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REVIEW

Biochemical pathways and targeted therapies in basal cell carcinoma: A systematic review

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Abstract: Basal cell carcinoma (BCC) is the most common type of human malignancy. It is a slow-growing skin cancer with little ability to metastasize, but it is aggressive and can cause local tissue destruction. Descriptions of Basal Cell Nevus Syndrome (BCNS), characterized by a predisposition to the formation of BCC and other neoplasms, and identification of the genetic defect in this syndrome, has led to significant advancement in our understanding of the pathogenesis of BCC. Unregulated expression of target genes in the sonic Hedgehog (SHH) signaling pathway plays a prominent role in the pathogenesis of BCC. An understanding of the signaling components has allowed for the development of pharmacologic agents that inhibit the SHH pathway. The first inhibitor of the SHH pathway approved by the Food and Drug Administration (FDA) for the treatment of BCC is vismodegib. In this review, we will discuss the biochemical pathways involved in BCC as targets of novel pharmacologic therapies.

Keywords: basal cell carcinoma; nonmelanoma skin cancer; Hedgehog signaling; vismodegib

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Introduction

Clinically, the prototypical nodular basal cell carcinoma BCC appears as a single pearly papule with telangiectasia. Histologically, BCC is characterized by a thickened epidermis with invasive buds and lobules of basaloid cells in the dermis with palisading nuclei (**Figure 1**).

Other subtypes of BCC include superficial and morpheaform BCCs, which have different clinical and histological findings. Basal cell carcinoma is the most common type of skin cancer in the world, with an incidence rate greater than 935/100,000 person-year in Southwestern United States, and with the rate increasing at 2% per year[1]. There is significant geographic variability, with

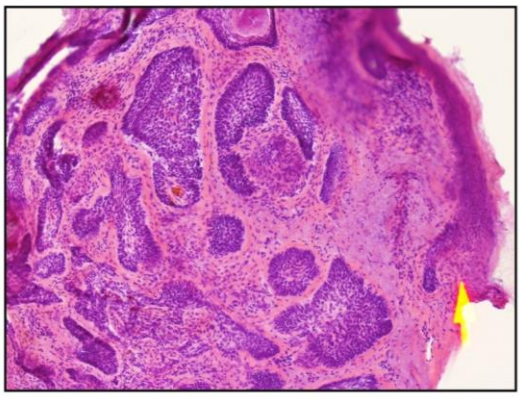

Figure 1. Hematoxylin and eosin stained slide demonstrating the histopathologic features of nodular BCC including invasive lobules of basaloid cells with clefting and palisading nuclei

the highest rates in Australia with an incidence of > 1,000/100,000 person-year compared to the lowest rates seen in parts of Africa with an incidence of < 1/100,000 person-year. Presumably, this is due to differences in skin pigmentation and ultra-violet (UV) light exposure. Indeed, risk factors related to UV and skin type include fair skin, red hair, blue or green eye color, Northern European ancestry, history of blistering sunburns, history of psoralen and UV-A treatment, exposure to arsenic, ionizing radiation, history of solid organ transplant, and certain genodermatoses[2]. BCC is thought to develop as a result of uncontrolled signaling due to mutations in the sonic Hedgehog pathway.

Methods

The identification of relevant articles was performed using the databases PubMed, CINAHL, and EMBASE in October 2015. Key search terms included "basal cell carcinoma," "vismodegib," and "hedgehog signaling". Language restrictions were not applied. Two reviewers identified potentially relevant studies. Furthermore, the reference sections of review articles were analyzed to harvest further citations.

Results

Hedgehog biochemical pathway

While important in embryologic development, the Hedgehog (Hh) pathway is considered to be mostly inactive in adults, save for a few important functions such as hair follicle growth[3], regulation of adult stem cells, and tissue maintenance and repair[4]. There are three mammalian homologs of the Hh ligand: Sonic Hedgehog (SHH), Indian Hedgehog, and Desert Hedgehog. Hh predominately functions in the skin but all bind its intended receptors with equal affinity[4].

