




Review

Hedgehog Signaling: Implications in Cancers and Viral Infections

Sidney Iriana [†], Kumari Asha , Miroslava Repak and Neelam Sharma-Walia ^{*,†} 

Center for Cancer Cell Biology, Immunology and Infection, Department of Microbiology and Immunology, Chicago Medical School, Rosalind Franklin University of Medicine and Science, North Chicago, IL 60064, USA; Sidney.iriانا@my.rfums.org (S.I.); asha.kumari@rosalindfranklin.edu (K.A.); miroslava.repak@my.rfums.org (M.R.)

* Correspondence: neelam.sharma-walia@rosalindfranklin.edu

† These authors contributed equally to this work.

Abstract: The hedgehog (SHH) signaling pathway is primarily involved in embryonic gut development, smooth muscle differentiation, cell proliferation, adult tissue homeostasis, tissue repair following injury, and tissue polarity during the development of vertebrate and invertebrate organisms. GLIoma-associated oncogene homolog (GLI) family of zinc-finger transcription factors and smoothened (SMO) are the signal transducers of the SHH pathway. Both SHH ligand-dependent and independent mechanisms activate GLI proteins. Various transcriptional mechanisms, post-translational modifications (phosphorylation, ubiquitination, proteolytic processing, SUMOylation, and acetylation), and nuclear-cytoplasmic shuttling control the activity of SHH signaling pathway proteins. The dysregulated SHH pathway is associated with bone and soft tissue sarcomas, GLIomas, medulloblastomas, leukemias, and tumors of breast, lung, skin, prostate, brain, gastric, and pancreas. While extensively studied in development and sarcomas, GLI family proteins play an essential role in many host-pathogen interactions, including bacterial and viral infections and their associated cancers. Viruses hijack host GLI family transcription factors and their downstream signaling cascades to enhance the viral gene transcription required for replication and pathogenesis. In this review, we discuss a distinct role(s) of GLI proteins in the process of tumorigenesis and host-pathogen interactions in the context of viral infection-associated malignancies and cancers due to other causes. Here, we emphasize the potential of the Hedgehog (HH) pathway targeting as a potential anti-cancer therapeutic approach, which in the future could also be tested in infection-associated fatalities.

Keywords: GLI transcription factors; cancer; virus; therapeutic



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1. Introduction

Hedgehog (HH) signaling is a necessary, evolutionarily conserved developmental process for human embryogenesis and organogenesis. First identified in *Drosophila melanogaster*, HH signaling is extensively used to explain the complex topic of cell segment number patterning. Advanced research identified its important morphogenic properties for cell proliferation, polarity, and differentiation [1]. Mammals have three HH homologs, Desert (DHH), Indian (IHH), and Sonic (SHH), of which Sonic is the best-studied ligand of the vertebrate pathway [1]. SHH signaling promotes adult stem cells' proliferation, including primitive hematopoietic [2], mammary, and neural stem cells [3]. Oncogenic mechanisms, however, can alter their fates in adult tissues and cause aberrant upregulation of the HH signaling pathway. Oncogenic mechanisms include cell proliferative capacity, angiogenesis, epithelial to mesenchymal transition (EMT), and invasive migration patterns typical of metastatic tissues [4–6]. With its first discovery in Gorlin syndrome, also known as nevoid basal cell carcinoma syndrome [7,8], HH signaling has been explored in gastrointestinal (GI), ovarian, brain, lung, skin, prostate, and breast cancers [9]. BCC and medulloblastoma tumors have constitutive activation of the HH pathway [10].

Downstream HH signaling protein families such as GLI have become the spotlight as targets for invasive epithelial cancers. HH pathway has been investigated for potential therapeutic antagonists as a strategy for cancer treatment, although the focus is limited to ligand-dependent effectors such as Patched 1 (PTCH1) and Smoothened (SMO); Frizzled class receptor [11,12]. In this review, we discuss the prospect of HH/GLI signaling in cancers due to viral infections and other causes.

2. Various Types of GLI

The GLI family includes three zinc finger proteins GLI1, GLI2, and GLI3 transcription factors identified as downstream targets of the HH signaling pathway—important in proper embryonic development, stem cell biology, and tissue homeostasis. Of the GLI proteins, GLI2 and GLI3 are the primary signal responders, with GLI2 mainly acting as a transcriptional activator and GLI3 predominantly acting as a repressor [13] (Figure 1). GLI1, a direct transcriptional target of HH signaling, is dispensable for mouse embryonic development [14,15]. HH signaling is GLI1 dependent in the spinal cord, and a combination of GLI2 and GLI3 is required to regulate motor neuron and early ventral spinal cord development [16]. Structurally, they share similar features, including conserved tandem zinc fingers, conserved N- and C-terminal domains, and regions of protein kinase A (PKA) binding. There is an increased level of complexity in GLI transcription factors' activation process as alternative splicing plays a significantly important role in controlling their activity. GLI1 alone functions as a transcriptional activator, whereas GLI2 and GLI3 have bifunctional transcription forms: full-length versions act as activators, and truncated N-terminal fragments act as repressors [13]. GLI2 and GLI3 display a repressor domain (RD), a processing determinant domain (PDD) [17], and a processing region (PR). N-terminal region of human GLI2 and GLI3 contains a domain with a transcriptional repressor, and removal of this domain enhances the transcriptional activity of GLI2 [16,18,19]. The balance between the GLI2/3 transcriptional activator and repressor actions dictates HH responses that are both tissue-specific and developmental stage-specific. During limb and ureter development, SHH acts mainly by opposing GLI3 repression [13,20–22]. During neural tube and skeletal development, integrated regulation of GLI2 activation and GLI3 de-repression has both overlapping and distinct functions. Both GLI2 and GLI3 constitutively traffic through primary cilia until activation of the HH pathway promotes the parallel accumulation of GLI2 and GLI3 at the tip of primary cilia [23]. This region acts as an organizational center for activated GLI proteins, which then traffic to target gene promoters in the nucleus. The balance between these functional forms in the cell environment—which depend on post-transcriptional and post-translational processing—determines the HH transcription's net direction and subsequent effects on tissue proliferation.

Figure 1 shows GLI family functional domains, their similarities at the transcriptional level. GLI proteins belong to the GLI-Kruppel family of transcription factors and have Kruppel-type zinc-finger (ZF) motifs in their DNA binding domains [24–26]. Suppressor of fused (SUFU) binding site is highly conserved across all three mammalian GLI proteins [24–26]. Localization of GLI1 is influenced by the presence of a nuclear export signal (NES), and GLI1 becomes constitutively nuclear when this signal is mutated, or nuclear export is inhibited [27]. SUFU is a conserved negative regulator of GLI1 signaling that may affect the nuclear-cytoplasmic shuttling of GLI1 or the activity of GLI1 in the nucleus and thereby modulate cellular responses [27]. Recently, a PY-type nuclear localization signal (PY-NLS) and the nuclear import factor karyopherin β 2 (Kap β 2) were discovered to regulate GLI ciliary localization and HH pathway activity [28]. PY-NLS acts in conjunction with the canonical NLS (a bipartite NLS) localized in the Zn-finger domain [29]. The canonical nuclear localization signal (NLS) in GLI plays a significant role, whereas the proline-tyrosine or PY-NLS has a minor role in targeting GLI to the nucleus. Interestingly, mutating the PY-NLS but not the canonical NLS impaired GLI ciliary localization and PY-NLSs interact with the Kap β 2, also known as transportin 1 (TRN1) or importin β 2 and transport PY-NLS-containing proteins to the nucleus [28]. GLI activity is restrained by the

phosphorylation of six conserved serine residues by protein kinase A (PKA) in the absence of HH ligands [30]. GLI protein functions are regulated via post-translational modifications such as phosphorylation by PKA, glycogen synthase kinase 3 (GSK3), and casein kinase 1 (CK1) or ubiquitination, SUMOylation, acetylation, or methylation [24–26]. Two isoforms of GLI1 are termed GLI1 Δ N and tGLI1 [31]. The full-length GLI1 is designated as GLI1FL [31]. However, GLI1 Δ N lacks the SUFU-binding domain. It can activate and turn on target genes similarly to GLI1FL [19]. tGLI1 has a deletion of 41 amino acids, but it preserves all the functional domains present in GLI1FL. tGLI1 efficiently translocates into the nucleus to activate gene transcription and responds to HH ligand stimulation as well [6].

