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REVIEW

New insights into pancreatic cancer stem cells

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Abstract

Pancreatic cancer (PC) has been one of the deadliest of all cancers, with almost uniform lethality despite aggressive treatment. Recently, there have been important advances in the molecular, pathological and biological understanding of pancreatic cancer. Even after the emergence of recent new targeted agents and the use of multiple therapeutic combinations, no treatment option is viable in patients with advanced cancer. Developing novel strategies to target progression of PC is of intense interest. A small population of pancreatic cancer stem cells (CSCs) has been found to be resistant to chemotherapy and radiation therapy. CSCs are believed to be responsible for tumor initiation, progression and metastasis. The CSC research has recently achieved much progress in a variety of solid tumors, including pancreatic cancer to some extent. This leads to focus on understanding the role of pancreatic CSCs. The focus on CSCs may offer new targets for prevention and treatment of this deadly cancer. We review the most salient developments in important areas of pancreatic CSCs. Here, we provide a review of current updates and new insights on the role of CSCs in pancreatic tumor progression with special emphasis on DclK1 and Lgr5, signaling pathways altered by CSCs, and the role of CSCs in prevention and treatment of PC.

Key words: Pancreatic cancer; Cancer stem cells; DclK1; Lgr5; Prevention; Treatment

Core tip: Despite aggressive treatment modalities, pancreatic cancer represents most lethal malignancy with uniform lethality. The pancreatic cancer stem cells (CSCs) have been found to be resistant to chemotherapy and radiation therapy. This review summarizes the important role of CSCs in pancreatic cancer tumor progression with emphasis on DclK1 and Lgr5 CSCs, molecular signaling altered by CSCs and the important role of pancreatic CSCs in prevention and treatment of pancreatic cancer.

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INTRODUCTION

Pancreatic cancer (PC) is a deadly disease with least survival compared to any other cancers. PC including pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer deaths in both genders (men and women) in the United States and the seventh world-wide[1,2]. Despite tremendous scientific effort for over three decades, PC remains almost uniformly lethal devastating disease with < 6% five-year survival. The incidence of PC has been increasing over the past ten years. In 2013, of 46420 people (23530 men and 22890 women) diagnosed with PC, 39590 people (20170 men and 19420 women) were expected to die in the United States[1]. Worldwide, 338000 people were diagnosed with PC in 2012[2]. Lack of early diagnosis and effective interventions are the major factors in the poor prognosis and dismal survival rates[3-5].

Recently, stem cells of pancreatic cancer (CSCs)/ or cancer/tumor initiating cells that often are resistant to treatment have been identified[6-9]. The CSCs occupying a very small part of the entire cancer tissue are the reasons for tumor resistance against conventional chemotherapy and re-growth of untreatable tumors. Although the CSCs exists a small population in the cancer tissues, very recent evidence shows that CSCs contribute to tumor initiation, growth, metastasis, and resistance to therapy[6-10]. Cancer stem cell (CSC) research has achieved much progress in a variety of solid tumors, including pancreatic cancer to some extent[11]. The identification of specific cell surface markers enabled purification of CSCs from different cell lines or clinical tissues/samples, leading to evaluate the nature of CSCs[12-14]. Understanding of pancreatic CSCs may improve existing therapies and deepen insight into the role of CSCs in pancreatic cancer progression[11].

In this mini-review, we will comprehensively focus on pancreatic CSCs with emphasis on DclK1 and Lgr5. Also, we review the signaling pathways altered by CSCs, and the role of CSCs in prevention and treatment of PC (Figure 1).

