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TOPIC HIGHLIGHT

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Therapeutic options for the management of pancreatic cancer

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Abstract

Since its initial characterization, pancreatic ductal adenocarcinoma has remained one of the most devastating and difficult cancers to treat. Pancreatic cancer is the fourth leading cause of death in the United States, resulting in an estimated 38460 deaths annually. With few screening tools available to detect this disease at an early stage, 94% of patients will die within five years of diagnosis. Despite decades of research that have led to a better understanding of the molecular and cellular signaling pathways in pancreatic cancer cells, few effective therapies have been developed to target these pathways. Other treatment options have included more sophisticated pancreatic cancer surgeries and combination therapies. While outcomes have improved modestly for these patients, more effective treatments are desperately needed. One of the greatest challenges in the future of treating this malignancy will be to develop therapies that target the tumor microenvironment and surrounding pancreatic cancer stem cells in addition to pancreatic cancer cells. Recent advances in targeting pancreatic stellate cells and the stroma have encouraged researchers to shift their focus to the role of desmoplasia in pancreatic cancer pathobiology in the hopes of developing newer-generation therapies. By combining novel agents with current cytotoxic chemotherapies and radiation therapy and personalizing them to each patient based on specific biomarkers, the goal of prolonging a patient's life could be achieved. Here we review the most effective therapies that have been used for the treatment of pancreatic cancer and discuss the future potential of therapeutic options.

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Key words: Pancreatic cancer; Pancreatic cancer stem cells; Microenvironment; Surgical resection; Neoadjuvant therapy; Adjuvant therapy; Chemotherapy; Radiation; Personalized therapy

Core tip: Pancreatic ductal adenocarcinoma has challenged researchers for decades. It remains one of the most deadly cancers due to the complex molecular and genetic makeup of its cancer cells and their surrounding microenvironment. In addition, there are no valid screening tests available to detect pancreatic cancer in its early stages. Yet, as knowledge of this cancer has evolved over time, so have novel methods for treating it. Researchers have a deeper understanding of pancreatic cancer now than ever before. The future holds much promise for new breakthroughs that will significantly improve patient outcomes.

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INTRODUCTION

Despite the improved survival rates noted in numerous cancers, including breast[1-3], prostate[4] and colon cancer[5], the overall survival rates for patients diagnosed with pancreatic cancer have shown little improvement over the past thirty years[6-8]. Pancreatic ductal adenocarcinoma (PDA) remains one of the most rapidly progressive and deadly malignancies worldwide[4]. The prevention of pancreatic cancer is difficult to assess, due to limited studies identifying potential risk factors compounded with the multifactorial, heterogeneous nature of the disease. Cigarette smoking has been noted to double the risk of pancreatic cancer, yet only accounts for 20%-25% of the cases[9,10]. Additionally, family history may also contribute a significant role as 5%-10% of individuals with pancreatic cancer report an incidence of pancreatic cancer in a close family member[11]. This risk is further substantiated when there is a larger number of family members with pancreatic cancer and a decrease in age of onset in kindred[12]. Other noted risk factors include alcohol abuse[13], a high-fat diet[14,15], and certain trace elements[16].

The challenge of diagnosing PDA at an early stage further contributes to the dismal five-year survival rate that is projected for patients. Located in the retroperitoneum of patients who present with non-specific symptoms, PDA is not diagnosed until it has reached an advanced clinical stage in 80% of patients[17]. In addition, lack of effective screening and early biomarker detection methods have prevented clinicians from identifying this cancer in a pre-malignant stage. Ideally, visual evaluation *via* computerized tomography (CT) and magnetic resonance imaging (MRI) should be incorporated upon suspicion of pancreatic cancer for detection and resectability assessment[18]. Although CT scan has often been utilized to detect pancreatic cancer[19-21], reliance on MRI, particularly in regard to assessing local invasion and metastasis, has increased[22]. Other imaging may also provide certain benefits, such as endoscopic ultrasound for investigating vascular invasion[23], fludeoxyglucose-positron emission tomography scanning for recurrent tumors[24], and laparoscopy for more accurate staging[25]. While the use of these techniques remains helpful to determine prognosis and treatment regimen for patients diagnosed with pancreatic cancer, none have been validated as effective screening tests for general or high risk populations.

Once diagnosed, a number of chemotherapy, radiation and combination therapy regimens have been used to treat patients with ductal pancreatic tumors. Unfortunately, the dynamic molecular and cellular makeup of individual pancreatic tumors, renders many of them resistant to the majority of these therapies. Although surgical resection has been shown to increase patient survival by 10 mo[26], the majority of patients who undergo these procedures experience comorbidities and recurrence. Current research has identified additional sources of therapeutic resistance in the microenvironment of these tumors. Characterized by stromal proliferation, reduced angiogenesis and a unique subset of cells known as cancer stem cells (CSCs), the tumor microenvironment has become a target of new therapeutic agents.

While improved understanding of pancreatic cancer biology has lead to several therapeutic breakthroughs in the treatment of PDA, major progress toward improving survival rates in patients has been extremely slow. However, as our understanding of this tumor's therapeutic resistant nature improves, so will future progress in treating pancreatic cancer.

CLINICAL PRESENTATION AND DIAGNOSIS

One of the greatest challenges in treating pancreatic ductal adenocarcinoma (PDA) is discovering it in the pre-malignant stage. The average patient diagnosed with pancreatic cancer is in their seventh decade of life and presents to their primary care physician with general symptoms of abdominal pain and weight loss[27]. Not only is the pancreas difficult to palpate due to its retroperitoneal location, but there are also no specific blood tests to confirm suspicion of malignancy. More specific symptoms, such as unexplained jaundice[28], onset of diabetes[29] and development of thromboembolic disease[30] are more diagnostic of pancreatic cancer, but do not present until later stages of the disease. The primary comorbidities associated with PDA include biliary obstruction, infection, ascites, pancreatic insufficiency and in advanced stages of the disease, cachexia[31]. Unfortunately, once a patient presents with these symptoms, the disease has often already reached its malignant stage and the patient may never be able to receive treatment.

Effective screening tests to provide early diagnosis of pancreatic cancer could potentially prevent these symptoms. The ones that do exist are not validated. For example, although endoscopic ultrasounds provide a higher yield of detecting pancreatic cancer in its early stages, the comorbidities associated with this procedure render it an unsuitable screening test in the general population. As a result, studies are currently underway to identify high risk individuals who may benefit from this invasive procedure[32-34]. Other techniques, such as cross-sectional imaging could be used to identify asymptomatic pancreatic neoplasms for surgical resection[34] as long as they are confirmed by CT or MRI techniques which provide better resolution between normal and neoplastic pancreatic tissue[35].

