Cancer Epidemiology 40 (2016) 152–157

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.cancerepidemiology.net

Hedgehog signaling pathway as a therapeutic target for ovarian cancer

Haixia Li, Jinghua Li, Limin Feng*

Department of Obstetrics and Gynecology, Beijing TianTan Hospital, Capital Medical University, China

ARTICLE INFO

Article history:
Received 31 July 2015
Received in revised form 3 October 2015
Accepted 5 November 2015
Available online xxx

Keywords:
Ovarian cancer
Hedgehog
Targeted therapy

ABSTRACT

Ovarian cancer is the most lethal cause of death among gynecological malignancies. Despite advancements in surgery and chemotherapy treatment strategies, the prognosis of ovarian cancer patients remains poor; a majority of patients relapse and eventually succumb to this disease. Therefore, novel therapeutic approaches to improve patient outcome are urgently needed. The hedgehog signaling pathway is vital for embryonic development and tissue homeostasis, and its deregulation is implicated in cancer cell growth, survival, differentiation, and metastasis. The critical role of hedgehog signaling in multiple biologic processes raises concerns about its potential therapeutic use in cancer. Consequently, many studies are focusing on hedgehog signaling as an attractive target in cancer treatment. In this review, we present an overview of the hedgehog pathway and its pathological aberrations in ovarian cancer. We also discuss inhibitors of the hedgehog signaling pathway that are currently being investigated in the laboratory and in early clinical trials; as well as the clinical challenges these inhibitors face.

Contents

* Corresponding author.
E-mail addresses: lucyfeng1966@163.com, lucyfeng66@163.com (L. Feng).

http://dx.doi.org/10.1016/j.canep.2015.11.014
1877-7821/

1. Introduction

The hedgehog (HH) signaling transduction pathway is originally discovered in *Drosophila* and has been shown to be highly conserved from *Drosophila* to humans [1]. The HH signaling pathway is a critical regulator of stem cell fate during embryonic development and, facilitates proliferation, regeneration and differentiation of somatic cells [2]. In the years since its discovery, studies have revealed that aberrant activation of the HH pathway is linked to many malignant tumors, such as ovarian [3], breast [4], gastrointestinal [5], hepatic [6], pancreatic [7], lung [8] and hematologic malignancies [9]. Deregulation of the HH pathway occurs in multiple human cancers, indicating that HH pathway inactivation is a prerequisite for tumorigenesis and cancer development. Thus, it is believed that inhibition of the HH pathway may be a novel therapeutic intervention for human cancer.

2. An overview of the hedgehog signaling pathway

The crucial role of HH signaling in embryo patterning and organogenesis during early development has been well established. The HH pathway is composed of highly conserved proteins (Sonic HH, Indian HH, and Desert HH), the HH receptors Patched (PTCH1 and PTCH2), the seven transmembrane proteins smoothened (Smo), and the five-zinc finger Gli transcription factors (Gli1, Gli2, and Gli3) [1]. Gli1 and Gli2 are considered as activators of hedgehog transcription, whereas Gli3 is a repressor. Full length Gli2 and Gli3, however, can be activators upon nuclear translocation. When PTCH inhibits Smo, Gli1 is completely degraded by the ubiquitin-proteasome system, whereas Gli2 and Gli3 are only cleaved, and their truncated forms translocate to the nucleus and suppress hedgehog transcription [10,11]. As shown in Fig. 1. In the absence of HH ligand binding, PTCH localizes to the base of the intact microtubule and constitutively inhibits the driving factor Smo, and proteasomes cleave Gli proteins to generate truncated repressor isoforms. HH signaling can also be activated by a ligand-dependent mechanism. In this mechanism, PTCH binds to a HH ligand, which then releases its inhibition of Smo, and activated Smo subsequently translocates from matrix vesicles to membrane cilia [12,13]. This activates Gli family transcriptions factors, Gli2 and Gli3 translocates to the nucleus, inducing transduction of downstream signaling cascades, that are involved in cellular survival, proliferation and differentiation [14,15].

A major negative regulator of the pathway, suppressor of fused (Sufu) binds to all three Gli members, to regulate Gli processing and/or degradation [16]. Sufu regulation of Gli is cilium-independent, and Sufu can promote Gli2 and Gli3 cleavage, and ultimately inhibit the HH pathway [17].

