TUMORIGENESIS

# Keeping a watchful eye

Disruptions in the delicate balance between keratinocyte proliferation and differentiation can contribute towards the development of squamous cell carcinoma (SCC) of the skin — a common human malignancy. It has been proposed that innate surveillants, molecules that promote terminal keratinocyte differentiation, exist in the skin to prevent carcinogenesis, but the conclusive identification of such proteins has not yet been achieved.

Inhibitor of nuclear factor κB kinase-α (IKKα, encoded by *CHUK*) is a promising candidate whose downregulation in mice leads to hyperproliferation of the epidermis and promotes chemically induced skin SCC development. But does IKKα loss cause SCC? New evidence suggests that this is indeed the case. The study, led by Yinling Hu and colleagues, used an inducible murine K15 promoter to obliterate *Chuk* specifically in the hair follicle keratinocytes of *Chuk*$^{flox/flox}$ mice. By 4 months, all mice had developed skin tumours resembling chemically induced papillomas and malignant carcinomas and, importantly, all tumours demonstrated *Chuk* loss. Closer examination of the epidermis of mutant mice revealed hyperproliferation of hair follicle keratinocytes and reduced expression of the terminal differentiation marker filaggrin. Together, these data asserted that the tumorigenic effect of *Chuk* ablation is linked to the induction of proliferation and the concomitant inhibition of differentiation.

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How was IKKα functioning? Vital clues were provided by the observed upregulation of epidermal growth factor receptor (EGFR) activity in the IKKα-null epidermis and the fact that both pharmacological and genetic inhibition of EGFR in IKKα-null cells blocked proliferation and induced terminal differentiation. These observations suggested that keratinocyte homeostasis was governed by cross-talk between EGFR and IKKα, but how were the two proteins communicating?

Prompted by the observation that IKKα-null keratinocytes expressed higher levels of mature EGF and heparin-binding (HB) EGF and lower levels of EGF and HBEGF precursors than wild-type cells, the authors hypothesized that IKKα somehow limited the production of mature EGF. Accordingly, mRNA levels of the Adam (a disintegrin and metalloproteinase) sheddases, which cleave EGF precursors to generate their active forms, were significantly upregulated in IKKα-null cells. Intriguingly, transcriptional regulation of the Adams is controlled by EGFR signalling, and chromatin immunoprecipitation experiments showed that IKKα exerted a double-pronged attack on this EGFR-driven circuitry by directly downregulating the activity of the *Egf*, and the *Adam12*, *Adam17* and *Adam19* promoters.

These data support a new innate surveillance role for IKKα, without which control of keratinocyte proliferation and differentiation are compromised by deregulated EGFR activity, providing a signalling milieu conducive to tumour formation. Given that IKKα downregulation has frequently been observed in human SCC, this study suggests that interference with EGFR might be a new therapeutic option for these patients.

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**ORIGINAL RESEARCH PAPER** Liu, B. *et al.* IKKα is required to maintain skin homeostasis and prevent skin cancer. *Cancer Cell* **14**, 212–225 (2008)