



Pancreatic neuroendocrine tumor cancer stem cells: potential novel therapeutic targets?

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Abstract: New therapeutic treatments are urgently needed for patients with pancreatic neuroendocrine tumors (PanNETs) that are insensitive or resistant to current therapeutic methods. The cancer stem cells (CSCs) in PanNETs may imply a promising and novel therapeutic approach to treat patients with advanced stage tumor and improve patient survival through targeting various molecular pathways. In this review, we define the process of identifying CSCs in PanNETs and address the potential therapeutic implications of targeting CSCs. The CSCs in PanNETs are marked by aldehyde dehydrogenases (ALDH) or CD90. We discuss the relevant molecular pathways in ALDH+ and CD90+ CSCs, including the Src, Notch, Hedgehog, Wnt/ β -catenin, mammalian target of rapamycin (mTOR), epidermal growth factor receptor (EGFR) and signal transducers and activators of transcription 3 (STAT3) signaling pathways. The function of Src signaling has been identified in a NET cell line, which suggests it could become a new therapeutic target in PanNETs. With the exception of the STAT3 signaling pathway, signaling pathways involved in the tumorigenicity of CSCs in many other cancers play a role in the pathophysiology of PanNETs. These molecular pathways may be potential targets for the treatment of PanNETs despite a lack of studies relating them to PanNET CSCs and more studies are needed to clarify the role of these signaling pathways in PanNETs. Additionally, targeting of the cellular surface markers CD47 and CD73 decreased the tumor growth of ALDH+ CSCs in PanNETs cell lines. In conclusion, the study of PanNET CSCs could aid in the development of novel therapeutic targets for PanNETs, and this review details the molecular pathways that might become new targets.

Keywords: Pancreatic neuroendocrine tumors (PanNETs); cancer stem cells (CSCs); molecular pathways; therapeutic targets

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Introduction

Pancreatic neuroendocrine tumors (PanNETs) are relatively rare, only accounting for 1–2% of all pancreatic neoplasms each year (1,2). The annual incidence per 1 million people is 1.8 in women and 2.6 in men (3). Nevertheless, the incidence of PanNETs has significantly increased over the past decades (1). Nonfunctional tumors, accounting for

85% of PanNETs (3), are usually diagnosed at late stages and have a significantly worse prognosis compared with functional PanNETs with evident hormonal syndrome (4). The increasing incidence of PanNETs and relatively poor prognosis of nonfunctional tumors emphasize the need for useful treatment methods for advanced tumors.

At present, surgery remains the first line of treatment.

The postoperative 5-year survival rate is 80% for patients with nonfunctional PanNETs (5). Due to distant metastasis or local extension of the tumor, surgery is often non-curative. In advanced cases, surgical extraction of PanNETs can only reduce symptoms related to tumor suppression and hormone production (6). For patients who are not candidates for surgery, systemic treatment plays an important role in controlling the disease (7), including targeted therapies, chemotherapy, somatostatin analogues and liver-directed therapies (8). The mammalian target of rapamycin (mTOR) inhibitor everolimus and the antiangiogenic agent sunitinib are new targeted agents for advanced, unresectable or metastatic PanNETs and both have demonstrated efficacy and safety in clinical studies (9,10). Nevertheless, primary and acquired resistance to these targeted therapies exists (11) and new anticancer strategies are urgently needed.

Cancer stem cells (CSCs) were first identified in a mouse tumor and later were found in solid tumors and leukemia (12-15). In 2011, CSCs were detected in gastrointestinal neuroendocrine tumors (16) and further confirmed to be present in PanNETs in 2016 (17). Properties of CSCs include self-renewal, dedifferentiation, tumorigenicity and inherent chemotherapy resistance (18,19), which may explain the drug resistance, metastasis and relapse risk of PanNETs. Recently, valid therapeutic strategies against CSCs have had confirmed efficacy against leukemia (20); thus, novel therapeutic strategies for targeting PanNETs CSCs might exist. The potential new therapies may improve drug sensitivity and inhibit invasion and metastasis of PanNETs. The purpose of the present review is to summarize current advances in the fields of PanNETs CSCs and their therapeutic implications.

