PIBB 生物化学与生物物理进展
Progress in Biochemistry and Biophysics
2023, 50(5): 1069~1076
www.pibb.ac.cn

Biomarkers for Early Detection of Pancreatic Cancer*

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Abstract Pancreatic cancer is one of the most difficult malignant tumors to be diagnosed and treated, with insidious onset, rapid progression and poor prognosis. Presently, surgery is still the preferred method for the treatment of pancreatic cancer. However, due to lack of early symptoms, approximately 70% of patients are diagnosed with local spread or distant metastasis, making it impossible to undergo surgical treatment. Development of effective approaches for better administration of the disease will be unmet and effective way for reducing the mortality and the morbidity. Unfortunately, detection of pancreatic cancer, especially at early stage, is challenged by the lack of highly sensitive and specific biomarkers. Imaging methods (CT, MRI, EUS, *etc*.) often fail to detect early lesions and is easily influenced by operator. Routine clinical markers such as CA19-9, CA125, CA242 and CEA were limited with unsatisfactory sensitivity or specificity. In recent years, extensive studies on biomarkers mainly focused on genetics, transcriptomics, and proteomics. Especially, non-protein coding RNA (ncRNA) consisting of microRNA (miRNA), long non-coding RNA (lncRNA) and circular RNA (circRNA) have proposed many new ideas about early detection of pancreatic cancer. However, the majority of them remain in the laboratory research stage. Few of them, to our knowledge, have gone into clinical practice. A mature study on biomarker may integrate data from genomics, transcriptomics, proteomics, or metabolomics, and combine with individual characteristics of patients (such as body mass index, history of diabetes, smoking, drinking and other risk factors) through large-scale, prospective and validation studies.

Key words early detection, pancreatic cancer, microRNAs, biomarker
DOI: 10.16476/j.pibb.2023.0149

According to the report from GLOBOCAN 2020[1], an estimated 495 773 patients were diagnosed with pancreatic cancer in 2020 worldwide, ranking pancreatic cancer 12th among all malignant tumors. The overall incidence rate was 6.4/10^5 globally, and 4.9/10^5 if adjusted by age. An estimated 466 003 deaths were attributed to pancreatic cancer in 2020. Pancreatic cancer is the seventh leading cause of cancer related death in both males and females worldwide because of its poor prognosis. Over the past several decades, its 5-year overall survival has marginally improved but still remains no more than 9%[2-3]. Due to the lack of typical early symptoms and its highly aggressive biological characteristics, most patients with pancreatic cancer are diagnosed at an advanced stage and are not eligible for curative surgery. However, the 5-year survival rate of patients with tumors limited to the duct epithelium can reach 100% when the tumors are smaller than 1 cm[4]. Thus, screening for early lesions of pancreatic cancer is crucial for improving its prognosis. It is well known that patients with pancreatic cancer at different stages

* This work was supported by grants from The National Natural Science Foundation of China (81770846, 81803024), Hirshberg Foundation for Pancreatic Cancer Research (GX20171003858, GX20191005878), Fundamental Research Funds from the Dalian Universities of Technology (DUT17ZD308), and Kante Seeds Grant (KD2020092201).

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Received: April 13, 2023 Accepted: April 18, 2023

exhibit dramatic outcomes in response to treatment. Most pancreatic cancers are characterized as pancreatic ductal adenocarcinomas (PDACs), which account for more than 85% of all malignancies of the exocrine pancreas[5]. Over the years, early detection of pancreatic cancer has always been the focus of research in the medical field, which is now mainly focused on imaging tests along with proteomics/genomics-based biomarker detection including miRNA and free DNA and other biomarkers. In this review, we reviewed the latest progression made in early detection of pancreatic cancer.

1 Imaging screening

Color Doppler ultrasonography is often used clinically as an important method for screening pancreatic cancer because of its non-invasive and low cost to patients. In recent years, endoscopic ultrasonography (EUS) guided fine needle aspiration (EUS-FNA) has improved the diagnosis rate of early pancreatic cancer and therefore has unique value in the diagnosis of pancreatic cancer, but is not suitable as the first choice of examination. Endoscopic retrograde cholangiopancreatography (ERCP) is commonly used in self-expanding cholangiopancreatic duct[6]. When ERCP bile drainage fails, EUS can be used to guide bile drainage, but its diagnostic value is very limited[7]. Magnetic resonance cholangiopancreatography (MRCP) and positron emission tomography (PET) are not suitable as screening tools for early pancreatic cancer due to their high cost. Some studies have found that EUS-FNA is more sensitive and accurate than PET/CT in the preoperative diagnosis of pancreatic cancer[8].

