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REVIEW

Hedgehog signaling pathway in colorectal cancer: function, mechanism, and therapy

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Chuanqing Wu
Xiaojie Zhu
Weizhen Liu
Tuo Ruan
Kaixiong Tao

Department of Gastrointestinal Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Abstract: Colorectal cancer (CRC) is one of the most common gastrointestinal cancers worldwide. It is a complicated and often fatal cancer, and is related to a high disease-related mortality. Around 90% of mortalities are caused by the metastasis of CRC. Current treatment statistics shows a less than 5% 5-year survival for patients with metastatic disease. The development and metastasis of CRC involve multiple factors and mechanisms. The Hedgehog (Hh) signaling plays an important role in embryogenesis and somatic development. Abnormal activation of the Hh pathway has been proven to be related to several types of human cancers. The role of Hh signaling in CRC, however, remains controversial. In this review, we will go through previous literature on the Hh signaling and its functions in the formation, proliferation, and metastasis of CRC. We will also discuss the potential of targeting Hh signaling pathway in the treatment, prognosis, and prevention of CRC.

Keywords: colorectal cancer, Hedgehog signaling pathway, cancer therapy

Introduction

Colorectal cancer (CRC) is one of the most common malignancies worldwide, which is related to significant morbidity and mortality. Despite the advancements in diagnosis and treatment of this tumor type, identification of new prognostic biomarkers continues to be a challenge.

The Hedgehog (Hh) signaling pathway plays an essential role in the patterning, growth, and differentiation in various tissues, including the gastrointestinal tracts.[1–5] In mammals, Hh signaling initiates with binding of one of the three ligands – Sonic Hedgehog (Shh), Indian Hedgehog (Ihh), and Desert Hedgehog (Dhh) – to the transmembrane receptor patched 1 (Ptc1), causing the release of the suppressed transmembrane protein Smoothened (Smo), which is a member of the seven transmembrane-receptor family, most closely related to the Frizzled family.[2] The release of Smo subsequently activates the Gli transcription factors.[3,6] Hh signaling pathway has been implicated in the pathogenesis of various human cancers; however, the role of the Hh pathway in CRC remains controversial.[6] There are two mechanisms of Hh activation: through Hh ligand-dependent activation or through ligand-independent activation, namely, by loss-of-function mutations in Ptc1 or gain-of-function mutations in the proto-oncogene *Smo*.[7] The Hh pathway is viewed as a cancer-related pathway and a potential therapeutic target.

In this review, we will go through previous literature on the Hh signaling pathway and its functions in the formation, proliferation, and metastasis of CRC. We will also discuss the potential roles of the Hh signaling pathway in the treatment, prognosis, and prevention of CRC.

Correspondence: Kaixiong Tao
Department of Gastrointestinal Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China
Tel +86 27 8572 1619
Email taokaixiong19@163.com

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Hh signaling pathway

Since first discovered in *Drosophila melanogaster*, the Hh signaling pathway has received extensive attention.[1–7] Massive research has confirmed its contributions in embryonic generation and postembryonic regulation of the development of various organs and tissues, including the patterning, growth, and differentiation in the gastrointestinal tracts.[1–5] The Hh signaling pathway is involved in the continuous renewal of the intestinal epithelial cells in adults, which leads to the speculation that dysregulation of the Hh signaling pathway would cause pathological hyperplasia of intestinal epithelial cells and contribute to the generation and progression of malignancies.[2,5,8]

There are three mammalian Hh homologs – Shh, Ihh, and Dhh – in vertebral animals that participate in the patterning and development of various tissues and organs.[2,8] These homologs are also functional in certain types of tissue regeneration and tumorigenesis.[9,10] In the gastrointestinal tracts, both Shh and Ihh are expressed, while Dhh expression appears to be restricted to the nervous system and testes.[10] The major components of the Hh pathway are localized to the cell membrane.[11] The transduction response to Hh ligands is regulated and conveyed by two transmembrane proteins: Ptc and Smo, and by the downstream transcription factors of the Gli family (Gli1, Gli2, and Gli3).[12]

