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MINIREVIEWS

Stem cells in gastrointestinal cancers: The road less travelled

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Abstract

Cancer stem cells (CSC) are thought to be malignant cells that have the capacity to initiate and maintain tumor growth and survival. Studies have described CSC in various gastrointestinal neoplasms such as colon, pancreas and liver and gastroesophageal tumors. The mechanism by which CSC develop remains unclear. Several studies have explored the role of dysregulation of the Wnt/β-catenin, transformation growth factor-beta and hedhog pathways in generation of CSC. In this review, we discuss the various molecular abnormalities that may be related to formation of CSC in gastrointestinal malignancies, strategies to identify CSC and therapeutic strategies that are based on these concepts. Identification and targeting CSC is an intriguing area and may provide a new therapeutic option for patients with cancer including gastrointestinal malignancies. Although great progress has been made, many issues need to be addressed. Precise targeting of CSC will require precise isolation and characterization of those cells. This field is also evolving but further research is needed to identify markers that are specific for CSC. Although the application of this field has not entered the clinic yet, there continues to be significant optimism about its potential utility in overcoming cancer resistance and curing patients with cancer.

Key words: Cancer stem cells; CD133+; WNT/β-catenin; Transformation growth factor-beta; Hedgehog; Notch

Core tip: Cancer stem cells (CSC) are thought to be malignant cells that have the capacity to initiate and maintain tumor growth and survival. Several studies have explored the role of dysregulation of the Wnt/β-catenin, transformation growth factor-beta and hedhog pathways in generation of CSC. The exact machismo of their development, however, remains unknown. Several investigators have researched modalities to identify and target CSC. In this review, we summarize the recent evidence exploring the mechanisms of development, identification and targeting of CSC in gastrointestinal malignancies.

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STEM CELLS IN GASTROINTESTINAL CANCERS: THE ROAD LESS TRAVELLED

Cancer is a disease of adult stem cells (SC). Adult SC are the only cells that persist in the tissue for a sufficient length of time to acquire the sufficient sequential genetic alterations for cancer development[1]. Adult SC have been traditionally relatively quiescent, a feature thought to protect them from the accumulation of DNA errors that may lead to carcinogenesis[1]. In the gastrointestinal tract,

the immediate stem cell progeny, however, proliferate rapidly to allow for tissue repopulation[1]. Their limited life span restricts the impact of any replication errors. It is worth noting that this concept has been challenged by recent studies that suggest that adult stem cells are in fact capable of rapid self-renewal[2]. Similarly, cancer stem cells (CSC) have the capacity to initiate and maintain tumor growth and survival[3]. Studies have described CSC in gastrointestinal neoplasms such as colon, pancreas and liver[4-6]. The mechanism by which CSC develop remains unclear[1]. Several studies have explored the role of dysregulation of the Wnt/β-catenin, transformation growth factor-beta (TGF-β) and hedhog pathways in generation of CSC[7-9]. In this review, we discuss the various molecular abnormalities that may be related to formation of CSC in gastrointestinal malignancies, strategies to identify CSC and therapeutic strategies that are based on these concepts.

