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Review

Epithelial–mesenchymal transition in pancreatic cancer: Is it a clinically significant factor?

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ABSTRACT

Pancreatic cancer is one of the most aggressive solid malignancies. This aggressiveness is partly attributable to extensive local tumor invasion and early systemic dissemination as well as resistance to chemotherapy. Epithelial–mesenchymal transition (EMT) plays fundamental roles in embryonic development and in the differentiation of normal tissues and organs. EMT also plays critical roles in tumor formation, dissemination and drug resistance in pancreatic cancer. Emerging data suggest that inhibiting EMT may reverse the EMT phenotype and enhance the efficacy of chemotherapeutic agents against pancreatic cancer cells. Thus, an understanding of the molecular biology of EMT in pancreatic cancer may provide insights into the mechanisms of tumor invasion and metastatic progression and facilitate the development of alternative therapeutic approaches to improve the treatment outcomes for patients suffering from pancreatic cancer.

Contents

Abbreviations: EMT, epithelial–mesenchymal transition; CSC, cancer stem cell; PSC, pancreatic stellate cell; TGF-β, transforming growth factor β; ZEB, zinc-finger E-box binding homeobox; HDAC, histone deacetylase; PDGF, platelet-derived growth factor; EGF, epidermal growth factor; HGF, hepatocyte growth factor; TNF-α, tumor necrosis factor α; IL, interleukin; COX-2, cyclooxygenase-2

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1. Introduction

Pancreatic cancer is the eighth most common cause of cancer-related deaths worldwide and has an extremely poor prognosis, with an overall 5-year survival rate of <5% [1]. The causes of pancreatic cancer are unclear. Many risk factors have been associated with an increased incidence of pancreatic cancer, including smoking, alcohol intake, diabetes, chronic pancreatitis, diet, obesity and family history [2]. Although notable improvements in survival have been achieved for many cancers in recent decades, pancreatic cancer survival has improved very little [3,4]. Pancreatic cancer is typically diagnosed at an advanced stage, with more than 80% of pancreatic cancer patients presenting with locoregional spread and/or distant metastasis; this delayed diagnosis is a major obstacle to long-term survival [5]. Therefore, an understanding of the molecular biology underlying the invasion and metastasis of pancreatic cancer is required to improve the rate of survival.

Epithelial–mesenchymal transition (EMT) plays fundamental roles in embryonic development and in the differentiation of multiple tissues and organs as well as in the metastasis of cancer cells [6]. Upon undergoing EMT, cells are endowed with migratory and invasive properties that allow them to migrate to distant organs through the extracellular matrix, enabling cell differentiation into multiple types during development and the metastatic initiation of cancer cells [7]. EMT is characterized by a loss of cell–cell contacts through the inhibition of epithelial markers, such as E-cadherin expression, and the acquisition of mesenchymal features, such as the up-regulation of the mesenchymal markers N-cadherin, vimentin, Twist, Snail1 and Snail2 [8].

Numerous data have indicated that EMT occurs in the development and progression of human solid tumors, including pancreatic cancer. This review presents the events in pancreatic cancer tumorigenesis, progression and prognosis. Finally, we discuss the impact of EMT on therapeutic resistance and explore potential approaches to improve the clinical management of pancreatic cancer.

2. EMT and pancreatic cancer tumorigenesis

Pancreatic cancer originates from the successive acquisition of several genetic changes that enable the malignant transformation of the pancreatic ductal epithelium to intraepithelial neoplasia and, eventually, to fully invasive cancer [2]. The mutational events of pancreatic cancer include the activation of the *KRAS* oncogene and inactivation of the tumor-suppressor genes *CDKN2A*, *TP53*, *SMAD4* and *BRCA2*. *KRAS* mutations occur in more than 90% of human pancreatic cancers, representing an essential event in the initiation of the malignant transformation of normal exocrine pancreas cells [4]. Pancreatic cancer cell lines harboring *KRAS* mutations tend to exhibit EMT induction, and the EGFR/Ras pathway correlates with the genesis and promotion of EMT-induced tumor-initiating cells [9–12]. Oncogenic *KRAS* activity affects the pancreatic tumor microenvironment by regulating the infiltration of immune cells as well as specific immune cytokines and cellular signaling pathways that also play an important role in the EMT process [13]. Extensive efforts have focused on inhibiting or reversing the expression of oncogenic *KRAS*. Some progress has been achieved in mouse models, in which blocking *KRAS* activity slows pancreatic cancer growth and even induces tumor regression [13,14]. Thus, inhibiting *KRAS* directly or its effectors, such as the Akt and MAPK signaling pathways as well as the inducers of EMT, may be promising therapeutic targets for pancreatic cancer.