The Hh signaling pathway begins with the production and secretion of Hh ligands.[13] The Hh ligands then bind to Ptc and subsequently activate the G protein–coupled receptor–like transmembrane protein Smo.[14] When Hh is absent, Ptc inhibits Smo via an unknown mechanism.[15] By binding to Hh, the Smo-repressing activity of Ptc is inhibited, thus freeing Smo to exhibit its signal activity intracellularly. Smo is located in primary cilia and signals intracellularly to mediate the three Gli zinc finger transcription factors.[16,17] Gli proteins are the last molecules of the pathway and the key final output of Hh. In vertebrates, there are three members in the Gli gene family: *Gli1*, *Gli*2, and *Gli3*. *Gli1* is an Hh response gene product that functions only as a transcriptional activator and is involved in a positive feedback circle upon pathway activation. Gli2 and Gli3 possess opposite functions: Gli2 functions primarily as a transcriptional activator, while Gli3 serves as the primary transcriptional inhibitor.[18] Smo is capable of activating two different intracellular signaling cascades: a non-canonical, ligand-independent pathway that modulates the cytoskeleton by modulating Rac1 and Rho1 GTPases and a canonical, ligand-dependent pathway through Gli2 activation.[18] Smo-regulated canonical signaling pathway involves intracellular activation of Gli2 by limited proteolysis. Full-length Gli2 resides in the cytoplasm linked to a suppressor complex composed of Fused kinase (Fu), Suppressor of Fused (SuFu), and Costal2. Smo activation releases Gli2 from the suppressor complex and transfers it to the nucleus to bind to the gene promoters induced by Hh signaling. Gli2-mediated Hh signaling requires the participation of its receptor Ptc, Hedgehog interacting protein (Hhip), and the transcription factor Gli1.[19] Thus, Gli1, Ptc, and Hhip are general transcriptional targets of canonical Hh signaling activity.[20] In the absence of Ptc ligand, Smo is inactive, thereby inhibiting the transcription of Gli1 and the release of Gli2, and Gli3 is cleaved to generate repressor isoforms (Gli3Rs). When Smo is activated by Ptc, Gli2 is released from the cytoplasm complex; Gli3 repressor function is inhibited; and Gli1 is transcriptionally active, combined together, the final output is generally transcription of Gli1 and Gli2 target genes (Figure 1).[16]

The inappropriate activation of Hh pathway is frequently found in various tumors, including basal cell carcinoma, medulloblastoma, pancreatic cancer, lung cancer, breast cancer, and gastric cancer.[12,18–21] Deregulation of the Hh pathway can occur in cancers either by mutations in key effectors of the canonical signaling pathway or by aberrant expression of Hh itself.[22,23] Some studies have also revealed that CRC cells, which frequently express Hh ligands, are believed to exert paracrine effects on the stromal component of the tumor.[24] However, the role of the Hh signaling pathway in CRC remains controversial.[6] The results vary among studies: according to currently available data, while most studies showed a correlation between Hh and CRC (98 out of 101 studies), there are three researches that claimed that Hh is not, or at least not directly, related to CRC.[25–27] Within the 98 studies, 92 studies confirmed upregulation effects and 5 revealed downregulation effects of the Hh pathway in CRC.[4–35,40,42,47–49,53–113] Moreover, among the studies in favor of a Hh-CRC correlation, its exact function in the formation, proliferation, drug resistance, and metastasis of CRC is not uniform.