2 Genomics−based screening

Large-scale genomic studies and genomic technologies, such as next-generation sequencing technology (NGS), have greatly promoted the early detection and screening of PDAC. The use of genomics helps in the early detection of individuals carrying alleles susceptible to cancer.

Kirsten rats arcomavirral oncogene homolog (KRAS) oncogenic mutations are the most common genetic mutations in pancreatic cancer and are detectable in more than 90% of PDAC patients. The activation point mutation in codon 12 of KRAS gene is the initial event in most cases of pancreatic cancer (70% to 95%), and KRAS G12D is more common. Point mutations in KRAS destroy the intrinsic GTp-enzyme activity of RAS, making GTP-activating protein (GAP) lose its inactivation effect on GTP (*i.e.* promoting the conversion of GTP to GDP). Therefore, KRAS protein binds to GTP permanently and continuously activates downstream signaling pathways to maintain cell survival and proliferation.

3 Transcriptomics biomarkers−based screening

RNA sequencing (RNAseq), real-time quantitative PCR (qPCR) or microarray techniques are commonly used in transcriptomic studies. The most common application of transcriptomics in PDAC studies is to compare gene expression differences between tumors and normal pancreatic tissues to look for transcripts whose expression were altered in tumors. ncRNAs refer to non-protein coding RNA, which have developed rapidly in the past decade, mainly consisting of microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs). Recent studies have found that ncRNAs can participate in chromosome modification, gene transcription, post-translational modification, and regulate intracellular signal transduction pathways, thus affecting the occurrence and development of tumors[9]. A series of ncRNAs have been discovered to be used in the detection of pancreatic cancer by a large number of scholars through clinical and basic studies. There are a line of studies showing potential transcriptomic biomarkers and their associated function in pancreatic cancer that was listed in Table 1.

Xue *et al*. [10] suggested there were 45 tRNA-derived small RNAs (tsRNAs) expressed at significant higher levels, 6 tsRNAs expressed at lower levels in PDAC patients, respectively, compared with healthy volunteers. TsRNA-ValTAC-41, tsRNA-MetCAT-37 and tsRNA-ThrTGT-23 expressed significant highly (P<0.05) in serum of PDAC patients in validation cohort. tsRNA-ValTAC-41 or tsRNA-MetCAT-37 combined with CA19-9 could increase the area under the receiver operating characteristic curves (*AUC*) of PDAC prediction (*AUC* =0.947 and 0.949 respectively), relative to CA19-9 test alone. Jin *et al*.[11] firstly identified a novel serum two-tsRNAs signature in PDAC patients, then demonstrated that serum tRF-Pro-AGG-004 and tRF-

Table 1 Potential transcriptomic biomarkers and their associated function in pancreatic cancer

Name	Dysregulation	Final result	Reference
tsRNA-ValTAC-41, tsRNA-MetCAT-37, tsRNA-ThrTGT-23	up	Take part in tumor progression and metastasis	［10］
tRF-Pro-AGG-004, tRF-Leu-CAG-002	up	tsRNAs overexpression promoted cell invasion	［11］
GAS8-AS1	down	Inhibited pancreatic cancer cell migration and invasion	［12］
let-7b-5p, miR-192-5p, miR-19a-3p, miR-19b-3p, miR-223-3p, miR-25-3p	up	—	［13］
miR-125a-3p, miR-5100, miR-642b-3p	up	—	［14］
miR-125a-3p, miR-4530, miR-92a-2-5p	—	—	［15］
miR-629	up	Promoted metastasis of pancreatic cancer cells by targeting FOXO3	［16］
miR-8073, miR-642	up	—	［17］
circRTN4	up	Promotes tumor growth and liver metastasis	［18］
circ-PDE8A	up	Lymphatic invasion	［19］
（hsa）_circ_0006215	up	Increase the migration and apoptosis of PANC-1 cells	［20］
Circ-IARS	up	Liver metastasis, vascular invasion, and tumor-node-metastasis (TNM) stage	［21］
hsa_circ_0000977	up	Pancreatic cancer cell proliferation and induced cell cycle arrest	［22］
CircPDK1	up	Promoted pancreatic cancer cell proliferation, migration	［23］

—: unknown.

Leu-CAG-002 could be used as novel promising biomarkers for pancreatic cancer diagnosis in early stage. Li *et al*.[12] showed that the level of plasma lncRNA GAS8-AS1 was lower in PDAC patients than in healthy controls. Downregulation of plasma GAS8-AS1 distinguished early-stage PDAC patients from healthy controls. Patients with low GAS8-AS1 plasma levels showed a significantly lower 5-year overall survival rate.

