TUMORIGENESIS

Flying beneath the radar

To enter and survive in enemy territory it is vital to remain undetected. Tumours somehow evade capture and destruction by the host immune system, which should suppress tumour growth. Hua Yu and colleagues report in *Nature Medicine* that constitutive activation of the Stat3 transcription factor in tumours inhibits dendritic cell (DC) maturation and prevents the immune system from eliminating the tumour.

The authors found that blocking Stat3 activation in the B16 mouse tumour cell line — by expressing Stat3β, dominant-negative Stat3, or using antisense oligonucleotides — increased expression of the pro-inflammatory cytokines interferon-β, tumour-necrosis factor-α (Tnf-α) and interleukin-6 (Il-6), and the chemokines Rantes and Cxcl10. By contrast, fibroblasts that were engineered to constitutively express Stat3 failed to express Il-6 or Rantes after stimulation with inflammatory mediators, confirming that Stat3 activation inhibits expression of cytokines and chemokines. So, exactly how does Stat3 activation in tumour cells affect the immune response?

There are two components of the immune response — innate and adaptive. Cytokines and chemokines amplify pro-inflammatory signals that are involved in the innate immune response. Blocking tumour-cell expression of Stat3 *in vitro* strongly induced Rantes and nitric-oxide production by macrophages, and Tnf-α production by neutrophils. Similar effects were seen *in vivo*, as disruption of Stat3 signalling by gene transfer of *Stat3β* into B16 tumours resulted in immune-cell infiltration. Innate immunity is crucial for the development of adaptive immunity, as it enhances maturation of DCs. As expected, DCs that were cultured with supernatants from Stat3β-expressing B16 cells — but not controls — increased levels of DC maturation markers. In addition, DCs that were exposed to supernatants from Stat3-inhibited B16 cells had increased proliferation of and cytokine release by antigen-specific T cells. Again, these observations were confirmed *in vivo*, as interruption of Stat3 signalling in B16 tumour cells caused infiltration and activation of tumour-specific $CD8^+$ T cells. Stat3 activation in tumour cells therefore blocks expression of inflammatory mediators, which are required to activate both arms of the immune system.

It is also possible that transformed cells directly block DC maturation, by secreting inhibitory factors that are induced by Stat3 activity. Maturation of bone-marrow-progenitor (BMP) cells into DCs was inhibited by supernatants from fibroblasts with activated Stat3. So, what are the tumour-derived factors, induced by Stat3, that inhibit this process?

Investigations indicate that these factors are diverse and depend on the tumour type. For example, vascular endothelial growth factor — a direct target of Stat3 — is crucial for DC inhibition, in the case of B16 tumours, whereas Il-10 seems to be a more important inhibitory cytokine produced by Src-transformed fibroblasts. Importantly, the diverse inhibitory factors seem to converge at a common point — Stat3 — in DCs, as tumour supernatants and Il-10 had no effect on the maturation of $Stat3^{-/-}$ BMPs. So, tumour inhibition of DC maturation involves a cascade of Stat3 activation — first in tumours and then in surrounding DCs.

This work demonstrates that constitutive Stat3 activation in tumours, which occurs at very high frequency, inhibits chemokine and cytokine production and induces factors that inhibit the adaptive immune response. Using targeted therapies against Stat3 could relieve this inhibition, allowing the immune system to detect and eliminate tumours.

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References and links

ORIGINAL RESEARCH PAPER Wang, T. *et al.* Regulation of the innate and adaptive immune responses by Stat3 signaling in tumor cells. *Nature Med.* **10**, 48–54 (2004)

FURTHER READING Dranoff, G. Cytokines in cancer pathogenesis and cancer therapy. *Nature Rev. Cancer* **4**, 11–22 (2004)

IN BRIEF

THERAPEUTICS

Suppression of breast cancer by chemical modulation of vulnerable zinc fingers in estrogen receptor.

Wang, L. H. *et al*. *Nature Med.* **10**, 40–47 (2004)

Breast cancer therapies that involve blocking ligand binding to the oestrogen receptor (ER) are limited, as the drugs used can activate the ER in some cancer cells. Wang *et al*. found that electrophilic agents that disrupt zinc fingers in the DNA-binding domain of the ER downregulate expression from oestrogen-responsive elements and inhibit the proliferation of breast tumour cells in a mouse xenograft model, indicating that these agents could be used as alternative treatments for ER-expressing breast cancers.

TUMOUR PROGRESSION

Role of thymosin β_4 in tumor metastasis and angiogenesis.

Cha, H.-J., Jeong, M.-J. & Kleinman, H. K. *J. Natl Cancer Inst.* **95**, 1674–1680 (2003)

Thymosin-β_4 expression is associated with increased metastatic potential in tumour cells, but the mechanisms underlying this are unclear. Cha *et al.* overexpressed thymosin-β_4 in tumour cells and saw increases in the numbers of blood vessels associated with tumours, and increased cell migration and expression of vascular endothelial growth factor (VEGF). So, thymosin-β_4 seems to promote tumour progression by stimulating angiogenesis — either directly or by increasing VEGF expression — and by promoting cell migration, which might be due to its actin-binding function.

CLINICAL TRIALS

Farnesyltransferase inhibitor R115777 in myelodysplastic syndrome: clinical and biologic activities in the phase 1 setting.

Kurzrock, R. *et al*. *Blood* **102**, 4527–4534 (2003)

Farnesylation is essential for the activity of several proteins, including the RAS oncoprotein. The farnesyltransferase inhibitor R115777 inhibits tumour growth *in vitro* and in animal models. Kurzrock *et al.* carried out Phase I clinical trials of R115777 in patients with myelodysplastic syndrome, a group of pro-leukaemic disorders in which *RAS* mutations are seen in ~25% of cases. Responses to R115777 were seen in 30% of patients, although only one-third of these had *RAS* mutations.

TUMOUR SUPPRESSORS

Arf tumor suppressor promoter monitors latent oncogenic signals *in vivo*.

Zindy, F. *et al*. *Proc. Natl Acad. Sci. USA* **100**, 15930–15935 (2003)

Activation of the tumour suppressor Arf is difficult to detect *in vivo*, probably because cells that express Arf die or undergo growth arrest. Zindy *et al.* made transgenic mice in which the *Arf* coding region was replaced by a green fluorescent protein (*GFP*) complementary DNA. They monitored GFP fluorescence to confirm that the *Arf* promoter is activated in response to a range of oncogenic signals.