Although a greater understanding of the molecular events in pancreatic cancer tumorogenesis has lead to the discovery of biomarkers that help to predict the tumor's response to treatment, there has been no use of these markers in cancer drug development[36]. The only biomarker

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Table 1 Cellular mechanisms of therapeutic resistance in pancreatic cancer

Cellular pathways	Mutated gene	Ref.
Cell-cycle control	*CDK2NA* (90%); *APC2*	Almoguera *et al*[54]; Schutte *et al*[71]; Hahn *et al*[72]
RAS	*KRAS* (90%); *MAP2K4*	Almoguera *et al*[54]; Hruban *et al*[56]; Pellegata *et al*[57]; Hezel *et al*[58]; Maitra *et al*[59]
DNA damage repair	*TP53* (75%-90%)	Almoguera *et al*[54]; Redston *et al*[67]; Olive *et al*[68]
TGF-β	*DPC4* (50%), *SMAD4*	Almoguera *et al*[54]; Yachida *et al*[73]
Apoptosis	*CASP10*; *CAD*	Jones *et al*[77]
Cell adhesion	*FAT*; *PCDH9*	Jones *et al*[77]
Hedgehog	*GLI1*; *GLI3*	Jones *et al*[77]
Integrin	*ILK*; *LAMA1*	Jones *et al*[77]
JNK	*MAP4K3*; *TNF*	Jones *et al*[77]
Small GTPases	*PLCB3*; *RP1*	Jones *et al*[77]
Wnt-β-catenin	*MYC*; *TSC2*	Jones *et al*[77]

APC: Adenomatous polyposis coli; CDK2NA: Cyclin-dependent kinase inhibitor 2 A; CAD: Carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase; CASP10: Caspase 10; DPC4: deleted in pancreatic cancer, locus 4; FAT: Fat tumor suppressor; GLI 1: Glioma-associated oncogene; GLI3: Glioma-associated oncogene 3; GTPases: Guanosine triphosphate; Wnt-B-catenin: Wingless type B-catenin; ILK: Integrin-linked kinase; JNK: c-Jun N-ternmial kinases; KRAS: Kristen rat sarcoma; LAMA1: Laminin A-1 chain; MAP2K4: Mitogen-activated protein kinase kinase 4; MAP4K3: Mitogen-activated protein-3 kinase-3: TNF: Tumor necrosis factor; MYC: Myelocytomatosis oncogene; PCDH9: Procadherin 9; PLCB3: Phospholipase C, beta 3; RP1: Retinitis pigementosa 1; SMAD4: Mothers against decapentaplegic homolog 4; TGF-β: Transforming growth factor β; TP53: Tumor protein 53; TSC2: Tuberous sclerosis 2; RAS: Rat sarcoma.

that has shown a great deal of promise in therapeutic monitoring and in identifying the recurrence of pancreatic cancer after treatment is the carbohydrate antigen 19-9 (CA 19-9), a sialylated Lewis blood group A antigen secreted by many pancreatic lesions[37]. Yet, CA 19-9 is not specific for pancreatic cancer and therefore cannot be used to screen for this tumor. Several other conditions, including hepatobiliary diseases, pancreatic diseases and gastrointestinal malignancies, bronchitis, congestive heart failure, cystic fibrosis, diverticulitis, lung cancer, ovarian cysts, pleural effusions, renal cysts and rheumatoid arthritis may present with elevated levels of CA 19-9[38]. In addition, approximately 10% of patients with pancreatic cancer are negative for Lewis antigen a or b. As a result, these patients are unable to synthesize CA 19-9 and will have no detectable levels of this biomarker, even in advanced stages of pancreatic cancer[39]. Although measurement of serum CA 19-9 levels has clinical significance in determining treatment and prognosis for patients with known pancreatic cancer, its usefulness as a diagnostic screening tool of the disease is not substantiated[40].

Upon diagnosis of pancreatic cancer, treatment and management of patients should utilize a multidisciplinary team including, primary care physicians, medical oncologists, radiation oncologists, surgeons, endocrinologists, radiologists and pathologists[41]. Cancer staging subsequently follows, with the American Joint Committee on Cancer providing the standard model, based upon the tumor-node-metastasis system[42]. However, not all criteria regarding tumor staging can be measured prior to surgical intervention. As a result, the majority of staging for pancreatic cancer incorporates imaging results and liver function tests. From these results, patients with pancreatic cancer can often be classified into three major cohorts: (1) patients with a resectable tumor or borderline resectable tumor; (2) patients with a locally invasive tumor without metastasis; and (3) patients with a systemically disseminated tumor.

Appropriately designating cases into the proper subgroup is vital to ensure appropriate treatment and management of patients presenting with pancreatic cancer. Often, fine needle aspiration guided by endoscopic ultrasonography is necessary to obtain histological confirmation[43,44], especially prior to the initiation of chemotherapy and radiation. Throughout the treatment process, CA 19-9 should be continuously measured[45,46]. Nonetheless, previous studies still support the usefulness of CA 19-9 in predicting patient response to chemotherapy[47,48], preoperative prognosis[49], as well as assessing treatment response[50,51], overall survival[51-53], and recurrence[51].

THERAPEUTIC RESISTANCE IN PANCREATIC CANCER

Cellular mechanisms of therapeutic resistance

In an effort to understand the therapeutic resistant (Table 1) nature of PDA, researchers have attempted to characterize the molecular and cellular components of the pancreatic cancer cells as well as the desmoplasia that surrounds them. Although pancreatic cancer displays pathologic and clinical heterogeneity, data suggests the majority of PDA express a successive accumulation of highly penetrant genetic alterations that occur at four genetic loci: K-ras, p53, cdkn2a and smad4/DPC4[54]. Originating in the ductal epithelium, pancreatic cancer evolves from a premalignant lesion to a highly invasive metastatic disease[55].