Zou *et al.*[13] identified 6 significantly upregulated miRNAs in the serum of patients with pancreatic cancer: let-7b-5p, miR-192-5p, miR-19a-3p, miR-19b-3p miR-223-3p, and miR-25-3p. A six-miRNA panel in serum was then established. The *AUC* of the panel was 0.910 for the combined training and testing phases, which showed higher diagnostic value than the individual miRNA. Salehi *et al.*[14] reported a promising three-miRNA panel (miR-125a-3p, miR-4530 and miR-92a-2-5p) in the plasma for noninvasive pancreatic cancer diagnosis. The *AUC*, the sensitivity and the specificity, of the panel, were achieved at 0.850, 0.804 and 0.872, respectively. The correlation model consisting of miR-125a-3p, miR-5100 and miR-642b-3p in another study showed a promising model in early detection of pancreatic cancer patients, as compared to healthy controls, with an *AUC* of 0.95, a sensitivity of 0.98 and a specificity of 0.97[15], which was further validated in a cohort study consisting of the microarray data from two other datasets (GSE112264 & GSE124158). Shi *et al*.[16] found that the expression level of miR-629 were significantly upregulated in both tissues and serum from patients with PDAC in comparison with matched normal tissues and healthy control, respectively. The study suggested that serum miR-629 may be used for efficiently detection of patients with pancreatic cancer (*AUC*=0.765). Importantly, diagnostic capability of serum miR-629 was significantly higher than that of CA19-9. Intriguingly, a combination of two molecules (CA19-9 and miR-629) showed higher diagnostic capacity as compared to single molecule. Another study showed that plasma level of miR-8073 may distinguish patients with pancreatic cancer from control with *AUC*, sensitivity and specificity values of 0.82, 0.77 and 0.78, respectively[17]. Wong *et al*.[18] found that circRTN4 was significantly upregulated in primary tumors from PDAC patients. *In vitro* and *in vivo* functional studies revealed that circRTN4 promoted PDAC tumor growth and liver metastasis.

Mechanistically, circRTN4 interacted with tumor suppressor miR-497-5p in PDAC cells. The upregulated circRTN4 promotes tumor growth and liver metastasis in PDAC through the novel circRTN4-miR-497-5p-HOTTIP pathway.

Li *et al*. [19] identified a circular RNA (circ-PDE8A) from liver-metastatic PDAC tissues by microarray analysis, and found that high circ-PDE8A expression was correlated with lymphatic invasion, tumor-node-metastasis (TNM) stages and a poor survival rate of patients with PDAC. circ-PDE8A may play an important role in tumor invasion, and exosomal circ-PDE8A may be a useful biomarker for PDAC diagnosis or progression. In Zhu *et al*.' s[20] study, human (hsa)_circ_0006215 was identified to be a candidate biomarker for pancreatic cancer using high-throughput sequencing. Circ-IARS expression was up-regulated in tissues and plasma exosomes of patients with metastatic pancreatic cancer[21]. Circ-IARS was found to enter HUVECs through exosomes and promote tumor invasion and metastasis. Circ-IARS expression was positively correlated with liver metastasis, vascular invasion, and TNM stage and negatively correlated with postoperative survival time. The study suggested that circRNAs in exosomes may be important indicator for early diagnosis and prognosis of PDAC. Silencing hsa_circ_0000977 suppresses progression of pancreatic cancer by interacting with hsa-miR-874-3p and inhibiting PLK1 expression[22]. Hsa_circ_0000977 may be a promising biomarker for diagnosis and treatment of pancreatic cancer. Lin *et al*. [23] found that circPDK1 was activated by HIF1A at the transcriptional level by modulating the miR-628-3p/BPTF axis and degrading BIN1. Exosomal circPDK1 is a promising biomarker for pancreatic cancer diagnosis and prognosis.

4 Proteomic biomarkers−based screening

Proteomics is a whole discipline of study from the perspective of protein localization, function, post-translational modification and protein-protein interaction. Cancer-related proteins or peptides in body fluids may be developed as effective biomarkers used for early detection of PDAC. With the development of proteomics technology, proteomics plays an important role in the discovery and validation of novel protein biomarkers. A number of peptide biomarkers have been developed for detection of PDAC at its early stages.

