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Basal cell carcinomas: attack of the hedgehog

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Abstract

Basal cell carcinomas (BCCs) were essentially a molecular 'black box' until some 12 years ago, when identification of a genetic flaw in a rare subset of patients who have a great propensity to develop BCCs pointed to aberrant Hedgehog signalling as the pivotal defect leading to formation of these tumours. This discovery has facilitated a remarkable increase in our understanding of BCC carcinogenesis and has highlighted the carcinogenic role of this developmental pathway when aberrantly activated in adulthood. Importantly, a phase 1 first-in-human trial of a Hedgehog inhibitor has shown real progress in halting and even reversing the growth of these tumours.

The fox knows many pathways, but the hedgehog knows how to cause basal cell carcinomas.

(With apologies to Archilochus, 7th century BC.)

Basal cell carcinomas (BCCs) are keratinocyte tumours that are so named because of their histological resemblance to the cells along the basement membrane — the 'basal' layer of the epidermis (FIG. 1). They are the most commonly diagnosed human cancer, at least among persons of European ancestry¹. Approximately 750,000 BCCs are treated each year in the United States alone. Despite this high frequency, the death rate from BCCs is extraordinarily low, a reflection perhaps of the excellent care provided by physicians and the fact that these tumours metastasize only extremely rarely. Nonetheless, they can cause significant tissue destruction by local invasion. In total, the cost of care for non-melanoma skin cancers (NMSCs) such as BCCs is the fifth highest for all cancers in the Medicare population in the United States². Our understanding of their molecular pathogenesis has advanced considerably in the past decade, and indeed these tumours now seem to have become the 'founding member' of an expanding group of human cancers in which deregulated Hedgehog (HH) signalling is of vital importance. I review here our current understanding of BCCs, including the environmental and genetic factors that contribute to their development, their molecular pathogenesis, the most obvious unanswered questions about them, and how new understanding might be translated into more effective prevention and treatment.

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Clinical aspects of BCCs

BCCs classically appear as slow-growing, translucent, elevated lesions on the sun-exposed skin of persons of fair complexion³ (FIG. 2). BCCs occur more commonly in men than in women, and they tend to occur after the age of 50. However, younger people may be developing more BCCs, perhaps correlated with the use of ultraviolet (UV) light sunbeds for cosmetic tanning purposes, especially among younger women^{4,199}. BCCs are often grouped together with skin squamous cell carcinomas (SCCs; see FIG. 1b) and with several other less common tumours as NMSCs. SCCs are considerably more likely to metastasize than are BCCs. Unlike SCCs, which are usually preceded by carcinoma *in situ* type lesions, BCCs have no detectable precursor lesion. Once individuals have developed a BCC, they have a much higher risk of developing additional BCCs: one estimate based on meta-analysis gives a 44% risk of a second BCC developing within 3 years in patients who have developed their first such tumour⁵. Usually, however, individual patients develop only one or a few BCCs. The incidence of development of new NMSCs is also high in those with cutaneous SCCs, and the second NMSC tends to be of the same type as the first⁶.

BCCs occur far more commonly in persons of European ancestry and in those who have had more sun exposure. Thus, in Kauai, the region of the United States with the highest incidence of skin cancers, the incidence of BCCs is 14-fold higher in persons of European ancestry than in those of Japanese ancestry⁷ and 34-fold higher than in those of Filipino ancestry⁸. Among persons of European ancestry, those of Celtic descent are especially prone to developing NMSCs. Patients with albinism, in which constitutional mutations prevent melanin formation, are highly susceptible to the development of BCCs as well as of SCCs and melanoma. By contrast, those of African or South Asian descent with dark skin colour are highly resistant to their development. Interestingly, this marked ethnic difference in susceptibility persists following organ transplantation, when patients become highly susceptible to the development of skin cancers. Thus, the incidence of BCCs may be tenfold higher in organ-transplant recipients of European ancestry than in persons of similar sun exposure who have not had an organ transplant. However, patients of East Asian ancestry have an extremely low incidence of these tumours even after organ transplant⁹.

As suggested by the inverse correlation of incidence with skin pigmentation, sunlight is an environmental factor that is important in BCC development. However, the exact relationship is complex — apparently far more so than for the development of SCCs. Thus, the incidence of SCCs rises with the total number of hours of sun exposure, especially when that amount approaches a cumulative 100,000 hours. To attain this much sun exposure, one must spend much of the day outdoors. By contrast, the incidence of BCCs peaks at approximately twofold at 10,000–35,000 hours total sun exposure and does not increase with further exposure^{10,11}. Similarly, the relative incidence of SCC:BCC rises with increasing sun exposure — this ratio is considerably higher in the southern parts of the United States than in northern parts. In addition, the use of sunscreens and other sunprotective measures has not yet been found to correlate with reduced BCC risk, unlike the reduction of SCCs associated with sun protection^{12–14}. Some have postulated that BCC development, like that of melanomas, may correlate better with intermittent sunlight exposure, such as that sustained by research oncologists who jog or cycle on weekends¹⁵. Additional environmental insults

that clearly correlate with BCC development are ionizing radiation and arsenic exposure^{16–18}.

Molecular genetics

BCCs and basal-cell nevus syndrome

The vast majority of BCCs occur sporadically, but there is one rare heritable disorder in which patients have a marked susceptibility to developing BCCs. This is basal-cell nevus syndrome (BCNS, also known as Gorlin syndrome or nevoid basal-cell carcinoma syndrome; see BOX 1).

