Review Article

Early Detection of Pancreatic Cancer: Challenges and Imaging Probes

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Abstract

Pancreatic cancer is a highly aggressive cancer, currently treated with limited success and dismal outcomes. It is the fourth leading cause of cancer related deaths in the U.S.A major cause for the high mortality rate is the difficulty in diagnosing the disease in early stage. New diagnostic and treatment strategies offer the potential to reduce cancer mortality; however, this strategy has not been significantly improved for pancreatic cancer patients compared to those with other types of cancer. Developing highly-specific non-invasive imaging modalities and probes is essentially needed for improving diagnostic accuracy, prognosis and monitoring therapeutic intervention for pancreatic cancer. In order to develop specific molecular imaging probes, it is necessary first to identify specific targets that are over expressed in the order of magnitude in pancreatic cancer cells, either on the cell surface or in the cytosolic components or in the microenvironment. Limited information is available on target identification and imaging probes for early detection of this cancer and monitoring therapy, especially modalities such as PET. This review briefly focuses on identification of specific targets and development of molecular imaging probes, including PET and SPECT.

ABBREVIATIONS

HIP/PAP: Hepatocarcinoma-Intestine-Pancreas/Pancreatitis–Associated Protein; PET: Positron Emission Tomography; SPECT: Single Photon Emission Tomography

INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States [1]. Pancreatic adenocarcinoma, by far the most common type of pancreatic cancer, is the 10th most diagnosed cancer in men and the 9th most diagnosed in women in the U.S. [2]. Despite improvements in survival rates for most cancers in recent decades [1,2], survival of patients with pancreatic cancer has changed little [3]. The most viable option for cure or longer survival in this disease is surgical resection, but a majority of patients who undergo surgery die of metastatic disease [4]. Early detection followed by treatment has been shown to have a positive impact on 5-year survival rates in many cancers [3,5,6]; however, early detection of pancreatic cancer is challenging because the disease is usually asymptomatic in the early stages. In almost all cases, pancreatic cancer is detected in the advanced stages when it is unresectable. Reliable methods for detecting pancreatic cancer in its early stages would allow for effective resection and improve patient outcomes.

While imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), or even ^{18}F-FDG–positron emission tomography (PET)/CT continue to improve in accuracy and utility, they lack the necessary sensitivity and specificity to detect small lesions that may be curable [7]. Highly specific, non-invasive imaging probes for pancreatic cancer are needed if we are to improve diagnostic accuracy and prognosis and meaningfully assess response to therapy. Before such specific molecular imaging probes can be developed, however, specific targets that are over expressed by orders of magnitude in pancreatic cancer cells, either on the cell surface or in the cytosolic components, must be identified. To date, few such targets have been identified for pancreatic cancer in the early stage. While many reviews have been published on various aspects of pancreatic cancer, including cancer biology [4], screening [8], and imaging [9], information on target identification and PET imaging probes for early detection and monitoring therapy response is limited [10]. This short review focuses on target identification and imaging probes for early detection of pancreatic cancer by non-invasive modalities, including PET.

Biomarkers: Specific targets

Biomarkers that can be assayed from biologic fluids have long been regarded as a gold standard for medical diagnostics [11]. An example of such a biomarker is carbohydrate antigen 19-9 (CA 19-9), a sialylated Lewis (a) glycoprotein expressed on

the surface of pancreatic cancer cells and in normal cells of the human pancreas and biliary duct. The concentration of CA 19-9 is typically elevated in the serum of patients with solid tumors of the pancreas, ovaries, liver, stomach, or colon. However, this marker is insufficiently sensitive for detecting small tumors, a significant limitation for detecting early-stage pancreatic cancer. A concerted antibody development program has resulted in development of a fully humanized antibody, 5B1 that targets CA 19-9 and thus has potential utility in the early diagnosis of pancreatic cancer [11]. Another monoclonal antibody that has been developed, MAb159, targets surface GRP78 and blocks its oncogenic functions [12].

Exosomes are also considered potential biomarkers in pancreatic cancer [13]. A cell surface proteoglycan, glypican-1 (GPC1) that is specifically enriched on cancer-cell–derived exosomes has been identified. Circulating GPC1 exosomes were detected in the serum of patients with pancreatic cancer with absolute specificity and sensitivity, accurately distinguishing healthy subjects from patients with early- or late-stage pancreatic cancers. While blood exosome analysis shows promise for early detection of pancreatic cancer [13], no diagnostic test has yet been clinically proven to be sufficiently accurate for this purpose.

The integrin $\alpha6\beta4$ has been reported as a promising target for pancreatic cancer and has been employed for single-photon emission computed tomography (SPECT) or near-infrared imaging for immunotargeting of pancreatic cancer [14]. An antibody against $\alpha6\beta4$ labeled with indium-111 or indocyanine green showed high levels of accumulation in tumors in an animal model [14].