CA19-9 is a class of Lewis' blood group antigen, mainly distributed on the cell membranes of pancreatic ducts, bile ducts and gallbladder epithelium that are positive for Lewis antigen, and its sensitivity and specificity for diagnosing pancreatic cancer can reach 80%[24]. However, some studies have shown that patients with some diseases also have elevated CA19-9 levels. For example, in a study by Tang *et al*.[25], 553 patients with biliary tract stones were tested for CA19-9 expression level, and the positive rate of serum CA19-9 expression reached 38.89% in patients with bile duct stones and 9.94% in patients with gallbladder stones. Therefore, it is still necessary to refer to other indexes when making a separate diagnosis of pancreatic cancer. In addition, there are other serological biomarkers such as CEA, CA242, CA50, CA195 and CA72-4 whose sensitivity and specificity are not ideal for pancreatic cancer diagnosis. Therefore, they are not used alone in clinical.

It has been reported that glypican-1 (GPC1) is highly expressed in pancreatic cancer[26-27]. Melo *et al.* [28] identified a cell surface proteoglycan, specifically enriched on cancer-cell-derived exosomes. GPC1+ circulating exosomes (crExos) were monitored and isolated using flow cytometry from the serum of patients and mice with cancer. GPC1+crExos were detected in the serum of patients with pancreatic cancer with absolute specificity and sensitivity, distinguishing patients with early- and late-stage pancreatic cancer from healthy subjects and patients with a benign pancreatic disease. A detection panel consisting of exosomal GPC1, CD82, and CA19-9 was employed for pancreatic cancer detection[29]. This panel exhibited excellent diagnostic performance (*AUC*=0.942) and could effectively distinguish patients with pancreatic cancer from healthy people and patients with pancreatitis. These results indicate that the combined detection of exosomal GPC1, exosomal CD82, and serum CA19-9 shows great promise as a standard method for pancreatic cancer detection.

Jin *et al*.[30] analyzed protein levels in pancreatic tissue from PDAC patients and normal people by immunohistochemical staining and Western blotting. RUNX2 showed a potential property to identify pancreatic cancer. Aberrant over-expression of LAMC2 was associated with poor prognosis of PDAC patients, tumor status and subtypes. The putative

diagnostic performance of three candidates, LAMC2, TNC and PTX3, was investigated by ELISA quantification in two cohorts of PDAC patients (n=200) eligible for surgery[31]. Circulating levels of LAMC2, TNC and PTX3 were significantly higher in PDAC patients compared to the healthy individuals (P<0.000 1). The ROC curve showed good sensitivity (1.00) and specificity (0.63 and 0.85) for LAMC2 and PTX3, respectively, but not for TNC, and patients with high levels of LAMC2 had significantly shorter overall survival (P=0.000 7). High levels of LAMC2 and PTX3 were detected at early stages (I−IIB) and in CA19-9-low PDAC patients.

Yang *et al*. [32] used an advanced multiplexed plasmonic assay to analyze circulating tumor-derived extracellular vesicles (tEVs) in more than 100 clinical populations. Using EV-based protein marker profiling, they identified a signature of five markers ($PDAC^{EV}$ signature, GPC1, EGFR, EPCAM, MUC1, WNT2) for PDAC detection. In prospective cohort, the accuracy for the $PDAC^{EV}$ signature was 84% (95%CI, 69% to 93%), but only 63% to 72% for single-marker screening. One of the best markers, GPC1 alone, had a sensitivity of 82% (95%CI, 60% to 95%) and a specificity of 52% (95%CI, 30% to 74%), whereas the $PDAC^{EV}$ signature showed a sensitivity of 86% (95%CI, 65% to 97%) and a specificity of 81% (95%CI, 58% to 95%). The $PDAC^{EV}$ signature of tEVs offered higher sensitivity, specificity, and accuracy than the existing serum marker (CA19-9) or single-tEV marker analyses.

5 Metabolic biomarker−based screening

Metabolomics is the qualitative and quantitative division of endogenous metabolites analysis, the detection of cells, tissues and organisms by nuclear magnetic resonance spectroscopy or mass spectrometry. Small molecule metabolites in the liquid track specific metabolites changes to further derive the physiological or pathological state of the organism. Metabolomics can look for potential responses that can be used in disease diagnosis, treatment, prognostic biomarkers.

Luo *et al*. [33] proposed a panel biomarker by integrating five individual metabolites (creatine, inosine, beta-sitosterol, sphinganine and glycocholic acid), demonstrating much higher accuracy and specificity to precisely diagnose pancreatic cancer than conventional biomarkers (CA125, CA19-9, CA242 and CEA).