The Hedgehog pathway is a network of multiple signaling interactions. The components of SHH signaling that serve as current pharmacologic targets are described in brief below:

1. Hedgehog protein has structural homology similar to a carboxypeptidase but instead of demonstrating hydrolytic activity, it has been found to directly bind to Patched (PTCH), a 12-pass transmembrane receptor located on the cell membrane during telophase at the base of primary cilia[5]. Hedgehog protein binds as an extracellular ligand in the ligand-dependent pathway[6]. The Hedgehog pathway uses primary cilium to process its components and amplify the SHH signal[7]. Normally PTCH sits in the cilium, but SHH ligand promotes the exit of PTCH from the cilium[8]. PTCH translocates and internalizes, causing the sterol pumps to be turned off. Oxysterols subsequently accumulate around a G-protein-coupled receptor known as Smoothened (SMO) and removes the inhibitory effect over SMO[4].

2. In the absence of SHH, PTCH constitutively inhibits SMO by preventing it from entering the cilium[4] (**Figure 2A**). This suppresses the initiation of downstream signaling events[4]. PTCH also removes oxysterols that were created by 7-dehydrocholesterol reductase, which inhibits the initiation of SMO pathway[4].

3. SMO is a 7-pass transmembrane G-protein-coupled receptor. It is a key pharmacologic target in Hedgehog pathway inhibition, and its biochemical structure is characterized when bound to a small molecular SMO inhibitor[9]. When PTCH is no longer in the cilium and inhibition is relieved, SMO and a Glioma-associated oncogene family protein (GLI) enter the cilium[8]. SMO activates GLI, a transcription factor (**Figure 2B**), by moving to the cell membrane of the cilium and cleaving the GLI family of transcription factors from the Suppressor of fused (SUFU) protein, a negative suppressor which prevents the transcription of GLI1 target genes[4].

4. GLI binds DNA and activates the transcription of SHH target genes (**Figure 2B**), which are involved in cell proliferation[10]. GLI is characterized by a nuclear localization signal that targets it to the nucleus, where it binds to GLI promoters via its repeated zinc finger motifs[4,11]. The kinase protein KIF7 positively and negatively regulates the SHH pathway. The promotion of SHH pathway via KIF7 occurs via antagonization of the activity of SUFU and KIF7, and negatively regulates the pathway by inhibiting GLI-dependent transcriptional activation[12].

Activation of the Hedgehog pathway has been extensively studied and three different mechanisms have been proposed: Type I ligand-independent signaling is driven by inactivating mutations of PTCH1 on chromosome 9q (**Figure 2C**), or activating mutations of SMO (**Figure 2D**), which leads to constitutive activation of Hedgehog signaling pathway in the absence of the Hedgehog (HH) ligand[13]. Type II ligand-dependent signaling in an autocrine or juxtacrine manner involves the secretion of the HH ligand from the same or neighboring tumor cells which activates the HH pathway. Type III ligand-dependent signaling involves a paracrine manner, in which the HH ligand is secreted from tumor cells. The ligand is received by remote cells in the stroma, which provide signals such as VEGF and IGF back to the tumor[4]. The Type I ligand-independent Hedgehog pathway is the proposed mechanism for the pathogenesis of basal cell carcinoma[4]. The clear role in the pathogenesis of basal cell carcinoma came from the studies of patients with genetic predispositions for developing BCC.