Evidence for CSCs especially PanNET CSCs

CSCs were first confirmed in leukemia patients when a study showed that leukemic cells that were CD34+ and CD38- had the capacity to initiate human acute myeloid leukemia in mice (21). The first solid tumor identified with CSCs was breast cancer (22), and a number of CSC markers exist in solid tumors, including CD44, CD133, receptor tyrosine kinases (RTKs), aldehyde dehydrogenases (ALDH), epithelial cell adhesion molecule/epithelial specific antigen (EpCAM/ESA), and ATP-binding cassette subfamily G member 2 (ABCG2) (23-25). These markers aided in identifying the CSCs, but there were no unique markers for specific cancers.

For gastroenteropancreatic neuroendocrine tumors, stem cell markers CD133 (26), DCLK1 (27), HES77 (28) and CD24 (29) were identified, implying the existence of CSCs in PanNETs. In 2011, CSCs were identified in gastrointestinal neuroendocrine tumors (16). ALDH was a marker of CSCs, and the number of ALDH+ cells ranged from 0.2–5.9% in PanNETs specimens (16). The existence of CSCs in neuroendocrine tumor was validated by sphere formation assays *in vitro* and tumorigenicity assays *in vivo*. However, in that study, the ALDH+ cells could only be tested in human PanNET specimens but not in cell lines due to a lack of PanNET cell lines at that time. In 2016, one study (17) developed a PanNET cell line, APL1, which was capable of growing *in vitro* and *in vivo*. In the study, PanNET CSCs were identified in the APL1 cell line through increased cell-surface protein CD90 expression and ALDH1 activity, both of which were novel markers of highly tumorigenic CSCs in the PanNETs (17).

Potential signaling pathways related to PanNET CSCs

Research of CSCs in PanNETs is a relatively new area compared to the study of CSCs in leukemia (20), in which therapy against progenitor populations has been applied to clinical settings. The identification of PanNET CSCs occurred only recently (16,17,30) and the molecular pathways regulating PanNET CSCs are not fully elucidated. In 2011, activation of the Src signaling pathway was identified in NET ALDH+ cells. Furthermore, *in vivo* Src inhibition resulted in decreased NET tumor size, providing the first link between the molecular pathway and GE-NET CSCs (16).

In addition to being markers of PanNETs CSCs, ALDH (16,17,30) and CD90 (17) were also reported in CSCs of other cancers and have been linked to many signaling pathways. Activated Notch signaling is important in maintaining ALDH+ CSCs in ovarian cancer, colon cancer, lung adenocarcinoma, breast cancer and pancreatic cancer (31-36). The Hedgehog pathway plays a critical role in the self-renewal and tumorigenicity of ALDH+ CSCs (37-41). In ALDH+ CSCs, inhibition of Wnt/ β -catenin signaling often leads to a reduction of CSCs in colorectal cancer, breast cancer, prostate cancer and liver cancer (42-45). Other pathways are also reported in ALDH+ CSCs, including mTOR signaling (46,47), epidermal growth factor receptor (EGFR) signaling (48,49) and STAT signaling (50-53). At the same time, CD90+ CSCs are also

associated with Notch signaling, the downregulation of which inhibited the proliferation of hepatocellular carcinoma (54,55).

Although important role of Notch signaling, Hedgehog signaling, Wnt/ β -catenin signaling, mTOR signaling, EGFR signaling and STAT3 signaling have been reported in ALDH+ CSCs, the role of these pathways is unclear for ALDH+ CSCs of PanNETs. Thus, we will discuss these mentioned molecular pathways and their potential relationship to PanNET CSCs.

Src pathway

Structurally, Src belongs to a family of nonreceptor tyrosine kinase proteins that is composed of c-Src, Yes, Fyn, Lyn, Lck, Hck, Fgr, Blk and Yrk (56). The structure of the c-Src protein includes seven regions: an SH4 domain, a unique domain, an SH3 domain, an SH2-SH3 linker, an SH2 domain, an SH1 (catalytic) domain, and a Cterminal negative regulatory region. Once activated, Src participates in the regulation of normal and oncogenic processes. It functions during tumor progression, with effects on apoptosis, cell adhesion, cell growth, cell migration and invasion (57).

