

# Therapeutics Progression in Pancreatic Cancer and Cancer Stem Cells

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## Abstract

**Pancreatic cancer (PC) is one of the most lethal malignant tumors, which often result from diagnoses of advanced stages and ineffective therapies. A main reason for this extremely poor prognosis is the cancer's tendency to invade adjacent tissues and metastasize to regional lymph at a relatively early stage. Nowadays, the resistance to conventional chemotherapy is becoming crucial in poor clinical outcomes of PC. In order to improve the prognosis and clinical outcomes of PC, there is a pressing need to develop new therapeutic strategies not only aimed at preventing invasion and metastasis, but also improving the resistance of chemotherapies. The resistance to conventional therapeutic agents in cancer may be sustained by a fraction of cancer cells within the tumor, which is called the cancer stem cells (CSCs). Combined therapies targeting CSCs and their progenies may represent the most promising approach for the future treatment of patients with PC.**

## Keywords

**Pancreatic Cancer, Cancer Stem Cells, Cancer Therapy**

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## 1. Introduction

Pancreatic cancer (PC) has one of the worst prognoses of any major malignancy (6.7% 5-year survival) [1]. Despite recent improvements in surgical and chemotherapeutic approaches, PC continues to have a poor prognosis due to the lack of early symptoms, which results in advanced stage and metastatic states of PC patients and makes their malignancy inoperable. Moreover, drug-resistance is also a main reason for the dismal prognosis with an average overall median survival of 4 - 6 months in PC patients [2] [3]. Nowadays, PC is the fifth most common cause of cancer death yearly in the United States and seventh cancer death in China [1] [4]. According to the report of Nation Cancer Institute (NIH), the number of new cases of PC was 12.3 per 100,000 men and women per year during 2007-2011, while 10.9 per 100,000 men and women dead of PC every year during

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2006-2010 [1].

Recent studies have shown that a small group of cells possess stem cell-like characters in various cancers [5]-[7]. These cells have been called cancer stem cells (CSCs) because of their stemness. CSCs have similar features as stem cells, including pluripotency with the function of self-renew and differentiation. CSCs mainly remain in the G0 phase of the cell cycle so that they are less sensitive to traditional radiotherapy and chemotherapy than proliferating cells [8]. Therefore, there is an emerging need to develop new strategies against CSCs. During the past few years, it has been demonstrated that CSCs are closely related to PC and play an important role in targeting therapeutic strategies [9] [10].

In this article, we reviewed the research status of pancreatic CSCs and recent progressions in CSC-related therapeutic strategies.

## 2. Cancer Stem Cells and Tumors

CSCs have been proved to possess the function of self-regenerate, proliferate and have multiple differentiation potentials [11]. They can differentiate to cancer cells and produce different phenotypes of non-tumorigenic tumor cells to enlarge tumor mass as well. They are also considered to be the only cells with metastatic ability in the tumor cell subset [12]-[14].

CSCs were first found in patients with acute myeloid leukemia. Bonnet and Dick found that some hematopoietic stem cells, which were similar to CD34+ CD38+ cells from tumor tissues, could self-renew, self-regenerate and become xenografts in nude mice [15]. Xenograft formation in nude mice was regarded as the gold standard of CSCs in cancer tissues. Breast cancer is one of the earliest tumors discovered to have CSCs. Al-Hajj and colleagues isolated a CD44+/CD24-/low cell line from breast cancer, which can form tumors in nude mice [16]. Ignatova et al first isolated CD133+ CSCs in human brain tumors, and found that an injection of CD133+ tumor cells can differentiate and proliferate into brain tumor [17]. However, even with injection of up to 500 times of CD133- cancer cells, there was no tumor formation. This provided strong evidence of the existence of CSCs. Thereafter, researchers proved the existence of CSCs in many solid tumors, including glioma [18], multiple myeloma [19], pancreatic cancer [20], colon cancer [21], liver cancer [22], prostate cancer [23], head and neck squamous cell carcinoma [24], malignant melanoma [25], and ovarian cancer [26].