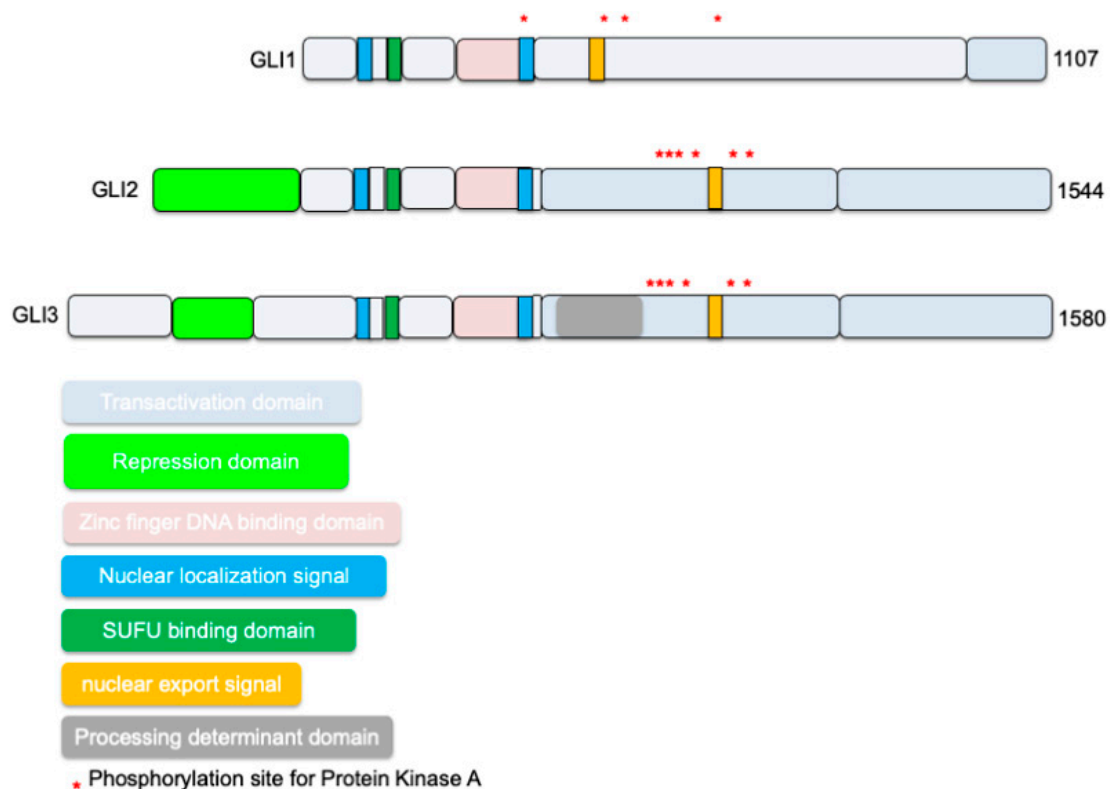


Figure 1. Schematic shows known full-length GLIoma-associated oncogene homolog (GLI) family functional domains at the transcriptional level. Similarities shared among all three types include Suppressor of fused (SUFU) binding sites, zinc finger DNA-binding domain, and activation domains. GLI1 has an additional SUFU binding site at the C-terminus, while GLI2/3 has repressor domains; additionally, GLI2 has an extra activation domain that supports its main feature of activating GLI-mediated transcription.

3. GLI and Hedgehog Signaling

The classical Hedgehog signaling pathway depends on the secretion of extracellular HH glycoproteins, Sonic HH (SHH), Indian HH (IHH), or Desert HH (DHH) [1]. SHH plays a critical role in maintaining normal embryogenesis, and abnormal fetal concentrations throughout its vast expression territory leading to the developmental defects, while its absence is lethal [32]. IHH, produced in hematopoietic cells, bone, and cartilage, has prominent HH signaling roles in the fetal liver [33]. DHH resides mostly in the peripheral nervous system and the testes, where its expression in pre-Sertoli cells serves as a marker for male sexual differentiation [34]. Despite the macroscopic arrangement and responsibilities of the HH family, canonical signaling remains conserved to the interaction of activated HH ligand binding and inactivating the cell-surface transmembrane protein, PTCH1 (Figure 2) [35]. In the inactive HH pathway, PTCH1 blocks the migration of SMO, a G protein-coupled receptor (GPCR), to the cell membrane. When the SHH ligand binds to PTCH1, inhibi-

tion upon SMO, a neighboring GPCR, is subsequently relieved, triggering downstream activation and nuclear localization of transcription factors like those in the GLI family to regulate the expression of target HH genes, effectively inducing cell proliferation, survival, differentiation, and angiogenesis. In the absence of HH ligand binding, GLI proteins are typically sequestered in the cytoplasm by the negative regulator called SUFU, which directly binds GLI to prevent activation of downstream pathway genes (Figure 2) [36]. PKA initiates a phosphorylation cascade for PKA, GSK3, and CK1 phosphorylate GLI3 [37]. Phosphorylation of GLI3 targets it for ubiquitination [37]. Kinesin family member protein 7 (KIF7) is a conserved regulator of the HH signaling. KIF7 localizes to the cilium tip, the site of microtubule plus ends. KIF7 must relay the signals from the membrane protein SMO to the GLI family transcription factors [38]. KIF7 affects HH signaling, both positively and negatively (Figure 2). It functions as a negative regulator of the SHH pathway by preventing GLI2 activation in the absence of ligand, and as a positive regulator by preventing the processing of GLI3 into its repressor form. FUSED (FU), the putative serine/threonine kinase, does not function in the mammalian HH signaling but plays a role in motile cilia [39] (Figure 2). The balance between activated and repressed forms of the GLI transcription factor determines the fate of target gene expression and cell phenotype.

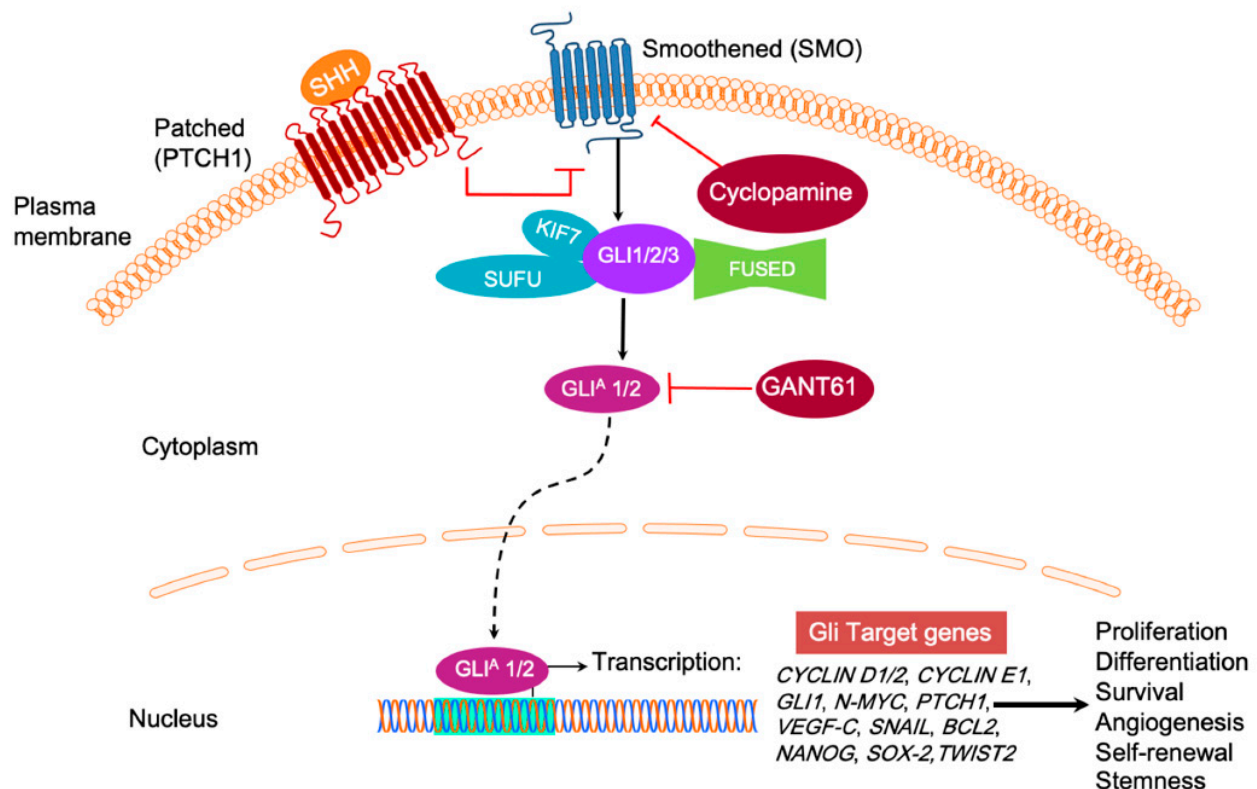


Figure 2. In the absence of Hedgehog (HH) ligand (SHH, IHH, and DHH), the Patched 1 (PTCH) transmembrane receptor at the base of the primary cilium maintains inhibition of Smoothed (SMO) G protein coupled receptor (GPCR) signaling. Upon HH binding, SMO inhibition is relieved and activates GLI transcription factors, usually sequestered by Suppressor of fused (SUFU), KIF7, and FUSED. GLIA refers to the transcriptionally active form of GLI. SMO is a popular drug target for cyclopamine, while GLI1 and GLI2-induced transcription can be inhibited by GANT61. It inhibits the HH signaling pathway downstream of SMO and SUFU, causing GLI1 nuclear accumulation. Target gene expression includes CYCLIN D1/2, CYCLIN E1, GLI1, N-MYC, PTCH1, VEGF-C, SNAIL, BCL2, NANOG, SOX-2, TWIST2 to upregulate cell proliferation and tumor survival.