Inhibition of Src along with STAT3 and FAK decreases tumorigenicity in breast cancer, supporting their function as inhibitors of CSCs (58). The Src/FAK/Snail axis also plays an important role in the epithelial-mesenchymal transition of hepatocellular carcinoma (59).

In PanNETs, Src kinase mediates the EGFR-transactivation induced by various gastrointestinal hormones/neurotransmitters, which indicates that Src plays a part in PNET cells growth (60). Src activity is also elevated in human PNET (61) and has a link to the mTOR pathway (62). Notably, Src is upregulated in ALDH+ cancer cells, and the Src inhibitor PP2 can decrease the development of ALDH+ cancer cells in NET (16). It is likely that the Src signaling pathway plays a role in PNET CSCs, and more study are needed to further explore this possibility.

Notch signaling pathway

The Notch pathway is essential in embryonic pancreatic development. Notch signaling is composed of four receptors (NOTCH 1-4) and five ligands (Delta-like-1, 3, and 4 and Jagged-1 and 2) (63). Notch1 is expressed in the endodermal epithelium at early embryonic stages, and Notch2 is

restricted to embryonic ducts, which might be the source of stem cells in a mouse model (64). Mice deficient for delta-like gene 1 (Dll1) showed accelerated differentiation of pancreatic endocrine cells and impaired normal pancreatic proliferation (65). In human beings, Notch signaling has been demonstrated to regulate the differentiation of stem and progenitor cells in the development of pancreas (66,67).

The role of Notch signaling in CSC is uncertain, partially because activated Notch signaling has been identified as both a tumor promoter and suppressor in different tissues (68). Activation of the Notch pathway is necessary to maintain the stemness of ACTH+ CSCs in ovarian cancer, colon cancer, lung adenocarcinoma, breast cancer and pancreatic cancer (31-36). The Notch pathway inhibitor can reduce the proliferation of breast CSCs (69) and tumor recurrence in colorectal cancer patients (34). Additionally, inhibition of the Notch/CDK2/CCNE pathway is necessary for ALDH to maintain the stemness of lung adenoma stem cells (70). At the same time, Notch signaling plays a role in regulating intestinal crypt fate (71). γ -secretase inhibitors blocking Notch signaling induce complete conversion of proliferative crypt cells into differentiated goblet cells. In intestinal adenomas with the mutational loss of Apc, the Notch and Wnt signaling pathways are essential to maintain the undifferentiated CSC states. Furthermore, inactivation of Notch1 in adult mice induces the skin tumor formation since Notch functions as a tumor suppressor (72).

In gastroenteropancreatic neuroendocrine neoplasm, Notch signaling might play the role of tumor suppressor. Notch1 inactivation leads to larger islet cell mass in mouse pancreatic endocrine tumors (73). The overexpression of activated Notch1 in carcinoid cells decreases neuroendocrine differentiation reflected by decreased expression of synaptophysin and chromogranin A, and inhibits BON cell growth (74). Furthermore, Notch1 expression is lacking in all malignant insulinomas (75) and metastasis specimens. The Notch signaling pathway could function as a tumor promoter in some other neuroendocrine tumors. miR-375 promotes neuroendocrine differentiation and inhibits aggressive cancer cell behavior by the inhibition of Notch signaling pathway in Merkel cell carcinoma (76). In lung cancer, Notch1 signaling activation contributes to not only the growth promotion of NSCLC (77) but also to the inhibition of SCLC (78).

The expression of Notch signaling pathway component is reflected in 34% of human PNETs (79), and 43.7% of patients with well-differentiated PanNETs demonstrated

positive Notch1 expression (75). The dual role of Notch signaling requires more studies to determine its function in PanNETs. In addition, the identification of CSCs in PNETs (17) provides a good platform to further study the relationship between Notch signaling and CSC and to identify the function of Notch signaling activation.