Like the normal stem cells, CSCs are the foundation and basis of the tumors. The expression of cancer-suppressing genes within CSCs is inhibited, and that of Sonic hedgehog (SHH), Notch, Wnt/ $\beta$ -catenin, and Hox signaling pathway is activated [27]-[30]. CSCs are regarded to be become drug resistant during conventional chemotherapy, and migrate and metastasize rapidly into novel tumors. All these findings are helpful for understanding tumors more comprehensively and developing more targeted cancer therapy.

### 2.1. Identification of Pancreatic Cancer Stem Cells

CSCs have been identified by a variety of biomarkers, some of which were previously associated with normal stem cells in the pancreas. But the detailed function of these markers remains uncertain.

### 2.2. CD44, CD24, EpCAM

CD44, CD24 and EpCAM (also called ESA) are often regarded as cell surface markers of CSCs in PC. Li first described population of pancreatic stem cells in 2007 [31]. Researchers injected a subpopulation of CD44+ CD24+ ESA+ cells from pancreatic ductal adenocarcinoma (PDAC) into immunodeficient mice and induced tumors, while their triple negative counterparts did not show tumorigenic capacity. In their studies, this population of CD44+ CD24+ ESA+ cells could initiate tumors much easier in 50% of transplanted mice. In contrast, as many as 100-fold triple negative cells were required to form tumors.

These triple positive cells could also re-establish the cell-surface profile of markers of the original tumors, which result from cell-renew and differentiation into triple-negative or single- and double-positive populations [32]. This process was considered to be related with SHH pathway, which is less activated in normal pancreatic cells, unsorted pancreatic cancer cells, and triple-negative cells. These findings indicated that this pathway might be important for the tumor-promoting functions of these cells.

### 2.3. CD133

CD133 could be found in CSCs from various tumors [33] [34]. Like CD44+ CD24+ ESA+ cells, CD133+ pan-

creatic CSCs also showed more aggressive behavior compared with CD133<sup>-</sup> cells, which include increased cell proliferation, migration, tumor invasion, and especially the presence of pancreatic stromal cells [35]. Compared with CD44 and CD24 positive cells, CD133<sup>+</sup> cells also show higher tumorigenic and metastatic potential [36]. Injecting  $5 \times 10^2$  CD133<sup>+</sup> cells into nude mice could induce tumor formation while no tumor growth was detected after inoculation of up to 2000 folds of CD133<sup>-</sup> cells [35]. Hermann also detected an overlap between CD133<sup>+</sup> and CD44<sup>+</sup> CD24<sup>+</sup> EpCAM<sup>+</sup>. However, none of the purging procedures for CSCs is currently capable of identifying single tumorigenic cells [35].

## 2.4. CXCR4

CXCR4 has been implicated in mediating pancreatic cancer invasion and metastases. Hermann and colleagues discovered a certain subpopulation of migrating both CD133 and CXCR4 positive CSCs, which is essential for metastasis in PC [35]. As the receptor for stromal-derived factor-1 (SDF-1/CXCL12), CXCR4 can strongly induce the migration for CD133<sup>+</sup> cancer cells *in vitro*. And the blockage of CD133<sup>+</sup>/CXCR4<sup>+</sup> cells could prevent metastasis of tumor xenografts in mice [35]. This indicates that modulating the SDF-1/CXCR4 axis might be potential pharmaceutical strategies in inhibiting metastasis of CSCs.

