Editorial

Hedgehog signaling in colorectal cancer: a spiny issue gets smoothened

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The Hh pathway has been recognized as one of the major regulators of cell growth and differentiation during embryogenesis and early development of vertebrates (1). Generally, it is inactivated in adults but reactivation via inappropriate mutation or deregulation of this pathway may play a crucial role in tumor development. Activation of canonical Hh signaling occurs when one of the ligands, i.e., Sonic (Shh), Desert (Dhh) or Indian (Ihh) Hedgehog binds to its receptor Patched 1 (PTCH1). This relieves the repression of Smoothened (SMO) by PTCH1, thereby initiating a signaling cascade that leads to the activation of the Glioma-associated oncogene (GLI) transcription factors, which will translocate to the nucleus and promote transcription of the Hh target genes. There are 3 different GLI proteins (GLI1, GLI2 and GLI3), of which only GLI1 is induced by Hh and constitutes a reliable marker of pathway activation. To date, numerous target genes have been described which are involved in feedback mechanisms (e.g., *HHIP*, *PTCH1*, *GLI1*), cell cycle regulation (e.g., *CYCLIN D1/2*), proliferation (e.g., *PDGFR*, *MYC*) apoptosis (e.g., *BCL2*), angiogenesis (e.g., *VEGF*, *ANG1/2*), epithelial-mesenchymal transition (EMT; e.g., *MMP9*, *SNAIL*) and self-renewal (e.g., *NANOG*, *SOX2*) (2), representing a broad spectrum of mechanisms by which the Hh signaling pathway can be involved in carcinogenesis.

To explain the role of Hh pathway in carcinogenesis, three mechanisms have been put forward in various types of cancers (3). First, in type 1, a ligand-independent signaling is driven by mutations mainly in the Hh pathway components. However, most tumors do not harbour recurrent driver somatic mutations in the Hh signaling pathway. Rather, these cancers demonstrate activation of ligand-dependent signaling in an autocrine (type 2) or paracrine (type 3) manner (3,4). The autocrine signaling refers to the mode that Hh ligand produced by tumor cells stimulates the Hh signaling in tumor cells; and the paracrine signaling is regarded as the one that tumor cell produced Hh ligand activates stromal and endothelial cells, which produce growth factors in microenvironment to support tumor growth and survival.

The importance of Hh signaling has been widely recognized among oncologists since the 2012 approval by the US Food and Drug Administration (FDA) of vismodegib (GDC0449; Roche), a small molecule anti-SMO, for the treatment of advanced basal cell carcinoma (BCC) (5). A Phase II randomized clinical trial of vismodegib in combination with FOLFOX1 or FOXFIRI in 195 patients with previously untreated metastatic CRC found no extension of progression-free survival (6). This disappointing outcome highlights the notion that the Hh pathway is highly complex and interactive with other signaling molecules in cells. Although disappointing, this result is consistent with preclinical observations that SMO inhibition has minimal cytotoxic activity in colon cancer cells (7,8). GLI1 inhibition has been suggested as an alternative toward an effective way to block the pathway with high cytotoxic efficacy (8) but this obviously needs further evaluation in clinical trials.

In the normal adult gastrointestinal tract, induction of the Hh pathway appears to protect the differentiated epithelial cells of the villous surface, counteracting the canonical Wnt signaling in the basal cells of the crypt (9).

Although aberrant activation of the Hh pathway has been demonstrated in the oncogenesis of human esophageal, gastric, and pancreatic cancers (10), its role in colon cancer has not been sufficiently clarified. The majority of sporadic and hereditary human colorectal tumors are believed to originate from constitutive activation of Wnt signaling by mutation of the APC or β-catenin genes (11), whereas the Hh pathway would oppose the proliferative effect of Wnt pathway on differentiated colonocytes (9). Recently, there has been evidence of the potential involvement of Hh signaling in cancer invasiveness (12), in colonic carcinogenesis (13,14), and in the metastatic dissemination of colorectal cancer (15). Nevertheless, approaches to elucidate the role of the Hh pathway in cancers are still limited, in particular in colon cancer where data have been controversial (7,16).

