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Targeting Cancer Stem Cells for Chemoprevention of Pancreatic Cancer

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Abstract

Pancreatic ductal adenocarcinoma is one of the deadliest cancers worldwide and the fourth leading cause of cancer-related deaths in United States. Regardless of the advances in molecular pathogenesis and consequential efforts to suppress the disease, this cancer remains a major health problem in United States. By 2030, the projection is that pancreatic cancer will be climb up to be the second leading cause of cancer-related deaths in the United States. Pancreatic cancer is a rapidly invasive and highly metastatic cancer, and does not respond to standard therapies. Emerging evidence supports that the presence of a unique population of cells called cancer stem cells (CSCs) as potential cancer inducing cells and efforts are underway to develop therapeutic strategies targeting these cells. CSCs are rare quiescent cells, and with the capacity to self-renew through asymmetric/symmetric cell division, as well as differentiate into various lineages of cells in the cancer. Studies have been shown that CSCs are highly resistant to standard therapy and also responsible for drug resistance, cancer recurrence and metastasis. To overcome this problem, we need novel preventive agents that target these CSCs. Natural compounds or phytochemicals have ability to target these CSCs and their signaling pathways. Therefore, in the present review article, we summarize our current understanding of pancreatic CSCs and their signaling pathways, and the phytochemicals that target these cells including curcumin, resveratrol, tea polyphenol EGCG (epigallocatechin-3-gallate), crocetinic acid, sulforaphane, genistein, indole-3-carbinol, vitamin E δ-tocotrienol, Plumbagin, quercetin, triptolide, Licofelene and Quinomycin. These natural compounds or phytochemicals, which inhibit cancer stem cells may prove to be promising agents for the prevention and treatment of pancreatic cancers.

Keywords

Cancer stem cells; signaling; DCLK1; natural compounds

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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INTRODUCTION

Pancreatic ductal adenocarcinoma continues to one of the deadliest cancers in the world. It is the fourth leading cause of cancer-related deaths in United States with the highest mortality rate among all cancers. With 5-year survival rate is <6%. The American Cancer Society has estimated that 43,090 Americans (22,300 men and 20,790 women) would die of pancreatic cancer in 2017 and 53,670 new cases for 2017 (27, 970 men and 25,700 women)[1]. In both men and woman, lifetime risk for developing pancreatic cancer is about 1 in 65 (1.5%). By 2030, it is predicted that pancreatic cancer will be the second leading cause of cancer-related deaths in United States [2]. Regardless of advances in molecular pathogenesis, pancreatic cancer has major unsolved health problem in the United States because of its drug resistance and susceptibility to metastasis [3, 4]. Moreover, delineation of several germline or acquired genetic mutations and the most common being K-Ras (90%), CDK2NA (90%), TP53 (75%–90%), SMAD4/DPC4 (50%), along with genomic and epigenetic alterations, also played an important role in poor prognosis of this disease. These mutations can direct us to focus on the precision medicine. In addition, tumor microenvironment, the chemo-resistant cancer stem cells, and the desmoplastic stroma have been the target for recent promising clinical investigations [5]. Previously, Gemcitabine was the treatment option for metastatic pancreatic cancer. Currently, two combination regimens for metastatic disease have been used for gold standard: 5-fluorouracil (5-FU)/leucovorin with irinotecan and oxaliplatin (FOLFIRINOX)[6, 7] and nabpaclitaxel with gemcitabine [8]. With these approaches, response rates range between 23% and 31%, progression-free survival rates are 5.5–6.6 months, and overall survival is between 8.5 and 11 months [8]. At this time, FOLFIRINOX and gemcitabine/nab-paclitaxel is being used in studies for metastatic disease, in both adjuvant and neoadjuvant setting, and also for the treatment of locally advanced but inoperable pancreatic cancers.