Ninety percent of tumors have point mutations that are specific for the KRAS2 oncogene, resulting in the constitutive production of the Ras protein[56-59]. Occurring early in tumorogenesis, these point mutations are essential for maintaining the malignant phenotype because once activated, Ras initiates a signal transduction cascade that activates proliferative and cell survival pathways and increases cell invasion[60,61]. The majority of the point mutations occur on codon 12 of the ras protein and give rise to pancreatic tumor-specific neo-antigens. Several studies demonstrated these antigens are recognized by helper T-cells and cytotoxic T-cells[62,63]. Using this knowledge, scientists developed personalized peptide vaccines corresponding to the K-ras mutations present in the tumors of patients enrolled in one clinical trial[64]. The vaccine was

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Table 2 Extracellular mechanisms of thereapeutic resistance in pancreatic cancer

Potential therapeutic targets	Extracellular response	Ref.
K-ras mutant oncogene	Proliferation of desmoplastic reaction (leukocytes, fibroblasts, endothelial cells, neuronal cells, collagen, hyaluron): upregulation of GM-CSF	Chu *et al*[78]; Neesse *et al*[79]; Ying *et al*[81]; Nolan-Stevaux *et al*[82]; Bayne *et al*[87]
Sonic hedgehog (SHH)	Growth and differenatiation of stromal fibroblasts	Bailey *et al*[83]; Tian *et al*[84]; Olive *et al*[85]
Tumor associated macrophages (TAMs); cancer associated fibroblasts (CAFs); regulatory T-cells (Treg); myeloid derived suppressor cells	Evasion of the immune system	Bayne *et al*[87]; Pylayeva-Gupta *et al*[88]
Desmoplastic reaction	Anti-angiogenesis; hypoxic tumor environment	Komar *et al*[86]

K-ras: Kinase-rat sarcoma; GM-CSF: Granulocyte macrophage colon-stimulating factor.

proven safe and tolerable and resulted in a more efficient immunologic attack on the tumor[65]. As a result, patients given the vaccine demonstrated a more favorable clinical outcome than those not given the vaccine. Combined with surgical resection, a long-term immune response initiated by the K-ras vaccine has resulted in a 10-year survival in some patients. These results may implicate a role for the K-ras vaccine as an adjuvant treatment option in the future[66,67].

Rather than being activated like the mutated KRAS2 oncogene, the p53 tumor suppressor gene is inactivated in 75%-90% of pancreatic tumors[68,69]. As a result, there is an impaired response to DNA damage in pancreatic epithelial cells, impaired apoptosis and impaired cell cycle control[70,71]. Two other tumor suppressor genes, *p16Ink4a* and *p15ARF* are encoded by the cdkn2a locus. Inactivation mutations in these genes are present in about 90% of human PDA[72,73].

A fourth common mutation seen in more than half of pancreatic cancers causes an alteration in DPC4[74]. These mutations confer a metastatic phenotype. The genetic makeup of the patient determines the number and combination of these mutations that will be present in their PDA. Patients with three or four mutated genes will have a much worse prognosis than those with one or two. The variable expressivity of these tumors presents a challenge in effectively treating them[75].

In addition to these four primary genetic alterations in PDA many other less-frequent mutations occur as well[76-78]. According to a comprehensive genetic analysis of 24 pancreatic cancers, an average of more than 60 genetic abnormalities, primarily point mutations, per tumor were noted in the PDA phenotype. While these mutations have been organized into 12 functional cancer-relevant pathways, not all tumors have alterations in each of these pathways. In addition, key mutations in select pathways appear to differ from one tumor to another[78]. These pathways may confer therapeutic resistance in the pancreatic tumor. Significant genomic instability in pancreatic cancer may also reduce the effectiveness of therapeutic agents by contributing to acquired chemoresistance.

Extracellular mechanisms of therapeutic resistance

Paracrine signals from pancreatic cancer cells stimulate the extracellular proliferation of leukocytes, fibroblasts, endothelial cells, neuronal cells, collagen and hyaluron (Table 2). This extracellular proliferation of cells is known as a desmoplastic reaction. It forms a thick stromal environment around the pancreatic cancer cells[79,80]. Studies have demonstrated that the signals that influence the proliferation of the desmoplastic reaction originate from the K-ras mutant oncogene in the epithelium of the pancreatic cancer cells[81,82].

In addition to the K-ras mutant signaling pathway, there has been an effort by researchers to understand the roles of other signaling pathways between the pancreatic cancer cells and their microenvironment. Sonic hedgehog (SHH) functions similarly to the K-ras mutant. Although it is over expressed in pancreatic cancer cells during the early stages of their development, SHH does not act on the SHH pathway in these cells[83]. Instead, it acts in a paracrine fashion in the extracellular fibroblasts, resulting in their growth and differentiation[84,85].

The desmoplastic reaction not only provides a mechanical barrier to the pancreatic cancer cells, but it is also thought to contribute to the anti-angiogenic environment that is characteristic of pancreatic ductal adenocarcinoma. Both properties directly affect therapeutic efficacy. Inadequate drug delivery to the site of the tumor is directly correlated with a negative patient outcome[86].

Researchers have also suggested a role for the tumor stroma in the T-lymphocyte depleted microenvironment of the PDA. Several cell types found in the desmoplastic reaction have been associated with tumor associated macrophages, cancer associated fibroblasts, regulatory T-cells and myeloid derived suppressor cells. In addition, a role for a K-ras dependent signaling molecule has been shown to up-regulate granulocyte-macrophage colony stimulating factor when activated. This cytokine promotes the maturation of immature myeloid progenitor cells into myeloid derived suppressor cells[87,88].

TREATMENT OF PANCREATIC CANCER

Surgical resection

Although surgical resection offers hope for curative therapy, only 20% of patients present with potentially resectable tumors[89,90]. It is important to note that surgical resection is only considered in patients with completely

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Table 3 Therapies for the management of pancreatic cancer

Therapeutic option	Subset	Ref.
Surgical resection	Cephalic pancreatoduodenectomy	Hidalgo[41]
	Distal pancreatectomy	
	Total pancreatectomy	
Chemotherapy	Neoadjuvant	Lemmens *et al*[101];
	Gemcitabine	Gillen *et al*[102];
	Adjuvant	Neoptolemos *et al*[108];
	Gemcitabine	Burris *et al*[118];
	5-Fluorouracil	Heinemann *et al*[119];
	Advanced disease	Reni *et al*[120];
	Gemcitabine	Moore *et al*[122];
	Gemcitabine + fluropyrimidines	Neesse *et al*[79]
	Gemcitabine + platinum analogs	
	Gemcitabine + erlotinib	
	FOLFIRINOX	
	Nab-paclitaxel	
Radiation therapy	Neoadjuvant	Pisters *et al*[131];
	Radiation + 5-fluorouracil	Hong *et al*[133];
	Radiation + paclitaxel	Yeo *et al*[140];
	Proton beam radiation + capecitabine	Regine *et al*[138];
	Adjuvant	Neoptolemos *et al*[137];
	Radiation + 5-Fluorouracil	Moertel *et al*[144];
	Radiation + gemcitabine	Schellenberg *et al*[147]
	Radiation + chemotherapy	
	Advanced	
	Radiation + 5-fluorouracil	
	Radiation + chemotherapy	
	Stereotactic body radiotherapy	
Personalized therapy	Target specific point mutations	Jones *et al*[77];
	Mitomycin C	Villarroel *et al*[153];
	Immune system stimulation	Yanagimoto *et al*[154]

resectable or borderline-resectable tumors (Table 3). Depending on the size and location of the tumor, three operative procedures are potentially utilized, as noted by Hidalgo[41], with additional removal of adjacent lymph nodes: (1) cephalic pancreatoduodenectomy (whipple procedure); (2) distal pancreatectomy; and (3) total pancreatectomy.

