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Importance of Cancer Stem Cell in Development of Pancreatic Cancer

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Abstract

Pancreatic cancer (PC) is an aggressive malignancy arising from the uncontrolled proliferation of pancreatic exocrine or neuroendocrine cells. It is currently the seventh leading cause of cancer-related deaths globally and the third in many developed nations, with an overall 5-year survival rate of approximately 10%. Pancreatic ductal adenocarcinoma (PDAC), the most prevalent form of PC, is particularly lethal, as most patients present with unresectable or metastatic disease at diagnosis. Two major biological models have been proposed to explain PDAC progression. The clonal evolution theory suggests that random driver mutations emerge within tumor cells, with selective clonal expansion of variants that confer a growth advantage. In contrast, the cancer stem cell (CSC) model highlights a small subpopulation of pancreatic cancer stem cells (PCSCs), characterized by $CD44^{+}CD24^{+}ESA^{+}$ markers (representing 0.2–0.8% of tumor cells), which exhibit high tumorigenicity, self-renewal capacity, and the ability to differentiate into heterogeneous cell populations reflective of the primary tumor. These PCSCs also show elevated expression of developmental signaling regulators such as Sonic Hedgehog and Bmi-1. The interplay between PCSCs and the highly complex tumor microenvironment contributes significantly to therapeutic resistance, metastasis, and tumor relapse. Therefore, comprehensive understanding of the tumor microenvironment and global gene-expression profiling of cancer stem cells is essential for developing targeted and more effective therapeutic strategies for PDAC.

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Cell surface marker, CSC (cancer stem cell), microenvironment, PC (pancreatic cancer), PDAC, tumor

Introduction

Pancreatic cancer is a highly lethal malignancy characterized by uncontrolled proliferation of exocrine or neuroendocrine pancreatic cells. Increasing evidence suggests that its initiation and progression are driven by a small subpopulation of aberrant cancer stem cells (CSCs), which contribute to tumorigenesis, metastasis, and resistance to therapy. Despite advances in diagnostic and therapeutic modalities, pancreatic cancer remains exceptionally difficult to treat, largely due to its aggressive biology, late clinical presentation, and the presence of therapy-resistant CSCs. This review aims to provide an improved understanding of pancreatic cancer stem cells (PCSCs) and their role in tumor initiation, progression, and therapeutic failure.

Prevalence

Pancreatic cancers are broadly classified into two major categories: exocrine pancreatic cancers, primarily pancreatic ductal adenocarcinoma (PDAC), and neuroendocrine pancreatic tumors. Exocrine cancers account for approximately 85% of all pancreatic cancer

cases, whereas neuroendocrine tumors represent less than 5% (Ilic and Ilic, 2016). According to GLOBOCAN 2018, pancreatic cancer ranks as the 11th most commonly diagnosed cancer worldwide (Bray *et al.,* 2018). SEER 2021 data reported 40,430 new cases and 48,220 pancreatic cancer–related deaths in the United States, with a persistently low 5-year survival rate of around 10% (Siegel *et al.,* 2021).

Several risk factors—including smoking, genetic predisposition, age, obesity, diabetes mellitus, and chronic pancreatitis—significantly increase disease susceptibility (Vincent *et al.,* 2011). Clinical manifestations are often absent until advanced stages, and symptoms such as jaundice, abdominal pain, unexplained weight loss, and pruritus frequently indicate metastatic or locally advanced disease. Given its silent progression and aggressive nature, pancreatic cancer continues to pose substantial clinical challenges. Understanding the origins and biology of PCSCs is therefore essential for improving therapeutic strategies and outcomes.

Cancer Stem Cells (CSCs)

Cancer stem cells (CSCs) possess defining properties similar to normal stem cells, including self-renewal, asymmetric division, and the ability to generate heterogeneous tumor cell populations. Additionally, CSCs demonstrate pronounced resistance to chemotherapy and radiotherapy, immune evasion, and sustained proliferative capacity (Clara *et al.,* 2020; Walcher *et al.,* 2020). Their capacity to acquire genetic mutations over time contributes to increased tumor aggressiveness (Bajaj *et al.,* 2020). CSCs can enter a quiescent G0 state, enabling them to survive treatments targeting rapidly dividing cells, and later re-enter the cell cycle under favorable conditions (Nguyen *et al.,* 2022; Talukdar *et al.,* 2019). The high expression of ATP-binding cassette (ABC) transporters, including ABCB1, ABCC1, and ABCG2, further contributes to multidrug resistance by actively effluxing chemotherapeutic agents (Cho and Kim, 2020).

