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Development of Pancreatic Cancer: Targets for Early Detection and Treatment

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Abstract
Background: Pancreatic ductal adenocarcinoma (PDAC) is the 4th leading cause of cancer death worldwide and compared to other malignancies its share in cancer mortality is expected to rise further. This is due to a lack of sensitive diagnostic tools that would permit earlier detection in a potentially curable stage and the very slow progress in finding effective drug treatments for pancreatic cancer. ***Key Messages:*** Aside from genetic predispositions and environmental agents, chronic pancreatitis is by far the greatest risk factor for PDAC. It also shares several etiological factors with pancreatic cancer and represents its most challenging differential diagnosis. Biomarkers that can distinguish between chronic pancreatitis and PDAC may therefore be suitable for the latter's early detection. Moreover, targeting the natural history of chronic pancreatitis would be one approach to prevent PDAC. Targeting tumor-cell signaling directly by interfering with receptor tyrosine kinases has shown some efficacy, although the results in clinical trials were less encouraging than for other cancers. Other compounds developed have targeted the formation of extracellular matrix around the tumor, the proteolytic activity in the tumor environment, histone deacetylases, hedgehog signaling and heat shock proteins, but none has yet found its way into routine patient care. Attempts to individualize treatment according to the tumor's somatic mutation profile are novel but so far impractical. ***Conclusions:*** Progress in the treatment of pancreatic cancer has been exceedingly slow and mostly dependent on improved pharmaceutical preparations or combinations of established chemotherapeutic agents. The promise of major breakthroughs implied in targeting tumor signal transduction events has so far not materialized.

Introduction

Pancreatic cancer is currently the 4th leading cause of cancer death and projected to become the 3rd leading cause of cancer-related death by 2030 due to delayed diagnosis and slow progress in treatment development [1]. The dismal prognosis of pancreatic cancer is caused by a variety of factors: (a) due to its location in the retroperitoneum, pancreatic cancer causes symptoms only when it has already grown to an advanced stage and is no longer locally resectable [2]. (b) Pancreatic cancer has a tendency to disseminate not only into the bloodstream and into the lymphatic tissue but also along nerve fibers, leading to an unusually high recurrence rate even after successful R0 resection [3]. For both these issues, a current consensus predicts that methods allowing earlier detection of pan-

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creatic cancer would be of benefit and improve survival [4]. (c) Pancreatic cancer is highly resistant to chemotherapy, radiation therapy and even targeted therapy [5].

Early Detection of Pancreatic Cancer

In the context of early detection methods and outside of imaging technologies, only very few biomarkers have been identified so far that could either distinguish pancreatic cancer from other disorders of the pancreas or detect it earlier than with currently available methods. The best established blood test for this purpose is carbohydrate antigen 19-9 (CA19-9), a Lewis antigen of the MUC1 protein-class. Unfortunately, CA19-9 can also be elevated in patients with nonmalignant diseases including liver cirrhosis, chronic pancreatitis and cholangitis as well as other gastrointestinal cancers [6]. CA19-9 has been reported to discriminate between pancreatic cancer patients and healthy controls with a sensitivity and specificity of slightly over 80% [7] and between pancreatic ductal adenocarcinoma (PDAC) and benign pancreatic disease with a sensitivity of 78% and a specificity of 83% [8]. However, CA19-9 is not expressed in Lewis blood type negative patients and this limits the optimum of any test relying on CA19-9 at a sensitivity of 92% under the best of circumstances. In up to one third of patients, the distinction between chronic pancreatitis and PDAC is inaccurate and the negative predictive value of diagnostic assays is often no better than 50–60% [1]. This has prompted a search for diagnostic biomarkers in blood and other body fluids (including saliva) for 2 purposes: to distinguish between benign pancreatic disease and pancreatic cancer and to detect PDAC earlier than currently possible with established imaging techniques. One very promising step in this quest is the detection of exosomes or microRNA patterns with a reasonable degree of specificity for PDAC [9]. Our group has taken a different approach and searched for metabolic biomarkers using a metabolomics approach including lipidomics. In more than 900 patients and appropriate controls, we were able to identify a distinct biomarker signature that can distinguish pancreatic cancer from chronic pancreatitis with greater sensitivity and specificity than CA19-9 and would improve the accuracy of the detection in 30% of patients [10]. Biomarker signatures (panels of multiple markers), rather than single individual parameters appear presently the most promising approach to early pancreatic cancer detection and thus the diagnosis in a potentially curable stage. Whether they can be employed in a population-based screening approach rather than being used only to make the distinction between clinically manifest benign and malignant pancreatic disorders has not been established and requires further studies.

