MMS of recurrent and high-risk NMSCs are most likely to impact the Mohs units that provide services to those most in need of this valuable but overused procedure.

CONFLICT OF INTEREST

The author states no conflict of interest.

REFERENCES

Chren MM, Linos E, Torres J *et al.* (2013) Tumor recurrence 5 years after treatment of cutaneous basal cell carcinoma and squamous cell carcinoma. *J Invest Dermatol* 133: 1188–96

Chren MM, Sahay AP, Bertenthal DS *et al.* (2007) Quality-of-life outcomes of treatments for cutaneous basal cell carcinoma and squamous cell carcinoma. *J Invest Dermatol* 127:1351–7

Connolly S, Baker D, Coldiron B *et al.* (2012) AAD/ACMS/ASDSA/ASMS 2012 appropriate use criteria for Mohs micrographic surgery: a report of the American Academy of Dermatology, American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and the American Society for Mohs Surgery. *J Am Acad Dermatol* 67:531–50

Donaldson M, Coldiron B (2012) Mohs micrographic surgery utilization in the medicare population, 2009. *Dermatol Surg* 38:1427–34

Essers B, Dirksen C, Nieman F *et al.* (2006) Cost-effectiveness of Mohs micrographic surgery vs surgical excision for basal cell carcinoma of the face. *Arch Dermatol* 142: 187–94

Essers B, Dirksen C, Prins M *et al.* (2010) Assessing the public's preference for surgical treatment of primary basal cell carcinoma; a discrete-choice experiment in the south of the Netherlands. *Dermatol Surg* 36:1950–5

Essers B, Nieman F, Prins M *et al.* (2007) Perceptions of facial aesthetics in surgical patients with basal cell carcinoma. *J Eur Acad Dermatol Venereol* 21:1209–14

Maxwell S, Zuckerman S, Berenson R (2007) Use of physicians' services under Medicare's resource-based payments. *N Engl J Med* 356:1853–61

Mosterd K, Krekels G, Nieman F *et al.* (2008) Surgical excision versus Mohs' micrographic surgery for primary and recurrent basal-cell carcinoma of the face: a prospective randomized controlled trial with 5-years' follow-up. *Lancet Oncol* 9:1149–56

Smeets N, Krekels G, Ostertag J *et al.* (2004) Surgical excision vs Mohs' micrographic surgery for basal-cell carcinoma of the face: randomized controlled trial. *Lancet* 364:1766–72

Stern RS (2010) Prevalence of a history of skin cancer in 2007: results of an incidence-based model. *Arch Dermatol* 146:279–82

Wennberg J, Gittelsohn A (1973) Small area variations in health care delivery. *Science* 182:1102–8

Wilson L, Pregenzer M, Basu R *et al.* (2012) Fee comparisons of treatments for nonmelanoma skin cancer in a private practice academic setting. *Dermatol Surg* 38:570–84

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"Patch"ing Up Our Tumor Signaling Knowledge

Scott X. Atwood[1,2], Ramon J. Whitson[1,2] and Anthony E. Oro[1]

The tumor suppressor Patched1 (Ptch1) possesses well-described roles in regulating sonic hedgehog (SHH) signaling in the skin and preventing the formation of basal cell carcinomas (BCCs). In this issue, Kang *et al.* extend their previous work to show that a naturally occurring allele of Ptch1 found in FVB mice promotes early squamous cell carcinoma (SCC) growth without aberrant activation of the SHH pathway. The study reveals new roles for Ptch1 that lie at the nexus between BCC and SCC formation.

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The sonic hedgehog (SHH) signaling pathway has key roles during embryonic development, cell fate decisions, and tumor formation (Hui and Angers, 2011; Ingham *et al.*, 2011). SHH binds to its receptor Patched1 (Ptch1), releasing Smoothened (Smo) inhibition that results in Gli-dependent transcription of SHH target genes. Inactivating mutations in Ptch1 in the skin promotes formation of basal cell carcinomas (BCCs) at high frequency and are the cause of Gorlin syndrome in the germline (Hahn *et al.*, 1996). Although Gorlin patients have well-characterized susceptibility to other SHH-dependent tumors, Ptch1 loss in these patients does not appear to contribute to excessive SCC development. Moreover, sporadic BCCs also rely on high levels of SHH target gene induction for tumor growth, providing the rational for development of a targeted therapy. Indeed, inhibition of the SHH pathway with Smo antagonists recently received Food and Drug Administration approval for the treatment of late advanced or metastatic BCCs, and they have shown impressive efficacy in Gorlin patients (Atwood *et al.*, 2012).

