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Mini-review

Pancreatic cancer: Stroma and its current and emerging targeted therapies

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ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal human malignancies with a 5-year survival rate of 8%. Dense, fibrotic stroma associated with pancreatic tumors is a major obstacle for drug delivery to the tumor bed and plays a crucial role in pancreatic cancer progression. Targeting stroma is considered as a potential therapeutic strategy to improve anti-cancer drug efficacy and patient survival. Although numerous stromal depletion therapies have reached the clinic, they add little to overall survival and are often associated with toxicity. Furthermore, increasing evidence suggests the anti-tumor properties of stroma. Its complete ablation enhanced tumor progression and reduced survival. Consequently, efforts are now focused on developing stromal-targeted therapies that normalize the reactive stroma and avoid the extremes: stromal abundance vs. complete depletion. In this review, we summarized the state of current and emerging anti-stromal targeted therapies, with major emphasis on the role of miRNAs in PDAC stroma and their potential use as novel therapeutic agents to modulate PDAC tumor-stromal interactions.

Introduction

Pancreatic cancer is one of the leading causes of cancer deaths in western societies, with the worst prognosis [1]. In the United States, it is the third leading cause of cancer deaths, and projected to become the second leading cause of cancer related deaths in just over a decade [2]. In 2016, it is estimated that 53,070 Americans will be diagnosed with pancreatic cancer, and 41,780 are expected to die from this lethal disease [3]. Pancreatic cancer originates from exocrine cells of the pancreas, and among all exocrine tumors, pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic neoplasm, accounting for more than 90% of pancreatic tumors [4]. In spite of intense research efforts and the development of numerous new cancer drugs and treatment strategies over the past four decades, there has been no significant improvement in overall patient survival, and death rates are almost equivalent to incidence rates [5].

Surgery, radiation, and chemotherapy are treatment options that may extend patient survival or reduce symptoms, but they seldom produce a cure. Surgical resection or surgery in combination with adjuvant therapy is the only curative therapy that improves overall patient survival [6]. However, <20% of PDAC patients are candidates for surgery because pancreatic cancer is usually not diagnosed until the cancer has spread to other parts of the body, and these advanced tumors are resistant to current therapeutic modalities [7,8]. Furthermore, there are no effective biomarkers for early detection of PDAC cases that could potentially benefit from curative therapeutic options. Although recent improvements in combination chemotherapy and patient selection strategies for radiation therapy have improved the outcome of advanced PDAC cases, the overall 5-year survival rate does not exceed 8% [3].

Developing therapies for advanced PDAC is much more complicated than targeting only the cancer cells. PDAC is characterized by a prominent fibrotic reaction where dense fibrotic tissue expands and surrounds the tumor and is known to play a critical role in pancreatic cancer progression [9–12]. This dense fibrotic

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stroma around the tumor causes hypovascularity and hypoxia, creating a major obstacle for drug delivery to the tumor bed [13,14]. Consequently, stromal biology and targeted therapies are under intensive investigation to improve the efficacy of chemotherapy and patient survival. Although some anti-stromal drugs and combination chemotherapeutic strategies have reached the clinic, they add little to overall patient survival, and they are also often associated with toxicity [15,16]. To date, the majority of the anti-stromal drugs that were evaluated in the clinic were intended to completely ablate the stroma. However, increasing evidence suggests that the stromal reaction acts to restrain tumor growth [17,18]. In preclinical studies, complete removal of the stroma led to more aggressive tumor types and decreased overall survival [19,20]. Given the failure of stromal depleting therapeutic strategies in clinic and the stroma's potential in restraining tumor growth, efforts are now intensely focused on developing novel stromal targeted therapies that appropriately modulate the stroma and avoid the extremes of ablation versus abundance [21,22]. In this review, we summarize the state of current and emerging anti-stromal targeted therapies, with a major emphasis on the role of microRNAs in pancreatic stellate cell-mediated stromal reaction and their potential use as novel therapeutic agents to modulate tumor-stromal interactions in PDAC tumor progression (see Ref. [22] for a more comprehensive review on pancreatic cancer stroma and therapy).

Stroma and its role in PDAC progression

Pancreatic cancer tumors are characterized by a profuse fibrotic stromal reaction called desmoplasia (Fig. 1), which is composed of cellular components such as pancreatic stellate cells, fibroblasts, vascular, and immune cells, and acellular components such as collagens and fibronectin, as well as cytokines and growth factors stored in the extracellular matrix [23,24]. A dynamic interaction between cellular and acellular components plays a critical role in pancreatic cancer progression and metastasis.

