Basal Cell Carcinoma: Hedgehog Pathway Inhibitors and Beyond

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An evolving theme in cutaneous oncology is targeted therapy. Blockade of the hedgehog signaling pathway has been a breakthrough in the management of patients with advanced basal cell carcinoma (BCC). Although promising results have been reported, recurrence and evolution of new tumors via circumvention of traditional pathways has occurred. In this column I will briefly review the hedgehog signaling pathway, tumorigenesis, and novel strategies for the development of next-generation drugs.

Basal cell carcinoma is the most common skin cancer and treatment generally includes surgical excision. Rarely, locally advanced and metastatic BCCs can occur, and rare genetic syndromes exist in which BCCs develop early in life and often are more aggressive than acquired malignancies.[1-3] Until recently, there were relatively few treatment options available for advanced BCC. Although the vast majority of BCCs are sporadic, the study of basal cell nevus syndrome (BCNS), a rare genetic condition, has led to a greater understanding of tumorigenesis. It is well established that dependence on the hedgehog pathway is necessary for BCC tumor growth in the majority of cases.[4,5] An understanding of the hedgehog signaling pathway has provided an opportunity for targeted therapy, which is highlighted by the recent US Food and Drug Administration approval of vismodegib, a smoothened (SMO) inhibitor representing an integral step along the hedgehog pathway.[6]

The Hedgehog Pathway

The story of the hedgehog pathway begins with a fruit fly called *Drosophila melanogaster* and 2 scientists, Christiane Nüsslein-Volhard and Eric Wieschaus, who identified genes that directly affect its embryonic development.[7] One such gene caused the *D melanogaster* larvae to grow spines, giving them the appearance of a hedgehog, and thus the hedgehog signaling pathway was named. The hedgehog signaling pathway was further recognized to be highly conserved from fruit flies to humans (similar genomes) and are now recognized as key regulators of embryonic development, cell proliferation, differentiation, and tissue patterning.[8] When the pathway goes awry, it has been linked to the development of many cancers, including BCC and medulloblastoma, as well as carcinomas of the pancreas, prostate, lungs, and breasts.[9]

The hedgehog proteins are ligands of the membrane receptors patched 1, *PTCH1*, and patched 2, *PTCH2*, and when they bind, they activate the hedgehog signaling pathway. Aberrant hedgehog pathway signaling leads to cancer, either by inactivating mutations in the *PTCH1* gene an estimated 80% to 90% of the time or, to a lesser extent, by activating mutations in SMO.[4,10,11] Normally, the 12 transmembrane receptor *PTCH1* actively inhibits SMO, a 7 transmembrane receptor. While under this active suppression, SMO is unable to signal downstream; however, when one of the extracellular ligands of the hedgehog pathway comes along and binds to *PTCH1*, SMO is no longer suppressed and is able to freely transmit signals through a variety of proteins, leading to the production of the Gli family transcription factors (Figure).[12]

Controlling the Hedgehog Pathway

The discovery of cyclopamine in the corn lily plant (*Veratrum californicum*) led to the development of a class of synthetic drugs designed to inhibit SMO. It

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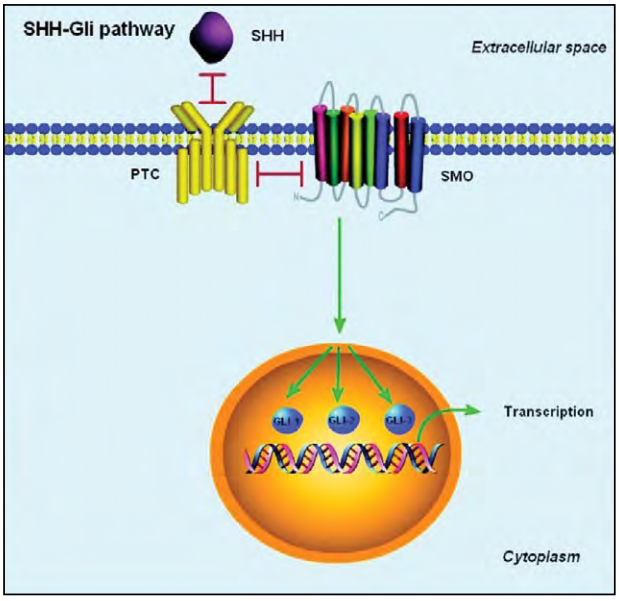
The author reports no conflict of interest.