Although the role for Ptch1 in BCC tumor suppression is clear, surprisingly little is known about how this enigmatic protein functions at a mechanistic level. Ptch1 is a member of the sterol-sensing domain family and shares identity with the ABC transporter family (Ingham *et al.*, 2011). Although this suggests it pumps key signaling molecules, none so far has been identified unequivocably. Moreover, Ptch1 function in suppressing Smo, arguably its most oft-written role, has not been delineated. Although it is clear that SHH binding to Ptch1 activates Smo, how the two proteins interact remains unknown. Initial studies suggested that the two proteins form a complex and argued for direct allosteric inhibition (Carpenter *et al.*, 1998; Murone *et al.*, 1999). However, later quantitative studies indicated that Ptch1 acts catalytically, suggesting it controls an enzymatic modifier of Smo function (Ingham *et al.*, 2000; Taipale *et al.*, 2002). Recently, entry into the primary cilium, a microtubule based organelle, has been shown to be important for Smo function, and Ptch1 appears to regulate ciliary entry in an as yet unknown manner (Rohatgi *et al.*, 2007).

Ptch1^{FVB} promotes Ras-induced skin tumorigenesis

Distinct from its role in controlling the SHH pathway, recent studies indicate a

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Clinical Implications

- Ptch1^{FVB} is a multifunctional protein that regulates hedgehog signaling and the Ras pathway.
- Ptch1 alleles can promote murine SCC development at the same time that they inhibit BCC growth.

growing role for Ptch1 in regulating apoptosis. The original role for SHH and Ptch1 in regulating cell survival came from work in the developing neuroepithelium, where SHH acts as a neuronal survival factor (Thibert *et al.*, 2003). This study demonstrated that Ptch1 induces apoptosis independent of Smo and Gli activity by acting as a dependence receptor, binding caspases, and inducing apoptosis.

Work from the Balmain lab illuminates a similar role for the multifunctional protein in skin cancer. Previously, Wakabayashi *et al.* (2007), in an elegant forward genetic screen for modifiers of SCC, found that a single-amino-acid variant of Ptch1 (T1267N) confers increased susceptibility to Ras-induced tumor formation in the FVB/N strain of mice. Overexpression of the *Ptch1*^{FVB} allele driven by the keratin 14 promoter (*K14Ptch1*^{FVB}) was sufficient to drive Ras-induced formation of SCCs in C57BL/6 mice. In this issue, Kang *et al.* (2013) show that forced overexpression of *K14Ptch1*^{FVB} results in developmental malformations consistent with diminished SHH signaling. Mice displayed shorter body lengths, lower body weights, ocular defects, and oligodactyly with fewer digits with higher *K14Ptch1*^{FVB} expression. Although low *K14Ptch1*^{FVB} expression did not show pronounced developmental defects, these mice were more stable, and they were used to expand upon the previously reported Ras-induced SCC formation. To determine the contribution of *K14Ptch1*^{FVB} in adult onset SCC, Ras was mutated by chemical means (7,12-dimethylbenz[a] anthracene followed by 12-*O*-tetradecanoylphorbol-13-acetate (TPA)) in the skin of adult mice, and tumor formation was measured. This system typically induces somatic mutation in H-Ras at codon 61 (CAA to CTA) at high frequency, causing constitutive activation and SCC formation similar to that which is observed in human skin tumors (Balmain *et al.*, 1984). The authors found that chemically induced SCC development increased and tumor latency decreased in *K14Ptch1*^{FVB} mice compared with wild-type mice, despite no significant change in SHH target gene expression. They concluded that the *K14Ptch1*^{FVB} allele contributes to Ras-induced skin tumor development in adult mice.