MOLECULAR PATHWAYS ASSOCIATED WITH CSCS IN GASTROINTESTINAL MALIGNANCIES

Notch signaling pathway

The Notch signaling pathway plays an important role in embryogenesis, cellular homeostasis-, differentiation and apoptosis[10-12]. While Notch mediates a number of biological processes through the "canonical "Notch signaling pathway, it also mediates a ligand- or transcription independent function known as the "non-canonical" pathway[12,13]. The canonical Notch pathway includes at least four Notch receptors (Notch 1-4) and five Notch ligands Delta-like 1,3 and 4 and Jagged 1 and 2[14]. When Notch ligand binds to a Notch receptor, Notch will be cleaved through a series of proteolytic cleavages by multiple enzymes leading to release of the active Notch fragment and activation of Notch target genes[15]. Notch target genes include Akt, mTOR (mammalian target of rapamycin, NF-κB, c-Myc and VEGF (vascular endothelial growth factor) and cyclin D1[16,17]. Activation of the Notch pathway can have tumor suppressor function in HCC but may play on oncogenic role in colon and pancreatic cancers[14]. Notch signaling has been found to play a pivotal role in CSC. Overexpression of Notch-1 and -2 was observed in pancreatic CSC and was associated with increased expression of CSC surface markers such as CD44 and EpCAM[15,17-19]. This observation suggests that Notch signaling may be involved in pancreatic CSC self-renewal but will need further confirmation.

WNT/β-catenin pathway

Notch signaling also perform a "non-canonical role" through antagonizing Wnt/β-catenin signaling[12,13]. Disrupted Wnt signaling is observed in a variety of gastrointestinal cancers which underscores its importance in carcinogenesis[20]. The Wnt pathway plays a crucial role in embryogenesis with signaling effects that regulate proliferation and apoptosis in developing cells[21]. Wnt pathway activation plays a fundamental role in maintenance of SC compartment and regulation of cellular differentiation[22]. The "canonical" Wnt pathway plays a crucial role in modulating the balance between self-renewal and differentiation in several adult CSC[21]. The "canonical" Wnt pathway describes a sequence of events beginning with the translocation of β-catenin from the cell membrane into the nuclear, where β-catenin then acts as a co-activator of the TCF/LEF family of transcription factors[23,24]. The signaling cascade is typically initiated when Wnt ligand binds to Frizzled (FZD), a transmembrane receptor[23]. The transcription factors activated by β-catenin subsequently regulate specific target genes including c-myc, cyclin D1 and survivin. FZD binding to Wnt ligand also promotes the escape of β-catenin from its association with E-cadherin[23,25]. The cytoplasmic elements of the activated Wnt pathway prevent β-catenin from being phosphorylated by degradation complex composed of a serine-threonine kinase, glycogen synthase kinase-3β (GSK3β), protein scaffolds, AXIN and adenomatosis polyposis coli (APC)[25]. Mutations of these proteins allow β-catenin to accumulate in the nucleus to enhance the transcription of its target genes which are found in many cancers[9]. For example, in hepatocellular carcinoma (HCC), mutations of β-catenin are located in exon 3 of CTNNB1 gene which is the phosphorylation site for GSK3B, AXIN1 and AXIN2 mutation[26]. It is worth noting that 20%-40% of human HCC exhibit abnormal cytoplasmic and nuclear accumulation of β-catenin by immunohistochemistry (IHC)[27]. B-Catenin can also undergo downregulation *via* the non-canonical Notch pathway. In this case, membrane-bound Notch forms a complex with active B-Catenin in the presence of Wnts. This action degrades active B-Catenin and thus inhibits its pathway. This process allows for regulation of SC and its dysfunction could lead to expansion of CSC[13]. Markers for elevated expression of Wnt include CD133+ and EpCAM+[28]. The knockdown of expression of EpCAM, in HCC stem cells resulted in decreased proliferation, colony formation, migration and drug resistance which highlight the role and Wnt signaling in tumor survival[28,29]. Additionally, knockdown of β-catenin resulted in inhibition of CSC[30]. Similarly mutations in APC gene acts to suppress Wnt signaling and result in familial adenomatous polyposis (FAP) syndrome[31]. In the majority of sporadic colorectal cancers, loss of APC or β-catenin mutations seems to be early events in carcinogenesis[32]. Of note, Apc 1638N has been shown to result in multiple intestinal tumors in mice[32].

