Review Article

Understanding pancreatic cancer stem cells and their role in carcinogenesis: a narrative review

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Objective: The purpose of this review article is to describe the pathogenesis of pancreatic cancer and to better understand the role of abnormal stem cells in the development of pancreatic cancer.

Background: Pancreatic cancer is a highly fatal disease that is caused by the uncontrolled proliferation of pancreatic exocrine or neuroendocrine glands. It is believed that pancreatic cancers arise from a small population of abnormal cancer stem cells (CSCs) that promote tumorigenesis, tumor metastasis and therapeutic resistance. The molecular markers CD133, CXCR4, DCLK1, c-MET, ABCG2 and Lgr5 are routinely used to detected and observe the behaviours of pancreatic cancer stem cells (PCSCs).

Methods: A comprehensive search was performed on PubMed, Google Scholar, Scopus, Clinicaltrials.gov and Web of Science using related keywords. Articles focusing on PCSCs and pancreatic cancer pathogenesis, biochemistry and clinical trials were selected.

Conclusions: Although very little is known about the exact cause of pancreatic cancer, PCSCs seem to play an important role in carcinogenesis. Mutated biochemical cascades include Sonic Hedgehog, K-RAS-JNK, DLL4/Notch and Nodal/Activin. Several clinical trials are trying to determine if the transplantation of hematopoietic stem cell or peripheral stem cells could be useful for the treatment of such an aggressive tumor.

Keywords: Pancreatic cancer; stem cells; pathogenesis; therapies; oncology

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Introduction and background

Pancreatic cancers are aggressive tumors which can be subdivided into two large categories: exocrine pancreatic cancers (e.g., adenocarcinoma) and neuroendocrine pancreatic cancers (1). Pancreatic adenocarcinomas represent approximately 85% of all pancreatic cancer cases and arise from pancreatic exocrine glands, whereas pancreatic neuroendocrine cancers represent slightly less than 5% of all pancreatic cancer cases and originate from endocrine tissues of pancreas (1).

According to GLOBOCAN 2018, pancreatic cancer is the 11th most common malignancy across the globe (2). It remains the seventh and third leading cause of cancer death worldwide and in the United States of America, respectively (2,3). A 2021 Surveillance, Epidemiology, and End Results (SEER) analysis estimated that there were 40,430 new cases of pancreatic cancer (79% men and 31% women) and 48,220 pancreas cancer-related deaths in the United-States (4). This disease has an overall poor 5-year survival rate (10%) and has a slightly higher mortality rate in men (12.7 per 100,000) than in women (9.6 per 100,000) (4).

The exact cause of pancreatic remains poorly understood, but involves a plethora of risk factors such as smoking status, genetic predispositions, advanced age, diabetes mellitus, obesity and a family history of chronic pancreatitis (5). The signs and symptoms of pancreatic cancer are mainly

dependent on two factors: (I) size/location of the tumor and (II) affected organs. Based on these parameters, pancreatic tumors can be assigned different numerical stages to describe their progression. If a pancreatic cancer is ≤2 cm (Ia) or >2cm (Ib) and only found in the pancreas, it is classified as a stage I neoplasm (5). Stage II cancers often grown nearby organs but have not infiltrated lymph nodes (5). A diagnosis of stage III pancreatic cancer indicates that the initial tumor is large and has invaded the lymphatic system but has not spread to distant sites (5). Stage IV pancreatic tumors are characterized by their ability to metastasize to distant organs (e.g., lungs or liver) (5). Unfortunately, a significant portion of patients remain asymptomatic until the advanced stage. Signs and symptoms include unintentional weight loss, nausea/vomiting, anorexia, and abdominal/back discomfort. The presence of jaundice, pale stools, dark urine and pruritus are signs that the underlying tumor might have metastasized or is exerting mass effect (5).

