Translational Therapeutic Opportunities in Ductal Adenocarcinoma of the Pancreas

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Abstract

Pancreatic ductal adenocarcinoma (PDA) remains a devastating disease with nearly equal incidence and mortality rates. Over the past few decades, a litany of randomized clinical trials has failed to improve the outcome of this disease. More recently, the combination chemotherapy regimen FOLFIRINOX has shown improvement in overall survival over the single agent gemcitabine, and nab-paclitaxel (an albumin-coated formulation of paclitaxel) in combination with gemcitabine has shown promising results in phase II studies. Despite limited impact on patient care as of yet, the molecular and biologic understanding of PDA has advanced substantially. This includes understanding the genomic complexity of the disease, the potential importance of the tumor microenvironment, the metabolic adaptation of PDA cells to obtain nutrients in a hypoxic environment, and the role of pancreatic cancer stem cells. These fundamental discoveries are starting to be translated into clinical studies. In this overview, we discuss the implications of biologic understanding of PDA in clinical research and provide insights for future development of novel approaches and agents in this disease. *Clin Cancer Res; 18(16); 4249–56. ©2012 AACR.*

Introduction

Pancreatic ductal adenocarcinoma (PDA), commonly referred to as pancreatic cancer, is a frequent and lethal disease ranking fourth as a cause of cancer-related death in Western countries. In 2012, it is estimated that a total of 43,920 patients will be diagnosed with pancreatic cancer and 37,390 will die of this disease in the United States (1). The causes of PDA remain largely obscure, with tobacco consumption, diabetes, and obesity recognized as risk factors. Approximately 10% of cases have a hereditary cause; another major risk factor is familial pancreatitis (2). The prognosis of PDA remains poor despite advances in the clinical management of the disease, including the introduction of systemic chemotherapy in the management of patients with operable disease, as well as the development of novel, more effective chemotherapeutic agents (2).

Over the past few years, a better understanding of the molecular biology of PDA has been gained. Critical to this progress has been the availability of preclinical models, including genetically engineered mouse models (GEMM) and patient-derived xenografts, that it is hoped may better recapitulate the biology of the disease (3–5). It appears clear that PDA, like most cancers, is a genetically diverse disease. The successive accumulation of mutations in key oncogenes and tumor suppressor genes leads to PDA that, once established, is a quite complex, heterogeneous, and genetically unstable disease (6–8). In addition, PDA is composed of multiple compartments. Together with the mature and differentiated cell compartment, some investigators believe there is a cancer stem cell compartment that, while numerically small, may be resistant to chemotherapy and radiation therapy and is involved in the process of cancer spread and treatment failure (9). PDA is also characterized by a dense and desmoplastic stroma composed of fibrillar elements such as collagen I, activated fibroblasts, and inflammatory cells among others (10). The interactions between the stroma and the cancer cells, largely ignored until recently, play critical roles in the process of tumor development and spread (as well as possible protection from the immune system). Furthermore, the poorly vascularized PDA stroma acts as a barrier to drug delivery in this disease and contributes to the creation of a hypoxic environment. Indeed, the mechanisms used by cancer cells to adapt to these conditions are starting to be elucidated and may represent potential therapeutic targets. In this article, we review the most salient biologic features of PDA with a focus on those that have clearer clinical applications.

Strategies to target the pancreas cancer cell

Evidence suggests that PDA results from the successive accumulation of mutations in oncogenes and tumor suppressor genes (6, 11). A summary of current concepts in PDA genetics is provided by Iacobuzio-Donahue and colleagues in this *CCR Focus* section (12). The cancer likely originates in the ductal epithelium and evolves from

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premalignant lesions to fully invasive cancer. A lesion called pancreatic intraepithelial neoplasia is the best characterized histologic precursor of PDA (13). It has been recently shown that these lesions harbor mutations in the same genes as invasive PDA, further supporting its role as a premalignant lesion (14). Fully established PDA almost universally carries 1 or more of 4 genetic defects (15). Ninety percent of tumors have activating mutations in the *KRAS2* oncogene. Transcription of the mutant *KRAS* gene produces an abnormal Ras protein that is "locked" in its activated form, resulting in aberrant activation of proliferative and survival signaling pathways. Likewise, 95% of tumors have inactivation of the *CDKN2A* gene with the resultant loss of the p16 protein, a regulator of the G_1–S transition of the cell cycle, and a corresponding increase in cell proliferation. *TP53* is abnormal in 50% to 75% of tumors, permitting cells to bypass DNA damage control checkpoints and apoptotic signals, thus contributing to genomic instability. The deleted in pancreatic carcinoma 4 gene (*DPC4*—also known as *SMAD4*/*MADH4*) is lost in approximately 50% of pancreatic cancers, resulting in aberrant signaling by the TGF-β cell surface receptor.