TGF-β pathway

TGF-β signaling is crucial for self-renewal and maintenance of SC and in the formation of gastrointestinal cancers[8,33]. TGF-β forms a complex with the serine-threonine kinase receptor type I and II[34]. The receptors are activated sequentially and subsequently phosphorylate one of the receptor-activated R-mads[35]. The activated R-mad will heterodimerize with Smad4 and then trans-

Table 1 Markers used in gastrointestinal cancer stem cell identification

Markers	Ref.
CD133+	[34]
CD44+	[55]
CD24+	[84]
Lgr5	[53]
mTert	[85]
Olfm4	[86]
Ascl2	[87]
ALDH	[79]
Sox9	[88]
Msi 1	[89]
Dcamkl1	[90]

CD: Cluster of differentiation; Ascl2: Achaete Scute-like 2; ALDH: Aldehyde dehydrogenase; Msi 1: Musashi1; Dcamkl1: Doublecortin and CaM kinase-like-1.

locate to the nuclear to regulate gene transcription[36]. Disruption of TGF-β signaling results in dysregulated gene expression and hence gastrointestinal malignancies are associated with suppressed activity of different members of TGF-β pathway[37,38]. For example, inactivation of Smad4 is seen in approximately 50% of patients with pancreatic cancer[39]. Similarly, reduced Smad4 expression and loss of ELF, a modulator of activity of Smad3, are observed in human colon and gastric cancer tissue[40,41]. Additionally, inactivating mutation of TGF-β II receptor was described in colon cancer[37].

Hedgehog pathway

The Hedgehog signaling pathway consists of a complex of molecules which regulate cell differentiation, regeneration and stem cell biology[9]. The pathway plays a central role in the development and homeostasis of the gut tissue[9]. The Hedgehog pathway is deregulated in gastrointestinal cancers[42]. Up to 60% of HCC samples express Sonic, the predominant ligand of the hedgehog pathway[42]. Additionally, genes involved in the hedgehog pathway are highly expressed in CD133+ liver cancer SC[43]. It is worth noting that suppression of Hedgehog pathway decreased HCC cell proliferation and sensitized HCC cells to treatment with 5-fluorouracil[44]. Hedgehog signaling has been shown to be essential for proliferation and survival of human colon cancers[45]. It is thought to affect both tumor growth and CD133+ CSC[45]. Similarly, HH signaling has been associated with pancreas cancer invasion and metastasis. Conversely inhibition of HH signaling inhibited pancreatic metastatic spread[46].

PTEN pathway

PTEN is a phosphatase that antagonizes PI3 kinase activity[47]. PTEN helps control the proliferative rate and the number of intestinal stem cells and its loss is associated with an increase in intestinal SC[47]. It is also thought that PTEN pathway controls SC activation *via* interaction with the Wnt pathway[48]. It is also proposed that PTEN pathway interacts with the TGF-β pathway described above[48]. Mutations in PTEN, result in a cancer syndrome (Cowden's syndrome) characterized by hamartomas in the gastrointestinal tract, central nervous system and skin in addition to tumors in the breast and thyroid gland[49]. PTEN deficient mice exhibit increase in intestinal SC which results in excess crypt formation[47].

Identification of CSCs

Eradication of CSC stems is an intriguing concept that provides hope in the possibility of finding a cure for cancer. Any therapeutic modality that targets CSC will require accurate identification and characterization of the CSC and differentiating them from normal SC. Isolation of cancer cells through the identification of pathognomonic surface markers has recently gained popularity and is an area of active investigation[50,51]. $CD133^+$ emerged as a promising surface marker for CSC[50]. Singh *et al*[51] used flow cytometry to successfully isolate $CD133^+$ CSC in human brain tumors and implanted them into forebrain of immunodeficient mice. Transplantation of as few as 100 cells produced tumors that were phenotypically similar to original tumors. Similar findings were reported in colorectal cancer. Several groups isolated subpopulations of cells, accounting for approximately 1% of total number of cells within a tumor, that were $CD133^+$ and we capable initiating cancer when transplanted in immunodeficient mice[5,52,53]. Other studies have identified new CSC markers (Table 1) that may be promising in isolation of CSC such as Lgr5, CD44, CD24 and epithelial specific antigen[54-57]. These markers were isolated in HCC and pancreatic cancer. This field is currently in evolution. Efforts have been made to identify surface marker "signatures " that are specific for each type of cancer (Table 2) It is worth noting that isolation of cancer cells is far from perfect and remains an area of controversy. Not all CSC express SC markers and some tumor cells that are not SC may also express those markers[1]. Great progress has been already made in this area but this more works remains to be done.