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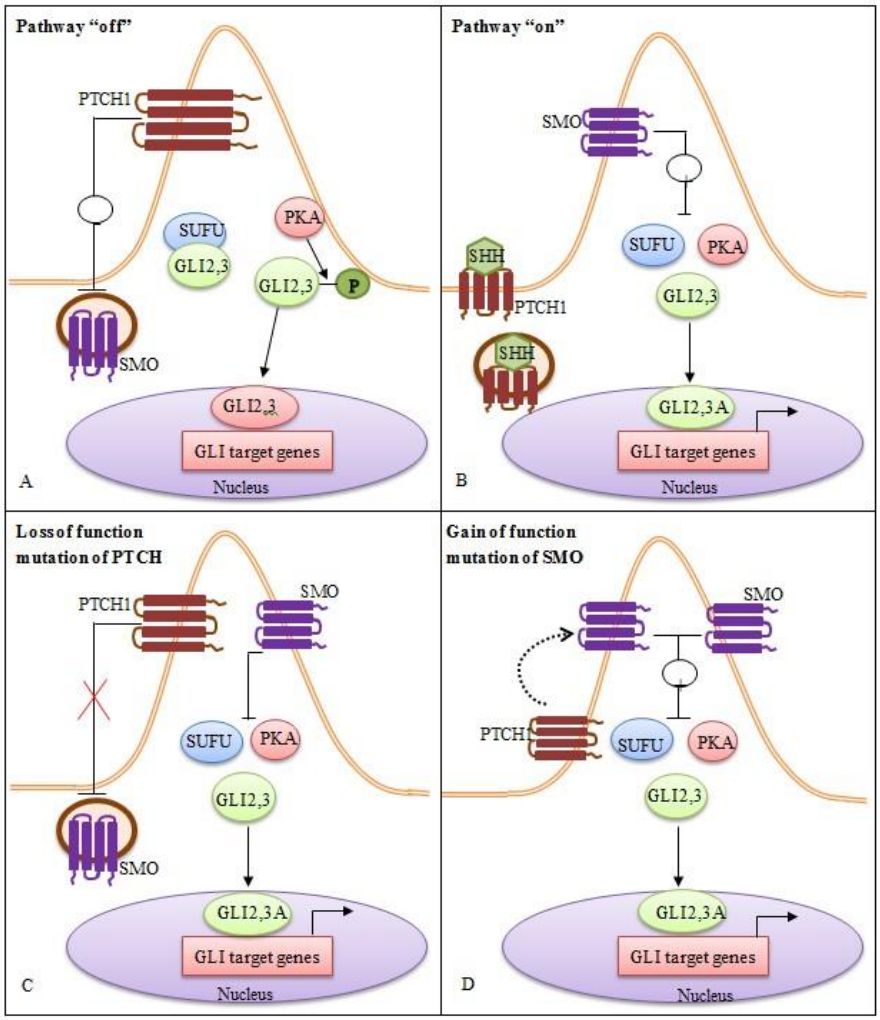

Figure 2. Simplified Hedgehog signaling pathway demonstrating Hedgehog signaling in physiologic and oncogenic states. **(A)** In the absence of SHH ligands, PTCH1 is located in the primary cilium and inhibits the activity of SMO. The GLI proteins together with GLI2 and GLI3 are phosphorylated by protein kinases such as PKA. SUFU inhibits GLIs in the cytosol which leads to its proteolytic cleavage to generate the repressor forms GLI2R and GLI3R. **(B)** In the presence of SHH ligand, PTCH1 exits the primary cilium, and SMO accumulates. The activation of SMO results in the dissociation of the GLI–SUFU complex and the transportation of activated GLI2 and GLI3 proteins to the nucleus. Activated GLI promotes expression of SHH target genes. **(C)** Loss-of-function mutation of PTCH results in unregulated SMO signaling and promotes tumor formation. **(D)** Gain-of-function mutation of SMO results in constitutive expression of SHH target genes, promoting tumor formation.

Genodermatoses

BCC is a prominent feature of several genetic syndromes (**Table 1**):

1. Basal Cell Nevus Syndrome (BCNS), also known as Gorlin syndrome, features multiple aggressive basal cell carcinomas, odontogenic cysts, skeletal abnormalities, ectopic calcifications, facial milia, coarse facial features, and palmoplantar pits[14]. It follows an autosomal-dominant inheritance pattern, and is caused by mutations in the Patched (*PTCH*) tumor suppressor gene on chromosome 9q22.3[15]. Presumably, a germline PTCH alteration increases the chances of a "second hit" mutation to cause loss of heterozygosity and loss of PTCH function. Without PTCH suppression, SMO has unchecked downstream signaling, which is thought to aid in the development of basal cell carcinoma.

2. Xeroderma pigmentosum (XP) features heightened photosensitivity of the skin resulting in BCC and other skin neoplasms, premature skin aging, ocular manifestations such as photophobia and cataract development, and neurologic manifestations such as microcephaly and sensorineural hearing loss[16]. It is inherited as an autoso-

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Table 1. Syndromes featuring BCC, genetic defect, and mode of inheritance

Syndrome	Mutation	Inheritance
Basal Cell Nevus Syndrome	*PTCH*	Autosomal Dominant
Xeroderma Pigmentosum	*XP*	Autosomal Recessive
Bazex-Dupré-Christol Syndrome	Unknown	X-linked Dominant
Rombo Syndrome	Unknown	Autosomal Dominant

mal recessive trait and is due to disorders of nucleotide excision repair and replication of damaged DNA caused by mutations in the XP genes[16].

