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TOPIC HIGHLIGHT

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Advances in pancreatic cancer research: Moving towards early detection

Xiang-Yi He, Yao-Zong Yuan

Xiang-Yi He, Yao-Zong Yuan, Department of Gastroenterology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200025, China
Author contributions: He XY collected all the references and drafted the article; Yuan YZ chose the topic, organized the structure and revised the article.
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Correspondence to: Yao-Zong Yuan, MD, PhD, Department of Gastroenterology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, 197 Ruijin Er Road, Shanghai 200025, China. yyz28@medmail.com.cn
Telephone: +86-21-64150773 Fax: +86-21-64150773
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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal forms of cancer. Substantial progress has been made in the understanding of the biology of pancreatic cancer, and advances in patient management have been significant. However, most patients (nearly 80%) who present with locally advanced or metastatic disease have an extremely poor prognosis. Survival is better for those with malignant disease localized to the pancreas, because surgical resection at present offers the only chance of cure. Therefore, the early detection of pancreatic cancer may benefit patients with PDAC. However, its low rate of incidence and the limitations of current screening strategies make early detection difficult. Recent advances in the understanding of the pathogenesis of PDAC suggest that it is possible to detect PDAC in early stages and even identify precursor lesions. The presence of new-onset diabetes mellitus in the early phase of pancreatic cancer may provide clues for its early diagnosis. Advances in the identification of novel circulating biomarkers including serological signatures, autoantibodies, epigenetic markers, circulating tumor cells and microRNAs suggest that they can be used as potential tools for the screening of precursors and early stage PDAC in the future. However, proper screening strategies based on effective screening methodologies need to be tested for clinical application.

Key words: Pancreatic ductal adenocarcinoma; Early detection; Diabetes mellitus; Pancreatic cancer

Core tip: Because pancreatic cancer is usually detected at an advanced stage and there is a lack of treatment strategies for advanced disease, it remains one of the most lethal solid tumors. Genetic and epigenetic alterations, miRNAs and tumor microenvironment promote the development of pancreatic cancer from precursor lesions to localized disease and further to metastatic disease in several years. An effective screening strategy for pancreatic cancer is therefore needed. New-onset diabetes mellitus associated with pancreatic cancer and recently identified novel circulating biomarkers should be explored as potential screening markers.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal forms of cancer. It is the 13th most commonly diagnosed cancer worldwide[1], and the eighth lead-

ing cause of cancer death. No early detection tests are available and most patients with localized disease have no recognizable symptoms or signs; as a result, most patients (80%-85%) are not diagnosed until late in the disease, when the cancer has metastasized to other organs[2,3]. Survival is better for those with malignant disease localized to the pancreas, because at present, surgical resection offers the only chance of cure. Because pancreatic cancer responds poorly to radiation and chemotherapy, and so far most of the targeted therapy agents have failed to show a substantial benefit, PDAC in the advanced stage is associated with an extremely poor prognosis[2,3]. Therefore, the early detection of PDAC has gained increasing attention with the aim of improving the outcomes of patients with this disease. Recent studies have improved our understanding of the pathogenesis of PDAC, the relationship between diabetes mellitus (DM) and PDAC, and the role of circulating biomarkers. The present review will discuss the possibility of using these data to detect PDAC in its early stage and propose future research directions.

RECENT ADVANCES IN THE UNDERSTANDING OF THE PATHOGENESIS OF PDAC

Despite the short lifespan of patients diagnosed with PDAC, the disease usually develops over a long period of time. Based on a genetic evolutionary model[4], it is estimated that 10-30 years are required from the initiating mutation until the patient's death. In this model, there are three critical periods in the genetic evolution of the disease: T1 is related to the formation of precursor lesions such as pancreatic intraepithelial neoplasia (PanIN) and lasts until the infiltrating carcinoma is first formed; T2 describes the period from that time until a metastatic subclone develops within the primary carcinoma; and T3 is the period of metastatic dissemination of that subclone until the patient's death. A conservative estimate of 11.7, 6.8 and 2.7 years per interval, respectively, has been reported[4].