However, the response rate to current chemotherapy is below 31% [8]. The extent of this problem mandates the need for novel preventive/therapeutic agents. Studies have suggested that CSCs may significantly influence drug resistance as well as metastasis [9]. The purpose of this review is to summarize our current understanding of cancer stem cells, highlighting recent advances and analyzing the preventing/therapeutic potential of targeting pancreatic cancer.

PANCREATIC CANCER STEM CELLS

Emerging evidence suggests that CSCs characterize a subset of cancer cells with distinct stemness features that permit them to drive tumorigenesis and metastasis [10, 11]. Moreover, studies have proven that CSCs have resistant to the current chemotherapy and radiation, which renders them a primary source for tumor recurrences after or even during treatment. Furthermore, primary tumors containing more number of CSC stem cell signature resulted in poor patient outcomes and higher rates of metastases [9].

Several proteins have developed as potential markers for the identification of pancreatic cancer CSCs (Fig. 1). One subpopulation of cells, marked by CD44+CD24+ESA+ (epithelial specific antigen) and represents between 0.2–0.8% of pancreatic cancer cells has

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a 100-fold increased tumorigenic potential compared with the rest of the cancer cells [12]. Also, CD133+[13, 14], c-MET+/CD44+ [15], increased 26S proteasome activity [16] and ALDH1 [17] have been reported to encode potential pancreatic CSC markers. Furthermore, Ischenko *et al.* demonstrated that a population of cells with surface markers expression of EPCAM+ CD24+CD44+CD133-Sca-bears CSC properties and metastatic potential [18]. Moreover, we have identified the expression of Doublecortin calmodulin-like kinase 1 (DCLK1) protein in a small proportion of cells in pancreatic cancer [19]. In addition, DCLK1 is found to be marked with a distinct subpopulation of cells in pre-invasive pancreatic cancer with characteristics of stem cells [20]. Furthermore, recent studies have also demonstrated that DCLK1+ cells initiate K-Ras mutant pancreatic tumors in the circumstance of pancreatitis and K-Ras and have shown that DCLK1 are candidates for the origin of pancreatic cancer [21–23].

CANCER STEM CELL SIGNALING PATHWAYS AND CHEMOPREVENTION

Multiple pathways have been identified to differentially activate in stem-like cells (Fig. 2). In this manuscript, we have focused on the key pathways and targeting them for prevention.

WNT SIGNALING

Aberrant Wnt/β-catenin signaling is one of the concerns in several cancers including pancreatic cancers [24, 25]. Around 65% of pancreatic adenocarcinomas shown to have active Wnt/β-catenin, but β-catenin gene mutations are also seen independently in most of the tumors [25]. Wnt/β-catenin signaling is mainly responsible for developmental process that regulates cell proliferation, differentiation, migration, polarity and asymmetric cell division [26]. β-catenin is an intracellular protein that is localized in cell membrane, cytoplasm and nucleus, an important molecule in this pathway. Wnt ligand binds to its receptors inhibits phosphorylation of β-catenin in the N-terminal region and prevent the protein from degradation which leads to accumulation of the protein in the cytoplasm, and subsequent translocation to the nucleus. Once β-catenin gets localized to the nucleus, it binds to target gene promoters interacting with T-cell factor/lymphoid enhancer factor (TCF/LEF) family members of transcription factors and induces their expression [27].

In pancreatic cancers, more than 65% of the tumors exhibit an increase in total β-catenin, which are enhanced membranous, cytoplasmic, and nuclear localization of which two have showed CTNNB1 mutation [25]. In addition, gene array analysis demonstrated that canonical arm of the Wnt pathway upregulated in pancreatic cancers [28]. Targeting the Wnt/β-catenin signaling pathway have shown to enhance the sensitivity of chemotherapeutic agents in pancreatic cancer> However, to completely understand the mechanism of action one would have to look at the various pathways affected by Wnt/β-catenin signaling including angiogenesis, cell cycle regulation, apoptosis and maintaining of highly resistant CSCs [29].