Hedgehog signaling pathway

The Hedgehog signaling pathway is composed of Hedgehog ligands (including SHh, DHh and IHh in mammals), the Patched receptor, Smo, and the Gli transcription factors. Binding of one of the three Hh ligands to the transmembrane receptor Patched initiates the activation of the Hedgehog signaling pathway. Smo, a 7-pass transmembrane-spanning protein, is activated by binding of Hh ligand to Ptc, which modulates the expression of the three Gli transcription factors. There are three Gli proteins in vertebrates. Gli1 acts as a transcriptional activator, Gli3 functions as a repressor, and Gli2 can be either a strong activator or suppressor of gene expression (80).

During embryonic development, Hedgehog signaling controls tissue polarity and stem cell maintenance. The role of Hedgehog signaling in regulating CSCs has been established in many human tumors including leukemia (81), pancreatic cancer (82), breast cancer (83) and multiple myeloma (84). Loss of Smo causes depletion of CSCs in chronic myelogenous leukemia, and activation of Hedgehog signaling in transgenic mice accelerates the CSC growth (81). Moreover, the SHh inhibitor vismodegib induced apoptosis and inhibited cell viability in pancreatic CSCs (82).

Hedgehog signaling also plays an important role in gastroenteropancreatic neuroendocrine tumors. Blockade of the Hedgehog pathway downregulates the Gli1, Ptch1, Snail and hASH1, and upregulates E-cadherin at the mRNA levels, in gastrointestinal neuroendocrine carcinomas (85). In neuroendocrine tumors of the ileum, Snail Hedgehog is found in 22 out of 37 (59%) of NET samples (86). PanNETs may occur sporadically or develop in association with inherited tumor syndromes, particularly multiple endocrine neoplasia type 1 (MEN-1). In MEN-1 tumors of mice, Hedgehog signaling has high expression (87). In sporadic PanNETs, positive PTCH1 staining is confirmed in 85% of sporadic PanNETs, with no significant difference from MEN-1 patients (88). Furthermore, pharmacologic inhibition of Hedgehog pathway largely reduces proliferation of insulinoma cells (87). The function of the

Hedgehog pathway in PanNETs provides a basis for further studying the role of the Hedgehog pathway in CSCs, which might open an effective therapeutic strategy for PanNETs by altering tumor cell nature.

Wnt/ β -catenin signaling pathway

The Wnt/ β -catenin signaling pathways have crucial roles in the regulation of diverse processes, including cell growth, differentiation, survival, migration and polarity (89). The Wnt signaling inactive state leads to phosphorylation of β -catenin by the destruction complex, which contains the scaffold protein Axin, APC and the kinases GSK3 β and casein kinase (CK1 α). Activation of Wnt signaling results in inhibition of GSK3 β activity and β -catenin releases from the CK1-GSK3 β -Axin-APC- β -catenin complex for stabilization. The accumulation of β -catenin in the cytoplasm results in its nuclear translocation. β -catenin forms an active complex with T-cell factor/lymphoid enhancer factor (TCF/LEF) family transcriptional factors and with legless family docking proteins (BCL9 and BCL9L) (90,91). The active complex is the effector to activate the transcription of several target genes and leads to alteration of multiple cellular processes (92).

Activation of the Wnt/ β -catenin signaling pathways plays a vital role in the function of CSCs (93). Due to activation of Wnt/ β -catenin signaling, LGR5-expressing breast cancers exhibit CSC-like properties, including the formation of self-renewing spheres and high tumorigenicity (94). In colorectal cancer, the expression of the CSC marker, CD44v6, is promoted by Wnt/ β -catenin signaling and results in increased metastatic capacity (95). Wnt/ β -catenin signaling is activated by *H. pylori* in a CgA-dependent manner and can promote stem-like properties of human gastric cancer cells (96).

The role of Wnt/ β -catenin signaling pathway in PanNETs CSC has not been settled, but the expression of Wnt/ β -catenin signaling pathway is confirmed in the PanNETs. PanNETs in patients with familial adenomatous polyposis (FAP) have abnormal nuclear β -catenin accumulation (97). In a PanNET transgenic mouse model, the activation of Wnt signaling is achieved through downregulation of the Wnt signaling inhibitor Dickkopf-1 (DKK1) and thus increases tumor angiogenesis (98). The Wnt/ β -catenin signaling pathway is characterized by accumulation of β -catenin in nuclei, where it regulates gene expression. The rate of detected nuclear or cytoplasmic β -catenin in neuroendocrine tumors is not high [about

15–29.7% (97,99)], but membranous β -catenin expression is strong in 55% of PanNETs. In summary, Wnt/ β -catenin signaling is able to drive tumor development in PanNETs, but more studies are required to explore its influence on PanNETs CSCs.