4. GLI Code

GLI expression is tightly regulated at the transcription level by multiple signaling inputs—in the context of phase activity—that converge on the GLI code and direct its fate.

Whether cells undergo healthy development, homeostasis, or have a dynamic expression of oncogenes and tumor suppressors during metastasis, GLI transcription responds appropriately to the cells' desired phenotype's instructional cues. For example, tumor suppressor p53 inhibits GLI1-induced neural stem cell self-renewal, proliferation, and tumor growth through repressing nuclear localization and transcription activity of GLI1 [40]. In contrast, the absence of p53, a hallmark event of most cancers, contributes to unregulated GLI1 expression and tumor progression [41]. Similarly, a human orthologue of the mouse tumor suppressor gene, *REN^{KCTD11}*, also antagonizes GLI-mediated transactivation, and its knock-down enhanced HH signaling and cell proliferation in medulloblastoma [42].

GLI transcription factors support tumorigenesis via cell signaling, cell proliferation, angiogenesis, and metastasis [9]. Several studies suggest a crosstalk between RAS-RAF-MEK, PI3K/AKT, and HH/GLI signaling pathways [43–46]. Not only does endogenous GLI1 activity require intrinsic AKT and MEK signaling function, but AKT1, in combination with N-RAS, enhances nuclear localization and transcription of GLI1 (Figure 3) [43]. Activated K-RAS can also genetically cooperate with activated GLI2 to induce undifferentiated pancreatic tumors [44,46]. A splice variant of p63, $\Delta Np63\alpha$, targets GLI2's promoter to increase expression and is an important event in osteosarcoma progression during rare breast cancer forms [47]. Mediating this bidirectional transcription response affecting GLI-level transcription determines the HH program's status and phenotype of cells in relevant tissues. HH pathway genes other than GLI1 include *PTCH1*, Wnt and TGF β superfamily proteins, cell cycle proteins (*CYCLIN D*), and stem-cell marker genes (homeobox protein *NANOG* and *SOX2*) [48–50]. RAS/RAF/MEK/ERK, PI3K/AKT/mTOR, epidermal growth factor receptor (EGFR), and NOTCH signaling pathways interact at the level of the GLI transcription factors, except for NOTCH, which interferes with the ligand SHH [51–53].

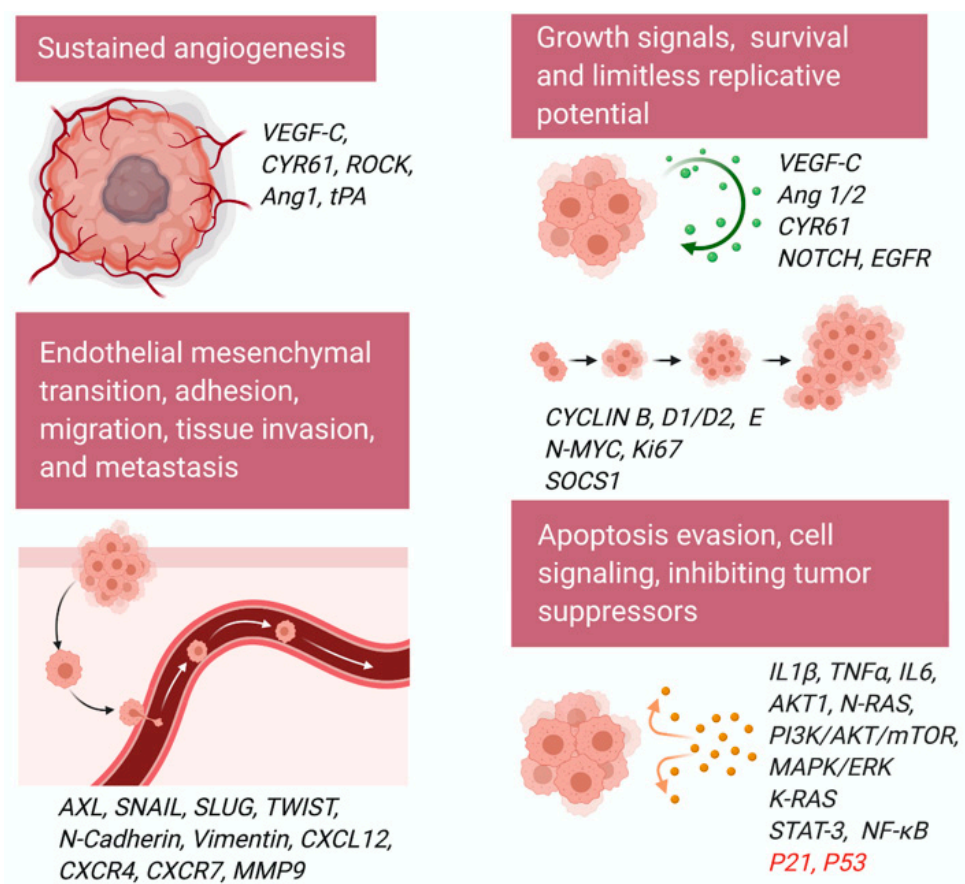


Figure 3. Schematic shows the role of GLI1 and GLI2 in cancer cell proliferation, migration, invasion, cell cycle regulation, angiogenesis, cell signaling, and survival kinases activation. Tumor suppressors downregulated by GLI are shown in red.

Constitutive canonical activation of the HH/GLI pathway is a classical representation of aberrant signaling and is typically localized to mutations of *PTCH1* (loss-of-function) and *SMO* (gain-of-function) [54,55]. Inactive HH precursors undergo post-translational modifications to form signal molecules consisting of cholesterol and palmitoyl residues, which enhances ligand activity and diffusion capacity [56]. Non-canonical signaling is often recognized as a deviation from the typical motif of HH signaling, independent of GLI activity, instead of acting through one of the multiple oncogenic pathways such as K-RAS, TGF β , PI3K-AKT, and PKC- α that target HH genes or are associated with a portion of the HH pathway [54,55,57]. Not only does this provide more prospects for aberrant HH signaling activity, but it also evades existing successful treatments for the canonical pathway such as SMO inhibitor, cyclopamine. In vivo, there may be a combination of canonical and non-canonical HH signaling that is regulated by crosstalk with other intracellular activity. The HH pathway plays an essential role in cell proliferation, differentiation, apoptosis, and migration, and it cross-talks with signaling pathways such as MAPK/ERK, PI3K/AKT/mTOR, EGFR, and NOTCH (Figure 3) [52,58–60]. tGLI1 has been reported as a stronger promoter of tumor migration and invasion as compared to GLI1 in glioblastoma and breast cancer [61].

5. Involvement of GLI in Cancers

In recent years, the HH signaling pathway has shown significant contributions to tumor initiation, progression to more advanced tumor stages, or low-grade to high-grade tumors [62–65]. Inappropriate HH signaling plays a role in more than 30% of human cancers [66]. GLI1 overexpression in breast cancer serves as a significant marker of aberrant activation of the SHH pathway driving the formation and progression of breast cancer [67–69]. SHH pathway activation promotes mammary epithelial cell mesenchymal transition (EMT) [68,69], and regulates mammary cancer stem cell (CSC) self-renewal, and facilitates angiogenesis [70]. Additionally, inhibiting the GLI1 expression could efficiently mitigate tumor growth and migration and showed its therapeutic potential in breast cancer management [71,72]. Studies reported no significant association between GLI1 expression and histological grade, T stage, clinical stage, and lymph node metastasis in breast cancer. A meta-analysis done in few studies explained GLI1 expression as one of the factors in aggressive biological behavior in breast cancer patients. Further, it elucidated the link between GLI1 expression and prognosis of breast cancer [67,73,74]. GLI1 works downstream of a protein lysine methyltransferase called SET7/9. The knockdown of SET7/9 promotes the proliferation, migration, and invasion of breast cancer cells in vitro and overexpression vice versa [75]. Investigation of the mechanism revealed that overexpression of SET7/9 inhibited GLI1 expression [75], suggesting that GLI1 expression in human breast cancer tissues negatively correlates with SET7/9 expression. Together, these results establish that SET7/9 inhibits oncogenic activities by regulating GLI1 expression in breast cancer [75]. High GLI1 expression in the claudin-low cells and tumors correlates with EMT markers and breast CSCs [76]. GLI1 knockdown in claudin-low cells reduced tumor growth of orthotopic xenografts, and treatment with nuclear factor κ B (NF- κ B) pathway inhibitor decreases GLI1 expression and protein levels in breast cancer [76].