Although additional palliative care is often utilized, controversy surrounds the potential benefits. For example, almost 80% of patients presenting with tumors in the pancreatic head exhibit jaundice due to biliary obstruction[91,92]. However, previous investigations have conflicting results regarding preoperative biliary drainage with certain studies reporting a decrease in perioperative morbidity and mortality[93] while others concluding recognizable benefit[94,95].

Preoperative biliary stenting doubled between 1992 and 2007 due to evidence demonstrating a higher risk of postoperative complications in patients presenting with a tumor in the head of the pancreas. Biliary drainage was further supported by evidence demonstrating its ability to improve liver function, nutritional status and cell-mediated immune function[93]. Despite intentions to reduce post-operative morbidity and mortality by improving liver function, extensive clinical studies have demonstrated preoperative biliary stenting prolongs time to operation, increases preoperative infection and is associated with overall increased complication rates after surgical procedures[94,95]. As a result, most studies have advised against routinely performing preoperative biliary drainage and have recommended that patients presenting with jaundice due to a resectable and non-metastatic tumor in the head of the pancreas should undergo early surgery without preoperative biliary resection[95]. Currently, the only indications for preoperative biliary decompression are for patients who present with severe jaundice, are undergoing neoadjuvant therapy, or have had their surgery postponed due to logistics[94,95].

Several poor predictors for successful resection have been identified, including lymph node involvement[96], high tumor grade[97], large tumor size[98], elevated CA 19-9 levels[46], and positive margins of tumor following resection[41]. These same factors also contribute to recurrence of pancreatic tumors. Even with surgical resection, 5-year survival rates remain dismal, at approximately 20% following surgery[90]. However, perioperative complications and mortality have significantly decreased over the past decade, likely due to greater hospital clinical volume through centralization[99,100].

Chemotherapy

Neoadjuvant therapy: Certain patients might receive neoadjuvant therapy, especially if the tumor presents with borderline resectability. In a study utilizing gemcitabine-based chemotherapy, improved tumor resection with increased survival rates was noted in border-line resect-

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able cases[101,102]. However, these effects may only occur in select tumors, with influences by both the genetic composition and microenvironment of the pancreatic cancer[103,104]. For example, White *et al*[105] noted p53 mutations were more common in patients with large residual tumors following treatment with chemoradiation. Moreover, outcomes for neoadjuvant therapy prior to surgically-resectable tumors did not differ when chemotherapy was provided post-operatively[106]. Chemotherapy with radiation has also been shown to improve survival, but not stage, of cases presenting with locally invasive tumors without metastasis[107]. However, previous studies do note that surgical interventions are more challenging and increased postoperative stay is associated with patients undergoing resection after neoadjuvant chemoradiation therapy for locally invasive cancer[106]. Since metastatic pancreatic cancer cannot be completely resected, surgical options are unavailable and hence no neoadjuvant therapy can be provided. Lastly, it is important to note that prior to initiating neoadjuvant therapy, histological confirmation of pancreatic adenocarcinoma is required, unlike surgical resection, which often relies solely on imaging.

Adjuvant chemotherapy: Even following complete, successful resection of pancreatic tumors, overall survival and prognosis remains discouraging. Hence, postoperative chemotherapy or chemoradiation is almost always incorporated in the therapeutic regimen. Postoperative chemotherapy often utilizes gemcitabine or 5-fluorouracil (with concurrent leucovorin as a rescue agent). Both drugs have demonstrated significant increases in patient survival, regardless of initial case presentation. These drugs may also be given simultaneously, however, significant toxicity (especially gastrointestinal) has been reported. Although gemcitabine has often been considered the standard, previous studies do differ on which agents are associated with the most optimal benefits. In a phase Ⅲ, randomized control trial, Neoptolemos *et al*[108] noted no significance difference in survivorship between gemcitabine and 5-fluorouracil (with folinic acid) in patients with resected tumors. In a separate study published in JAMA, the authors concluded that gemcitabine alone should be favored over 5-fluorouracil with leucovorin due to its decreased toxicity[108].

Developments of other complementary agents to enhance chemotherapeutic effects are currently under review. For example, possible inhibition of Hedgehog signaling[84] or concurrent use of Smac mimetics[109], microRNAs[110], Resveratrol[111], capecitabine[112], thymoquinone[113] or heat-shock protein complements[114] may promote tumor uptake and damage of administered drugs, such as Gemcitabine administered with concurrent curcumin may also be a potential option, especially in tumors exhibiting gemcitabine-resistance[115]. In addition to utilizing CA 19-9 and imaging to monitor patient response to chemotherapy, other markers, such as human equilibrative nucleoside transporter 1 levels have also shown to be useful[116]. Other gene expression levels, as noted in Fujita *et al*[117], may also be predictive of treatment efficacy, particularly with gemcitabine. Further investigation is required as to whether adjuvant chemotherapy should be administered if prior neoadjuvant therapy before surgery had already been provided.

Chemotherapy for advanced disease: Due to its poor detection rate, 60%-70% of patients present with metastatic pancreatic cancer upon initial diagnosis. In the advanced stage of disease, pancreatic cancer causes imminent mortality for the majority of affected patients and median survival rate is typically 6-8 mo. Therefore, treatment of patients with metastatic pancreatic adenocarcinoma incorporates chemotherapy, targeted-therapy, comorbid conditions, intensive supportive treatment and psychosocial support.

