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Mini-review

Current status of biomarker and targeted nanoparticle development: The precision oncology approach for pancreatic cancer therapy

Lei Zhu [a], Charles Staley [a], David Kooby [a], Bassel El-Rays [b], Hui Mao [c], Lily Yang [a, c, *]

[a] Department of Surgery, Emory University School of Medicine, Atlanta, GA 30322, United States
[b] Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA 30322, United States
[c] Department of Radiology and Imaging Sciences, Emory University School of Medicine, Atlanta, GA 30322, United States

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ABSTRACT

Pancreatic cancer remains one of the major causes of cancer-related mortality. The majority of pancreatic cancer patients are diagnosed at the advanced stage with unresectable and drug resistant tumors. The new treatments with the combination of chemotherapy, molecular targeted therapy, and immunotherapy have shown modest effects on therapeutic efficacy and survival of the patients. Therefore, there is an urgent need to develop effective therapeutic approaches targeting highly heterogeneous pancreatic cancer cells and tumor microenvironments. Recent advances in biomarker targeted cancer therapy and image-guided drug delivery and monitoring treatment response using multifunctional nanoparticles, also referred to as theranostic nanoparticles, offer a new opportunity of effective detection and treatment of pancreatic cancer. Increasing evidence from preclinical studies has shown the potential of applications of theranostic nanoparticles for designing precision oncology approaches for pancreatic cancer therapy. In this review, we provide an update on the current understanding and strategies for the development of targeted therapy for pancreatic cancer using nanoparticle drug carriers. We address issues concerning drug delivery barriers in stroma rich pancreatic cancer and the potential approaches to improve drug delivery efficiency, therapeutic responses and tumor imaging. Research results presented in this review suggest the development of an integrated therapy protocol through image-guided and targeted drug delivery and therapeutic effect monitoring as a promising precision oncology strategy for pancreatic cancer treatment.

Introduction

Pancreatic cancer is the fourth leading cause of cancer death in the United States [1,2]. In 2016, it is estimated that 53,070 new cases of pancreatic cancer will be diagnosed in the US, and 41,789 pancreatic cancer patients will die as a result of this disease [1]. Pancreatic ductal adenocarcinoma (PDAC) is the most common cancer type (over 95%) [2]. Because of its aggressive biological nature and the ineffectiveness of current treatments, PDAC has a mortality rate almost equal to its incidence with a five-year survival rate of 5%. One important reason for the poor survival is that the majority (over 85%) of the patients are diagnosed with advanced diseases and have a poor prognosis [1]. Only few patients (approximately 15%) are diagnosed when they are at the earliest-stage of PDAC and are candidates for the potentially curative surgery [3].

A challenge for screening and early detection of PDAC is that patients lack specific clinical symptoms at the early stage and the risk factors are not well known except for smoking and family history [4]. A major problem is that human pancreatic cancer is highly heterogeneous with a tumor mass from a single patient containing 63 genetic alterations and 12 core signal pathway abnormalities. There are also heterogeneity in tumor biomarker expression among different cancer patients [5]. Currently, blood-test based on biomarkers and imaging methods are clinical standard due to the ease of operation, and relatively noninvasive nature [4,6]. Tumor biomarkers that allow for the reliable diagnosis of pancreatic cancer have yet to be identified. However, investigations are ongoing to evaluate the effect of several biomarkers for pancreatic cancer detection. So far, the levels of serum carbohydrate antigen (CA 19-9), CA-125, ICAM-1, CEA, mutant Kras DNA,

* Corresponding author. Department of Surgery, Emory University School of Medicine, Atlanta, GA 30322, United States.
E-mail address: lyang02@emory.edu (L. Yang).

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miRNAs, and glypican-1 in exosomes [7,8] have been evaluated as serum biomarkers for the detection of pancreatic cancer. However, many of those biomarkers are not specific for pancreatic cancer since they are also expressed in other tumor types and some of them on normal and premalignant tissues. It is likely that the combination of serum biomarker detection with the biomarker targeted molecular imaging to localize and characterize pancreatic cancer lesions will improve sensitivity and specificity of the early detection of pancreatic cancer.

At present, various targeted imaging probes have been developed for non-invasive tumor imaging using different imaging modalities. For example, nanoparticle imaging probes targeting plectin-1, mesothelin, uPAR, EGFR, and IGF-1R are under investigations for the detection of pancreatic cancer [9–12]. With the development of nanomedicine, it is expected that nanomaterials modified with PDAC targeting ligands can facilitate the early diagnosis of PDAC so that personalized therapeutic strategy can be designed and applied timely to the patients. Additionally, biomarker targeted imaging nanoparticles are not only promising imaging contrasts for tumor detection, but also for the evaluation of the biomarker expression in primary and metastatic pancreatic cancers for stratifying the patients with biomarker positive tumors for targeted therapy.