Inflammatory breast cancer (IBC), a rare (<5%) form of all breast cancers diagnosed in the US, is the most aggressive and lethal form of primary breast cancer targeting young women. IBC is characterized by a higher risk of early recurrence, distant metastases, and spread to the central nervous system than non-inflammatory, locally spread breast cancer [77–79]. HH pathway has been studied in the context of pathophysiology in triple-negative breast cancer (TNBC), especially IBC [71]. GLI1 plays a role in proliferation, survival, and migration of IBC cell line SUM149PT, and direct targeting of GLI1 transcription is proposed as a novel and promising strategy for IBC [71]. Mechanisms of crosstalk between HH signaling and TNBC cell survival have potential implications for HH targeting interventions [80].

GLI1 was discovered in human glioma [81], and its signaling pathways have been reported in medulloblastoma [82–84] and rhabdomyosarcoma [85]. Loss of tumor suppressor SNF5 (SMARCB1) induces aberrant activation of GLI1 in malignant rhabdoid tumors (MRTs) [86]. SMARCB1 is localized to the upstream regions of the transcription start sites of GLI1 and PTCH1 [86]. shRNA mediated knockdown of SMARCB1 upregulated GLI1 and PTCH1 and activated SHH signaling pathway, whereas reexpression of SMARCB1 in MRT cell lines repressed GLI1 expression [86].

Pancreatic cancer is one of the most lethal malignancies that require innovative treatments targeting CSCs. Inhibition of HH pathway using GLI inhibitor GANT61 reduced the expression of stem cell marker CD133, and sphere formation of pancreatic cancer cells [87]. The double blockage of HH/GLI and mTOR signaling was also very useful for pancreatic cancer cells [88]. Pancreatic ductal adenocarcinoma (PDAC), the most aggressive human malignancy, thought to be initiated by K-RAS activation, involves transcriptional activation of GLI transcription factors [46]. Ectopic GLI1 activation in the mouse pancreas accelerated K-RAS driven tumor formation, underscoring the importance of GLI transcription factors in pancreatic tumorigenesis [46]. Interestingly, GLI-regulated I κ B kinase epsilon (I κ BK ϵ) and NF- κ B activity were critical for PDAC cell transformation and survival, demonstrating the mechanism of GLI-NF- κ B oncogenic activation in pancreatic cancer (Figure 3) [46].

Prostate tissues in the embryonic phase require the HH pathway for healthy prostate development that involves ductal morphogenesis through concentrated SHH expression at bud formation sites [35]. SHH null mice exhibit a congenital disorder cyclopia, neural tube malformation, and absence of distal limb structures as developmental defects [89]. Adult tissues require constant SHH activity for epithelial cell turnover, phase regulation, and prostatic growth, branching morphogenesis, and epithelial differentiation [90]. SHH overexpression adds to the metastatic potential with a probable interaction between epithelial and stromal cells and aberrant differentiation of epithelial cells [90].

Colorectal cancer is one of the leading causes of cancer death among young adults in the US [91]. Increased levels of GLI1 and GLI2 cooperatively represent a hallmark of unregulated HH activity in colorectal tumor progression. High GLI2 expression stems from an initial genetic mutation acts as a marker for high HH signaling. It predicts poor prognosis and suggests that the potential epigenetic reprogramming is an underlying natural metastatic transition [92]. A novel variation in HH signaling that sustains the colon tumor microenvironment inhibits the repressor form of GLI3 called GLI3R. SUFU, which typically sequesters GLI proteins in the absence of HH ligand binding, can also bind to GSK3 β to form the trimolecular complex GLI3/SUFU/GSK3 β . This complex activates phosphorylation of GLI3 and subsequent processing/cleavage, which represses the HH pathway [93–96]. High levels of GSK3 β found in colon cancer tissues up-regulate non-canonical HH signaling through maintaining the activator form of GLI3, thus effectively promoting cancer cell survival [93–96].

HH signaling downstream regulators are over-expressed in both squamous and adenocarcinomatous esophageal cancers [97]. GLI1 binds to the caudal type homeobox 2 (CDX2), responsible for maintaining the intestinal phenotype promoter, activating the site independently of SMO, which supports a non-canonical transition from squamous to columnar epithelium metaplasia in Barrett's-associated adenocarcinoma cells [98]. A study by Yang et al. found increased HH pathway activation in precancerous esophageal lesions (Barrett's esophagus and squamous dysplasia), suggesting HH signaling as an early event esophageal cancer development [99]. The same study stated that high levels of SHH, PTCH1, and GLI2 are focally expressed in the epithelium of carcinoma in situ, suggesting potential early screening possibilities for unusual HH signaling activity [99]. Many presentations of gastric cancer are epithelial-derived and manifest in the interstitium or more diffusely as adenocarcinomas. El-Zaatari et al. demonstrated that GLI1 knock-down in mice had reduced expression of a pre-neoplastic phenotype with low IL1 β , TNF α , IL6, phosphorylated signal transducer and activator of transcription 3 (STAT3), and proliferative marker Ki67 [100,101]. Studies that introduce GLI2 specific negative regulators in

gastric cancer cell lines informed a decrease in cell proliferation, migration, invasion, and an increase in cell apoptosis [102,103].

Previous work in mouse models has shown that GLI2 over-expression in the skin leads to the development of basal cell carcinoma (BCC), with sustained or aberrant upregulation of SHH/GLI cascade for cancer growth [104–106]. GLI2 acts as a direct upstream activator of GLI1 via binding to its promoter site and initiates a positive feedback loop in HH signaling.

HH signaling is also involved in ovarian cancer, bladder cancer, endometrial cancer, rhabdomyosarcoma, pancreatic tumorigenesis, non-small-cell lung cancer (NSCLC), melanoma, and hematological malignancies such as acute myeloid leukemia (AML), diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), Hodgkin's lymphoma (HL), ALK+ anaplastic large cell lymphoma (ALCL), mantle cell lymphoma (MCL), multiple myeloma (MM) and chronic myeloid leukemia (CML) [66,107–115]. Dysregulation of SHH, the most potent and widely expressed HH ligand, is characteristic of basal cell nevus syndrome, also known as Gorlin syndrome. [116,117]. Gorlin syndrome is an autosomal dominant neurocutaneous disease mainly triggered by PTCH1 gene mutations [118]. *PTCH1* gene mutations permit SMO transposition and enhance the expression of GLI that drives cell proliferation and tumor growth [118]. SHH dysregulation increases the risk of developing BCC, medulloblastoma, and meningioma. Activating or loss of function mutations in the HH pathway genes SMO and PTCH1 occur in human gastric tumors [119], sporadic BCC [120], medulloblastoma, nevoid basal cell carcinoma syndrome (NBCCS), and colorectal cancer [121].

6. GLI and Hallmarks of Cancer

6.1. Angiogenesis

Initial stages in preparing the tumor microenvironment include a breakdown of the vascular membrane and extracellular matrix (ECM), proliferation, and migration of endothelial cells (Figure 3). High expression of a common factor initiating angiogenesis, vascular endothelial growth factor-C (VEGF-C), is often correlated to increased vascularity in Glioma formation [122]. There is a potential link between elevated HH signaling and increased transcription of VEGF-C (Figure 3). Another factor, cysteine-rich angiogenic inducer 61 called CYR61, is an ECM associated signaling molecule that promotes the adhesion of endothelial cells through interaction via integrin. CYR61 contains pro-angiogenic characteristics at the embryonic and wound healing properties at adult levels [123,124]. SHH-expressing breast cancer cells exhibit unregulated levels of CYR61 at the transcript level. A GLI1 binding site exists upstream of the CYR61 transcription start site, and mutation or deletion of this GLI1 binding site results in diminished activity of the CYR61 promoter in the presence of GLI1 [125]. SHH influences angiogenesis in endothelial cells directly through the Rho/RhoA and Rho kinase (ROCK) signaling pathway [126]. SHH induces the expression of matrix metalloproteinase 9 (MMP9) and osteopontin (OPN) [126]. MMP9 is involved in the degradation of the ECM [126]. OPN, also known as bone sialoprotein I (BSP1), is a highly chemotactic glycoprotein involved in bone remodeling, bone mineralization, immune cell activation, and anti-apoptosis in various cancers and viral infections [126]. Genetic ablation of the tissue plasminogen activator (tPA) in mouse brain endothelial cells (MBECs) impaired tube formation and downregulated VEGF and angiopoietin 1 (Ang1). Addition to rh SHH to tPA^{-/-}, MBECs partially restored the tube formation and upregulated Ang1, but not VEGF, although rh SHH increased VEGF and Ang1 expression on wild-type MBECs. Complete restoration of tube formation in tPA^{-/-} MBECs was observed when both exogenous SHH and tPA were added, demonstrating the role of SHH-induced in vitro cerebral angiogenesis during the brain repair after stroke [127].