ROLE OF CSC IN PC

Little has changed over last three decades for 5-year pancreatic cancer survival despite introduction of new and targeted chemotherapeutic agents[15]. It is primarily due to highly aggressive nature of the PC disease as majority of the patients' present late stage disease and doesn't respond to therapy thereby showing chemoresistance[15]. Recently, attention has been focused on pancreatic CSC levels to find better ways to combat PC. Cell membrane markers have made possible the identification of CSCs. Pancreatic CSC populations account for less than 1% of all pancreatic cancer cells[14]. The pancreatic CSCs identified so far are CD133, CD24, CD44, EPCAM, ESA, c-Met, Aldh1, and more recently DclK1 and Lgr5[9-18]. These pancreatic CSC markers are well known based on several xenograft studies. All these markers may mark themselves or co-express to show the CSC properties[19-21]. CD133 pancreatic CSC cells co-express the CXCR4 receptor at the invading margins of human pancreatic ductal tumors[14,19]. Other CSC markers that co-express ($CD24^+$/$CD44^+$/EPCAM and $CD133^+$) show CSC properties making them often resistant to chemo and radiotherapy. However, complete overlap may not be found between these different CSC markers[22].

Most drugs are unable to eradicate these pancreatic CSCs, and this is postulated to be one of the primary reasons for failure of chemotherapy that will lead to tumor relapse and metastasis. The pancreatic CSCs markers CD24, CD44, CD133, CXCR4, ESA and nestin were reported in pancreatic intraepithelial neoplasia and PDAC[23]. Pancreatic CSC populations expressing the cell surface markers CD24, CD44, and ESA[14,19,24] were observed to maintain their cell surface marker phenotype after repeated passages in immunocompromised xenografts mice[12,14,19]. In another study, c-Met positive cells readily formed *in vitro* spheres/but not the c-Met negative cells[14,25]. Similarly, it was noted that cells expressing combinations of CD44 and c-Met showed increased tumor formation ability and to renew[25]. Kim *et al*[18] reported that irrespective of CD133 status, the pancreatic cancer cells with high ALDH1 activity were resistant to chemotherapy-induced cell death and are highly tumorigenic[14,18]. The MiaPaCa-2 sphere derived CSC like cells obtained from the xenograft tumors of the mice showed high expression of EpCAM, CD44 and EZH2[14,26]. All of these CSCs have been reviewed elsewhere for pancreatic cancer. However, there are recent studies showing the CSC properties for two important makers DclK1 and Lgr5 in pancreatic cancer.

DclK1 and pancreatic cancer

Dclk1 (Doublecortin-like kinase 1, formerly known as DCAMKL-1 or doublecortin and CaM kinase-like 1) initially was identified as a putative intestinal stem cell marker. Earlier studies have suggested that Dclk1 may mark tumor-initiating cells in a variety of tumor types[27-39]. DclK1 regulates several key oncogenes like c-MYC, KRAS, NOTCH1 and EMT[32,33,39]. Moreover, DclK1 is also reported to be a pancreatic cancer stem cell marker and its expression is found to be upregulated in PDAC[9,39]. In the pancreas and intestines, Dclk1 has also recently been described as an undefined tuft/brush cell marker[36,37]. We have empirically shown DclK1 expression in both murine and human pancreatic intraepithelial neoplasia (PanIN) and PDAC[9]. DCLK1 is also expressed by isolated cells in the pancreatic duct and islets of normal mouse pancreas, and prior studies have suggested that these non-neoplastic Dclk1-expressing pancreatic cells were associated with progenitor-like function[31]. Further, it was shown that DCLK1HI/AcTubHI mouse PanIN cells display specialized morphology, unique patterns of gene expression, and enhanced PanIN