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HEDGEHOG SIGNALING

Abnormal hedgehog signaling has been shown in many types of human cancers including pancreatic cancers. Three different types of hedgehog genes reported so far are desert hedgehog (DHH), Indian hedgehog (IHH) and sonic hedgehog (SHH). These genes function as ligands for the 12-pass transmembrane receptor, patched (PTCH1) [30]. Hedgehog signaling plays a dual role, it can act as mitogen or can promote differentiation. Increased hedgehog signaling has been shown to alter the behavior of the tumor microenvironment and stroma in pancreatic carcinogenesis. Therefore, hedgehog signaling pathway can be an important target to treat pancreatic cancer [31]. Once hedgehog ligands bind its receptor PTCH1, it results in the internalization and degradation and release of Smoothened (SMO), a G-protein coupled receptor (GPCR) and subsequent dissociation of the suppressor of fused (SUFU)-GLI complex. GLI1 and GLI2 transcription factors translocate to the nucleus and induce the transcription of target genes. GLI3, however, acts as repressor in a normal situation but is degraded during the transcription function[32]. Furthermore, recently it has been shown that mutant K-Ras are involved in the development of pancreatic intraepithelial neoplasia and also in the maintenance and progression of pancreatic cancer in mouse models. Deletion of a single allele of GLI1 resulted in characteristic inflammatory response and improper remodeling of stroma associated with pancreatic cancer in this mouse model. Studies have shown that loss of Gli1 has been identified in cytokines IL6, IL8, monocyte chemoattractant protein-1 (MCP1), and macrophage colony-stimulating factor MCSF which are Gli1 target genes. These studies have also shown that canonical hedgehog signaling are essential for pancreatic recovery. Thus, both GLI1 and hedgehog signaling are critical for regulation of the pancreatic microenvironment [33]. Hedgehog signaling also plays a role in regulation of cellular proliferation, stemness, cell fate determination, and cellular survival [34]. Its downstream target Smo and GLI transcription factors are involved in noncanonical activation of hedgehog signaling [35]. In noncanonical activation the GLI proteins can dodge the inhibition of Smo result in lesser efficacy and also leads to resistance of Smo inhibitors. The family of transcription factors GLI genes transcriptionally regulate downstream targets in hedgehog-dependent survival. Gli1 as a transcriptional target of GLI2, is a primary activator of hedgehog signaling pathway and this may be involved in amplification of hedgehog-induced target gene expression [36]. GLI1 and GLI2 increase transcription of overlapping and distinct sets of target genes [36, 37]. GANT61 is a small molecule inhibitors GLI1-mediated transcription, was identified by cell-based screening. It blocks GLI function in the nucleus, thereby reducing the GLI1- and GLI2-mediated transcription, and inhibits GLI1-DNA binding[38, 39].

Cyclopamine, a natural compound found in the plant *Veratrum californicum*, commonly called the corn lily which was the first phytochemical identified to inhibit the hedgehog pathway [40]. Cyclopamine inhibits the activation of Smo, which is the target of the sonic hedgehog[40]. In addition, treatment with cyclopamine significantly reduced GLI1 expression in pancreatic cancer cells [41]. Furthermore, Cyclopamine effectively targets pancreatic CSCs[42]. In addition, studies have demonstrated that pancreatic CSCs are effectively eliminated by hedgehog/GLI inhibitor GANT61 in combination with mTOR inhibition [43]. In pancreatic cancer, CSCs have elevated expression of Sonic hedgehog