The development of PDAC involves multiple steps. It may originate from four distinct precursors, *i.e.*, mucinous cystic neoplasm (MCN), intraductal papillary mucinous neoplasm (IPMN), PanIN, and the newly added intraductal tubular papillary neoplasms (ITPNs)[5]. All four harbor varying degrees of dysplasia and stepwise accumulation of genetic alterations, suggesting progression of these lesions from benign toward malignant neoplasms. MCNs have a characteristic ovarian-type stroma. Approximately one-third of MCNs are associated with invasive carcinoma of a ductal phenotype. IPMNs are recently established clinical entities with characteristic features of mucin hypersecretion and duct dilatation. Some IPMNs are associated with invasive carcinoma and IPMNs are recognized as precursors to pancreatic cancer. ITPNs are rare premalignant tumours, with a concomitant invasive component, and were included for the first time in the 2010 World Health Organization classification[5]. PanINs are microscopic proliferative lesions arising from any part of the pancreatic duct system. Low grade PanINs are commonly found in the pancreatic ducts of older individuals, whereas high grade PanINs, previously called carcinoma *in situ*/severe ductal dysplasia, may eventually give rise to invasive pancreatic cancer. PanINs are divided into four categories based on the degree of dysplasia (1A, 1B, 2, and 3). Appropriate clinical management is critical for patients with MCNs, IPMNs and PanINs. The progression from PanIN to invasive PDAC has been intensively studied and reviewed elsewhere[6]. The established model describes the stepwise progression of PanINs to PDAC through the accumulation of several important genetic aberrations. KRAS mutation may be the first step driving this progression, and it is detected in approximately 99% of PanIN-1 lesions[7]. In addition, to overcome oncogene-induced senescence, loss of function of CDKN2A, and genetic inactivation of TP53, SMAD4, and BRCA2 are also required for the development of PDAC[8]. Further investigation of these precursor lesions is expected to reduce the mortality from pancreatic cancer.

The development of PDAC involves multiple genes. In 2008, detailed, global, genomic analyses found that a large number of genetic alterations (an average of 63) affect a core set of 12 signaling pathways and processes that are each genetically altered in 67%-100% of cases of pancreatic cancer[9]. However, the pathway components that are altered in any individual tumor vary widely. The 12 core pathways[9] are apoptosis, DNA damage control, regulation of G1/S phase transition, Hedgehog signaling, homophilic cell adhesion, integrin signaling, c-Jun N-terminal kinase signaling, KRAS signaling, regulation of invasion, small GTPase-dependent signaling (other than KRAS), TGF-β signaling and Wnt/Notch signaling. In addition to the core pathways described above, more recent data indicate that chromatin regulation[10] and axon guidance[10,11] are additional cellular processes that play a crucial role in pancreatic cancer. The pathways involved in each patient often vary. This finding may help account for the heterogeneous nature of tumors and offer insights into why agents targeting a specific gene in a pathway rarely result in a therapeutic advantage in more than a minor percentage of patients. Therefore, identification of the core players of each pathway and the factors connecting them is important. In addition to whole genomic alterations, numerous investigators have focused on particular PDAC-associated genes through laboratory and patient studies. Our group demonstrated that Periostin[12], X chromosome-linked inhibitor of apoptosis (XIAP)-associated, factor 1 (XAF1, a novel XIAP modulator)[13], angiotensin-converting enzyme 2[14], bone morphogenetic protein-2[15], eEF1A2[16], L1 cell adhesion molecule (L1-CAM)[17], and DJ-1[18] are associated with PDAC proliferation, apoptosis, invasion and/or progression.

MicroRNAs (miRNAs) are a highly conserved family of 18-24-nucleotide RNA molecules that regulate the sta-

bility or translational efficiency of complementary target mRNAs. More than 20 miRNAs involved in pancreatic adenocarcinoma biology have been identified and shown to affect tumor growth, metastatic potential, and chemosensitivity[19]. Combinations of miRNAs can be used to differentiate between pancreatic adenocarcinoma and other pancreatic pathologies, as well as to assess prognosis. Manipulations of miRNAs can decrease the rate of growth or reinstall chemosensitivity to certain chemotherapeutic agents. The most extensively studied miRNA, as far as pancreatic cancer is concerned, is miR-21, which has been associated with cell proliferation, metastatic ability, decreased gemcitabine sensitivity, and poor overall survival (OS)[20-23]. Other PDAC associated miRNAs were discussed elsewhere. Recently, several other miRNAs (miR-196a[24,25], 130b[26], 92a[27], 198[28], 221[29,30], 23b[31], 29a[32,33]) were shown to play an important role in PDAC.

