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TOPIC HIGHLIGHT

2016 Pancreatic Cancer: Global view

Molecular targets for the treatment of pancreatic cancer: Clinical and experimental studies

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Abstract

Pancreatic cancer is the fourth most common cause of cancer deaths worldwide. Although recent therapeutic developments for patients with pancreatic cancer have provided survival benefits, the outcomes for patients with pancreatic cancer remain unsatisfactory. Molecularly targeted cancer therapy has advanced in the past decade with the use of a number of pathways as candidates of therapeutic targets. This review summarizes the molecular features of this refractory disease while focusing on the recent clinical and experimental findings on pancreatic cancer. It also discusses the data supporting current standard clinical outcomes, and offers conclusions that may improve the management of pancreatic cancer in the future.

Key words: Pancreatic cancer; Targeted therapy; Tyrosine kinase inhibitors; Microenvironment; Cancer stem cell

Core tip: Pancreatic cancer-related mortality is almost consistently caused by local recurrence and metastasis. The survival of patients after surgical resection remains poor, and the results of adjuvant chemotherapy and radiotherapy are still unsatisfactory. Therefore, new treatments are urgently needed. Recent developments in our knowledge of the underlying biological features of pancreatic cancer may be useful in establishing molecularly targeted therapy as a new strategy, similar to those used to treat other types of malignancies.

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INTRODUCTION

Pancreatic cancer is the fourth most common cause of cancer deaths, resulting in 330000 deaths per year worldwide[1]. Many patients with pancreatic cancer are diagnosed at advanced incurable stages because of the absence of screening. Although advances in a variety of approaches have improved the management of pancreatic cancer, the 5-year survival rate remains lower than 5%[1]. Surgical resection is currently the only potentially curative treatment. However, even after resection, the 5-year survival rate is less than 20% due to the high frequency of distal metastasis and local recurrence[2].

The treatment of inoperable pancreatic cancer has traditionally involved the use of gemcitabine with low response rates and a marginal survival benefit. The failure of clinical treatment in patients with pancreatic cancer is often due to the heterogeneous nature of the disease. This type of tumor involves not only cancer cells, but stellate cells and stroma, which were known as microenvironment. Stromal proliferation and reduced angiogenesis have been shown to contribute to therapeutic resistance despite the efficacy in experimental studies utilizing cell lines or animal models. A recent European study found that the combination chemotherapy of FOLFORINOX and gemcitabine is more effective than the use of gemcitabine alone. Albumin-bound paclitaxel (nab-paclitaxel), which was approved by the FDA in 2013, can also be used in conjunction with gemcitabine to treat pancreatic cancer[3]. However, in most patients with advanced stages of the disease, these treatments only prolong survival by a few months, while combination therapy can also lead to significantly increased toxicity[4]. The development of effective pancreatic cancer treatments is urgently needed to overcome these obstacles.

To date, knowledge of the molecular basis of tumor initiation has led to the use of various kinds of targeting agents to produce better prognoses for some types of solid tumors. These agents, including those targeting the angiogenesis pathways, the epidermal growth factor receptor (EGFR), the mitogen-activated ERK kinase (MEK), the fibroblast growth factor receptor (FGFR), the phosphatidylinositol-3 kinase/protein kinase-B/mammalian target of rapamycin (PI3K/mTOR), and the cancer stem cell compartment, may lead to significant advancements in pancreatic cancer treatment. In this study, we will review the current clinical and experimental results regarding molecular targets for the treatment of pancreatic cancer, and discuss potential future treatments.

GENE ALTERATION AND MOLECULAR PATHOLOGY OF PANCREATIC CANCER

Recent studies have shown that pancreatic cancers include an average of 63 genetic alterations[5]. Therefore, in order to develop effective treatments for pancreatic cancer, the complicated gene alterations and pathological features of this tumor type need to be elucidated. The molecular analysis of pancreatic cancer has often shown the involvement of known cancer genes and traditional cancer signaling pathways. The *KRAS* gene, which encodes a small GTPase that regulates the downstream signaling of growth factor receptors, is a known mutated oncogene found in most pancreatic cancers at advanced stages[6]. Missense mutations in the *KRAS* cluster have been found in specific hotspots (most generally codon 12)[7]. Recent studies have demonstrated that KRAS mutations are one of the earliest genetic events seen in human pancreatic intraepithelial neoplasia (PanIN) progression[8,9]. In addition to *KRAS* mutations, alterations in tumor suppressor genes such as *INK4A*, *BRCA2*, and *LKB1* occur frequently in pancreatic cancer. The tumor suppressor gene, *P16/CDKN2A*, which encodes a critical cell cycle regulator, is inactivated in > 90% of pancreatic cancer[10]. Mutation of the p53 gene is closely associated with cellular responses to cytotoxic stress by contributing to both cell cycle arrest and cell apoptosis[11]. Mutations in p53 are also common in pancreatic cancer, as these have been reported in approximately 75% of patients and most frequently characterized by small intragenic mutations coupled with a loss of heterozygosity[5]. The missense mutation of SMAD4, a tumor suppressor gene that encodes the transforming growth factor beta (TGFβ) signaling pathway, is found in approximately 55% of patients with pancreatic cancer[12]. Mutations in SMAD4 are associated with a poorer prognosis and widespread metastases, which suggests potential clinical implications[13]. The mismatch repair gene, *MLH1*, and the cationic trypsinogen gene, *PRSS1*, are also often mutated in pancreatic cancer[14]. Based on the typical age of onset related to the aforementioned mutations, these genetic lesions are thought to impact malignant progression rather than cancer initiation.

