Review Article

Hedgehog signaling pathway and ovarian cancer

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Abstract: Epithelial ovarian carcinoma (EOC) is the most common form of ovarian malignancies and the most lethal gynecologic malignancy in the United States. To date, in spite of treatment to it with the extensive surgical debulking and chemotherapy, the prognosis of EOC remains dismal. Recently, it has become increasingly clear that in many instances, the signaling and molecular players that control development are the same, and when inappropriately regulated, drive tumorigenesis and cancer development. Here, we discuss the possible involvement of Hedgehog (Hh) pathway in the cellular regulation and development of cancer in the ovaries. Using the *in vitro* and *in vivo* assays developed has facilitated the dissection of the mechanisms behind Hh-driven ovarian cancers formation and growth. Based on recent studies, we propose that the inhibition of Hh signaling may interfere with spheroid-like structures in ovarian cancers. The components of the Hh signaling may provide novel drug targets, which could be explored as crucial combinatorial strategies for the treatment of ovarian cancers.

Key Words: Hedgehog signaling; ovarian cancer; targeted therapy

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Introduction

Epithelial ovarian carcinoma (EOC) is the most common form of ovarian malignancies and the most lethal gynecologic malignancy in the United States, accounting for almost 90% of all ovarian malignant tumors, with approximately 22,000 new cases and 16,000 deaths occurring annually (1,2). It is diagnosed often in advanced stage, owing to the absence of specific signs and clinically significant symptoms and the lack of effective screening programs including appropriate tumor markers, which contributes to the low 5-year relative overall survival of ovarian cancer patients at 46%. As we know, if diagnosed at the localized stage, the 5-year survival rate would be up to 93% (2). To date, the major clinical problems associated with ovarian cancers remain unresolved including malignant progression and rapid emergence of drug resistance. Despite intense scientific research and improved clinical technology, once EOC enters into late stage, even with the extensive surgical debulking and chemotherapy, its prognosis remains dismal (3).

As an important regulatory module during development, the Hedgehog (Hh) signaling pathway can control a variety of developmental processes such as proliferation, differentiation and organogenesis (4). Recently, it has become increasingly clear that in many instances the signaling and molecular players that control development are the same, and when inappropriately regulated, drive tumorigenesis and cancer development (5-13). Here, we discuss the possible involvement of this pathway in the physiologic process and development of cancer in the ovaries. The components of the Hh signaling may provide novel drug targets, which could be explored as crucial combinatorial strategies for the treatment of ovarian cancers.

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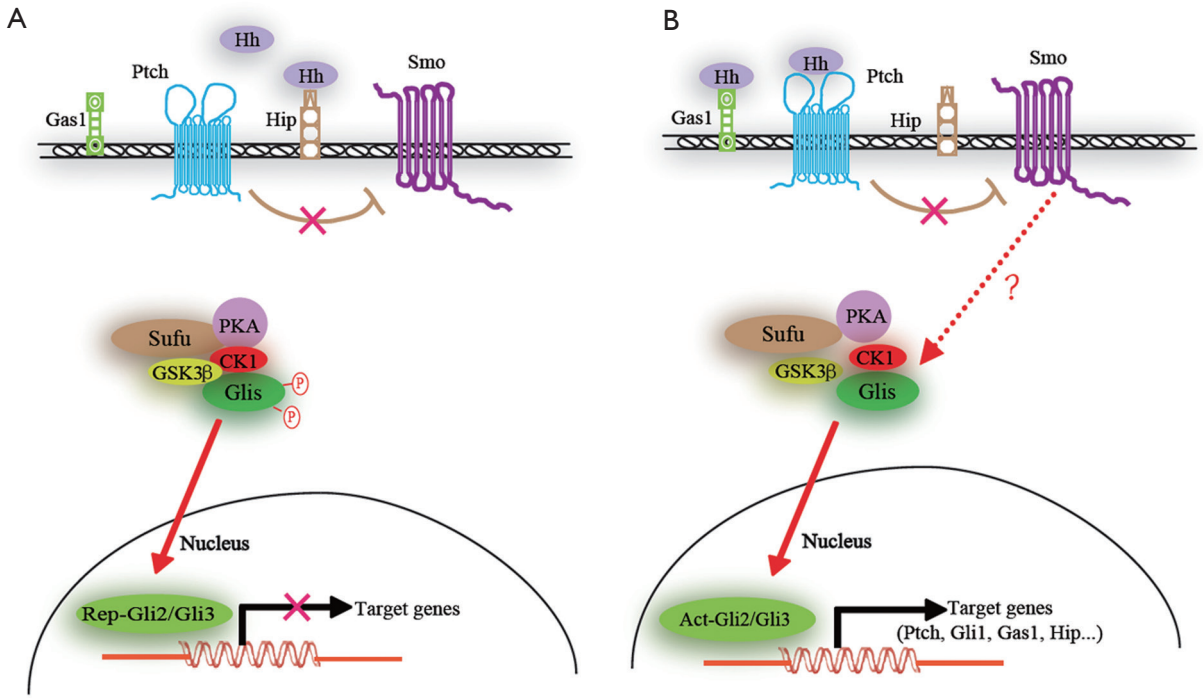