The full mutational landscape of PDA was initially determined in a study that reported an extensive and comprehensive genetic analysis of 24 PDAs (6). The results from this study showed that PDA is extremely complex and heterogeneous. The average number of likely relevant genetic abnormalities per tumor was 63 in this study, mainly point mutations, which may be organized in 12 functional cancer-relevant pathways. However, not all tumors have alterations in all pathways, and the key mutations in each pathway appear to differ from one cancer to another (6). More recently, 2 studies analyzed the genomic characteristics of primary and paired metastatic lesions (7, 8). These studies showed that the clonal populations that comprise the distant metastases are present in the primary tumor and appear to have evolved genetically over a long period of time. Genomic instability frequently persists after cancer dissemination, resulting in ongoing, parallel, and even convergent evolution among different metastases.

The genetic diversity of PDA is also manifested at the transcription level. On the basis of gene expression profiling, it has been recently proposed that PDA may be classified in 3 phenotypic groups, including a classical group, a group with endocrine features, and a quasi-mesenchymal group. These 3 groups not only carry different prognoses but also respond differently, at least *in vitro*, to drugs commonly used in the therapy of PDA, such as gemcitabine and erlotinib (16).

Recent discoveries deciphering the genetic changes are beginning to be exploited Clinically, it has been a real challenge however, because most of the mutations encountered in PDA, such as *KRAS* or *CDKN2A*, at present, are not directly targetable. Different strategies to circumvent this problem are being studied. With regard to KRAS mutations, for example, one approach is to target the downstream signaling pathways activated by Ras. Currently, there is a large portfolio of agents in clinical development against RAF, ERK, MEK, PI3K, and Akt, to name a few, some of which have shown activity, either alone or in combination, in patients with PDA in early clinical studies.

One ramification that has become clearer after looking further at the data elucidating PDA genomics is the need for personalized or precision medicine. This is well exemplified by the global genetic analyses of PDA. Although no recurring drug targets were encountered, some individual patients harbored mutations in genes that could be therapeutically exploited. Thus, a mutation in the *PALB2* gene found in one cancer suggested that this cancer could be sensitive to DNA-damaging agents. Indeed, although anecdotal, treatment of this individual with alkylating agents resulted in marked tumor regression and long survival (17). The hope that a detailed analysis of a patient's genome may lead to individualized treatment in PDA as in other cancers is being incorporated in prospective clinical studies using designs such as the one depicted in Fig. 1. In a preliminary report from one of these trials, assessment of well-known drug targets such as ERCC1, Topo 1, and Topo 2 in a cohort of 35 patients with PDA led to specific treatment recommendations (18). Furthermore, in-depth analysis of copy number variation in patients with metastatic pancreas cancer showed several genomic abnormalities that could be treatment targets (19). However, several important challenges must be addressed before this approach can be incorporated into the clinic. One is the need for high-quality tumor tissue at the time of diagnosis. Second, the complexity of PDA genetics requires sophisticated bioinformatic analysis of the data to select the most relevant targetable mutations. Because these types of studies and *in silico* analyses usually identify several potential treatment options, systems to experimentally test their effectiveness and eliminate false positives are needed. In this regard, the so-called "Avatar" mouse models may be useful and are being evaluated by several research groups (20). Finally, and perhaps the most challenging, is that even if new targets are discovered, there are often no drugs for the targets discovered.