## 2.5. c-Met

c-Met, belongs to the group of receptor tyrosine kinases, is one of the novel detected pancreatic CSC markers. With the function of mediating cell growth, angiogenesis and metastasis, c-Met is named as the mesenchymal-epithelial transition factor and membrane receptor (MET) [37]. Combined with its physiological ligand, the hepatocyte growth factor (HGF), c-Met is required for normal mammalian development and plays an important role in epithelial-mesenchymal interactions during organ morphogenesis. Using xenografts and injecting pancreatic cancer cells from patients, Li *et al* show that these cells express high levels of c-Met. c-Met was particularly informative when combined with CD133 or CD44. Moreover, it was interesting that using both c-Met and CD44 could identify a population of cells with strongest tumorigenic potential. These double-positive cells could generate subcutaneous tumors and were highly metastatic [38].

It was also reported that inhibition of c-Met activity with the kinase inhibitor XL184 (cabozantinib) could reduce tumorsphere formation, growth of tumor xenografts, and metastasis in intracardiac injection models [39]. This indicates that c-Met activity is required to maintain a CSC population.

## 2.6. ALDH1 (Acetaldehyde Dehydrogenase-1)

ALDH1, a marker of normal and malignant breast stem cells [40] and lung CSC [41], has also been used for isolating tumorigenic cells in the human pancreatic line L3.6pl [42]. ALDH1 expression could predict for poor outcome and ALDH1<sup>+</sup> cells presented enhanced migratory and invasive potential compared to ALDH1<sup>-</sup> cells [43]. ALDH1 could also be functional marker of pancreatic CSCs. Studies suggest that high expression of ALDH1 protects pancreatic cancer cells from chemotherapy-induced cell death [44]. Xenograft tumors exposed to gemcitabine become enriched for ALDH1<sup>-</sup>positive cells [45], indicating that they can withstand chemotherapy.

## 3. Targeting Therapies against Pancreatic Cancer Stem Cells

Nowadays, the therapeutic strategies against PC are facing two main problems. One of them is drug resistance. Recent researches have revealed that CSCs, especially pancreatic CSCs, play crucial roles in drug resistance which often impairs the successful use of chemotherapies [35] [46]-[48]. Zhang *et al.* found that pancreatic cancer stem-like cells were more resistant to gemcitabine, commonly used against pancreatic carcinoma, and those cells were more invasive [49]. Pancreatic CSCs were proved to contribute to drug resistance of gemcitabine as well [50]. Another problem is that most therapies for pancreatic cancer do not affect pancreatic CSCs, which can then re-establish tumors after treatment. New approaches are therefore needed to debulk existing tumors and eliminate pancreatic CSCs, to prevent relapse. So targeting therapies, which could eliminate pancreatic CSCs and reduce drug resistance, are emerging needs in PC therapies.

## 4. Recent Approaches for Targeting Pancreatic Cancer Stem Cells

Minnelide, a water-soluble prodrug of triptolide, is currently under phase I clinical trial. By decreasing CD133<sup>+</sup>

tumor-initiate cells (TICs or CSCs) as well as non-TIC population, Minnelide could reduce tumor burden, which might point out a potential and effective therapy against PC [51].

Sulforaphane could inhibit the growth of pancreatic CSCs orthotopically implanted in NOD/SCID mice by inhibiting SHH pathway and also inhibits the marker of EMT in human pancreatic CSCs [52].

The dual endothelin1/VEGF signal peptide receptor, DEspR, is detected in microvessels and tumor cells in PDAC. It can be found in CSCs isolated from PDAC-Panc1 cells as well. Researches demonstrated that DEspR-inhibition could decrease Panc1-CSC xenograft tumor growth in nude rats by impacting CD133+ CSCs, suggesting that DEspR-inhibition defines a novel targeting therapy for pancreatic cancer [53].

Disulfiram, an irreversible inhibitor of ALDH, was found to play a key role in resistance to anticancer therapies for PDAC. Kim *et al* found human PDAC-derived cells, expressing high levels of ALDH, could show CSC features. Disulfiram is sensitive to this gemcitabine-resistant subpopulation and removes ALDH-high cancer cells and inhibits tumor growth [54].