Figure 1 The constitutive components and the transduced mechanisms of Hh signaling pathway. A. In the absence of Hh ligand, the latent Gli transcription factors Gli2/3 are bound to a multiprotein complex with the negative regulator Sufu. Phosphorylation of Gli2/3 by PKA, GSK3β and CK1 targets latent Gli proteins to proteasome-dependent repressor formation (Rep-Gli2/Gli3) that cannot activate target gene transcription upon binding to DNA in the nucleus; B. Upon binding of Hh ligand to its receptor Ptch, Ptch translocates out of the primary cilium, losing its ability to inhibit Smo, which moves into the cilium, thus stimulating the pathway and preventing Gli2 and Gli3 cleavage. The activated forms of Gli2 and Gli3 bind to Gli-promoters in the nucleus and stimulate transcription of the ubiquitous mammalian target genes

Constitutive components and transduced mechanisms of Hh signaling

In comparison with *Drosophila*, in humans, Hh/Gli signaling pathway consists of three ligands, Sonic hedgehog (Shh), Indian hedgehog (Ihh) and Desert hedgehog (Dhh), which can all bind to the 12-pass transmembrane receptor Patch (Ptch) and are expressed at different stages of tumorigenesis in different tissues and may have distinct biological functions (4). When the processed and lipid modified Hh ligand binds to its receptor Ptch, the canonical Hh signal transduction is initiated, resulting in that the inhibitory function of Ptch on the 7-pass transmembrane protein Smoothened (Smo) is abolished and then Smo activates the final arbiter of Hh signaling, the Gli family of transcription factors. Ultimately, the Gli family of Gli1, Gli2 and Gli3, transcriptionally regulates Hh target genes by binding to the specific elements in promoter sequences (14-16). The exact mechanism of signal transduction within the cascade from Smo to Gli proteins is unclear, and the emerging data suggest that primary cilium serves as the processing sites for Gli transcription factors (17), involving a multi-protein complex comprising of a subset of intraflagellar transport proteins, protein kinase A (PKA), glycogen synthase kinase 3β (GSK 3β), casein kinase 1 (CK1), the suppressor of fused (Sufu) and so on (18-21) (*Figure 1*). Of these, Sufu is thought to play a key role in negatively regulating Hh/Gli signaling, since targeted disruption of the murine Sufu gene leads to the similar phenotype caused by an excess of Hh signaling (22,23).

Gli proteins seem to have context-dependent repressor and activator functions. Gli1 functions as the terminal and thus a critical transcriptional activator of the Hh pathway and its function is reinforced by a positive feedback loop as its transcription is induced by Hh signaling (24,25). Gli2 can act as an activator or repressor, whereas Gli3 can serve as a weak activator, mainly functions as a repressor of transcription (26). Gli1 and Gli2 have been shown to have distinct as well as overlapping functions. Three Gli proteins operate together

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to integrate intercellular Hh signaling and other input, and each can have positive or negative effects (27,28).

Different states of the Gli code can give rise to different or partially overlapping sets of target gene expression profiles, then further facilitate distinct cellular responses (29,30). It is not surprising that deregulation of Hh signaling can cause various diseases including malformations and tumors because of its broad range of direct or indirect targets in different cellular contexts.

Many feedback regulatory mechanisms are employed in Hh signaling pathway. Ptch, Hedgehog interacting protein (Hip), growth arrest specific protein1 (Gas1) and Gli1 are not only the components of the Hh signaling pathway, but also its target genes. Ptch and Hip can negatively regulate the Hh signal, while Gli1 can positively regulate it. Hh signal can downregulate the expression of Gas1, simultaneously, Gas1 functions as the positive regulator of the Hh signal. Aberrant regulations can result in abnormal Hh signal and the expression of specific genes that promote cell proliferation or differentiation.

