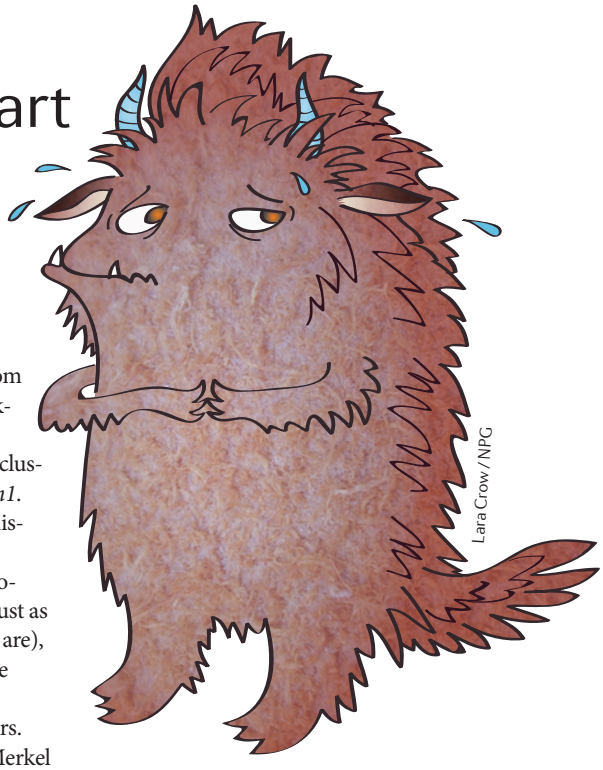
TUMORIGENESIS

A hairy and nervous start



Lara Crow / NPG

Basal cell carcinomas (BCCs) are Hedgehog (HH)-driven tumours that have been thought to arise from follicular and interfollicular epidermal basal keratinocytes, although the identity of the cell of origin of this type of tumour and the compartments in which these cells reside remain controversial. Now, Peterson *et al.* have found that BCCs primarily arise from stem cells within hair follicles, whereas most stem cells within the interfollicular epidermis (IFE) do not form tumours with the exception of an innervated subset of IFE cells known as touch dome epithelia.

BCC is characterized by frequent loss of the gene encoding Patched homologue 1 (PTCH1), which normally suppresses HH activity. Given that BCC has long been thought to originate at the hair follicle — which is maintained by several independent stem cell populations — the authors tested whether these different populations were able to form tumours upon loss of *Ptch1* and found that BCC-like tumours can originate from progenitor populations in different sections of the hair follicle.

The authors then assessed whether BCC could also originate from the surface epidermis by using mice in which *Ptch1* is deleted in progenitor cells of the IFE but not in the hair follicle. These mice did not develop tumours in the epidermis. However, mice in which *Ptch1* was deleted specifically in *Gli1*-expressing cells did develop lesions that extended from the epidermis at sites close to guard hairs (the long outer hair that protects the underfur in certain animals), where the touch dome cells reside.

As touch dome epithelial cells also have activated HH signalling during homeostasis, the authors investigated whether the epidermis-associated tumours might derive from touch dome cells by tracking keratin 17-positive touch dome-derived cell clusters upon deletion of *Ptch1*. They found that epidermis-associated tumours were lined by innervated neuroendocrine Merkel cells (just as normal touch dome cells are), whereas Merkel cells were not found near any hair follicle-associated tumours.

Tumour-associated Merkel cells are innervated by sensory afferents, and surgical nerve ablation has been reported to cause loss of both normal touch dome and Merkel cells in mice. The authors sought to investigate whether denervation could also impair HH signalling using mice in which lacZ expression can be detected upon HH pathway induction. Denervation of one side of the mice showed reduced HH signalling in touch dome cells compared with the other side that had been left intact as a contralateral control, suggesting that cutaneous nerves maintain HH pathway activity in the touch dome. Importantly, denervation also inhibited touch dome-derived tumours, and this effect was site-specific, as nerve ablation did not affect adjacent hair follicle-associated lesions.

But how does the perineural microenvironment promote a pro-tumorigenic niche in the touch dome? The authors investigated the possibility that paracrine signals released by nerves can promote HH signalling. Indeed, dissection of the ganglia in the dorsal area — where cutaneous sensory nerves are located — showed that these nerves express higher levels of all three HH ligands than do skin epithelia.

Apart from establishing the cell and place of origin of BCCs, the results by Peterson *et al.* confirm the role of the nervous system in promoting tumorigenesis in mice. In humans, recent studies in the prostate and intestines have also pointed to a possible role for nerves in stimulating tumorigenesis, and specific subtypes of BCC have been associated with Merkel cells. Together, these studies shed light on cancers with unexpected nervous inclinations.

M. Teresa Villanueva

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ORIGINAL RESEARCH PAPER Peterson, S. C. *et al.* Basal cell carcinoma preferentially arises from stem cells within hair follicle and mechanosensory niches. *Cell Stem Cell* **16**, 400–412 (2015)