Using family-based linkage studies of kindreds with BCNS, the locus carrying the causative mutant gene was mapped to human chromosome 9q22 (REF.19) and then to the patched 1 (*PTCH1*) gene^{20–22}. This finding was especially instructive for several reasons. First, there was previously only minimal insight into the molecular underpinnings of this cancer — p53 mutation in a sizable fraction of sporadic BCCs was essentially the only previously known molecular abnormality²³, and p53 mutations are common in non-cancerous skin of BCC patients as well²⁴. This lack of knowledge was due, at least in part, to the difficulty of growing human BCCs in tissue culture or as xenografts and to the lack of a satisfactory animal model. Mice treated with UV or ionizing radiation, or with chemical carcinogens, develop papillomas and carcinomas of the squamous but not basal cell lineage. rats treated with ionizing radiation do develop BCCs but they also develop other skin cancers in greater abundance. Second, the function of *PTCH1* was broadly clear — its sequence identified it as the homologue of an already well-studied inhibitor of the HH signalling pathway that was known to be crucial for development in *Drosophila melanogaster*, and was found subsequently to occupy a similarly crucial role in mammalian development. Hence, it was straightforward to predict and demonstrate that its biallelic inactivation produced constitutive upregulation of HH signalling. Thus, *PTCH1* functions as a classic tumour suppressor gene. Third, not only was HH signalling found to be upregulated in all studied sporadic BCCs, but also this upregulation is frequently accompanied by, and at least in part based on, mutations in *PTCH1*. Currently, it is thought that upregulation of HH signalling is the pivotal abnormality in all BCCs, and indeed there is some evidence that little more than HH upregulation is required for BCC carcinogenesis^{25,26}. Approximately 90% of sporadic BCCs have identifiable mutations in at least one allele of *PTCH1* (often loss of the portion of chromosome 9q harbouring *PTCH1*), and an additional 10% have activating mutations in the downstream smoothed (*SMO*) protein, which presumably render *SMO* resistant to inhibition by *PTCH1* (REFS 27–30).

Hedgehog signalling

Although a complete description of the intricacies of HH signalling is outside the focus of this review (see REFS 31–33 for reviews), some background information is necessary (FIG. 3). The HH signalling pathway is named after the family of extracellular HH ligands, of which there are three in mammals: sonic hedgehog (SHH), Indian hedgehog (IHH) and desert hedgehog (DHH). *PTCH1* is the receptor to which the HH ligands bind, and such binding relieves the inhibition of the pathway induced by unbound *PTCH1*, specifically

through SMO in a non-stoichiometric manner. Once relieved of inhibition, SMO sends signals through a series of interacting proteins, including suppressor of fused (SUFU), culminating in activation of the downstream Gli family of transcription factors, Gli1, Gli2 and Gli3, the founding member of which was identified as a gene amplified in glioblastoma³⁴. These transcription factor proteins exist in various forms, and Gli2 and Gli3 can be activators or suppressors of transcription; Gli1 seems to have only activator functions. The stability of these molecules is controlled by phosphorylation and ubiquitylation–proteolytic destruction, and processing from inactive to active suppressor or activator forms is accomplished, at least in part, by proteolysis^{35–38}.

The interactions of the components of the HH signalling machinery can occur at the cilium^{39–42}. SMO seems to be excluded from this structure when inactive, but resides within the cilium when signalling is activated⁴³. Target genes whose expression is upregulated directly by HH signalling in BCCs include PTCH1, providing a negative feedback that dampens of the pathway, GLI1, providing a positive feedback for the pathway, and HHIP, which encodes a HH binding protein^{44,45}. The expression of mRNAs encoding these proteins is routinely increased in BCCs.

Somatic mutations in BCCs

In general, BCCs seem to have relatively stable genomes — the few published studies suggest that they have lower levels of genomic instability than do many extracutaneous cancers⁴⁶. As noted above, BCCs routinely carry mutations in PTCH1 and TP53 and, in 10% of instances, in SMO^{47,48}. Mutations in several other genes encoding components of HH signalling have been sought but few have been identified, let alone confirmed⁴⁷. The mutations identified in PTCH1 and TP53 are frequently of a type that is consistent with their having been produced by UV radiation. This is true for BCCs that arise sporadically, and even more so for those large numbers of BCCs that arise in patients with xeroderma pigmentosum (XP), suggesting that repair of UV-induced DNA damage normally does reduce BCC carcinogenesis^{49–51}. Furthermore, this suggests that one reason for the increased incidence of BCCs in older people might be the reported reduction of DNA repair with ageing⁵².

Predisposing constitutional genetic variants

Because UV irradiation is a significant risk factor for BCC development, genes that control the extent of UV-induced DNA damage and those whose protein products effect repair of that damage are prime candidates for risk-modifying genes.

Variation in constitutive pigment and ability to tan seem to be correlated inversely with BCC development. Hence, it is not surprising that studies have been undertaken of the melanocortin 1 receptor gene (MC1R), the major known genetic variant contributing to the degree of skin pigmentation. MC1R encodes the receptor of α -melanocyte-stimulating hormone (α MSH), a proteolytic product of the larger protein encoded by the pro-opiomelanocortin gene (POMC). MC1R is highly polymorphic among normal individuals and is a prime contributor in determining whether the skin produces brown–black pigment (eumelanin) or red–yellow pigment (pheomelanin). Non-functional MC1r variants result in

the production of pheomelanin and, in particular, the phenotype of red hair⁵³. Because people with red hair and fair pigment have an increased risk of skin cancers, those with variant *MC1R* alleles are at increased risk both of melanomas and of BCCs, and the increased risk is dose-dependent, that is, higher in carriers of two variant alleles than in carriers of a single variant allele^{54–57}. However, in both BCCs and SCCs of the skin, the association of variant alleles and increased risk persists even when corrected for skin pigmentation, thus suggesting a role for *MC1R* in susceptibility to skin cancers that is mediated by mechanisms other than control of pigmentation. Similarly, *MC1R* variants seem to contribute to susceptibility to melanoma by mechanisms beyond their effects on skin pigmentation^{58–60}. Indeed, some have suggested that α MSH can directly modulate keratinocyte proliferation and differentiation⁶¹. Furthermore, UV irradiation of keratinocytes can enhance POMC and α MSH production, which suggests a possible paracrine role for this hormone^{62–64}. Variation in BCC incidence is also associated with variants in the genes encoding tyrosinase, the rate-limiting enzyme in melanin formation, and agouti signalling protein, which inhibits the interaction of α MSH and MC1r. As with MC1r variants, their effects on pigmentation do not seem to explain all of their effects on BCC susceptibility⁶⁵.

