Hedgehog Pathway in Basal Cell Carcinoma

Dr Gurleen Kooner,
MMBS, FY2, Department of breast and Skin Surgery Royal Surrey County Hospital NHS Foundation Trust.

Mr Farrokh Pakzad,
Consultant Oncoplastic Breast and Skin Cancer Surgeon, Department of Breast and Skin Surgery, Royal Surrey County Hospital NHS Foundation Trust.

Correspondence address:
Mr F Pakzad
E: f.pakzad@nhs.net

Basal cell carcinoma (BCC) is the most common malignant neoplasm of the skin worldwide, and its incidence is increasing. Although generally slow-growing, locally invasive tumours may cause tissue destruction, disfigurement and severe morbidity. Surgical resection is the mainstay of treatment. Other treatments may include photodynamic therapy, topical cytotoxics such 5-fluoruracil, immune modulators such as Imiquimos, cryotherapy and radiotherapy. Where such treatments are ineffective (eg: those with recurrent disease, refractory to radiotherapy, or with metastatic spread), treatment options maybe limited and highly destructive surgery becomes the only hope. More recently, inhibiting the Hedgehog pathway has opened avenues in targeted systemic treatment for BCC and potentially other cancers.

Hedgehog pathway – overview

The Hedgehog (Hh) pathway comprises a group of proteins involved in the regulation of cell growth, differentiation and promoting stem cell proliferation. It was discovered for its role in organogenesis in Drosophila, where the lack of the hedgehog gene resulted in failure of organ development and migration [1]. The resultant 'spiky' appearance of defective embryos lead to the pathway being named Hedghog. In humans, as well as facilitating embryonic growth, the Hh pathway is an important regulator of adult stem cell function involved in maintenance and regeneration of adult tissue.

Hedgehog (Hh) proteins are secreted paracrine molecules that are ligands for the trans-membrane receptor known as Patched (PTCH). In the resting cell, PTCH has a tonic inhibitory effect on a G-protein coupled membrane receptor called Smoothened (SMO). Binding of Hh to PTCH releases this inhibition, allowing SMO to initiate a cascade of events resulting in the transcription of genes that promote cellular proliferation. Of the three hedgehog proteins identified, Sonic hedgehog (SHH) has been the most well characterised, the others being Desert Hedgehog and Indian Hedgehog homologues.

In a healthy adult cell, the hedgehog pathway will be activated in the presence of SHH (see fig1). GLI activation downstream from SMO has been shown to have a number of effects. It increases expression of cyclins D1 & B1, promoting progression through cell cycle and suppressing apoptosis. E-cadherin expression is decreased, reducing cell adhesion and the integrity of tight junctions and encouraging cell separation and the development of metastases. It also increases angiopoietin-1 and angiopoeitin-2 expression, promoting angiogenesis [2].

Mutations in PTCH or SMO result in SHH-independent or constitutively activated pathways, leading to uncontrolled proliferation of basal cells in BCC. Congenital mutations in PTCH have been linked to Basal Cell Naevus Syndrome (also known as Gorlin syndrome), which predisposes to the development of BCC. Defects in the Hh-signaling pathway have also been implicated in over 90% of sporadic BCC [3]. The development of medulloblastoma, rhabdomyosarcoma and pancreatic cancer have all been linked to overactive hedgehog signaling, thus targeting this pathway may potentially lead to treatment for a variety of cancers [3].

Inhibiting hedgehog pathway signals

Cyclopamine, the first identified inhibitor of the Hh pathway is a naturally occurring alkaloid derived from the extract of the corn lilly plant. Its teratogenic effects were discovered in sheep grazing on corn lilly leaves, where amongst a number of congenital malformations, cyclopia was frequently seen (hence the name Cylopamine) [4]. Subsequent attempts at developing drugs that inhibit the hedgehog pathway have been modeled on its structure. Saridegib and Vismodegib are small molecule, synthetic analogues of Cyclopamine that inhibit SMO. Saridegib initially showed promise in phase I trials involving a range of advanced or metastatic solid tumours. However, phase II trials in chondrosarcoma and metastatic pancreatic cancer were terminated early, due to unfavorable results as compared to the placebo arms [5]. The potential use of Saridegib in treating BCC is yet to be explored. Vismodegib (trade name Erivedge) is the first and currently the only, hedgehog pathway inhibitor that has been licensed for use in BCC's that are not amenable to surgery or radiotherapy. A 2-pyridyl amide molecule with oral bioavailability as once daily 150mg dose, it blocks hedgehog signaling by selectively inhibiting SMO, consequently preventing the induction of the target genes, which underlie BCC growth.