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protein [12], which are believed to be mediators of pancreatic tumor invasion and metastasis [13]. Cyclopamine and gemcitabine combination therapy resulted in inhibition of metastatic spread and reduced primary tumor burden in pancreatic orthotopic xenografts [44]. Moreover, curcumin, an active ingredient of the spice turmeric has been shown to inhibit Sonic hedgehog-GLI1 signaling pathway by downregulating Sonic hedgehog protein and its downstream targets GLI1 and Ptch1 [45]. Furthermore, curcumin, can reverse the epithelial-mesenchymal transition in pancreatic cancer by suppressing the Hedgehog signaling pathway [46]. In addition, curcumin treatment reduces hypoxia-induced pancreatic cancer metastasis, thereby inhibiting the hedgehog signaling pathway [47]. Studies have shown that resveratrol can also reduce proliferation and induce apoptosis through the inhibition of GLI1 and Ptch1 [48, 49]. Sulforaphane also inhibits self-renewal of pancreatic CSCs by suppressing the Sonic hedgehog-GLI pathway [50]. Similarly, the combination of (−)-epigallocatechin-3-gallate and Quercetin can synergistically inhibit the self-renewal capacity of CSCs through reduction of TCF/LEF and GLI activities. Together, these studies suggest that targeting CSCs and sonic hedgehog pathway may improve the outcomes of patients with pancreatic cancer [51]. Recent studies demonstrated that Crocetinic acid isolated from saffron inhibits hedgehog signaling to inhibit pancreatic cancer stem cells [52]. These studies suggest that plant polyphenols or natural compounds target CSCs self-renewal properties can highlight a potential for cancer prevention.

NOTCH SIGNALING

Notch signaling pathway plays an important role in the differentiation and maintenance of stem cells [53]. It has shown that aberrant activation of Notch signaling is linked to the development of many cancers including pancreatic cancers [54]. There are four transmembrane notch receptors (notch 1–4) which upon binding with its ligands (JAG1, JAG2, delta-like 1–4) undergo cleavage, releasing notch intracellular domain that further translocates to nucleus and interacts with its target genes, including Hes-1 and Hey1 [55], cyclin D1[56], $p21^{CIP1}$[57], NF-κB[58] and c-myc[59]. γ-secretase is a multiprotein intramembrane-cleaving proteases which has four components presenilin, nicastrin, Pen2, and Aph1 and they are all thought to be essential for activity [60]. Presenelin is responsible for the catalytic activity and nicastrin plays critical role in substrate recognition.

Curcumin has been shown to inhibit Notch signaling pathway in several cancers [61–65]. Similarly, resveratrol a compound found in grapes, berries and peanuts has been shown to exhibit anti-cancer properties by affecting the Notch pathway [66]. In addition, genistein has been shown to inhibit cells growth and induce apoptosis in pancreatic cancer cells by down-regulating Notch-1 [67]. By inhibiting Notch and CXCR4 activities, genistein has been shown to reduce the number of pancreatic CSCs [68]. Furthermore, sulforaphane from broccoli gained attentions of researchers for developing a combination therapy for targeting pancreatic cancer stem cells. a combination treatment of Sulforaphane and gemcitabine inhibits ALDH1 activity because of suppression of Notch-1 and c-Rel expression in pan-creatic cancer [69]. Recent studies have also demon-strated that the Quinoxaline antibiotic Quinomycin A inhibits pancreatic CSCs by inhibiting Notch signaling pathway [70].

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HIPPO SIGNALING

The Hippo signaling pathway is essential to maintain tissue homeostasis, organ size, and tumorigenesis. There are two sets of core kinases Mst1/2 and Lats1/2, whose functions are controlled through Sav and Mob. When Hippo signaling is active, Yes associated protein 1 (YAP1) phosphorylate or TAZ transcriptional coactivators by Lats1/2which leads to cytoplasmic sequestration and degradation. On the other hand, inactivation of Hippo signaling can facilitate unphosphorylated YAP/TAZ to enter into the nucleus and thereby one of the four TEAD family members activates transcription. Verteporfin, is a porphyrin molecule which blocks YAP1-TEAD complex formation by binding to YAP1 and result in conformational change of the complex [71]. Dysregulation of the pathway is implicated in many types of cancers. YAP1/TAZ and TEAD are upregulated in a several human tumors and the mechanisms involved through gene amplification and silencing of upstream components of hippo pathway. TAZ is a transducer of the Hippo pathway which has shown to induce epithelial-mesenchymal transition and thereby promote progression and development of pancreatic cancer [72]. It is reported that both YAP1 and TAZ can control the direct activation of JAK-STAT3 signaling pathway, thereby initiating pancreatic cancer in mouse models [73]. YAP has also shown as a critical oncogenic K-Ras effector and a promising therapeutic target for pancreatic cancer [74]. Recent study demonstrated that 14-3-3σ can interact with YAP1, thereby inducing gemcitabine resistance along with promoting ribonucleotide reductase expression [75]. Furthermore, YAP overexpression promotes the epithelial-mesenchymal transition and chemo-resistance in pancreatic cancer cells [76]. Therefore, Hippo signaling protein YAP/TAZ is important target to develop a novel compounds for prevention and treatment of pancreatic cancer.