Resistance of CSCs to anticancer therapy

Several studies demonstrated that CSC exhibit resistance to chemotherapy agent[2,58]. One of the widely accepted theories is that the elevated levels of ATP-binding cassette (ABC) transporters mediate resistance to chemotherapy[2,3,58,59]. ATP transporters are membrane transporters that can pump small molecules including cytotoxic drugs out of cells in exchange for ATP hydrolysis[59]. CSC as well as normal SC appear to express high levels of ABC transporters[60]. This characteristic can lead to multidrug resistance and enhanced tumorigenesis. Evolving evidence suggests that numerous cell lines and tumors contain CSC, referred to as side population (SP) cells that possess a differentially greater capacity to resist chemotherapeutic agents and invade surrounding tissues[2,61-63]. This phenomenon, however, may allow for development of therapies that could target ATP transporters in CSC.

Table 2 Surface markers of gastrointestinal cancer stem cell

Tumor type	Phenotype of CSC markers	Ref.
Liver	CD133+, CD49f+, CD90+	[1,6,91]
Colon	CD133+, CD44+, CD166+, EpCAM+, CD24+	[5,45,52]
Pancreatic	CD133+, CD44+, EpCAM+, CD24+	[57]
Stomach	CD44+, CD133+, NESTIN, CD90+, CD54+, ALDH1	[79]

CSC: Cancer stem cell.

Targeting CSCs

Targeting CSC is an intriguing concept that may offer several therapeutic advantages. Targeting the inherently resistant CSC may overcome resistant to chemotherapeutic agents. Most patients with metastatic gastrointestinal cancers tend to experience treatment failure and resistance to palliative chemotherapy[64-66]. Additionally, targeting CSC may, not only improve efficacy of treatment but may also reduce therapy-related toxicity through developing treatment that are selective for CSC and not toxic to healthy tissues. Novel treatment strategies are, therefore, being developed that target surface markers on CSC, ATP-binding cassettes, key signaling pathways or their tumor microenvironment[1].

Targeting surface markers: Since $CD133^+$ is expressed in CSC in gastrointestinal cancer, it represents an interesting target to selectively inhibit CSC. A recent study demonstrated that carbon nanotubes conjugated with CD133+ monoclonal antibodies caused photothermolysis of $CD133^+$ glioblastoma cells when affixed to an anti-CD133 antibody that selectively targeted those cells[67]. This study represents an encouraging proof of concept that gastrointestinal CSC can be possibly targeted with similar strategies.

Targeting cancer stem cell pathways: Targeting signaling pathways that are thought to be active in CSC is an ongoing area of active research. Lin et al demonstrated that a curcumin analogue, GO Y030, may have clinical activity against colorectal cancer SC *in vitro* and *vivo*[68]. They identified aldehydehehydrogenase (ALDH) positive and $CD133^+$ colorectal CSC using flow cytometry. The demonstrated that isolated CSC exhibited STAT-3 (signal transducers and activators of transcription-3) activation and treated them with GO-Y030. GO-Y030 inhibited STAT3 phosphorylation and reduced STAT3 downstream target gene expression resulting in induction of apoptosis in colon CSC. Additionally, GO-Y030 suppressed tumor and CSC growth of SW480 and HCT-116 colon cancer cell lines *in vivo* in mouse models. Interestingly, Curcumin has been shown to also inhibit cell growth and apoptosis in pancreatic cancer cells. Its effect was associated with down-regulation of Notch-1 expression, which suggests that Curcumin may be associated with potential advantageous activity against pathways that are upregulated in CSC[18]. Other attempts to target Notch signaling in gastrointestinal CSC have, however, not been very successful. Gamma-secretase inhibitors (GSI) are thought to antagonize Notch signaling through blocking of Notch receptor cleavage[69]. Evaluation of the effect of GSI in two gastric cancer cell lines did not result in any appreciable antitumor effects[70]. These results were surprising since GSI have shown promising antitumor potential in leukemia, breast and glioblastoma multiformes models[71-73].