Patients with XP have constitutional inactivating mutations in both alleles of certain genes that encode DNA repair proteins, in particular those involved in nucleotide excision repair, a process that is of crucial importance for removing UV-induced photoproducts from keratinocyte DNA. In patients with XP, this molecular importance is attested to clinically by the huge increase in relative risk of developing BCCs and other skin cancers and the onset of these cancers on average 50 years earlier than in those without such genetic impairment⁶⁶.

This finding raises the question of whether more common variants in genes encoding proteins involved in DNA repair might contribute to the relative risk of developing BCCs in patients without XP. Numerous studies have investigated the repair capacities of cells from patients with BCC and control patients, as well as the effects of common coding variants (predominantly single nucleotide polymorphisms) on BCC relative risk. In general, studies in patients with various cancers indicate some reduction of DNA repair⁶⁷. One group has published several studies that favour a reduced DNA-repair capacity (using the host cell reactivation assay) in lymphocytes from patients with BCC as opposed to controls⁶⁸, although their findings were not confirmed in a small independent study⁶⁹.

Similarly, a recent small study found reduced *in vivo* clearance of UV-induced photoproducts from DNA extracted from the skin of patients with BCC compared with DNA extracted from a control group without skin cancer⁷⁰. However, the overlap between individuals in the two groups was large, so variations in DNA repair, at least as captured by the assay used, cannot account for a large proportion of any differential susceptibility to BCC in the Finnish population studied.

Associations between DNA repair gene variants and BCC relative risk that reach (or at least closely approach) statistical significance have been reported for several DNA repair genes. Perhaps the most studied of these is the gene polymorphism that underlies the T241M substitution in *XRCC3*. Some studies^{71–73} but not all^{74,75} have found that this substitution is associated with a reduced relative risk for BCCs. Counterintuitively, this substitution is also

associated with an increased risk for breast cancer⁷¹ and it does not seem to change DNA repair capacity, at least by the assay used. The usual explanation for such findings is that the identified polymorphism is not causative, but is simply located near (is in linkage disequilibrium with) the causative mutation, or it could be that the reported association results are spurious.

Studies of polymorphisms in other DNA repair genes have also suggested associations with the relative risk of developing BCCs, but other studies have failed to find the same association. Clearly, the relationships between identified associations and changes in DNA repair are confusing (BOX 2). Such uncertainties argue for the potential of unbiased, genome-wide association studies to identify polymorphisms that confer a relative susceptibility to BCC formation, and to uncover greater understanding of the mechanisms underlying BCC development.

A common variant in *TP53* occurs at codon 72, and the two alleles encode either arginine or proline (Pro). Taken together, at least some of the published studies imply that the Pro allele enhances susceptibility to BCC, but perhaps only in people who are relatively more resistant to developing these tumours — those with darker skin pigmentation and a lack of variant *MC1R* alleles^{76,77}. There are similar published results for an association between this variant and susceptibility to cutaneous melanomas⁷⁸. Again, as with other studied polymorphisms, conflicting data arguing for no association have also been published⁷⁹. A further complication of the analysis is an association of the Pro allele with resistance to childhood sunburn. Thus, *TP53* alleles may control not only susceptibility to skin cancer but also to sunburn, and the effects of one allele may be opposite on these two phenotypes and in counterintuitive directions. A biologically active polymorphism in *MDM2*, which influences p53 protein stability, was found not to be associated with BCC relative risk in one study that assessed more than 1,000 subjects⁸⁰.

One common polymorphism at exon 23 of *PTCH1* encodes either Pro or leucine at codon 1315. In patients with more severe BCCs (multiple tumours, early onset), two studies have found an association with the genotype encoding Pro/Pro^{55,81}. However, in one study that was not restricted to patients with greater BCC severity, the individual single nucleotide polymorphism was not associated with BCC relative risk, although one haplotype that included this polymorphism was so associated. Possible associations with the many other genes encoding members of the HH pathway and/or genes encoding controls of this pathway remain to be studied. Finally, Balmain and colleagues reported the surprising finding that a *Ptch1* polymorphism in the mouse is an important controlling factor in the susceptibility to mutant HRAS-induced skin tumours of the squamous lineage. They suggest that such polymorphisms may control the relative susceptibility to formation of SCCs versus BCCs⁸².

Molecular analyses are therefore consistent with the idea of genetic control of susceptibility versus resistance to BCC carcinogenesis. In particular, such analyses are consistent with the idea that resistance is associated with better protection against mutagenesis and with better repair of whatever DNA damage does occur. However, we have yet to identify convincingly the genetic underpinnings beneath the wide range of clinical outcomes in some people of northern European ancestry with pale complexions who sunbathe: some get many BCCs,

some get many SCCs, some get fewer tumours, some get only precancerous carcinomas *in situ*, some get only wrinkles and some sustain no clinically apparent skin damage at all.

Pathway interactions and expression changes

Several groups have assessed genome-wide expression in keratinocytes in which HH signalling has been activated experimentally⁸³ and directly in BCCs. A question with the latter is the choice of control cells against which the BCC expression results are compared. Published studies have compared expression patterns of whole tumour with those of whole normal skin^{84–86} or of cells at the periphery of BCC nests with those of cells of the basal layer of the interfollicular epidermis⁸⁷. Overall, perhaps as expected, many differences in expression have been found, but so far the field has not progressed sufficiently to enable firm conclusions to be drawn about which findings are reproducible across different platforms and investigators, and which changes are crucial to the aberrant behaviour of the BCC cancer cells.