3. Bazex-Dupré-Christol syndrome features basal cell carcinomas and nevi, follicular atrophoderma, and diffuse congenital hypotrichosis[17]. Its hereditary pattern is X-linked dominant[17]. The genetic defect involved in the pathogenesis of the basal cell neoformations has not yet been defined.

4. Rombo syndrome presents with BCCs, milia, hypotrichosis, vermiculate atrophoderma ("worm-eaten" appearance), and peripheral vasodilation with cyanosis[18]. It is inherited in an autosomal dominant fashion. It is distinguished from Bazex syndrome by the skin redness, although its genetic defect is similarly unknown[19]. There are multiple other syndromes that may feature or be associated with the development of basal cell carcinoma. Certainly, areas of future research will include defining the genetic defects in syndromes featuring BCCs.

Molecular pathogenesis

In sporadic BCC, the gene-encoding tumor suppressor protein 53 (TP53) has been found to be mutated even in the absence of PTCH1 alteration[20]. TP53 is involved in cell cycle regulation, DNA damage repair, and apoptosis. It is mutated in approximately half of all human malignancies[21]. With regard to the SHH pathway, BCC-like tumors have been induced in a transgenic mouse model with overexpression of SHH[22]. As we have observed in the loss of function of PTCH1 in BCNS, unregulated transcription of SHH target genes promotes BCCs. Downstream of PTCH, activating mutations in SMO have also been found to result in BCC formation (**Figure 3**)[23]. Finally, GLI overexpression has been shown to induce BCC in a mouse model[24]. SHH signaling does not occur in isolation; cross-talk has been demonstrated with other cell signaling cascades including epidermal growth factor receptor (EGFR), transforming growth factor beta (TGFβ), tumor necrosis factor (TNF), and wingless (Wnt), and these pathways are well summarized in a recent review article[25]. As the mechanisms for these signaling interactions are further elucidated, there may be identification of novel targets for inhibiting the growth and development of basal cell carcinoma.

Interestingly, BCC has a low tendency to metastasize. On the molecular level, the distant spread of a cancer cell is inhibited by metastasis suppressors (MSPs), which are proteins defined by its ability to inhibit a cancer cell's capacity to metastasize without affecting primary tumor growth[26]. BCC's low metastatic potential may be due to the maintained expression of MSPs NM23-H1, NDRG1, and E-cadherin[27]. Despite this, metastasis does occur, with an incidence of 0.0028%–0.55%[28]. Unfortunately, metastatic BCC (mBCC) carries a poor prognosis with a median survival of ten months[29]. With the recent advances in systemic therapies targeting components of the SHH pathway, there is hope for improvement of symptoms and survival in mBCC.

Treatment of basal cell carcinoma is dependent on the risk of recurrence, which involves clinical features of the tumor, such as anatomic site and borders; patient risk factors, including immunosuppression from solid organ transplant; histopathologic features such as morpheaform or micronodular subtypes; and evidence of perineural invasion[30].Therapies range from topical imiquimod or 5-fluorouracil, photodynamic therapy, radiation, electrodessication and curettage, standard surgical excision with post-operative or intra-operative margin assessment, to Mohs micrographic surgery[31]. While surgery is the mainstay of therapy, targeted inhibitors of hedgehog signaling increase the medical armamentarium in the treatment of advanced and mBCC.

SMO inhibition

Cyclopamine was the first pharmacological inhibitor of SHH signaling described and its timeline in the development of SHH inhibitors in humans has been recently reviewed[32]. Briefly, the phenotype of cyclopia, or having one eye, was discovered in lambs whose mothers grazed on corn lilies. The teratogen in this plant was identified and named as cyclopamine. In humans as well, it was realized that cyclopia was caused by defective SHH signaling during embryogenesis. Further studies revealed that cyclopamine binds SMO and inhibits SHH signaling. Small-molecule screens identified other SMO inhibitors with more favorable pharmacology. Cyclopamine has low affinity to the receptors and poor bioavailability[4]. A more soluble and stable derivative—IPI 269609—has been developed[4].