6.2. Epithelial to Mesenchymal Transition (EMT)

Downstream effects of GLI family activation such as EMT transform adult tissues to a mesenchymal-like state, losing polarity and adhesive properties while gaining migratory characteristics that encourage the invasive nature of cancer cells (Figure 3) [128]. This includes stem-cell features such as non-adherent growth, changes in the expression of cell-surface glycoproteins, and surface marker expression of stem cells [129]. The net structural transition of epithelial cells is from an attachment to the underlying ECM to migration into the matrix [130,131]. HH signaling induces the trans-differentiation of epithelial cells by decreasing E-Cadherin expression levels, increasing β -catenin and vimentin expression, tissue invasion, migration, and colony formation; it also transcribes necessary EMT regulators such as SNAIL, SLUG, and TWIST via GLI1 in adult human placentas [132]. In mouse models of gastric adenocarcinoma, EMT seems to be a particular phenotype of activated GLI2 [133]. These metastatic cells undergo rapid proliferation and differentiation typical of tumor heterogeneity and become locally invasive through basement tissues and manifest as tumor islands in the gastric mucosa—features only present with activated GLI2. Normal E-cadherin levels maintain cell attachment and layered phenotype of the villous cytotrophoblast. In contrast, EMT-induced reduction of E-cadherin and redistribution at cell junctional regions promotes loosened cell-to-cell connections and apicobasal polarity [132].

Further evidence in human melanoma cells suggests that GLI2 is directly responsible for turning off the E-cadherin gene (*CDH1*) expression during EMT in addition to enhancing the transcription of other EMT activators [134]. While this mesoderm expression process is an essential precursor to the differentiation of multiple tissue types and generation of organs in embryogenesis, it also enables a microenvironment of asymmetrical cell division leading to macroscopic metastases in adult tissues. Various target molecules regulate the proliferation pathway of HH signaling (Figure 3). Ectopic expression of Rab23 acts as a negative regulator of HH signaling at the level of GLI1 and GLI2 mRNA expression [135,136]. Interestingly, Rab23 upregulates the repressor form of GLI3, which endogenously inhibits the HH signal cascade [137]. EMT cells increase breast cancer metastasis via paracrine GLI activation in neighboring tumor cells and triggering HH/GLI signaling cascade [138]. GLI3 repressor (GLI3R) inhibits HH signaling, and GLI3R is essential for response to SMO antagonist glasdegib in AML [139]. GLI3 is silenced in most AML patients [139]. GLI3R represses AML growth by downregulating AKT expression [140]. GLI3R plays an essential role in SMO-independent HH signaling in AML and suggests that GLI3R could serve as a potential biomarker for patient selection in SMO antagonist clinical trials. GLI3 inactivation results in additional digit formation in vertebrates [140]. GLI3 works as a negative modulator of the proliferative expansion of digit progenitors by restricting the G1 to S cell-cycle transition by regulating CDK6 and constrains S phase entry of digit progenitors [140].

6.3. Cell Cycle

Aberrant HH signaling triggers a series of vasculogenic and angiogenic processes that endorse tumorigenesis and tumor growth in adult tissues. Several proposed that feedback loops regulate HH pathway activity (Figure 3). IFN- γ /STAT1 signaling has tumor suppressor function and is inactive in at least one-third of all melanoma and lung adenocarcinoma cell lines in mice [141]. SOCS1, an IFN- γ /STAT1 inhibitor, is activated by HH signaling pathway itself to create a negative feedback loop and a downstream target of GLI1 and GLI2, which upregulates its transcriptional activity and subsequently relieve the IFN- γ /STAT1 from obstructing tumor growth [142]. Common cell cycle genes turning on via the HH pathway include *CYCLIN D* and *E*, which are necessary to induce G1-to-S transition in the cell cycle, and *CYCLIN B*, which activates mitosis promoting factors (Figure 3). HH signaling opposes normal stimuli for epithelial cell cycle arrest such as *P21* and inhibits the *P53* tumor suppressor gene [143,144].

6.4. Migration/Adhesion/Invasion/Metastasis

Mechanisms of HH induced metastasis are understood at a broad level, but specific phases remain under deliberation. Upregulation of G-protein coupled receptors (GPCRs), chemokines CXCR4 and CXCR7 enhance the directional migration of breast cancer cells in lung metastasis by way of CXCL12 [145], which is a highly-secreted signaling protein of metastatic organs [146]. HH pathway upregulation of GLI1 enhances the CXCL12 induced migration of cancer cells [147]. Administering CXCR4 specific inhibitors or knock-down treatments suppress cancer cell migration patterns in breast and pancreatic cancer in mouse models and in vitro [145]. Part of the migration effectiveness depends on the EMT-programmed loss of cell-cell adhesion that leads to motility. GLI1 activates EMT by inducing SNAIL expression. SNAIL causes fibroblastic conversion, malignant transformation, and loss of a cell-cell adhesion molecule called E-cadherin [148]. Once the adhesive properties of the membrane are compromised, metastatic cells invade the matrix. The EMT program upregulates the expression of essential invasion factor AXL, which is required to maintain SNAIL, SLUG, and TWIST expression in pancreatic adenocarcinoma cells [149]. Interestingly, these same factors potently induce AXL expression, contributing to a positive feedback loop that continues the proliferation of malignant mesenchymal tumor cells [149]. GLI2 knockdown studies supporting its role in migration and invasion in osteosarcoma, prostate cancer, and hepatocarcinoma cell lines underscores the metastatic potential of GLI [150,151].

GLI2 expression directly enhances tumorigenesis in a model of myofibroblastic cells representing reactive stromal prostate cancer cells [152]. There is still some controversy regarding the exact model of hormone signaling in prostate tissues: paracrine versus autocrine. Paracrine signaling from the epithelium supports stromal differentiation during prostate development and sustains the stroma in the adult prostate [153,154]. In xenograft tumors, SHH is localized to the prostatic epithelium, while GLI1 mRNA is localized to the stromal compartment suggesting paracrine HH signaling [155]. Other studies support the idea of a shift to autocrine SHH signaling during pathogenesis and progression of prostate carcinoma [156]. There may be some interplay between these two forms of hormone activity in vitro, at least during the introduction of tissue metastasis, if not during the tumor progression.

7. HH Signaling Pathways during Infections and Viral Malignancies

Besides controlling processes involved in embryogenesis, there are broader implications of HH signaling. Recent studies revealed that aberrant activation of HH signaling leads to pathological consequences [157]. Viruses enter the host by interacting via their surface proteins, hijacking host replication machinery, targeting several signaling pathways concurrently, and overturning host immune mechanisms and evolutionary benefit from the host cell machinery. The virus makes copies of itself and spreads those copies to new hosts. Many viruses have evolved to stimulate host HH signaling to control their life cycle and pathogenesis [157,158]. There is considerable speculation of pathogens to use HH signaling to regulate their life cycle.

Here, we discuss influenza-A, hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), human papillomavirus (HPV), Merkel cell polyomavirus (MCPyV), human T-cell leukemia virus, type 1 (HTLV-1), Epstein-Barr virus (EBV) and Kaposi's sarcoma herpesvirus (KSHV) infection to highlight the plausible involvement of HH pathway players in the viral life cycle. We discuss the possible role of HH signaling in viral latency, virus reservoir maintenance, entry, replication, pathogenesis, infected cell proliferation, infection progression, pathogen recognition in the host, and the immune response of the host, exit of the pathogen and memory of the host immune mediators (Figure 4).