Colorectal cancer

CRC is one of the most common gastrointestinal cancers in the world. It is a complicated and often fatal cancer.[28,29] Despite the overall therapeutic improvements, there is still a high disease-related mortality (about 33%).[30] Approximately 90% of the mortality was caused by the metastasis of CRC.[31] Current clinical statistical data show less than 5% 5-year survival for metastatic CRC.[32] The most common type of CRC is sporadic CRC, which makes up to nearly 80%–85% of all CRC cases.[33]

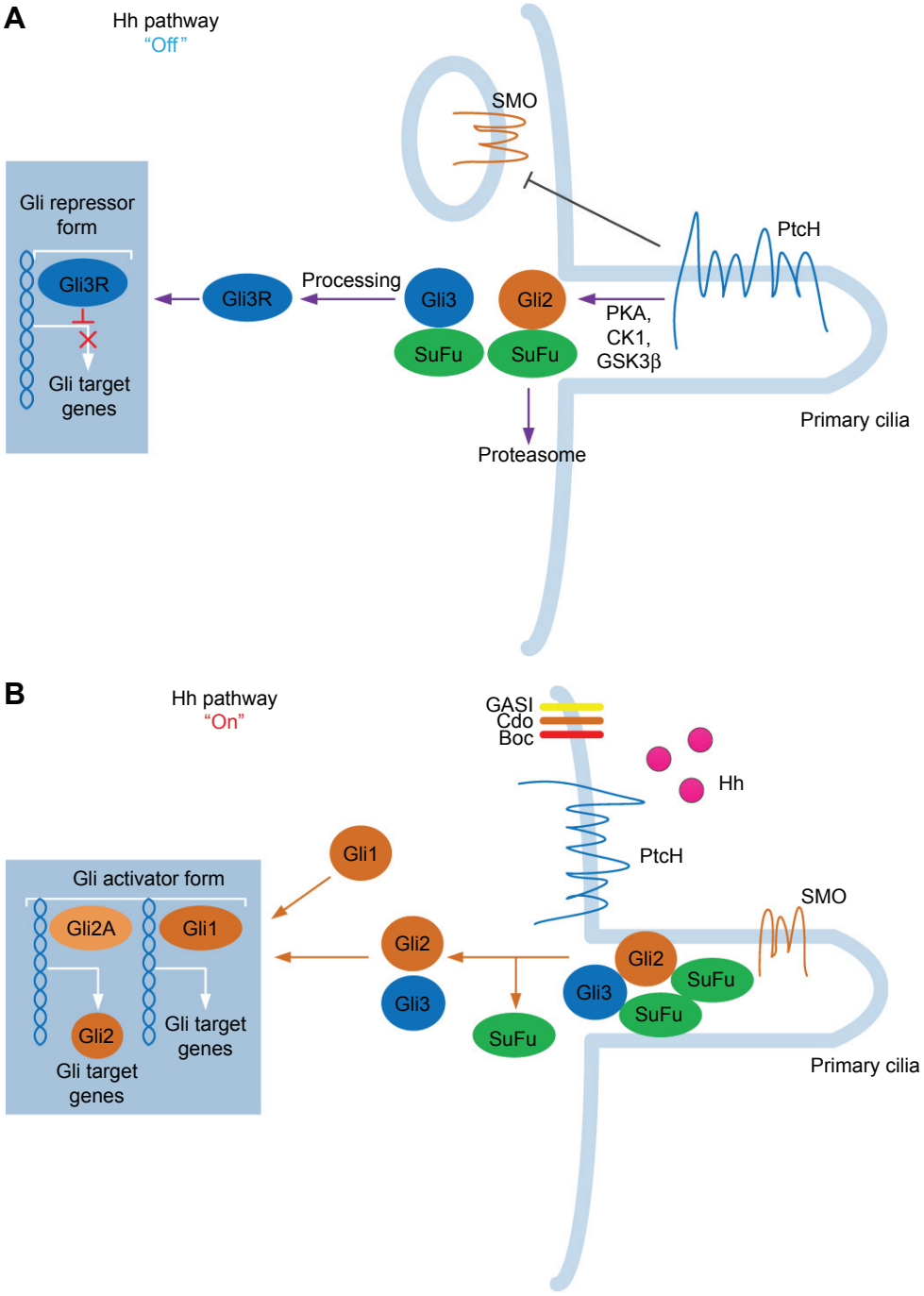

Figure 1 The sketch of Hedgehog (Hh) signaling pathway. The Hh signaling pathway contains three Hh homologs: Sonic Hh, Indian Hh, and Desert Hh. (**A**) When the ligand is absent ("Off" state), the patched (Ptc) receptor inhibits the downstream protein Smoothened (SMO). Henceforth, glioma-associated oncogene homolog (Gli) proteins are sequestered by Suppressor of Fused (SuFu). The Hh pathway is, generally, inhibited at "Off" state. (**B**) After activation of the Hh ligand, Hh proteins are released from the signaling cell. Hh then subsequently binds ("On" state) to PtcH, removing the inhibition and further activating SMO. SMO then regulates the downstream transduction molecules of Gli proteins (Gli1, Gli2, and Gli3). Gli proteins are subsequently transferred to the nuclei and they exert their transduction functions.

The cause of CRC is still not clear; however, there are multiple factors involved in the formation and development of CRC, including age, dietary habits, genetic alteration (mutational activation of oncogenes and inhibition of several tumor suppressor genes), epithelial-to-mesenchymal transformation (EMT) and its reversal in cancer invasion and mucosal healing, and angiogenesis in tumor growth and metastasis.[34–36] Extensive studies have been conducted to explore the molecular mechanisms underlying the tumorigenesis of CRC. Various signaling mutations have been confirmed to contribute to CRC development, including KRAS, MYB, and BRAF (Table 1).[17,19–21] Moreover, Gut

Table 1 Mutations that are correlated in colorectal carcinogenesis

Gene	Chromosomal location	Type of mutation	Prevalence (%)	Function of gene product
KRAS	12p12	Point mutation (codons 12, 13 of exon 2)	40	Cell proliferation and survival
PIK3CA	3q26	Point mutations (E545K on exon 9, H1047R on exon 20)	15–30	Cell proliferation and survival
CDK8	13q12	Gene amplification	10–15	β-Catenin activation
EGFR	7p12	Gene amplification	5–15	Cell proliferation and survival
