• Review Article •

Hedgehog signaling in selected ocular and adnexal tumors: biological roles and therapeutic advances

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Abstract

● The Hedgehog signaling pathway is a key regulator of embryonic development, cell proliferation, differentiation, stemness, and tissue homeostasis, and its aberrant activation has been implicated in the development and progression of multiple ocular tumors. This review summarizes the molecular alterations, biological functions, and therapeutic relevance of Hedgehog signaling in eyelid and periocular basal cell carcinoma, sebaceous carcinoma, retinoblastoma, and ocular melanoma. Overall, the biological and clinical significance of Hedgehog signaling varies across ocular tumor types. Further studies integrating multi-omics analyses, functional validation, predictive biomarkers, and prospective clinical investigation are needed to clarify pathway dependence, mechanisms of resistance, and the therapeutic value of Hedgehog pathway targeting in ocular tumors.

● **KEYWORDS:** Hedgehog signaling pathway; periocular basal cell carcinoma; sebaceous carcinoma; retinoblastoma; ocular melanoma; vismodegib

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INTRODUCTION

Tumors of the eye and ocular adnexa comprise a heterogeneous group of benign and malignant neoplasms arising in or involving the eyelid, conjunctiva and caruncle, lacrimal apparatus, orbit, optic nerve, and intraocular structures[1]. Due to the delicate anatomy of the eye, the confined anatomical space, and the close relationship between ocular tissues and adjacent structures, clinical management is highly complex, as it requires not only effective tumor control but also preservation of visual function and facial appearance. Despite advances in surgical resection, radiotherapy, chemotherapy, and immunotherapy, the mechanisms underlying some malignant tumors remain incompletely understood, while conventional treatments still have limitations in terms of efficacy and safety. Therefore, further elucidation of the molecular mechanisms involved in the initiation and progression of ocular tumors, together with the identification of molecular targets with diagnostic, prognostic, and therapeutic value, has become an important area of research in this field.

The origins of Hedgehog signaling research can be traced to the systematic genetic screens performed by Nüsslein-Volhard and Wieschaus[2] in *Drosophila melanogaster*, reported in 1980, which identified *hedgehog* among the genes required for proper embryonic segment patterning. Molecular cloning and characterization of the *Drosophila hedgehog* gene in 1992 revealed that it encodes a protein targeted to the secretory pathway and provided key evidence for its role in developmental positional signaling[3]. In 1993, vertebrate Hedgehog homologs, including Sonic hedgehog (SHH), were identified, and seminal studies implicated SHH as a key signaling molecule in embryonic patterning, particularly in ventral neural tube patterning[4]. A major conceptual advance came in 1996, when Patched 1 (*PTCH1*) mutations were identified in patients with Gorlin syndrome and associated tumors, providing genetic evidence that the loss of *PTCH1* function contributes to basal cell carcinoma development[5-6]. These discoveries provided a mechanistic link between dysregulated Hedgehog signaling and human tumorigenesis and ultimately paved the way for therapeutic targeting of the signaling pathway. This translational trajectory culminated in the Food and Drug Administration (FDA) approval of the Smoothened (SMO) inhibitor vismodegib in 2012 for patients with metastatic or locally advanced basal cell carcinoma[7].

The Hedgehog signaling pathway is now recognized as an essential regulator of embryonic development, cell proliferation, and tissue differentiation, and it plays an important role in the normal development of the eye and ocular adnexa[8-10]. In adult tissues, Hedgehog signaling is

generally maintained at a low level or under tight regulation, while retaining important roles in tissue homeostasis[11]. Aberrant Hedgehog signaling has been associated with tumor cell proliferation, maintenance of cancer stemness, epithelial–mesenchymal transition, therapeutic resistance, and tumor progression[12-13]. Despite growing evidence linking dysregulation of Hedgehog signaling to individual ocular neoplasms, its alterations and clinical implications across tumors of the eye and ocular adnexa have not yet been comprehensively synthesized. Accordingly, this review systematically summarizes alterations in the Hedgehog signaling pathway across different tumors of the eye and ocular adnexa and their clinical significance, and further discusses the translational potential and therapeutic applications of Hedgehog pathway-targeted strategies, with the aim of providing new perspectives on the research and treatment of ocular tumors.