The tumor microenvironment

A characteristic of PDA is the formation of a dense stroma, termed a desmoplastic reaction composed of cellular and fibrillar elements (Fig. 2; refs. 10, 21). Pancreatic stellate cells play a critical role in the formation and turnover of the stroma. Upon activation by growth factors such as TGF-β1, platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF), these cells become activated myofriblobasts and secrete collagen and other components of the extracellular matrix. Stellate cells also appear to be responsible for the poor vascularization of PDA (22, 23). Furthermore, stellate cells regulate the reabsorption and turnover of the stroma, mainly though the production of matrix metalloproteinases (24). The stroma is not only a mechanical barrier but also constitutes a dynamic compartment critically involved in the process of tumor formation, progression, invasion, and metastasis (10, 21). Stromal cells express multiple proteins, such as Cox-2, PDGF receptor, VEGF, stromal-derived factor, chemokines, integrins, secreted

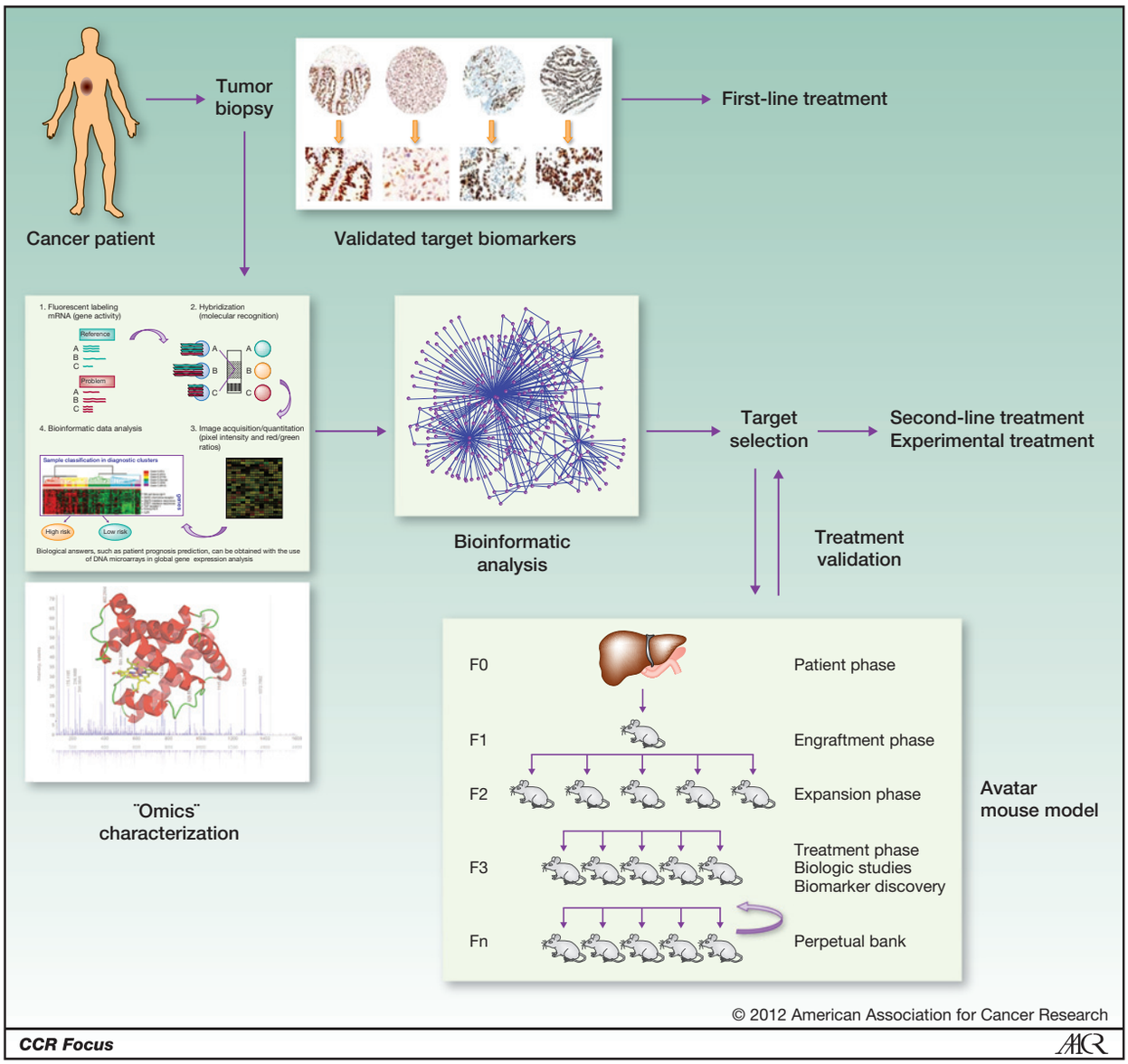

Figure 1. Schematic approach to PDA personalize treatment. Depicted in this figure is the approach followed by the Stand Up To Cancer Dream Team in pancreas cancer to personalize treatment. This included selection of first-line treatment based on readily available and easy-to-measure biomarkers coupled with complete "omic" characterization, bioinformatic analysis for target and pathway identification, and Avatar mouse model preclinical testing for ranking selected treatments and prioritization of clinical trial participation.

protein acidic and rich in cysteine (SPARC), and hedgehog pathway elements, among others, that have been associated with a worse prognosis and resistance to treatment.

