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Review

Strategies for discovering novel pancreatic cancer biomarkers☆

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ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related deaths in both men and women in Canada and the United States and has the most dismal survival rates among any solid malignancy. Most patients are diagnosed with pancreatic cancer once the disease has progressed into an advanced or metastatic stage, making the only curative approach of resection surgery impossible. The persistent delayed or missed diagnosis of pancreatic cancer can be attributed to the absence of early symptoms and the lack of efficient non-invasive screening or diagnostic tests in clinical practice. Given that earlier diagnosis is critical for ameliorating patients' survival rates, there is an urgent need for biomarkers with enough sensitivity and specificity to help diagnose pancreatic cancer early. Serological biomarkers provide a minimally invasive and efficient way of detecting pancreatic cancer, however, there is currently no marker with sufficient diagnostic sensitivity and specificity to identify early cancer patients. This review focuses on the classical tumor markers for PDAC as well as emerging markers. In addition, we will discuss an integrative proteomic approach used in our lab to identify a panel of biomarkers that have the potential to allow the early detection of PDAC.
This article is part of a Special Issue entitled: From protein structures to clinical applications.

Contents

Abbreviations: PDAC, Pancreatic ductal adenocarcinoma; CT, computerized tomography; EUS, endoscopic ultrasound; ERCP, endoscopic retrograde cholangiopancreatography; CA, Carbohydrate antigen/cancer antigen; CEA, carcinoembryonic antigen; EGTM, European Group on Tumor Markers; ASCO, American Society of Clinical Oncology; NACB, National Academy of Clinical Biochemistry; MUC, mucin; DIGE-MS/MS, difference gel electrophoresis and tandem mass spectrometry; FDA, Food and Drug Administration; APRIL, a proliferation-inducing ligand; TNF, tumor necrosis factor; PanIN, pancreatic intraepithelial neoplasia; HSP, heat shot protein; ULBP2, UL16 binding protein 2; CM, Conditioned media; HPDE, Human pancreatic ductal epithelial cell line; ELISA, Enzyme-linked immunosorbent assays; ROC, receiver operating characteristic; ARG2, anterior gradient homolog 2; OLFM4, olfactomedin-4; SYCN, Syncollin; PIGR, polymeric immunoglobulin receptor; COL6A1, collagen alpha-1 (VI) chain; AUC, area under curve; SCX, strong cation exchange.

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1. Introduction

Despite the increase in research interest and advancement in the understanding of pancreatic cancer over the past few decades, it remains one of the deadliest solid malignancies affecting mankind. It has a 5-year relative survival rate of less than 5%, a median survival rate of less than 6 months and is the fourth leading cause of cancer-related deaths in men and women in Canada and the United States despite being only the tenth most common form of cancer [1,2]. The mortality is almost identical to its incidence rate for this devastating disease and it is estimated that there will be 43,920 new cases and 37,390 deaths from the disease in the U.S. in 2012 [1]. There are several types of pancreatic cancer, the most common being pancreatic ductal adenocarcinoma (PDAC), which accounts for approximately 90% of all pancreatic cancers [3] and for which this review will focus on.

The poor prognosis of PDAC is the result of its silent nature, high metastatic potential and resistance to conventional therapies. To date, the only potentially curative treatment is surgical resection, with the overall five-year survival rate improving to 40% if the tumor is detected at less than 20 mm and to 75% when tumors are detected at less than 10 mm [4]. Unfortunately only approximately 20% of the PDAC patients have their cancers detected at a stage at which surgical resection remains a viable option [5]. Once the disease has progressed into an advanced stage, chemotherapy, radiation or any combinatorial therapies are mostly palliative and have minimal improvement on the patient survival [6].

The inability to detect pancreatic cancer in its early treatable stage is a critical clinical problem. Unfortunately, early PDAC is characterized by a lack of clinical symptoms and when symptoms are present they are generally non-specific (back pain, weight loss, and digestive problems) and do not lead to disease detection. Although a standardized screening strategy is still maturing, the current screening practice commonly includes high risk individuals carrying genetic abnormalities associated with pancreatic cancer, with more than 2 first degree relatives diagnosed with pancreatic cancer, however, such patients only account for less than 5% of all pancreatic cancer [7]. Increasing evidences have shown that new-onset diabetes is present in approximately half of the pancreatic cancer patients, and its occurrence is prevalent even in early stage, asymptomatic pancreatic cancer patients [7]. Therefore, new-onset diabetes may represent a high risk population group to screen for asymptomatic pancreatic cancer [7]. Given that type 2 diabetes is common and pancreatic cancer is rare in the general population, screening all new-onset diabetic patients for pancreatic cancer is not cost-effective without a reliable marker to differentiate between pancreatic cancer-associated diabetes from the more prevalent type 2 diabetes [7]. There have been studies attempting to identify potential candidate biomarkers for pancreatic cancer-associated diabetes, however there is currently no specific marker available since they were either unsuccessful in consequent validation studies or remain to be validated [7–10]. Even if such a marker is found, it may not detect pancreatic cancer in patients without pancreatic cancer-associated diabetes. This leads to the urgent need of the discovery and validation of biomarkers that can help detect PDAC at an early stage in all patients and improve the survival of pancreatic cancer patients.

Although it has been commonly believed that pancreatic cancer progresses and develops metastases too rapidly for early detection to be practical, new research indicates otherwise. Two recent studies analyzing the progression of PDAC using mathematical analyses of tumor genetic sequencing data showed that it may take up to about 10 years after tumor initiation for pancreatic cancer cells to acquire the metastatic capacity to spread to distant organs [11,12]. Based on this finding, there appears to be a long window of opportunity for the detection of pancreatic cancer at an early stage, reinforcing the importance for researchers to discover and validate novel methods for the early detection of pancreatic cancer (Fig. 1).

Diagnostic tests of pancreatic cancer include computerized tomography (CT) scan, endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) [13,14]. Owing to the fact that these imaging parameters are costly, potentially invasive and time consuming, they are usually performed only after the onset of symptoms. These imaging methods are powerful, yet they are not designed to detect early premalignant lesions, or PDAC when the tumor is small and potentially resectable. In addition, it is often difficult to differentiate chronic pancreatitis from pancreatic cancer. Due to their low cost, and minimal invasiveness, serum based biomarkers remain an ideal method for which to detect PDAC in its early stages. The past decade has seen a plethora of advancements in the field of proteomics, which coupled to the interest in early PDAC detection, and has led to numerous publications on the identification of potential biomarkers for clinical use in pancreatic cancer detection. This review focuses on the most widely used PDAC biomarker CA19-9, emerging novel protein markers and our identification of a biomarker panel using an integrative proteomic approach.