-Review-

Activation of the hedgehog pathway in gastroesophageal cancers

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Abstract

The hedgehog pathway is a major regulator for cell differentiation, tissue polarity and cell proliferation in embryonic development and homeostasis in adult tissue. Studies from many laboratories reveal activation of this pathway in a variety of human cancer, including basal cell carcinomas, medulloblastomas, leukemia, gastrointestinal, lung, ovarian, breast and prostate cancers. It is thus believed that targeted inhibition of hedgehog signaling may be effective in treatment and prevention of human cancer. Even more exciting is the discovery and synthesis of specific signaling antagonists for the hedgehog pathway, which have significant clinical implications in novel cancer therapeutics. In this review, we will summarize major advances in the last two years in our understanding of hedgehog signaling activation in human gastroesophageal cancer, and their potential in clinical treatment with hedgehog pathway inhibitors.

Key words:

Hedgehog; Inhibitor; Gastroesophageal cancer; Human cancer therapy

INTRODUCTION

The hedgehog (Hh) gene was identified in 1980 through genetic analysis of segmentation of fruit fly *Drosophila*. [1] In early 90's, three homologues of the Hh gene were identified in vertebrates. [2-6] Overall, the general signaling mechanisms of the Hh pathway is conserved from fly to the humans. [7] The seven transmembrane domain containing protein smoothened (SMO) serves as the key player for signal transduction of this pathway, whose function is inhibited by another transmembrane protein Patched (PTC) in the absence of Hh ligands. In the presence of active Hh ligands, binding of Hh to its receptor PTC releases this inhibition, allowing SMO to signal downstream, eventually to Gli transcription factors. As transcription factors, Gli molecules can regulate target gene expression by direct association with a specific consensus sequence located in the promoter region of the target genes. [8,9] Figure 1 shows the simplified diagram of Hh signaling in the presence or absence of Hh.

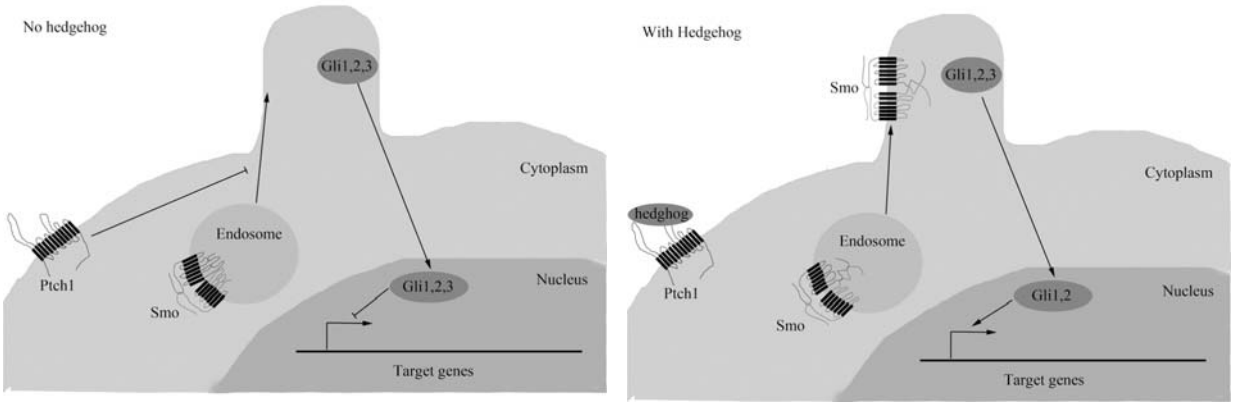

Figure 1 A simplified diagram of Hh signaling in vertebrates.In the absence of Hh ligands, PTC somehow inhibits SMO signaling, which results in formation of repressor forms of Gli transcriptional factors Gli2 and Gli3. In the presence of Hh ligands, SMO no longer affected by PTC, is signaling to downstream effectors, leading to formation of active forms of Gli transcriptional factors and ultimately activation of the target genes.