BRAF	7q34	Point mutations activating kinase activity (most commonly V600E)	5–10	Cell proliferation and survival
CMYC	8q24	Gene amplification	5–10	Cell proliferation and survival
CCNE1	19q12	Gene amplification	5	Cell proliferation and survival
NRAS	1p13	Point mutation	<5	Cell proliferation and survival
CTNNB1	3p22	Stabilizing point mutations and in-frame deletions near N terminus	<5	Regulation of Wnt pathway target genes that promote tumor growth and invasion
ERBB2 (*HER2*)	17q21	Gene amplification	<5	Cell proliferation and survival
MYB	6q22-q23	Gene amplification	<5	Stimulates growth of intestinal stem cells

flora disorder and inflammatory diseases also contribute to CRC generation.[22]

It has now been well illustrated that CRC is derived from the intestinal epithelium and arises as a consequence of the progressive accumulation of genetic and epigenetic changes that drive the transformation and progression of normal colorectal epithelial cells to carcinoma.[37,38] In CRC, cells follow an ordered sequence of events called "adenoma-carcinoma sequence", which starts with the transformation of normal colorectal epithelium to an adenomatous intermediate and then to the adenocarcinoma phase.[39] The pathogenesis of CRC generally ends with the formation of invasive carcinomas that usually metastasize to the liver.[32]

Growing evidence supports the concept that epithelial cancers, including CRC, are diseases driven by the pluripotent, self-renewing cancer stem cells (CSCs).[40] CSCs represent the apex in the hierarchical model of tumor genesis, heterogeneity, and metastasis. They possess the capacity of unlimited self-renewal through symmetric cell division, the ability to give rise to progeny cells through asymmetric division, and an innate resistance to cytotoxic therapeutics.[41] Wnt, Notch, Hh, and/or TGF-β signaling pathways are involved in proliferation and maintenance of CSCs, and dysregulation of these pathways might cause the development of CRC.[42–45] Despite the advancements in diagnosis and targeted and combined treatment, the advanced and metastatic stage of CRC still remains untreatable. Further development in targeting treatment and prevention is one of the major challenges.[36] Prevention of CRC includes various measures including lifestyle modification, identification and early intervention of individuals at risk, and treatment of pre-neoplastic lesions.[37] Some drugs such as aspirin are also reported to be effective in CRC prevention; however, the clinical usage of such drugs was limited due to some side effects.[38]

