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Invited review article

Hedgehog signaling in basal cell carcinoma

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ABSTRACT

Basal cell carcinoma (BCC), the most common type of skin cancer, is occasionally aggressive with deep invasion, destruction of adjacent structures, recurrence and, on very rare occasions, regional and distant metastases. Mutations that occur in BCC in hedgehog (Hh) pathway genes primarily involve the genes encoding patched homolog (PTCH) and smoothened homolog (SMO). Several animal models have demonstrated the functional relevance of genetic alterations in the Hh pathway during tumorigenesis. Recently, targeted therapy has become available both commercially and in the context of human clinical trials. Interestingly, Hh pathway inhibitors not only suppress BCC progression but also promote acquired immune responses. Since immune responses are crucial for long-term tumor control, new clinical trials, such as those involving a combination of Hh inhibitors with immune modifiers, are needed to supplement standard methods of tumor control.

Contents

1. Introduction

Basal cell carcinoma (BCC) is the most common cancer type and its incidence rate is increasing [1]. BCC characteristically arises in body areas that are exposed to the sun and is most common on the head and neck (80%), followed by the trunk (15%) and arms and legs [2]. BCC has also been reported in unusual sites, including the axillae, breasts, perianal area, genitalia, palms, and soles [3].

BCC is generally characterized by slow growth and minimal soft tissue invasiveness [4]. Since BCC has low metastatic potential, treatment focuses on local control. Treatment of BCC can be surgical or nonsurgical, such as conventional surgical excision or micrographic surgery, radiotherapy, photodynamic therapy, cryosurgery, or topical treatment, including 5-fluorouracil or toll-like receptor agonist imiquimod [5].

BCC is occasionally aggressive with deep invasion, destruction of adjacent structures, recurrence and, on very rare occasions, regional and distant metastasis [6]. A previous report showed that BCCs comprised 6.6% moderate (640 of 9652) and 0.6% (58 of 9652) of severe cases [7]. In 2012, the United States Food and Drug Administration (FDA) approved vismodegib as a first-generation hedgehog (Hh) pathway antagonist for the treatment of advanced or metastatic BCC. Vismodegib was also approved in the European Union, Switzerland, Canada, Australia, Mexico, Israel, South Korea and other countries in 2013. Vismodegib is an effective therapy that shrinks tumors to a manageable size. In this review, we will

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discuss the Hh pathway in BCC and new insights into Hh pathway inhibitors in adaptive immunity for BCC treatment.

2. Hh signaling

The Hh pathway plays a crucial role in patterning and organogenesis during early development, and is largely inactive in adults, except for its function in tissue repair and maintenance [8]. The central components of the Hh pathway consist of three secreted ligands (Sonic Hh, Indian Hh, and Desert Hh), a negative regulatory receptor (Patched [PTCH]), a positive regulatory receptor (smoothened [SMO]), and glioma-associated oncogene (GLI) transcription factors (GLI1, GLI2, and GLI3) [8,9]. The primary cilium is a microtubule-based organelle that protrudes from the plasma membrane and acts as a sensor for extracellular signals, including the Hh pathway [10].

The precise mechanism of Hh signaling through SMO has been well studied. In the absence of Hh ligand, PTCH localizes in the cilia and represses SMO activity by preventing its trafficking and localization to the cilia (Fig. 1A). GLI transcription factors are sequestered in the cytoplasm by several protein mediators, including protein kinase A (PKA) and suppressor of fused (SUFU) [11]. GLI undergoes proteasomal cleavage and the resulting repressor from GLI translocates to the nucleus and inhibits the translation of Hh target genes. On ligand binding, PTCH is displaced from the cilia, thereby allowing ciliary accumulation and activation of SMO. Activated GLIs, the final effectors of the pathway, translocate into the nucleus to induce the expression of various context-specific genes, which regulate cellular differentiation, proliferation, and survival (Fig. 1B) [11].

3. Hh signaling in BCC

The relationship of Hh pathway activation and cancer has been examined since the report of germline loss-of-function mutations in PTCH in patients with nevoid basal cell carcinoma syndrome (NBCCS, Gorlin syndrome) [12]. NBCCS is an autosomal-dominant disease that is characterized by multiple developmental abnormalities and a predisposition to tumors, specifically BCC, medulloblastoma (MB), embryonal rhabdomyosarcoma, and meningioma [13]. Somatic mutations in PTCH have been identified in 90% of sporadic BCC [14], and gain-of-function mutations in SMO have been detected in BCC [15]. In particular, recurrent mutations in SMO and functional studies have demonstrated that these mutations, leading to aberrant activation of Hh signaling, promote tumor development (Fig. 2A) [15]. Recently, Hh pathway mutations have been identified in large-scale whole-genome and whole-exome deep-sequencing studies across a wide range of cancers. Interestingly, somatic mutations in PTCH have been detected in other cancer types, such as ovarian and endometrial cancers [16]. In contrast with BCC and MB, these mutations are mainly missense. Their relevance in tumor development remains to be determined.

