TUMOUR IMMUNOLOGY

Multi-tasking by STAT3

The link between inflammation and cancer is well described, as shown by the increased risk of colorectal cancer in patients with inflammatory bowel disease. A common finding in inflammation-associated cancers is hyperactivation of signal transducer and activator of transcription 3 (STAT3) in various cell types, but the mechanisms linking inflammation and cancer through STAT3 are unclear.

As STAT3 mediates both the expression of and response to inflammatory cytokines, it is thought that STAT3 activity in tumour cells could promote cytokine-induced tumour growth, whereas STAT3 activity in immune cells could modulate cytokine production to inhibit tumour-specific immune responses or inflammation. Three papers in *Cancer Cell* explore these possibilities.

To investigate the role of STAT3 in tumour cells during inflammation-associated tumorigenesis, Bollrath *et al.* and Grivennikov *et al.* generated *Stat3*$^{\Delta IEC}$ mice, which lack STAT3 expression specifically in intestinal epithelial cells (IECs). In the colitis-associated cancer (CAC) model — in which administration of the mutagen azoxymethane is followed by the induction of chronic inflammation through epithelial injury by the toxin dextran sodium sulphate (DSS) — the *Stat3*$^{\Delta IEC}$ mice developed fewer and smaller tumours than STAT3-sufficient mice. Both groups showed that STAT3 activity in IECs upregulates the expression of anti-apoptotic proteins and cell cycle genes that increase the survival and proliferation of pre-neoplastic azoxymethane-mutagenized IECs in DSS-treated mice.

However, the increased apoptosis and decreased proliferation of IECs in *Stat3*$^{\Delta IEC}$ mice was associated with more severe intestinal inflammation after DSS treatment as a result of less effective repair of damage to the intestinal epithelium. This suggests that IEC proliferation mediated through STAT3 signalling is a normal wound-healing response that could result in abnormal cell proliferation and tumour growth if STAT3 becomes hyperactivated.

Bollrath *et al.* confirmed the relationship between STAT3 activation in IECs and tumorigenesis using mice in which STAT3 is constitutively activated by a mutant form of the gp130 subunit of the interleukin-6 (IL-6) receptor in response to IL-6 or IL-11. These mice were protected against DSS-induced colitis, which correlated with increased IEC proliferation, but had increased size and frequency of CAC tumours. Grivennikov *et al.* showed that IL-6-deficient mice, which had decreased activation of STAT3 in IECs, had increased levels of intestinal injury and reduced number and size of CAC tumours.

Taking a different approach, Kortylewski *et al.* looked at the role of STAT3 signalling in immune cells in the tumour microenvironment. In a tumour-challenge model, conditional knockout of *Stat3* in haematopoietic cells resulted in decreased production of IL-23 by tumour-associated macrophages and increased production of IL-12 by tumour-associated dendritic cells through direct effects on gene transcription. The STAT3-dependent production of IL-23 by tumour-associated macrophages was shown to activate STAT3 in regulatory T (T_{Reg}) cells, resulting in increased production of the immunosuppressive cytokine IL-10.

These three studies support a model in which STAT3 activation during tumorigenesis is both a tumour-cell-autonomous mechanism that links inflammatory cytokines (such as IL-6 or IL-11) in the local environment to the proliferation of tumour cells and an immune-regulatory mechanism that shifts the balance of cytokine production from anti-carcinogenic IL-12 (which activates natural killer cells and T helper 1 cells) to pro-carcinogenic IL-23 (which activates T_{Reg} cells).

Kirsty Minton

ORIGINAL RESEARCH PAPERS Bollrath, J. *et al.* gp130-mediated Stat3 activation in enterocytes regulates cell survival and cell-cycle progression during colitis-associated tumorigenesis. *Cancer Cell* **15**, 91–102 (2009) | Grivennikov, S. *et al.* IL-6 and Stat3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. *Cancer Cell* **15**, 103–113 (2009) | Kortylewski, M. *et al.* Regulation of the IL-23 and IL-12 balance by Stat3 signaling in the tumor microenvironment. *Cancer Cell* **15**, 114–123 (2009)
FURTHER READING Yu, H., Kortylewski, M. & Pardoll, D. Crosstalk between cancer and immune cells: role of STAT3 in the tumour microenvironment. *Nature Rev. Immunol.* **7**, 41–51 (2007)