Sonic hedgehog (SHH)–Gli pathway. Normally, patched 1 (*PTCH1*) inhibits smoothened (SMO). When hedgehog ligands bind to *PTCH1* (PTC in figure), it disinhibits SMO regulation leading to signal transduction and nuclear activation of Gli (GLI in figure) proteins, which regulate target genes. Reprinted with permission, ©2011 American Society of Clinical Oncology.[12]

was observed during droughts in the early 1950s that sheep grazing in Idaho were giving birth to lambs with severe malformations, including cyclopia or the development of only 1 eye in the mid forehead.[13,14] Further investigation revealed that the sheep had grazed on the corn lily plant during the drought, which contained cyclopamine, a steroidal alkaloid. Cyclopamine was discovered to interact with SMO, inhibiting its activity.[15] The pharmacologic properties of cyclopamine are not ideal for human treatment, and the pursuit of synthetic, small molecule inhibitors of SMO began.[16,17]

Vismodegib Enters the Picture

The efficacy of vismodegib, a small molecule inhibitor of SMO, was demonstrated in a phase 1 clinical trial published in 2009. Among the 33 participants, vismodegib was found to have objective response rates in 18 participants (2 complete and 16 partial). Of the remaining 15 participants, 11 were stable and 4 progressed.[18] A nonrandomized phase 2 study designed to establish safety profiles in 96 participants with either metastatic BCC (n=33) or locally advanced BCC (n=63). The results demonstrated response rates of 30.3% (10/33) and 42.9% (27/63), respectively.[19] Side effects were common, occurring in more than 20% (20/96) of participants, and included muscle spasms, alopecia, dysgeusia, nausea, diarrhea, fatigue, decreased appetite, arthralgia, constipation, vomiting, and ageusia. These adverse events appear to be related to inhibition of the hedgehog pathway and are so-called class-related side effects.[19] As such, they seem to be an unavoidable consequence and may prove to be intolerable for long-term use or as maintenance therapy in patients with BCNS. In a separate study, 41 participants with BCNS who were treated with vismodegib were noted to develop on average only 4 new tumors per year compared to 24 new tumors in participants taking a placebo, and existing skin lesions shrank drastically; however, 54% (14/26) of participants discontinued treatment due to adverse events. Interestingly, other cutaneous manifestations of BCNS (eg, palmar pitting) also regressed during treatment with vismodegib.[20] After discontinuing treatment, patients with BCNS were noted to have recurrence of BCCs within 3 months of stopping treatment.[21] Thus far, trials have only included patients 18 years and older, and it remains to be seen if inhibition of the hedgehog pathway will be safe for younger patients with BCNS. However, this investigation is unlikely to occur in the near future, as hedgehog pathway inhibition in young animals has been associated with permanent defects in skeletal development.[22]

Newer synthetic, small molecule inhibitors of the hedgehog pathway, hopefully with fewer side effects, currently are in clinical trials.[23-25] Another possible avenue to circumvent adverse effects is intermittent dose scheduling, with the hypothesis that adverse effects may not be continuous or cumulative.[24]

Topical application of vismodegib would circumvent many systemic side effects. However, a recent study of topical application of a hedgehog pathway inhibitor (CUR 61414) revealed disappointing results due to suboptimal penetration in human models.[26] Newer formulations may prove to have greater efficacy.[27] A study of topical 0.75% LDE225 cream (erismodegib) applied to BCCs in patients with BCNS for 4 weeks was well tolerated and showed either a complete response (n=3) or partial response (n=9) clinically in 13 lesions treated. Histologic examination revealed residual tumor in all lesions, with an average reduction in volume of 56% after 4 weeks of topical application. It remains to be seen if these results are durable.[27]

Neoadjuvant therapies to decrease the size of tumors prior to excision or Mohs micrographic surgery may be another promising application, and Stanford University, California, currently is enrolling patients in one such trial.[23] A concern that arises is that hedgehog pathway inhibitors may inadvertently select for a subpopulation of tumor cells that are not

sensitive to the drug or, as in the case of histologic basosquamous cell carcinomas, they might inadvertently select for squamous progression while controlling the BCC. Recent data indicate that heterogeneity in tumor cells exists at the time of diagnosis, and these drug-resistant clones, initially present in low numbers, become the dominant clone as they gain growth advantage in the treated tumor.[28,29] Indeed, the initial phase 2 studies of vismodegib revealed a median progression-free survival of 9.5 months.[19] A widely metastatic, *PTCH1*-mutant medulloblastoma in 1 patient from the phase 1 study of vismodegib who experienced rapid tumor regression and then recurrent disease was identified to be associated with an acquired tumor-specific mutation in SMO that inhibited vismodegib binding.[30] Understanding tumor resistance may lead to more refined targeted therapy or combination therapies in the future. Inhibitors of downstream pathways such as Gli transcription factors and S6K1 (ribosomal protein S6 kinase) may help delay tumor resistance.[31,32]

Another area of interest is the use of other hedgehog pathway inhibitors, such as itraconazole and arsenic, that are distinct in their mechanisms from those of SMO inhibitors.[33,34] Both drugs have been found to inhibit the hedgehog pathway by another mechanism than SMO inhibition in murine models; oral capecitabine also has been used in a patient with BCNS with notable clinical regression of cutaneous disease.[12]

Conclusion

Although the field of cutaneous oncology seemed for a brief moment to have found a cure for cancer, it remains to be seen if these advances will be curative or palliative.

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