Some pancreatic cancers harbor activating mutations of BRAF rather than KRAS[15]. BRAF encodes RAF, a serine/threonine kinase belonging to a family of MEK (Figure 1A). MEK activates ERK, which forms the MAPK signaling pathway. Thus, active mutations of KRAS and BRAF eventually result in triggering the MAPK signaling, which is critical for the development of pancreatic cancer. Activation of the MAPK pathway is found not only in benign lesions, but also in late-stage pancreatic cancer[16]. Overexpressed MAPK through a constitutively active form of RAF results in PanIN/pancreatic ductal adenocarcinoma formation; conversely, the silencing of MAPK signaling inhibits tumor initiation[17,18]. PI3K signaling is another important pathway that has been studied in great detail in pancreatic cancer along with the MAPK pathway. The PI3K signaling mediates cell growth

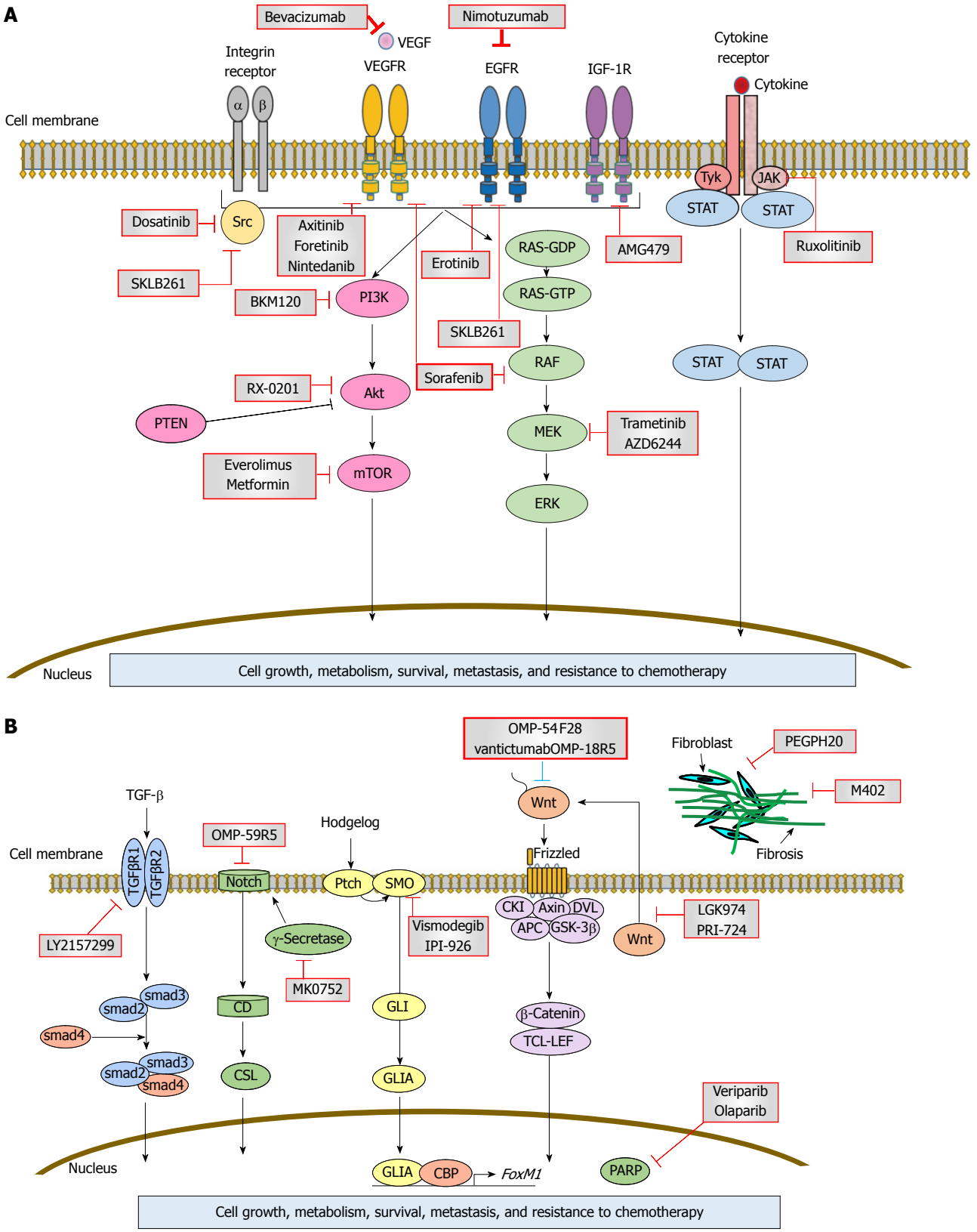

Figure 1 Signaling cascade (A) and therapeutic inhibitor (B) in pancreatic cancer. Black circles indicated the critical signaling for the development of pancreas cancer. Red squares indicated the molecularly targeted agents for the treatment of pancreatic cancer. Adapted from Matsuoka T *et al*.

and survival *via* several downstream substrates such as Akt, p70-S6K, and mTOR (Figure 1A). Similar to the MAPK pathway, the consistent activation of PI3K has been shown to be closely associated with the carcinogenesis of pancreatic cancer[19]. The PI3K downstream effector, *Akt*, is amplified in 10%-20% of pancreatic cancers, providing genetic evidence to support the importance of this pathway in this

type of cancer[20]. Several growth factor receptors, including vascular endothelial growth factor (VEGF) and insulin-like growth factor 1 receptor (IGF1R), are aberrantly expressed in pancreatic cancer[21]. These pathways mediate the important genes involved in a variety of cellular functions such as growth, apoptosis, differentiation, and metastasis *via* these two pathways (Figure 1A).

MOLECULARLY TARGETED AGENTS FOR PANCREATIC CANCER TREATMENT

Within the last decade, numerous targeted agents have been examined individually or in combination with cytotoxic agents for the treatment of pancreatic cancer. The growth stimulating signaling described above has been targeted by molecular therapies for many kinds of cancer. Taken together, a number of paracrine signaling pathways, such as Hedgehog, Wnt, Notch, and TGFβ, might also contribute to cancer stem cell signaling and tumorigenesis (Figure 1B)[22]. These characteristics of pancreatic cancer may contribute to the development of molecularly targeted therapies. Figure 1 schematically summarizes the current understanding of inhibitors in pancreatic cancer. Table 1 summarizes clinical trials using molecular targeting agents.