Literature Search Relevant literature was searched in PubMed/MEDLINE, Embase, and Web of Science from database inception to October 8, 2026. The main search strategy combined terms related to the Hedgehog signaling pathway with terms related to ocular and adnexal tumors. Additional combinations including "Hedgehog inhibitor" and "vismodegib" were used to identify studies on the therapeutic application of Hedgehog pathway inhibitors. Reference lists of relevant original studies and reviews were manually screened to identify additional publications. Studies were selected based on their relevance to the molecular alterations, biological functions, clinicopathological significance, and therapeutic implications of Hedgehog signaling in ocular and adnexal tumors, with emphasis on recent and clinically relevant evidence. As this is a narrative review, the literature search was intended to provide a broad and up-to-date overview rather than a formal systematic review.

Components and Signal Transduction Mechanisms of the Hedgehog Pathway Aberrant activation of the Hedgehog signaling pathway has been implicated in the initiation and progression of various human cancers[14]. Hedgehog proteins are secreted signaling ligands that undergo dual lipid modification with cholesterol and palmitate[8]. In humans, the Hedgehog ligand family comprises three homologous proteins: SHH, Indian hedgehog, and Desert hedgehog[15]. In vertebrates, canonical Hedgehog signal transduction primarily depends on the primary cilium and is ultimately mediated by glioma-associated oncogene (GLI) transcription factors[16]. GLI1 functions mainly as a transcriptional activator, GLI2 predominantly exerts activating effects, whereas GLI3 mainly functions as a transcriptional repressor through its proteolytically processed truncated form[12]. Downstream of SHH signaling, GLI3 can mediate activation of the GLI1 promoter, while GLI2 can directly bind to the GLI1 promoter and induce GLI1 expression[17-18]. GLI1 functions as a transcriptional activator and further amplifies Hedgehog signaling through a positive-feedback loop[19].

Suppressor of fused (SUFU) binds GLI proteins and constrains their transcriptional activity (Figure 1)[20]. In the absence of Hedgehog signaling, protein kinase A-mediated phosphorylation primes GLI3 for additional phosphorylation by glycogen synthase kinase 3β and casein kinase 1, promoting beta-transducin repeat-containing protein-dependent ubiquitination and proteasomal processing[21-22]. This mechanism efficiently converts GLI3 into its C-terminally truncated transcriptional repressor form, GLI3R, whereas GLI2 is processed much less efficiently and is more frequently destabilized or completely degraded[23]. When SHH binds to PTCH1, PTCH1-mediated inhibition of SMO is relieved[24]. Multisite phosphorylation of SMO by casein kinase 1α and G protein-coupled receptor kinase 2 promotes its accumulation in the primary cilium and induces its active conformation[25]. Activated SMO promotes the ciliary recruitment and dissociation of SUFU–GLI complexes[26]. Hedgehog signaling suppresses the processing and degradation of GLI2 and inhibits the proteolytic conversion of GLI3 into GLI3R, thereby favoring the accumulation of transcriptionally active full-length GLI proteins[23,27]. Nuclear GLI activators subsequently induce Hedgehog target genes, including GLI1 and PTCH1[17,28].

Role of the Hedgehog Pathway in Tumors of Eye and Ocular Adnexa

Eyelid and periocular basal cell carcinoma Aberrations in the Hedgehog signaling pathway are closely associated with basal cell carcinoma of the eyelid and periocular skin. Immunohistochemical analysis demonstrated significantly lower PTCH1 expression in cutaneous eyelid basal cell carcinoma than in conjunctival squamous cell carcinoma, supporting the involvement of PTCH1 alterations in the pathogenesis of eyelid basal cell carcinoma[29]. A recent multi-omics study further demonstrated that Hedgehog pathway abnormalities in eyelid basal cell carcinoma vary across histological subtypes. GLI2-dominant pathway upregulation is observed mainly in the tumor tissue and surrounding stroma of morphoeic basal cell carcinoma. By contrast, although nodular basal cell carcinoma shows statistically significant alterations in Hedgehog-related genes at the mutational level, it does not exhibit corresponding pathway upregulation at the transcriptomic level, and the expression of pathway-related proteins does not exceed the level of physiological activation[30].