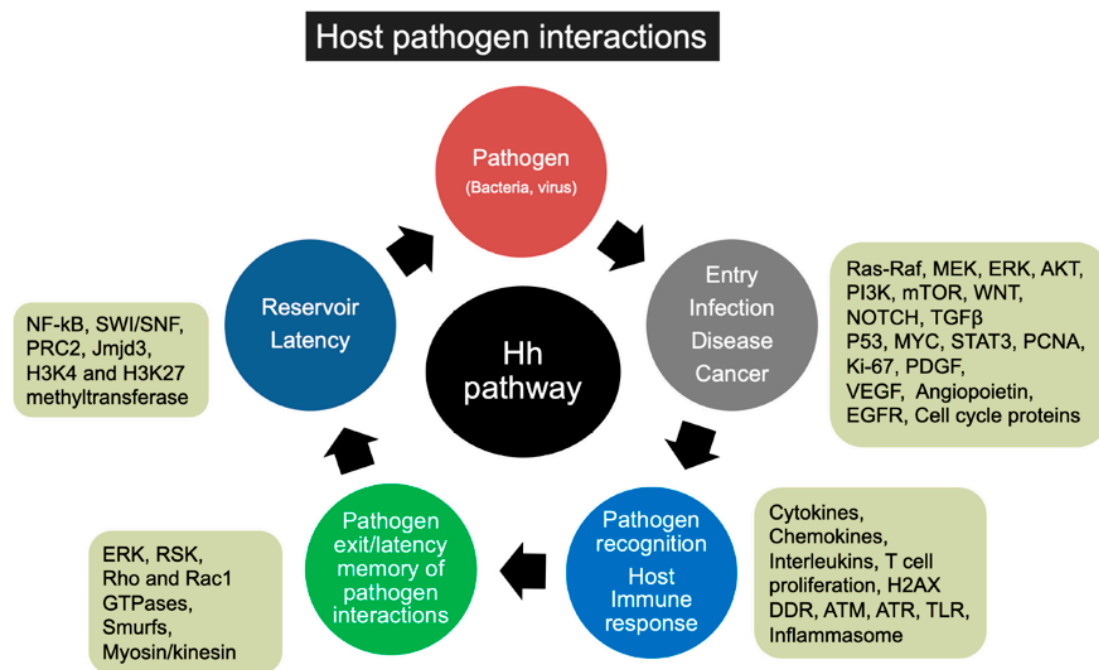


Figure 4. Schematic shows various stages and consequences of host-pathogen interactions. It also shows multiple signaling cascades, and transcription factors are demonstrated to be regulated by the HH pathway. Signaling molecules and transcription factors regulated by HH signaling could contribute to pathogen (virus or bacteria) entry, infection, pathogenesis (angiogenesis, fibrosis, inflammation), and activation of host foreign recognition network, host immune response, pathogen exit/elimination, and pathogen latency in the host.

HIV [159,160], HCV [161,162], HBV [163], EBV, and KSHV [164–166] utilize VEGF to maintain the vascularity of the tumors and infected cell proliferation. HH signaling plays an indispensable role in vascular development in mouse embryos via VEGF and NOTCH signaling [167]. SHH regulates the angiogenic VEGF and angiopoietin (Ang 1 and Ang 2) in astrocytes by activating the nuclear receptor subfamily 2 group F member 2 (NR2F2) transcription factor [168] (Figure 3). HIV [169], HCV [170], HBV [171,172], EBV and KSHV [173–176] infection promotes angiopoietin expression. Maturation of VEGF-induced new vessels in the cornea involves a platelet derived growth factor (PDGF)-SHH axis that mediates PDGF-BB-mediated smooth muscle cell (SMC) migration by inducing ERK1/2 and PI3K γ activation [177]. Elegant studies described that KSHV utilizes host PDGF receptor- α (PDGFR α) to drive its tumorigenesis and is prominently active in murine and human AIDS-associated-Kaposi's sarcoma (AIDS-KS) development [178]. Exclusively blocking PDGFR α signaling could impede murine KS tumor formation [178]. There is a strong correlation between the HH pathway and hypoxia and hypoxia-inducible factor 1 (HIF1). Hypoxia induces upregulation and secretion of SHH in the human pulmonary arterial smooth muscle cells (HPASMCs) [179]. SHH expression depends on HIF1 in the HPASMCs, and hypoxia stimulates GLI1 nuclear translocation [179]. Overall, hypoxia induces HPASMC proliferation, and the HH signaling pathway regulates apoptosis in the HPASMCs subjected to hypoxia [179]. HIV [180], EBV [181], and KSHV [182–186], HCV [187], and HBV [182] utilize the host HIF1 factor for redox signaling during their life cycle.

HH signaling is a potential target for manipulating viruses, as this pathway plays a fundamental role in cell survival and proliferation [188–190]. The HH target gene PTCH1 is one of the critical host genes involved in influenza infection and favors viral dissemination [191,192]. Nonstructural protein 1 (NS1), one of the multifunctional proteins, limits the lung's injury to preserve the viral habitat in the host. HH signaling plays a significant role in branching morphogenesis during pulmonary development [193]. Immunohistochemical analyses have indicated increased TGF β 1 expression at the epithelial site of fibrosis, such as cryptogenic fibrosing alveolitis and bronchiectasis. SHH antagonizes TGF β 1 by inducing

epithelial repair [194]. Patients with scarring in distal lung secondary to bronchiectasis show prominent perinuclear staining for SHH, thus relating the SHH staining to the level of injury [195].

Moreover, the HH receptor, PTCH1, is expressed in infiltrating and circulating lymphocytes (CD4 and CD8) at both protein and mRNA levels. It is evident that immune cells are equipped to respond to the HH ligand secreted from the inflamed area [196]. HH signaling thus plays an essential role in repairing damaged lung tissue by remodeling the epithelium directly or in concurrence with activated immune cells and regulates the communication of immune cells. Therefore, controlling the HH response may help the host to avoid the harmful consequences of viral infection. A similar study on larval *Drosophila melanogaster* has shown that the effect of the NS1 on the HH pathway is conserved between the species. A point mutation (A122V) was identified in *Drosophila*, which could reduce the HH-dependent activity of the NS1 in flies and transfected cells [191]. However, the same mutation, when incorporated into a mouse-adapted influenza-A virus, intensified the expression of some HH targets in the mouse lung and significantly accelerated lethality. No mutation at position 122 of NS1 has been recognized in any influenza strains, and thus NS1 protects the host. This muting of HH signaling may be utilized to diminish the harmful effects that could be caused by HH signaling to ensure optimal viral maturation before dissemination.

HIV [197], HCV [198], and HBV [199], EBV [200], and KSHV [201–203] are well-known to program their genes selectively to modulate the DNA damage response (DDR). KSHV manipulates DDR either via activation of ataxia telangiectasia mutated (ATM) pathway or by phosphorylating factors associated with the DDR, such as tumor suppressor protein P53 [201–203]. Interestingly, canonical HH signaling or ectopic expression of GLI1 causes genomic instability and cancer predisposition by faulting the S-phase checkpoint, DNA repair mechanisms, and inhibiting DNA double-strand breaks (DSBs)-mediated DDR [204]. ATM and Ataxia telangiectasia and RAD3 related (ATR) protein serine-threonine kinases involved in cell-cycle checkpoint signaling are regulated by HH signaling [205]. GLI inhibitor GANT61 induces DNA damage. GANT61 treatment increases the nuclear foci of γ H2AX and activates ATM and Chk2 in human colon carcinoma cells [206].

HH signaling also contributes to the epigenetic regulations. HH target genes are poised and are marked by an active (H3K4me3) and a repressive (H3K27me3) mark maintained by the H3K27 methyltransferase polycomb repressive complex 2 (PRC2) [207]. SHH induction recruits the Jumonji domain-containing protein D3 (Jmjd3), a histone H3K27 demethylase, which dislodges PRC2, removes H3K27me3, and enlists the Set1/MLL H3K4 methyltransferase complex to initiate gene expression [207]. DNA viruses exploit epigenetic regulation in maintaining viral episomes through the generation of chromatin, controlling viral gene transcription and replication or evading of the host innate immune response [208]. Excitingly, HIV [209], HCV [210], HBV [211,212], EBV [213,214] and KSHV [215,216] employ host methyltransferases, histone modification enzymes, histone acetylases, deacetylases, and demethylases, etc., for their chromatin remodeling, reactivation from latency, and viral life cycle propagation.

HBV and HCV are associated with liver cirrhosis and hepatocellular carcinoma (HCC) worldwide [217]. Pereira et al. showed increased hepatocyte production of HH ligands in patients with chronic HBV and HCV infection [218]. HH pathway activation often occurs during fibrogenic repair of liver damage due to chronic viral hepatitis [218]. HH-responsive cells facilitate hepatocarcinogenesis and disease advancement in chronic viral hepatitis [218]. Another study further confirmed the increased expression of HH targets in a GLI-dependent manner when liver cells were treated in vitro with the whole HBV replicon or with serum from HCV-infected patients [219]. This caused pro-fibrotic effects [219]. Hepatitis B virus x (HBx), one of the HBV viral proteins, increases GLI1 protein nuclear accumulation [220]. HBx protein stimulates the HH-GLI activation through protein stabilization and nuclear localization of GLI1 in liver cancer cells while the exact role of GLI1 protein translocation for these viral activities remains to be discovered [220]. Blocking HH signaling delayed

hepatocarcinogenesis induced by HBx protein (Table 1) [221]. HH signaling in liver cells is associated with increased permissiveness for HCV replication and viral production [222].

Table 1. Therapeutic strategies against viral diseases.

Hh Inhibitors	Disease	Mechanism of Action
Vismodegib (<i>GDC-0449</i>)	HBV and HCV	Decreases liver fibrosis in human Decreases tumor formation in a mouse model of fibrosis-associated HCC
		Reduces the growth of HBV X-expressing tumor xenografts in nude mice and HCC formation in transgenic mice expressing the HBV X protein
GLI inhibitors: GANT-61	EBV and EBV linked Nasopharyngeal cancer	Reduces the pro-fibrotic effects Inhibits autophagy in HCV-exposed fibroblasts
	HPV	Reduces tumor-sphere formation in several EBV-infected cell lines Decreases the proliferation of Human Papilloma Virus-derived cervical cancer cells
GLI agonist	HIV	Targeted against local uninfected environment
Smoothened agonist		Targeted against HIV infected Cells. Limits viral niche.