Signaling pathway

Angiogenesis pathway: Angiogenesis is crucial for the growth of malignancies. Anti-angiogenic therapies have shown efficacy in renal cell carcinoma, colorectal cancer, lung cancer, glioblastoma, and ovarian epithelial cancers[23]. VEGF is one of the key factors of angiogenesis that promotes tumor growth and metastasis[24]. VEGF is overexpressed in over 90% of patients with pancreatic cancer[25], thus providing justification for VEGF-targeted therapy for pancreatic cancer. In contrast, a randomized phase Ⅲ trial (CALGB 80303) found no improvements in the survival of patients who were given a combination of bevacizumab, which is a monoclonal antibody to VEGF, and gemcitabine, compared to the results of those treated with gemcitabine and a placebo, despite promising outcomes in phase Ⅱ[26]. Taken together, efforts to use targeted agents such as sorafenib and axitinib have been unfavorable[27-29]. A phase Ⅱ trial using TL-118, a novel anti-angiogenic drug, combined with gemcitabine to treat metastatic pancreatic cancer (NCT01509911) is currently ongoing (Table 1). Foretinib was developed as an ATP-binding site competitor to inhibit receptor tyrosine kinases with reported activity against VEGFRs, RON, c-Met, c-KIT, FLT-3, and platelet-derived growth factor receptors (PDGFRs)[30]. Mounting evidence has indicated that foretinib targets multi-additional kinases, resulting in the growth inhibition of tumors. Since hepatocyte growth factor (HGF) and c-MET are frequently overexpressed in pancreatic cancer[31], targeting these pathways has attracted much attention. A recent study concluded that foretinib inhibits tumor growth, angiogenesis, and lymphangiogenesis in xenograft animals by inhibiting not only c-MET but VEGFR-2, VEGFR-3, and TIE-2 signaling as well. These results suggest that simultaneous inhibitory effects to reduce pancreatic tumor growth can be expected from multikinase inhibition[32].

EGFR pathway: EGFR, a transmembrane tyrosine kinase receptor of the ErbB family, plays an important role in tumor cell behavior. Aberrant EGFR activity leads to receptor dimerization and subsequently activates downstream signals, including members of the RAS and PI3K/Akt/mTOR pathways[33]. Overexpression of this growth factor receptor is seen in over 90% of pancreatic cancers[34]. Sustained EGFR activation has been reported in pancreatic cancer cell lines, and EGFR inhibitors have been found to lead to decreased proliferation[35]. Thus, EGFR pathway activation seems to provide a rationale for EGFR-targeted inhibition strategies. However, clinical trials using the anti-EGFR and anti-Erbb2 antibodies have yielded negative results[36,37]. In contrast, a large randomized phase Ⅲ in which patients with pancreatic cancer were assigned to receive gemcitabine with or without erlotinib[38] reported that the patients who received the combination treatment had a modest but statistically significant improvement in overall median survival (OS) (P = 0.038) and progression-free survival (P = 0.004). The data from a subset analysis of this trial failed to indicate whether the KRAS mutation status or EGFR was a predictive marker for the therapeutic response to erlotinib[39]. Even though the median OS was only prolonged by 2 wk, this trial is remarkable because it is the only one to have shown an improvement in survival outcomes with combination gemcitabine/erlotinib in metastatic pancreatic cancer. On the other hand, the oncogenic benefit of erlotinib should be balanced with its potential complications, some of which have been reported to be fatal[40]. Another EGFR monoclonal antibody, nimotuzumab, achieved survival benefits when added to gemcitabine (8.7 mo *vs* 6.1 mo) with tolerable toxicity in a recent phase Ⅱ trial involving patients with locally advanced pancreatic cancer (*J Clin Oncol* 2013;31:abstr 4009). Clinical trials to evaluate the effects of nimotuzumab combined with gemcitabine are ongoing in patients with the RAS wild type of locally advanced or metastatic pancreatic cancer (NCT 02395016).

IGF1R pathway: IGF1R belongs to the insulin receptor family. IGFR1 signaling is highly expressed in pancreatic cancer, and this activation leads to a signaling cascade that triggers pathways such as ERK and PI3K/Akt/mTOR. It also plays a role in cancer survival and proliferation through RAS-dependent and -independent pathways. Inhibition of IGF1R signaling