Hh signaling pathway and carcinogenesis

The Hh signaling pathway is a morphogenesis signaling pathway, which is crucial for the growth and patterning of various tissues during embryonic development (31-36). Cancers occur in various organs after adolescence, suggesting that they are derived from cells harboring mutations that generally occur in genes that control embryonic morphogenesis after the embryonic stage. In the adult, the Hh signaling is significantly reduced, with the remaining activity mostly involved in tissue maintenance and repair, and regulating stem cell behavior in several instances (37,38). Hh signaling has been reported to be reactivated in many types of cancers in ligand-dependent manner (39-42) or ligand-independent manner (5-7,43-45), contributing to carcinogenesis and cancer progression. Whereas the former activation is caused by the overexpressed Hh ligand derived from tumor cells or stroma cells, the later activation is due to mutations of the components within the Hh signaling pathway such as Ptch, Smo and Sufu. Non-canonical Gli activation mediated by epithelial epidermal growth factor receptor (EGFR) or transforming growth factor-β (TGF-β) signaling further activate their downstream targets (46,47) (*Figure 2*). It therefore renders cancer cells resistant to Smo antagonists.

Recent studies of human tumors, such as glioblastoma, pancreatic adenocarcinoma, chronic myeloid leukemia and colon cancer, suggest that Hh signaling regulates cancer stem cell (38,48-52). Both the clonogenicity and tumorigenesis of human cancer stem cells depend on sustained Hh-Gli signaling. It was demonstrated that the Hh signaling components Ptch1, Gli1 and Gli2 are highly expressed in normal human mammary stem/progenitor cells and that these genes are downregulated when differentiation is induced in these cells (53). Thus, the Hh signaling pathway might play a critical role in the continuous self-renewal of tissues from stem cells.

The Hh signaling pathway is known to contribute to cancer invasiveness and metastasis. A report showed that Notch and Shh facilitate neovascularization, angiogenesis, and epithelial-mesenchymal transition (EMT), and contribute to the maintenance of highly-metastatic tumor stem cells (54). Recently, Souzaki M *et al.* found that the Hh signaling pathway mediates the progression of non-invasive breast cancer to invasive breast cancer (55). It is known that the activation of Hh signaling is involved in the cell cycle progression and invasion of various tumors, including prostate cancer, pancreatic cancer and gastric carcinoma and so on (56-58). Among these, the contribution of Hh pathway to invasiveness was first documented in prostate cancer. As to gastric cancer, the report suggested that Shh signaling promotes motility and invasiveness of it through TGF-β-mediated activation of the Alk5-Smad3 pathway. Combined, these studies suggest that Hh signaling affirmatively contributes to cancer invasion and metastasis.

Cancer therapy targeting hedgehog signaling

Because of the widespread involvement of the Hh pathway in cancers that controls fundamental cellular processes such as cell growth and death, the promising therapeutic strategies against cancers may be developed through the modulation of the Hh pathway in the near future. Several approaches to block this pathway are under development. Sustained application of specific Hh pathway inhibitors has been proven effective in preventing growth of many tumors *in vitro* (49,59) and in xenografts (60,61).

Small molecular modulators of Hh signaling have been an intense interest in recent years, and the last few years have brought a significant increase in the identification of related inhibitors (62-66). The natural product alkaloid cyclopamine was one of the first small-molecule inhibitors of the Hh pathway to be reported (67). To date, the majority of reported Hh pathway inhibitors target Smo including cyclopamine, IPI-926, GDC-0449, BMS-833923 and so on, and several have advanced to human clinical trials,