Vismodegib (GDC-0449) is likely the most well-known SHH pathway inhibitor. In 2009, a phase I clinical trial revealed the clinical promise of this small molecule antagonist of SMO in cases of advanced BCC[33].

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Given its continued success in a phase II trial, the drug was approved by the Food and Drug Administration (FDA) in 2012 for the treatment of locally advanced (laBCC) or mBCC[34,35]. In a recent efficacy and safety outcome update from the ERIVANCE BCC study, in which patients were assessed after an additional 12-month follow-up from the primary analysis, the mBCC objective response rate improved from 30.3% to 33.3%[36]. The laBCC objective response rate improved from 42.9% to 47.6%. The median overall survival period for patients with mBCC was 24.1 months but the survival period for laBCC patients was not yet able to be estimated. However, there was an increase in adverse events. The treatment-emergent adverse events (TEAEs) included dysgeusia, muscle cramps, alopecia, weight loss, fatigue, and nausea[36]. Vismodegib has also been studied for use as neoadjuvant chemotherapy 12 months prior to Mohs surgery for BCC lesions. Approximately 42% of patients demonstrated complete histological and clinical clearance, but there was only a 16% histological clearance rate and 36% complete clinical clearance rate 24 weeks post- vismodegib[37]. These studies help to underscore the importance of vismodegib. According to a search in www.clinicaltrials.gov in October 2015, there are 25 ongoing studies on the effects of vismodegib on BCC. The results will hopefully provide further insight into its efficacy.

In addition to vismodegib, there are multiple different drugs in development and in clinical trials that inhibit SMO and other components of the SHH pathway. An overview of the SMO inhibitors follows (**Figure 3**).

SMO inhibitors

1. Saridegib (IPI-926) is a systemic, selective SMO inhibitor that is a derivative of cyclopamine. It is found to have activity in patients with BCC. A phase I trial identified a regimen of 160 mg of saridegib daily in 28-day cycles as the recommended dose and schedule for phase II trials[38]. The patients with vismodegib-naive BCCs showed response to the drug but disease progression ultimately developed. There are ongoing clinical trials for saridegib.

2. Sonidegib (LDE225) is a second SMO inhibitor that has been approved by the FDA for laBCC. The BOLT phase II clinical trial showed a 47% objective response rate in patients taking 200 mg for laBCC and a 35% response rate in patients taking 800 mg for laBCC[39]. The drug has not proven to be very useful for mBCC. The response rate for patients taking the 200 mg mBCC arm was 15%, whereas those taking the 800 mg arm had a 17% response rate. Essentially all patients in both arms encountered side effects but the 200 mg arm had lower adverse events, a lower discontinuation rate, and longer duration of treatment; therefore, it was more favorable. In the 12-month follow-up, the 200 mg arm patients had a 58% response rate as opposed to the 800 mg arm patients who had a 44% response rate[40]. At the 12th month mark, approximately 78% of patients discontinued treatment, mostly due to adverse events. Currently, there are three active clinical trials evaluating the efficacy of sonidegib and BCC.

3. CUR61414 is another SMO inhibitor that has been studied in a topical formulation that showed promise in pre-clinical studies in SHH signaling blockade in mice, but had no clinical activity in human BCC during a phase I clinical trial[41]. Lauressergues *et al.* found CUR61414 to be a low potency inhibitor compared to other SMO antagonists[42].

4. BMS-833923 (XL-139) is a SMO inhibitor that decreases *GLI* and *PTCH* mRNA expression and reduces cell viability[43]. It has also been shown to have strong receptor-ligand interaction and binding affinity against SMO receptor[44]. It showed a clinical partial response in a patient with BCNS in a phase I trial, but was complicated by pancreatitis[45]. Currently, there is a phase I study of BMS-833923 in subjects with advanced or metastatic BCC and in two patients with BCNS.

5. MK4101 is a SMO inhibitor which has been used in preclinical studies in lung cancer cell lines that have been reported to have increased SHH signaling[46].