Table 1 Current clinical trials for pancreatic cancer

Target molecule	ClinicalTrials.gov identifier	Sponsor	Agent	Treatment setting	Study phase	Comments
EGFR	NCT00561990	Oncoscience AG	Nimotuzumab	First line	Ⅱ / Ⅲ	GEM ± nimotuzumab
	NCT02395016	Biotech Pharmaceutical	Nimotuzumab	First line	Ⅲ	GEM ± nimotuzumab
MEK	NCT01222689	National Cancer Institute	selumetinib	First line	Ⅱ	Selumetinib + erlotinib
PI3K	NCT01571024	UNC Lineberger Comprehensive Cancer Center	BKM120	First line	Ⅰ	BKM120 + mFOLFOX6
Akt	NCT01028495	Rexahn Pharmaceuticals	RX-0201	First line	Ⅱ	RX0201 + GEM
mTOR	NCT00981162	Roswell Park Cancer Institute	Everolimus	Second line	Ⅰ / Ⅱ	Everolimus + sorefenib
Angiogenesis	NCT01509911	Tiltan Pharma Ltd	TL-118	First line	Ⅱ	TL-118 + GEM
Src	FOLFOX-D, NCT01652976	University of Florida	Dasatinib	First line	Ⅱ	5-Fluorouracil + leucovorin + oxaliplatin + dasatinib
Jak	NCT01423604	Incyte Corporation	Ruxolitinib	Second line	Ⅱ	Ruxolitinib + capecitabine
	NCT01822756	Incyte Corporation	Ruxolitinib	First line	Ⅰ	Ruxolitinib + gemcitabine or nab-paclitaxel
Notch	NCT01098344	Cancer Research UK	MK0752	First line	Ⅰ	MK0752 + GEM
Hedgehog	NCT01130142	Infinity Pharmaceuticals, Inc.	IPI-926	First line	Ⅰ / Ⅱ	IPI-926 + GEM
Wnt	NCT01351103	Novartis Pharmaceutical	LGK974	First line	Ⅰ	LGK974 alone
	NCT01302405	Prism Pharma Co., Ltd.	PRI-724	First line	Ⅰ	PRI-724 alone
	NCT02050178	OncoMed Pharmaceuticals, Inc	OMP-54F28	First line	Ⅰ	GEM + nab-paclitaxel + OMP-54F28
	NCT02005315	OncoMed Pharmaceuticals, Inc	Vantictumab (OMP-18R5)	First line	Ⅰ	GEM + nab-paclitaxel + vantictumab
Stroma	Halo-109-202, NCT01839487	Halozyme Therapeutics	PEGPH20 (hyaluronidase)	First line	Ⅱ	GEM + nab-paclitaxel ± PEGPH20
	S1313, NCT01959139	Southwest Oncology Group	PEGPH20	First line	Ⅰ / Ⅱ	FOLFIRINOX ± PEGPH20
PARP	NCT01585805	National Cancer Institute	Veriparib	First line	Ⅱ	GEM + cisplatin ± veriparib
	NCT01296763	Sidney Kimmel Comprehensive Cancer Center	Olaparib	First line	Ⅰ / Ⅱ	Irinotecan + cisplatin + mitomycin C ± olaparib
Others	NCT01210911	Academisch Medisch Centrum	Metformin	First line	Ⅱ	Erlotinib + metformin + GEM
	NCT01373164	Eli Lilly and Company	LY2157299 (TGF-b inhibitor)	First line	Ⅱ	LY2157299 + GEM
	NCT01621243	Momenta Pharmaceuticals, Inc	M402 (heparan sulfate)	First line	Ⅰ / Ⅱ	GEM + nab-paclitaxel ±M402
	NCT01783171	National Cancer Institute (NCI)	Dinaciclib	First line	Ⅰ	Dinaciclib + MK-226

GEM: Gemcitabine.

enhances the cytotoxicity of gemcitabine in pancreatic cancer xenografts[41]. However, the IGF1R inhibitor, AMG-479, and the monoclonal antibody, cixutumumab, failed to provide any survival benefits in a previous study (NCT01231347) (*J Clin Oncol* 2012;30:abstr 198). Meanwhile, the use of IGF1R in conjunction with ErbB would appear to be a good strategy for overcoming the chemoresistance common in pancreatic cancer. A previous study demonstrated that the simultaneous blockade of IGF1R and EGFR/Her-2 synergistically inhibits the pancreatic tumor growth and completely abolishes the activation of IRS-1, Akt, and MAPK phosphorylation. These results suggest that the combined application of these two inhibitors averts the resistance associated with monotherapy[42].

RAS pathway: The RAS/RAF/MEK/ERK (MAPK) pathway is activated by numerous growth signals *via* their receptors, including EGFR, and is crucial in mediating uncontrolled growth and survival[43]. As previously discussed, MAPK plays a crucial role in the development of pancreatic cancer. Although trametinib, a MEK inhibitor, is currently approved for the treatment of melanoma, this drug has failed to show survival benefit when combined with gemcitabine in advanced pancreatic cancer (*J Clin Oncol* 2013;31:abstr 291). A phase Ⅱ trial of another MEK inhibitor, AZD6244, in combination with erlotinib as a second line treatment of advanced pancreatic cancer is currently underway (NCT01222689).

PI3K/Akt/mTOR pathway: Upon activation by RAS or EGFR, PI3K activates Akt, which subsequently triggers multiple downstream targets such as mTOR, leading to the regulation of many essential cellular processes, including cell growth, metabolism, survival, metastasis, and resistance to chemotherapy[44]. The PI3K-Akt pathway is activated in 59% of patients with pancreatic cancer[45]. Deregulation of this pathway through absent or reduced expression of PTEN (phosphatase and tensin homolog, a natural antagonist of PI3K) is frequently found in pancreatic cancer[46]. A phase Ⅱ trial is currently testing the combination of an Akt antisense oligonucleotide, RX-0201, with gemcitabine in metastatic pancreatic cancer (NCT01028495). A phase I study of BKM120, a pan-class 1A PI3K inhibitor, with mFOLFOX6 in patients with metastatic pancreatic cancer is also now

recruiting (NCT01571024). Everolimus, an mTOR inhibitor, has shown antitumor activities, including the inhibition of cell proliferation, apoptosis, and angiogenesis, and displayed synergistic effects when combined with other anticancer agents[47]. A phase Ⅱ study was conducted to explore treatment activity of the combination of capecitabine with everolimus in patients with advanced pancreatic cancer. The results revealed a response rate (RR) of 6.5% and an OS of 8.9 mo, suggesting that this combination therapy might enhance the efficacy of capecitabine[48]. Sorafenib, a multikinase inhibitor targeting Raf-1, BRaf, VEGFR1, VEGFR2, VEGFR3, and PDGFRβ, has been confirmed to be efficacious against advanced hepatocellular carcinoma[49]. It acts by inhibiting Raf-1 and BRaf as well as the activities of VEGFR1, VEGFR2, VEGFR3, and PDGFRβ. A phase Ⅰ/Ⅱ combination trial of sorafenib and everolimus in advanced pancreatic cancer has been completed, but the results have yet to be released (NCT00981162). Metformin, an antidiabetic drug that has direct metabolic effects through the activation of adenosine monophosphate-activated protein kinases, can inhibit the mTOR pathway by activating the tumor suppressor gene, TSC2. A randomized phase Ⅱ study exploring the activity and safety of erlotinib and metformin combined with gemcitabine in patients with metastatic pancreatic cancer is also currently underway (NCT01210911).