It is hoped that our increasing understanding of the PDA stroma will have therapeutic implications, and several complementary approaches are currently undergoing clinical evaluation (Fig. 2). One key factor in the greater understanding of the role of the stroma in PDA biology and therapeutics has been the development of GEMMs of PDA that are characterized by dense murine stroma more similar to the clinical scenario. As shown in Fig. 2, the study of tumor microenvironment is providing important therapeutic targets that will have to be validated. For example, quiescent pancreatic stellate cells express hormone receptors such as vitamin D and retinoic acid receptor that may prevent activation of these cells to active, matrix-secreting myofibroblasts. Studies have also shown several important targets in the activated myofibroblast such as PDGF, TGF-β, FGF, Cox-2, hedgehog ligand, matrix metalloproteinases, and CTGF among others. In preclinical models, therapeutic targeting of some of these receptors and enzymes is associated with antitumor effects. One of the most highly sought targets is the hedgehog pathway. In preclinical studies, strategies that block smoothened result in marked

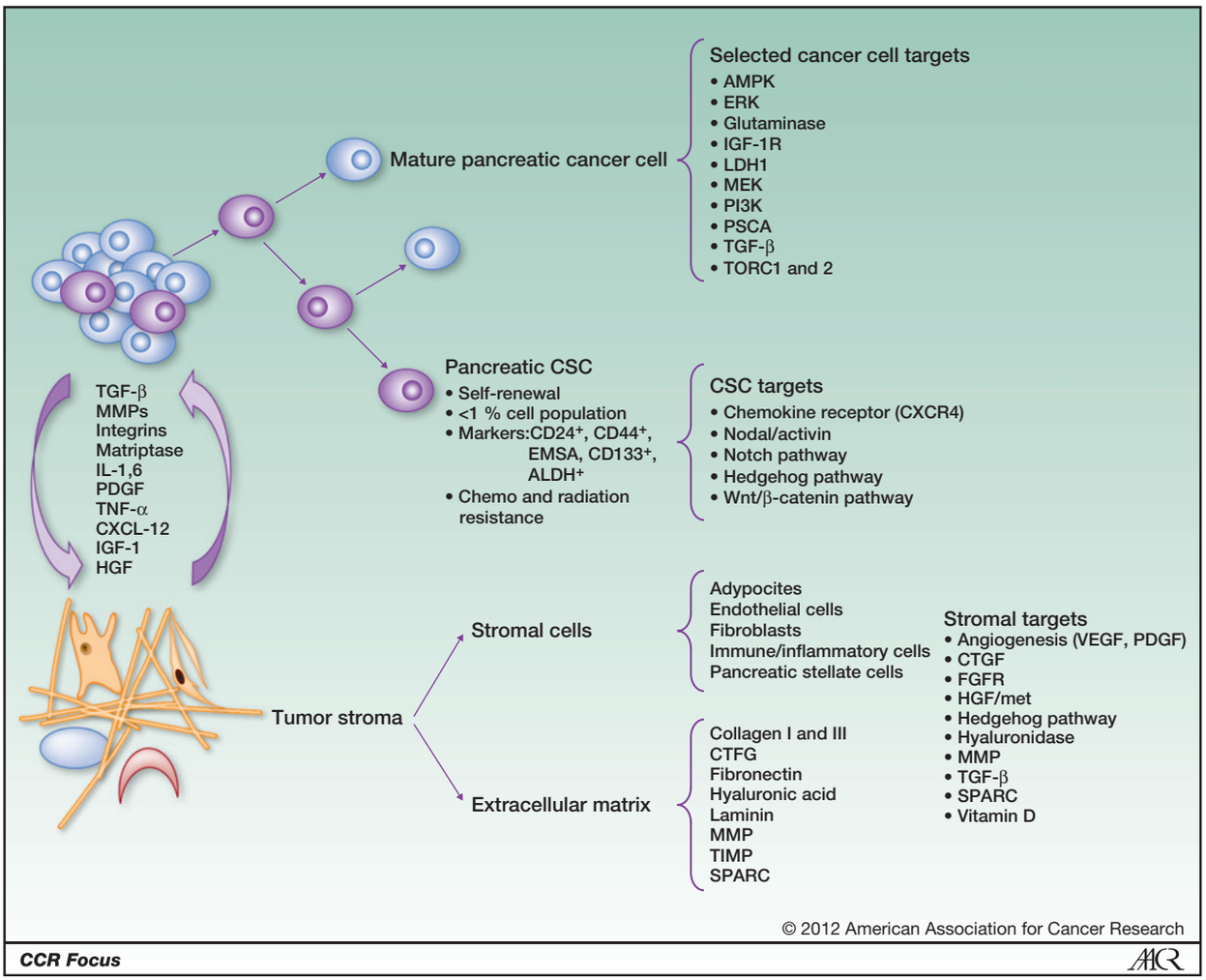

Figure 2. Selected new targets in PDA. Current and immediate future targets in PDA are shown including their predominant compartment localization. CSC, cancer stem cell. Figure adapted from Hidalgo (2).

elimination of the stroma and this in turn is associated with better perfusion and increased delivery of gemcitabine (25).

The notion that depletion of the PDA stroma could lead to better delivery of anticancer drugs has been the focus of recent attention (discussed by Feig and colleagues in this *CCR Focus* section; ref. 26). The 2 most exploited targets thus far are SPARC and hyaluronic acid. SPARC, also known as osteonectin, is an extracellular matrix protein that has been associated with poor prognosis in pancreatic cancer patients as well as with invasion and metastasis in preclinical PDA models (27, 28). Recent studies suggest that SPARC functions as a stromal chaperone playing a critical role in collagen turnover in pancreatic cancer. SPARC is a target of albumin-bound nab-paclitaxel. In a phase I/II study of this agent in patients with PDA, a combination with gemcitabine showed promising results with a median survival of 12.8 months in patients with advanced disease. In parallel mechanistic studies nab-paclitaxel, in addition to its cancer cell–directed effects, has