Another target that has been identified for pancreatic cancer is hepatocarcinoma-intestine-pancreas/pancreatitis–associated protein (HIP/PAP), which is expressed in the peritumoral region of pancreatic cancers [15-17]. The *HIP/PAP* gene was found to be over expressed in peritumoral acinar tissue adjacent to infiltrating pancreatic adenocarcinomas compared to normal pancreatic acini [18,19], and the expression of HIP/PAP was 130-fold greater in peritumoral pancreatic tissue than in normal pancreas [18]. Although HIP/PAP is over expressed in peritumoral cells, its level of expression in the serum is not sufficiently elevated for use as a biomarker in pancreatic adenocarcinoma. These findings, while promising, demonstrate that a suitable biomarker that can be used for routine screening for pancreatic cancer has not yet been found.

Imaging modalities for early detection of pancreatic cancer

Many of the imaging modalities currently available have been applied for diagnosis of pancreatic pathology, including optical and bioluminescence imaging[20], ultrasound [21], CT [20], MRI [22], PET [23,24], and SPECT [25]. PET with glucose derivative ^{18}F-FDG is considered to be the most useful of the common imaging technologies for the diagnosis and staging of pancreatic cancer [23,24]. Detecting specific sites of tumor and identifying small cancer deposits with PET remains a challenge, however, because the resolution of clinical PET scanners is about 5 mm [7], while early-stage tumors are typically 2-3 mm in size. Furthermore, ^{18}F-FDG/PET has many other drawbacks and is considered unsuitable for detection of pancreatic cancer [26,27].

^{18}F-labeled lactose derivatives have shown promise for early detection of pancreatic cancer by PET [15-17]. Two different analogues of ^{18}F-labeled lactose have shown encouraging results in animal models [15-17]. The tracer ethyl β-D-galactopyranosyl-(1,4)-2-fluoro-D-glucopyranoside (^{18}F-FEDL) effectively targeted and imaged HIP/PAP expression, highlighting the tumor/peritumoral region of pancreatic tumor xenografts. Accumulation of ^{18}F-FEDL in the peritumoral tissue was confirmed by autoradiography and immune histochemical analysis of HIP/PAP expression in the adjacent tissues. A high level of ^{18}F-FEDL radioactivity was seen in the peritumoral pancreatic tissue but not in the tumor lesion itself [15]. These findings demonstrated ^{18}F-FEDL to be a potential imaging agent for early detection of pancreatic cancer [15].

Another analogue of lactose that targets HIP/PAP, ^{18}F-fluoroethyl lactose (^{18}F-FEL), was synthesized and tested in an orthotopic tumor xenograft mouse model of pancreatic cancer. Preliminary data on the efficacy of ^{18}F-FEL in detection of early-stage pancreatic cancer by targeting HIP/PAP were reported to be promising [17]. Comparison of ^{18}F-FEL-PET/CT images with MRI images showed very clear correlation, indicating that ^{18}F-FEL accumulated in the region where tumor was detected by MRI. Autoradiography and immune histochemical analyses confirmed HIP/PAP expression in the peritumoral tissue that was visualized by PET/CT [17]. Most recently, ^{18}F-FEL was tested in a subcutaneous pancreatic cancer model in nude mice [28]. That study demonstrated that tumors established by subcutaneous inoculation with T3M4 pancreatic cancer cells could be visualized by ^{18}F-FEL/PET. These results conflict with the hypothesis that the lactose analogue binds with HIP/PAP that is over expressed in the peritumoral tissue. However, these results support the potential of ^{18}F-FEL for imaging pancreatic cancers via a currently unknown target, and further studies on the use of ^{18}F-FEL/PET in early detection of pancreatic cancer are warranted. The greatest advantage of targeting HIP/PAP is its expression in the tissue surrounding the pancreatic tumor, which enhances and increases the target volume, overcoming the limitation of the PET scanner's resolution.

SUMMARY AND CONCLUSION

The imaging modalities used for diagnosis and staging of pancreatic cancer have improved in the last several years [29]. However, no imaging technique has achieved sufficient accuracy to precisely assess tumor resectability in pancreatic cancer [30]. Radio labeled monoclonal antibodies is evolving for use in early diagnosis of pancreatic cancer, but further work is needed. The ^{18}F-labeled lactose analogues targeting HIP/PAP has potential in early detection of pancreatic cancer by PET. This modality may have some advantage over the others, such as target volume amplification and detection of early-stage pancreatic cancer through recognition of the stage at which the pancreatic cancer cell begins to differentiate and grow. However, this approach requires further development.

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