Gemcitabine is currently considered the chemotherapeutic standard of care in treatment of advanced pancreatic cancer[118]. It has been shown to prolong the average survival rate by 4 mo. In an attempt to improve survival rates, several phase Ⅱ and phase Ⅲ trials combined Gemcitabine with fluoropyrimidines and platinum analogs. Most of these combinations failed to show statistically significant survival benefit, however compared to Gemcitabine alone[119]. In another attempt to prolong patient survival, scientists have developed several Gemcitabine-based polychemotherapy regimens involving 3-4 cytotoxic agents. When Reni *et al*[120] performed a randomized trial to test the cisplatin, epirubicin, fluorouracin and gemcitabine (PEFG-regimen) against gemcitabine alone, those patients treated with the PEFG saw a significant decrease in cancer progression, when compared to those treated with gemcitabine alone[120]. Yet in regards to survival, the infusional 5-FU/folinic acid, irinotecan, and oxaliplatin (FOLFIRINOX) regimen has been shown to be superior to the PEFG-regimen.

According to Conroy *et al*[121], FOLFIRINOX is the new standard in the treatment of advanced stage pancreatic cancer. Compared to gemcitabine alone, FOLFIRINOX demonstrated a better objective response rate, progression-free survival, overall survival and one-year survival. While the toxicity levels associated with FOLFIRINOX are greater than those caused by gemcitabine, the effects did not seem to have a significant impact on quality of life. In addition, few toxic deaths have been reported.

Inhibitors of epidermal growth factor receptor (EGFR) have also been tested for treatment of metastatic pancreatic cancer. Cetuximab, an anti-EGFR directed antibody and erlotinib, an oral EGFR tyrosine kinase inhibitor have been tested in several randomized trials. However, Moore *et al*[122] demonstrated that combining gemcitabine with erlotinib is the only targeted-therapeutic agent that has clinical efficacy. Compared with gemcitabine alone, gemcitabine plus erlotinib showed significant decrease in tumor progression and concurrently increased overall survival rates.

Other targeted therapies have focused on targeting

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the desmoplastic stroma, one of the key components of pancreatic cancer that may contribute to impaired drug delivery and thus chemotherapy resistance[79]. Nab-paclitaxel is one therapy that has been developed to diminish this stromal tissue network. Studies have demonstrated that albumin interacts with secreted protein acidic and rich in cysteine (SPARC), a matrix glycoprotein that has a role in tumor invasion, facilitating the uptake of paclitaxel by the tumor[123]. Infante *et al*[124] have demonstrated that overexpression of SPARC in peritumoral fibroblasts was a negative prognostic indicator in patients with advanced pancreatic cancer[124]. In a phase Ⅰ/Ⅱ trial, Von Hoff *et al*[125] demonstrated the ability of nab-paclitaxel to increase median survival rate in patients with metastatic pancreatic cancer.

Similar to the mechanism of action of nab-paclitaxel, new therapies are being developed that target the peritumoral stroma in order to increase tumor perfusion. One such preclinical strategy inhibits the hedgehog signaling pathway, depleting the stroma and increasing angiogenesis to improve delivery of chemotherapeutic agents to the tumor[126].

Phase Ⅱ clinical trials have demonstrated a benefit of second-line treatment for patients who are resistant to gemcitabine treatment[127]. Second-line treatments typically consist of fluoropyrimidines in combination with oxaliplatin[128]. Limited data exists on how to treat patients who do not tolerate FOLFIRINOX as a first-line therapy. However, Conroy *et al*[121] have demonstrated the benefit of using gemcitabine-based therapies in these instances.

The primary prognostic indicators for patient survival are both patient and tumor related. Based on the genetic and morphologic heterogeneity that exists within each individual pancreatic tumor, therapy, dose and length of therapy administration will need to be customized for each Individual patient to ensure optimal treatment.

Radiation

Neoadjuvant radiation therapy: Many studies have demonstrated the important roles for chemotherapy and radiation therapy in preventing the recurrence and improving the resectability of pancreatic tumors. While surgery is currently the only potential curative treatment modality for pancreatic cancer, more than 80% of patients who undergo surgical resection will experience tumor recurrence within 12 mo of their procedure[129]. Therefore, a great deal of focus has not only been placed on developing effective neoadjuvant and adjuvant therapies, but also on effective preoperative staging techniques to determine candidates who will benefit most from surgical resection[130]. Since surgery is associated with high rates of morbidity and mortality, many patients do not begin adjuvant therapy until after they have recovered. As a result, there is a long delay before they receive adjuvant therapy. In order to begin more potent treatments earlier and to potentially shrink the tumor before surgery, researchers developed neoadjuvant therapeutic regimens.

Multiple trials of 5-fluorouracil-based chemoradiation have been done to date. At the conclusion of these studies, researchers determined that a combined treatment modality with preoperative rapid-fractionation chemoradiation, Whipple procedure, and intra-operative radiation therapy resulted in minimal toxicity and a small recurrence rate[131]. In a follow-up study, paclitaxel replaced 5-fluorouracil and was used to treat 35 patients who presented with resectable pancreatic tumors[132]. Based on the results of this study, researchers concluded that preoperative paclitaxel-based chemotherapy with rapid-fractionation chemoradiation, Whipple procedure and intraoperative radiation therapy resulted in similar outcomes as the previous study, but toxicity levels were greater than those from 5-fluorouracil. In another study, researchers treated patients who presented with tumors in the head of the pancreas with a neoadjuvant chemoradiation regimen of capecitabine with proton beam radiation[133]. No dose limiting toxicities were observed and the authors concluded that this form of neoadjuvant therapy was feasible. In several other prospective neoadjuvant chemoradiation trials in patients with resectable pancreatic cancers, the rate of resection was high in all studies, ranging from 87%-100%[107,134,135].

Adjuvant radiation therapy: The median survival rate of patients who undergo surgical resection of a pancreatic tumor is 15-22 mo. Only 20% of patients survive for five years following surgery[136]. The most common site for pancreatic cancer recurrence is the retroperitoneum. Therefore, adjuvant therapy is needed to improve patient prognosis. In the United States, adjuvant therapy is currently delivered in the form of chemotherapy, chemoradiotherapy or chemotherapy followed by chemoradiotherapy. Standard adjuvant treatment in Europe is chemotherapy alone. These guidelines were based on previous randomized trials that showed improved survival in patients given adjuvant therapy following surgical resection.

The first prospective trial for adjuvant chemoradiotherapy was conducted by the Gastrointestinal Tumor Study Group in 1985. The trial enrolled patients with resectable pancreatic cancer. The protocol called for external beam radiation delivered with 5-fluorouracil. The patients were then given a maintenance dose of 5-fluoruracil for an additional two years following initial treatment. Patients treated with adjuvant chemoradiation achieved a longer median and 2-year survival rate than those not treated with adjuvant therapy. As a result, adjuvant chemoradiation became the most frequently used adjuvant treatment for resectable pancreatic cancer in the United States.