Pancreatic cancer remains a disease that is very hard to treat despite the availability of various treatment options. It is assumed that this neoplasm arises from a small population of irregular stem cells that divide uncontrollably. The purpose of this narrative review is to shed some light on the genomic complexity of pancreatic cancer and to better understand the role of pancreatic cancer stem cells (PCSCs) in tumor development. We present the following article in accordance with the Narrative Review reporting checklist (available at https://sci.amegroups.com/article/view/10.21037/sci-2021-067/rc).

Methods

A thorough investigation was performed using the following search engines: PubMed, Google Scholar, Scopus, Clinicaltrials.gov and Web of Science. The most recent query was performed in December 2021 while reviewing the article. The selected articles were either basic research, clinical research, or translational research papers. Keywords such as “pancreatic cancer”, “pancreatic cancer stem cells”, “stem cells”, “pancreatic cancer biochemical cascades”, “pathogenesis” and “pancreatic cancer clinical trials” were used. A paper was only included if it followed one or more of the following criteria: (I) written in English; (II) published the data of *in vitro* or *in vivo* studies that discussed the behaviour of cancer stem cells (CSCs) in pancreatic cancer; (III) published data on drugs targeting PCSCs. A total of 48 articles were used for the creation of this literature review.

PDAC subtyping

Molecular subtypes

Bailey *et al*. postulated that pancreatic adenocarcinomas (PDACs) can be subdivided into four different categories based on their expression patterns (6). The *squamous* subtype was associated with a poor prognosis because it harbored mutations in several important tumor suppressor genes (e.g., *TP53* and *KDM6A*) which led to a complete loss of endodermal identity (6). The *pancreatic progenitor* subtype was characterized by its preferential expression of *PDX1*, *MNX1* and *FOXA2/3* (6). These genes play an important role in the early development of the pancreas via the regulation of glycosylation, fatty acid oxidation and steroid hormone/drug metabolism (7). Although the *immunogenic* subtype is similar to the *pancreatic progenitor* subtype in terms of genetic expression patterns, it defined by remarkable immune cell infiltration due to aberrancies in B-cell signalling pathway, antigen presentation and Toll-like receptor (TLR) signalling pathways (6). The aberrantly differentiated endocrine exocrine (*ADEX*) subtype was caused by genes involved in exocrine function (e.g., *NR5A2* and *RBPJL*), endocrine differentiation (e.g., *NEUROD1* and *NKX2-2*) and mutant *KRAS* activation (6).

Immune subtypes

According to Liu *et al.*, PDACs can be separated into three different immune clusters (C1-3) (8). Subtype C1 pancreatic cancers are viewed as immune-cold because they lacked several key immune modulators such as INF-γ and TGF-β (8). In contrast, subtype C2 cancers have an immune-suppressive phenotype as they are associated with elevated TGF-β enrichment scores and low lymphocyte enrichment scores (8). Subtype C3 pancreatic tumors are immune-hot cancers because they display an abundance of inflammatory markers and are linked with severe immune cell infiltration (8).

Cancer stems cells and pancreatic cancer

Cancer stem cell hypothesis and tumorigenesis

It is hypothesized that all cancers originate from a very small population of abnormal pluripotent stem cells also known as CSCs or tumour-initiating cells (9). The ability of CSCs to self-renew indefinitely and differentiate into various cells is an important feature in tumor formation, progression, metastasis, and therapy resistance (10-12). Although scientists

are still trying to determine the exact origin of CSCs, it is thought that CSCs arise from non-malignant progenitor cells that have acquired various somatic mutations (9). Another hypothesis is that CSCs are the product of differentiated cells re-acquiring stem-cell like properties via the epithelial-to-mesenchymal transition (EMT) (13). Markopoulos *et al.* have noticed that inflammatory cytokines (e.g., TNFα, TGFβ, IL-1 and IL-6) may accelerate this phenomenon by activating master transcription factors (TFs) such as Smads, STAT3 and NF-kB and EMT-inducing TF families such as Snail, Twist and Zeb (14).

