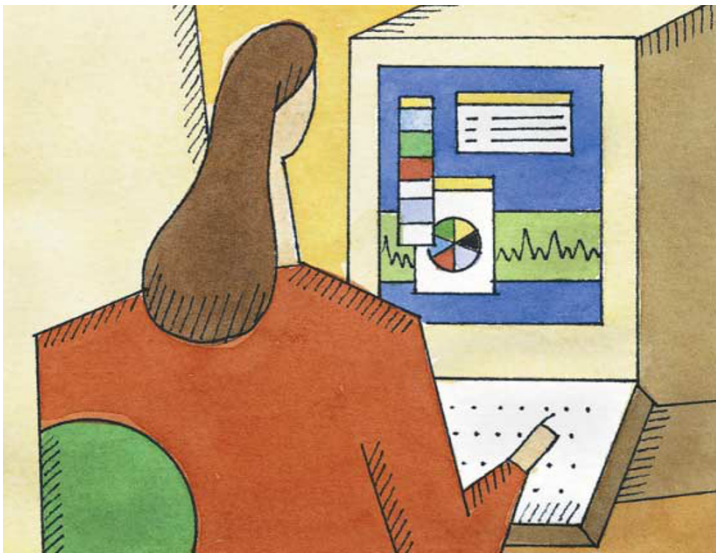
ONCOGENES

Keeping track of STATs



Signal transducer and activator of transcription 3 (STAT3) has been shown to be constitutively activated in several human epithelial malignancies, although its requirement in the *de novo* development of tumours had not been demonstrated. John DiGiovanni and colleagues now show that this transcription factor is not only required for skin tumorigenesis, but is essential for maintaining the proliferation and survival of cancer cells.

STAT3, which normally resides in the cytoplasm, becomes activated in response to a range of growth-factor signalling pathways through tyrosine phosphorylation. This leads to its dimerization and translocation to the nucleus. DiGiovanni and colleagues had previously shown that STAT3 becomes activated in the mouse epidermis following topical treatment with a range of tumour-promoting agents, so they set out to determine if this molecule was required for carcinogenesis.

They used mice in which *Stat3* was disrupted only in the epidermis and showed that this protected mice against the epidermal proliferation usually observed after skin treatment with the tumour promoter 12-*O*-tetradecanoylphorbol-13-acetate (TPA). The skin of STAT3-deficient mice expressed much lower levels of MYC and cyclin D1 in response to TPA treatment, indicating that these important regulators of proliferation are transcriptional targets of STAT3. Furthermore, STAT3-deficient keratinocytes were over five times more likely to undergo apoptosis in response to treatment with the DNA-damaging agent 7,12-dimethylbenz[*a*]anthracene (DMBA) than controls. This apoptosis was frequently observed in the bulge region of the hair follicle, where keratinocyte stem cells reside. DiGiovanni's group believes that STAT3 is therefore involved in maintaining the survival of keratinocyte stem cells following DNA damage.

Most importantly, STAT3-deficient mice were completely resistant to skin tumour development when DMBA was applied as a tumour initiator, followed by TPA as a tumour promoter. STAT3 activity could also be blocked with decoy oligonucleotides, which prevent its interaction with its DNA-binding site. The authors showed that these oligonucleotides inhibit the proliferation of HRAS-transformed cells in culture, as well as the early development of skin papillomas in *Hras*-transgenic mice.

Recent evidence indicates that keratinocyte stem cells are especially susceptible to DNA damage and transformation in response to carcinogen treatment. STAT3 might mediate these effects, as its transcriptional targets in these cells not only include a range of genes that regulate proliferation, but also cell survival. So, STAT3 inhibitors would not only be useful anticancer agents, but also useful in the prevention of epithelial cancers, because of the role of STAT3 in the earliest stages of tumorigenesis.

Kristine Novak

References and links

ORIGINAL RESEARCH PAPER Chan, K. S. *et al.* Disruption of Stat3 reveals a critical role in both the initiation and the promotion stages of epithelial carcinogenesis. *J. Clin. Invest.* **114**, 720–728 (2004)

FURTHER READING Yu, H. & Jove, R. The STATs of cancer — new molecular targets come of age. *Nature Rev. Cancer* **4**, 97–105 (2004)

WEB SITE
John DiGiovanni's lab:
http://sciencepark.mdanderson.org/documents/jDigiovanni/Digiovanni.html