To further assess adjuvant radiation therapy for resectable pancreatic cancer, the European Study Group for Pancreatic Cancer (ESPAC-1) conducted the largest randomized trial to date in 2004[137]. In order to evaluate the effects of chemoradiotherapy and chemotherapy on patient survival following surgical resection, patients with resectable pancreatic ductal adenocarcinoma were divided into one of four groups: chemotherapy alone;

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chemoradiotherapy alone; chemoradiotherapy followed by chemotherapy; or no further treatment. Patients who received chemotherapy followed by chemoradiotherapy had a 5-year survival rate that was 10% less than those who received chemotherapy alone. In addition, patients who received chemotherapy treatment showed a 5-year survival benefit when compared to those who received no chemotherapy. As a result of these findings, the standard of adjuvant treatment in Europe shifted towards chemotherapy only, abandoning postoperative chemoradiation.

A phase Ⅲ trial was conducted by the Radiation Oncology Group and GI Intergroup around the same time as the ESPAC-1 trial[138]. This trial compared the 5-fluorouracil-based chemoradiation to gemcitabine-based chemoradiation. Patients receiving gemicitabine-based chemoradiation had a median survival of 20.6 mo, 3.5 mo more than those given 5-flurouracil-based chemotherapy. The Charite Onkologie Clinical Studies in GI Cancer 001 (CONKO-001) trial in Germany and Austria showed similar median survival in patients given gemicitabine-based chemotherapy alone[139].

Additionally, reports from several institutions, including the Mayo Clinic, Johns Hopkins Medical Center and Virginia Mason University have all reported the benefit of adjuvant chemoradiation therapy following resectable pancreatic cancer compared to those who received surgery alone[140-142].

Management of locally advanced pancreatic cancer: Patients with locally advanced pancreatic cancer achieve little benefit from surgical resection because their cancer meets the criteria for unresectable cancer: (1) distant metastasis and/or pancreatic lymph node involvement; (2) encasement or occlusion of the superior mesenteric vein or superior mesenteric vein/portal vein confluence; and/or (3) direct involvement of the celiac axis, aorta, inferior vena cava, or superior mesenteric artery[143]. As a result, chemoradiation is recommended for these patients based on data from several studies.

A 1981 trial conducted by the Gastrointestinal Tumor Study Group compared the effects of high-dose radiation therapy alone; moderate dose radiation combined with 5-flurorouracil and high dose radiation combined with 5-fluorouracil in 194 patients with locally advanced pancreatic cancer. Researchers found that patients administered 5-fluorouracil in combination with low or high dose radiation showed a greater median survival than those treated with radiation alone[144]. In a follow-up study, the same group demonstrated that chemotherapy, when combined with radiotherapy afforded patients with locally advanced pancreatic cancer a greater median survival when compared to combination chemotherapy alone[145]. These results were verified by the ECOG trial as well, which demonstrated an increased median survival rate in patients treated with gemcitabine and radiotherapy together as opposed to those treated with gemcitabine alone[146].

Although chemoradiation has been shown to provide an increased median survival in patients with locally advanced pancreatic cancer by 9-13 mo, many of these patients progress to the metastatic stage of disease shortly after therapy. Perhaps a better approach to these patients would be to begin a chemotherapy regimen, restage their cancer after completion of initial treatment, and follow up with chemoradiation in patients who do not demonstrate metastatic disease progression. Radiation in these patients could relieve pain associated with disease by slowing local progression.

Stereotactic body radiotherapy: An evolving radiation therapy for treatment of locally advanced pancreatic cancer is stereotactic body radiation therapy. This newer technique uses image guidance to deliver toxic radiation doses directly to tumors. As a result, there is less systemic involvement, and patient outcomes are improved without having to undergo daily treatments. However, the major challenge of this novel therapy is accurately characterizing the tumor in terms of size, number and location. In order to do so, precise diagnostic tests and real-time imaging techniques are used. In addition, each treatment regimen is tailored to each individual patient. To date, scientific literature suggests sterotactic body radiotherapy does slow local progression in patients with locally advanced pancreatic cancer[147-149]. However, it does not increase overall survival rate because patient mortality is due to distant metastases.

Advances in radiation therapy techniques: Over the past decade, major advances in radiation therapy have been in treatment planning and more precise delivery methodologies. One technique, intensity-modulated radiotherapy, decreases systemic toxicities in patients by modifying radiation dose delivery specifically to the tumor sites, sparing surrounding normal tissue[150,151]. Another technique, image-guided readiotherapy, has provided more accurate visualization and real-time tracking of viscerally-located tumors and thus has enabled more precise delivery of high-dose therapeutic beams of radiation to these tumors and prevented adverse effects in normal tissue[152].

In order to improve patient outcome and prolong median survival rate, additional studies are needed to define the optimal role of adjuvant and neoadjuvant treatment in patients with resectable pancreatic cancer. As radiation therapies become more precise and customized to individual patients, it will be necessary to continue to investigate their future role in the treatment of pancreatic adenocarcinoma, especially as a greater understanding of the molecular pathways involved in the carcinogenesis and progression of this disease are understood.

Personalized therapy: In an article published in *Science*, Jones *et al*[77] performed a comprehensive genome assessment on 24 different pancreatic cancers. Results revealed an average of 63 genetic mutations per cancer, spanning 12 separate signal transduction pathways. This study sup-

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ports the notion of pancreatic cancer being a genetically heterogeneous malignancy, partially accounting for its notable resistance to therapy as well as varied responses to treatment. Moreover, this finding likely explains why no candidate gene has been identified in the treatment of pancreatic cancer. This heterogeneity will likely dictate an individualized, unique approach for each particular case, which has already shown to be effective against even advanced pancreatic cancer stages. In one such case report, Villarroel *et al*[153] identified Mitomycin C, a DNA-damaging agent, as a highly effective agent by utilizing a xenograft derived from the patient's tumor. Upon administration of this drug, the patient exhibited notable clinical benefits for over three years, despite the tumor previously being gemcitabine resistant. Personalized immune system stimulation may also be a viable option in treatment of unresectable disease. For example, Yanagimoto *et al*[154] incorporated a vaccine containing individualized, reactive peptides with concurrent gemcitabine treatment, noting a significant correlation between immune boosting and survivorship.

