SIGNALLING

Without the sun

MACMILLAN AUSTRALIA

> targeting PDE4 is a suitable strategy for skin cancer prevention.

The second messenger cyclic AMP (cAMP) has a key role in numerous cellular processes. In response to melanocyte-stimulating hormone (MSH) cAMP enhances skin pigmentation and protects against ultraviolet (UV)-induced damage, features that imply it would be an attractive skin cancer prevention agent. However, preliminary data in humans revealed that forskolin, which activates adenyl cyclase to induce cAMP synthesis, exhibits inadequate skin penetration, a finding that has prompted a search for viable alternatives.

David E. Fisher and colleagues turned their sights to a group of enzymes that metabolize cAMP: the phosphodiesterases (PDEs). A link between cAMP, PDEs and melanocytes was suggested by the finding that the expression of two PDEs correlated with the expression of MITF, a transcription factor that is induced by MSH–cAMP signalling to regulate melanocyte development. The stimulation of primary human melanocytes with forskolin consistently upregulated the *PDE4D3* isoform. Small interfering RNA (siRNA)-mediated knock down of *MITF*, luciferase assays with forskolin and chromatin immunoprecipitation together confirmed that *PDE4D3* is a direct target of MITF and that it is the main PDE in the cAMP–MITF pathway in melanocytes.

The cAMP-dependent, lineage-specific induction of *PDE4D3* suggests that it could facilitate a negative feedback loop in pigment cells. Exploring this possibility, the authors noted that PDE4 inhibition by rolipram prolonged expression of MITF. Furthermore, initial treatment of melanocytes with forskolin induced subsequent resistance to the compound that was reversed by *PDE4D3* knockdown or by the PDE4 inhibitors rolipram or Ro 20–1724. To determine whether this homeostatic circuit modulates skin pigmentation *in vivo*, a mouse strain that is prone to sunburn and thus highly susceptible to skin cancer was used. Pigmentation induction through the production of melanin was observed following topical application of either of the PDE4 inhibitors, and this was robust following the application of the inhibitors together with forskolin.

Fisher and colleagues have identified a MITF–PDE4D3 negative feedback circuit in melanocytes and found that PDE4 inhibition drives melanocyte development probably by obstructing this loop. Thus, targeting PDE4 is a suitable strategy for skin cancer prevention.

Kira Anthony, Editor, NCI–Nature Pathway Interaction Database

ORIGINAL RESEARCH PAPER Khaled, M. *et al.* Control of melanocyte differentiation by a MITF–PDE4D3 homeostatic circuit. *Genes Dev.* **24**, 2276–2281 (2010)