Tumors are complex tissues in which mutant cancer cells have conscripted and subverted normal cell types to serve as active collaborators in their neoplastic agenda. Recent studies have shown that PDAC is one of the most stroma-rich cancers. The tumor microenvironment surrounds most of the tumor mass and consists of a dynamic assortment of extracellular matrix components and non-neoplastic cells including fibroblastic, vascular and immune cells. Recent work has revealed that the PDAC stroma supports tumor growth and promotes metastasis, and simultaneously serves as a physical barrier to drug delivery[34]. Pancreatic stellate cells (PSCs) identified in 1998, have the ability to trans-differentiate from a "quiescent" retinoid/lipid storing phenotype in the normal pancreas to an "activated" a-smooth muscle actin producing myofibroblastic phenotype[35]. The activated PSCs produce the extracellular matrix proteins that comprise the pancreatic tumor stroma, to facilitate pancreatic cancer development[35]. Sonic hedgehog signaling has been shown to be restricted to the stromal compartment and enhance the desmoplastic reaction[36]. Findings[36] suggest that increased HIF-1α produced by hypoxic tumors triggers the desmoplastic reaction in pancreatic cancer.

The genetic evolutionary model of PDAC suggests a detection window of several years (T1 + T2) for this disease. The visualization of PDAC precursor lesions using currently available imaging methods is limited; therefore, the detection of precursors is difficult. Improving our understanding of the mechanisms of precursors and PDAC development may help identify tumor biomarkers for this disease.

DM AND PDAC

Because of the low incidence of PDAC in the general population, population-based screening is not recommended. It is more practical to screen individuals at increased risk for PC based on their family history or identifiable genetic predisposition, or patients with diseases known to increase the risk of pancreatic cancer, such as chronic pancreatitis and type Ⅱ DM. Patients with a family history of pancreatic cancer or mutation carriers (germline mutations in the *BRCA2*, *PALB2*, *p16*, *STK11*, *ATM*, *PRSS1* genes and Lynch syndrome or Peutz-Jeghers syndrome) should be screened for pancreatic cancer according to the recommendations of the International Cancer of the Pancreas Screening consortium[37]. Here, we will discuss the relationship between DM and PDAC and the possibility of using new-onset DM as a marker for the detection of PDAC.

Increasing evidence suggests that DM is related to PDAC. It is now recognized that although long-standing diabetes is an etiological factor for pancreatic cancer, new-onset diabetes is its manifestation[38-40]. Epidemiological investigations have found that long-term type 2 DM is associated with a 1.5-fold to 2.0-fold increase in the risk of pancreatic cancer[40]. The evidence suggesting that new-onset diabetes is the manifestation of PDAC, or in other words, caused by PDAC, is that: (1) new-onset diabetes is associated with a high prevalence of PDAC; (2) diabetes associated with pancreatic cancer is predominantly new-onset; (3) pancreatic cancer resection ameliorates diabetes; and (4) experimental data. A meta-analysis[41] conducted in 2005 that included 17 case-control and 19 cohort and nested case-control studies published between 1996 and 2005 demonstrated that the combined age-adjusted and sex-adjusted odds ratio (OR) for pancreatic cancer associated with diabetes was 1.8 (95%CI: 1.7-1.9) and was lower still (OR = 1.5) in patients with a ⩾ 5 year history of diabetes. In a pooled analysis[42] of 2192 patients with pancreatic cancer and 5113 cancer-free controls in three large case-control studies conducted in the United States, diabetes was associated with a 1.8-fold increase in the risk of pancreatic cancer (95%CI: 1.5-2.1). Risk estimates decreased as the number of years with diabetes increased[42]. A study from our group[43] included 1458 patients with PDAC and 1528 age-, sex- and sociodemographic matched controls and showed that compared with controls, patients with long-standing diabetes (⩾ 2-year duration) had a moderately increased risk of PDAC, with an OR (95%CI) of 2.11 (1.51-2.94). Interestingly, a significantly higher risk was observed among cases with new-onset DM (< 2-year duration), with an OR of 4.43 (3.44-5.72) compared to controls without DM. On the other hand, the reported prevalence of DM in pancreatic cancer varies from 23% to 75%, with the majority being new-onset[44]. Our data also showed that 44.7% of PDAC patients harbor DM, and almost 2/3 are new-onset[45]. Data from our group and other groups showed that resolution of DM after pancreatic resection occurs in 41%-57% of PDAC patients with new-onset DM, in contrast to most patients with longstanding DM, who remain diabetic postoperatively[44-46]. Recognition of new-onset diabetes as an early manifestation of pancreatic cancer could improve the detection of asymptomatic, early-stage pancreatic cancer[38].