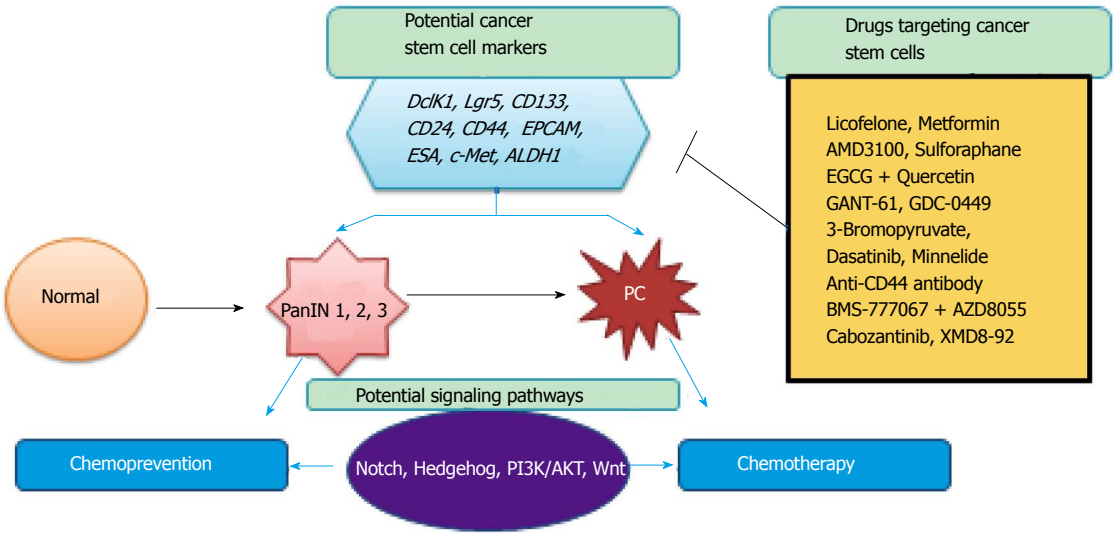

Figure 1 Schematic representation of the role of cancer stem cells markers during pancreatic cancer development, signaling pathways involved and cancer stem cells inhibition by various drugs by chemoprevention and/or chemotherapy. PC: Pancreatic cancer.

sphere-forming ability[6]. The lineage tracing techniques using alternate DNA recombinases (*e.g.*, Dre, Flp) or the development of non-Cre/lox-based methods for Kras activation in the murine pancreas will further the progress in this area. Multiple pathways that contribute to the CSC properties of DCLK1HI/AcTubHI pancreatic cancer cells were identified by using whole genome transcriptome analysis[6]. Studies identified ABL1 and IGF1R to be highly expressed in DCLK1HI/AcTubHI cells, complementing ongoing preclinical and clinical evaluation of ABL1 and IGF1R pathway inhibition as new forms of targeted therapy for pancreatic cancer[38,39]. These studies suggest that both invasive and preinvasive PC may depend on DCLK1 expressing cells with cancer stem cell capabilities. As in the case of intestinal tumorigenesis, targeting this cell population may have therapeutic potential in the treatment and/or chemoprevention of pancreatic cancer. Further, NPsiDCLK1 (nanoparticle-encapsulated siRNA) knockdown of Dclk1 in the mouse xenograft lead to downregulation of important markers of pluripotency like SOX2, NANOG, OCT4 and KLF4 and EMT, and angiogenic factors[40]. These data clearly supports a central regulatory role of Dclk1 in pancreatic tumorigenesis[39]. However, further studies are underway to evaluate the potential of Dclk1 as pancreatic CSC and specifically target DclK1 along or in combination with other CSC markers.

Lgr5 and pancreatic cancer

Lgr5 also known as G-protein coupled receptor 49 (GPR49) or G-protein coupled receptor 67 (GPR67) or Leucine-rich repeat-containing G-protein coupled receptor 5 (LGR5) is the Wnt target gene that marks Wnt driven actively dividing stem cells[41-43]. In the stem cell hierarchy, LGR5 is on a higher level than CD133, however, its expression and function in the tissues of pancreatic cancer is unclear. Recent studies investigated tissue expression of LGR5 and CD133 in resected pancreatic ductal adenocarcinoma who underwent resection and demonstrated cytoplasmic expression of LGR5 in the PC cells[17].

The maturation lineages of proximal peribiliary glands to the distal pancreatic ductal glands start near duodenum where cells express pluripotency markers (SOX2, OCT4 and NANOG), self-replication, proliferation and early hepato-pancreas commitment (Lgr5, PDX1, SOX17, SOX9)[44]. A biological framework for life-long pancreatic organogenesis is constituted by the biliary tree-derived stem cells and their connections to committed progenitors of the pancreas[40]. In the normal pancreas, LGR5 is co-localized with insulin and Nanog in the beta cells clusters and is exclusively expressed in the islets of the Langerhans[45].