As an essential developmental signaling pathway, the Hh pathway is critical for maintaining tissue polarity and stem cell population. Inactivation of this pathway causes developmental defects such as holoprosencephaly,[10] whereas hyperactivation of this pathway is found in most basal cell carcinomas (BCCs) and many extracutaneous cancers. [11-13] In pancreatic cancer for example, activation of the Hh pathway is found in both early tumors and metastatic cancer[14-18]. In support of there findings, transgenic mice with pancreatic-specific expression of Shh or Gli2 develop pancreatic tumors.[16,19] Pancreatic-specific deletion of SMO did not affect formation of pancreatic ductal adenocarcinoma (PDAC) whereas Gli2 expression resulted in undifferentiated pancreatic tumors. [20,21] These studies indicate that activation of the hedgehog pathway is important but not sufficient for tumor formation of PDAC. It was shown that Kras directly activates the Hh pathway in PDAC cells. [22] Activation of the Hh pathway is detected in stem cell-like subpopulation in pancreatic adenocarcinoma. [23-25] Hh pathway inhibitors cyclopamine, [26] IPI-269609 [27] have effect in pancreatic cancer mouse model. Combination of Hh pathway inhibitor IPI-926 and gemcitabine, [28] SMO antagonist SANT-1 and histone deacetylase inhibitor SAHA, [29] Hh pathway inhibitor cyclopamine and inhibitor of epidermal growth factor receptor (EGFR) Iressa [30] inhibit tumor cells in pancreatic cancer. The emerging role of Hh signaling in human cancer further emphasizes the relevance of studying this pathway to human health.

Cyclopamine, a plant-derived steroidal alkaloid, binds directly to SMO and inhibits Hh signaling.[31] The discovery of small molecule antagonist of SMO has opened up exciting new prospects for target therapy and prevention of human cancers associated with Hh signaling. Six Hh pathway inhibitors (e.g. GDC-0449, BMS-833923, IPI-926 and PF-04449913) have been used in clinical trials for treatment of basal cell carcinoma (BCC), medulloblastoma, ovarian cancer, lung cancer. [32] GDC-0449, which was developed by Curis and Genentech, had great effects in therapy of advanced BCC and medulloblastoma. [33,34] However, to our disappointment, clinical trials of GDC-0449 treatment in ovarian cancer and colorectal cancer have been suspended due to limited benefits for the patients. The remarkable differences in effectiveness of Hh pathway inhibitor in some types of cancer indicated that the Hh pathway plays different roles in different types of cancer. Therefore, in the future, thorough study is required before Hh pathway inhibitors are advanced into clinical trials. In this review, we will summarize major advances in Hh signaling activation in human gastroesophageal cancer to provide in-depth information for evaluation of clinical treatment with Hh pathway inhibitors.

ACTIVATION OF THE HH PATHWAY IN ESOPHAGEAL CANCER

Esophageal cancer is the 6th cause of cancer-related death worldwide and the 7th cause of cancer-related death in American men. [35] The two types of esophageal cancer, squamous cell carcinoma (ESCC) and adenocarcinoma of esophagus (ACE), have different incidence in different geographic regions: squamous cell carcinoma of esophagus is still the predominant type worldwide. The incidence of adenocarcinomas is rising in the United States and several European countries.[36-38] China is one of the countries with the highest incidence of esophageal cancer. [39] It is known that the etiology of esophageal adenocarcinoma includes long standing acid/bile reflux esophagitis and development of Barrett's esophagus, an intestinal type metaplasia of the normal squamous epithelium which further progresses to

dysplasia and carcinoma. Similarly, ESCC is considered to arise from multiple steps through progression of precancerous lesion-squamous dysplasia to invasive ESCC. Most esophageal cancers are diagnosed in the advanced stage, resulting in a high mortality. Current treatments of esophageal cancer include surgery, neoadjuvant chemotherapy or neoadjuvant radiochemotherapy followed by surgery, or surgery plus chemotherapy. The overall 5-year survival rate of esophageal cancer (<10%) has not changed since 1980. Therefore, identifying sensitive and specific biomarkers for esophageal cancer will help early diagnosis and may help to design novel strategies for more effective targeted therapy for patients with advanced diseases.

Hh signaling activation has been reported in esophageal cancer. Previously, we and others found activation of Hh signaling in esophageal cancer.[40-42] Elevated expression of sonic hedgehog (Shh) and its target genes have been found in several esophageal cancer cell lines and esophageal cancer specimens. [42-45] Studies also suggest that Hh signaling activation is associated with poor prognosis[44] of esophageal caner. Crosstalks among Hh signaling, the epithelial-mesenchymal transition pathway, [46] the phosphinositide-3 kinase pathway and mitogen-activated protein kinase pathway [47] have been reported in esophageal cancer.