Kang *et al.* (2013) begin to shed light on how Ptch1^{FVB} promotes SCC formation through regulation of Ras-induced apoptosis (Figure 1). *Ptch1*^{FVB} expression suppresses HRAS-induced apoptosis and Tid1, a tumor suppressor involved in apoptosis, differentially binds Ptch1^{FVB} weaker than Ptch1^{B6} (Wakabayashi *et al.*, 2007). The authors confirm the strong Tid1–Ptch1^{B6} and weak Tid1–Ptch1^{FVB} binding, and they show that binding between Tid1–Ptch1^{B6} decreases after TPA treatment to levels seen between Tid1–Ptch1^{FVB}. However, how Ras influences the Tid1–Ptch1 interaction needs to be explored further, as expression of *V12HRAS* partially inhibits Tid1–Ptch1^{B6} and partially promotes Tid1–Ptch1^{FVB} binding. The authors suggest that stimulation of mitogen-activated protein (MAP) kinase signaling from TPA treatment may also influence Tid1–Ptch1 binding, as Ptch1 can activate extracellular signal–regulated kinase (ERK) independently of Smo (Chang *et al.*, 2010). In light of the observation that TPA promotes P-ERK in the presence of Ptch1^{B6}, but inhibits P-ERK when Ptch1^{FVB} is expressed, additional work is needed to determine whether Ptch1 influences MAP kinase signaling directly.

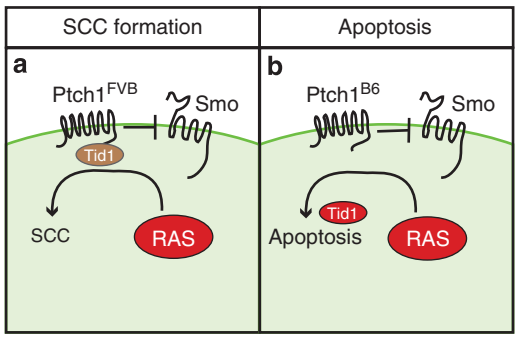

Figure 1. Diagram of Patched1 (Ptch1)-dependent squamous cell carcinoma (SCC) tumor formation. (**a**) High levels of active RAS and inhibition of Tid1 by Ptch1^{FVB} results in SCC tumor formation but not maintenance. (**b**) SCC tumor formation is suppressed in the Ptch1^{B6} background, where Ptch1^{B6} is unable to inhibit Tid1 and results in an increase in Ras-induced apoptosis. Smo, smoothened.

Ptch1 lies at a nexus between BCC and SCC formation

Identification of the *Ptch1*^{FVB} allele suggests that Ptch1 can have roles in both BCC and SCC development, inhibiting BCCs and promoting SCCs. Interestingly, both tumors appear to share a common cell of origin, with the interfollicular epidermis, hair follicle bulge, and hair germ giving rise to both tumors, depending on the genetic environment (Epstein, 2011; Lapouge *et al.*, 2011; White *et al.*, 2011). In mice, p53 loss instigates tumor growth along with activating signals from either RAS or SHH. Toggling expression of RAS or SHH through Ptch1^{FVB}, where more Ptch1 leads to inhibition of SHH signaling and promotion of Ras signaling, provides an interesting and simple way in which tumor lineages can use the multiple functions of a single protein to generate distinct outcomes. Although the current study focuses on murine skin cancer, alterations in the Ptch1 locus in human SCCs appear frequently but are of unknown significance. Ptch1 function in preventing apoptosis may be generalizable to other SHH-dependent and well as SHH-independent cancers.

Additional studies of the enigmatic Ptch1 protein are likely to unveil novel and illuminating cancer mechanisms.

CONFLICT OF INTEREST

The authors state no conflict of interest.

REFERENCES

Atwood SX, Chang ALS, Oro AE (2012) Hedgehog pathway inhibition and the race against tumor evolution. *J Cell Biol* 199:193–7

Balmain A, Ramsden M, Bowden GT *et al.* (1984) Activation of the mouse cellular Harvey-ras gene in chemically induced benign skin papillomas. *Nature* 307:658–60

Carpenter D, Stone DM, Brush J *et al.* (1998) Characterization of two patched receptors for the vertebrate hedgehog protein family. *Proc Natl Acad Sci USA* 95:13630–4

Chang H, Li Q, Moraes RC *et al.* (2010) Activation of Erk by sonic hedgehog independent of canonical hedgehog signalling. *Int J Biochem Cell Biol* 42:1462–71

Epstein EH (2011) Mommy - where do tumors come from? *J Clin Invest* 121:1681–3

Hahn H, Wicking C, Zaphiropoulous PG *et al.* (1996) Mutations of the human homolog of Drosophila patched in the nevoid basal cell carcinoma syndrome. *Cell* 85:841–51

Hui C-C, Angers S (2011) Gli proteins in development and disease. *Annu Rev Cell Dev Biol* 27:513–37

