown to regulate metabolism and oncogenic signaling. SRC-3 is a scaffold protein bringing together nuclear receptors and other coregulators to form transcriptional complexes (71). SRC-3 levels are increased with the progression of PDAC, low in healthy pancreatic tissue, medium in PanIN lesions, and high in metastatic PDAC (72). SRC-3 also has nuclear receptor independent roles and some of these functions in other cancers include cell cycle, tumorigenesis, apoptosis, and invasion and migration (73).

SRC-3 has been well studied in endocrine cancers, for example breast cancer, but its role in pancreatic cancer is not well understood. Microarray data suggests knockdown of SRC-3 influences AKT, P38 MAPK, ERK1/2, ubiquitin C, and NF-kB signaling affecting a variety of cellular functions. In addition to this SRC-3 has been shown to induce a pro-inflammatory microenvironment via the stabilization of mucins, MUC1 and MUC4, in pancreatic cancer (74). Inhibiting SRC-3 with small molecule bufalin displays anti-tumor activity in an orthotopic mouse model of pancreatic cancer but exhibits cardiotoxicity in humans decreasing its usefulness in the clinic (75). Since the discovery of bufalin as a small molecule inhibitor of SRC-3, the small molecule inhibitor SI-2 and small molecule stimulator MCB-613 have been optimized through medicinal chemistry and exhibit anti-cancer activity in breast cancer. In breast cancer cells, SI-2 has low nanomolar activity. Also in an orthotopic breast cancer mouse model, SI-2 administration inhibits tumor growth (76). Additionally, pan-SRC overstimulation inhibits tumor growth by inducing ER stress and ROS production (77).

Metastasis-associated protein (MTA1) can act as both a corepressor and coactivator depending on whether it is acting with or independently of nucleosome remodeling and deacetylation (NurD) complex components. MTA1 is a known oncogene, overexpressed in many cancers. Recent

studies found that MTA1 activates HIF-α and VEGF signaling in pancreatic cancer metastasis (78). High levels of MTA1 are found in samples having increased lymph node metastasis and worse survival (79). The antioxidant pterostilbene has been shown to inhibit pancreatic cancer cell growth *in vitro* and *in vivo* (80). Also, studies in hepatocellular carcinoma suggest the anti-cancer activity of pterostilbene is due to destabilization of the MTA1-NuRD complex (81). Additionally, the coactivating activity of MTA1 with E2F1, which results in increased HA production and reduced infiltration of macrophages, can also be targeted with small molecule argatroban (82).

Yes-associated protein (YAP) is a transcriptional coregulator that acts as an effector in Hippo signaling via the TEAD transcription factor during embryonic development of the pancreas (83). In pancreatic cancer, YAP is overexpressed in patient tissue samples compared to normal tissue and high YAP levels correlate with poor survival (84). *In vitro* studies suggest that YAP signaling results in pancreatic cancer invasion and metastasis and promotes desmoplasia (85,86). A novel YAP inhibitor shows preclinical efficacy in esophageal cancer, and multiple independent studies have suggested statins can interfere with YAP activity in PDAC models (87,88). The FDA approved photosensitizing agent verteporfin has tumoricidal activity in pancreatic cancer by disrupting the YAP-TEAD complex, but other studies suggest verteporfins activity is not YAP selective and has anticancer activity independent of YAP signaling (89,90). Further experimental and preclinical studies investigating transcriptional coregulators as pancreatic cancer therapeutics are warranted before clinical trials are proposed, but studies in recent years suggest targeting transcriptional coregulators as a valid approach.

Tumor microenvironment in PDAC also reduces therapeutic efficacy

In addition to its varied genetic background, the tumor microenvironment in pancreatic cancer adds another level of complexity and heterogeneity. Complex interactions occurring between pancreatic cancer cells, endothelial cells, and immune cells in the stroma have presented barriers in therapeutic design and delivery unique to this cancer type. Pancreatic tumors seem to have an innate resistance, compared to the acquired resistance occurring against independent breast cancer therapies, to radiation and chemotherapy in part due to the stroma and its unique biophysical attributes (91). For example, microenvironment components like hyaluronan have been shown to lead to poor vascularization which then leads to poor drug delivery (92). Additionally, fibronectin secreted from PSCs has been shown to induce resistance to gemcitabine by inducing ERK1/2 activity (93).