Treatments Resistance of Pancreatic Cancer

The issue of therapy resistance is even harder to address. Some progress has been made over recent decades in identifying chemotherapy regimens that increase the overall survival of patients with pancreatic cancer. The most notable success was to establish that adjuvant chemotherapy in pancreatic and ampullary cancer can double the survival of patients after successful resection of the tumor [11, 12]. However, the fact that this merely represents an improvement from 10% to approximately 20% overall survival after 5 years only highlights the extensive treatment resistance and almost limitless recurrence potential of this tumor. For patients in whom surgery is not an option because the tumor is locally advanced, usually with artery encasement beyond a resectable stage, or because of metastasis formation, palliative chemotherapy is currently the only therapeutic option. Improvements in overall survival have been achieved in recent years, albeit the extent is limited. One regimen that was found to confer a survival benefit was the combination of several long established cytotoxic compounds such as 5FU, irinotecan and oxaliplatin [13]. Another used a new albumin-encapsulated preparation of paclitaxel in combination with gemcitabine and found it superior to the long-standing standard regimen of gemcitabine alone [14]. A similar approach to improving the tumor penetrance of established chemotherapeutic agents was taken with irinotecan, a liposomal preparation of which has resulted in encouraging initial studies [15] and will probably be approved for pancreatic cancer within the next months. These regimens have improved the median overall survival from 5 months to no more than 11 months and thus represent a much lesser treatment advance than achieved for patients with colorectal cancer or other solid tumors. A summary of currently available treatment options can be found in table 1.

Potential and Established Treatment Targets

A variety of structures have been targeted in pancreatic cancer such as the EGF receptor, the VEGF receptor, fibroblast activation protein α5β1-Integin, and others

Table 1. Life expectancy in patients with pancreatic cancer

5-year overall survival of all patients, %	0.4
5-year overall survival after resection and adjuvant chemotherapy, %	20
Median survival, months	
All patients, best supportive care	5
Chemotherapy with gemcitabine	6
Chemotherapy with gemcitabine plus capecitabine	7
Chemotherapy with gemcitabine plus nab-paclitaxel	9
Chemotherapy with gemcitabine plus erlotinib (in case of rash)	10
Chemotherapy with FOLFIRINOX	11
Resection without adjuvant chemotherapy	16
Resection with adjuvant chemotherapy (gemcitabine or 5 fluoruracil)	23
Current average gain in life expectancy by surgery, months	12–17

Gudjonsson B: Cancer 1987;60:2284–2303 [52]
Neoptolemos JP, et al: N Engl J Med 2004;350:1200–1210 [53]
Moore MJ et al: J Clin Oncol 2007;25:1960–1966 [16]
Conroy T, et al: N Engl J Med 2011;364:1817–1825 [13]
Neoptolemos JP, et al: JAMA 2010;304:1073–1081 [11]
Burris HA 3rd, et al: J Clin Oncol 1997;15:2403–2413 [54]
Cunningham D, et al: J Clin Oncol 2009;27:5513–5518 [55]
Goldstein D, et al: J Natl Cancer Inst 2015;pii:dju413 [14]