The best documented Gli target genes are Gli1 and PTCH1, and both proteins regulate the HH pathway positively and negatively. HH signaling also interacts with other important oncogenic pathways, including the MAPK, PI3K, EGFR, and TGF-β pathways, which are involved in cellular proliferation, apoptosis, and angiogenesis [18–20].

3. HH signaling is aberrantly activated in cancer

Aberrant activation of the HH signaling pathway has been implicated in tumorigenesis. The relevance of HH pathway to cancer has been established by the the early 1980s discovery of heterozygous loss-of-function mutations that influence PTCH in sporadic basal cell carcinoma and cause abnormal activation of HH signaling transduction [21]. So far, HH pathway mutations have been studied in several cancers by genome-wide sequencing. In particular, data from the Cancer Genome Atlas validate PTCH mutations in medulloblastoma [22–24]. Essential roles of HH signaling in other tumors, such as pancreatic adenocarcinoma and lung, gastric, and hepatic cancer have also been demonstrated [5–9].

Aberrant HH signaling in human cancers has three primary modes of action: (a) ligand-independent signaling. Cancers of this type are mainly driven by activating mutations in HH pathway components, such as loss-of-function mutations in PTCH and, Sufu, gain-of-function mutations in Smo, and missense mutations in Gli1 and Gli3, which have been observed in basal cell cancer and medulloblastoma. (b) ligand-dependent autocrine signaling. Cancer cells can secrete HH ligand, and the ligand binds to the receptor on the same cells, resulting in cell autonomous pathway activation, as is observed in lung cancer, pancreatic cancer and prostate

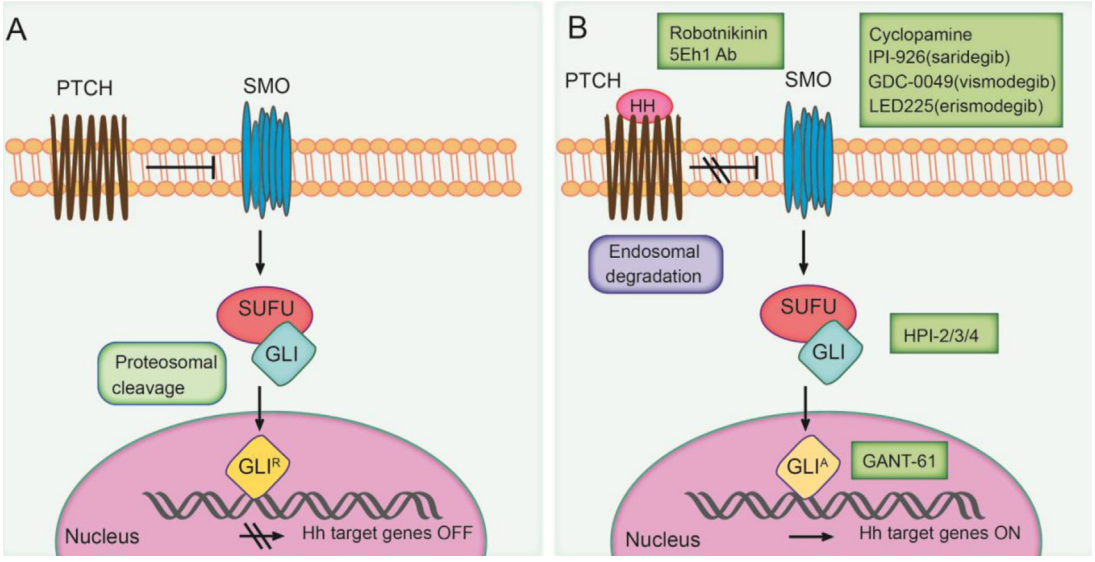

Fig. 1. Schematic overview of the hedgehog signaling pathway and some inhibitors of the pathway in preclinical and clinical studies. (A) In the absence of HH ligands,PTCH inhibits the function of SMO, and GLI proteins are converted by proteosomes to the transcriptional repressor form (GLI^R). (B) Interaction of HH ligands with PTCH unrepresses SMO and generates activated GLI factors (GLI^A) which induce transcription of downstream HH genes. The bound of HH/PTHC complex becomes internalized in the endosome and degraded.