Zhao *et al*. [34] conducted nontargeted metabolomics analysis in tissue samples of 51 PDAC tumors, 40 noncancerous pancreatic tissues (NT), and 14 benign pancreatic neoplasms (BP) as well as serum samples from 80 patients with PDAC, 36 with BP, and 48 healthy controls (Ctr). Upregulated levels of fatty acids and lipids and downregulated amino acids were observed in tissue and serum samples of PDAC patients. Proline, creatine, and palmitic acid were identified as a panel of potential biomarkers to distinguish PDAC from BP and Ctr (OR=2.17, 95%CI 1.34−3.53). AUC of the panel was 0.854 and 0.865, respectively, for the comparison of PDAC *vs* Ctr and PDAC *vs* BP. In the validation set, the values were improved to 0.949 and 0.909 when CA19-9 was added to the model. Cao *et al*. [35] constructed a 2-metabolites-model (isoleucine and adrenic acid) for stage-I PDAC. The AUC value was 0.93 in the discovery set and 0.90 in the independent validation set. Especially, the serum metabolite model had a better diagnostic performance than CA19-9 (AUC=0.79). Sahni *et al*.[36] identified a six-metabolite panel (trigonelline, glycolate, hippurate, creatine, myoinositol and hydroxyacetone), which demonstrated high potential to diagnose PDAC, with AUC of 0.933 and 0.864 in the discovery and validation cohort, respectively. Notably, the identified panel also demonstrated great potential to diagnose early-stage (I and II) PDAC patients with an AUC of 0.897. These results demonstrate that the selected metabolite signature could be used to detect PDAC and will pave the way for the development of a urinary test for diagnosis of PDAC. Mayerle *et al*.[37] identified a biomarker signature for the differential diagnosis between PDAC and CP. The biomarker signature (proline, sphingomyelin, phosphatidylcholine, isocitrate, sphinganine-1-phosphate, histidine, pyruvate, ceramide, sphingomyelin) distinguished PDAC from CP in the training set with an AUC of 0.96 (95%CI 0.93−0.98). When fixed the specificity on 85%, the biomarker showed a sensitivity of 94.9% (95%CI, 87.0%−97.0%). In the test set, an AUC of 0.94 (95%CI, 0.91−0.97), a sensitivity of 89.9% (95%CI, 81.0%−95.5%) and a specificity of 91.3% (95%CI, 82.8%−96.4%) were achieved.

6 Conclusion and future perspectives

The early diagnosis of pancreatic cancer is complex, and the identification of reasonable and reliable diagnostic biomarkers is particularly important. The current clinical methods for early detection of pancreatic cancer have limited sensitivity and specificity. Research on early tumor cell characteristics of pancreatic cancer has identified a large number of diagnostic markers with clinical translation potential. In the future, artificial intelligence with deep learning capabilities can integrate data from genomics, transcriptomics, proteomics, metabolomics and other dimensions, and combine with large-scale, prospective and validation studies to achieve risk classification and early diagnosis of pancreatic cancer, which can greatly improve the detection capacity of pancreatic cancer at early stage.

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胰腺癌早期检测的生物标志物*

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摘要 胰腺癌症是最难诊断和治疗的恶性肿瘤之一，其特点是发病隐匿、进展迅速、预后差。目前，手术治疗仍然是首选治疗方法。然而由于缺乏早期症状，大约70%的患者在确诊时已经出现局部扩散或远端转移，从而无法进行手术治疗。由此看来，早期检测是提高患者治疗效果和预后的有效途径。临床上使用的成像方法（CT、MRI、EUS等）通常无法检测早期病变，并且很容易受到操作员的影响。常规临床标志物如CA19-9、CA125、CA242和CEA受到限制，其敏感性或特异性不令人满意。因此，寻找新的具有高敏感性和特异性的标志物是实现胰腺癌早期检测的关键。近年来，对生物标志物的广泛研究主要集中在遗传学、转录组学和蛋白质组学上。特别是由microRNA（miRNA）、long non-coding RNA（lncRNA）和circRNA（circRNA）组成的非蛋白质编码RNA（non-protein coding RNA，ncRNA）为胰腺癌的早期检测提出了许多新思路。然而，其中绝大多数仍处于实验室研究阶段。而一项成熟的生物标志物研究应该整合基因组学、转录组学、蛋白质组学或代谢组学的数据，并结合患者的个体特征（如体重指数、糖尿病史、吸烟、饮酒和其他危险因素）进行大规模、前瞻性和验证性研究。

关键词 早期检测，胰腺癌，microRNAs，生物标志物
中图分类号 R735 **DOI**：10.16476/j.pibb.2023.0149

* 国家自然科学基金（81770846，81803024），胰腺癌研究Hirshberg基金（GX20171003858，GX20191005878），大连理工大学基础研究经费（DUT17ZD308）和康德种子基金（KD2020092201）资助项目。
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收稿日期：2023-04-13，接受日期：2023-04-18