Src pathway: Src, a family of proto-oncogenic non-receptor protein tyrosine kinases, plays a pivotal role in regulating multiple signal transduction pathways *via* its interactions with a number of proteins, including receptor tyrosine kinases and G-protein coupled receptors. C-Src is frequently overexpressed and/or aberrantly activated in a number of malignancies including 70% of pancreatic cancers[50]. Dasatinib, a compound related to saracatinib, was examined in a phase Ⅱ trial in patients with metastatic pancreatic cancer; however, encouraging results were not obtained. A phase Ⅱ trial to explore the efficacy of dasatinib combined with 5-fluorouracil, leucovorin, and oxaliplatin against metastatic pancreatic cancer is currently recruiting subjects (FOLFOX-D, NCT01652976).

JAK/STAT pathways: Activation of the Janus kinase/signal transducer and transcription (JAK/STAT) pathway has been found in many human cancers[51]. JAKs are a family of cytoplasmic tyrosine kinases, comprised of four members-JAK1, JAK2, JAK3, and Tyk2. JAK activation occurs upon the binding of a ligand to cell surface receptors, which leads to the creation of sites for interaction with proteins that contain phosphotyrosine-binding Src homology 2 (SH2) domains. STATs, a family of downstream transcription factors for JAKs[52], contain a tyrosine residue phosphorylated by JAKs, leading to nuclear translocation. In the nucleus, STATs serve as transcription factors that initiate the transcription of downstream target genes. Abnormalities of the JAK/STAT pathway contribute directly to cellular transformation, increased cell proliferation, apoptosis, and angiogenesis. JAK mutations and STAT activation have been reported in pancreatic cancer[53,54]. In a randomized phase Ⅱ study of capecitabine plus either ruxolitinib or placebo, patients with metastatic pancreatic cancer demonstrated an improvement in survival (NCT01423604). An early phase clinical trial of ruxolitinib and gemcitabine with or without nab-paclitaxel is also currently underway (NCT01822756).

Cancer stem cells

A small population of pancreatic cancer stem cells (CSCs) has been suggested to be resistant to chemotherapy and radiation therapy. CSCs are believed to be responsible for tumor carcinogenesis, progression, and metastasis in cancers including the pancreatic type[55,56]. Hedgehog, Notch, and Wnt have been shown to play a pivotal role in the development of pancreatic cancer stem cells[57]. Remarkable progress in understanding the involvement of CSCs in pancreatic cancer might highlight these cells as attractive targets for therapy.

Notch signaling: Recent evidence has suggested that Notch signaling is implicated in tumor growth and survival as well as involved in the development and function of many organs[58]. This pathway is thought to sustain a pool of pancreatic progenitor cells at an early stage of pancreatic development, and regulates pancreatic ductal cell differentiation[59]. Notch ligands and receptors have been shown to be highly expressed in pancreatic cancer; they also promote epithelial-mesenchymal transition (EMT) by regulating several transcription factors such as Snail, Slug, and TGFβ[60]. A number of studies have shown that chemotherapy-resistant pancreatic CSCs are related to Notch signaling activation[61]. The ALPINE trial is a phase Ib study exploring the anti-Notch2/3 inhibitor, OMP-59R5, in combination with nab-paclitaxel and gemcitabine in patients with untreated metastatic pancreatic cancer (*J Clin Oncol* 2014;32:abstr). This study showed good tolerability and positive responses (partial response = 46%, durable complete response = 77%). One appealing target for blocking this pathway is the γ-secretase enzyme, which causes proteolytic cleavage and controls the release of the Notch intracellular domain as well as the production of its active form. Clinical trials are currently underway to investigate the effects of MK0752, a γ-secretase inhibitor, combined with gemcitabine in patients with advanced pancreatic cancer (NCT01098344).

Hedgehog signaling: The Hedgehog (HH) pathway regulates embryogenesis, which is undetectable in normal pancreatic tissue. HH binds to the extracellular receptor and the transcriptional target gene, Patched

(Ptch), the latter of which releases the Smoothened seven-transmembrane protein (SMO). This allows SMO to translocate to the cell surface and results in the activation of GLI transcription factors and the consequent induction of HH target genes, including GLI and Ptch1 (Figure 1B). The pathological behavior of HH signaling is well known, and an increased expression has been observed during pancreatic tumorigenesis[62]. It has been found that hedgehog signaling is phosphorylated in earlier pancreatic tumor lesions, and the expression of pathway substrates becomes elevated during the progression to an advanced stage[63]. HH signaling has also been shown to be closely associated with KRAS mutations, which drive the early stages of pancreatic neoplasia[64]. Interestingly, HH signaling in pancreatic cancer is localized to the stromal compartment, and the overexpression of sonic HH in the pancreas is sufficient to initiate precancerous lesions in transgenic mice, which contributes to maintaining the tumor microenvironment[65,66]. Interestingly, the attenuated action of sonic HH has resulted in improved gemcitabine delivery, the depletion of dense stroma, and an enhanced vascularization of the tumors in mouse models[67], suggesting that this pathway could be an appealing target for drug development. GDC-0449, also known as vismodegib, a small-molecule SMO antagonist, inhibits the HH signaling pathway. A pilot study evaluating the effects of GDC-0449 in combination with gemcitabine was performed in patients with metastatic pancreatic adenocarcinoma; however, the joint use of GDC-0449 and gemcitabine was not found to be superior to the sole use of gemcitabine in the treatment of metastatic pancreatic cancer[68]. Similarly, a randomized phase Ⅱ trial of gemcitabine with or without vismodegib in treating patients with recurrent or metastatic pancreatic cancer also yielded disappointing results (NCT01064622). A phase Ⅱ randomized study evaluating IPI-926, a small molecule SMO antagonist, in combination with gemcitabine in metastatic pancreatic cancer patients was recently completed, and the publication of its results is highly anticipated (NCT01130142).