In addition to the SMO-dependent pathway, phosphatidylinositol 3-kinase (PI3K) also promotes Hh signaling in oncogenesis. S6 kinase 1 (S6K1) and atypical protein kinase C (aPKC), components that are downstream from PI3K, are reported to promote GLI-dependent transcription. S6K1 is also downstream of the mammalian target of rapamycin (mTOR) pathway and was found to be elevated in esophageal cancers resistant to SMO antagonists [17]. In addition, PI3K can promote 3-phosphoinositide-dependent kinase 1 (PDK1) activation and PDK1 can promote mTOR and S6K1 activation. S6K1 promotes GLI-dependent transcription by phosphorylating GLI1, which prevents an inhibitory interaction with SUFU that allows GLI to enter into the nucleus and turn on target genes. aPKC is an Hh target gene that phosphorylates GLI1 at distinct sites from S6K1, activating GLI1 DNA binding and transcriptional activity to generate a positive-feedback loop that amplifies GLI-dependent transcription in BCC (Fig. 2B) [17].

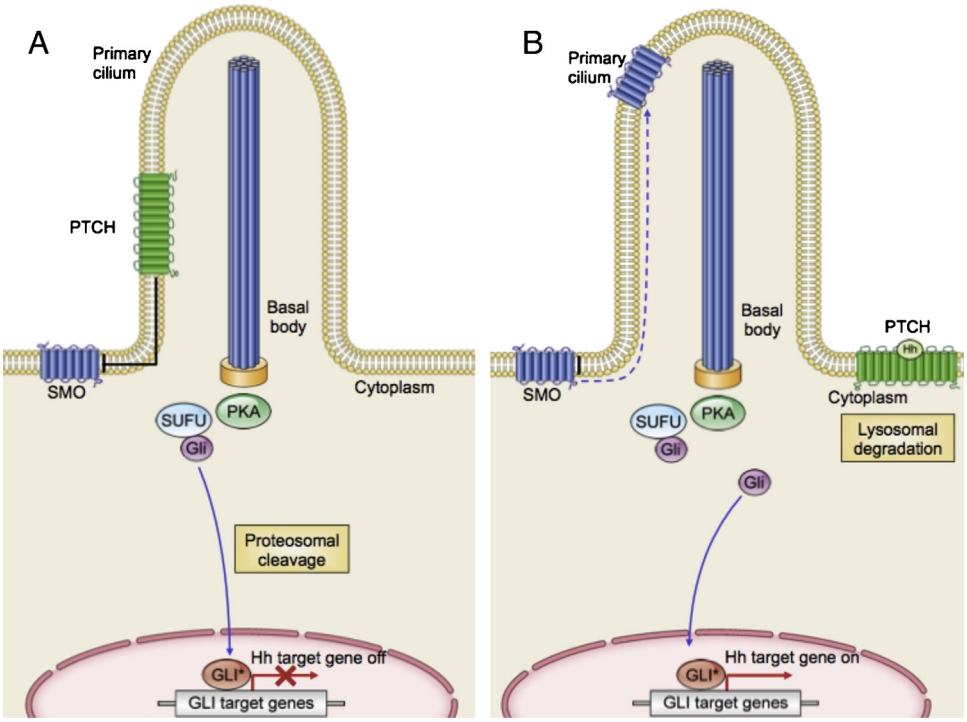

Fig. 1. Mechanism of the Hh pathway. (A) In the absence of Hh ligand, PTCH localizes in the cilia and represses SMO activity by preventing its trafficking and localization to the cilia. GLI transcription factors are sequestered in the cytoplasm by several protein mediators, including PKA and SUFU. GLI undergoes proteasomal cleavage and the resulting repressor form GLI translocates to the nucleus and inhibits the translation of Hh target genes. (B) On ligand binding, PTCH is displaced from the cilia, thereby allowing ciliary accumulation and activation of SMO. Activated GLIs, the final effectors of the pathway, translocate into the nucleus to induce the expression of various context-specific genes that regulate cellular differentiation, proliferation, and survival.