Since, Lgr5 is a stem cells marker in various organs and acts as Wnt-agonistic R-spondins receptor, the Lgr5 positive stem cells from intestine, liver and stomach form organoids in three dimensional cultures that resemble the tissues of origin[42,46,47]. In a normal adult pancreas, Lgr5 is not expressed when Wnt signaling is inactive under normal conditions[48]. However, upon the injury, Wnt pathway is activated by partial duct ligation, and Lgr5 is concomitantly expressed in the regenerating ducts[49]. It was observed that pancreatic duct or fragments in the RSPO-1 cultures initiate Lgr5 expression and develop into organoids that can clonally expand containing Lgr5 stem/progenitor cells[49]. The histoanatomical distribution, prevalence, and tumor biological significance of LGR5 in gastrointestinal tract tumors (including pancreatic cancer) was tested on transcriptional and translational level in tissues of 127 patients (malignant and non-malignant). It was noted that the non-neoplastic tissue usually had very few scattered LGR5 positive cells. The corresponding malignant pancreatic cancers showed significantly more LGR5 positive cells at protein and mRNA levels compared with the non-neoplastic tissue[50]. Lgr5 co-

expressed with other CSC markers Mushashi-1, CD44 and ADAM17 and the patients with high Lgr5 positive cells had shorter median survival[50]. Future studies are required to understand the role and clarify the prognostic value of Lgr5 in the pancreatic cancer.

SIGNALING PATHWAYS ALTERED BY CSCS

Pancreatic cancer cells and pancreatic CSCs share many characteristics of the carcinogenesis process including self-renewal, proliferation and immortality and several signaling pathways. Researchers have identified several CSC specific markers. In a recent study, investigators detected high expression of CD24, CD44, Dclk1, CXCR4, ESA, and Nestin-positive cells in the low-grade PanIN, high-grade PanIN, and PDAC (pancreatic ductal adenocarcinoma) tumors with fewer in normal ducts[9,12,13,51,52]. These studies clearly demonstrate that pancreatic CSCs correlate with the step-wise progression of pancreatic intraepithelial neoplasias (PanINs) (PanIN1-2-3) to PC (Figure 1). During this process of early tumorigenesis after Kras mutations, several of the transcription factors like Oct4 and Nanog gets overexpressed linearly with the PanIN progression to PDAC[53]. Oncogenic Kras mutations in the pancreas activate important signaling pathways such as sonic hedgehog, Wnt, PI3K/AKT, Notch and PTEN, Bmi1 that lead the transformation of the normal pancreas to the malignant PanINs and PDAC[54-59].

Researchers have observed aberrant expression of Hedgehog during the PC initiation followed by progression of the pancreatic precursor PanIN lesions to pancreatic adenocarcinoma[60]. This clearly underscores the importance of hedgehog signaling in a sequential development of PC. Recently, mounting evidence supports hedgehog signaling activation in pancreatic CSCs. Hedgehog pathway plays a significant role by regulating pluripotency maintaining factors like Oct4, Nanog, c-Myc, and Sox2 to the maintenance of stemness[61-66]. Apart from hedgehog, increasing evidence suggests that Notch signaling activation was associated with molecular characteristics of CSCs in PC cases[67,68]. This was shown by the studies that overexpression of Notch1 leads to increasing in the formation of pancreatospheres along with expression of the CD44 and EpCAM CSC surface markers. Other studies reported that expression of Oct4, Nanog, and PDX1 in Notch2 positive human pancreatic adenocarcinoma cells[69]. The Oct4, Nanog and PDX1 are also considered as markers of self-renewal of pancreatic CSCs. Also, the expression of ALDH1 was associated with poor overall survival durations in PDAC patients[70].