In the normal pancreas, connective tissue, resident fibroblasts, pancreatic stellate cells (PSCs), immune cells, and vascular cells play a critical role in tissue repair and wound healing. In response to pancreatic injury/tissue damage, injured acinar cells secrete pro-inflammatory and pro-angiogenic growth factors/cytokines, and activate immune cells (adaptive and innate), PSCs/fibroblasts, and vascular cells to engage immune surveillance, synthesize extracellular matrix proteins/connective tissue, and generate blood vessels respectively, to restore normal pancreatic function [25]. However, in the presence of oncogenic mutations, genetically altered epithelial cells transform into cancer cells and disrupt normal cell–cell communications between PSCs, immune cells, and vascular cells, controlling their function to create a favorable microenvironment for cancer progression [25,26].

In the PDAC tumor microenvironment, cancer cells secrete variable amounts of pro-inflammatory growth factors/cytokines, including TGF-β1, PDGF, TNFα, and IL-1/6 and activate PSCs/fibroblasts. Activated PSC/fibroblasts transform into a myofibroblast-like phenotype, and secrete large amounts of extracellular matrix (ECM) proteins, comprised of collagens, fibronectins, and laminins in periacinar regions to form fibrous tissue [27,28]. In addition, activated PSC/fibroblasts produce pro-inflammatory growth factors/chemokines that act in an autocrine fashion to maintain their sustained activity and produce fibrotic stromal ECM proteins [29,30] (Fig. 1). Excessive ECM deposition in periacinar regions distorts normal parenchyma (Fig. 2), causes compression of the vasculature, and leads to hypovascularity and hypoxia of tumors [13,14]. Tumor hypoxia is also known to activate PSCs and helps maintain and perpetuate the hypoxia-fibrosis cycle [31]. In addition, dense fibrotic stroma and dysfunctional vasculature impair drug delivery to the cancer cells and reduce their therapeutic efficacy [13]. PSCs are known to closely interact with cancer cells, promote local tumor growth, and co-migrate with cancer cells to distant metastatic sites, establishing stromal abundant tumors beyond the pancreas [32–34]. Additionally, activated PSCs and cancer cells produce pro-angiogenic factors, which promote neoangiogenesis and support cancer cell growth and survival under a hypoxic tumor-microenvironment [14].

In the normal pancreas, immune cells protect the pancreas from microbial infection and eliminate the damaged/genetically altered epithelial cells. In the dense fibrotic tumor microenvironment, cancer cells activate a wide variety of signaling pathways and suppress both innate and adaptive immune systems by decreasing cytotoxic CD8 T cells and increasing the presence of immunosuppressive macrophages (M2), neutrophils (N2), and T-regulatory

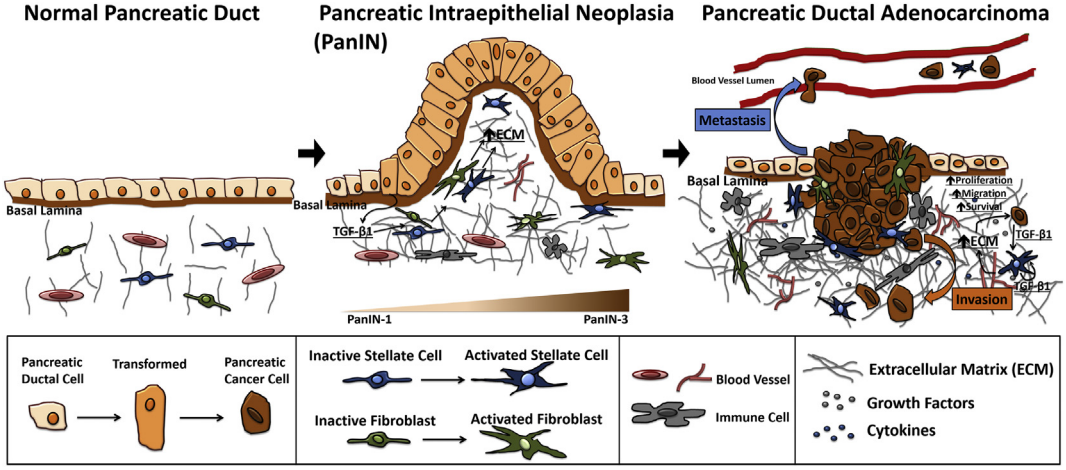

Fig. 1. Illustration demonstrates the progression of pancreatic ductal adenocarcinoma (PDAC) from normal pancreatic duct, to precursor pancreatic intraepithelial neoplasm (PanIN), to invasive/metastatic cancer (left to right). During carcinogenesis, normal ductal epithelial cells (tan cells) acquire oncogenic mutations (e.g. Kras) (light orange cells) early and develop into hyperplastic ductal lesions called PanINs which progress through various grades (PanIN-1A, PanIN-2A, PanIN-2, and PanIN-3), eventually developing into fully invasive and metastatic pancreatic cancer (dark brown cells). Pancreatic cancer cells (dark brown) and pancreatic stellate cells (blue) release TGF-β1 and other pro-inflammatory cytokines/growth factors that activate pancreatic stellate cells to produce ECM proteins and increase fibrotic stromal deposition. A close interaction between stellate cells, cancer cells, and pro-inflammatory growth factors/cytokines contribute to PDAC progression and metastasis. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)