without resulting in a significant clinical benefit. Neither overexpression of TNFα nor the use of broad spectrum receptor tyrosine kinase inhibitors has met the high expectations of patients and physicians. The only tyrosine kinase inhibitor found to confer a survival advantage so far was erlotinib, a small molecule originally designed to interfere with EGF receptor signaling but probably also effective against more than 20 other RTKs [16]. Not every patient benefits from treatment with erlotinib but only those who develop a prominent skin rash. The skin rash therefore serves as a biomarker sign and can be used to determine whether or not a continuation of the treatment beyond a few weeks is of any benefit to the patient. Other RTKs [17] are currently under investigation as potential treatment targets and it is much hoped that novel compounds directed against them can match or surpass the results achieved with erlotinib.

Since more than 90% of pancreatic cancer specimens carry somatic mutations in the proto-oncogene *KRAS* this has turned into an attractive target. The disadvantage of the RAS pathway is that it is vital for cellular survival in all tissues and not only cancer cells. This poses a number of difficulties for developing tumor-specific anti-RAS therapies. Other targets that are currently under investigation include polo-like kinase and heat shock protein 70, the latter of which appears to be involved in tumor cell resistance to apoptosis [18]. The dissemination of tumor cells into neighboring organs depends on the function of intact cell–cell adhesions [2], which impair metastasis formation. Histone deacetylases HDAC1 and HDAC2 are potent regulators of cell-contact protein formation and have therefore (including their inhibitors) become a much investigated target for pancreatic cancer treatment modalities [19]. The jury is still out as to whether or not they are of any benefit to patients. Once the appropriate target has been identified, there remains the challenge of how to deliver the compound to the tumor cells in a cancer that produces abundant extracellular matrix, an often severe impediment to drug delivery. To address this challenge a number of techniques including microspheres and the abovementioned albumin- or liposome encapsulation of compounds have been invented. Other strategies target the tumor stoma directly.

Targeting Extracellular Matrix Deposition

One of the well-researched explanations why pancreatic cancer is so resistant to chemotherapy is the fact that it produces extensive extracellular matrix [20] encapsulating the tumor, a phenomenon it shares with chronic pancreatitis [21], and that any systemically administered medication can simply not reach the tumor across this barrier [22]. This assumption has prompted the development of several strategies intended to overcome the matrix barrier and to degrade or digest its components in pancreatic cancer [23]. Recent experimental evidence suggests that this may not necessarily be beneficial and could even render the exposed tumor cells more aggressive [24, 25]. Inhibition of the hedgehog pathway, regard-

ed as crucial for pancreatic cancer desmoplasia and matrix deposition, also resulted in disappointing outcomes [26]. The longstanding discussion of whether the extracellular matrix protects the patient from a dissemination of his tumor or whether it protects the tumor from the penetration of chemotherapeutic agents or tumor-lytic inflammatory cells appears not to be settled for the moment.

Precision Therapy

Pancreatic cancer is known to carry a multitude of somatic mutations affecting a finite number of signal transduction pathways. A strategy has therefore been developed; it is broadly based on the concept of individualized medicine, more recently termed precision medicine. The approach involves taking a tumor biopsy, analyzing the tumor genome and characterizing the signaling pathways that have undergone pathological alterations. Based on these findings, an individually confectioned cocktail of antiproliferative agents or inhibitors of signal transduction pathways shall then be administered. Investigators have so far screened for established molecular targets such as *HER2* amplification, *KRAS* wild-type, and mutations in DNA damage repair pathways (*BRCA1*, *BRCA2*, *PALB2*, *ATM*). The first pilot results are not encouraging but the greatest impediments are mostly technical. They include the need to obtain a sufficient number of tumor cells on biopsy or the delay of 3 weeks until final results are translated into a therapy, which resulted in an unacceptable dropout rate in one study [27]. However, these difficulties will most likely be overcome by technical improvements and only then can individualization of therapy according to the genomic tumor profile be assessed with a sufficient degree of robustness.