The prognosis of CRC varies according to factors such as the stage at diagnosis, treatment quality, and individual health status. Identification of new prognostic biomarkers could be a useful tool in predicting disease development and making personalized treatment plans.[48] With the help of TCGA data and other approaches, now studies have located numbers of molecules that might be used as biomarkers.[114–117] Besides the expected biomarkers such as SMAD family member 4, APC, tumor protein p53, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, and KRAS proto-oncogene (KRAS) mutations, frequent mutations in AT-rich interaction domain 1A, sex determining region Y-box 9, and FAM123B/WTX were detected in CRC, indicating that these could be used as specific biomarkers for CRC.[116]

The most important prognostic indicator is stage at diagnosis. The 5-year relative survival of patients diagnosed with CRC is 90% for patients with disease localized to the original sites, 69% for patients with regional spread, and less than 12% for patients with metastasis.[37] CRCs are classified according to local invasion depth (T stage), lymph node involvement (N stage), and distant metastases (M stage).[38] These TNM stages provide most valuable prognostic information and basic treatment guidance. Nevertheless, the outcome and response of individual patient to therapy are variable.[39]

Hh signaling pathway in CRC

Aberrant activation of the Hh signaling pathway is associated with tumorigenesis in various tissues.[46] Up until

now, however, the role of the Hh signaling pathway in the formation and progression of CRC still remains controversial among the studies and researches.[44,47–49] Its exact involvement in the formation, growth, and metastasis of CRC remains enigmatic. Some studies showed no direct correlation between abnormal Hh pathway activation and CRC cells.[25–27] Chatel et al examined the Hh signaling pathway component expression in 7 CRC cell lines and found that aberrant activation of the Hh signaling pathway is not involved in CRC cell lines.[26] Alinger et al also concluded that Hh signaling is involved in differentiation and renewing of the colonic lining epithelium instead of cancer formation, growth, or proliferation.[27] However, such studies either lacked large quantity samplings or failed to acquire a coherent conclusion, and thus are unconvincing.

Through decades of studying and researching, the mainstream idea concerning the role of the Hh signaling pathway in CRC can be concluded by the following aspects: 1) different types of CRCs and CRC cells exhibit different expressions of components in the Hh signaling pathway; 2) the Hh pathway may function in gene mutation, EMT and metastasis, angiogenesis to alter the cell malignancy in CRC; 3) the roles of Hh signaling pathway differ at each stage during the adenoma-to-adenocarcinoma development of CRC; 4) Shh would promote the development of CRC, whilst Ihh would inhibit CRC formation; and 5) the downstream component of the Hh signaling pathway, Smo, may have the most important role in Hh regulation of CRC.[21,48–50]

Hh signaling pathway participates in tumorigenesis of CRC

Despite some studies that fail to conclude a positive correlation of Hh signaling pathway and the development of CRC, the major body of concerning studies has provided a positive correlation between them. Most studies specify that the Hh signaling pathway participates in oncogenesis of CRC. Hh signaling regulates colonic enterocyte differentiation, and the Hh mRNA and protein are highly expressed in CRC cell lines.[51–53] An active Hh-Gli pathway is also found to be displayed in epithelial tumor cells in most human CRC cell lines.[54] Most scholars agreed that a high Hh-Smo-Gli activity is acquired in CRC for tumor cell survival and metastasis, and that the Hh signaling is activated by both canonical signaling (via Smo) and non-canonical activation (via the RAS/RAF pathway) in colon cancers.[32,55,56]