Other relative pathways

mTOR is a serine threonine kinase located downstream of the PI3K/AKT signaling pathway (100), and PI3K/AKT/mTOR signaling has been shown to be frequently hyperactivated in the majority of cancers, including PanNETs (101). In colorectal cancer, the capacity for sphere formation as well as ALDH activity is largely decreased by mTOR inhibitors (47). Combined inhibition of the mTOR and Hh pathways results in decreased proliferation of ALDH+ cells in biliary tract cancer (102). Furthermore, mTOR and AKT are activated in ALDH+ stem cells of midgut carcinoid cell lines in spite of low expression (16). Although the relationship between mTOR signaling and PanNETs CSC is unclear, it is worthwhile to explore the effect of mTOR inhibitors on PanNETs CSCs. The potential mechanism of PI3K/AKT/mTOR signaling related to CSCs might explain the phenomena that some PanNETs are insensitive or resistant to mTOR inhibitor.

EGFR signaling pathways may also be potential targets for treatment of PanNETs CSCs. Inhibition of EGFR as well as heat shock protein 27 suppresses the vasculogenic mimicry activity in ALDH+ cells and decreases the formation of vessel-like structures (103). EGFR inhibition abrogates the age-related proliferation of ALDH1+ colon cancer stem-like cells. The expression of EGFR is immunohistochemically detected in 49% (104) to 50% (105) of patients with PanNETs and it is significantly higher in poorly differentiated endocrine carcinomas (105). Both EGFR and COX-2 are detected in the human pancreatic carcinoid cell line BON, and combined treatment with the COX-2 inhibitor celecoxib and EGFR antagonist AG1478 greatly induced cell apoptosis, which was more useful than separate monotherapy. EGFR signaling may present additional chemotherapeutic targets in PanNETs and its role in PanNETs CSCs needs further research.

Signal transducers and activators of transcription 3 (STAT3) is a cytoplasmic transcription factor that regulates gene expression by conveying signals from the cell membrane to the nucleus. The STAT3 signaling pathway is involved not only in embryonic stem cell differentiation (106) but also the proliferation and survival

of CSCs (107,108). The STAT3 pathway is associated with maintenance of ALDH1A3+ CSC tumorigenicity in non-small cell lung cancer (50), and STAT3 inhibitors reduce the ALDH(+) subpopulations of breast cancer cells (52). ALDH+/CD133+ stem cell-like colon cancer cells greatly decrease after FLLL32 inhibition of the expression of the STAT3 pathway (53). Currently, there are no studies directly relating the STAT3 pathway and PanNETs or PanNET CSCs. Considering the important role of STAT3 pathway in the ALDH(+) CSCs, it might be important to explore the relationship between the STAT3 pathway and PanNETs.

Potential therapies targeting CSCs in PanNETs

PanNETs are tumors with great heterogeneity and not all patients are compatible with the existing therapies; thus, it is necessary to find new therapeutic targets. CSCs give much hope for future therapies and have been identified in PanNETs though there are limited studies to support potentially therapeutic molecular targets. Many conventional chemotherapeutic agents kill both cancerous and normal cells because of their nonspecific distribution and they are not effective in eliminating CSCs, thus recurrence and metastasis are common after treatment (109). Emerging evidence suggests that CSCs are more resistant to cancer therapy than normal cancer cells. Thus, the elimination of CSCs is very important in curing malignant diseases (110,111).

In PanNETs, some novel therapeutic methods are believed to kill CSCs through cellular surface marker targets, but they are still under experimental evaluation. Additionally, one oncogenic signaling target has also been discussed in gastrointestinal neuroendocrine tumors and has a great possibility of becoming a potential molecular target. Thus, both the cellular surface markers and the oncogenic signaling target are summarized below.