OTHER STEM CELL RELATED SIGNALING PATHWAYS

JAK-STAT PATHWAY

The Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathway are involved in various cytokines and growth factors signaling pathways and affects various cellular functions, including cell proliferation, angiogenesis, metastasis, and immune response. JAK-STAT pathways are known to be upregulated in various cancers, including pancreatic cancer [77–79] constitutively activate STAT3 expression, have shown in human pancreatic cancer specimens but the activation is relatively low in normal pancreatic tissues [80]. Recent study demonstrated that gemcitabine treatment enhances the CD24+ and CD133+ cells ratio and also expression of stemness-associated genes Bmi1, Nanog, and Sox2, suggesting that gemcitabine promotes pancreatic cancer stemness by activating Nox/ROS/NF-κB/STAT3 signaling cascade [81]. Therefore, simultaneous targeting of Notch and JAK2/STAT3 signaling pathways may be better than either one alone [82]. In addition, combination of Notch inhibitor GSI IX and JAK2/STAT3 inhibitor AG-490 have shown to be potential as a therapeutic modality for pancreatic cancer [82]. Indole-3-carbinol (I3C) and genistein combination treatment significantly inhibits constitutive activated STAT3 expression in pancreatic cancer cells [80]. Curcumin downregulate the expression of survivin/BIRC5 gene and inhibits constitutive STAT3 phosphorylation in human pancreatic

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cancer cell lines [83]. Similarly, resveratrol inhibits STAT3 phosphorylation in pancreatic cancer cells *in vitro* [84].

PI3K/Akt/mTOR SIGNALING

PI3K/Akt and mTOR signaling pathways are important for many physiological and pathological conditions, such as cell proliferation, angiogenesis, metabolism, differentiation and survival[85]. Most importantly, this pathway acts as a master regulator of cancer. During tumorigenesis, it plays a major role in growth, proliferation, motility, survival and angiogenesis [86, 87]. A recent study demonstrated that the combined inhibition of PI3K/Akt/mTOR and Shh pathways resulted in reduced human pancreatic cancer stem cell characteristics and tumor growth [88]. Shin-Kang et al have looked at the effects of the Vitamin E δ-tocotrienol in pancreatic cancer cells. They observed that Vitamin E δ-tocotrienol inhibits the activation of Akt, ERK/MAP kinase and also its downstream mediator RSK (ribosomal protein S6 kinase) [89]. γ-tocotrienol showed to suppressed the activation of AKT resulted in downregulation of p-GSK-3β and upregulation along with nuclear translocation of FoxO3. Moreover, vitamin E δ-tocotrienol have shown to induce apoptosis and also suppress cell survival and proliferative pathways such as PI3-kinase/AKT and ERK/MAP kinases, which occurred in part by suppressing Her2/ErbB2 expression [89]. Similarly, plumbagin promotes cell cycle arrest and autophagy in pancreatic cancer cells. However, more importantly, the compound suppresses epithelial to mesenchymal transition by inhibiting PI3K/AKT/mTOR and p38 MAPK mediated pathways, and activation of 5′-AMP-dependent kinase [90]. It would be fascinating to evaluate effects of these compounds on cancer stem cells, and also to study understanding mechanism of action for prevention and treatment of pancreatic cancer.

