Hedgehog Pathway

Subjects: Oncology

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The hedgehog pathway, which plays a significant role in embryonic development and stem cell regulation, is activated in gastrointestinal cancers. Chemotherapy is widely used in cancer treatment. However, chemoresistance becomes a substantial obstacle in cancer therapy.

Keywords: the hedgehog pathway ; chemotherapy ; resistance ; gastric cancer ; colorectal cancer ; pancreatic cancer

1. Introduction

The hedgehog (HH) pathway plays a crucial role in embryonic development, tissue homeostasis, and carcinogenesis [1][2]. HH ligands activate signaling by binding to receptor patched 1 homolog (PTCH1). In the absence of HH ligands, PTCH1 prevents smoothened (SMO) from transducing a signal to the downstream glioma-associated oncogene homolog (GLI) transcription factors. HH ligands bind to PTCH1, and relieve PTCH1's inhibition on SMO, allowing SMO to signal downstream effectors GLI, which activates the target genes via specific genomic DNA sequences (TGGGTGGTC) [3][4].

Activation of GLI proteins via the HH–PTCH1–SMO axis is regarded as the canonical HH signaling pathway. In addition to the canonical pathway, some molecules can bypass the ligand-receptor signaling axis to activate GLI, and these types of regulation are regarded as non-canonical HH signaling. Non-canonical HH signaling is found in malignant diseases. KRAS signaling [5][6], transforming growth factor β (TGFβ) [7], AKT [8], protein kinase C (PKC) [9], and SOX2-bromodomain-containing protein 4(BRD4) [10] are reported to regulate HH signaling via non-canonical pathways.

Chemotherapy is widely used in cancer treatment, and significant improvement is achieved in the prognosis of patients. However, not all patients benefit from it. Chemoresistance becomes a substantial obstacle in cancer therapy due to intrinsic resistance, which occurs at the beginning or even before the treatment, or acquired resistance after initial response to treatment, resulting in relapse [11][12]. Platinum, 5-Fluorouracil (5-FU), and gemcitabine are the most commonly used drugs in the chemotherapy of gastric, colorectal, and pancreatic cancers, and the underlined mechanisms of drug resistance have been studied. Mechanisms of chemoresistance include cancer stem cells(CSCs), tumor microenvironment, and ATP-binding cassette (ABC) transporter family proteins [13][14][15].

Our group studied drug resistance in gastrointestinal cancers and found the HH pathway contributes to drug resistance.

2. New Drugs and Therapeutic Strategy

The HH inhibitors vismodegib and sonidegib have been approved by the Food and Drug Administration to treat recurrent, locally advanced basal cell carcinoma (BCC) or metastatic BCC, or for those who are not eligible for surgery or radiotherapy. The efficacy and safety of vismodegib and sonidegib have been reviewed in [16]. Vismodegib and sonidegib are also used in clinical trials for other solid tumors (medulloblastoma, prostate cancer, pancreatic cancer, and small cell lung cancer) and hematologic malignancies (actively reviewed in [17][18]).The results from these clinical trials show that the HH inhibitors only promote treatment efficacy in HH-driven cancers.

Since current therapy is still far from satisfactory, novel drugs and new therapeutic strategies were developed to improve the treatment. Novel HH inhibitors also have been developed. GDC0449 analog MDB5 [19] and GLI1 inhibitor NanoHHI [20] overcame SMO mutation and improved the treatment effect. Other drugs, such as curcumin, sensitized colorectal cancer to chemotherapy through downregulating HH signaling [21], and Dpc [22], ormeloxifene [23], Patched 1-interacting peptide [24], and metformin [75] targeted HH signaling was found to reduce the tumor-associated stromal tissue in pancreatic cancers.

Due to dense stromal tissue, chemotherapeutic and targeted drugs, immune cells are hard to get to cancer cells; therefore, targeting stromal cells is a new promising strategy in pancreatic cancers. Since the HH pathway contributes to the development of the dense stromal tissue, several studies combined SMO inhibitors with either cytotoxic

chemotherapeutic drugs [25][26][27] or a targeted antibody [28] to increase the delivery of the drugs and promote tumor infiltration of the CD8 T cells. Inhibition of the HH pathway increased intratumoral vasculature density. Some studies found that SMO inhibitors reduced collagen, α-SMA, and GLI-1 expression [25][28]. However, another study found that SMO inhibitor did not decrease the α-SMA-positive fibroblasts and type I collagen in the stroma [26], indicating more studies should be performed to identify the mechanisms how SMO inhibitors increase the delivery of drugs. Furthermore, research suggested that combined the hepatocyte growth factor (HGF)/c-Met and HH pathways inhibitors overcame the resistance to the single-inhibitor treatment and led to sensitization to the gemcitabine treatment [29]. Despite the promising results above and the excellent responses to sonidegib in a mouse model [30], vismodegib does not show improvement in metastatic pancreatic adenocarcinoma (NCT01088815, NCT01064622, [31]). The preclinical model may not accurately reflect the tumor context of patients; patient-derived xenografts, and maybe in the future, patient-derived 3D culture models with tumor cells and a microenvironment, are better materials for studying the efficacy and mechanisms of action of therapeutic drugs.

3. Conclusions and Perspectives

Accumulating data suggest that the HH pathway plays an important role in chemoresistance in gastrointestinal cancers. CSCs are the well-known cause for drug resistance and are extensively studied in gastric, colorectal, and pancreatic cancers, and the HH pathway is a promising target for eradicating CSCs. Due to the dense stromal tissue in pancreatic cancers, the role of HH signaling in PSCs is actively being investigated. Inhibition of the HH pathway in PSCs reduces stromal tissue and increases drug delivery, suggesting that HH signaling may also play a mechanical role in chemoresistance. However, studies focused on the HH pathway in the TME of gastric and colorectal cancer chemoresistance are relatively scarce. Despite the different pathological characteristics in gastric, colorectal, and pancreatic cancers, the HH pathway regulates the ABC transporter family proteins in all three types of cancer.

Studies from gastrointestinal cancers and their CSCs provide evidence for the existence of both canonical and non-canonical HH signaling, which do sound the alarm to us. Inhibition of SMO may not inhibit HH activation, and this may partially explain the dismal results of vismodegib in some clinical trials for advanced solid tumors. Identifying how HH signaling is activated, caused by either a ligand-dependent or ligand-independent mechanism, may help us choose the correct inhibitors to attenuate activation of the HH pathway in different cancer contexts.

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