The HH pathway maintains and controls stem cells and policies of hematopoiesis and lymphopoiesis to maintain immune cells [223–226]. Increased GLI1 expression in EBV infection decreases the level of human leukocyte antigen (HLA) and helps the virus to escape cytotoxic T cell recognition [227]. The HH pathway is activated in EBV derived nasopharyngeal carcinoma (NPC) tissue, NPC-derived cell lines, and in EBV infected epithelial cells [228]. HIV-related nephropathy presented increased expression of GLI and associated proteins of the HH pathway [217]. EBV latent membrane protein 2A (LMP2A) utilizes Gli1 to downregulate HLA in gastric cancer cells [229]. The same was observed in a human podocyte cell line infected with HIV [217]. These aberrant pathway activities decrease host defense by increasing proliferation and migration markers, loss of kidney filtration barrier function, and increased permeability. All these changes observed could seemingly boost viral dissemination and increase host infectivity [217]. HIV infection is linked to the elevated level of immunoregulatory cytokine TGF β 1 that leads to the suppression of host protective immune responses [230]. GLI2 regulates TGF β 1 at the transcriptional level in human CD4+ T cells during HIV infection [230]. Human SMO inhibits HIV-1 replication and disease [231]. The role of the HH pathway was tested in HIV-induced EMT, which is critical for the progression of kidney injury [217]. The blockade of the HH pathway with GANT 58 (GLI antagonist, a specific blocker for GLI1-induced transcription) treatment could dramatically decrease HIV-induced podocyte EMT, permeability, and fibrosis of the kidney (Table 1) [217].

HH regulates the expression of OPN in nonalcoholic steatohepatitis-related liver fibrosis as GLI directly interacts with the GLI-binding sites in the OPN promoter [232]. A decrease in either HH signaling or OPN decreases fibrosis [232] as OPN is a direct transcriptional target of the HH pathway [232]. Treatment with GLI1 inhibitor or cyclopamine plays a protective role in a mouse model of renal fibrosis following injury and expressing the activated HH signaling pathway [232]. Some viruses may promote HH signaling to induce fibrotic damage to ensure viral spread [157,217,233]. Other pathogens, such as the influenza virus, limit fibrotic tissue formation, thereby allowing more time for replication, maturation, and dissemination of infection [157,191]. However, to maintain progeny, these viruses make sure to support viable hosts available for reinfection.

Merkel cell polyomavirus (MCPyV) is detected in approximately 80% of Merkel cell carcinoma (MCC), an aggressive neuroendocrine skin cancer mostly occurring in the elderly. Reactivation of HH signaling later in life can cause tumors. 29 MCPyV-positive and 21 MCPyV-negative MCCs were stained for SHH, IHH, PTCH1, SMO, GLI1, GLI2, and

GLI3 and expression of the HH signal pathway players associated with MCPyV infection and prognosis of MCC [234].

HPV oncogenes (E6/E7) and estradiol, major etiologic factors associated with cervical cancer, could induce GLI activity in the cervix and the skin in mice [235]. Treatment with a putative novel HH inhibitor itraconazole, could not diminish HH signaling, but it reduced growth at an early stage of cervical carcinogenesis (Table 1) [235]. While these studies suggested the possible involvement of HH signaling in cervical carcinogenesis, the mechanism is not known [235]. GLI1 and GLI2 overexpression serve as a prognostic factor for overall and disease-free survival in patients with locally advanced HPV negative head and neck cancer undergoing surgery and postoperative radiotherapy [236]. The human poliovirus receptor CD155 gene acts as a transcriptional target of SHH and is activated by SHH in neuroectodermal tumors [237].

Tumor cells of Hodgkin lymphoma (HL) are derived from mature B cells. The lineage infidelity of Hodgkin/Reed-Sternberg cells (HRSs) often causes diagnostic problems as HRS markers are also favorable for follicular dendritic cells (FDCs). Investigation of the expression of FDC markers in HL and anaplastic large cell lymphoma (ALCL) revealed GLI3, fascin (actin-bundling protein found in membrane ruffles), and TUBB3 (a member of the beta-tubulin protein family) as the most sensitive markers, which were diffusely positive in HL [238]. A recent study from our lab reported the increased expression of GLI1 in KSHV infected primary effusion lymphoma (PEL) cells [239].

Anti-inflammatory lipoxin A4 treatment in PEL cells downregulated GLI1 expression [239]. The decrease in GLI1 and PTCH1 expression was not dependent on SHH ligand activity, as we did not observe any significant change in SHH expression in the solvent or lipoxin A4 treated PEL cells. Interestingly, we found increased phosphorylation of GLI1 at Thr 1074 and decreased phosphorylation of AKT/mTOR proteins in lipoxin A4 treated PEL cells. GLI1 phosphorylation at Thr 1074 led to the degradation of GLI1 through 5' adenosine monophosphate-activated protein kinase (AMPK) activation (through the phosphorylation of AMPK at Thr 172) and reduced the oncogenic potency of GLI1 by preventing the transcription of target genes GLI1 and PTCH1. We are testing the therapeutic potential of GLI inhibitors in KSHV related cancers, including KS and PEL.

HTLV1 expression is activated by the interaction of a viral transactivator protein, TAX, and cellular transcription factor, CREB (cyclic AMP response element-binding protein), binds to the long terminal repeat (LTR). The human homolog of a member of the GLI oncogene family, GLI2 (also termed hGLI2), helps HTLV1 infection progression as the simultaneous binding of hGLI2 and CREB seems critical for TAX protein to activate transcription [240]. HIV [241], HCV [242], HBV [243,244], EBV [245], and KSHV [246] utilize MYC and cellular STAT3 for infected cell proliferation, the persistence of herpesviruses latency, and inhibition of viral reactivation. HIV [247], HCV [248], HBV [249], EBV and KSHV [250,251] infected cells secrete cytokines and chemokines to regulate viral pathogenesis, evade host immune response (Toll-like receptors; TLRs and inflammasome), angiogenesis, and selectively chemoattracts T cells, activation and migration of immune cells. HIV1 envelope protein R5 gp120 exposure to immature monocyte-derived DCs (MDDCs) resulted in the CCR5-dependent production of interleukin-6 (IL6) cytokine via mitogen-activated protein kinase (MAPK)/NF- κ B pathways [252]. IL6 could activate STAT3 by an autocrine loop, further contributing to IL6 secretion [252]. HH pathway has been demonstrated to act synergistically with interleukin-6 to drive the growth of basal cell carcinoma via STAT3 activation [253]. Mechanistically, IL6 and HH/GLI signaling integration occur at the level of cis-regulatory sequences by co-binding of GLI and STAT3 to common HH-IL6 target gene promoters and HH-IL6 pathway combinatorial blockade could efficiently arrest cancer growth in BCC patients [253]. These transcription factors, signaling pathways mediating IL6 induction have not been tested in the context of viral infections, which depend significantly on the IL6 for survival and progression of infection such as KSHV [254], H1N1 influenza A infection [255], Pneumovirus infection; closely related to a respiratory syncytial virus [256], Hepatitis B Virus [257], and EBV [258].

HH signaling is also regulated by MAPK and NF- κ B cascade and HH/GLI1, MAPK (KRAS-MEK-ERK) cascade and NF- κ B cooperate to regulate growth and cell proliferation [259], and apoptosis resistance in many tumors [260]. These studies provide a potential link that could be playing an important role in the lifecycle of many viruses, which activate MAPKs and NF- κ B in host cells upon binding, entry, or during the stage of viral gene expression. Similar to MAPK, ERK, PI3K, and NF- κ B, HH/GLI pathway plays an important role in the induction and sustenance of Rho-GTPases and stimulates cell migration [261,262]. HIV [263], HCV [264], HBV [265], EBV [266] and KSHV [267–269]. These viruses utilize signaling pathways such as ERK, RSK, PI3K, Rho, and Rac1 GTPases for cell cycle progression, viral entry, cellular transformation, expression of viral genes, and the establishment of infection. HIV [270], HCV [271,272], HBV [273–275], EBV, and KSHV [276–279] exploit host AKT, PI3K, mTOR signaling pathways for the evasion of apoptosis, infected cell survival, and proliferation, viral replication, production, vesicle formation, intracellular motility and activation of transcription factors. HIV [280], HCV [281], HBV [282], EBV [283], and KSHV [269] utilize myosin/kinesin for viral transmission, virion transcytosis, virus entry, intracellular viral transport, and formation of highly metastatic and invasive tumors with the leading edge.

Not only viruses, but bacterial infections such as *Salmonella enteritidis* ST183 [284] *Escherichia coli* [285], and *Helicobacter pylori* [286] are also inclined to use the HH signaling pathway to control the infection progression and the infected cell microenvironment [284,285,287,288] (Figure 4). *Helicobacter pylori* infection mediated inflammation and repair process involving macrophage recruitment activates transcription factor NF- κ B and also upregulates HH proteins [286].