MAPK-ERK PATHWAY

MAPK pathway plays an important role in regulating wide variety of signals which leads to numerous cellular responses such as inflammation, growth, differentiation and cell death. In pancreatic cancer, K-Ras transduces MAPK signaling, which regulates cell proliferation, differentiation, and apoptosis [91]. K-Ras mutation constitutively hyperactivate downstream signaling pathways, including extracellular signalregulated kinase (ERK), PI3K, and the Ral guanine nucleotide exchange factor [92], which subsequently leads to cell transformation and tumorigenesis [93]. MAPK signaling activation results in resistance to TGF-β–induced apoptosis in CD133+ cells as compared to CD133− cells [94]. In addition, CD133+ CSCs specifically show increased activation of ERK1/2 as a result of increased MAPK signaling. Moreover, the CCL21/CCR7 axis is involved in the increased metastatic properties of CD133+ pancreatic cancer stem-like cells thorough EMT and Erk/NF-κB pathways [95]. Furthermore, Chai *et al.* demonstrated that P70S6K phosphorylation was associated with ERK1/2 phosphorylation, and that metformin is able to suppress this activation, thereby inhibiting proliferation of CD133+ cells proliferation in pancreatic cancer [96].

Chemo-preventive Agents and Pancreatic Cancer Stem Cells—Recent studies demonstrated that cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) inhibitor licofelone, significantly decreased DCLK1+ cells, as well as inflammation and proliferation in a mouse model of pancreatic cancer [97]. In addition, simultaneous targeting of 5-LOX-

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COX by licofelone and EGFR by gefitinib significantly reduced DCLK1+ CSCs, thereby blocking progression of pancreatic ductal adenocarcinoma [98]. Furthermore, metformin significantly reduced pancreatic cancer stem cell marker proteins CD44, CD133, ALDH1 and EPCAM expression and mTOR signaling pathway, thereby preventing the progression of pancreatic cancer [97]. It has been shown that sulforaphane inhibits self-renewal of pancreatic cancer stem cells through inhibition of Sonic hedgehog-GLI pathway [50]. PanC-1 sphere cells have observed to be more resistant to conventional chemotherapy which shows the presence of significantly increased level of CSC markers. Metformin and curcumin target these pancreatic CSCs [99]. Recent study demonstrated that Triptolide inhibits pancreatic CSCs by reducing the spheroid formation, and ALDH1 expression (100). In addition, it also reduced proliferation and mesenchymal cells along with upregulation of markers for apoptosis and epithelial cells [100]. It has been shown that Minnelide can reduce CD133+ side population and effectively eliminates pancreatic CSCs [101]. Moreover, crocetinic acid, which was purified from Saffron, significantly reduced the expression of pancreatic cancer stem cell markers DCLK1 and CD133 and spheroid formation[52]. Furthermore, the Quinoxaline antibiotic Quinomycin also inhibited pancreatopshere formation, and the number of DCLK1+ cells, as well as suppressing the levels of CSC markers DCLK1, CD44, CD24 and EPCAM in pancreatic cancer cells. In addition, this compound reduced expression for DCLK1, CD44, CD24 and EPCAM in pancreatic cancer tumor xenografts. These data show that Quinomycin may be a potent suppressor of pancreatic cancer that targets the stem cells by inhibiting the Notch signaling pathway [70]. Chemopreventive and natural compounds that inhibit pancreatic cancer stem cells are shown in Fig. (1).