Currently, the Hedgehog pathway inhibitor vismodegib has been used in patients with locally advanced basal cell carcinoma of the eyelid or periocular region[31-32]. Recent

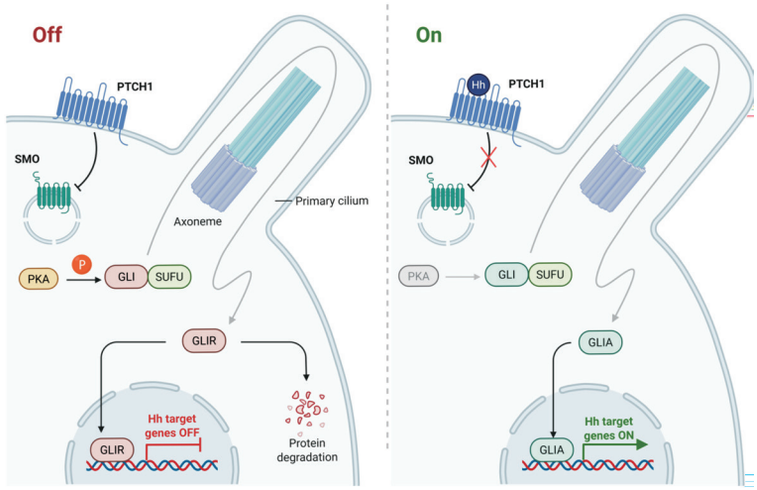


Figure 1 Typical Hedgehog signal transduction in the absence and presence of Hedgehog ligand In the absence of Hedgehog ligand (Off state), PTCH1 suppresses SMO activity and prevents SMO accumulation in the primary cilium. SUFU binds GLI proteins and restricts their transcriptional activity. GLI proteins undergo phosphorylation-dependent processing, resulting in the generation of transcriptional repressor forms (GLIR), which enter the nucleus and inhibit Hedgehog target gene expression. Upon Hedgehog ligand binding to PTCH1 (On state), PTCH1-mediated inhibition of SMO is relieved. Activated SMO accumulates in the primary cilium and promotes dissociation of the SUFU–GLI complex, allowing the formation and nuclear translocation of transcriptionally active GLI proteins (GLIA), which induce Hedgehog target gene expression. Hh: Hedgehog; PTCH1: Patched 1; SMO: Smoothened; PKA: Protein kinase A; GLI: Glioma-associated oncogene; SUFU: Suppressor of fused; GLIR: GLI repressor; GLIA: GLI activator. The figure was created with BioRender.com.

evidence supports the tumor-reducing and globe-preserving potential of vismodegib in selected patients with locally advanced periocular or orbital basal cell carcinoma; however, level I and II evidence remains lacking[33]. Gill *et al*[34] prospectively enrolled seven patients with recurrent, locally advanced periocular basal cell carcinoma, four of whom had secondary orbital involvement. Following vismodegib treatment, two patients achieved complete clinical regression, two demonstrated greater than 80% partial clinical regression, two demonstrated less than 35% partial clinical regression, and one experienced disease progression. Among the four patients with orbital involvement, three showed partial responses ranging from 15% to 90%, whereas one experienced disease progression. de Giorgi *et al*[35] evaluated 15 patients with advanced periocular basal cell carcinoma treated with Hedgehog pathway inhibitors, including vismodegib and sonidegib. Three patients treated with vismodegib discontinued therapy after achieving complete responses following a mean treatment duration of approximately 12mo. Another five patients achieved partial responses but discontinued treatment because of adverse events after a median of five treatment cycles. After treatment withdrawal, four patients remained stable, whereas one experienced disease progression approximately 3mo later, suggesting that tumor control may not always be maintained after discontinuation of Hedgehog pathway inhibitors.