The impact of DM on the long-term outcomes of patients with PDAC has also been intensively studied recently, although the results are controversial. In patients

with stage I -IV pancreatic cancers, DM does not confer a worse prognosis; in fact, diabetics have a statistically significantly superior median survival[47]. A retrospective study of 344 patients who underwent surgical resection of pancreatic cancers showed that perineural invasion was significantly more common in diabetics, with a poor OS[47]. A multi-institutional retrospective study[48] reported a shorter OS and disease-free survival (DFS) in patients with preoperative DM. By stratifying DM into different groups (long-term/new-onset pre-surgical diabetes, resolved/unresolved post-surgical diabetes), we found that the heterogynous DM groups have different impacts on PDAC outcomes: longstanding DM is predictive of poor postoperative DFS and OS, whereas postoperatively resolved new-onset DM is associated with longer DFS and OS[45].

There are several possible mechanisms to explain the effect of diabetes on promoting PDAC progression, including the cellular proliferative effects of hyperglycemia, hyperinsulinemia, abnormalities in insulin/IGF receptor pathways, oxidative stress and inflammatory responses[40]. A prospective nested case-control study that included 449 case patients and 982 control subjects showed that the highest and the lowest quintiles of HbA1c, insulin, and proinsulin were associated with an increased risk for pancreatic cancer. However, in mutually adjusted models, only circulating markers of peripheral insulin resistance (proinsulin), rather than hyperglycemia (HbA1c) or pancreatic β-cell dysfunction (insulin), were independently associated with pancreatic cancer risk[49]. By comparing the proteome of PDAC with and without DM, our previous study indicated that regenerating gene (REG) I α may be one of the connections between DM and PDAC[50]. The number of REG I α positive cancer cells was significantly higher in pancreatic cancer patients with diabetes (n = 38) than in subjects without diabetes. Overexpression of the REG I α protein in pancreatic cancer cell lines resulted in accelerated cell proliferation and consequently tumor growth, both *in vitro* and *in vivo*[50]. The IQ motif containing GTPase activating protein 1-exocyst axis is a growth factor- and nutrient-sensor that couples cell growth and division. It may function at the interface of cancer and diabetes[51].

Several preclinical and observational studies have shown that anti-diabetic medications may modify the risk of pancreatic cancer. A case-control study showed that diabetics treated with metformin had a significantly lower risk of pancreatic cancer (OR = 0.38; 95%CI: 0.22-0.69, P = 0.001)[52]. Metformin significantly decreased pancreatic cell growth[53]. These effects could be attributed to disruption of the crosstalk between insulin receptor and GPCR signaling[54], or up-regulation of miR-26a or other factors[53]. However, in a recent meta-analysis that included eleven studies, 1770 cases of pancreatic cancer in 730664 patients with DM were reported, indicating no significant association between metformin, insulin, or TZD use and risk of developing pancreatic cancer, and use of sulfonylureas was associated with a 70% increase in the risk of developing pancreatic cancer[55].

CIRCULATING BIOMARKERS FOR PDAC

Because PDAC develops over a long period of time and the curative response is significantly better in patients with early disease, an early diagnostic marker could positively impact the outcome of patients. Circulating biomarkers are always preferred over others because of their ease of collection and relatively noninvasive nature. The current standard serum marker, sialylated Lewis blood group antigen CA19-9, is widely used, but its use is limited to monitoring responses to therapy and not as a diagnostic marker because of its poor sensitivity (41%-86%) and specificity (33%-100%)[56]. CA19-9 can arise among patients with benign pancreaticobiliary disorders, notably cholestasis, and 5% to 10% of the population does not express Lewis antigens.

In the last two decades, many biomarkers have been tested for PDAC detection, some of which have higher specificity and sensitivity than CA19-9. These are new antibodies such as PAM4 recognizing MUC-1[57], soluble iC3b[58], REG4[59], serum phosphoproteins extracellular signal-regulated kinase (p-ERK1/2)[60], CEACAM1, a proliferation-inducing ligand[61], DJ-1[62], and laminin, gamma 2[63]. Further validation studies including a large number of cases are required for the clinical application of these biomarkers.