6. PF-04449913 is a targeted SMO inhibitor that underwent a phase I clinical trial in patients with advanced solid tumors, which resulted in no partial or complete responses; however, some patients had prolonged stable disease[47]. It has been studied in the use of hematopoietic malignancies and has shown to inhibit hematopoietic precursor cells in Drosophila and to modulate self-renewal signatures and cell cycle progression[48,49]. There are many clinical trials that are evaluating the use of PF-04449913 in hematologic malignancies.

7. LEQ506 is a second-generation targeted inhibitor of SMO currently in a phase I clinical trial for advanced solid tumors including BCC[50,51].

8. TAK-441 is a SMO inhibitor found to have *in vitro* activity against a mutant form of SMO that is vismodegib-resistant[52]. A phase I dose-escalation trial of TAK-441 in patients with advanced solid tumors concluded that TAK-441 had a maximum tolerated dose of 1600 mg/day. Out of 34 patients, one BCC patient showed partial response and seven patients with various tumors showed stable disease progression[53]. There is currently a clinical trial evaluating TAK-441 in adult patients with advanced non-hematologic malignancies.

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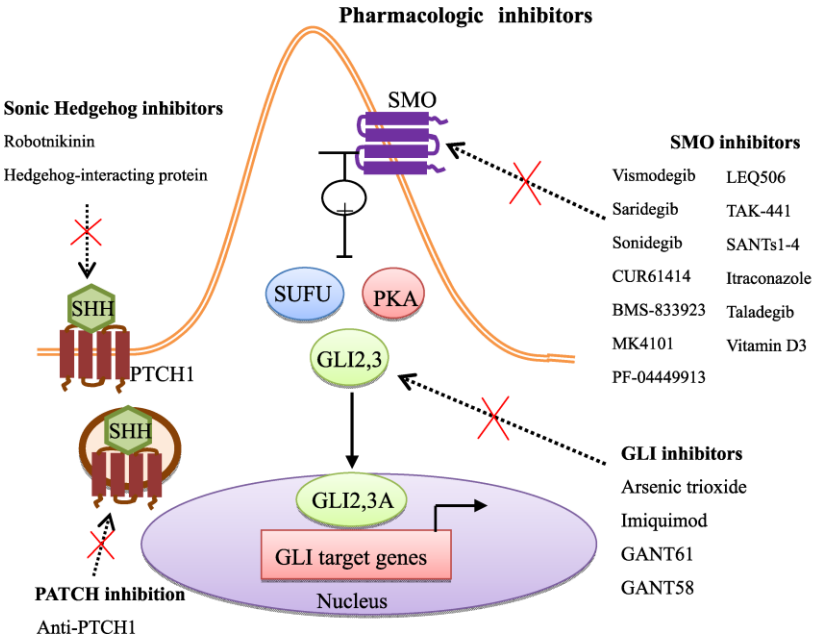

Figure 3. Hedgehog signaling pathway demonstrating pharmacologic inhibitors of the signaling cascade and its molecular targets

9. SANTs1-4 are four pre-clinical small molecule inhibitors of SMO that are structurally distinct from cyclopamine and were identified in cell-based assays[54].

10. Itraconazole is an antifungal agent found to inhibit SHH signaling during a screen of drugs that have been previously tested in humans[55]. It decreases cell proliferation, *GLI1* mRNA, and tumor size[55]. It has also been shown to have activity against mutant SMO resistant to vismodegib[56]. In a clinical trial, itraconazole showed a 23% reduction in BCC size, a 45% reduction in neoplastic proliferation, and a 65% reduction in SHH pathway activity[57]. The combination of itraconazole and arsenic trioxide (ATO) antagonizes the SHH pathway at sites that are distinct from SMO inhibitors. In five patients with relapsing mBCC after SMO inhibitor treatment, three showed stable disease progression after undergoing three treatment cycles of the combination. The remaining patients discontinued treatment. However, the combination therapy demonstrated reduced *GLI* mRNA by 75% from baseline[58]. There are currently five clinical trials that are testing itraconazole specifically in patients with BCC, including one with a combination treatment of arsenic trioxide and itraconazole.