Gerling *et al*. (17) shed light on the role played by Hh in colorectal tumorigenesis. Using Gli1 reporter mice in the AOM/DSS model of colitis-associated colon cancer, they provided evidence that downstream Hh signaling activity is reduced in murine colon tumors stroma despite high Ihh expression in the tumor cells. This might be the result of alterations in stromal gene expression programs that render stromal cells indifferent to epithelial ligands or of insufficient ligands concentrations to activate downstream Hh signaling in the stroma, due to disrupted tissue architecture during tumorigenesis. Moreover, the stromal downstream Hh signal was diminished in areas of high epithelial Wnt activity and low epithelial BMP signaling. Furthermore, Gerling *et al*. showed that Vismodegib administration to wild type mice or the use of inducible epithelial specific Ihh knockout mice led to increased tumor burden in the AOM/DSS model, thus demonstrating that Hh inhibition can fuel colon tumorigenesis. On the other hand, the specific activation of Hh signaling in Col1a2 expressing stromal cells had a protective effect on colorectal carcinogenesis, largely mediated in a Smo-dependent manner. Gene expression analysis revealed that Hh activation led to reduced expression of colonic stem cell-signature genes and a marked reduction in secreted BMP inhibitors such as Gremlin 1 (GREM1). BMP signaling has been regarded as tumor-suppressive in colorectal cancer (CRC) by reducing cancer cell proliferation and invasion, and by impairing epithelial-to-mesenchymal transition (EMT) (18). The authors assumed that loss of stromal BMP inhibitors due to the activation of stromal Hh signaling may have the potential to restrain colonic tumor initiation and progression. Indeed, the stroma specific activation of Hh signaling in established tumors caused an increase in epithelial BMP signal activity and resulted in a permanent macroscopic growth arrest and, in the case of smaller lesions, in regression, whereas tumors in control animals progressed. Finally, the authors re-assessed Hh expression in different CRC cohorts, including the pathway downstream targets. The analysis confirmed that human colon cancer harbours a marked decrease in Hh downstream target gene expression despite upregulated expression of the ligand SHH.

Gerling's data (17) point to the possibility that treatment with Hh antagonists could increase the risk for several solid malignancies including CRC and caution should be warranted particularly when using Hh antagonists in patients with inflammatory bowel disease, who are at increased risk of CRC. Moreover, these data may explain the negative results of the recent trial on patients with metastatic pancreatic cancer, in which the addition of vismodegib to gemcitabine did not improve overall response rate, progression free survival, or overall survival independently to drug delivery or treatment efficacy (19). There would be requirement of drugs that specifically control the stromal hedgehog signals, though they may not have a complete beneficial therapeutic response as the tumors have variable needs depending on the activation of stromal components induced by hedgehog pathway. Moreover, sporadic colorectal carcinogenesis is characterized by, and is dependent on, a complex inflammatory cell infiltrate. A role for Hh in modulating the immune infiltrate in the colon cannot be excluded and previous studies have suggested that stromal Hh signals can act as modifiers of the intestinal immune response (20,21). Emerging preliminary evidence implicates Hh signaling activation in immune system suppression as a result of the pathway ability to downregulate MHC I which suppresses cytotoxic T cell tumor cell clearance, upregulate SOCS1 which inhibits STAT1 signaling, and upregulate STAT6 which promotes T cell polarization toward the Th2 phenotype. All three properties result in diminished immune system function against tumors and the promotion of pro-tumorigenic functions by T cells (22). Though Hh signaling seems to be connected to impaired T cell activation, some reports confirm Hh activation is linked to cytotoxic T cell activation; this T cell-induced cytotoxicity was abolished upon using SMO and GLI inhibitors (23). This dual activity is unsurprising for Hh signaling, as it is important in T cell development (24); however, in the presence of pathological conditions, the functions of the pathway could shift. Indeed, in a tumor-like hypoxic environment, the Hh

inhibitor cyclopamine significantly inhibited monocyte-derived dendritic cell induction, migration, chemotaxis, phagocytosis, maturation, IL-12 p40 or p70 secretion and the allogeneic lymphocyte stimulation activity (25). Hh signaling is evidently involved in suppressing host immunity to promote tumor growth by activating T regs, MDSCs, and the Th2 phenotype that promote angiogenesis and extracellular matrix remodeling (22).

Although Hh inhibitors effectively treat BCC, their usage in treating other tumor types potentially carries significant risks, therefore, the mechanisms of Hh signaling should be critically evaluated in specific tumor types prior to commencing Hh inhibitor clinical trials in patients.

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Footnote

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