Compared with study of the Hh pathway in esophageal cancer, little is known about Hh signaling activation in precancerous lesions of esophageal cancer. Recent study indicates that Shh is induced in Barrett's esophagus to mediate paracrine Hh signaling. [48] We also found that expression of PTCH1 is associated with occurrence of severe squamous dysplasia/ carcinoma *in situ* and Barrett's esophagus (our unpublished data). Consistent with the human specimen data, we found a high percentage of Hh signaling activation in precancerous lesions in rat models (our unpublished data). These data indicate that the Hh pathway activation is an early molecular event in the development of esophageal cancer and may be a target for early diagnosis and novel therapy for esophageal cancer. Activation of the Hh pathway in esophageal adenocarcinoma is much higher than in esophageal squamous cell carcinoma (our unpublished data), which may caused by more activation of the hedgehog pathway in Barrett's esophagus compared with squamous dysplasia and different etiology between ESCC and ACE, indicating that the Hh pathway in esophageal cancer may be context dependent and affected by tumor heterogeneity. Without knowing the status of Hh signaling, it will be difficult to predict the outcomes of Hh signaling inhibitors in cancer treatment. Several animal models have been used in the study of esophageal cancer, including surgical bilious reflux injury induced rat/mouse esophageal cancer model,[48,49] NMBA induction of rat esophageal squamous cell carcinoma model[50] and esophagogastroduodenal anastomosis induced rat esophageal adenocarcinoma model. [51] These are useful tools in evaluation of effects of the Hh pathway inhibitors for esophageal cancer development and progression.

ACTIVATION OF THE Hh PATHWAY IN GASTRIC CANCER

The incidence and mortality have fallen dramatically over the past 70 years. [52] However, gastric cancer is the fourth leading cancer following lung, breast, and colorectal cancer and the second cause of cancer related death worldwide after lung cancer.[53,54] In 2002, approximately 930,000 people were diagnosed with gastric cancer and about people 700,000 died of this cancer. [55] The best treatment option for gastric cancer is surgical removal of the tumor at early stages. Most patients with gastric cancer are diagnosed later in tumor progression, making it impossible to do surgery. Other therapeutic approaches include neoadjuvant chemotherapy, neoadjuvant chemoradiotherapy and adjuvant chemotherapy and palliative therapy, with only a slight improvement of patient survival or reduced pain of the patients. Event with the best intent to cure from clinicians, the overall 5-year survival of gastric cancer patients is 5%-15%.

Recent studies have shown that the Hh pathway is involved in gastrointestinal development and gastric regeneration. [56-60] Molecules such as the transcriptional factors GATA-4, GATA-6, [61] FoxF1, FoxL1, [62] COUP-TFII, [63] E-cadherin, [64] ERK[65] and epithelial-mesenchymal transition pathways, [66] are reported to be associated with Hh signaling in this process. Paracrine Hh signaling is found in gastric patterning throughout murine embryonic and adult life. [67] Gastric acid induces Shh gene expression.[56,68,69] Aberrant expression of Shh is involved in the pathogenesis of gastric diseases such as gastric atrophy,[70,71] hypergastrinemia and hyperproliferation of surface mucous cells. [72] All these studies will help us to better understand the molecular mechanism of gastric diseases and optimize the strategy of treatment.

Increasing evidence shows that Hh signaling plays a role in gastric cancer. It is estimated that about 90% of gastric cancers are adenocarcinomas. According to Lauren Classification, there are two major types of gastric adenocarcinoma: intestinal and diffuse type. Several studies on activation of the Hh pathway in these two types show inconsistent results. Hh signaling is found to be more frequently and highly activated in the diffuse form, not the intestinal type. [57] Low expression of Shh and high level of Cdx2 are found in metaplasia columnar epithelium. [73] Shh expression is down regulated by Cdx2 in intestinal metaplastic mucosa of stomach from Cdx2-transgenic mice. [74] Another study reports that