CONCLUSION AND FUTURE DIRECTION

It has become increasingly clear that pancreatic cancer remains one of the deadliest cancers worldwide and the fourth leading cause of cancer-related deaths in the United States. By 2030, it is expected that pancreatic cancer will be the second leading cause of cancerrelated deaths in the United States [2]. Pancreatic tumors have distinct type of cells, which are resistant to conventional therapies and lead to metastasis. One of the small subsets of these cells is CSC in the tumor which is responsible for the growth and metastasis. CSCs might have signaling pathways that are potentially unique to them, such as hedgehog, Wnt/β-catenin, and Notch signaling. If we can identify natural compounds that can specifically target cancer stem cells, then these could be the scaffolds for developing new generations of anti-pancreatic cancer drugs. However, one of the biggest questions in the field is identifying the CSC. Multiple markers have been identified some of which include three cell surface proteins, such and CD44, CD24 and EpCAM [12]. We and others have clearly demonstrated that DCLK1 marks a rare group of cells in the tumor and that these cells have the ability to develop new tumors [19]. Other markers that have been presented are CD133 and ALDH1A1 [13, 17]. We are currently looking for both natural compounds and synthetic compounds that can target DCLK1. Once such compounds are identified, these compounds either alone or in combination with conventional therapy would be a significant step in clinical trials, and could provide a novel approach for prevention and treatment of pancreatic cancers.

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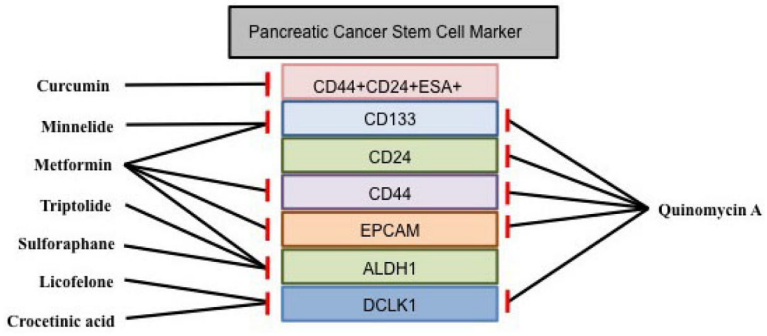

Fig. (1).
Chemopreventive agents and pancreatic cancer stem cells.

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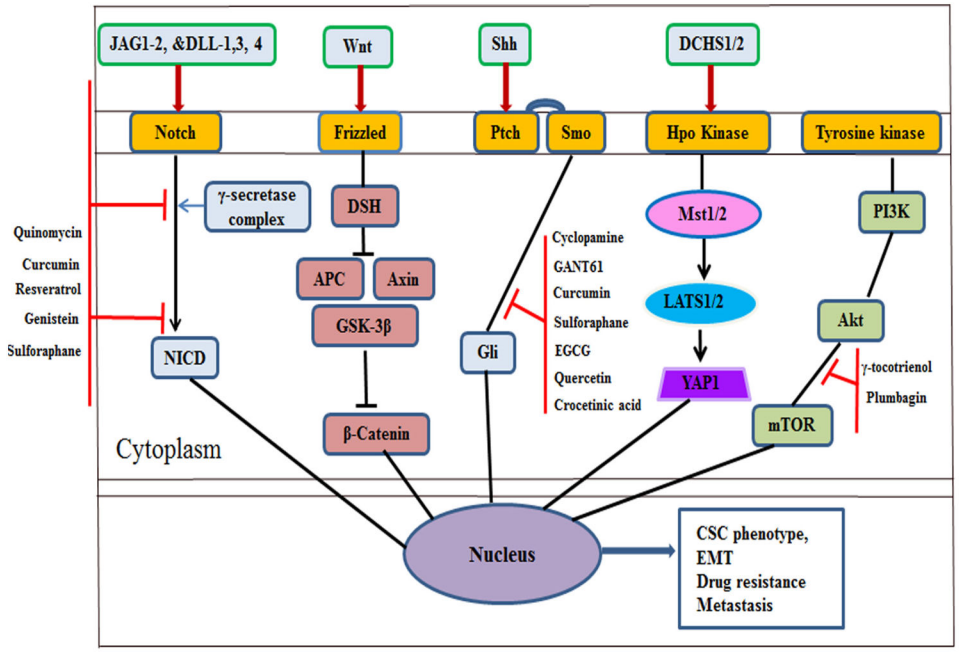

Fig. (2).

A pictorial representation of natural compounds targeting major pancreatic CSCs signaling pathways.