The Erivance BCC trial found tumour shrinkage in 30% and 43% of patients with metastatic and locally advanced BCC respectively. Of the patients with

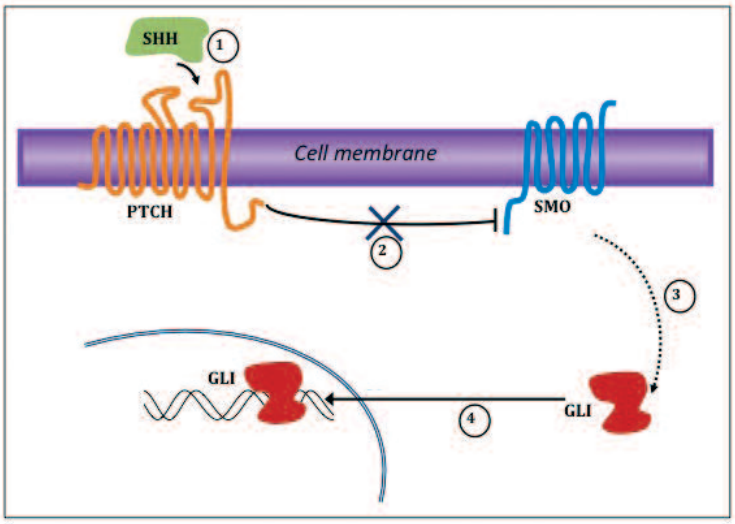

Figure 1:
1. SHH binds to the extracellular portion of PTCH1.
2. PTCH1 inhibition of SMO is relieved.
3. SMO initiates a signaling cascade, which activates the GLI (Glioma Associated Oncogene) family of transcription factors.
4. GLI enters the nucleus to regulate the expression of genes, which promote cell survival.

Figure 2: Corn lily (veratrum spp.) from which cyclopamine is derived.

locally advanced BCC, 54% had no residual disease in biopsy specimens obtained during treatment with Vismodegib, indicating a complete response [6].

Although no control group was utilised in this study, given the lack of alternative effective therapies available and the improbability of spontaneous resolution, the therapeutic potential is evident. Another phase II randomised, placebo-controlled study recruited patients with Gorling's syndrome. Vismodegib was shown to significantly reduce the size of existing BCCs compared with the placebo (reduction of 65% in treatment group versus 11% in placebo arm), as well as decreasing the incidence of new BCC lesions (2 cases / group / year vs 29 in the placebo group) [7].

Adverse drug reactions to Visemodegib appear to be common. In the Erivance trial, all enrolled patients reporting at least one adverse effect. While majority of these were minor side effects (most commonly gastrointestinal disturbances, anorexia, alopecia), 25% were grade 3 / 4 reactions that included muscle spasms, weight loss and fatigue. For 13 patients (12%), Visemodegib was discontinued due to adverse effects, with this figure being much higher (54%) in patients in the BCNS study. In patients with BCNS, rebound recurrence after cessation of Vismodegib has also been reported [8]. This has fueled concerns over the use of Visomodegib in this population, where the rate of drug intolerance appears to be high. Vismodegib is hightly teratogenic as well as ebryogenic. Therefore highly effective forms of birth control measures are advised for both male and female patients on treatment (and up to 7 months for women and 2 months for men after the last dose given).

Resistance to Vismodegib therapy due to mutated SMO has been encountered in trials for medulloblastoma [9]. The antifungal agent Itraconazole has been explored for its potential in blocking the hedgehog pathway via an as yet unclear mechanism that is independent of SMO inhibition. Pre-clinical studies have suggested that this may offer an option in resistant disease [10].

Summary

Vismodegib is an oral inhibitor of the hedgehog pathway and the first systemic treatment for patients with locally advanced or metastatic basal cell carcinoma that is not amenable to surgery and radiotherapy. Data on overall survival with Vismodegib is currently limited, however, response demonstrated in early clinical trials has been promising.

To date, inappropriate activation of the hedgehog signaling cascade has been implicated in many other types of cancer. There is also emerging evidence to support crosstalk between the Hh pathway and other cancer pathways. As such, the synergistic role of targeted Hh-inhibition with EGFR, MEK, mTOR or PI3K inhibitors is currently being investigated in a range of solid and hematological malignancies [11]. ●

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