METASTASIS

Tipping the balance

The regulation of gene activation or repression is a balancing act involving the integration of signals from a complex network, which results in the recruitment of specific chromatin-remodelling complexes and transcription factors. Jung Hwa Kim and colleagues report in *Nature* that the transcription regulation of the metastasis-suppressor gene *KAI1* is regulated in a tissue-specific manner by such a balance, which pivots on the transcription factor nuclear factor-κB (NF-κB).

KAI1 is a known NF-κB-responsive gene, so the team wondered whether NF-κB could regulate the metastasis-suppressive function of *KAI1*. PCR after reverse transcription of RNA (RT-PCR) showed that *KAI1* mRNA is increased in normal as well as tumorigenic but non-metastatic prostate (RWPE) cells following treatment with the NF-κB activator interleukin-1β (IL-1β). However, *KAI1* shows no increase in response to IL-1β in a highly metastatic prostate cancer cell line (LNCaP). Restoring expression of *KAI1* to the LNCaP cells markedly decreased the number of metastases that formed in the lungs of mice orthotopically injected with these cells.

To tease out the mechanisms of *KAI1* transcriptional regulation in prostate cancer, Kim *et al.* used a chromatin immunoprecipitation (ChIP) assay to identify factors bound to the *KAI1* promoter. In RWPE cells, IL-1β treatment led to the release of an NCo-R transcriptional co-repressor complex from the promoter, and the recruitment of TIP60, an androgen-receptor co-activator implicated in the development of prostate cancer. In LNCaP cells, however, once the NCo-R was released, the TIP60 co-activator complex was not recruited.

TIP60 forms a complex with the chromatin-remodelling proteins pontin and reptin, and as the RWPE ChIP experiments showed that histone H3 and H4 were acetylated following IL-1β treatment, the team next focused on the involvement of these proteins in the regulation of *KAI1*. In the non-metastatic cells, TIP60 and pontin bound to the *KAI1* promoter after exposure to IL-1β; in the metastatic LNCaP cells, however, they did not. Instead, reptin was recruited to the promoter along with β-catenin, another transcriptional regulator that interacts with both pontin and reptin.

At the protein level, the metastatic cells showed less TIP60 and more β-catenin than the non-metastatic ones. Together with the ChIP experiment, this indicated a transcriptional balance between repression, mediated by a β-catenin–reptin complex, and activation through a TIP60 complex. This theory was borne out by expression of a constitutively active mutant of β-catenin in the non-metastatic cells that was sufficient to downregulate *KAI1*. Increasing TIP60 expression restored *KAI1* expression. Moreover, a two-step ChIP assay showed that β-catenin–reptin was recruited only to promoters that were TIP60-negative.

The effects of β-catenin, on *KAI1* at least, seem to be mediated through NF-κB. Using a minimal promoter containing binding sites for the NF-κB DNA-binding protein p50, the authors found that recruitment of both β-catenin and TIP60 was dependent on p50.

But does this transcriptional balance between TIP60 and β-catenin actually modulate metastasis in prostate cancer cells? To test this, the researchers altered the ratio of TIP60 to β-catenin and measured the ability of the cells to traverse a Matrigel-coated membrane. Overexpression of TIP60 or knocking down β-catenin in IL-1β-treated LNCaP cells does indeed decrease invasion of the Matrigel compared with controls. So it seems that this pathway could be central to the metastatic potential of these cells.

Helen Dell

References and links

ORIGINAL RESEARCH PAPER Kim, J. H. *et al.* Transcriptional regulation of a metastasis suppressor gene by Tip60 and β-catenin complexes. *Nature* **434**, 921–926 (2005)

IN BRIEF

ANGIOGENESIS

Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion.

Orimo, A. *et al. Cell* **121**, 335–348 (2005)

Weinberg and colleagues have identified how carcinoma-associated fibroblasts (CAFs) contribute to the tumour microenvironment using a tumour xenograft model. CAFs express abnormally high levels of stromal-cell-derived factor 1 (SDF1). SDF1 production helps recruit endothelial progenitor cells, thereby promoting tumour angiogenesis, as well as directly stimulating cell growth by interacting with its cognate receptor, CXCR4, on carcinoma cells. Inhibiting SDF1–CXCR4 signalling would therefore be an excellent therapeutic target.

CANCER VACCINES

Recruitment of latent pools of high-avidity CD8$^+$ T cells to the antitumour immune response.

Ercolini, A. M. *et al. J. Exp. Med.* 9 May 2005 (doi:10.1084/jem.20042167)

Peripheral tolerance prevents a reaction against normal self antigens but probably causes the poor response of patients to antitumour vaccines. In the *Erbb2*-N mouse model of breast cancer, cyclophosphamide treatment in combination with an ERBB2-targeted vaccine produces tumour protection in 10–30% of vaccinated mice. Cylophosphamide acheives this by inhibiting the host's CD4$^+$CD25$^+$ regulatory T cells. High-avidity ERBB2-specific CD8$^+$ T cells are not deleted as previously thought, and can be recruited to illict a potent antitumour response.

TUMORIGENESIS

Protein farnesyltransferases in embryogenesis, adult homeostasis, and tumour development.

Mijimolle, N. *et al. Cancer Cell* **7**, 313–324 (2005)

Protein farnesyltransferase (FTase) modifies proteins with a carboxy-terminal CaaX motif, enabling protein–protein interactions or association with membranes. FTase inhibitors have been developed to prevent the activation of proteins, such as RAS, at the membrane. This paper demonstrates that FTase is essential for embryogenesis, but is dispensible in the adult. Moreover, a lack of FTase does not prevent RAS-induced tumorigenesis, but does inhibit tumour progression.

THERAPEUTICS

Indirubin derivatives inhibit Stat3 signaling and induce apoptosis in human cancer cells.

Nam, S. *et al. Proc. Natl Acad. Sci. USA* 10 May 2005 (doi:10.1073/pnas.0409467102)

Signal transducer and activator of transcription 3 (STAT3) is constitutively active in many human cancers. This paper shows that derivatives of indirubin, a herbal constituent of traditional Chinese medicine, inhibit STAT3 signalling in human breast and prostate cancer cells. One derivative also inhibited the kinase SRC, which activates STAT3, indicating that the antitumour activity of these compounds is due, in part, to inhibition of this signalling pathway.