Newer studies illustrated involvement of PI3K/AKT signaling in pancreatic CSCs proliferation. In this direction, a recent study showed that CSCs like CD133 showed high levels of mTOR signaling in pancreatic adenocarcinoma. This underlines that the PI3K/AKT pathway plays a prominent role in pancreatic CSCs[71] consistent with significant inhibition of CD133 cells by the mTOR inhibitor rapamycin[71]. However, the functions of Wnt signaling in pancreatic CSCs are less and poorly understood. Lgr5 is the Wnt target gene that is being recently explored as pancreatic CSC. Like other important signaling pathways, the Wnt/β-catenin signaling pathway play a critical role in the pancreatic cancer development and progression.

ROLE OF PANCREATIC CSCS IN PREVENTION AND TREATMENT

Advances in the identification and characterization of pancreatic CSCs have created new opportunities for genetic targeting in treatment applications. Pancreatic CSCs are essential drivers for cancer progression and metastasis and are responsible for therapeutic resistance. Targetable cellular markers including CD24, CD44, CD133, ESA, ALDH1, c-Met, EPCAM, nestin, Lgr5 and DclK1 have been employed to characterize pancreatic CSCs[9-14,64]. Studies suggest that the use of the drugs that target PI3/AKT/mTOR, Hedgehog, c-Met and other developmental signaling pathways might deplete the populations of CSCs. Conceivably, multidrug combinations and multitargeting approaches will produce maximal anti-tumor efficacy by depleting resistant CSCs in PC[72]. So far, no clinical studies have been aimed at targeting pancreatic CSCs specifically in PC patients. The pancreatic cancer precursors, PanINs, progress slowly over many years to the development of invasive PC[3-5]. Hence, developing novel strategies to delay or inhibit progression of pancreatic cancer targeting CSCs are warranted. The K-rasG12D genetically engineered mouse (GEM) is an excellent model that shows the development of lesions closely resembling human PanIN's with progression to PDAC and it has been used successfully for chemoprevention studies[5,8,72-78]. We have shown that licofelone, a dual COX-5-LOX inhibitor, exhibits chemopreventive efficacy against pancreatic cancer in $p48^{Cre/+}$-LSL-$Kras^{G12D/+}$ mice in part by inhibiting CSCs[72]. We have also shown that metformin, an anti-diabetic drug significantly prevents progression of pancreatic cancer by targeting in part CSCs[8].

To date, there are no specific CSC inhibitors tested preclinically using GEMs or clinically in PC patients. Pharmacological or genetic inhibition of JNK leads to loss of stem cell properties in the pancreatic CSCs both *in vitro* and tumor. Furthermore, loss of Kras in kras mutant pancreatic CSCs led to the loss of stem cell characteristics by downregulation of the JNK pathway[79]. Pancreatic cancers contain 1%-3% of CD133 positive cancer cells, some of which show high expression of CXCR4, a pro-invasive marker[14]. The selective inhibition of CXCR4 signaling in $CXCR4^+$ CSC cells by AMD3100 blocks tumor tissue invasion[13,14], suggesting a potential role of CXCR4 in pancreatic tumor metastasis[14]. Accordingly, it remains

possible that there is more than one type of CSC sub-population in pancreatic cancer tissues, which would be consistent with the known heterogeneity of most-human tumors[14,24]. More preclinical animal and human clinical studies are warranted to evaluate the drugs for their specificity in targeting CSCs to inhibit the progression of PC. Combination of epigallocatechin-3 gallate (EGCG) and quercetin, and, Sulforaphane inhibited the self-renewal capacity of pancreatic CSCs *via* attenuation of the Hedgehog pathway[62-65]. The GANT-61 is a Gli transcription factor inhibitor that inhibits pancreatic CSC viability and induces apoptosis[61]. Together, blockade of hedgehog and mTOR signaling along with standard chemotherapy was found to eliminate pancreatic CSCs[80]. Another hedgehog antagonist Vismodegib (GDC-0449), inhibits pancreatic CSC characteristics *in vitro*[81]. Using GDC-0449, a human phase I clinical trial is ongoing[82], which preliminarily suggest that GDC-0449 has good safety profile and antitumor activity for some of the locally advanced or metastatic solid tumors. Pancreatic cancer progression was inhibited by sulforaphane, green tea catechins and quercetin by inducing let7a miRNA and inhibiting Kras and ALDH1 activity[82]. The 3-Bromopyruvate, a glycolysis inhibitor blocked CSC signaling in PC cell lines and the spheroids derived from patients[83]. Also, chloroquine (antimalarial agent) decreased CSCs *in vitro* and *in vivo* in combination with gemcitabine by inhibiting the hedgehog signaling[84].