CSCs also display activated signaling pathways such as PI3K/AKT, Wnt/β-catenin, and NOTCH, which promote survival and inhibit apoptosis (Phi *et al.,* 2018). The tumor microenvironment (TME), composed of stromal cells, extracellular matrix components, and signaling molecules, plays a pivotal role in supporting CSC maintenance and mediating treatment resistance (Lee *et al.,* 2020).

CSCs were first identified in 1994 by Lapidot *et al.,* in acute myeloid leukemia, where $CD34^{+}CD38^{-}$ cells were shown to maintain leukemic growth in SCID mice, establishing the concept of "leukemia-initiating cells" (Lapidot *et al.,* 1994). In solid tumors, epithelial-to-mesenchymal transition (EMT) has been strongly linked to CSC generation and metastatic potential. During EMT, epithelial cells lose polarity and cell–cell adhesion, acquire mesenchymal properties, and express stemness markers such as SOX2, OCT4, KLF4, alongside CSC surface markers including CD44, CD24, EpCAM, and CD133—several of which are prominent in PDAC.

The origins of CSCs remain debated. They may arise from normal tissue stem cells due to their inherent longevity and capacity for mutation accumulation (Brunner *et al.,* 2012). Alternatively, early progenitors or even differentiated cells may acquire stem-like characteristics through genetic or epigenetic reprogramming (Dalerba *et al.,* 2007; Lopez, 2015). In gastrointestinal cancers, CSCs have been shown to originate predominantly from normal stem cells (Barker *et al.,* 2009), while other studies demonstrate that mesenchymal stem cells (MSCs) can spontaneously transform into CSC-like cells in vitro (Burns *et al.,* 2005). These findings underscore the biological heterogeneity and complexity of CSC origin across tumor types.

Isolation and Characterization of CSCs

The existence of a distinct subpopulation of pancreatic cancer stem cells (PCSCs) has been well documented, with early studies indicating that only 0.2–0.8% of tumor cells simultaneously express the surface markers CD44, CD24, and ESA/EpCAM (Li *et al.,* 2007). These cells exhibit a markedly enhanced tumorigenic capacity—nearly 100-fold higher than their $CD44^{-}/CD24^{-}/ESA^{-}$ counterparts—and possess the ability to self-renew through both symmetric and asymmetric division. In addition, PCSCs overexpress key developmental signaling molecules such as Sonic Hedgehog (SHH), further supporting their role in driving tumor progression (Li *et al.,* 2007). Beyond the canonical $CD44^{+}CD24^{+}EpCAM^{+}$ phenotype, several other markers have been identified for PCSCs, including CD133, ALDH1, DCLK1, CXCR4, ABCG2, c-Met, and Lgr5, each contributing additional insights into tumor biology and heterogeneity (Immervoll *et al.,* 2008; Rasheed *et al.,* 2010; Ito *et al.,* 2016; Morita *et al.,* 2020; Wang *et al.,* 2009; Li *et al.,* 2011).

CSCs were initially isolated from breast tumors in 2003 using similar membrane markers, providing a foundational framework for CSC identification across solid cancers (Haji *et al.,* 2003). Following this approach, Li *et al.,* (2007) conducted a pivotal study analyzing primary and metastatic pancreatic cancer specimens using CD44, CD24, and EpCAM as cell surface markers (Figure 2). Their work demonstrated that individual marker-positive populations—such as $CD44^+$ cells—possessed significantly greater tumorigenic potential than marker-negative cells when injected into NOD/SCID mice. Notably, the $CD44^+CD24^+EpCAM^+$ subset exhibited the highest tumor-initiating capacity: as few as 100 cells were sufficient to generate pancreatic tumors, whereas hundreds to thousands of negative cells failed to do so. Tumors derived from these cells recapitulated the full histological heterogeneity of the patient's primary tumor, confirming their stem-like properties. This landmark study firmly established the presence of a highly tumorigenic PCSC subpopulation that drives pancreatic cancer initiation, progression, and phenotypic diversity (Li *et al.,* 2011).