Due to the ongoing advances in DNA sequencing, personalized genomic therapy appears more plausible. Moreover, as scientists continue to identify regions of the genome with high potential for tumor-pathogenesis, this method will only become more efficient. Upon identification, cases can be distributed into cohorts based upon their tumor's genetic composition and administered treatment previously demonstrated to be effective in that particular subgroup. This method would not only identify pertinent biomolecules in pancreatic pathogenesis, but also lead to tumor-specific treatment, which is likely necessary if we are to see any significant improvement in the prognosis of pancreatic cancer.

FUTURE PERSPECTIVES

Despite decades of effort by the scientific community to design sophisticated chemotherapeutic and radiation techniques to combat pancreatic ductal adenocarcinoma, less than 5% of patients with this disease have a 5-year survival rate. The majority of patients have a median survival period of 4-6 mo[155,156]. A combination of factors including few early symptoms, few accurate biomarkers for early detection, rapid metastasis to the lymphatic system and distant organs, and few effective treatment options, makes this disease one of the most deadly cancers today[157,158]. Although current therapeutic agents have had limited effects on patient care, there has been substantial advancement in the understanding of the molecular and biological makeup of pancreatic adenocarcinoma. This knowledge has the potential to lead to the development of novel therapies that could significantly improve the lifespan of individuals suffering with this disease.

Such advances in understanding this complex disease have been achieved with genetically-engineered mouse models and patient-derived xenografts. These studies have demonstrated the genetic diversity of pancreatic ductal adenocarcinoma results from successive accumulation of mutations in several primary oncogenes and tumor suppressor genes, leading to its heterogeneity, instability and early tumor metastasis[77]. Pancreatic ductal adenocarcinoma is composed of several compartments. In addition to a mature cancer cell population, some researchers have characterized cancer cells that display stem cell properties and are resistant to chemotherapy and radiation therapy, potentiating their ability to metastasize[56]. Another area of interest is the dense tumor microenvironment that surrounds the pancreatic cancer cells. Composed of collagen I , activated fibroblasts, and inflammatory cells, it has been shown to interact with pancreatic cancer cells in order to foster tumor development, act as a barrier to optimal drug delivery and aid the tumor in invasion and metastasis[59]. Furthermore, this dense stroma creates a hypoxic microenvironment that pancreatic cancer cells thrive in[159]. However, the mechanisms by which these cancer cells adapt to these conditions are currently being identified and may serve as additional therapeutic targets in the near future.

Pancreatic cancer cells

Pancreatic ductal adenocarcinoma most likely originates in the ductal epithelium of pancreatic cells[160]. Neoplastic cells contain one or more of four primary genetic mutations that will ultimately give rise to the invasive form of this disease. Ninety percent of these tumors have mutations in the KRAS2 oncogene, resulting in the activation of proliferative survival signaling pathways. Ninety-five percent have a mutation in the CDKN2A tumor suppressor gene, resulting in the loss of the p16 protein and thus loss of regulation of the G_1-S transition of the cell cycle. An abnormal *TP53* gene has been identified in 50%-75% of characterized cancer cells, allowing cells to avoid DNA damage control checkpoints and subsequently, apoptotic signals. Another 50% have a deleted SMAD4/MADH4 gene, resulting in aberrant signaling by the TGF-β cell surface receptor[153].

One study performed genetic analysis on 24 pancreatic ductal adneocarcinomas and reported that each tumor has an average of 63 clinically relevant genetic abnormalities. While these abnormalities differ from one cancer to another, they all seem to play a role in 12 functional cancer-related pathways[161]. Recently, two studies compared the genetic makeup of distant metastases to their primary metastatic lesions. They found that over time, the distant metastases accumulated additional mutations to those present in the clonal cells from which they arose, adding to the complexity this disease[162]. Such genetic diversity not only results in different prognoses for patients, but also causes individual tumors to respond differently to common therapeutic agents used in treating pancreatic ductal adenocarcinoma[163].

The varying degrees of genetic instability that exist between individual pancreatic ductal adenocarcinomas present a greater need for genomic sequencing of individual tumors, followed by personalized therapies to target spe-

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cific genes and pathways that have been altered[164]. Several clinical trials have begun exploring this idea[165]. In order to incorporate this treatment modality into the clinical setting, several criteria must be met: (1) a high quality tumor tissue sample must be attained at the time of diagnosis; (2) sophisticated bioinformatic analysis of the data must be performed to identify the most relevant mutations in each tissue sample; and (3) model systems must be designed to experimentally test varying treatment options to determine the most effective one for the patient. Perhaps the greatest challenge lies in developing a drug once specific genetic abnormalities have been identified.

Pancreatic cancer stem cells

Recently, investigators have characterized pancreatic cancer cells with stem cell properties[162] . Known as pancreatic cancer stem cells, these cells have the ability to regrow new tumors when placed into naïve mouse models and are able to maintain long-term tumorigenic potential[163]. Studies have shown that pancreatic CSCs are not only capable of self renewal, but may also confer therapeutic resistance, and play a role in tumor formation and disease progression[164,165]. In addition, different cancer stem cell populations perform different biological functions. One of the most recent findings has demonstrated that these cells may transition between epithelial and mesenchymal states, contributing to their highly metastitc potential[165]. Therefore, eliminating or inhibiting these CSCs with new therapeutic designs could significantly improve patient outcomes. Current therapies have already been designed to target cancer stem cell-specific antigens in order to inhibit their roles in cell survival, adhesion, self renewal and differentiation. A greater understanding of individual CSC populations and how they interact with one another will enable further progress in the treatment of pancreatic cancer[164,165].

Therapeutic targets of pancreatic ductal adenocarcinoma cancer stem cells include genes located in developmental pathways such as hedgehog, Wnt, Notch, CXCR4 and Met. In addition, targeting apoptotic pathways such as DR5 and nodal-activin could have a significant therapeutic implications. Several preclinical trials have been conducted to target these pathways in models of human pancreatic ductal adenocarcinoma cancer stem cells. By inhibiting these pathways, investigators were able to confer longer-term tumor control when compared to current standard chemotherapeutic regimens, in which tumor regression was significantly shorter-lived. In one recent trial, salinomycin was shown to induce cell death in epithelial-mesenchymal transition-induced cancer stem cells[124].