Transcriptional regulation of the Hh signaling response is mediated by Gli genes (*Gli1*, *Gli2*) downstream of Smo, which are also activated by oncogenic signaling pathways. Switching off Hh signaling at the level of Gli induces extensive cell death, in contrast to targeting Smo upstream of Gli.[57] Sénicourt et al further confirmed the participation of the Hh signaling pathway by finding that cilia are present in CRC cells with high expression of Smo and Gli.[58]

Different types of CRCs and CRC cells exhibit different expression of components in Hh signaling pathway

From previous studies we can find that the activation of the Hh pathway is highly incongruent in different CRC types and CRC cell lines, implying that the function of the Hh pathway may be variable according to different CRC cancer types.

For instance, Li et al[1] discovered that Smo expression was not statistically correlated with CRC-specific or overall survival, while in CpG island methylator phenotype-high tumors, CRC-specific survival was distinctively associated with higher Smo expression.[67] The study by Stefanius et al revealed no correlation between Hh and colorectal serrated adenocarcinomas.[59] Hu et al also reported that Hh signals were more frequently expressed in the microsatellite instable group, compared with the microsatellite stable group in CRC.[60] All those studies described that the activation of the Hh signaling pathway is restricted in several types of CRC, but not in other types of cancer.

The Hh signaling pathway may function in gene mutation, EMT and metastasis, cell differentiation, and angiogenesis to alter the malignancy in CRC

The Hh signaling pathway was shown to be multi-functional in the formation of CRC. The involvement of the Hh pathway in gene mutation, EMT and metastasis, apoptosis, and angiogenesis was discovered. Oku et al found that Hh signal is correlated with dedifferentiation at the initial metastasis sites of CRC.[62]

Activation of the Hh signaling pathway is also reported to be associated with Gli1-induced lymphangiogenesis and tumor cell regeneration in CRC, which is correlated to the metastatic ability and drug resistance in chemotherapy of CRCs.[46,63,64]

The participation of Hh signaling pathway differs at each stage in the adenoma-adenocarcinoma process

The development of CRC is now commonly proved by most studies to go through the adenoma-adenocarcinoma process.

Accordingly, the role and importance of Hh signaling pathway vary during each stage of the process.[49,65] Zhang et al found that Smo and Gli1 expressions were enhanced gradually from the normal colon to colonic adenoma and then to the CRC, implying that the role of the Hh pathway may be increasingly enhanced during the process of CRC tumorigenesis.[44] Xu et al noticed that expression of Shh, Ptc, and Gli1 mRNA was gradually increased along the Peutz-Jeghers polyposis (PJP)-adenoma-adenocarcinoma sequence.[66] Peng et al also suggested that aberrant methylation of the Ptc1 promoter would inhibit the expression of Ptc1, which may be an early, initiating event of colon carcinogenesis.[67]

Shh would promote the development of CRC, whilst Ihh would inhibit CRC formation

The Hh signaling pathway conducted by two homologs of Shh and Ihh is of central relevance in cancer genesis.[68,69] Most studies have confirmed the stimulatory function of Shh and inhibitory function of Ihh in CRC formation.[70]

Shh pathway has been reported to have stimulatory function in the process of angiogenesis, cell proliferation, inhibition of tumor suppression genes, and metastasis.[71–74] Many studies have proved that Shh is expressed in CSCs and CRC cell and tumor masses and showed a positive correlation between Shh overexpression and CRC tumorigenesis.[47,75–80] Xu et al examined the expression of Shh, Ptc, and Gli1 in 20 normal tissues and 75 colorectal lesions (25 PJPs, 25 adenomas, and 25 adenocarcinomas) and found that overexpression of Shh may be responsible for the elevated expression of Gli1 in colorectal neoplasms.[66] The results of the clinical trial conducted by Yoshikawa et al indicated that Shh can contribute to the process of adenoma-adenocarcinoma aggravation.[81]