Pancreatic Cancer and Chronic Pancreatitis

Chronic pancreatitis is not only the single most significant risk factor for the development of pancreatic cancer but also an important differential diagnosis [28]. Particularly patients suffering from the hereditary variety of chronic pancreatitis that is associated with mutations in the cationic trypsinogen (*PRSS1*) gene have a 40–70% lifetime risk of developing pancreatic cancer [29]. They further double their cancer risk if additional environmental factors such as cigarette smoking contribute to this condition [30]. It seems presently unlikely that acute pancreatitis [31] can contribute to the pancreatic cancer risk, but for autoimmune pancreatitis, a possible association has not been ruled out [32, 33].

Chronic pancreatitis and pancreatic cancer share a number of underlying mechanisms and risk factors. Common to all forms of pancreatitis is a prominent role of trypsin, a digestive protease that is prematurely activated in the early disease phase [34, 35] and mutations in one of the isoforms of which (*PRSS1*) confer the greatest risk of developing hereditary pancreatitis [28, 29], the disease variety burdened with the greatest risk of developing pancreatic cancer [29, 30]. Interestingly, trypsin is also immunogenic and has been implicated in the pathogenesis of autoimmune pancreatitis [36]. The role of trypsin in pancreatic cancer is less clear, but several studies have implicated this digestive protease as either a biomarker [37] or a pathogenetic factor [38] for adenocarcinoma of the pancreas. The same connection applies to another group of proteases, lysosomal cathepsins, secreted by the exocrine pancreas in significant quantities [39, 40], play a prominent role in the activation of trypsin during pancreatitis [41, 42], but have also been identified in pancreatic cancer tissue, where their presence appears to be a biomarker for a poor prognosis [43]. Their pathogenetic role in cancer is assumed to require an involvement in the interaction between cancer cells and extracellular matrix.

Another common mechanism between pancreatitis and cancer deals with the functional impairment of cell–cell contacts [44], which not only permits the translocation of inflammatory cells into the pancreas [45, 46], but at the same time allows for the dissemination of malignant cells from the tumor to peripheral organs [2]. Among the cell contact, protein families that have been shown to be involved in tumor development are claudins [47], mutations in which have recently been reported to also represent a risk factor for chronic pancreatitis [48].

The last factor on this incomplete list worth mentioning, and presently the most puzzling, is the ABO blood type. Blood types are a surrogate for the degree to which certain cellular proteins, and not only those on red blood cells, undergo surface glycosylation. It has been shown that the blood type B not only increases the lifetime risk of developing pancreatic cancer [49], but also doubles the risk of developing chronic pancreatitis [50]. Whether or not the underlying mechanisms indicated by blood type B only signals an unspecific cellular stress (ER-stress) response as common denominator for pancreatitis and cancer or rather points to a distinct set of proteins that need to undergo specific glycosylation events for the dis-

ease risk to materialize is presently unknown. Studies that attempt to solve this question are ongoing.

At present it appears plausible that any target that is common to pancreatitis and pancreatic cancer has the greatest potential for leading to a preventive strategy. As shown for other inflammatory disorders such as ulcerative colitis and hepatitis, it is likely that approaches with a beneficial effect on the natural disease course of pancreatitis will have an impact on the development of pancreatic cancer. Currently there is none, and therapy for chronic pancreatitis remains strictly symptomatic or complication oriented. This needs to change before greater progress in the management of patients with pancreatitis and in the prevention of pancreatic cancer can be expected [51]. Pancreatic cancer surgery is, in all but a tiny minority of patients, as much a palliative approach as conventional chemotherapy. It is at present just the better palliation and prolongs the patients live significantly longer. For medical therapy of pancreatic cancer to be more successful, two issues need to be resolved: (a) how to target tumor cells or tumor stem cells more specifically, effectively and sustainably and (b) how to deliver this therapy to a tumor across a highly impenetrable extracellular matrix barrier. A large-scale concerted effort by the research community and its funding agencies is required to make this deadly disease not only a non-surgical disorder but also a curable condition.

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