Drug tolerability is an important factor limiting the continuation of treatment. In the case series reported by Gill *et al*[34], adverse events occurred in six of the seven patients. Alopecia, dysgeusia, and muscle spasms were each reported in 29% of patients, whereas decreased appetite occurred in 14%. During treatment, two patients also developed new, well-differentiated keratoacanthoma-type squamous cell carcinomas at previously unaffected sites. The authors emphasized the need for close surveillance for newly developed cutaneous squamous cell carcinomas during vismodegib treatment. However, given the small sample size and the absence of a control group, this study cannot establish a causal relationship between vismodegib treatment and the occurrence of these lesions.

Taken together, the available evidence suggests that Hedgehog pathway inhibitors can reduce the tumor burden in some periocular and orbital lesions and may facilitate globe or eyelid preservation and reduce the extent of surgery. However, treatment responses are not consistently sustained, and adverse events may result in treatment interruption. Following treatment, residual disease and the need for subsequent local therapy should therefore be carefully assessed. A systematic review identified evidence supporting vismodegib as a neoadjuvant treatment option for locally advanced periocular basal cell carcinoma when surgery and/or radiotherapy are contraindicated, with the potential to facilitate ocular preservation[36].

Eyelid Sebaceous Carcinoma Hedgehog signaling plays an important role in sebaceous gland development and sebocyte cell-fate determination[37]. Animal studies have demonstrated

that inhibition of activator protein-1 activity can reprogram squamous tumor cell identity toward a sebaceous lineage by modulating Wnt/β-catenin and Indian hedgehog/Hedgehog signaling programs, resulting in the formation of sebaceous adenoma-like tumors[38]. Molecular studies have identified alterations in several signaling pathways in eyelid sebaceous carcinoma, including Wnt/β-catenin, Hedgehog, epidermal growth factor receptor, p53, and p21 signaling, suggesting that its development and progression involve multiple molecular mechanisms[39].

Current evidence suggests that Hedgehog signaling may be involved in the biological progression of eyelid sebaceous carcinoma. Immunohistochemical analysis demonstrated expression of multiple SHH pathway-related proteins in eyelid sebaceous carcinoma, including SHH, GLI proteins, and ATP-binding cassette subfamily G member 2 (ABCG2). A positive correlation between SHH and ABCG2 expression has also been observed, supporting the aforementioned view. Higher levels of SHH and ABCG2 expression were detected in tumors from patients with metastasis, and elevated ABCG2 expression has been associated with a higher cumulative incidence of metastasis, indicating that dysregulation of SHH signaling may be associated with aggressive behavior and metastatic potential of sebaceous carcinoma[40]. A recent study compared SMO expression among periocular non-nodular basal cell carcinoma, squamous cell carcinoma, and sebaceous carcinoma. SMO expression was significantly higher in the tumor tissue than in the surrounding stroma in all three tumor types, whereas no significant differences in expression levels were observed among the groups. Apart from this, higher SMO expression was associated with a higher Ki67 proliferation index across all three tumor types, while a positive correlation with mitotic count was observed only in basal cell carcinoma[41]. Notably, another study using nodular basal cell carcinoma as the comparator simultaneously examined PTCH1, SMO, GLI1, and GLI2. Expression of several Hedgehog pathway components, including PTCH1, SMO, and GLI2, was higher in sebaceous carcinoma than in nodular basal cell carcinoma, while PTCH1, SMO, and GLI2 expression was also increased compared with normal periocular tissue controls. In addition, PTCH1 and GLI2 expression was elevated in the stroma surrounding sebaceous carcinoma, suggesting that these abnormalities may involve multiple levels of the pathway as well as tumor–stromal interactions[42]. The differences between these two studies may be related to the histological subtype of basal cell carcinoma used as the comparator and the range of Hedgehog pathway components examined. The former included non-nodular basal cell carcinoma and focused only on SMO expression, whereas the latter used nodular basal cell carcinoma as the comparator and evaluated multiple Hedgehog pathway components, including PTCH1, SMO, and GLI transcription factors. Current evidence supports the presence of Hedgehog-related alterations in sebaceous carcinoma; however, whether these alterations are more prominent than those in basal cell carcinoma may depend on the histological subtype of the basal cell carcinoma comparator and the specific pathway components assessed.