expression of Shh is stronger in the intestinal type than in the diffuse type. [75] Consistent with the role of Hh signaling in gastric cancer, loss of Gli3, an inhibitory component of the Shh pathway, results in intestinal transformation of gastric epithelium. [59] Expression of Shh, Ihh, pathway components and target genes increases in gastric cancer,[38,43,45] and gastric lesions are associated with the methylation status of the sonic hedgehog (Shh) promoter. [76] Nuclear translocation of Gli1 was higher in undifferentiated-type tumors and positively correlated with lymph node metastasis in gastric carcinoma. [77] Hh signaling was found to promote gastric cancer cells proliferation, [78] epithelial-mesenchymal transition, [66] mobility and invasiveness[79] and inhibit apoptosis.[43,80]

Helicobacter pylori (*H. pylori*) infection is one of the major carcinogens in gastric cancer. *H. pylori* infection suppresses expression of Shh in gastric mucosa prior to neoplastic transformation[81] and eradication of the infection restore Shh expression. [82-84] *H. pylori* infection is also implicated in activation of the Hh pathway in gastric cancer.[85,86] These studies indicate that *H. pylori* have different roles in Shh pathway in temporal and spacial dependent manners during gastric carcinogenesis.

Crosstalk between the Hh pathway and other signaling in gastric cancer has been reported. Mitogen-activated protein kinase cascade promotes activation of the Hh pathway in gastric cancer cells. [87] Activation of the Wnt pathway is reversely correlated with activation of the Hh signaling in gastric cancer, [88,89] probably through inhibition of the Wnt pathway by Hh target gene sFRP1.[89,90] A recent study provides evidence that the estrogen receptor-alpha pathway promotes gastric cancer cells proliferation by activating the Hh pathway. [91] Expression of Shh signaling components is also found in precancerous lesions of gastric cancer, [75] indicating that the Shh pathway is involved during early gastric carcinogenesis.

Hh SIGNALING IN GASTROESOPHAGEAL CANCER STEM CELLS

The definition of cancer stem cell, "a cell within a tumor that possesses the capacity to self-renew and to cause the heterogeneous lineages of cancer cells that comprise the tumor", was reported in AACR Workshop on Cancer Stem Cells in 2006. [92] Study of acute myeloid leukemia in 1997 found that a subpopulation could initiate cancer in NOD/SCID mice resemble of histology of cancer from donors, [93] which provided evidence for the existence of cancer stem cells. Currently, there are four methods to detect cancer stem cell, including cell surface markers, side population, tumorspheres formation and inoculation in NOD/SCID mice. Since cell surface markers or side population alone may not represent the cancer stem cells in solid tumors, it is necessary to use more than one method to detect cancer stem cells.

Several cell surface markers are found to be potential markers to separate gastric cancer stem-like cells in cancer cell lines and specimens. CD44+ subpopulation in gastric cancer cell line MKN-45, MKN-74 and NCI-N87, [94] CD44, CD24 and CD133 positive HGC-27 cell line[95] forms tumorspheres *in vitro* and initiates tumor *in vivo*. Expression of CD133 and Bmi-1 are detected in cancer specimens, and CD133 is correlated to invasion and prognosis of gastric cancer. [96,97] Side population cells isolated from cancer cell lines MKN-45, OCUM-2M, OCUM-2D, OCUM-2MD3 possess the characteristics of cancer stem-like cells.[98,99]

Studies have revealed the several possible origins of gastric cancer stem cell. Chronic inflammation induced by *H. pylori* infection recruits bone marrow-derived cells, and these cells go through metaplasia, dysplasia to cancer. [100,101] Gastric epithelial stem cells may be the cellular origin of gastric cancer.[102,103] Under mucosal injury and inflammation, mature gastric chief cells act as cryptic progenitors and reacquire the ability of proliferation. [104]

Study of Hh signaling in gastric cancer stem cells has just begun. Tumorspheres of HGC-27 cancer cell line and specimens express high level of Ptch and Gli1. Hh signaling blocked by 5E1 or cyclopamine causes reduction in self-renewing capacity. [95] The Hh pathway is widely studied in cancer stem cells of glioma, [105-107] breast cancer,[108,109] myeloid leukemia,[110,111] and find that the Hh pathway is essential to maintain characteristics of cancer stem cells. Therefore, we believe that the mechanism how Hh signaling involved in the gastric cancer initiation and progress through regulating gastric cancer stem cells will be revealed soon in the future.