Currently, therapeutic options applicable to PDAC are still limited to surgery, chemotherapy and radiotherapy. Most PDAC patients have advanced diseases and are treated by chemotherapy. However, most chemotherapeutics are not very effective with minimal impact on survival in most cases. For example, advanced PDAC patients receiving gemcitabine (2′-2′-difluorodeoxycytidine) or the combination of fluorouracil, oxaliplatin, irinotecan (CPT-11) and folinic acid (FOLFIRINOX) treatment, still have median survival less than 12 months [13]. One reason for this unfavorable treatment outcome is the presence of “desmoplasia” in PDAC, which is known as tumor stroma with characteristics of abnormal and poorly functioning vasculatures, altered extracellular matrix, infiltrating macrophages and proliferation of active fibroblasts. Intense tumor stroma consisting of 50–85% of the PDAC tissues creates a drug delivery barrier for many therapeutic agents, including small molecules, higher molecular weight antibody-based drugs, and nanoparticle formulations. In addition, PDAC cells are highly resistant to chemotherapy drugs [14], because of abnormal levels of gene expression, genetic mutations, activation or inhibition of cellular signal pathways, tumor hypoxia, and the stroma-rich tumor microenvironment [15]. Therefore, new and more potent therapeutic agents and novel treatment protocols will improve the clinical outcomes of pancreatic cancer. Since pancreatic tumor microenvironment plays critical roles in tumor biology, drug delivery and response to therapy, it is necessary to consider the stroma effect for designing and evaluation of new therapeutic agents [16].

In this article, we will provide an overview of the current research regarding potential biomarkers or molecular targets in pancreatic cancer for the development of targeted therapy and imaging for pancreatic cancer PDAC with a particular focus on nanoparticle or theranostic nanoparticle drug carriers.

Pancreatic cancer biomarkers and molecular targets

Over the years, intensive efforts have been devoted to identify biomarkers and molecular targets for the development of targeted molecular imaging and therapeutic approaches [17]. In comparison with other solid tumors, PDAC has unique pathological characteristics to consider when developing imaging and drug delivery agents. Several molecules that are currently under evaluation for PDAC targeted treatment based on their roles in tumorigenesis and progressions will be reviewed here (Fig. 1). Although these biomarkers may not be specific for PDAC, the detection of the presence of high levels of the biomarkers in suspected pancreatic lesions should not only provide supportive information for diagnosis of pancreatic cancer, but also identify the cell surface molecular targets for the development of biomarker targeted nanoparticle drug carriers, or theranostic nanoparticles. The following are examples of cell surface biomarkers that are highly expressed in pancreatic cancer for the development of tumor targeted imaging and therapeutic agents:

Mesothelin

Mesothelin is a membrane type protein that is normally expressed in mesothelial cells of pleura, peritoneum and pericardium. A high level of mesothelin is detected in various types of cancers, including mesothelioma, non-small cell lung, ovarian and pancreatic cancers [18]. Studies so far have reported that mesothelin is related to cell survival, migration, invasion and tumor progression [19,20]. It was also uncovered that silencing the expression of mesothelin suppressed tumor growth [21], implying that mesothelin can be a potential marker for cancers, including PDAC [22]. Indeed, mesothelin was detected in PDAC tissues but not in normal pancreas and chronic pancreatitis [23]. It was reported that significantly elevated levels of circulating mesothelin protein were detected in 73 of the 74 patients with pancreatic adenocarcinoma, and in all five patients with benign pancreatic disease, but not in the healthy controls [24]. As the most of the other PDAC biomarkers, mesothelin is not a PDAC specific biomarker but can be combined with other biomarkers for confirming diagnosis of PDAC [25]. Recent studies have shed light on the possible role of mesothelin as an antigen for immunotherapy. A positive correlation between prognosis and the presence of a humoral response to mesothelin has been shown in pancreatic cancer patients [26]. It has been reported that modification of imaging agents and drug-delivery systems with anti-mesothelin antibody would improve diagnostic and therapeutic efficiency in mesothelin overexpressing

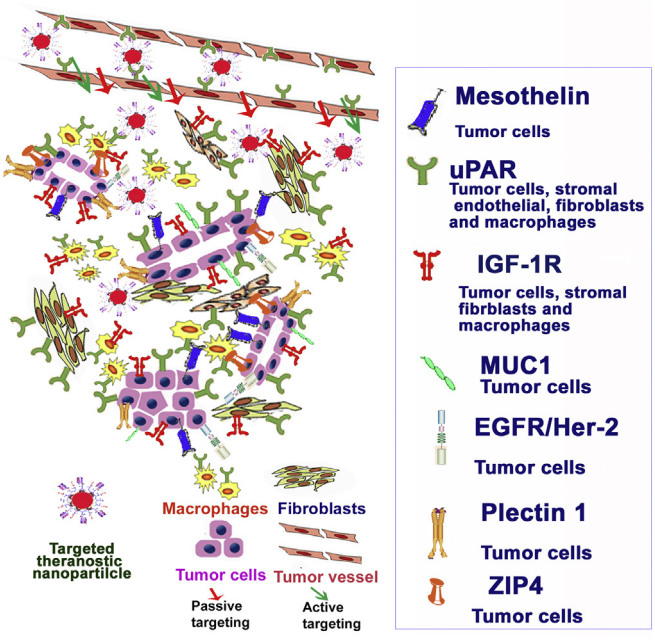

Fig. 1. Molecular biomarkers for the development of targeted nanoparticle drug carriers and theranostic nanoparticles for pancreatic cancer therapy.