Ingham PW, Nystedt S, Nakano Y *et al.* (2000) Patched represses the Hedgehog signalling pathway by promoting modification of the smoothened protein. *Curr Biol* 10:1315–8

Ingham PW, Nakano Y, Seger C (2011) Mechanisms and functions of Hedgehog signalling across the metazoa. *Nat Rev Genet* 12:393–406

Kang HC, Wakabayashi Y, Jen K-Y *et al.* (2013) *Ptch1* overexpression drives skin carcinogenesis and developmental defects in *K14Ptch*^{FVB} mice. *J Invest Dermatol* 133:1311–20

Lapouge G, Youssef KK, Vokaer B *et al.*Identifying the cellular origin of squamous skin tumors (2011) *Proc Natl Acad Sci* 108:7431–6

Murone M, Rosenthal A, de Sauvage FJ (1999) Sonic hedgehog signaling by the patched-smoothened receptor complex. *Curr Biol* 9:76–84

Rohatgi R, Milenkovic L, Scott MP (2007) Patched1 regulates hedgehog signaling at the primary cilium. *Science* 317:372–6

Taipale J, Cooper MK, Maiti T *et al.* (2002) Patched acts catalytically to suppress the activity of smoothened. *Nature* 418:892–7

Thibert C, Teillet MA, Lapointe F *et al.* (2003) Inhibition of neuroepithelial patched-induced apoptosis by sonic hedgehog. *Science* 301:843–6

Wakabayashi Y, Mao J-H, Brown K *et al.* (2007) Promotion of Hras-induced squamous carcinomas by a polymorphic variant of the Patched gene in FVB mice. *Nature* 445:761–5

White AC, Tran K, Khuu J *et al.* (2011) Defining the origins of Ras/p53-mediated squamous cell carcinoma. *Pro Natl Acad Sci* 108:7425–30

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Applications of Nanoparticles for Treating Cutaneous Infection

Astrid M. Westendorf[1]

Today, nanotechnology is finding applications in medicine. The unique physical and chemical properties of nanoparticles can overcome barriers and allow them to gain access to biological systems. Because of the increasing prevalence of microbial resistance to conventional therapies, the development of novel antimicrobials is imperative. Creating nanotechnology-based drug delivery systems with antibacterial and immunomodulatory activities may lead to novel treatments for cutaneous pathogens.

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Nanotechnology is the design and control of matter that ranges in size from ~1 to 100 nm. The application of nanotechnology to medicine, known as nanomedicine, involves the use of precisely engineered materials in this size range to develop novel therapeutic and diagnostic modalities. The unique physical and chemical properties of nanoparticles, in particular their small size and their high surface-to-volume ratio, can overcome barriers and allow them to gain access to biological molecules and systems. These properties can be used to overcome some of the limitations of conventional therapeutic and diagnostic agents. Therefore, nanoparticles can be engineered to serve as vehicles that carry various therapeutic agents and may be useful in medical applications, including targeted drug delivery, vaccine delivery, antimicrobials, and immunomodulation (Prow *et al.*, 2011; DeLouise, 2012).

Antimicrobial nanoparticles

Several studies have shown that nanoparticles are advantageous in several dermatological applications (Papakostas *et al.*, 2011; DeLouise, 2012). One important application with respect to the increasing frequency of microbiological resistance to conventional therapies is the nanotechnology-based drug delivery with antimicrobial agents.

Acne is a chronic inflammatory disease of the pilosebaceous unit. It results from an androgen-induced increase in the production of sebum, alterations in keratinization, inflammation, and bacterial colonization of hair follicles on the face, neck, chest, and back by *Propionibacterium acnes*. The Gram-positive bacterium *P. acnes* is a ubiquitous member of the skin microbiota and is found in sebaceous follicles located on the face and back of most humans. *P. acnes* is generally regarded as a commensal of the skin, but certain properties suggest that it has a pathogenic role in acne vulgaris. Treatment of acne with antimicrobial agents has been found to be associated with the development of resistance to these agents by *P. acnes,* leading to treatment failure. Because acne often requires long-term treatment with antibiotics, there are concerns that the development of resistance by *P. acnes* may be associated with the development of resistance by other organisms, such as *Staphylococcus aureus* and *S. pneumoniae*. Judicious use of antibiotics is important, especially for a common condition such as

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