been shown to increase the delivery of gemcitabine. Additional studies showed that this might be because of stromal depletion and/or modification of the catabolism of gemcitabine (29). Likewise, administration of pegylated hyaluronidase to mouse models of PDA eliminates hyaluronic acid content, alleviates intratumoral pressure, normalizes blood vessels, and increases the delivery and efficacy of gemcitabine (30, 31). These 2 strategies are currently in clinical development.

An additional characteristic of the PDA stroma is that it contributes to an immunosuppressive tumor microenvironment that can interfere with antitumor immunity. Consequently, there has been interest in reversing this phenomenon therapeutically. Because CD40 activation can reverse immune suppression and drive antitumor T-cell responses, clinical studies have tested the combination of an agonist CD40 antibody with gemcitabine chemotherapy in patients with surgically incurable PDA and have shown tumor regressions. Mechanistic studies showed that this agent

works by stimulating the infiltration of tumor macrophages that deplete the cancer stroma (32).

Hypoxia is another consequence of the tumor microenvironment. Recently Borad and colleagues reported encouraging results with the hypoxia-activated alkylating agent TH302 (33). If these findings are confirmed in a follow-up phase III trial, this may prove valuable against this disease.

Optimal therapeutic targeting of the PDA stroma may need specific clinical trial design (Fig. 3). Most new drugs in PDA, as in other tumor types, are introduced in late stages of the disease. One issue, however, is that while PDA has a very rich and hypovascular stroma, metastases arising from PDA do not and are not different from other tumors. This may explain why, thus far, inhibitors of the hedgehog pathway tested in patients with advanced disease have not proved beneficial. Thus, the best opportunity for a stromal-directed agent may be patients with locally advanced disease, particularly tumors with wild-type DPC4, as these are known to be less prone to metastasize and possess a higher stromal content. Clinical endpoints may include (in addition to response rate) time to disease progression, overall survival, and the proportion of patients whose tumors are rendered operable after treatment. This setting could also benefit from innovative imaging studies such as ^{18}fluoro-misonidazole positron emission tomography (MISO-PET) to assess hypoxia and elastography to determine tumor stiffness (34).