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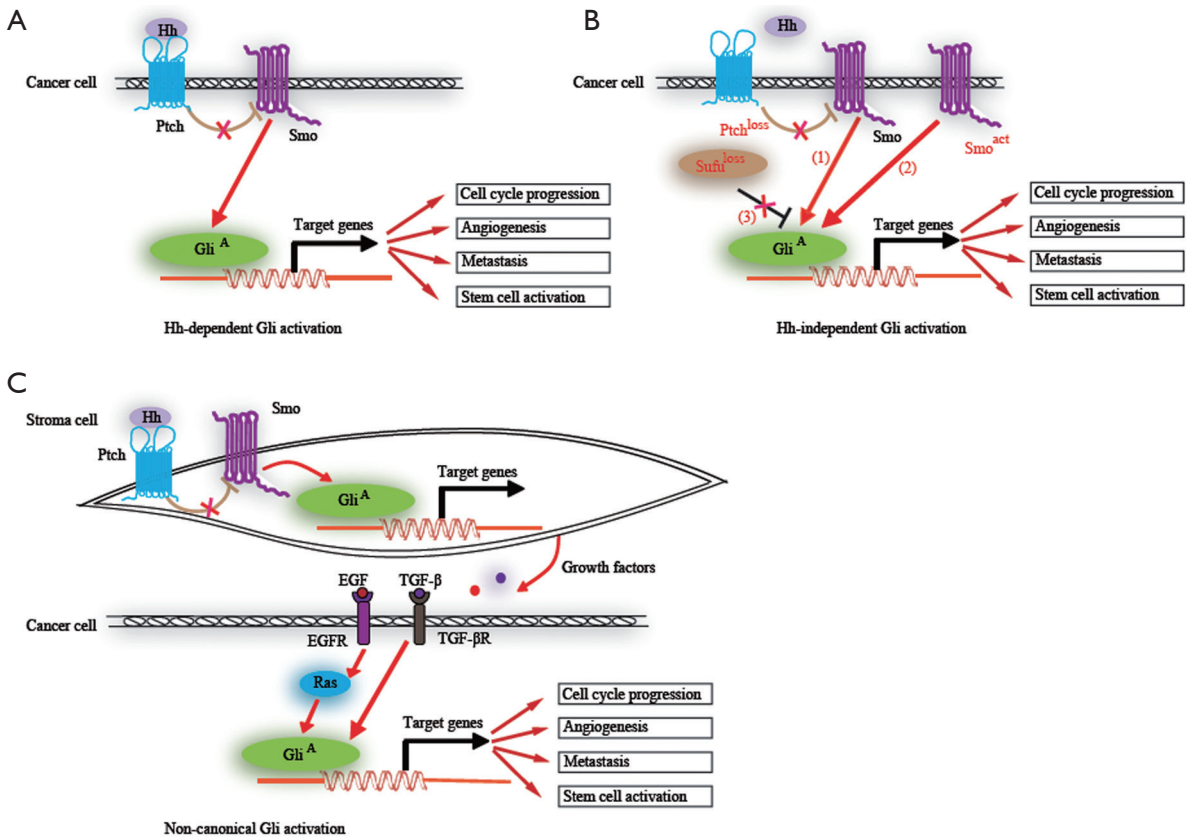

Figure 2 The different models of Hh signaling pathway activation in cancer. A. Hh-dependent Gli activation. Prostate, lung and pancreatic cancer have been shown to depend on the presence of Hh ligand. These tumors display constitutively elevated activity that is likely to be due to increased ligand (Hh^{high}) and Smo (Smo^{high}) expression; B. Hh-independent Gli activation. Ligand-independent tumor growth has been shown to arise from loss of Ptch or Sufu repressor function ($Ptch^{loss}$, $Sufu^{loss}$) or activating mutations in the Hh-effector Smo (Smo^{act}); C. Non-canonical activation. In epithelial tumor cells, TGF-β signaling has been shown to activate the transcription of Gli, whereas epidermal growth factor (EGF) and/or Ras signaling promotes Gli^{A} function through the kinase cascade. In these models, ligand-dependent, ligend-independent and non-canonical activation are characterized by an increase in Gli^{A} activity and Gli target gene expression. Possible oncogenic routes activated downstream of Hh/Gli such as proliferation, and survival, metastasis and stem cell activation are driven by (direct) transcriptional stimulation of key regulators of these processes

which have different molecular mechanisms respectively. The impact of terminating Hh signaling at the level of Gli genes on the tumorigenesis is little known. Few agents are available that target Gli genes, which constitute the final step in the Hh pathway, whereas, GANT61 was identified as a more effective small molecular inhibitor of Gli in comparison with Smo, which induced extensive cell death or apoptosis in cancer cell lines *in vitro* and prohibited additional tumor growth in the xenograft assays through inhibiting the expression of the target genes downstream of Gli (10,60). More recently, as the first reported inhibitor of Shh, robotnikinin was identified to bind to the transmembrane receptor Ptch, reversing its inhibitory effect on Smo (68,69). Collectively, these Hh signaling inhibitors have brought about the expectation that the Hh signaling pathway could provide effective approaches for cancer therapy. In order to implement the individualized therapy with all Hh pathway-dependent cancers, we must select the appropriate inhibitors corresponding to the molecular mechanism of altered Hh pathway.