Stromal cells can play both a protumorigenic role or an antitumorigenic role in a context dependent manner (94). Stromal components can promote tumor proliferation and migration. These components include a variety of cell types likes PSCs, leukocytes, and endothelial cells, along with extracellular matrix components like HA and collagen. PSCs are the major source of cancer-associated fibroblasts (CAFs). In the normal pancreas, these PSCs are quiescent but can be activated into CAFs (aka as activated PSCs or aPSCs) by tumor secreted factors such as platelet-derived growth factor (PDGF), TGF-β, TNF-α, macrophage inhibitory factor (MIF), IL-1, IL-6, IL-8, IL-10. Upon activation of PSCs, the secretion profile changes into a pro proliferation, inflammation, motility, invasion phenotype (95,96).

Ras mutations play a multifactorial role in PDAC and also have been shown to promote dense stromal desmoplasia via paracrine signals. If mutated KRAS is switched to unmutated KRAS using genetic approaches, the desmoplasia proliferation rate slows down after a few days (97). Desmoplasia is the proliferation of fibroblasts surrounding epithelial cells and this complex reaction involves multiple cells types in the microenvironment including leukocytes, fibroblasts, endothelial cells, and ECM components like collagen and hyaluronan. Many clinical trials have been conducted to address stromal implications of pancreatic cancer and disease progression (98). Targeting the stroma may facilitate the delivery of other therapeutics in combination by decreasing desmoplasia and increasing vascularity. The most promising stromal target is hyaluronan. Other attempts include targeting the sonic hedgehog pathway, matrix metalloproteases, and VEGF but with little success over gemcitabine treatment.

Sonic hedgehog (SHH) signaling activates stromal fibroblasts in cancer cells aiding in high levels of desmoplasia. Attempts to target Smoothened signaling downstream of SHH have resulted in multiple stopped or unsuccessful clinical trials (99). Follow-up studies investigating the lack of success demonstrate that genetic knockout or inhibition of smoothened leads to increased epithelial-mesenchymal transition, metastasis, and morbidity in mouse models (94). This suggests there is a balance between too much and too little when it comes

to stromal elements in pancreatic cancer. SHH inhibitors have been tested in clinical trials but with little success. Modulation of SHH signaling and co-administration with cytotoxic agents may still be useful therapeutically but will require a fine balance to be useful clinically. MMP inhibitors have also not been successful in clinical trials with tanomastat performing worse than gemcitabine and newer analogs showing musculoskeletal toxicity (100). Knockdown studies in mouse models also show that the absence of MMP-9 leads to PDAC progression and metastasis (101). VEGF inhibitors, for example bevacizumab, target angiogenesis but also show no advantage over gemcitabine in phase 3 clinical trials (102).

Immune therapy has gained increased interest after the success of checkpoint inhibitors in melanomas, but as a monotherapy has proven ineffective in pancreatic cancer. The immunosuppressive microenvironment is the basis of resistance to immune therapies in pancreatic cancer (103,104). Pancreatic tumors are classified as "non-inflamed" or immune cold, lacking T cell infiltration (105). A major contributor to this is stromal secreted factors that recruit immunosuppressive cells like regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages (106). T cell recruitment to the tumor and tumor cell recognition and killing by tumor-infiltrating lymphocytes are necessary for effective antitumoral immune response. To overcome these challenges, efforts are being made to combine checkpoint inhibitors with agents that increase tumor immunogenicity allowing the recruitment and activation of effector T cells (103).

Metabolism

Generating energy to maintain uncontrolled cell proliferation by metabolic reprogramming is a hallmark of cancer (107). Normal cells metabolize glucose to enter the tricarboxylic acid cycle and produce ATP via oxidative phosphorylation. Cancer cells, in addition to meeting energy needs via ATP, must also produce the building blocks for the synthesis of proteins, nucleic acids, and lipids to match their proliferation rates.