Wnt signaling: Evidence that the Wnt signaling pathway plays a pivotal role in the regulation of stem cells has been accumulating[69,70]. Recent studies of Wnt signaling have suggested its roles in tumor biology and the pathogenesis of pancreatic cancer. Based on findings, it is plausible that the dysregulation of Wnt signaling pathway is closely associated with pancreatic cancer chemoresistance[71]. Wnt signaling inhibitors such as LGK974 and PRI-724 are currently under investigation in active phase Ⅰ clinical studies on advanced solid tumors including pancreatic cancers (NCT01302405 and NCT01351103, respectively). An open-label phase 1b dose-escalation study to elucidate the safety and tolerability of OMP-54F28 (NCT02050178) and Vantictumab/OMP-18R5 (NCT02005315) when combined with nab-paclitaxel and gemcitabine is currently in progress.

TGFβ: TGF-β is intimately involved in regulating numerous physiological processes, including cellular differentiation, homeostasis, and EMT in pancreatic cancer[72]. A phase Ⅱ study of gemcitabine in combination with LY2157299, a specific type 1 receptor inhibitor of TGFβ, or a placebo is currently being implemented (NCT01373164).

Stromal environment

One of the most important obstacles that impairs the effects of anticancer agents is the extracellular matrix (ECM) and stromal cells[73]. It has been reported that tumor-stroma interactions result in a complicated signaling network that leads to tumor progression in many kinds of solid cancers[74,75]. Pancreatic cancer shows abundant stroma in the tumor microenvironment[76]. Pancreatic cancer is uniquely characterized by a rich tumor stroma that might interfere with the delivery of agents to tumors and induce a complex interplay of intercellular signaling. Stromal depletion strategies such as the degradation of hyaluronic acid could potentially facilitate drug delivery to tumor sites[67]. Currently, there is a randomized phase Ⅱ trial comparing the treatment effects of PEGPH20, a pegylated formulation of recombinant hyaluronidase, in combination with nab-paclitaxel and gemcitabine comparing the treatment effects of PEGPH20 with the treatment effects of nab-paclitaxel alone in metastatic pancreatic cancer (Halo-109-202, NCT01839487). A partially randomized phase Ⅰ/Ⅱ evaluation of modified FOLFIRINOX with or without PEGPH20 in patients with newly diagnosed metastatic pancreatic cancer is also now under testing (S1313, NCT01959139). Heparan sulfate proteoglycans (HSPGs) are complex polysaccharides that regulate several aspects of cancer biology, including tumorigenesis, tumor development, and metastasis[77]. HSPGs have been shown to be associated with the tumor microenvironment by binding to factors that support tumor proliferation. M402, a mimetic of heparan sulfate, blocks the multiple interactions associated with heparan sulfate[77]. A phase Ⅱ clinical trial evaluating the effects of M402 in conjunction with standard chemotherapy is actively ongoing (NCT01621243).

Alternative poly (ADP-ribose) polymerase pathway

Breaks in the DNA double-strand are generally repaired by homologous recombination, which is mediated by BRCA1 and BRCA2 proteins that sustain genomic stability and cell death. The poly (ADP-ribose) polymerase pathway takes on the main role in DNA repair when BRCA dysfunction occurs[78]. The PARP proteins undertake roles in a wide range of cellular functions including DNA transcription, DNA damage response, genomic stability maintenance,

and cell cycle regulation. Inhibitors of PARP enzymes result in synthetic lethality in cancers with DNA repair failure or homologous repair deficiency. They have also been shown to be clinically effective in cancers with poor DNA repair due to germ-line mutations in BRCA1 and BRCA2, which are estimated to be 5%-7% of patients with pancreatic cancer. A randomized phase Ⅱ trial of cisplatin plus gemcitabine with or without veliparib, which is a selective PARP inhibitor, in locally advanced or metastatic pancreatic cancer patients is ongoing (NCT01585805). Another PARP inhibitor, Olaparib, at 100 mg b.i.d. with 600 mg/m^2 of gemcitabine is tolerated in patients with advanced pancreatic cancer[79]. A randomized multi-center phase Ⅰ/Ⅱ trial is currently investigating the effects of irinotecan, cisplatin, and mitomycin C combined with olaparib in patients with advanced pancreatic cancer (NCT01296763). Conversely, a randomized, double blind phase Ⅲ study of olaparib monotherapy in patients with BRCA1/2 mutated metastatic pancreatic cancer who have not progressed from first line platinum-based chemotherapy is also now underway (NCT02184195).

RECENT EXPERIMENTAL STUDIES ON THE TREATMENT OF PANCREATIC CANCER

Despite numerous clinical trials utilizing known targeted agents, the overall advancement made in pancreatic cancer treatment has been relatively modest in comparison to the advancement made in the treatment of other types of tumors. Therefore, the exploration of novel agents targeted at certain signaling pathways is one of the most important undertakings to improve the outcome of patients with lethal pancreatic cancer. In this section, we will focus on the recent experimental studies that may open the door to the development of novel and hopefully more effective strategies for the treatment of pancreatic cancer. A list of novel therapeutic targets and drugs is presented in Table 2.