Additional Characterization of PCSCs & Clonal Evolution Theory

Several subsequent studies have further characterized this rare and highly tumorigenic subpopulation of pancreatic cancer stem cells (PCSCs). Hermann *et al.,* (2007), for example, identified a distinct PDAC stem cell population with intrinsic metastatic potential. Their hypothesis was based on the premise that if CSCs can initiate and maintain primary tumors, they may also drive invasion and metastasis. Using flow cytometry, they isolated $CD133^+$ cells—a marker previously associated with normal and malignant stem cells across multiple embryonic lineages.

Their findings demonstrated that $CD133^+$ pancreatic CSCs displayed markedly enhanced tumorigenicity compared with $CD133^-$ or unsorted bulk tumor cells: as few as 500 $CD133^+$ cells were sufficient to initiate tumors in nude mice, underscoring their potent tumor-initiating ability.

Building on early discoveries involving CD44 as a PDAC stem cell marker, Li *et al.,* later identified c-Met as another critical PCSC marker. c-Met, a receptor tyrosine kinase implicated in proliferation, invasion, and metastasis, was found to be enriched in aggressive CSC populations. By examining multiple established markers—$CD44^+/CD24^+/EpCAM^+$, $CD133^+$, and others—they observed substantial overlap among CSC subsets. Notably, the c-Met^high/$CD44^+$ fraction exhibited the strongest tumorigenic potential, with as few as 50 cells able to induce tumor formation in NOD/SCID mice. The proportion of c-Met and c-Met^high cells varied between 2–16% across patient samples. Importantly, gemcitabine treatment—the standard chemotherapeutic agent for PDAC—resulted in a significant expansion of the CSC population by up to 50%, providing a potential explanation for therapy resistance and frequent relapse. To evaluate whether c-Met itself sustains the CSC pool, Li *et al.,* utilized XL184 (cabozantinib), a potent c-Met inhibitor. Combination therapy with gemcitabine and XL184 significantly reduced tumor burden, suppressed metastasis for over 30 days post-treatment, and strongly inhibited spheroid formation. These findings highlight the necessity of therapeutic strategies that simultaneously target both the tumor bulk and the CSC compartment to improve PDAC outcomes.

Understanding Cancer Stem Cells and Their Role in Carcinogenesis

Clonal Evolution of Tumor Populations

Two major models have been proposed to explain tumor initiation, progression, and intratumoral heterogeneity. The first is the classical clonal evolution theory, introduced by Peter Nowell in 1976 and grounded in Darwinian evolutionary principles. According to this model, random genetic and epigenetic alterations arise within tumor cells, and clones that acquire advantageous driver mutations outcompete neighboring cells, ultimately dominating the tumor population. This model implies that *any* cancer cell has the potential to acquire additional mutations and give rise to new clonal expansions, suggesting that all tumor cells possess comparable tumorigenic potential (Nowell, 1976; Vega *et al.,* 2023).

The second, non-mutually exclusive model is the cancer stem cell (CSC) hypothesis, which posits that tumorigenesis is sustained by a small, hierarchically organized subset of cells with stem-like properties—including self-renewal, asymmetric division, and the ability to regenerate heterogeneous tumor cell populations.

These CSCs, rather than all tumor cells, are responsible for long-term tumor maintenance, therapeutic resistance, and metastatic spread.

PCSC Origin & Tumor Microenvironment

Origin of Pancreatic Cancer Stem Cells (PCSCs)

Multiple studies have demonstrated that the major pancreatic cell lineages arise from a common pool of progenitor cells that express the transcription factor pancreatic and duodenal homeobox 1 (Pdx1). These multipotent progenitors have the capacity to differentiate into all mature pancreatic cell types; however, they disappear during development, and adult pancreatic regeneration does not rely on their presence (Gu *et al.,* 2002; Zhou *et al.,* 2007; Stanger *et al.,* 2007). Although true stem cells in the adult pancreas remain limited, recent evidence from engineered mouse models (Byrnes *et al.,* 2018) and single-cell RNA sequencing studies (Yu *et al.,* 2019) indicates the existence of rare progenitor-like subpopulations within cultured pancreatic cells. Additionally, a distinct epithelial niche known as the pancreatic ductal gland (PDG) compartment has been identified as a potential reservoir of stem-like cells responsible for ductal epithelial maintenance (Yamaguchi *et al.,* 2015). However, the PDG compartment does not appear to contribute substantially to regeneration following inflammatory injury of terminal ducts or acinar tissue.