In many studies, downregulation of Ihh has been observed as an early event in the formation of CRC.[82,83] van den Brink et al found that loss of Ihh expression precedes the development of dysplasia in colon carcinogenesis.[51] Gerling et al concluded that Ihh is mainly expressed in stromal tissue in colon. Increased Ihh expression will inhibit the formation of CRC, and stromal Hh can be used as a tumor suppressor.[84] The mechanism of the inhibitory function of Ihh in CRC tumorigenesis is still not quite lucid. van den Brink et al specifically pointed out that Ihh antagonizes Wnt signaling in colonic epithelial cell differentiation.[51] Further studies also confirmed that the activation of Wnt might contribute to the downregulation or loss of Ihh expression in colorectal tumors.[85] Some also raised a hypothesis that upregulation of Ihh expression may work against CRC by inducing differentiation of tumor cells and abrogating the Shh signaling that drives CRC growth.[86]

The downstream components of Hh signaling pathway, such as Smo and Gli, may have the most important role in Hh regulation of CRC

Plenty of studies have pointed out that the downstream components of the Hh signaling pathway are the key to the tumorigenesis of CRC, and the cooperation of Smo and Gli has the most important role in Hh regulation of CRC.[30,66,87–89] Further studies also confirmed that the Hh signaling pathway components Smo and Gli exhibit coordinated expression in colon cancer cell lines.[90] These results give rise to the idea that the downstream components of the Hh pathway may play even more important roles in the tumorigenesis of CRC than the upstream components such as Hh and Ptc, which provides the theoretical basis for the potential of targeting inhibition of Hh signaling at the level of the Gli genes, downstream of Smo, in the treatment of human colon carcinoma cells.[91]

Hh signaling pathway may network with other mechanisms and signaling transductions to cooperate in the tumorigenesis of CRC

The development of CRC is a complicated process involving various mechanisms and factors, and requires a complex of network among different signal transductions. The Hh signaling pathway is also involved in the signaling transductions to orchestration in the tumorigenesis of CRC.[71,92]

Early events in the progression of 90% of sporadic CRCs depend on constitutive activation of Wnt signaling.[93] The role of Wnt signaling is well established in colorectal carcinogenesis.[94,95] Activation of both Wnt/β-catenin and Hh/Gli1 signaling pathways results in the overexpression of cancer-related genes such as *cyclin D* and *Myc* (*c-Myc*), which are involved in cancer development of several malignancies.[96] Both the Wnt and Hh signaling pathways are essential for the normal development of gastrointestinal tissues, and most studies are prone to the thought that they are related to tumorigenesis in gastrointestinal tumors, including CRC.[15,97–100] A study found out that Hh signaling pathway is seldom activated in CRC due to inhibitory regulation by the canonical Wnt signaling pathway, suggesting that Wnt may play a regulating role in the Hh pathway in CRC.[14]

Moreover, several studies proved that Ihh functions as an antagonist of Wnt signaling during colorectal tumorigenesis, and the Hh signaling pathway was recently shown to antagonize the constitutive activity of Wnt pathway that drives proliferation and metastasis of CRC cells, thus establishing an initial antagonizing counterpart between Ihh and Wnt pathways.[12,15,33,37] In human CRC, enhanced Gli1 represses Wnt-TCF targets and is involved in the metastasis of CRC.[101–105] Hh signaling in intestinal epithelium represses canonical Wnt signaling to restrict expression of Wnt target genes in stem or progenitor cells.[48] The current research supports the idea that downregulation of Ihh–Ptc–Gli1 signaling is essential to allow unrestrained Wnt signaling and progression to adenocarcinoma.[18] Some studies also reported that Smo can increase Wnt signaling.[87,106]