CSCs are enriched in the side population (SP) cells, which overexpresses stem cell markers as well as pluripotency maintaining factors, such as Nanog, Sox2, Oct4, c-Myc, signaling molecule Notch1, and drug resistant gene ABCG2. Some scientists established a combination of Sox2/Oct4/c-Myc targeting agent, which could suppress all CSC properties and phenotypes, and reduce the tumorigenic capability of the SP cells and the resistance to conventional chemotherapy [55].

Inhibiting c-Met with XL184 or Alk-4/7 with SB431542 [56] reduces the number of CSCs in tumors and has synergistic effects with gemcitabine. While Gemcitabine treatment results in an increase of the c-Me-high CD44+ population, c-Met inhibition with XL184 leads to a decrease in c-Methigh CD44+ cells. Combination treatment prevents the increase in the CSC population observed with Gemcitabine alone and also contributes to a decrease in c-Methigh CD44+ population, suggesting that XL184 targets the CSC population specifically.

## 5. Immunotherapy against CSCs

Nowadays, a series of immunotherapies are induced and directly targeting towards specific antigens expressed by tumor cells including CSCs. A recent study by Huang and colleges shows an anti-CD3/anti-CD133 bispecific antibody (BsAb) bounding with cytokine-induced killer (CIK) cells could target and kill CD133 high CSCs. The killing of CD133 high pancreatic (SW1990) by the effect cells (BsAb-CIK cells) was significantly ( $p < 0.05$ ) higher than the killing by the parental CIK or by CIK cells bound only with anti-CD3 (CD3-CIK) and inhibited CD133 high tumor growth significantly. The findings introduce a novel immunotherapy for patients with cancer containing CD133 high CSCs by selectively targeting this population [57].

Immunotherapy with unconventional T cells such as  $\gamma\delta$  T cells is based on their potent HLA-nonrestricted cytotoxicity against different tumor entities and their additional capacity to recognize and present antigens to  $\alpha\beta$  T cells [58] [59]. Oberg [60] demonstrated how bispecific antibodies that selectively recruit  $\gamma\delta$  T cells to tumor antigens expressed by cancer cells illustrate the tractable use of endogenous  $\gamma\delta$  T cells for immunotherapy. They isolated  $\gamma\delta$  T cells from patients with PDAC tumor infiltrates lyse pancreatic tumor cells after selective stimulation with phosphorylated antigens and designed bispecific antibodies that bind CD3 or V $\gamma$ 9 on  $\gamma\delta$ T cells and Her2/neu (ERBB2) expressed by pancreatic tumor cells. Both antibodies enhanced  $\gamma\delta$ T-cell cytotoxicity with the Her2/Vg9 antibody also selectively enhancing release of granzyme B and perforin and reduced growth of pancreatic tumors grafted into SCID-Beige immunocompromised mice.

As mentioned above, high level of ALDH was related with pancreatic CSCs. Visus *et al.* [61] used ALDH as a marker for identifying and selectively targeting pancreatic CSCs as well. They generated ALDH1A1-specific CD8+ T cells in order to eliminate ALDH+ CSCs, which induced growth inhibition of CSCs and reduction of metastasis. However, ALDH1A1-specific CD8+ T cells are not CSCs-specific. They could target normal ALDH+ stem cells as well.

## 6. Conclusion

The discovery of pancreatic CSCs has introduced an important concept to cancer biology. Targeting therapies for cancer treatment are much more important when conventional therapies are effortless. According to recent studies, pancreatic CSCs appear to be critical for the processes of cancer cell invasion and metastasis. Therefore, targeting strategies for pancreatic CSCs could be crucial for the prevention of cancer progression and metastasis. However, the mechanism of the resistance of Pancreatic CSCs to radiation and chemotherapy still remains un-

clear. We also should keep on sighting pancreatic CSCs gene expression profiles and the overall complexity of the tumor microenvironment.

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