Instead, pancreatic injury triggers an alternative repair mechanism driven by cellular plasticity, particularly in acinar cells—the most plastic cell type in the pancreas. Through acinar-to-ductal metaplasia (ADM), acinar cells undergo dedifferentiation to an embryonic-like state before re-differentiating into ductal or other cell types as needed. This process has been strongly implicated as an early event in the initiation of pancreatic ductal adenocarcinoma (PDAC), supported by evidence from transgenic mouse models and 3D human organoid systems. ADM-derived cells can progress to pancreatic intraepithelial neoplasia (PanIN-1 or PanIN-2), although additional genetic and microenvironmental alterations—such as activation of EGFR or NOTCH pathways, macrophage recruitment, and pro-inflammatory signaling—are required for malignant transformation. Notably, early PanIN lesions expressing DCLK1 exhibit functional similarities to CSCs, further linking ADM to PCSC origin (Storz, 2017; Westphalen, 2016).

Growing evidence suggests that CSCs may undergo epithelial-to-mesenchymal transition (EMT), a process that enhances their motility and metastatic capability. While many studies support acinar cells as the principal origin of PDAC—mediated by ADM and EMT—ductal cells may also give rise to PDAC through intraductal papillary mucinous neoplasms (IPMN). Ductal cells can undergo dedifferentiation with re-expression of progenitor markers such as Pdx1 and HNF4A, generating a population capable of forming metastatic PDAC (Roy *et al.,* 2015). Single-cell sequencing analyses of primary PDAC and adjacent normal tissue further strengthen the notion that both acinar and ductal compartments contribute to tumor initiation under specific pathological contexts (Peng *et al.,* 2019).

Tumor Microenvironment (TME) in Pancreatic Cancer Development

The tumor microenvironment (TME) plays a pivotal role in the initiation, progression, and therapeutic resistance of pancreatic cancer. First conceptualized by Virchow in 1889 through his observations linking chronic inflammation to carcinogenesis, the TME comprises both acellular and cellular components that coexist in a dynamic and highly interactive ecosystem.

The acellular components include cytokines, chemokines, extracellular vesicles, growth factors, and a dense extracellular matrix (ECM) rich in collagen, hyaluronic acid, and fibrotic elements. These components contribute to the hallmark desmoplastic stroma characteristic of PDAC and create a physical and biochemical barrier that impedes drug penetration.

The cellular compartment consists of both malignant and non-malignant cells, including tumor-associated macrophages (TAMs), cancer-associated fibroblasts (CAFs), dendritic cells (DCs), tumor-associated neutrophils (TANs), myeloid-derived suppressor cells (MDSCs), T cells, B cells, natural killer (NK) cells, endothelial cells, and pericytes. Among these, CAFs represent the most abundant stromal population and play critical roles in ECM remodeling, immune suppression, angiogenesis, and CSC maintenance. Collectively, these components cooperate to create an immunosuppressive, highly fibrotic, and therapy-resistant niche that enables tumor progression and shields CSCs from chemotherapeutic agents.

The TME not only facilitates immune evasion but also modulates key signaling pathways that promote EMT, stemness, metastasis, and recurrence, underscoring its importance as a therapeutic target in PDAC.

The tumor microenvironment (TME) plays a fundamental role in the initiation, progression, and

therapeutic resistance of cancer. It is a dynamic ecosystem characterized by continuous bidirectional communication between malignant and non-malignant cells, influencing key processes such as tumor initiation, maintenance, metastasis, immune evasion, and resistance to chemotherapy and radiotherapy. The acquisition and preservation of cancer hallmarks are strongly dependent on the regulatory influence of the TME.