Hh inhibitors in the treatment of CRC

Although the relationship between the Hh pathway and CRC remains inconclusive, the application of Hh inhibitors has been practiced in cellular, animal, and clinical experiments.[107] For instance, Meng et al reported that overexpression of SuFu, an inhibitory regulator of the Hh signaling pathway in SW480 (APC^{mut}) colon cancer cells, could inhibit cancer cell growth and tumor formation in nude mice.[108]

The most widely used Hh inhibitor in clinical practice is cyclopamine. Various trials have been conducted to testify the effectiveness of cyclopamine in treating CRC. Many showed promising results, and some found that cyclopamine can significantly reduce apoptosis and decrease proliferation in CRC cells.[31,32] Qualtrough et al found that cyclopamine treatment can induce the expression of E-Cadherin in both benign and malignant colorectal tumor cell lines and can reduce the invasion ability in SW480 cells.[109] Besides cyclopamine, cabozantinib is also reported to effectively reduce EMT potential on another CRC cell line HCT-116's spheres and tumor size and angiogenesis, and suppressed the expression of vascular endothelial growth factor in tumor tissues.[110,111] Moreover, one trial on the oral investigational Hh signaling pathway inhibitor TAK-441 in patients revealed an antitumor activity of the Hh inhibitor TAK-441 in advanced CRC.[113]

Nevertheless, some studies reported that Hh inhibitor cyclopamine did not affect viability of these colon cancer cell lines.[15] Some even showed opposite conclusion and pointed out that Hh antagonists may promote colonic carcinogenesis, induce hypergastrinemia, and lead to increased numbers of Paneth cells with unknown effects on mucosal immunity and that Hh agonists may instead be effective in preventing or treating colon cancer.[18]

In conclusion, Hh inhibitor is promising in treating gastrointestinal carcinoma, but more details about the mechanism of Hh inhibitors in the process of the Hh signaling pathway are needed. Inhibition of different sites in the pathway could be useful in different types of CRC, and thus requires deeper development in Hh inhibitors, more various types of Hh inhibitors and more extensive research into the treatment effect of Hh inhibitors in CRC.[112] Nevertheless, most of the currently available research on the anti-oncogenic effects of Hh inhibitors in CRCs are limited to in vitro and in vivo levels. Further explorations of the effectiveness in human are required to confirm the clinical effect and acquire more knowledge on Hh functions of tumorigenesis.

Discussion

Based on all the researches and findings, we concluded that the Hh signaling pathway may play a crucial role in the tumorigenesis of CRCs.[4–35,40,42,47–49,53–113] Although its exact role remains controversial, the expression of the Hh pathway in CRC tissues is much higher than in normal colon tissues, especially Shh and its signaling pathway components. Removals of certain parts in Shh pathway could lead to failure of cell development, proliferation, metastasis, and tumor sustenance in CRC, according to multiple studies.[17–24]

Shh is now considered to likely promote formation and metastasis of CRCs.[24,35] It is believed that overexpression of Shh and its downstream components is highly correlated with the formation and metastasis of CRCs, whereas it's detailed mechanism remains unclear. Some studies revealed that it is a paracrine factor and works with the inhibition of anti-oncogenes, like p53.[41] More studies showed that it is also linked to other important signaling pathways, like Wnt/beta-catenin; together they perform the function of sustaining and proliferation of CRC cells and lead to the final formation of CRCs.[11,14,37] Ihh is another important ligand in Hh family. Research shows that it is mainly expressed in stromal tissues in the colon, and it has the suppressive effect of CRC.[92] More studies are required for further exploration of the Hh pathway and its function in CRCs.[66]

Hh inhibitor is considered as one of the therapeutic methods in treating cancers. Its application in treating CRC has been reported and received promising results, implying that the development of signaling pathway targeting treatment in CRC is a promising path for antitumor treatment.[27,113] More details about the mechanism of Hh inhibitors in the Hh pathway are needed. Inhibition of different sites in the pathway could be useful in different types of CRC.[89]

Thus, deeper development of Hh inhibitors, more various types of Hh inhibitors and more extensive research on the treatment effect of Hh inhibitors in CRC is needed.

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Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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