Box 1

Gorlin syndrome

Patients with this syndrome, also known as basal cell nevus syndrome (BCNS), had been described previously on numerous occasions but it was the dentist Robert Gorlin who realized most clearly half a century ago that multiple abnormalities occurred in the same patients, thus justifying the ‘syndrome’ designation. This condition is inherited as an autosomal dominant affliction and can produce many, varied phenotypical abnormalities¹⁶⁵, most prominent among which are the development of tens, hundreds or even thousands of basal cell carcinomas (BCCs) starting in adolescence or occasionally even in childhood. Patients with BCNS also characteristically develop odontogenic keratocysts, the encroachment of which into the jaws often being the aspect that is most troublesome to the patient. Other tumours to which they are particularly prone are medulloblastomas. Approximately 1–2% of patients with medulloblastomas have BCNS and approximately 3–5% of patients with BCNS develop medulloblastomas, mostly during childhood¹⁶⁶. Ovarian fibromas can also occur, sometimes in early childhood or even infancy¹⁶⁷. More rarely occurring in BCNS patients, but probably at an incidence greater than in non-BCNS individuals, are meningiomas, rhabdomyosarcomas, cardiac fibromas and mesenteric cysts. The lifespan of patients with BCNS, barring medulloblastomas, seems to be close to normal, but no compilation of their ages or causes of death has been published. Thus, we do not know whether or not these patients have any small increase in incidence of any of the more commonly fatal cancers, including those in which aberrant Hedgehog signalling has been described. Among the more intriguing phenotypical abnormalities in these patients is a strong propensity to develop BCCs after therapeutic ionizing radiation, whether given for treatment of BCCs or of medulloblastomas. BCNS is most often diagnosed on the basis of clinical findings, and major and minor phenotypical criteria for diagnosis have been proposed¹⁶⁸.

Currently, the best-studied downstream mediators remain those on which investigators have chosen to focus as candidate targets. Among these are upregulated platelet-derived growth

factor receptor- α (PDGFR α)⁸⁸, the upregulated apoptosis inhibitors BCI2 (REFS 89,90) and CASP8 and FADD-like apoptosis regulator (CFIAR)⁹¹ and the downregulated apoptosis inducers CD95 (FAS)^{92,93} and BMI1 (REFS 94,95). The ‘wiring’ downstream of HH signalling activation seems to differ in various tissues. Thus, inhibition of mitogen-activated protein kinase signalling inhibits the growth of HH pathway-stimulated BCC cells but not that of cerebellar granule precursor cells^{88,96}. But, in truth, we have only a limited understanding of which downstream expression changes are actually crucial for HH-induced BCC carcinogenesis. More data have been published during the past few years indicating that other signalling pathways may have profound effects on HH signalling in cancers (see below and BOX 3), although most of these studies did not address BCCs specifically.

PI3K–Akt—Interactions of the HH signalling pathway and the phosphoinositide 3-kinase (PI3K)–Akt pathway are suggested by models in which HH-induced tumorigenesis is enhanced by concomitant PI3K–Akt signalling activation⁹⁷ or responses to HH ligands are enhanced by concomitant insulin-like growth factor (IGF) ligand. Indeed, *Ptch1^{+/-}Igf2^{-/-}* mice fail to develop rhabdomyosarcomas⁹⁸, but no data about the dependence of BCC formation on Akt signalling have been published. These two classical pathways may interact at several levels. First, activation of HH signalling in some systems can affect PI3K–Akt signalling^{99–102}. Second, PI3K–Akt signalling can affect HH signalling: activated PI3K–Akt can stabilize GII2 through inhibition of protein kinase A (PKA)-mediated phosphorylation that normally results in ubiquitin-targeting and degradation¹⁰³.

FOXM1—FOXMI, which encodes a member of the forkhead box of transcription factors, is expressed in BCCs at higher levels than in normal keratinocytes¹⁰⁴. This gene is more generally expressed in all proliferating cells, its expression is higher in transformed cell lines and its overexpression contributes to carcinogenesis and to more malignant behaviour in various cancer models^{105–109}. Its transcriptional activity can be activated by DNA damage through CHK2 phosphorylation and consequent protein stabilization and, in turn, its expression stimulates the expression of the DNA repair enzymes XrCC1 and BrCA2 (REF. 110). FOXMI is a HH target gene, and its loss rescues entry into mitosis in cells specifically driven by HH signalling¹¹¹. Expression of FOXM1 is crucial for normal mitosis, and its loss can cause chromosomal instability, mitotic catastrophe and consequent cell death¹¹². FOXM1 transcriptional activity can be inhibited by ARF¹¹³, and pharmacological inhibition of FOXM1 with a cell-penetrating ARF peptide¹¹⁴ or with a small molecule¹¹⁵ has an anticancer effect in model systems. We do not yet know the degree of dependence of BCCs on FOXM1 expression.

In addition, another FOX family member, FOXEL, is expressed in human epidermis and at a higher level in human BCCs¹¹⁶. Its loss is associated with abnormal development of the hair follicle in a pattern consistent with it being a HH target gene and with it mediating downstream effects of HH signalling¹¹⁷. Again, its downstream target genes and the role it has in BCC carcinogenesis are unknown.

Wnt signalling—Although previous studies have drawn conflicting conclusions regarding the role of Wnt signalling in BCC carcinogenesis, a recent study presents convincing evidence for the requirement for activated Wnt signalling to be downstream of HH

signalling in these tumours, in both mice and humans¹¹⁸. These findings suggest yet another target for therapeutic intervention.

In summary, we still have only a dim idea of the factors that control BCC keratinocyte HH signalling, other than driver mutations, and of the ‘wiring’ downstream of this pathway. Often impressive results in model systems suggest that such knowledge could point to potential targets for therapies, which could perhaps be useful in combination with the specific HH inhibitors now under development, especially because modulators of these other pathways are also under development. Hence, a global assessment of these in BCCs remains a high priority.