DJ-1 is up-regulated in 68.5% of PDAC specimens and correlates with tumor invasion and metastasis. The secretion of DJ-1 by tumor cells implies its potential as a biomarker[64]. Our data showed that the area under the curve (AUC) of serum DJ-1 is higher than that of CA 19-9 in certain patients with PDAC, and serum DJ-1 level also predicts poor patient outcome. Other groups confirmed our results[65] and showed the increase of DJ-1 in pancreatic juice[66].

The sensitivity and specificity of these biomarkers, which may be insufficient when used alone, can be improved by using them in combination or together with CA19-9. In a recent study[67], CA19.9 showed a better AUC in combination with SYCN, REG1B and AGR2 than when used alone. When analyzed in combination, three panels [CA19.9 + REG1B (AUC of 0.88), CA19.9 + SYCN + REG1B (AUC of 0.87) and CA19.9 + AGR2 + REG1B (AUC of 0.87)] showed a significantly better AUC (P < 0.05) than that of CA19.9 alone (AUC of 0.82). The superiority of the combination of biomarkers was also shown by our group and others[64,68].

Several recent reports showed that aberrant miRNA production is an early event in the development of PanIN lesions[69,70]. MiRNAs 21[71,72], 155[71], 16[73], 196a[73], 1290[74], 221[30], 375 (lower in PDAC)[30], and 18a[75] were identified by using miRNA expression profiling or other methods as potential biomarkers of PDAC alone or in combination with CA19-9 and each other[72,73]. A recent meta analysis of three blood based miRNA studies reported that the median specificity and sensitivity were 0.91 and 0.96, respectively[72]. Our group together with other centers[71] in China screened differentially expressed serum miRNAs with Illumina's sequencing by synthesis technology

using pooled serum samples followed by RT-qPCR validation of a large number of samples arranged in multiple stages in 97 PDAC cases and 158 age- and sex-matched cancer-free controls. We established 7 miRNA-based biomarker model (miR-20a, miR-21, miR-24, miR-25, miR-99a, miR-185, and miR-191) for PDAC diagnosis. These biomarkers had high sensitivity and specificity for distinguishing various stages of pancreatic cancer from cancer-free controls and also accurately discriminated pancreatic cancer patients from chronic pancreatitis patients (AUC = 0.993). In 26 stage I pancreatic cancer cases, the positive rate of pancreatic cancer detection by the 7 miRNA-based biomarker set was 96.2%, which was significantly higher than that of CA19-9 (46.2%) or CEA (30.8%) in the same sample set. In 48 stage Ⅱ pancreatic cancer cases, the positive rate was 91.7%, which was also higher than that of CA19-9 (62.5%) or CEA (31.3%). Although miRNA detection is not currently used as a criterion for PDAC diagnosis, recent investigations indicated that they may be promising biomarkers in the near future.

Circulating tumor cells (CTCs) are tumor cells that have acquired the ability to enter the circulatory system. Studies have reported the presence of CTCs in peripheral blood in 40%-100% of pancreatic cancer patients[76,77], and their potential as biomarkers of PDAC was demonstrated recently[76-83]. CTCs have the potential to provide a surrogate for "real-time biopsy" of tumor biological activity. However, as CTCs are extremely rare, both enrichment and sensitive methods of detection are required for their enumeration[79]. Recently, using a modular system with innovative features, EpCAM positive CTCs were isolated from PDAC patients at high purity (> 86%) and with excellent yields (mean = 53 CTCs per mL)[76]. However, the high cost and involved procedure associated with this system constitute an obstacle to its clinical application.

CONCLUSION

The early detection of pancreatic cancer may benefit patients with PDAC. The slow development and progression of pancreatic cancer are closely associated with the activation of oncogenes, inactivation of tumor suppressor genes, altered expression of miRNAs, and activated tumor microenvironment. Therefore, a better understanding of the pathogenesis of PDAC may help detect PDAC or PDAC precursors at the early stages of the disease. However, a low rate of PDAC incidence and the limitations of current screening strategies make early detection difficult. A cost-effective screening strategy is required. The association of DM with PDAC may provide clues for early diagnosis and assessment of the progression of PDAC. Advances in the identification of novel circulating biomarkers including serological signatures, autoantibodies, epigenetic markers, circulating tumor cells and miRNAs have provided potential tools for the early detection of PDAC. However, there are currently no prospective studies investigating screening methods for PDAC in patients with new-onset DM, and biomarkers useful for this purpose or their combinations remain unidentified. Therefore, further studies are required in this field of research.

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