An SRC inhibitor, dasatinib in combination with gemcitabine significantly reduced ALDH1 in MiaPaCa parental and gemcitabine resistant cells[85]. A drug under phase 1 trial, Minnelide efficiently decreased CD133 cells in the tumors[86]. Triptolide (plant derived Chinese medicine) is generally used for arthritis and cancer. In clinical trials it inhibited hypoxia-induced transcriptional signaling and EMT and CSC features in cell lines, decreased tumor growth *in-vivo*, and inhibited CSCs from patient tumors[87].

Vaccine or antibody approaches are recently explored for pancreatic cancer inhibition. In the xenograft models and *in-vitro* cultures, anti-CD44 monoclonal antibodies decreased growth, metastasis and CSCs including downregulating *CSC* genes *Sox-2*, *Nanog* and *Rex1*[88]. BMS-777067 (tyrosine kinase inhibitor) in combination with AZD8055 (mTOR inhibitor) successfully inhibited chemoresistant cancer cells and CSCs. However, BMS-777067 alone induces the polyploidy in the CSCs making them insensitive to the therapy[89]. Cabozantinib downregulated c-Met, SOX2 and CD133 in the drug resistant PC cells and CSC spheroids and induced apoptosis[90]. A kinase inhibitor XMD8-92 was shown to down-regulate Dclk1 and its downstream targets including KRAS, ZEB1, ZEB2, c-MYC, NOTCH1, OCT4, SOX2, SNAIL, SLUG, NANOG, KLF4, LIN28, VEGFR1, and VEGFR2 in the tumors of the xenografts[90,91].

IMPLICATIONS AND FUTURE DIRECTIONS

It is now well-established that pancreatic CSCs contribute to aggressive tumor phenotype resistant to radiation and chemotherapy[8,14]. The molecular and pathological characteristics of the pancreatic CSCs are yet to be fully elucidated. Knowledge gained from the GEM models, and, isolation and identification of specific cancer stem cell markers and their characterization in tumor tissues will provide deep insights that will be of value in designing effective strategies for the development of chemoprevention and chemotherapy drugs that reduce tumor aggressiveness by specifically targeting CSCs[8,14]. Although some pathways such as Notch and c-Met signaling are important for pancreatic CSC maintenance, other pathways like Wnt (Lgr5) and pathways related to Dclk1 that are required for pancreatic CSC activity must also be elucidated. Drugs targeting CSCs and their markers might modulate function of these CSCs[8,14]. The validity of this approach was suggested by the finding that metformin, an anti-diabetic drug, displays anti-tumor effects due to the partially targeted elimination of CSCs in pancreatic cancer[8,14]. Additional clinical and preclinical work is required to demonstrate conclusively the therapeutic benefit of metformin[8,14,88], and CSC-targeting drugs in general, for the management of particular cancers[8,14]. As such, CSCs are one of the best targets for cancer treatment. However, we need to improve our understanding of pancreatic CSCs and pancreatic cancer biology to develop optimal treatment (Chemoprevention and Chemotherapy) regimens. Effective treatment of pancreatic cancer could require the continued administration of conventional chemotherapeutic agents in combinations or along with agents that specifically deplete pancreatic CSCs. Pancreatic cancer could be effectively treated if the above conditions are met.

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