Hh signaling pathway and ovarian cancer

Hh signaling has not been found in the mature vertebrate

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ovary (70), while it was identified to act specifically on the stem cells in *Drosophila* ovary (71). These stem cells are responsible for the regulated repair of the surface epithelium after the ovulatory rupture (72). Under abnormal conditions that lead to enhanced Hh signaling, these stem cells might ultimately transform into cancer stem cells and lead to malignant progression (73,74).

It is generally accepted that ovarian epithelial cancer derives from ovarian surface epithelium (OSE) that covers the ovary. As we know, by comparison with mesothelia elsewhere, OSE is a simple, rather primitive mesothelium with both epithelial and mesenchymal characteristics, which retains the properties of relatively uncommitted pluripotent cells and has the ability to differentiate diversely in response to different stimuli (75). Apart from other cancers, OSE becomes more committed to an epithelial phenotype in association with increased E-cadherin expression (75,76) when it progresses to malignancy, through adherens junction mediated by E-cadherin, tumor cells can often aggregate and form spheroid-like structures that followed by implanting and invading into intra-abdominal tissues (76-78). Ray A *et al*. demonstrated that Hh signaling pathway can regulate the growth of ovarian cancer spheroid forming cells, which have the properties of cancer stem cells of self-renewal, differentiation, and chemoresistance (79).

Recently, aberrant activation of Hh signaling pathway has been reported in ovarian cancers (80). In this report, the authors indicated that Hh signaling pathway is activated in ovarian carcinomas, concerning cell proliferation, while, its inhibition precipitates growth suppression and cancer cells apoptosis. They found that Dhh expression was correlated with poor prognosis of patients with ovarian carcinoma. Bhattacharya R *et al*. found that the upregulation of the Hh pathway was present in primary ovarian tumors and all of the human ovarian cancer cell lines tested. They proposed that the Hh pathway can help maintain the clonal growth of human ovarian carcinoma-derived cell lines (81). Liao X *et al*. showed for the first time that overexpression of Gli1 and Patched was correlated with poor clinical outcome in ovarian cancers, which provided a molecular basis for the role of Hh pathway in ovarian cancers (82). In contrast to previous reports, Yang L *et al*. documented that they only detected a small proportion of ovarian cancers with Hh signaling target gene expression. They suggested that activation of the Hh pathway would not be frequent in ovarian cancers (83). Schmid S *et al*. found that a subset of patients with ovarian cancer (25%) in their study had increased expression of the Hh signaling and transcription factors Gli2 (84). The published data concerning the Hh signaling pathway in ovarian cancer are contradictory, which is probably resulted from the cross talk between Hh and other signaling pathways.

As mentioned above, abnormal Hh signaling plays important roles in the development and progression of ovarian cancers, which has been further verified through some *in vitro* and *in vivo* studies. Accordingly, the inhibition of Hh pathway might be a valid therapeutic strategy for ovarian cancers. Treatment with a monoclonal antibody against Shh resulted in a dose-dependent decrease in cell proliferation (81). Similarly, treatment of cultured ovarian cancer cells with the Smo inhibitor cyclopamine has been found to induce cell cycle arrest in G1 and promote apoptosis (80). McCann CK *et al*. showed that inhibition of Hh signaling by the inhibitor IPI-926, a derivative of cyclopamine with increased oral bioavailability and a longer half-life, antagonized serous ovarian cancer growth in a primary xenograft model (85). In addition, ovarian carcinoma cell lines-derived xenografts are also susceptible to Hh pathway inhibition as their growth is markedly impaired following treatment with cyclopamine (81). To date, all studies that determine the effect of the Hh inhibitors on growth and progression of ovarian cancer were targeted to Smo. Less is known about whether the therapeutic approaches targeted to downstream genes of Smo might be more promising.

Prospect

Significant progress has been made in understanding the pathogenesis and targeted therapy of ovarian cancer, especially in last 5 years. Cognition on the genetics and Hh pathways in both epithelial cells and stromal cells at the molecular levels allows us to interfere with ovarian cancers using defined pathway inhibitor through the *in vitro* and *in vivo* assays. Further dissection of the role of Hh pathway in the initiation and progression of ovarian carcinoma will create new drug targets for its therapeutic intervention.

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