Oncogenic *KRAS* expression is the most commonly mutated gene in PDAC and is also pivotal to metabolic reprogramming. Thus far KRAS has been a difficult drug target, but there may be therapeutic benefit in targeting its role in metabolism. In PDAC mouse models, KRAS activation leads to increased glucose uptake and subsequent glycolysis, increased hexosamine biosynthesis for glycosylation, and increased nonoxidative pentose phosphate synthesis for ribose synthesis (108). Additionally, KRAS G12D mutations are necessary to recycle building blocks necessary to sustain tumor growth. Autophagy and micropinocytosis are dependent upon KRAS activation and these processes allow for increased uptake of metabolites. Additionally, KRAS mutations lead to increased glucose uptake via upregulation of GLUT1 and subsequent flux through the non-oxidative arm of the pentose phosphate pathway to generate nucleotide precursors (109).

An additional difference between cancer metabolism and normal metabolism is through ion transport. Metal ions like zinc are used by metalloenzymes and transcription factors. The Li group has identified a key role of zinc transporter (ZIP4) in mediating pancreatic tumor growth, signaling transduction and metabolism. *In vivo* studies have demonstrated that overexpression of ZIP4 increases tumor volume (110). Additional studies show that genetic knockdown of ZIP4 inhibited pancreatic cancer invasion and migration *in vivo* by modulating known regulators of cell migration and invasion (111). Further studies are needed, but ZIP4 may be a potential target for the development of either small molecule based or RNAi based therapeutics (112).

Using metabolite profiling, in conjunction with other omics based methods, a few different stratifications have been proposed. Pancreatic cancer exhibits both large intratumoral (within the same tumor) and intertumoral (between patients) heterogeneity. Intratumor heterogeneity between histological samples shows a large difference in transcriptional profile (more than 1,000 genes) between tumor center and periphery (113). Despite this, tumor subtyping based on DNA, RNA, and metabolite profiling has been attempted but with little overlap between the studies (114). Transcriptome studies based on RNA signature have proposed 3 subtypes: quasi-mesenchymal, exocrine-like, and classical subtype from most aggressive to least aggressive (115). The metabolite profiling is divided into three subtypes: a slow-growing subtype, a glycolytic subtype with quasi-mesenchymal phenotype, and a lipogenic subtype with the classical phenotype (116). Metabolite profiling performed in PDAC cell lines may correlate with RNA based subtyping in tumors with advances in tumor metabolomics in the future. Metabolic clustering in PDAC cell lines identified profiles associated with glycolysis dependent, lipogenesis dependent, and redox dependent pathways. Based on the metabolic signature, cancer cell lines were either more or less sensitive to aerobic glycolysis inhibitors (116).

Conclusions

Pancreatic cancer is a challenging disease to treat and continued progress in understanding this disease is imperative. As the focus shifts to more personalized medicine, the current understanding of this disease must be used to stratify patients in clinical trials. Better design in clinical trials is also important. Patient stratification based on molecular/biomarker strategies only occurs in 8.6% of new study protocols registered between 2015–2018 (117). There is also the possibility that due to poor stratification of patients in the original planning of clinical trials, a therapeutic that is responsive in one or a few patients may be seen as an anecdote instead of having a true clinical benefit (118). Drugs targeted to specific subtypes may not improve general patient outcome but may greatly improve the outcome of patients with that particular tumor type. Also, immunotherapy is showing increased potential in other solid tumors and may be a promising approach for pancreatic cancer in the future (119,120). Pancreatic cancer cells secrete immunosuppressive factors to escape immune surveillance as recently reviewed by Neoptolemos and others (121). Early detection techniques also are imperative. The stepwise progression from low-grade PanIN (expressing MUC5 and harboring mutations in KRAS/CDKN2A) to high-grade PanIN (expressing MUC1 and mutant p53/SMAD4) is driven by the activation of KRAS. The window of opportunity is large with some studies analyzing the genetic evolution of disease suggesting at least 15 years between the initiating mutation and metastatic ability (122). With a better understanding of the disease, the translation into efficacious clinical trials is attainable.

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