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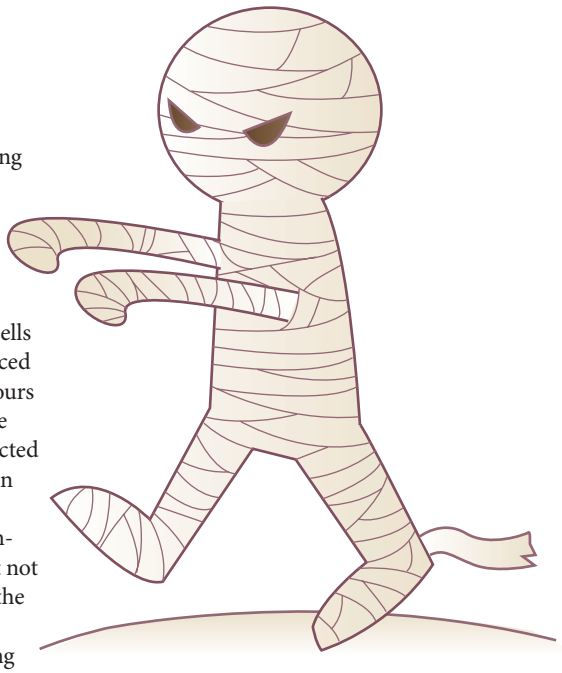
TUMORIGENESIS

Wound-up tumours



Cancer development and wound healing share common features that have led to the view that tumours are wounds that do not heal. Indeed, an increased risk of basal cell carcinoma (BCC) has been associated with both chronic and acute wounds, but the mechanisms underlying this association are unknown. Two articles recently published in *Proc. Natl Acad. Sci. USA* have provided some answers as to how these two processes are linked.

BCC is thought to arise from stem cells of the hair follicle and is associated with the misactivation of the Hedgehog (HH) signalling pathway. As mutations in Smoothened (*SMO*), a central mediator of the HH pathway, are commonly found in BCCs, Sunny Wong and Jeremy Reiter investigated whether activating this pathway in follicular stem cells was sufficient to trigger BCC. To do so, they generated mice that expressed a conditional oncogenic allele of *Smo* (*SmoM2*) in the keratin 15 (*K15*)-expressing cells of the follicular bulge, cells which have previously been shown to be follicular stem cells. These mice did not develop tumours. However, wounds administrated to the backs of the mice induced the appearance of multiple BBC-like tumours. These lesions were composed of follicular stem cells that had migrated to the epidermal margin of the wound. The authors then assessed whether activating HH in cells of the interfollicular epidermis (IFE) would have the same outcome. In the absence of wounds, IFE cells expressing *SmoM2* formed tumours, and wounding did not increase their tumorigenic capacity. Thus, these authors conclude that mobilizing tumorigenic follicular stem cells can account for wound-induced tumorigenesis. Why do tumours form in the IFE but not in the bulge cells? The authors detected *SmoM2*-induced upregulation of the HH target gene, and a positive regulator of this pathway, *Gli1*, only in the IFE but not at the bulge, suggesting that the HH pathway was blocked in the bulge cells, thus protecting against oncogenesis.

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Similar conclusions were reached by Rune Toftgård and collaborators, who were interested in the effect of wounding in BCC-like tumours. They developed two mouse models mainly targeting cells from the bulge region: mice overexpressing human *GLI1* in basal cells under the keratin 5 promoter (K5–*GLI1*), and mice in which the negative regulator of HH patched 1 was inactivated in cells that expressed K5 (K5Cre–*Ptch1*$^{fl/fl}$). Both models developed the same BBC-like lesions, which were composed of follicular stem cells and IFE cells. When wounds were introduced in the dorsal skin, the authors found that the K5–*GLI1* mice showed a significant increase in the size of the tumours in the wounded area, probably owing to a general increase in cell proliferation associated with wound healing, but no increase in the number of lesions. By contrast, K5Cre–*Ptch1*$^{fl/fl}$ mice showed an increase in both size and number of BBC-like tumours. This could be attributed to the recruitment of cells with an ability to initiate tumours that emigrate from the hair follicle.

These papers raise interesting questions regarding how stem cell niches restrict tumorigenesis and how wounds ‘call’ stem cells out of their niches — questions that will require further investigation to answer.

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ORIGINAL RESEARCH PAPERS Wong, S. Y. & Reiter, J. F. Wounding mobilizes hair follicle stem cells to form tumors. *Proc. Natl Acad. Sci. USA* (doi:10.1073/pnas.1013098108) | Kasper, M. *et al.* Wounding enhances epidermal tumorigenesis by recruiting hair follicle keratinocytes. *Proc. Natl Acad. Sci. USA* (doi:10.1073/pnas.1014489108)