CSCs increase in number by undergoing symmetric cell division which generates two identical pluripotent daughter cells (15). CSCs can also self-renew through asymmetric cell division, but this process produces a tumor progenitor cell (TPC) and a daughter cell possessing stem-cell properties (15). The delicate balance between symmetric and asymmetric cellular division is tightly controlled by various oncogenes that employ the Hedgehog, Notch and Wnt signalling mediators (16,17).

PCSCs

In 2007, Li *et al.* first defined PCSCs by observing the behaviour of human PDAC cells transplanted into immunosuppressed mice (18). There was a small subpopulation of PCSCs, which represented 0.2-0.8% of all the tumor cells, which simultaneously expressed the CD44, CD24 and ESA/EpCAM (epithelial specific antigen) surface markers (18). These neoplastic cells displayed a 100-fold increase in tumorigenic potential compared to their $CD44^-CD24^-ESA^-$ counterparts and were able to generate the development signal molecule sonic hedgehog (SHH) and undergo symmetric as well as asymmetric cellular division (18). Other known PCSC markers include CD133, ALDH1, DCLK1, CXCR4, ABCG2, c-Met, and Lgr5 (19-24).

Also known as prominin-1, CD133 is a pentaspan transmembrane glycoprotein that serves as a biological marker for stem cells and CSCs (25). Although the exact role of CD133 in the progression of cancer remains elusive, a study by Hermann *et al.* revealed that a population of $CD133^+/CXCR^+$ CSCs were able to sustain pancreatic tumor growth and were essential for metastasis (26). CD133 is thought to confer a metastatic phenotype by upregulating the expression of N-cadherin via the Src signalling pathway, which plays a critical role in the EMT regulatory loop (27,28). Moreover, the expression of CD133 in PDACs was associated with tumorigenesis and resistance to chemotherapy (26). The chemokine receptor CXCR4, once bound to its primary ligand CXCL12, has also been implicated in pancreatic cancer tumorigenesis, infiltration, and metastasis (29). Billadeau *et al.* proposed that this process, in part, involves the activation of ERK-mediated biochemical cascades which control the expression of different angiogenesis-related genes such as VEGF, CD44, HIF1α and IL8 (30). As part of the ALDH super-family, ALDH1 is a cytosolic enzyme that plays a vital role in the detoxification of exogenous and endogenous aldehydes (31). This protein marker was first described by Ginestier *et al.* in 2007 and is now used as a functional marker for normal stem cells (32). Rasheed *et al.* noticed that increased expression of ALDH1A1 in pancreatic cancer cells was associated with a worse prognosis (20). Furthermore, ALDH1 has been shown to regulate the proliferation of PDACs and provide them with gemcitabine and cyclophosphamide resistance (33). DCLK1 is a serine/threonine-protein kinase belonging to the doublecortin (DCX) family that plays an important role in PCSC biology. Several studies noticed that DCLK1 was overexpressed in PCSCs displaying invasive and metastatic properties (21). This tumor marker accelerates the development of malignant features in CSCs by robustly upregulating genes (e.g., SNAI2, *CDH2* and *VIM*) that modulate EMT (34). Furthermore, it is postulated that DCLK1 overexpression might sustain neoplastic growth as a study by Westphalen *et al.* discovered that DCLK1+ cells were necessary for the regeneration of pancreatic tissue following injury (35). The hepatocyte growth factor (HGF)/c-MET axis is one of many signalling pathways that is necessary for the expression of DCLK1 in tumor cells. It facilitates pancreatic cancer progression by mediating the interaction between PCSCs and stromal pancreatic stellate cells (PSCs) (36). Although ABCG2 and Lgr5 have also been implicated in the development of PDACs, very little is known about their precise role in development of pancreatic cancer tumorigenesis (37,38).