Mouse models of BCC carcinogenesis

As discussed earlier, classical mouse skin carcinogenesis models readily produce tumours of the squamous lineage but none of the BCC lineage. The identification of the pivotal role of HH signalling in BCC carcinogenesis stimulated the engineering of several models in which HH signalling could be manipulated and BCCs could be produced, some of which carry inactivating mutations in genes encoding inhibitors of HH signalling, and some of which carry activated mutants or overexpressed wild-type positive regulators of this pathway (TABLE 1). These models have allowed studies of interventions — chemoprevention and chemotherapy — as well as more basic investigations into BCC tumorigenesis.

The first lesson derived from the models is that deregulated HH signalling is indeed crucial to BCC carcinogenesis. Thus, either constitutive or conditional overexpression of GII1 (REF. 119) or of GII2 (REF. 120) in keratinocytes can produce BCC-like proliferations in the skin. Similarly, expression of SMO carrying the activating mutations identified in human BCCs also can produce murine BCCs²⁹. Furthermore, *Ptch1*^{+/-} mice develop BCCs, and those BCCs often have deletion of the wild-type copy of *Ptch1* as well as upregulation of HH signalling¹²¹. Similarly, mice carrying one inactivated, mutant allele of the HH suppressor *Sufu* are also susceptible to BCC development¹²². Thus, mice carrying mutations in genes that encode at least four different components of the HH signalling machinery develop BCCs, or at least skin tumours resembling BCCs.

Box 2

Defects in DNA repair genes that might affect development of basal cell carcinomas

Studies investigating a possible link between defects in DNA repair genes and basal cell carcinomas (BCCs) have yielded conflicting results. For example, a single nucleotide polymorphism in *XPA* reported to be associated with increased relative risk of BCCs is also associated with increased, not decreased, DNA repair capacity¹⁶⁹; *XRCC1* polymorphisms have been reported to be associated¹⁷⁰ or not to be associated¹⁷¹ with BCC relative risk; and studies of associations of BCC relative risk with *XPD* (also known as *ERCC2*) polymorphisms are in conflict^{172–175}. These disparate results suggest that the effects of any single gene polymorphism may be weak but they do not exclude the possibility of stronger effects of combinations of polymorphisms, and remind us of our

lack of knowledge about how the efficiency of DNA repair is controlled in normal individuals. Such controls seem to include not just polymorphisms in the genes encoding these and other DNA repair genes (for example, DNA polymerase- η ¹⁷⁶), but also potentially polymorphisms in genes encoding other proteins that affect the level of DNA repair, such as interleukin 12, which enhances this process and can apparently affect susceptibility to ultraviolet (UV)-induced skin cancers¹⁷⁷. In addition, we have only a partial understanding of the mechanisms by which UV induces skin cancers. These mechanisms probably include not only direct DNA damage but also indirect DNA damage through the production of free radicals and UV-induced immunosuppression¹⁷⁸, which may impair putative immune defences against skin cancer development¹⁶¹.

The second lesson is that it seems that the degree of activation of HH signalling is correlated with the histological appearance — the stronger the activation, the more the tumours resemble human BCCs¹²³. With weaker activation, the tumours more closely resemble human tumours that are more hair-follicle-like.

A third striking finding is that p53 loss markedly enhances HH-driven tumorigenesis. This was shown first by the development of medulloblastomas in almost 100% of *Ptch1*^{+/-};*Trp53*^{-/-} mice as opposed to an incidence of less than 10% in *Ptch1*^{+/-} mice that have wild-type p53 (REF. 124). Similarly, we have found that *Ptch1*^{+/-} mice in which p53 is deleted conditionally in K14-expressing keratinocytes have a marked enhancement of BCC carcinogenesis. Therefore, the high incidence of p53 mutations in human BCCs is probably not simply caused by the fact that BCCs usually arise in sunexposed skin, but rather reflects the ability of p53 loss to contribute to the development of BCCs and perhaps to that of other HH-driven tumours as well.

Finally, results of pharmacological interventions in the *Ptch1*^{+/-} mouse seem so far to correlate well with results of the same interventions in humans. For example, topical application of the retinoid tazarotene, a retinoic acid receptor- β/γ ligand that is widely used for treatment of acne, (see later) inhibits BCC development in the *Ptch1*^{+/-} mouse and has clear anti-BCC efficacy in humans. Similarly, we have found that systemic non-steroidal anti-inflammatory drugs, such as celecoxib, weakly inhibit BCC carcinogenesis in both human and mouse PTCH1^{+/-} individuals (J. Tang *et al.*, unpublished observations).

Interventions

Prevention

Although the use of sunscreens has not so far been associated with a reduction in BCCs, there is hope that their use earlier in childhood might reduce later BCC carcinogenesis. Clinical trials addressing this hypothesis will not be completed in the near future, and so counselling of sun avoidance must currently rely on ‘best guesses’. One alternative to sun-protection measures is that of artificial tanning by systemic administration of α MSH¹²⁵, and indeed tanned skin is less susceptible to UV-induced DNA damage¹²⁶. As compared with UV-induced tanning, α MSH-induced tanning would seem to have the advantages of being non-mutagenic, non-promoting and non-immunosuppressive, but its clinical practicality has

yet to be demonstrated, and current development efforts involve parenteral drugs, a route of administration that is not likely to gain universal acceptance for UV protection.

Oligonucleotides that mimic the free ends of telomeres enhance DNA repair, stimulate tanning¹²⁷ and have anticancer efficacy in various cancer models, including UV-treated *PtchI*^{+/-} mice¹²⁸. Another strategy to enhance DNA repair capacities is to apply extra copies of DNA repair enzymes. Surprisingly, such proteins applied in liposomes can penetrate skin and accumulate in the nucleus of UV-damaged cells in an apparently catalytically active form such that significant reduction in UV-induced skin changes, including experimental carcinogenesis, can be seen¹²⁹. Such topical applications over one year significantly reduced the development of new skin cancers in patients with XP¹³⁰.