Evolving evidence suggests that targeting the Hedgehog pathway may be a feasible strategy to inhibit CSC. Cyclopamine, a naturally occurring hedgehog inhibitor has shown promising potential[46]. As a single agent cyclopamine suppressed the invasion of pancreatic cancer cells[4]. Cyclopamine reduced the percentage of cells expressing the pancreatic CSC markers such as ALDH[74]. In combination with gemcitabine, cyclopamine resulted in reduction of metastasis in an orthotopic xenograft model[74]. To further clarify this observation, Yao *et al*[74] demonstrated that cyclopamine dowregulated the expression of CD44 and $CD133^+$ in gemcitabine-resistant pancreatic cancer cells indicating that it may be an effective modality for reversing gemcitabine resistance in pancreatic CSC. A similar observation was made in gastric CSC where blocking of Hedgehog pathway with cyclopamine decreased self-renewing properties and enhanced sensitivity of gastric cancer cells to chemotherapeutic agents[75]. Additionally, Feldmann *et al*[76] demonstrated that IPI-269609, a novel Hedgehog inhibitor, inhibited growth and metastasis of pancreatic cancer mostly through targeting of the CSC.

Since the Wnt pathway is also deregulated in CSC, it represents an intriguing target for cancer treatment. Anti-Wnt therapy is in early stages of clinical development[77]. He *et al*[77] demonstrated that a monoclonal antibody against Wnt-1 induced apoptosis in human cancer cells. Also, Salinomycin, an antibiotic commonly used in poultry firmly, is thought to suppress Wnt/β-catenin signal transduction[78]. In gastric cancer, salinomycin, selectively inhibited gastric CSC *in vitro*[79]. Wnt inhibitors also are being investigated in phase I clinical trials. Oral LGK974[80] is a potent and specific inhibitor of O-acyltransferase Porcupine (Porcn) that acetylates Wnt proteins required for their biological activities is being investigated in a phase I clinical trial in patients with malignancies dependent on Wnt ligands. This trial is enrolling patients with pancreatic and colon adenocarcinoma.

Targeting ATP-driven efflux transporters has been explored in preclinical and early phase clinical trials. The first drug efflux pump inhibitor is verapamil. Simultaneous treatment with verapamil and chemotherapy resulted in promising antitumor activity. Other agents such as Dofequidar Fumarate (MS-209), Biricolar (VX-710), and tariquidar are in various stages of clinical development[81-83]. Most of the experience with these agents is derived from lung and breast cancer trials but these agents, to our knowledge, have not been investigated in gastrointestinal cancers.

CONCLUSION

Identification and targeting CSC is an intriguing area and

may provide a new therapeutic option for patients with cancer including gastrointestinal malignancies. It is a rapidly evolving area in the treatment of gastrointestinal and other tumors. Although great progress has been made, many issues need to be addressed. The CSC model does not fully explain the observed genetic heterogeneity of many tumors. This criticism may however be explained by the fact that even CSC may evolve over time and give rise to cells that are both genetically and functionally heterogeneous[1]. Furthermore, accurate targeting of CSC will require precise isolation and characterization of those cells. This field is also evolving but further research is needed to identify markers that are specific for CSC. Nevertheless, there continues to be significant excitement about this field and hope that it may represent a new treatment modality in patients with cancer.

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