Pancreatic cancer stem cells

Several parallel studies, using primary tumor xenograft models, have identified a subset of pancreas cancer cells that some investigators believe have stem cell properties (9, 35). As summarized by Penchev and colleagues, these cells, whose phenotypic identification is still a matter of debate, may have different biologically important characteristics, such as the capacity to self-renew and divide asymmetrically (36). In PDA, early data suggest that the identification of these putative cancer stem cells in primary tumors is associated with shorter overall survival, resistance to the standard cytotoxic agent gemcitabine, and enhanced metastatic potential (35, 37). Cancer stem cells are also heterogeneous, with different cell populations having different functional properties. One important recent observation is that the putative cancer stem cells are very plastic and can transition between different states, such as epithelial and mesenchymal states, that may be involved in the metastatic spread of PDA (38).

An interesting observation is that PDA cancer stem cells have unique therapeutic targets (39–42). These include genes found in developmental pathways such as hedgehog, Wnt, Notch, CXCR4, and Met, as well as apoptotic pathway

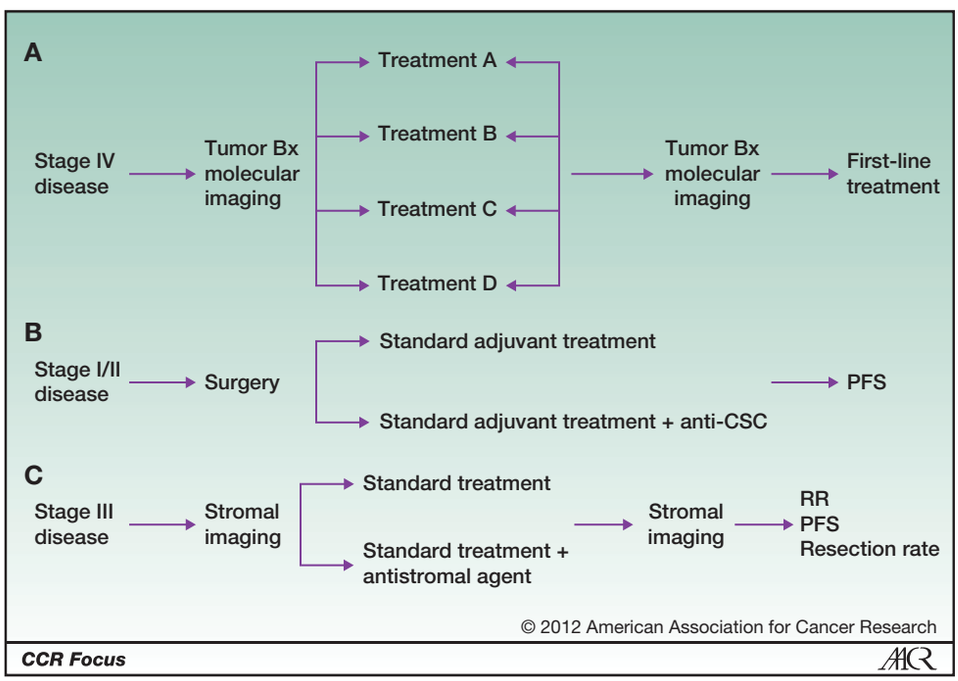

Figure 3. Potential clinical trial designs in PDA. A, screening trial of new agents in patients with advanced disease. After a tumor biopsy with or without molecular image, patients are randomized to receive 1 of several new agents for a short period of time followed by a second tumor biopsy and appropriate imaging. Patients then proceed to receive first-line treatment. Analysis of paired tumor biopsies and molecular imaging allows selection of molecularly active drugs to be further developed. B, trial design to test anticancer stem cell therapeutics. Rather than stage IV disease, these agents are more likely to be effective in situations of minimal disease such as the adjuvant setting. C, clinical trial design for drugs targeting the cancer stroma. Because of the preponderance of tumor stroma in patients with locally advanced disease, this represents an ideal clinical scenario to test stroma-modulating drugs. Bx, biopsy; CSC, cancer stem cell; PFS, progression-free survival; RR, response rate.

targets such as DR5 and novel pathways such as nodal–activin (Fig. 2). In preclinical models of human PDA, targeting these pathways results in prolonged tumor control compared with the short-lived tumor regressions with conventional chemotherapeutic agents. More recently, salinomycin has been shown to induce cell death in epithelial–mesenchymal transition–induced cancer stem cells (43).