Numerous studies have demonstrated that cancer cells actively manipulate surrounding stromal and immune populations by releasing cytokines, growth factors, extracellular vesicles, and other signaling molecules that promote metastatic dissemination, remodel the extracellular matrix, and recruit immunosuppressive cells. These interactions between cellular and acellular components contribute significantly to intratumoral heterogeneity and clonal evolution, ultimately shaping a more aggressive tumor phenotype (Baghban *et al.,* 2020). Within the TME, distinct specialized niches have been identified—each characterized by unique biochemical or physical features that support tumor adaptation and survival. At least six such niches have been described: the hypoxic niche, acidic niche, mechanical niche, innervated niche, metabolic niche, and immune niche (Figure 4). These microenvironmental niches have been particularly implicated in promoting therapeutic resistance and enabling tumor cells, especially cancer stem cell subsets, to evade immune surveillance and persist following treatment.

Tumor Microenvironment: Specialized Niches in Pancreatic Cancer

Hypoxic Niche

Rapid cellular proliferation combined with aberrant and insufficient vascularization leads to regions of oxygen deprivation, giving rise to hypoxic niches within tumors. Hypoxia-inducible factor-1 (HIF-1) is the central regulator of cellular adaptation to low oxygen levels, orchestrating the shift from normoxia to hypoxia and modulating downstream survival pathways (Heddlestone *et al.,* 2010). Hypoxic niches are characterized by the expression of stemness-associated transcription factors, including SOX2, KLF4, NANOG, MYC, and OCT4, which collectively promote cancer cell survival, dedifferentiation, and therapeutic resistance.

Elevated expression of these markers is frequently associated with poor prognosis and enhanced tumor aggressiveness (Zhang *et al.,* 2021).

Acidic Niche

Cancer cells undergo profound metabolic reprogramming, preferentially relying on aerobic glycolysis even in the presence of oxygen—a phenomenon known as the Warburg effect (Warburg, 1956; Vander Heiden *et al.,* 2009). Although glycolysis facilitates rapid ATP production, it leads to excessive lactate accumulation, acidifying the tumor microenvironment. Initially cytotoxic, this acidic milieu becomes advantageous once cancer cells adapt, enabling them to outcompete healthy cells, induce apoptosis in surrounding normal tissues, and promote invasion, metastasis, and immune evasion (Sattler *et al.,* 2010).

Mechanical Microenvironment (MME)

The mechanical microenvironment is a highly specialized niche influenced by cytoskeletal components (e.g., vimentin, actin, neurofilaments) and extracellular matrix (ECM) components such as collagen (Nagelkerke *et al.,* 2015). Mediated largely by cancer-associated fibroblasts (CAFs), the secretion of matrix metalloproteinases (MMPs) drives ECM remodeling, enhancing stiffness and facilitating epithelial-to-mesenchymal transition (EMT). This mechanotransduction environment enables tumor cells to acquire invasive and metastatic capabilities (Calvo *et al.,* 2013; Xiong *et al.,* 2020). The MME plays a critical role in shaping tumor architecture and fostering a pro-metastatic phenotype.

Innervated Niche

Emerging evidence demonstrates that the nervous system significantly influences tumor development and progression. Neurotransmitters and neuropeptides released by pre-existing nerves or newly formed tumor-induced neural networks stimulate cancer cell proliferation, invasion, and metastasis (Magnon *et al.,* 2013; Ayala *et al.,* 2008). Tumor innervation provides physical conduits that facilitate cancer cell dissemination to distant organs (Jobling *et al.,* 2015; Liebig *et al.,* 2009). Additionally, neural progenitors can migrate from the central nervous system to tumors and differentiate into neurons, further contributing to tumor innervation (Mauffrey *et al.,* 2019; Cervantes, 2020). Innervated niches have been documented in multiple malignancies—including pancreatic, breast, prostate, colorectal, ovarian, and head and neck cancers—and are strongly associated with aggressive behavior and poor treatment outcomes (Zahalka & Frenette, 2020). Because

neural–tumor crosstalk promotes therapeutic resistance, the innervated niche represents a promising target for anti-neurotrophic therapeutic strategies.