Bone marrow-derived cells contribute to esophageal squamous cell[112,113] and metaplasia of BE,[113,114] which is similar to chronic inflammation induced bone marrow-derived cells involved in gastric cancer. Due to current knowledge, there is one and three possible derivation of cancer stem cells for esophageal and gastric cancer, respectively. Because of heterogeneity and different etiology of two tumors, more types of cancer stem cells will be revealed in the future. A subpopulation of esophageal basal cells has characteristics of stem cells. [115] Studies of cell surface markers identifying

esophageal cancer stem-like cell are preliminary. Lgr5 (an intestinal stem cell marker), [116,117] P75 neurotrophin receptor[118-120] are potential candidate biomarkers. Previously established cancer stem cell markers, CD24, CD29, CD44 and beta-catenin, were not the markers for cancer stem cells in EAC. [121] Side population cells from EC9706, EC109 cells[122], primary ESCC tissue, [123] possessed the properties of cancer stem cell. NS398, a cyclooxygenase-2 inhibitor, enhanced the radiosensitivity of esophageal cancer stem-like cells by down regulating beta-catenin. [124] However, roles of the Hh pathway in esophageal cancer stem-like cells have not been reported. We are looking forward to the progression on this subject.

IMPLICATIONS OF THE Hh PATHWAY IN GASTROESOPHAGEAL CANCER THERAPY

Hh signaling plays crucial roles in initiation, proliferation, metastasis and survival in gastroesophageal cancer, which provide novel target for therapy. Activation of the Hh pathway after chemoradiotherapy in esophageal cancer promotes tumor reoccurrence,[125,126] and associates with the resistance to chemoradiotherapy, [127] indicating that combination of Hh pathway inhibitor and chemoradiotherapy may improve prognosis of esophageal cancer. Recent study finds that Gli1 is a novel target of ursodeoxycholic acid-aspirin combined treatment. [128]

Cyclopamine, a SMO antagonist, inhibits proliferation of gastric cancer cells, [43] however, in acid environment reduced efficiency of cyclopamine is found. [129] Therefore, design of acid-proof cyclopamine analogues, such as IPI-926, may help to improve treatment in gastric cancer. Additionally, tumorspheres from gastric cancer cell line HGC-27 has higher chemoresistance than adherent cells. Blocking Hh signaling enhances the efficacy of chemotherapeutic drugs in tumorspheres. [95]

GDC-0449, an Hh pathway inhibitor, had great effects in therapy of advanced BCC and medulloblastoma. [33,34] A medulloblastoma patient developed a D473H resistance mutation in SMO during the treatment of GDC-0449 and ultimately relapsed. Further analysis revealed that substitution of D473 with positively charged residues showed potential oncogenic property and identified several inhibitors against these resistant mutations. However, up-regulation of Gli2 and cyclin D1 (target gene of the Hh pathway) were found in other resistant models, suggesting that components downstream of SMO may also develop the resistance. Interestingly, the GDC-0449 resistant models regained sensitivity to PI3K inhibition. [130] Studies indicate that there is limitation applying Hh pathway inhibitors alone in cancer treatment. In addition, the Hh pathway is crucial in sustain cancer stem cells which are resistant to chemoradiotherapeutic drugs. Therefore, efficacy of combination of Hh pathway inhibitors with conventional therapy is evaluated in various cancer models (Table 1). Hh pathway inhibitors, mostly SMO antagonists, showed synergistic effects with chemoradiotherapeutic agents and inhibitors of pathways and molecular in cancer treatment. However, not all the combination therapy conferred more efficiency. Combination of hepatocyte growth factor neutralization antibody L2G7 with Shh neutralization antibody 5E1 or cyclopamine failed to improve survival in medulloblastoma mouse model compared with L2G7 treatment. [131] This reminds us that combination therapy should depend on the context of cancers and perform preclinical test to make sure the activity of targeted pathways.

SUMMARY

In summary, increasing evidence indicate that Hh signaling is involved in gastroesophageal cancers. Understanding of the Hh pathway provides great opportunities for developing novel therapeutic strategies for human gastroesophageal cancers with activated Hh signaling.