Due to the heterogeneity of the cancer stem cell population, future drugs designed to target pancreatic ductal adenocarcinoma stem cells may require clinical trials in which therapies are designed specifically for pancreatic tumors in each individual patient. These customized therapies could potentially serve as adjuvant treatment options for patients following pancreatic tumor resection. Similar to previous clinical trial designs, adjuvant therapies targeting cancer stem cells could be given to patients with or without current conventional chemotherapy and/or chemoradiation to determine which option confers the greatest overall survival rate in patients following surgical resection.

Tumor microenvironment

One of the primary characteristics of pancreatic ductal adenocarcinoma is the dense stroma surrounding the pancreatic cancer cells. Composed of fibroblasts, collagen I and other fibrillar elements, this desmoplastic reaction has become a primary target of current drug therapies[125]. The key players in the formation and turnover of this dense stroma are pancreatic stellate cells. Certain growth factors [TGF-β1, platelet-derived growth factor (PDGF) and fibroblast growth factor] activate these cells to myofibroblasts. Not only do these activated myofibroblasts secrete components of the extracellular matrix, but they are also responsible for the poor vascularization of the pancreatic tumor[166,167]. In addition to forming a mechanical barrier around the pancreatic cancer cells, the stroma has an important role in tumor formation, progression, invasion and metastasis[168]. Many proteins expressed by stromal cells have been directly correlated with poor prognosis and resistance to current therapies [Cox-2, PDGF receptor, VEGF, stromal-derived factor, chemokines, integrins, secreted protein acidic and rich in cysteine (SPARC), and hedgehog elements].

Pre-clinical models have demonstrated that targeting these receptors and enzymes is associated with antitumor effects. Perhaps one of the most promising targets to date is the hedgehog signaling pathway. Some studies have demonstrated that targeting smoothened resulted in a depletion of the stroma and thereby increased delivery of gemcitabine to the tumor cells[169]. Another target for therapeutic trials has been SPARC (osteonectin) and hyaluronic acid. SPARC is an extracellular matrix protein that plays a role in collagen turnover in the dense stroma. It is associated with invasion and metastasis in pancreatic ductal adenocarcinoma, and thus poor prognosis in patients with elevated levels[170]. As mentioned previously, SPARC is the target of the albumin-bound chemotherapy agent, nab-paclitaxel. Phase Ⅰ/Ⅱ clinical trials have shown that administration of this drug breaks down the stroma and improves delivery of the chemotherapeutic agent to the site of the tumor[171]. In addition, in a mouse model of pancreatic ductal adenocarcinoma, investigators demonstrated that administration of pegylated hyaluronidase eliminated hyaluronic acid content, thereby relieving pressure on the blood vessels surrounding the tumor and allowed for increased perfusion of the chemotherapeutic agent to the site of the tumor[172].

The immunosuppressive nature of the tumor microenvironment has been another stromal characteristic targeted by recent therapeutic development. Using a CD40 antibody combined with gemcitabine chemotherapy, researchers have attempted to reverse immune suppression and drive antitumor T-cell responses in patients with non-resectable pancreatic ductal adenocarcinoma. Studies

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have shown that this agent results in tumor regression by stimulating tumor macrophages to attack and deplete the pancreatic cancer stroma[173].

To date, targeting pancreatic ductal adenocarcinoma has proved most effective when treating patients with locally advanced disease, especially patients with tumors characterized by wild-type DPC4. These tumors are known to be less prone to metastasis and possess higher stromal content. Other tumors, especially those in late stages of the disease, characterized by distant metastases, have not been effectively treated with current stromal-targeting therapeutic agents. This is due to the fact that although pancreatic ductal adenocarcinoma has a rich and hypovascularized stroma, metastases arising from this cancer do not and are not different from other tumors. Therefore, patients who may benefit most from treatment with agents targeting the dense stroma microenvironment would be those with resectable tumors that have not progressed to the advanced stages of disease[174].

Metabolic pathways

Another conventional way to target pancreatic ductal adenocarcinoma would be to inhibit its major metabolic pathways. In order to do so, researchers would need to prevent its supply of glucose and glutamine; interrupt the pathways that enable it to exist in a hypoxic environment[175]; and prevent its ability to digest intracellular organelles for energy[176].

Investigators have identified several key metabolic enzymes to target [hexokinase, pyruvate kinase, lactate dehydrogenase A (LDHA) and ampicillin-activated protein kinase (AMPK)]. Several preclinical trials have demonstrated the anti-tumor effects of agents directed against these enzymes. One study demonstrated a potential clinical application for the LDHA inhibitor, FX11. By blocking the conversion of lactate to pyruvate in cells with p53 mutations, FX11 has antitumor potential. However, to date, there are only two therapies that have shown potential for targeting pancreatic ductal adenocarcinoma metabolism. One of these medications, metformin, is an activator of AMPK. It has been shown to decrease the potential for patients with diabetes to develop pancreatic cancer and to increase survival in diabetic patients with this disease[177,178]. The other drug used to target the metabolic pathways of is rapamycin. An inhibitor of mTOR, rapamycin has been shown to decrease glucose uptake by reducing levels of Glut1 in pancreatic cancer[179,180].

In order to inhibit autophagy, a significant mechanism for pancreatic cancer cell survival, investigators have used chloroquine, the antimalarial drug[181]. In preclinical trials with both allografts and xenografts, chloroquine has been shown to decrease tumorigenesis in a transgenic model and is currently being tested in clinical trials.

CONCLUSION

A greater understanding of the molecular and cellular makeup of pancreatic cancer over the past four decades has resulted in innovative therapeutic designs to target this aggressive malignancy. We now know that pancreatic cancer is a dynamic, heterogenous and genetically unstable tumor that results from successive mutations early in disease and gives rise to metastases that continue to garner mutations as they travel to distant locations. An equally important understanding of the role the peritumor microenvironment, composed of a dense desmoplastic stroma, plays in tumor development, metastases and as a barrier to chemotherapy delivery has been elucidated over the years. More recently, a role for pancreatic cancer stem cells in resistance to chemotherapy and radiation therapy was discovered. In addition, a deeper understanding of the metabolic pathways responsible for adaptation of pancreatic cancer cells to hypoxic environments has significant implications for future therapeutic development.

While some of these discoveries have resulted in novel therapeutic targets and treatment strategies and others are currently being tested in preclinical trials, efficient and effective drug development to combat pancreatic ductal adenocarcinoma is a necessity for the future. The majority of clinical trials have been conducted in patients with advanced stage disease. In the future, it will be necessary to design clinical trials to enroll patients with earlier stages of pancreatic cancer in an attempt to cure their cancer before it can metastasize.

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