Exosome-Mediated Communication

Extracellular Vesicles (EVs), including exosomes, are nanoscale membranous structures that mediate intercellular communication by transporting proteins, lipids, RNA, and DNA fragments (Aliuno *et al.,* 2020; Jayasinghe *et al.,* 2021). EVs originate either through plasma membrane shedding or via exocytosis (Cocucci *et al.,* 2009; Denzer *et al.,* 2000) and are conserved across prokaryotic and eukaryotic organisms (Colombo *et al.,* 2014). Exosomes (50–150 nm) play a pivotal role in tumor progression, with cancer cells producing significantly higher levels compared to normal cells (Bebelman *et al.,* 2018). These vesicles modulate multiple aspects of the tumor microenvironment, promoting hypoxic adaptation, EMT, angiogenesis, and autophagy. Cross-talk mediated by exosomes between CAFs, macrophages, and cancer cells further strengthens the hypoxic niche and enhances survival under stress conditions (Yang *et al.,* 2021; Xu *et al.,* 2021).

Metabolic Microenvironment

The metabolic microenvironment reflects nutrient availability and metabolic pressures within the tumor ecosystem. Reactive oxygen species (ROS), generated by both cancer and stromal cells, contribute to DNA damage and genomic instability (Weinberg *et al.,* 2010). However, tumor cells often adapt to elevated ROS levels, developing a phenomenon known as ROS addiction that drives proliferation and metabolic rewiring (Mao *et al.,* 2018). ROS also regulate immune cell recruitment and function, influencing populations such as MDSCs, TAMs, and regulatory T cells (Qu *et al.,* 2012; Sena *et al.,* 2013; Costa *et al.,* 2014). This metabolic reprogramming further reinforces tumor heterogeneity and immune suppression.

Modern Biotechnology: Single-Cell RNA Sequencing (scRNA-seq) in PDAC

Over the past decade, single-cell RNA sequencing (scRNA-seq) has revolutionized tumor biology by enabling high-resolution analysis of cellular heterogeneity, transcriptional dynamics, and lineage evolution. Its integration with complementary technologies such as scDNA-seq, scATAC-seq, spatial transcriptomics, and multimodal proteogenomics has transformed the understanding of pancreatic ductal adenocarcinoma (PDAC) (Casado *et al.,* 2022; Jia *et al.,* 2022).

Recent profiling studies have revealed distinct stromal, immune, and tumor epithelial subpopulations in PDAC, reinforcing earlier observations of structural, inflammatory, activated, and immunomodulatory stromal compartments (Puleo *et al.,* 2018; Moffitt *et al.,* 2015). Using CyTOF, scRNA-seq, and multiplex immunohistochemistry, Steele *et al.,* identified a highly complex immune-suppressive interaction network, highlighting the need for personalized immunotherapeutic strategies (Steele *et al.,* 2020).

Single-cell sequencing has also uncovered diverse CAF subtypes. Elyada *et al.,* identified three major CAF lineages—myofibroblastic CAFs (myoCAFs), inflammatory CAFs (iCAFs), and a newly discovered antigen-presenting CAF population characterized by high MHC-II expression—capable of directly interacting with CD4+ T cells. Moreover, Chan-Seng-Yue *et al.,* identified five molecular tumor subtypes, demonstrating the coexistence of classical-like and basal-like cells within the same tumor and establishing a link between basal-like states and EMT programs associated with poor clinical outcomes.

These multimodal single-cell studies have fundamentally reshaped our understanding of PDAC biology and continue to guide the development of precision therapeutic strategies.

Ongoing Clinical Trials and Future Directions

Current clinical trials targeting pancreatic cancer stem cells (PCSCs) are predominantly focused on hematopoietic stem cell transplantation (HSCT) and stem-cell–directed interventions. One Phase I trial evaluates a chemotherapeutic regimen combining melphalan, carmustine (BCNU), and vitamin therapy followed by autologous HSCT in BRCA1/2-mutated metastatic pancreatic adenocarcinoma to assess safety and toxicity outcomes.

A Phase II study conducted by the Medical College of Wisconsin and MIT is investigating the potential of doxycycline to selectively eliminate metakaryotic PCSC populations in previously treated pancreatic adenocarcinoma. In addition, a Phase I clinical trial initiated by Shenzhen University General Hospital is assessing the efficacy and safety of CD276-targeted

CAR-T cells in refractory pancreatic cancer, representing a promising advancement in stem-cell–directed immunotherapy (Sambly & Landry, 2022).

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