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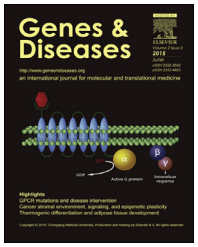

REVIEW ARTICLE

Pancreatic cancer stromal biology and therapy

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Abstract Pancreatic cancer is one of the most lethal malignancies. Significant progresses have been made in understanding of pancreatic cancer pathogenesis, including appreciation of precursor lesions or premalignant pancreatic intraepithelial neoplasia (PanINs), description of sequential transformation from normal pancreatic tissue to invasive pancreatic cancer and identification of major genetic and epigenetic events and the biological impact of those events on malignant behavior. However, the currently used therapeutic strategies targeting tumor epithelial cells, which are potent in cell culture and animal models, have not been successful in the clinic. Presumably, therapeutic resistance of pancreatic cancer is at least in part due to its drastic desmoplasis, which is a defining hallmark for and circumstantially contributes to pancreatic cancer development and progression. Improved understanding of the dynamic interaction between cancer cells and the stroma is important to better understanding pancreatic cancer biology and to designing effective intervention strategies. This review focuses on the origination, evolution and disruption of stromal molecular and cellular components in pancreatic cancer, and their biological effects on pancreatic cancer pathogenesis.

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Introduction

Pancreatic cancer is one of the most lethal malignancies with a 5-year survival rate below 5%.[1,2] Although surgery remains the best choice for pancreatic cancer treatment, most cases are diagnosed at an advanced stage, making patients poor candidates for surgical treatment.[3–6] Major reasons for the dismal prognosis for pancreatic cancer include lack of early appreciable symptoms, tendency of rapid local or distant metastasis, and intrinsic resistance to conventional chemotherapeutics.[4–7] Because effective systemic therapy capable of controlling the aggressive pancreatic cancer biology is currently lacking, the need for a better understanding of detailed mechanisms underlying pancreatic cancer development and progression is urgent.[3,8–10]

Recent studies on pancreatic cancer genetics and epigenetics have led to the identification of notable genetic alterations, such as *K-ras*, *p53*, *Smad4*, and *p16*.[11–16] These signature genetic events, combined with accompanying histopathological alterations, suggest a sequential transformation roadmap of pancreatic cancer from normal pancreatic epithelium to increasing grades of pancreatic intraepithelial neoplasia to, ultimately, invasive pancreatic adenocarcinoma.[17] However, targeting these signature genetic and epigenetic alterations has not resulted in useful preventive and/or therapeutic modalities in clinic, while gemcitabine remains the first-line chemotherapeutic agent for pancreatic cancer.[3,18]

Recently, paradigm of pancreatic cancer research has shifted from parenchyma to stroma.[19–21] Evidently, tumors with identical germline mutations exhibit diverse formations of stroma and the degrees of stromal reaction predict aggressive phenotype.[11–14] In fact, histological hallmark of pancreatic cancer is its pronounced desmoplastic reactions (Fig. 1). In general, pancreatic cancer stroma could account for more than 90% of the total tumor volume. Many signaling pathways have been proposed to mediate interactions between cancer cells and stroma.[21,22] Identification of the pivotal role that the stroma plays in pancreatic cancer development and progression has led to the development of potential targeted therapies for pancreatic cancer, some of which appear to be promising and exhibit synergistic efficacy in combination with gemcitabine.[18] This review focuses on the origination, evolution and disruption of stromal molecular and cellular components in pancreatic cancer, and their biological effects on pancreatic cancer pathogenesis.

Pathogenetic basis of pancreatic cancer

Histopathological studies on pancreatic neoplasms have identified three major precursor lesions, which have the potential to evolve into highly malignant and invasive pancreatic cancer (PDAC): pancreatic intraepithelial neoplasia (PanIN), mucinous cystic neoplasms (MCN), and intraductal papillary mucinous neoplasms (IPMN).[23,24] PanIN is the most common precursor pancreatic lesion.[25] It is believed that the precursor lesions evolve step-wisely into invasive pancreatic cancer.[17] This PanIN-to-PDAC progression model has been supported by thorough genetic analyses and molecular profiling studies.[26,27]

Mutational activation of *K-ras* is the most notable oncogene identified in pancreatic cancer cells. Although occasionally occurring in normal pancreatic tissue and only about 30% of pancreatic cancer lesions at the earliest stage,[28] the frequency of *K-ras* activation increases as the disease progresses and is found in nearly all pancreatic cancer cases.[29] Other major genetic alterations include inactivation of tumor-suppressive genes, *e.g.*, *p16/CDKN2A*, *TP53*, and *SMAD4*. Most recently, a landmark study of sequencing of 23,219 transcripts representing 20,661 protein-coding genes in 24 pancreatic cancer cases has detailed a large number of genetic alterations (an average

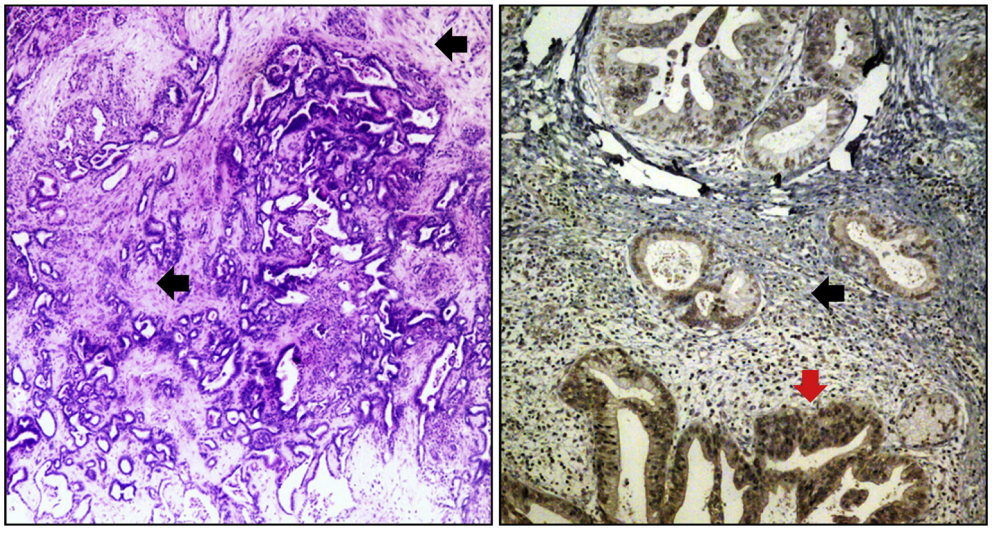

Figure 1 Pancreatic cancer stroma. Shown are tissue sections of both mouse (left panel) and human (right panel) pancreatic cancer. The mouse pancreatic cancer is from a L-KrasG12D/+; L-p53R172H; pdx1-Cre+ (KPC) mouse (stroma is indicated by black arrows). In human pancreatic cancer, FOXM1 is highly expressed in the invasive lesion (indicated by a red arrow, see Ref. 10 for more information).