Systemic retinoids have been reported to be effective against new BCC development in patients with BCNS^{131,132} or XP¹³³, but have shown no protective effect in trials in patients who are at high risk of developing sporadic BCCs^{134,135}. Surprisingly, prolonged topical application of tazarotene can cure 25—50% of sporadic human BCCs^{136–138}. Topical tazarotene effectively prevents BCC carcinogenesis in the *PtchI*^{+/-} mouse^{139,140}, and we (D. Bickers and E.H.E.) are now conducting a multicentre clinical trial of its efficacy in patients with BCNS. Finally, one clinical trial of dietary intervention in patients who were at high risk of developing new sporadic skin cancers found that a low-fat diet (20% of calories as fat as opposed to the usual 35—40%) was associated with a reduction in the number of new BCCs¹⁴¹.

Treatment —narrowing the hedgehog's powers

Surgical excision of BCCs is currently by far the most commonly used treatment, and control approaches 100%. However, this high cure rate is accompanied by the inevitable discomfort and scarring of surgery, and the high frequency of BCCs makes them an expensive effort for those who foot the bill. As PDGFR α has been reported to mediate some of the downstream effects of HH signalling in BCCs, use of approved agents that inhibit this receptor kinase would be sensible⁸⁸. These include sorafenib and imatinib (Gleevec) but no study of their efficacy in BCC has been published. One systemic chemotherapy reported to have some efficacy for locally uncontrollable BCCs is the combination of paclitaxel and carboplatin¹⁴². With the evidence for HH activation in many types of visceral cancers, the rationale for development of HH inhibitors (HHIs) has become compelling. Consequently, at least half a dozen pharmaceutical companies have embarked on HHI development, and BCCs that are not controllable by local therapies are potential targets for trials of HHIs.

Box 3

Signalling pathways implicated in HH-induced tumours

Phorbol esters, which activate protein kinase C (PKC), are the most extensively studied promoters of squamous cell carcinogenesis, so it is not surprising that members of the PKC family have been investigated in relation to basal cell carcinomas (BCCs). Initial reports indicated that although PKC α is expressed in the epidermal and hair follicle basal layers, it is not expressed in BCC tumour nests^{179,180}. In model cell systems *in vitro*, PKC α inhibits the activity of the Gli family of transcription factors. By contrast, PKC δ

increases Gli activity, and sonic hedgehog (SHH) activation of Gli in at least some contexts seems to require PKC δ activity^{181,182}. The effects of PKC δ seem to be downstream of suppressor of fused (SUFU) but upstream of GLI1 (REF. 182). PKC also may act through activation of the MAPK kinase (MEK) to control Gli transcriptional activity itself. Like PKC α , PKC δ seems not to be expressed in BCC tumour nests but both are expressed in BCC stroma¹⁸⁰. One of the cancer-stimulatory genes downstream of PKC is ornithine decarboxylase (ODC), and in the *Ptch1*^{+/-} mouse model, ODC inhibitors reduce UV-induced BCC carcinogenesis and reduce expression of hedgehog target genes¹⁸³. However, ODC activity can be controlled by other pathways as well¹⁸⁴.

Epidermal growth factor receptor¹⁸⁵⁻¹⁹⁰ and transforming growth factor receptor β ¹⁹¹⁻¹⁹⁶ pathways can influence HH signalling markedly in model systems, but there is little evidence for their possible roles in BCC carcinogenesis. Surprisingly, because Notch activation can drive some human leukaemias, Notch loss in mice can activate GLI2 expression and produce skin tumours, including BCCs^{197,198}.

The first well-studied HHI is the plant alkaloid cyclopamine¹⁴³. Indeed, one intrepid group applied cyclopamine topically and reported regression of four sporadic BCCs¹⁴⁴. Cyclopamine is a competitive inhibitor of SMO signalling, binding directly to the protein¹⁴⁵⁻¹⁴⁷, and inhibits the growth of malignant cells driven by HH activation¹⁴⁸. Infinity Pharmaceuticals in Cambridge, Massachusetts, USA is developing cyclopamine derivatives with better pharmacological and inhibitory properties as potential HHIs, and the company expects to launch a phase 1 trial of one of these in 2008.

The first HHI tested in phase 1 trials was a Curis-Genentech compound (Curis 61414), which produced neither clinical changes in the tumours nor reductions of mrNA encoding the HH target gene *GLI1* when applied topically to sporadic human BCCs (see [Curis website 2006 press release](#) in Further information). However, GDC-0449, a second Curis-Genentech HHI molecule, seemed to have minimal toxicity and to cause clinically significant benefit in eight out of nine patients with metastatic or locally advanced BCCs when administered orally in a phase 1 trial¹⁴⁹. Genentech expects shortly to initiate phase 2 trials of this molecule in patients with advanced BCCs and in patients with advanced colorectal and ovarian cancers.

The practical barriers to the development and use of HHIs in localized BCCs include the high cure rate with surgery, despite the unattractive aspects of such procedures described earlier. If systemic delivery of HHI were to be used, the agent would have to be essentially 100% free of adverse extracutaneous effects. One potential on-target adverse effect might be on normal tissue stem cells such as those of the brain, the maintenance of which in mice is supported by HH^{150,151}. loss of these brain stem cells in mice has been reported to give cognitive defects¹⁵². Indeed, the minimally annoying dysgeusia (distortion or loss of the sensation of taste) and alopecia seen in the systemic HHI trial could be caused by on-target effects of inhibition of HH function normally required for maintenance of the olfactory bulb, tongue papillae and hair follicle^{150,153-155}. Such therapy-induced loss occurring in humans with pancreatic cancer might be tolerable; not so for patients with the usual BCCs. HHIs also can cause premature closure of epiphyses¹⁵⁶, a reminder that development is not

complete at birth and a potential contraindication to HHI treatment of childhood medulloblastomas.

Unanswered questions

Why are BCCs so much more common than other human cancers?