SMAD4 inactivation occurs in approximately 50% of pancreatic cancers, resulting in changes in the cell signaling pathway of transforming growth factor β (TGF-β). Members of the TGF-β family, which are involved in angiogenesis and regulate cell proliferation, differentiation and apoptosis, are the main and best-characterized inducers of EMT in embryonic development as well as in tumor pathogenesis [15]. The role of TGF-β in pancreatic cancer is complex. Deregulated TGF-β signaling is a common event in pancreatic cancer development and progression and is thought to promote tumor-associated pathways and the development of a tumor microenvironment [16]. TGF-β inhibitors block and even reverse the EMT process and prevent tumor metastasis *in vivo* [17]. Interestingly, *KRAS* mutations appear to be early events that occur in intraepithelial neoplasias with low- to intermediate-grade dysplasia, while *SMAD4* mutations appears to be relatively late events that occur in intraepithelial neoplasias with high-grade dysplasia and in aggressive neoplasms [4]. Mouse studies indicate that *KRAS* activation cooperates with *SMAD4* inactivation to accelerate the initiation and development of pancreatic tumors [18].

Recent studies have demonstrated that a small group of pancreatic cancer cells appear to have cancer stem cell (CSC) features, as identified by the expression of specific cell surface markers including CD44, CD24, CD133, epithelial-specific antigen (ESA), and hepatocyte growth factor (HGF), some of which may promote cell-to-cell interactions and activate many EMT-related pathways [19]. CSCs possess certain unique properties, including unlimited self-renewal, asymmetric division and differentiation into other cell types, that distinguish them from the majority of cancer cells and fuel the maintenance of tumor growth [2]. Emerging evidence suggests that EMT generates cells with stem cell properties, promotes the CSC phenotype, and therefore enhances pancreatic cancer tumorigenic and metastatic ability [19,20].

EMT programs can also be triggered by many growth factors and cellular signaling pathways, including platelet-derived growth factor (PDGF), Notch and Wnt signaling, some of which are essential for the regulation of pancreatic tumor growth (Table 1) [15,21,22]. Thus, EMT plays an important role in tumor initiation and progression in pancreatic cancer, and EMT regulators are promising candidate therapeutic targets for pancreatic cancer (Table 1) [23,24].

3. EMT and pancreatic cancer progression

3.1. E-cadherin loss and its repressors

The loss of contact inhibition of cell proliferation, a hallmark of cancer, is thought to be associated with cadherin-mediated cell–cell attachments [25]. E-cadherin is expressed in epithelial cells and plays a vital role in cell adhesion and movement. E-cadherin loss can stabilize tumor cells in the mesenchymal state, producing single migratory cells derived from epithelial tumor cells [26–28]. The loss of E-cadherin function or expression is considered a crucial step in the progression of incipient neoplasia to invasive carcinoma and a fundamental event in EMT [29]. Partial or complete loss of E-cadherin expression is particularly evident in patients with undifferentiated, noncohesive pancreatic cancers, indicating that E-cadherin loss plays an essential role in the invasive and metastatic process of pancreatic cancer cells [30–32]. E-cadherin loss can be caused by genetic or epigenetic modifications and gene promoter silencing, but the regulation of E-cadherin expression in pancreatic cancer remains unclear [33–35].

Some factors, including Snail family members, ZEB family members, bHLH family members and HDACs, are inducers of EMT as well as potent repressors of the E-cadherin promoter (Table 1) [36]. Snail-induced EMT accelerates tumor lymph node invasion and distant metastasis by repressing E-cadherin expression, enhancing the invasive ability of cancer cells and inducing immunosuppression [36–39]. Snail also alters cell proliferation and protects against cell death, which are essential for the metastatic process in tumor cells [39]. *In vivo* experiments have demonstrated that the Snail/HDAC1/HDAC2 complex promotes the pancreatic cancer metastatic process by suppressing E-cadherin expression to induce EMT in human pancreatic cancer cells, while the inhibition of HDAC *via* drug treatment restores E-cadherin expression [31]. *In vitro* studies have indicated that ZEB1 cooperates with HDAC1 and HDAC2 to bind and modify the *CDH1* promoter, while HDAC inhibition and ZEB1 knockdown cause E-cadherin expression and attenuate pancreatic cancer cell proliferation and migration [40]. These findings reveal a complex