Therefore, despite the established efficacy of Hedgehog pathway-targeted therapies in basal cell carcinoma, their application in sebaceous carcinoma remains unsupported by sufficient clinical and biological evidence. Given the current lack of clinical trials specifically investigating sebaceous carcinoma, as well as the possibility that its pathway dependence and drug sensitivity differ from those of basal cell carcinoma, the therapeutic relevance of Hedgehog pathway targeting in this disease requires further evaluation through functional studies and clinical evidence.

Retinoblastoma Although retinoblastoma 1 (RB1) inactivation represents the initiating event in most retinoblastomas, additional molecular alterations may contribute to cellular transformation, tumorigenesis, and tumor progression[43-44]. Dysregulation of SHH signaling has been proposed as a potential contributor to retinoblastoma progression[45-46]. A study of 79 retinoblastoma specimens showed that SHH was expressed in the vast majority of retinoblastoma specimens, being detected in 78 of 79 cases (98.7%), and the high expression of related proteins was also confirmed in retinoblastoma cell lines. The expression of GLI1, GLI2, and ABCG2 proteins was significantly associated with undifferentiated tumors, whereas high SHH expression was associated with local invasion and metastasis[45]. These findings suggest that dysregulation of SHH signaling may be involved in the pathogenesis and progression of retinoblastoma and may be associated with aggressive clinicopathological features.

Moreover, Song *et al*[47] found that SHH promotes retinoblastoma cell growth, whereas SHH silencing reduces cell viability and induces apoptosis. Mechanistically, SHH knockdown suppressed phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signaling, and activation of this pathway by insulin-like growth factor 1 partially rescued the effects of SHH depletion, suggesting that SHH contributes to retinoblastoma progression partly through PI3K/AKT pathway activation.

MicroRNAs (miRNAs) can function as oncogenes or tumor suppressors and play important roles in the pathogenesis of retinoblastoma[48-50]. miR-361-3p and miR-186 have been shown to regulate retinoblastoma by targeting Hedgehog signaling. One study demonstrated that miR-361-3p exerts tumor-suppressive effects during the development and progression of retinoblastoma by targeting SHH signaling,

thereby markedly inhibiting tumor cell proliferation and stemness[51]. Another study found that miR-186 expression was downregulated in retinoblastoma tissues, whereas ATPase family AAA domain-containing protein 2 (ATAD2) and Hedgehog pathway-related genes were upregulated. Further experiments demonstrated that miR-186 directly targets and downregulates ATAD2, thereby suppressing Hedgehog signaling, inducing apoptosis, and inhibiting retinoblastoma cell viability, invasion, migration, and angiogenesis[52]. Collectively, current findings indicate that multiple miRNAs may influence the initiation and progression of retinoblastoma through the Hedgehog pathway. Although no drugs directly targeting these miRNAs are currently available, these observations suggest that miRNAs may serve as potential biomarkers for retinoblastoma and that miRNA-based approaches may provide new opportunities for targeted therapy.

Ocular melanoma In uveal melanoma, two commonly used human cell lines express components of the Hedgehog signaling pathway, including SMO and GLI1. Pharmacological inhibition or knockdown of SMO downregulates GLI1, suppresses cell proliferation, colony formation, migration, and epithelial–mesenchymal transition-related phenotypic changes, and induces G1-phase cell-cycle arrest and apoptosis. It also reduces vascular endothelial growth factor (VEGF) expression and VEGF-related proangiogenic activity[53]. These findings suggest that the SMO–GLI1 axis may contribute to the progression of uveal melanoma and provide *in vitro* evidence supporting the potential therapeutic value of SMO inhibitors.