The answer to this question traditionally has been that they arise in an organ that is subject to enormous mutagenic insults exogenously and endogenously as a 'cost' of the continued lifelong high turnover of the epidermis. Viewed in molecular terms, it might also be the case that, unlike in the development of many visceral cancers, disruption of merely one anticancer mechanism — restraint of HH signalling — seems to be enough to allow their growth. However, viewed in another context (prostate cancer in the elderly, for example), perhaps their frequency is not so high after all. Moreover, the apparently high incidence might be, in part, a product of the fact that these lesions are obvious to the naked eye. Indeed, as we have been able to examine internal tissues more closely, the incidence of 'incidentalomas' rises dramatically, with the accompanying quandary of what is the proper medical intervention. If the diagnosis of BCCs were to depend on organ dysfunction rather than appearance, their incidence might plummet to less than that of many classical visceral cancers. In this context, the skin may serve as a useful model for how medicine will learn to deal with the increasing numbers of 'incidentalomas' that our improving diagnostic acumen uncovers.

Why does the incidence of BCCs not rise proportionally to the amount of UV exposure as in SCCs?

One possibility for this comes from the observation that sun exposure activates DNA repair mechanisms¹⁵⁷: perhaps mutations of *PTCH1* are more susceptible to repair than mutations in the genes that underlie SCCs. However, no evidence for such differential repair is available. One alternative is suggested by the observation that vitamin D inhibits HH signalling through binding to SMO protein¹⁵⁸. Thus, more frequent UV exposure might maintain a level of keratinocyte vitamin D that is sufficient to inhibit the growth of BCCs but not of SCCs. A potential flaw in this is that one study suggested that chronic sun exposure fails to increase cutaneous vitamin D levels even while increasing internal levels¹⁵⁹. Consistent with this idea, however, is the finding that skin production of 7-dehydrocholesterol, the precursor molecule that UV radiation converts to vitamin D, wanes in the elderly, and this parallels the increasing incidence of BCCs with ageing¹⁶⁰. More generally, the increasingly studied and discussed anticancer effects of vitamin D stores might also have some anti-BCC carcinogenesis effect. Another possibility might be that the photoimmunosuppression that occurs with sun exposure affects SCCs more than BCCs; indeed, in immunosuppressed organ transplant patients, the incidence of SCCs increases considerably more than the incidence of BCCs. However, at least in *Ptch1*^{+/-} mice, anti-rejection drugs can allow more robust BCC carcinogenesis¹⁶¹, and so the immune system ordinarily may provide at least some protection against BCC as well as SCC carcinogenesis. Better understanding might come were we able to identify clinically inapparent precursor lesions.

Why do BCCs so rarely metastasize?

Not only do BCCs essentially never spread to distant regions, but also the limitation of their growth to that by local extension allows careful, microscopically controlled surgical excision to give a cure rate approaching 100%. One possibility might be that physicians remove BCCs before they grow to a size that allows the accumulation of the additional mutations needed to metastasize. Yet patients with BCNS may have hundreds of BCCs; commonly, BCCs in these patients are removed only when they impinge on sensitive structures such as the eye, and most are treated with a 'wait and see' approach. Another possibility would be that activated HH signalling is incompatible with metastasis. But prostate cancer metastases have higher HH signalling activity than do the primaries from which they arose¹⁶², suggesting that this might not be the answer. A third possibility might be that specialized abnormal stroma is required, and indeed there is some evidence that BCCs are especially dependent on stroma, at least for their experimental transplantation to other sites in humans¹⁶³. In addition, loss of specialized stroma might be one reason for the marked downregulation of HH signalling when experimental BCCs or medulloblastomas are transferred from the host to tissue culture. But in most patients with BCCs, there would seem to be no lack of UV-damaged stroma available as a 'soil' for BCCs to find if this were the main cause of their lack of metastasis. Finally, BCCs tend to have relative genomic stability, and perhaps it is this that provides the barrier to further DNA abnormalities that might confer metastatic potential. But why do BCCs not acquire genomic instability? Might such instability be incompatible with their successful local growth?

What can we learn about BCCs that may further inform our knowledge of visceral cancers?

If hedgehog activation at first induces keratinocyte senescence, as has been suggested in experimental models of HH signalling activation¹⁶⁴, why does senescence not occur with physiological HH signalling during development, hair follicle cycling and experimental models with conditional Gli overexpression?²⁵ A greater understanding of the HH pathway and the induction of senescence is needed to address this question. It is possible that the degree of deregulation of HH signalling found in human cancer is enough to overcome induction of senescence. Indeed, it will be interesting to determine how much HH signalling is required to drive cancer development in different tissues. Analysis of tissues from the recent phase 1 clinical trials of HHIs in patients with BCC will also provide important data on whether a complete absence of HH signalling is required for a clinical response or whether a reduction is all that is needed. later stage trials of HHIs in BCC will also be able to address whether relapse or resistance occur in patients with advanced BCC. Finding mechanisms of resistance, should they occur, might help the development of HHIs for other cancers such as medulloblastoma, in which HH signalling is deregulated. As BCCs seem to have relatively little genomic instability, it is reasonable to hope that mutations may not be as frequent a mechanism of resistance as is the case with more genetically unstable cancers. Finally, it will be important to establish the signalling pathways downstream of the Gli transcription factors that drive carcinogenesis. These might provide opportunities for development of drugs with perhaps a better therapeutic index (for example, sparing stem cells that, at least theoretically, might be the target of collateral damage with HH inhibition) than that of direct inhibition of HH signalling.

Conclusions

In little more than one decade, thanks to the work of many investigators, our understanding of the molecular pathogenesis of BCCs has gone from close to zero to a fairly significant body of information. Certainly, we still have only a rudimentary knowledge of the genetic underpinnings that determine which people develop BCCs and which do not, and of the wiring that drives keratinocytes to BCC carcinogenesis. But it does seem that we already have enough information to have a reasonable chance of translating our molecular understanding to real clinical benefit. The successful molecularly targeted treatment of BCCs with HHI might be only the first of the clinical benefits that result from the vanquishing of the evil hedgehog.

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Medicare

The US federal government medical insurance programme that covers all citizens over the age of 65.