Novel tyrosine kinase inhibitor

There is growing evidence to suggest that novel tyrosine kinase inhibitors can target multiple different pathways and/or signaling processes that have never been seen before in pancreatic cancer. As previously explained, utilizing the multikinase inhibitor, foretinib, may provide a simultaneous inhibitory effect on pancreatic cancer[32]. SKLB261 is a multikinase inhibitor obtained recently through lead optimization with reported activity against EGFR, Src, and VEGFR2. The application of SKLB261 has resulted in more potent antitumor activities than that of dasatinib, gemcitabine, or erlotinib in pancreatic cancer xenografts as well as more prolonged survival in mice compared with gemcitabine-treated groups[80]. Nintedanib, a triple angiokinase inhibitor that targets the VEGFR1/2/3, FGFR1/2/3, and PDGFRα/β pathways, has been shown to strongly inhibit the growth of pancreatic cancer cell lines in addition to enhancing the inhibitory effects of gemcitabine. Nintedanib also induces apoptosis in pancreatic cancer cells associated with stromal cells, providing a strong rationale for the clinical evaluation of nintedanib combined with conventional cytotoxic agents[81].

Masitinib, a multi-targeted protein tyrosine kinase inhibitor with possible anticancer activity, selectively binds to and inhibits both the wild-type and mutated forms of the stem cell factor receptor (c-Kit; SCFR), PDGFR, and FGFR3. In the recently conducted randomized phase Ⅲ trial, masitinib combined with gemcitabine prolonged the survival of patients in subgroups defined by an overexpression of acyl-CoA oxidase-1 (ACOX1) in secondary analyses. In the ACOX1 subgroup, the patients treated with masitinib plus gemcitabine showed a median OS of 11.7 mo (95%CI: 8.3-19.9) compared with a median OS of 5.6 mo (95%CI: 3.7-12.9) for the placebo plus gemcitabine treatment-arm[82].

Hypoxia inducible factor-1 (HIF-1) is a principal mediator of cell adaption to hypoxia, and is extensively expressed in 88% of pancreatic tumors[83]. PX-478, an HIF-1 inhibitor, has been shown to promote the anti-cancer effects of gemcitabine, which are closely associated with immunogenic cell death in pancreatic cancer[84]. Recent studies have demonstrated that GSK3β is closely related to pancreatic cancer cell growth, providing a rationale for targeting GSK3β in the treatment of patients with pancreatic cancer[85]. GSK3β inhibition has been shown to induce apoptosis by a mechanism involving JNK-cJUN activation[86]. CXCR4 (CXC chemokine receptor type 4), a G-protein coupled receptor of CXCL12 (SDF-1), has been found to promote GSK3β expression and the invasion ability of pancreatic cancer cells by Akt signaling. This finding suggests that CXCR4 inhibition may open a new therapeutic avenue that will impact the capacity to effectively treat pancreatic cancer patients[87]. Forkhead box M1 (FOXM1) is a transcription factor in the FOX protein superfamily containing a conserved winged helix DNA-binding domain[88]. FOXM1 is an important transcription factor for many genes key to regulating a variety of processes in tumor pathogenesis, such as tumor cell survival, growth, and EMT. Several bodies of evidence have demonstrated that FOXM1 plays a crucial role in pancreatic cancer progression[89]. A recent paper asserted that FOXM1 contributes to the development of pancreatic cancer by enhancing the *uPAR* gene transcription and subsequently the EMT of cancer[90]. These findings suggest that the deregulation of FOXM1 signaling may be a new attractive strategy in the development of novel therapeutic targets to

Table 2 Recent experimental studies of targeted therapy for pancreatic cancer

Targeted therapeutics	Ref.	Cell lines (cell type)	Main results
Multikinase inhibitors			
Foretinib	Chen *et al*[32]	Panc-1(P)	Foretinib inhibited tumor growth, angiogenesis and lymphangiogenesis in xenograft animals, by inhibiting c-MET but VEGFR-2, VEGFR-3, and TIE-2 signaling
SKLB261	Pan *et al*[80]	BxPC-3 (P), Panc-1 (P), AsPC-1 (S), HPAC (P)	Application of SKLB261 resulted in more potent antitumor activities than dasatinib, gemcitabine, or erlotinib in pancreatic cancer xenografts
Nintedanib	Awasthi *et al*[81]	AsPC-1 (S), BxPC-3 (P), Panc-1 (P), MIA-PaCa-2 (P),	A triple angiokinase inhibitor, nintedanib inhibited growth of pancreatic cancer cell lines, with gemcitabine enhancing inhibitory effects
Dual inhibition			
Lapatinib and trametinib	Lindberg *et al*[101]	MAD 08-608, 08-738, 09-366 (P)	Dual anti-EGFR and anti-HER2 therapy significantly enhanced the growth inhibitory effects of the MEK1/2 inhibitor trametinib
ZSTK474 and RO5126766	Van Dort *et al*[99]	Panc-1 (P)	PI3K inhibitor and the Raf/MEK inhibitor RO5126766 resulted in high in vitro inhibition of both PI3Kand MEK1 also decreased cellular viability in pancreatic cancer cell line
NVP-AEW541 and lapatinib	Urtasun *et al*[42]	NP-9, -18, -29 (P) CP15T, ,15A (p)	Combined treatment with the IGF-IR and EGFR/Her-2 inhibitors synergistically inhibited pancreatic cancer cell growth which is associated with abolishment of Akt, Efk, and IRS-1 activity
Novel pathways			
PX-478 (HIF-a)	Zhao *et al*[84]	CFPAC-1 (S), BxPC-3 (P), Panc-1 (P), MIA-PaCa-2 (P)	Combined treatment with gemcitabine/PX-478 significantly enhanced the anti-tumor effect which is associated with immunogenic cell death
SB216763(GSK-3b)	Marchand *et al*[86]	Panc-1 (P), MIA-PaCa-2 (P), BxPC-3 (P)	Inhibition of GSK-3βn induced apoptosis by mechanism involving
Micro RNA			
miR-142-3p	MacKenzie *et al*[95]	MIA-PaCa-2 (P), Capan-1(S), HEK-293 (P), S2-013 (P)	A unique HSP70 inhibiting compounds, miR-142-3p regulate triptolide-induced inhibition of pancreatic cancer growth
miR-146a	Li *et al*[96]	AsPC-1 (s), Panc-1 (P)	miR-146a takes significant roles in pancreatic cancer invasion and metastasis but lower expressed in pancreatic cancer compared with normal pancreatic tissue
miR-494	Li *et al*[97]	Colo357 (s), Panc-1 (P)	miR-494, identified to affect levels of FOXM1 in pancreatic cancer cell lines and act as a negative regulator of this transcriptional activator, blocked nuclear translocation β-catenin

VEGF: Vascular endothelial growth factor; EGFR: Epidermal growth factor receptor; HER2: Human epidermal growth factor receptor 2; MEK: Mitogen-activated ERK kinase; PI3K: Phosphatidylinositol-3 kinase; IGF-1R: Insulin-like growth factor 1 receptor; FGFR: Fibroblast growth factor receptor; HSP: Heat shock protein; FOXM1: Forkhead box M1; P: Primary; S: Secondary.

control pancreatic cancer.