Like agents targeting stroma, the potential of therapeutics directed at these putative cancer stem cells might require specific clinical trial designs. One possible scenario in PDA is in the postoperative setting. Despite the best current efforts including surgery, chemotherapy, and radiation therapy, the outcome of patients with resected PDA is poor, with a median time to progression of approximately 12 to 14 months (44–46). Thus, one clinical trial design might randomize patients to conventional treatment with or without a cancer stem cell antagonist with the expectation that disease-free survival would increase with the cancer stem cell antagonist (see Fig. 3).

Nutritional requirements of PDA

Like other cancers, PDA cells rely on fuel sources for homeostasis and proliferation; as such, interrupting the use of 2 major nutrients, glucose and glutamine, may provide new therapeutic avenues. In addition, PDA cancer cells are particularly suited to grow under low oxygen conditions (47). Another unique characteristic of PDA cells is their autophagy activity, which allows energy procurement from digestion of intracellular organelles (see Le and colleagues in this *CCR Focus* section, ref. 48).

Detailed analysis of key metabolic enzymes has identified several putative targets, such as hexokinase, pyruvate kinase, LDHA, glutaminase, and AMPK, among others. In preclinical studies, agents directed against these targets are associated with antitumor effects. For example, the LDHA inhibitor FX11 has shown antitumor effects in cells harboring mutant p53 proteins by selectively blocking the conversion of lactate to pyruvate. So far, however, the only 2 agents with the potential to interfere with the metabolism of PDA in the clinic are metformin and the mTOR inhibitors. Metformin, an activator of AMPK, reduces the risk of PDA in patients with diabetes and exerts antitumor effects in preclinical PDA models (49, 50). In a retrospective analysis of diabetic patients with PDA, metformin increased overall survival (51). The precise mechanism of action of this effect is not known, but reduction of glucose uptake may be important. In this regard, mTOR inhibition with rapamycin has been shown to decrease glucose uptake by reducing the levels of Glut 1 in pancreas cancer (52, 53).

Another point of interest is autophagy, because PDAs display significant autophagic activities for survival. Indeed, Ras-transformed cells depend on autophagy for survival (54). Hence, inhibition of autophagy with the antimalarial agent chloroquine has resulted in significant preclinical responses of pancreatic cancer xenografts and allografts in treated mice as compared with control animals. Chloroquine also diminishes pancreatic tumorigenesis in a transgenic model and is currently been tested in clinical studies.

Summary

Over the past few years, our molecular understanding of pancreatic cancer has advanced dramatically. These advances include genetic diversity and the notion that metastases are genetically unstable and heterogeneous and occur early in the disease. Another important development is the realization of the importance of the stroma for both cancer development and progression and as a barrier to the optimal delivery of chemotherapy. A group of pancreatic cancer cells with stem cell properties have been found to be resistant to chemotherapy and radiation therapy. Finally, insights into the mechanism responsible for cancer adaptation to hypoxic environments and nutrient procurements are also providing new therapeutic targets.

Some of these findings are already resulting in new therapeutic targets and treatment strategies. However, rapid and effective drug development in PDA may need new clinical trial designs. In the past, agents have only been tested in patients with advanced disease in large randomized trials with a survival outcome. This is not a very productive strategy, and not surprisingly dozens of these trials failed. More effort should be placed in understanding the molecular effects in early studies and to select the disease stage most likely to benefit from a particular situation. As an example, Fig. 3 shows the clinical trial design used by the Stand Up To Cancer Pancreas Cancer Dream Team to interrogate the effects of several potential molecular leads with the goal to prioritize phase III candidate approaches.

We still have a long way to go. The Editors hope the readers enjoys this special *CCR Focus* section on pancreatic cancer and that it gives colleagues additional ideas of ways to pursue what is still a deadly disease.

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Authors' Contributions

Conception and design: M. Hidalgo, D.D. Von Hoff
Development of methodology: M. Hidalgo
Writing, review, and/or revision of the manuscript: M. Hidalgo, D.D. Von Hoff

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