Conflicting Interest: The authors have no conflicting interest to declare.

Table 1 Summary of Hh pathway inhibitor combined therapy in cancer treatment.

Type of cancer	Model	Hh pathway inhibitor	Combined therapy	Efficacy	Reference
Hepatocellular carcinoma	HA22T, Sk-Hep1 cell line	Shh antibody or Gli-1 RNAi	Ionizing radiation	Enhance the radioresponse	Chen, *et al* 2011 [103]
Pancreatic adenocarcinoma	Panc-1, BxPC-3 cell line	Smo antagonist SANT-1	Histone deacetylases inhibitor SAHA, Gemcitabine	Increase Gemcitabine cytotoxicity	Chun, *et al* 2009 [29]
Glioma	cancer cell line	Blocking Hh pathway	VCR, VP16, CDDP and ACNU	Enhance cytotoxicity of chemotherapertic agents	Cui, *et al* 2010 [132]
Mantle cell lymphoma	JVM2 cell line	Cyclopamine	Doxorubicin	Increase susceptibility to doxorubicin	Hegde, *et al* 2008 [133]
Pancreatic cancer	Direct xenograft model	Cyclopamine	Gemcitabine	Induce tumor regression and decrease in cancer stem cell markers	Jimeno, *et al* 2009 [134]
Leukemia, B-cell lymphoma	Acute leukemia and B-cell lymphoma cell lines	Cyclopamine	Quercertin	Suppress the growth of cancer cells	Kawahara, *et al* 2009 [135]
Prostate cancer	LNCap, DU145 and PC3 cell line	Cyclopamine	Epidermal growth factor receptor inhibitor gefitinib, docetaxel	Improve the cytotoxic effects of docetaxel	Mimeault, *et al* 2007 [136]
Pancreatic cancer	in vitro and in vivo models	Cyclopamine/ CUR199691	Mammalian target of rapamycin inhibitor rapamycin, chemotherapy	Combined inhibition of Hh and mTOR pathway together with chemotherapy reduces the number of cancer stem cells	Mueller, *et al* 2009 [137]
Androgen-independent prostate cancer	PC-3 xenograft	Gli2 antisense oligonucleotide	Paclitaxel	Delay tumor progression and enhanced paclitaxel chemosensitivity	Narita, *et al* 2008 [138]
Leukemia	T-cell acute lymphoblastic leukemia cell lines, acute myeloid leukemia cell lines	Cyclopamine	Notch inhibitor GSI-XXI, Wnt inhibitor quercetin	combination with cyclopamine or quercetin promotes anti-leukemic effects of GSI	Okuhashi, *et al* 2011 [101]
Pancreateic ductal adenocarcinoma	mouse model	IPI-926	Gemcitabine	Enhance delivery of gemcitabine	Olive, *et al* 2009 [139]
Medulloblastoma and glioblastoma (GBM)	GBM and medulloblastoma cell lines, primary human GBM cultures	Cyclopamine	Gamma-secretase inhibitor MRK-003	More effective at eliminating GBMs cells	Schreck, *et al* 2010 [140]
Androgen-independent prostate cancer	LNCaP C4-2B cell line	Cyclopamine	ErbB signaling inhibitors gefitinib and lapatinib	Synergistic antiproliferation effects	Shaw and Prowse 2008 [141]
Pancreatic cancer	PANC-1, SUIT-2 and ASPC-1	Cyclopamine	Epidermal growth factor receptor inhibitor Iressa	Induce growth inhibitory and apoptosis	Hu, *et al* 2007 [30]
Cholangiocarcinoma	Cholangiocarcinoma cell lines	Cyclopamine	MEK inhibitor U0126	Decease proliferation and survival	Jinawath, *et al* 2007 [142]
Prostate cancer	LNCaP-C33, LNCaP-LN3, LNCaP-C81, DU145 and PC3 cell line	Cyclopamine	Epidermal growth factor receptor inhibitor gefitinib,	Growth arrest and apoptosis	Mimeault, *et al* 2006 [143]
Esophageal cancer	SEG-1,BE-3 cell line	Cyclopamine	Ionizing radiation	Enhance radiation cytotoxicity	Sims-Mourtada, *et al* 2006 [126]

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