11. Taladegib (LY2940680) is a SMO inhibitor that binds to the extracellular end of the transmembrane-helix bundle of SMO and inhibits SMO mutants that are vismodegib-resistant[9,59]. There are eight active studies on taladegib.

12. Vitamin D3 is thought to directly bind to SMO to inhibit the SHH pathway[60]. A phase II study of the combination of topical diclofenac 3% and calcitriol of 3 μg/g on superficial basal cell carcinoma (sBCC) and nodular basal cell carcinoma (nBCC) has just been completed. The post-treatment expression levels of anti-apoptosis (B-cell lymphoma Bcl-2) immunohistochemical and proliferation (Ki-67) markers were measured. Combination therapy showed a significant decrease in Ki-67, and complete histologic tumor regression was seen in 43.8% of those with sBCC. However, there were no significant changes in patients with nBCC[61].

SHH ligand inhibitors

1. Robotnikinin is a small molecule which binds the extracellular SHH protein that inhibits PTCH[62]. While of interest on a mechanistic level, it seems that blocking this interaction will not be clinically relevant, given that the mutations in BCC tend to occur downstream of this signaling step.

2. Hedgehog-interacting protein (Hhip) sequesters the extracellular SHH ligand and is part of a negative feedback mechanism during embryologic development[63]. For the reasons stated above, it may not be an important pharmacologic inhibitor of the SHH pathway.

3. 5E1 is a monoclonal antibody to SHH that blocks SHH binding to PTCH[64]. It has been shown to reduce tumor stroma in pancreatic cancer xenografts[65].

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However, there are currently no clinical trials to evaluate its efficacy in humans.

GLI inhibition

1. Arsenic trioxide is an FDA-approved drug for the treatment of acute promyelocytic leukemia, but it directly inhibits GLI in the SHH pathway[66]. It inhibits GLI2 ciliary accumulation and promotes its degradation. Since ATO and itraconazole act at sites different from SMO inhibitors, the combination has proven useful for treatment in those that are resistant to vismodegib[56]. As stated previously, there is currently a study underway that analyzes the effectiveness of ATO and itraconazole. Also, a study has just been completed by Stanford University in which arsenic alone was used to treat BCC. The results are not yet published[67].

2. Imiquimod is currently approved for use as a topical treatment for superficial BCC on the trunk and extremities[68]. It has been shown to directly decrease SHH signaling by decreasing GLI activity[69]. In a three-year follow-up for a randomized controlled trial of photodynamic therapy *vs.* imiquimod *vs.* fluorouracil for the treatment of superficial basal cell carcinoma, imiquimod was shown to have the highest probability of tumor-free survival (79.7%) at three years post-treatment[70]. There are multiple clinical trials analyzing the efficacy of imiquimod as treatment of BCC.

3. GANT61 is a GLI inhibitor that has been shown to reduce GLI expression in a rhabdomyosarcoma model[71]. However, more recently, a study demonstrated *in vitro* that GLI expression was not significantly decreased by the treatment with GANT61 in the leukemia cell lines but GANT61 inhibited proliferation of the cell lines and the viability of the cells[72].

4. GANT58 is a GLI inhibitor that has been shown to reduce GLI expression and tumor cell viability in an acute T-cell lymphoma model[73].