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At a glance

- Basal cell carcinomas (BCCs) are keratinocyte tumours that resemble the basal layer of the epidermis, and are the most commonly diagnosed human cancer among persons of European ancestry.
- Despite this high frequency, the death rate is extraordinarily low, a reflection perhaps of the excellent care provided by physicians and of their vanishingly rare propensity to metastasize.
- The vast majority of BCCs occur sporadically, but patients with the rare heritable disorder basal cell nevus syndrome (BCNS) have a marked susceptibility to developing BCCs.
- Family based linkage studies of kindreds with BCNS identified the patched 1 (*PTCH1*) gene, an inhibitor of the hedgehog signalling pathway, as being mutated in these patients. p53 is also mutated in some patients with sporadic BCCs.
- Downstream signalling pathways that are deregulated in patients with BCCs are currently being investigated.
- Surgery is curative for most patients with BCCs. However, for those few that develop locally advanced or metastatic BCC, for which there is currently no effective treatment, Phase I clinical trials with inhibitors of the hedgehog signalling pathway have produced promising results.

Linkage disequilibrium

When alleles at two or more genetic loci occur more frequently in the population than expected given the known allele frequencies and recombination fraction between the two loci. This indicates that the loci are tightly linked; that is, sufficiently close together on the same chromosome to be co-inherited more than 50% of the time.

Parenteral

Administration of a drug by injection, such as subcutaneous, intramuscular or intravenous, rather than administration through the alimentary canal.

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Cyclopamine

The teratogenic component of corn lilies that is responsible for the cyclopean (one-eyed) phenotype of lambs born of dams eating this plant.

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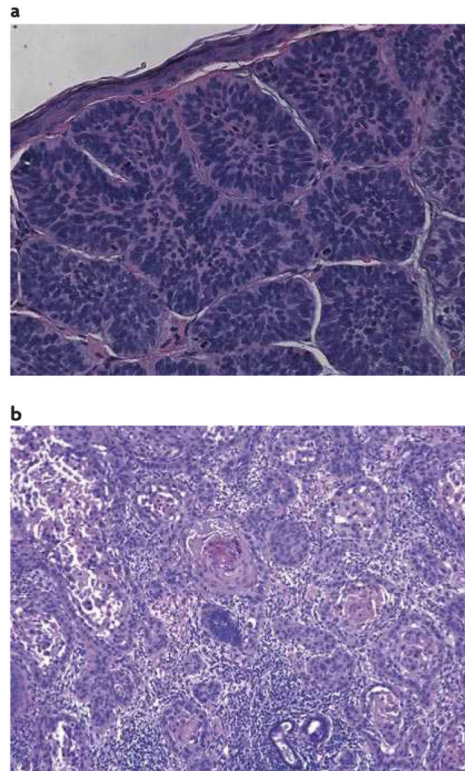


Figure 1. Histological sections of basal cell carcinoma and squamous cell carcinoma of the skin
a | Basal cell carcinomas (BCCs) are keratinocyte tumours that are so named because of their histological resemblance to the cells along the basement membrane — the ‘basal’ layer of the epidermis. **b** | Often BCCs are grouped as non-malignant skin cancer together with squamous cell carcinomas of the skin (shown) and several other less common tumours.



Figure 2. The cutaneous appearance of basal cell carcinoma
BCCs classically appear as slow-growing, translucent, elevated lesions on the sun-exposed skin of persons with ‘fair’ skin and occur more commonly in men than in women.

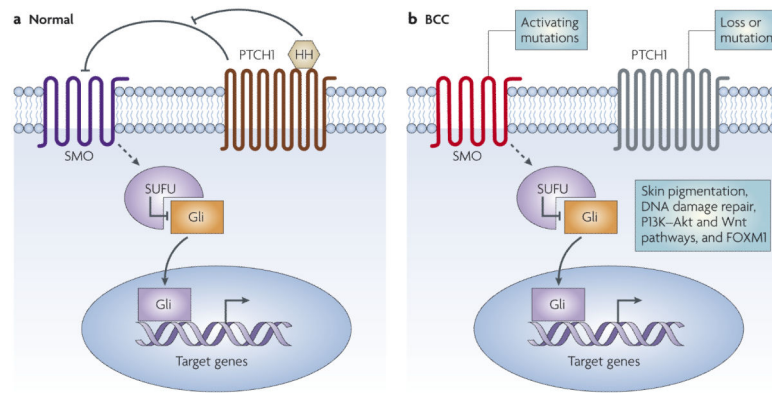


Figure 3. A basic schematic of the Hedgehog (HH) signalling pathway

a | The family of extracellular HH ligands, of which there are three in mammals (sonic hedgehog (SHH), Indian hedgehog (IHH) and desert hedgehog (DHH)) bind to the patched 1 (PTCH1) receptor. This relieves the inhibition of smoothened (SMO) by PTCH1, and SMO sends signals through a series of interacting proteins, including suppressor of fused (SUFU), resulting in activation of the downstream Gli family of transcription factors: GLI1, GLI2 and GLI3. **b** | Loss of *PTCH1* in patients with basal cell nevus syndrome predisposes them to basal cell carcinoma (BCC) development. Sporadic BCCs routinely carry mutations in *PTCH1* and *TP53*, consistent with their having been produced by ultraviolet radiation and, in 10% of instances, in *SMO*. Other mutations have been implicated in BCC development, including genes that regulate skin colour, DNA damage repair genes, members of the phosphoinositide 3-kinase (PI3K)–Akt and the Wnt pathways and FOXM1.

Table 1

Occurrence of basal cell carcinoma (BCC) in mouse models

Gene	BCC as a result of overexpression (transgenic)	BCC as a result of knockout
<i>Shh</i>	Yes	No
<i>Ptch1</i>	No	Yes
<i>Smo</i>	Yes	No
<i>Sufu</i>	No	Yes
<i>Gli1</i>	Yes	No
<i>Gli2</i>	Yes	No

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