Aberrant biochemical pathways causing therapy resistance

Tumors are composed of a heterogenous mix of active tumor cell lines and clonal stem cells; the latter being subdivided into CSCs and tumor initiating cells (TICs). While CSCs tend to remain quiescent in the periphery, TICs are responsible for the continued proliferation of the tumor progeny (16,17). Experiments by Hermann *et al.* found that PCSCs have profound resistance to very high concentrations of gemcitabine (up to 100 micrograms/mL) (26). These

Table 1 Molecular pathways involved pancreatic cancer stem cell resistance

Study	Pathway	Therapy	Conclusion
Mueller *et al.* [2009]	Sonic Hedgehog (SHH), mTOR	Cyclopamine/CUR199691 Rapamycin	Blockade of either SHH or mTOR alone were insufficient; combined inhibition of both pathways as a supplement to CTx led to reduced CSCs
Jimeno *et al.* [2009]	Sonic Hedgehog (SHH)	Cyclopamine	Tumors pre-treated with gemcitabine then randomized to gemcitabine alone, SHH inhibitor alone, or combined therapy showed that combined therapy induced tumor regression and decrease in PCSC markers
Singh *et al.* [2011]	Sonic Hedgehog (SHH)	GDC-0449 (Vismodegib)	Inhibition of cell viability and induction of apoptosis in PCSC
Yen *et al.* [2012]	DLL4/Notch	Anti-hDLL4 (21M18) Anti-mDLL4 (21R30)	Combined therapy as adjuvant to gemcitabine increases programmed cell death, delays tumor recurrence, and reduces levels of TICs
Lonardo *et al.* [2011]	Nodal/Activin	Anti-Alk4/7	Inhibition of Alk4/7 reverses chemoresistance of PCSC by reducing or eliminating their self-renewal capacity; combined targeting with SHH inhibitors gives long-term, progression-free survival
Okada *et al.* [2014]	K-RAS-JNK	Anti-JNK	K-ras plays a significant role in JNK activity and self-renewal; combined inhibition of K-ras-JNK axis reduced TICs by dysregulation of self-renewal

CSC, cancer stem cell; PCSC, pancreatic cancer stem cell.

same concentrations were able to induce apoptosis in virtually all other tumor cell lines. In fact, gemcitabine notably led to selective pressure of CD133+ PCSCs, leading to the chief hypothesis that pancreatic treatments may expand the tumorigenic cell population by producing a relapsed progeny of resistant tumor cell types. Early studies of hematopoietic stem cells by Goodell *et al.* in 1996 suggested that stem cell resistance to therapy is likely linked to their quiescent nature, enhanced repair of DNA damage, and anti-apoptotic mechanisms such as efflux membrane transporters, specifically, ABC transporters (39).

Since the discovery of PCSCs as potential drivers of therapeutic resistance, several studies (*Table 1*) have researched the proposed molecular pathways. Hedgehog signaling through the SHH pathway was identified as a mediator of tumorigenesis by Thayer *et al.* in 2003 (40). Hedgehog signaling is essential in pancreatic embryonic pathways and its misexpression was shown to lead to the development of precursor lesions and the subsequent development of mutations in K-RAS and HER-2/neu (40). Several studies evaluating the inhibition of this pathway suggest that PCSCs may be induced to undergo apoptosis, thus serving as an adjuvant to chemotherapy (41-43).

The Notch signaling pathway is responsible for stem cell renewal, differentiation, and survival and is an important driver of pancreatic embryonic development. Overexpression of Notch proteins by CD133+ PCSCs has been shown to promote self-renewal through vascular development and is key in therapeutic resistance (44). Hoey et al. had previously shown that targeting delta like ligand 4 (DLL4), an important component of Notch signaling, in colon and breast cancer reduced the frequency of TICs (45). They expanded this knowledge to pancreatic cancer in 2012 and found that combining anti-human DLL4 and anti-murine DLL4 had pronounced reductions in TICs, likely by the induction of dysfunctional vasculature within the tumor microenvironment (44).

