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Pancreatic cancer stem cells: Association with cell surface markers, prognosis, resistance, metastasis and treatment

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A B S T R A C T

In this review, we will discuss the recent advances in understanding the pancreatic cancer stem cells. Identification and characterization of pancreatic cancer stem cells may aid our ability to improve diagnosis and treatment of pancreatic cancer. Novel approaches are necessary for the earlier diagnosis of pancreatic cancer as well as improved treatment to prevent distal metastasis. Key markers for the identification of pancreatic cancer stem cells include CD133, ALDH, side population cells and the triplet combination CD44+ CD24+ESA+. The roles of these proteins as markers for stemness in pancreatic cancer as well as recent studies with the c-Met proto-oncogene will be discussed. The ability of these markers to predict survival of pancreatic cancer patients is being examined clinically. Stemness and resistance to chemotherapy and radiotherapy may be linked. Expression of some of these markers may be associated with distant metastasis. Treatment of pancreatic cancer patients by targeting the pancreatic cancer stem cells holds promise.

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Introduction

Pancreatic cancer is the ninth most common cancer in the United States, causing approximately 250,000 deaths worldwide (Siegel et al., 2013). It has the highest mortality of any cancer and will become the second most common cause of cancer deaths in the United States by 2020 (Rasheed and Matsui, 2012). The lethality of this disease has improved little over the last 40 years (Muniraj et al., 2013). The mechanisms behind the lethality of pancreatic cancer are not entirely elucidated; however, its contributing factors include locally advanced presentation, early metastasis, and few patients are candidates for curative intent surgery (Zakharova et al., 2012; Muniraj et al., 2013). Indeed, pancreatic cancer can be contended to be, most often, a systemic disease at presentation.

Pancreatic cancer is often incurable at presentation, is minimally responsive to chemotherapy, and has a propensity for local, regional and distance recurrence. These properties may be in part attributable to cancer stem cells (Rasheed and Matsui, 2012). In the traditional cancer model, i.e., the stochastic model, all cells are thought to have malignant potential (Fanali et al., 2014). In contrast, the cancer stem cell model contends that cancers behave similar to complex organs where few cells have cancer initiating potential. Cancer stem cells have properties similar to normal stem cells: the ability of multi-linage differentiation, asymmetrical division, and self-renewal.

Cancer stem cells

Putative cancer stem cells have been identified for multiple neoplasms including liver, hematopoietic, head and neck, ovarian, prostate, brain, bladder, breast, colorectal, and pancreatic cancer (Reya et al., 2001; Li et al., 2007; McCubrey et al., 2012; Xia et al., 2012; Li et al., 2013). In such validation studies, putative stem cells are often identified from human cancers or cell lines using surface markers such as CD44, CD24, CD34, epithelial specific antigen (ESA) and CD133 (Xia et al., 2012; Li et al., 2013). Classically, these cells are isolated using techniques, such as flow cytometry, and implanted in immunocompromised mice (Duan et al., 2013). Recapitulation of the neoplasm is considered validation of stemness. The most common i*n vitro* model used as surrogate for *in vivo* growth is tumor sphere formation in a low adhesion environment (Ricci-Vitiani et al., 2007; Huang et al., 2009). *Another model for growth of human pancreatic cells is in the anterior eye chamber of an immunocompromised mouse (Barker et al. 2013).*

Pancreatic cancer stem cells

Stem cells have been implicated in pancreatic cancer cancerogenesis, prognosis, and resistance to therapy. As such, these cells are attractive therapeutic targets. Cancer stem cells are likely regulated by similar developmental pathways as normal stem cells including Hedgehog, Notch, Wnt, BMI-1, and PTEN (Rasheed et al., 2010; Abel et al., 2014). Multiple markers for pancreatic cancer stem cells have been identified; however, a universal marker is elusive (Herreros-Villanueva et al., 2014). In order to advance the understanding and treatment of pancreatic cancer stem cells, we must better understand markers of stemness and cell fraction association with prognosis, metastasis, and resistance to therapy.

Markers of stemness in pancreatic cancer

Markers that have been utilized to identify neoplastic and non-neoplastic stem cells include CD44, CD24, CD133, ESA, aldehyde dehydrogenase (ALDH) and Hoechst dye exclusion (side population) (Rasheed and Matsui, 2012; Richard et al., 2013). The key markers for pancreatic cancer stem cells are CD133, ALDH, side population cells and the triplet combination CD44+ CD24+ESA+. Two independent teams identified pancreatic cancer stem cells in 2007. Investigators at the University of Michigan identified the cell surface marker combination of CD44+CD24+ ESA+ as indicative of stemness in human pancreatic cancers (Lee et al., 2008). In a series of experiments, these investigators used fluorescence-activated cell sorting (FACS) to identify cells in primary human cancers that were CD44+CD24+ESA+ (0.2%–0.8% of the total cell population), and implanted them in immunocompromised mice. Tumors were consistently recapitulated with a small volume of cells. Cells not