Micro RNA

Recently discovered micro RNA (miRNA) are short non-coding RNAs involved in the negative regulation of miRNAs translation. It is important to note that miRNAs mediate a variety of cellular functions and their dysregulation is a crucial event in tumor initiation[91]. The expression of miRNAs in pancreatic cancer cells differs from those in normal pancreatic cells and in patients with chronic pancreatitis. Over 130 miRNAs have been proven to be deregulated in pancreatic cancer[92]. Several of these miRNAs play a role in new therapeutic prospects in the treatment of pancreatic cancer. It has been shown that nanomolar concentrations of antisense miR-21 and miR-221 oligonucleotides significantly repress their targets and reduce the growth of pancreatic cancer cell lines[93,94]. A unique HSP70 inhibiting compound, miR-142-3p, regulates the triptolide, a diterpene triepoxide extract from the Chinese herb Tripterygium wilfordii, -induced inhibition of pancreatic cancer growth[95]. The miR-146a compound plays a significant role in pancreatic cancer invasion and metastasis[96]. Interestingly, miR-146a has been shown to restore the proteolytic activity of pancreatic cancer cells but with less expression in pancreatic cancer than in normal pancreatic tissue. Utilizing isoflavones or 3,3′-diindolylmethane has been found to increase the expression of miR-146a, which may be a promising approach to blocking the invasion of pancreatic cancer. MicroRNA-494 (miR-494) is known to affect levels of FOXM1 in pancreatic cancer cell lines and act as a negative regulator of this transcriptional activator. It has also been shown to block nuclear translocation of β-catenin, which leads to cell proliferation, migration, and the increase of the sensitivity of pancreatic cancer cells to gemcitabine[97].

CONCLUSION

Pancreatic cancer illustrates genetic heterogeneity, and the complications in molecular signaling crosstalk

cause the failure of existing treatment strategies. Currently, only a few targeted agents, including erlotinib, have yielded a significant survival benefit for patients with pancreatic cancer. To overcome these obstacles, a considerable effort needs to be put into investigating the effective use of these therapies. Another challenge in evaluating novel targeted therapies in pancreatic cancer treatment is to identify underlying pathological features and incorporate them into trials with molecular biomarkers. Analysis of pancreatic cancer pathogenesis with its molecular characteristics may help to identify the biomarker-defined subsets of patients that can be targeted to optimize the therapeutic benefit[98].

The identification of effective targeted combination therapies may be useful for generating enhanced strategies of treating pancreatic cancer. For instance, suppression of the PI3K/Akt /mTOR pathway may result in an escape *via* the MAPK pathway as well as in diminished effects due to the intensive crosstalk between these pathways. Therefore, a combination of agents that inhibit separate pathways may be crucial for achieving the desired efficacy against tumors. A recent study found that the application of a prototype dual-acting agent designed using the PI3K inhibitor, ZSTK474, and the Raf/MEK inhibitor, RO5126766, resulted in high *in vitro* inhibition of both PI3K and MEK1 as well as decreased cellular viability in pancreatic cancer cell lines[99]. In a previous study, the combined effect of the cyclin-dependent kinase inhibitor, dinaciclib, and the pan-Akt inhibitor, MK-2206, dramatically inhibited tumor growth and metastasis in eight pancreatic cancer models. Remarkably, several complete responses were induced by this combination treatment. These results suggest that blocking RAF in combination with other effector pathways downstream from KRAS may provide increased efficacy in pancreatic cancer treatment[100]. Notably, preclinical studies predicting the effects of combination therapies with EGFR and other pathway inhibitors in pancreatic cancer xenografts have presented promising results. A recent study asserted that dual anti-EGFR and anti-HER2 therapy significantly enhanced the growth inhibitory effects of the MEK1/2 inhibitor, trametinib, in different patient-derived pancreatic cancer xenografts. This highlights the importance of designing therapeutic interventions that target not only the EGFR-HER2 but also the KRAS pathways to achieve maximal therapeutic efficacy[101].

Selecting drug combinations with novel agents that target not only tumor initiation but also the surrounding stroma may be one such approach. There is growing evidence to suggest that proteins expressed by stromal cells (Cox-2, stromal-derived factor, integrins, secreted protein acidic and rich in cysteine, and HH elements) are related to poor outcomes and the resistance to current therapies[102]. In the meantime, it is also essential to pay attention to the toxicity resulting from the use of targeted agents with conventional chemotherapy or agents targeting other pathways. A thorough understanding of the underlying mechanisms involved in toxicity will be crucial to furthering the development of pancreatic cancer therapies.

Thus far, most clinical trials involving targeted therapies for pancreatic cancer have not yielded successful results. The lack of effectiveness of several targeted agents in pancreatic cancer, despite their success in treating other types of malignancies, suggests that pancreatic cancer has particularly challenging biological characteristics that have yet to be well defined. As discussed in this review, several experimental studies have demonstrated promising new pathogeneses and efficacy in the treatment of pancreatic cancer. Therefore, continuing to develop and investigate treatments that fight pancreatic cancer from as many angles as possible will likely increase the chances of achieving positive outcomes for patients.

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