Nodal/Activin are components of the TGF-beta superfamily and are chiefly responsible for the regulation of embryonic stem cells. Lonardo *et al.* found that nodal/activin were highly expressed in PCSCs and the inhibition of their activin-like (Alk) 4/7 receptor reduced or eliminated the capacity for their self-renewal (46). This effect was enhanced by co-blockade with SHH inhibitors and ultimately showed reversal of chemoresistance of PCSCs. The c-Jun NH2-terminal kinase (JNKs) is a sub-group of the mitogen-activated protein kinases, which are often dysregulated in many cancer types. JNKs have been shown to be crucial to

Table 2 Ongoing clinical trials involving pancreatic cancer stem cells

Study	Intervention/treatment	Primary outcome
NCT04150042	Drug: melphalan; drug: BCNU (carmustine); drug: vitamin B12, vitamin C, ethanol; device: autologous hematopoietic stem cells	Rates of toxicity; rates of adverse events
NCT02775695	Drug: doxycycline 100 mg twice daily for 8 weeks	Efficacy of doxycycline in inducing metakaryotic (stem cell) death
NCT02744287	Biological: BPX-601; autologous T-cells genetically modified with retrovirus containing PSCA-specific CAR and an inducible MyD88/cluster designation (CD) 40 (iMC) co-stimulatory domain; drug: rimiducid; dimerizer infusion to activate the iMC of the BPX-601 cells for improved proliferation and persistence	Dose-limiting toxicity; treatment emergent and serious AE; maximum tolerated dose
NCT05143151	Biological: CD276 CAR T-cells	Objective response rate

stem cell self-renewal in human glioblastoma, which led to their evaluation by Okada *et al*. in PCSCs (47,48). Inhibition of the JNK axis deprived the PCSCs of their ability to sustain tumor growth. Additionally, K-ras mutations were shown to contribute to the maintenance of the PCSCs, and combination therapies which targeted K-Ras-JNK significantly reduced TICs and tumor bulk growth (48).

Ongoing clinical trials and future directives

Most clinical trials currently investigating PCSCs are largely focused on hematopoietic stem cell transplant (HSCT) or the transplantation of peripheral stem cells (*Table 2*). A phase I, single-arm trial evaluating metastatic pancreatic adenocarcinoma with BRCA 1 or 2 mutation is treating patients with a drug combination of melphalan, BCNU (carmustine), and vitamins in association with autologous HSCT. The primary outcomes of this study are the evaluation of toxicity and adverse events. The medical college of Wisconsin (through collaboration with Massachusetts Institute of Technology) is evaluating whether the antibiotic doxycycline can kill a significant fraction of metakaryotic (PCSCs) cells in pre-treated pancreatic adenocarcinoma. This phase 2 trial will administer doxycycline during radiation treatment and following neoadjuvant chemotherapy. Patients will then undergo surgical resection.

Researchers are currently studying the feasibility and safety profile of PSCA-specific CAR-T cells (BPX-601) with concurrent administration of rimiducid in PSCA-positive advanced solid tumors. This is a Phase I/II dose escalation and expansion trial which will evaluate the safety and efficacy in metastatic pancreatic and prostate cancer. A Chinese study sponsored by Shenzhen University General Hospital is currently recruiting for a Phase I trial studying the efficacy and safety of CD276-targeted CAR-T cells in refractory pancreatic cancer. This biologic is a member of the B7 co-stimulatory family and has been shown to be overexpressed in many cancer types and is associated with a poorer prognosis.

Conclusions

Pancreatic tumor heterogeneity is driven by sub-groups and functional differences within sub-group clones. PCSCs and their counterparts, tumor-initiating cells, are largely responsible for this diverse tumor microenvironment and often play crucial roles in the recurrence and chemoresistance seen in advanced pancreatic cancer. Many of the molecular pathways involved in the self-renewal and function of stem cells have been identified and their co-inhibition coupled with standard therapeutic regimens may improve progression, recurrence, and overall survival.

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Footnote

Reporting Checklist: The authors have completed the

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