8. GLI Inhibition and Implications as Anticancer Therapeutics

Currently, small molecule modulators such as SMO and GLI1 inhibitors of HH signaling have been used in basic research to detect links between signaling and specific phenotypes of interest [289]. Few inhibitors are now in use to treat certain malignancies associated with viral infections (Table 1), BCC and certain leukemia, whereas many others are still in clinical trials [290]. Till now, vaccines and antivirals, which are specific to rapidly mutating viral proteins, have been used, but now with the use of HH inhibitors, a broad spectrum of strains can be targeted. Since the HH signaling controls many critical cellular processes, simultaneously, there is a need to target a specific pathway component selectively. This process may require combinatorial drug usage targeting different HH-dependent processes, which may further regulate signaling in the infected cells. An in-depth understanding of the precise mechanism by which viral factors would interact with the HH pathway players would prove beneficial for targeted therapies.

Aberrant HH signaling has been found responsible for chemo-resistance in aggressive cancers [291,292]. Much work has already shown the worth of the GLI family as emerging targets for cancer therapy [293]. GLI1 inhibitors have demonstrated the broadest therapeutic potential so far as a target in advanced and metastatic tumors [293]. GLI1 expression has been used as a potential prognostic factor for survival in bladder and colon cancer [294]. Inhibition of upstream MEK1/2-ERK1/2 activity with U0126 inhibitor in human HT29 colon cancer cells suppress GLI transcriptional activity and subsequent protein expression [96]. GLI1 also supports a correlation between low expression and more prolonged survival in patients with oral squamous cell carcinoma [295]. Breast tumor cells upregulate GLI2 expression during bone metastasis, stimulating bone resorption, activating TGF β , and subsequent tumor proliferation [296]. Aberrant HH signaling activation promotes the growth of BCC, medulloblastoma, colorectal cancer, and small lung cell cancer [289]. This has led to a large repertoire of small molecule inhibitors developed for the treatment of cancers dependent on the HH pathway.

Among SMO inhibitors, GDC-0449 and LDE-225 are in the clinic for the treatment of advanced BCC with aberrant HH activity due to loss of the functional allele of PTCH [297,298] The steroidal alkaloid, cyclopamine, has progressively shown therapeutic potential as an

inhibitor for HH signaling. The mechanism of cyclopamine action suggests an interaction with the SMO heptahelical bundle, promoting a protein conformation through small endogenous molecules rather than direct protein-protein interaction [292,299]. In Glioma-derived neurospheres, cyclopamine blocked overall growth rate by 30–70% [291,300]. Vismodegib (trade name Erivedge) is another SMO inhibitor that effectively terminates HH signaling. Vismodegib is also an FDA approved treatment for basal cell carcinoma in adult patients [301]. There is less support for cyclopamine and its analogs as therapies in cancers with bone metastases such as IBC, wherein GLI2 needs to be inhibited further downstream from the HH receptors [302]. LDE-225 (Erismodegib/Sonidegib/Odomzo), HH pathway inhibitor, received FDA approval to treat cancer patients [303,304]. Many phase I and phase II trials for Erismodegib as a monotherapy and in combination are underway, treating malignancies including advanced gastroesophageal adenocarcinoma, small cell lung cancer, myelofibrosis, advanced/metastatic HCC, and relapsed medulloblastoma [305,306].

IPI-926 (Saridegib), CUR61414 binds to SMO and prevents its activation, BMS-833923/XL139 (binds SMO), PF-04449913; Glasdegib (SMO inhibitor), PF-5274857 (SMO antagonist), TAK-441 (SMO inhibitor), LY2940680; Taladegib (SMO antagonist), MRT-92 (anti-SMO activity by blocking several overlapping sites of the SMO transmembrane domain), Jervine (binds to SMO and preventing its conversion to an active state), RU-SKI 43 (SHH Inhibitor), and SHH Monoclonal Antibody 5E1 (SHH Inhibitor) is SMO or SHH Inhibitor in clinical trials [305,306].

A well-known small molecule inhibitor, GANT61, reduces GLI1, GLI2, and PTCH1 mRNA expression in human colon carcinoma cell lines [96]. GANT61 appears to be a more potent treatment in colon carcinoma cell lines than its upstream-acting counterpart, cyclopamine. Another study found that cells treated with GANT61 accumulated at G1/S followed by early S and finally underwent cell death at 48h, and cyclopamine treated cells demonstrated minimal effects on cell cycle distribution or cell death [96]. Arsenic Trioxide (ATO) is an FDA approved inhibitor of GLI1 and GLI2 transcription factors for acute promyelocytic leukemia treatment [303]. In esophageal adenocarcinoma (EAC), elimination of S6K1 activation by mTOR pathway inhibitor enhances the killing effects of the HH pathway inhibitor [52]. In EAC, the activated mTOR/S6K1 pathway promoted GLI1 transcriptional activity and oncogenic function through S6K1-mediated GLI1 phosphorylation at Ser84, which released GLI1 from its endogenous inhibitor, SUFU.

SHH pathway is highly activated in pancreatic CSCs and plays an essential role in cancer initiation, progression, and metastasis [88]. Sanguinarine, an anti-inflammatory and antioxidant compound isolated from the roots of *Macleaya cordata* and *M. microcarpa*, could inhibit cell proliferation, colony formation, self-renewal capacity, and induced apoptosis in human pancreatic CSCs through oxidative damage. Sanguinarine inhibited the SHH-GLI pathway, leading to modulation of GLI target genes in pancreatic CSCs. Sanguinarine inhibited the binding of NANOG with promoters of CDK2, CDK6, FGF4, c-MYC, and OCT4, suggesting the direct involvement of NANOG in the cell cycle, pluripotency, and self-renewal of pancreatic CSCs via SHH-GLI-NANOG pathway [304]. Aspirin (acetylsalicylic acid, ASA), the most widely used drug for its analgesic, antipyretic, and anti-inflammatory properties, has a broad-spectrum antitumor effect in pancreatic cancer, colorectal adenomas, hepatocellular carcinoma, etc. [307]. Recently, aspirin was reported to exert its antineoplastic property in glioma by abrogating the tumorigenic effect of the SHH/GLI1 signaling pathway, especially sensitizing the malignant glioma cells resistant to temozolomide (TMZ) therapy [307].

9. Perspectives

GLI transcription factors interact with multiple signaling pathways. Therefore, many combination treatment modalities are under clinical trials, including PI3K inhibitor (BKM120 or BEZ235) and SMO inhibitor (LDE225), an mTOR inhibitor and GANT61, simultaneous targeting of GLI1 and HIF2 α . LDE225/Sonidegib and GDC-0449/Vismodegib SMO inhibitors are FDA approved for treating basal cell carcinoma. Clinical trials are ongoing to evaluate

the efficacy of this novel class of targeted therapy in various malignancies. The paracrine mechanism plays an essential role in upregulating the HH signaling in a tumor animal model, suggesting the need to consider the stroma-tumor interactions in HH/GLI signaling in the experimental models [105]. HH signaling and GLI transcription factors gain attention and interest in host-pathogen communications and are emerging as a pathogenic target that calls for further investigation. Recent studies highlight the role of HH/GLI signaling in the modulation of the anti-tumoral immune response. These studies have uncovered the functions of HH/GLI in immunosuppression and the production of immunosuppressive cytokines. This exciting development and novel research findings warrant future evaluation of the combination of cancer immunotherapy with HH/GLI inhibitors.

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Abbreviations

ALCL	Anaplastic large cell lymphoma
ATO	Arsenic Trioxide
CDH1	E-cadherin gene
CSCs	Cancer stem cells
CREB	cyclic AMP response element-binding protein
CYR61	Cysteine-rich angiogenic inducer 61
DHH	Desert HH
EBV	Epstein–Barr virus
ECM	Extracellular matrix
EMT	Epithelial to Mesenchymal Transition
FDCs	Follicular dendritic cells
GLI	Glioblastoma-associated-protein
GSK3 β	Glycogen Synthase Kinase 3 Beta
HH	Hedgehog
HTLV-1	Human T-cell leukemia virus type 1
HBV	Hepatitis B
HCV	Hepatitis C
IBC	Inflammatory Breast Cancer
IHH	Indian HH
IL6.	Interleukin-6
KSHV	Kaposi's sarcoma herpesvirus
LTR	Long terminal repeats
MAPK	Mitogen-activated protein kinase
MCPyV	Merkel cell polyomavirus
NSCLC	Non-small-cell lung cancer
NLS	Nuclear localization signal
NES	Nuclear export signal
PTCH1	Patched1
SMO	Smoothed
SHH	Sonic HH
SUFU	Suppressor of fused
VEGF-C	Vascular endothelial growth factor-C

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