Targeting cellular surface markers

Antibodies, which bind specific antigens, are often used for fighting against tumor surface markers to enhance the specificity of therapeutic strategies. Monoclonal antibodies have shown efficacy against CSC surface markers in human cancer xenograft mice (112). The effect of anti-CD47 monoclonal antibodies and CD73 inhibitors has been shown in PanNETs through not only PanNETs cell lines but also in xenograft mouse models (17,30).

CD47 is a widely expressed cell surface molecule in all human solid tumor cells and binds signal regulatory protein alpha (SIRP α) on phagocytic cells. The CD47-SIRP α interaction then initiates signal transduction resulting in inhibition of phagocytosis and functions as a “don’t eat me” signal (113). Thus, CD47 expression is needed to suppress tumor cell phagocytosis and elimination, and anti-CD47 antibodies inhibit tumor growth in mouse models (114). In PanNETs, high expression of CD47 is observed in the CD90^{high} cells (similar to CSCs) and is related to decreased survival of PanNET cells. *In vitro*, anti-CD47 monoclonal antibody treatment inhibits tumor growth, prevents metastasis to liver and prolongs mouse survival compared with a control group. Furthermore, the anti-tumor activity of anti-CD47 therapy is increased when combined with anti-EGFR monoclonal antibodies (17). CD47 therapy might become a valid method to treat PanNETs but preclinical studies relating CD47 with PanNETs are rare. Therefore, more attention should be paid to research of the function of CD47 in PanNETs.

As a cell surface glycoprotein regulating cellular external and internal environments (115), extracellular-5'-nucleotidase (CD73) also participates in the development of PanNET CSCs. In both human PanNET cell lines QGP1 and MIN6, CD73 is expressed in the ALDH+ cells, which are CSCs. When the CD73 inhibitor APCP is used in QGP1 cell lines, the CSC properties of ALDH+ cells are inhibited (sphere-forming and scar migration are decreased). At the same time, tumor growth is significantly decreased in murine xenograft models treated with APCP compared with control group (30). Actually, broad distribution of CD73 is seen in normal tissues, and CD73 is often upregulated in some solid tumor tissues including breast cancer and colon cancer (116,117). High expression of CD73 has been associated with poor prognosis (117), and CD73 antibody can increase anti-tumor immunoreaction and decrease tumor metastasis of breast cancer (118). Thus, the further study of the role of CD73 signaling in the PanNETs is promising.

Targeting crucial signaling pathways

The Src family kinase inhibitor PP2 targets ALDH+ cells gastrointestinal NET, and ALDH+ cells shows a significant reduction in cell number after 72-hour treatment with PP2. Furthermore, siSrc-DOPC treatment decreases the CSCs and reduces NET tumor size. Src inhibitors treat some other tumors in preclinical models of cancer, and some of

them have entered clinical trials (119). Dasatinib has been licensed for the front-line treatment in chronic myeloid leukemia (120). Despite the lack of clinical trials of Src inhibitors in the PanNETs and limited studies reporting the link between Src and PanNET CSCs, future studies should be aimed at filling this gap.

Conclusions

In the past few years, significant advances have been made in the field of PanNETs CSCs. PanNETs are certain to contain tumor-initiating cell populations that are ALDH+ or CD90+. The molecular pathways altered in ALDH+ or CD90+ CSCs mainly include Src, Notch, Hh and Wnt/ β -catenin. The Src signaling pathway is reported to be related to carcinoid tumor CSCs, and it may apply to PanNETs CSCs. The Notch, Hh and Wnt/ β -catenin signaling pathways are largely shown to participate in the activity of PanNETs and further study is required to clarify the relationship between the pathways and PanNET CSCs. Other signaling pathways, such as mTOR, EGFR and STATs, also participate in the regulation of ALDH+ or CD90+ CSCs and require further study to clarify their roles in PanNET CSCs. Targeting of the cellular surface markers CD47 and CD73 or of crucial signaling pathways to inhibit CSCs might become a novel potential therapeutic treatment for PanNETs. More studies are needed to clarify the molecular pathways related to PanNET CSCs in the hope that novel approaches to treating PanNETs will be found and will ultimately improve the survival of PanNET patients.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2016.12.07>). The authors have no conflicts of interest to declare.

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