SUFU is a negative regulator of the Hedgehog signaling pathway in vertebrates[54]. SUFU contributes to ocular melanocyte homeostasis and regulates melanoblast migration[55]. Ocular melanocytosis is a recognized risk factor for uveal melanoma[56]. A prevalence-based analysis estimated that approximately 1 in 400 White individuals with ocular or oculodermal melanocytosis would develop uveal melanoma during their lifetime, compared with approximately 1 in 13 000 individuals in the general population[57]. Further investigation revealed that patients with melanocytosis who developed uveal melanoma had a significantly higher risk of metastasis than those without melanocytosis[58]. SUFU is essential for maintaining melanocyte homeostasis, and its disruption leads to ectopic migration of melanoblasts into the anterior segment of the eye during development, resulting in ocular melanocytosis and anterior segment malformation[55]. Another study identified recurrent deletions involving chromosome region 10q24.32–26.2 in conjunctival melanoma. This region encompasses several tumor suppressor genes, including neuralized E3 ubiquitin protein ligase 1, SUFU, programmed cell death 4, and chromosome 10 open reading frame 90, and deletions of this region were significantly associated with aggressive tumor features, including metastasis, lymphatic invasion, increased tumor thickness, and B-Raf proto-oncogene, serine/threonine kinase mutations[59]. Although the role of the Hedgehog pathway in ocular melanoma has not yet been fully elucidated, the available evidence suggests that this pathway may represent a potentially important molecular target in ocular melanoma.

Research Limitations and Future Perspectives Current evidence regarding the Hedgehog pathway in tumors of the eye and ocular adnexa remains uneven. Although a certain amount of clinical evidence has accumulated for periocular basal cell carcinoma, studies of sebaceous carcinoma, retinoblastoma, and ocular melanoma are still largely limited to tissue expression analyses, cell-based experiments, and animal models, and are therefore insufficient to support clinical application. In addition, existing studies have mainly focused on individual pathway components, such as SHH, PTCH1, SMO, and GLI. Systematic investigations into the interactions between canonical and noncanonical Hedgehog signaling, the tumor microenvironment, and other pathways, including Wnt and PI3K/AKT signaling, remain limited, and the underlying mechanisms require further clarification. Pathway activity and drug sensitivity may also vary within the same tumor and among different histological subtypes. Therefore, protein expression alone may be insufficient to determine pathway dependence or accurately predict treatment response. Although Hedgehog pathway inhibitors can reduce tumor size in some patients with locally advanced periocular basal cell carcinoma, not all patients achieve durable responses because of individual variability and heterogeneous treatment efficacy. Moreover, adverse events such as dysgeusia, muscle spasms, alopecia, and weight loss may lead some patients to interrupt or discontinue treatment, while recurrence or disease progression may still occur after treatment withdrawal. Future studies should therefore include prospective, multicenter investigations and integrate multi-omics analyses, functional validation, and diagnostic prediction models to further clarify pathway dependence, mechanisms of resistance, predictive biomarkers of treatment response, and appropriate combination treatment strategies across different tumor subtypes.

In conclusion, the Hedgehog signaling pathway is involved in the development and progression of various tumors of the eye and ocular adnexa by regulating cell proliferation, differentiation, stemness maintenance, and the tumor microenvironment. However, its biological roles and clinical significance vary considerably among tumor types. In eyelid and periocular basal cell carcinoma, Hedgehog pathway abnormalities represent a relatively well-established molecular basis, and pathway inhibitors have demonstrated some clinical

therapeutic value. By contrast, studies of eyelid sebaceous carcinoma, retinoblastoma, and ocular melanoma have mainly identified associations between pathway alterations and tumor biological behavior. Overall, the Hedgehog pathway provides an important perspective for understanding the molecular heterogeneity of ocular tumors and may become an important target for their clinical diagnosis and treatment in the future.

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