Discussion

The Hedgehog pathway serves as a key role in the treatments used for multiple malignancies. However, the components of the Sonic Hedgehog pathway have successfully been pharmacologic targets in the treatment of BCC. The inhibition of the SHH ligand leads to unregulated PTCH. PTCH can then continue to inhibit SMO and thus cause downregulation of the transcription factor GLI. Drugs that act as SMO inhibitors are the most numerous and have proven to be vital for BCC therapy. Vismodegib has shown a 48% and 33% response rate in laBCC and mBCC, respectively. 200 mg of sonidegib had a 43% and 15% response rate in laBCC and mBCC, and 38% and 17% response rate for 800 mg of sonidegib in laBCC and mBCC, respectively[74]. Although the drugs effectively inhibit SMO, there are concerns about SMO mutations and vismodegib resistance. Resistance to vismodegib after an initial successful treatment has developed predominately through SMO (D473H and G497W) mutations as well as PTCH, SHH, and GLI[8,75-77]. SMO D473H is a result of aspartic acid mutating to tyrosine at position 473 whereas G497W is a mutation of glycine to tryptophan[76]. Upregulation of the IGF-1R/PI3K pathway has also been demonstrated in resistant tumor samples, as well as disruption of ligand responsiveness and autoinhibition[77,78]. Mutations in SMO and concurrent copy number mutations in SUFU and GLI are in many cases of the relapsed tumors. In untreated Gorlin syndrome, the SMO mutations were absent; in 15% of sporadic BCCs, they were present[78,79]. Shimizu has found that TAK-441 is able to potently inhibit the SMO- D473H mutation because the dissociation rate of TAK- 441 was much smaller than that of vismodegib or cyclopamine[80]. An open-label study analyzed sonidegib in nine patients with laBCC who were resistant to vismodegib treatment. The results showed that only three patients had stable disease and five patients had disease progression[81]. However, patients with mBCC will have a higher likelihood of acquired resistance with a rate as high as 21% [75].

Although many of the SHH therapies used for BCC were successful, most patients experienced adverse effects and some discontinued the treatment as a result. The most common treatment-emergent adverse events (TEAEs) included dysgeusia, muscle cramps, alopecia, weight loss, fatigue, and nausea[36]. Given that SHH plays a role in hair follicle development, it is understandable that the blockade of this pathway results in alopecia. An interim analysis of a large clinical trial on the safety and efficacy of vismodegib (STEVIE) reported that 36% of their participants discontinued the drug due to adverse events[82]. However, 67% showed partial or complete response. The side effects are difficult to avoid since they exhibit the “class effect”. They are directly caused by Hedgehog pathway inhibition and are thus “on-target”[83]. Notably, vismodegib was also shown to reduce tumor burden in patients with BCNS, although the side effects resulted in a high rate of discontinuation of therapy[84]. Sofen *et al.* put patients on two courses of vismodegib for eight weeks, each with a four-week break in-between, but this did not improve the adverse events[37]. Vismodegib was found to be teratogenic in rats at doses that were 20% of the recommended dosage[4]. It caused absent or fused digits, craniofacial anomalies,

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and an open perineum. It is a pregnancy Category D drug[4]. Side effects from systemic SHH inhibition may in fact elucidate other functions of SHH signaling in adults that are yet to be discovered[32].

The next steps for further developing SHH medications include finding long term treatment options, circumventing side effects, providing tailor-made therapy for the patient, and reducing the financial toxicity of treatment. Some patients may not fit neatly into the locally advanced or metastatic BCC categories while others may be perfect candidates but are not willing to tolerate the side effects. Treatments should target individuals based on a multitude of factors that not only include the molecular mechanisms of cancer etiology and progression, but incorporate additional aspects such as tumor resistance, adverse events, and patient adherence. Another consideration is the economic burden of new medications. A one-month supply of once-daily capsules of vismodegib from Genentech is USD7,500. If the expected length of treatment is 10 months, the total cost could be upwards of USD75,000. By the year 2022, the sales predictions in Europe are projected to peak at USD533 million[85]. Although vismodegib has proven to be successful so far, the financial burden should be taken into account.

Conclusion

In summary, basal cell carcinoma is an important clinical entity. Its molecular pathogenesis is driven by excessive signaling through the Hedgehog pathway. Advances in our understanding of hedgehog and other cell signaling cascades have resulted in the development of novel drugs in the treatment of human malignancy. There are certain frontiers that need to be pushed to develop newer therapies for BCC. Discovering alternative SHH targets can help avoid adverse events and SMO resistance. More clinical trials on the efficacy of cheaper drugs such as itraconazole can guide us toward alleviating an economic burden. For now, vismodegib is the mainstay of medical treatment, but further elucidation of these biochemical pathways will undoubtedly lead to increasing medical management of advanced and mBCC.

Author contributions

BAP Tran and AK Somani were involved in the overall study concept and design. Acquisition, analysis, and interpretation of data were performed by BAP Tran and T Alexander. BAP Tran and T Alexander also drafted the manuscript. Critical revision of the manuscript's content was done by BAP Tran and AK Somani.

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Conflict of interest

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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