CARCINOGENESIS

A marked loss

Tamoxifen is used to treat breast cancer, but its use is associated with an increased incidence of endometrial cancer. Wu *et al.* have now identified the oestrogenic pathway through which tamoxifen achieves this carcinogenic effect.

Given that both tamoxifen and oestrogen bind to oestrogen receptors to mediate their effects, the authors used microarrays to compare their effects on gene expression in endometrioid carcinoma samples. There was an overlap in the sets of genes that were regulated by the two molecules, but two-thirds of each set was unique. This implies that oestrogen and

tamoxifen operate through distinct pathways.

The authors then looked at the genes that were regulated by both molecules and found that one upregulated gene, paired box gene 2 (PAX2), significantly increased proliferation when overexpressed in endometrioid tumours. In addition, silencing of PAX2 reduced proliferation in tumours that had been stimulated by oestrogen or tamoxifen.

These results imply that PAX2 mediates tamoxifen-stimulated carcinogenesis, so the authors looked at the expression pattern of PAX2 in carcinomas. They found that expression

of PAX2 correlates with that of oestrogen receptor- α (ER α) and that ER α binds to the upstream regulatory region of PAX2.

In addition, the authors found that the PAX2 promoter was hypomethylated in carcinoma samples, whereas it is hypermethylated in normal endometrial tissue. They suggest that this loss of methylation is the reason why tamoxifen-bound ER α can activate PAX2 expression. How this hypomethylation occurs requires further study, but the identification of the role of PAX2 offers a potential new drug target.

Patrick Goymer

ORIGINAL RESEARCH PAPER Wu, H. *et al.*

Hypomethylation-linked activation of PAX2 mediates tamoxifen-stimulated endometrial carcinogenesis. *Nature* **438**, 981–987 (2005)

FURTHER READING Robson, E. J. D. *et al.* A PANorama of PAX genes in cancer and development. *Nature Rev. Cancer* **6**, 52–62 (2006)

LEUKAEMIA

Crisis talks

The aggressive blast crisis phase of BCR-ABL⁺ chronic myeloid leukaemia (CML) can only be temporarily delayed by treatment with the BCR-ABL kinase inhibitor imatinib mesylate (Gleevec). Danilo Perrotti and colleagues have now shown that activation of the tumour suppressor protein phosphatase 2A (PP2A), which is normally activated in the earlier chronic phase of the disease but inactivated in blast crisis, inhibits the oncogenic BCR-ABL kinase and thereby impairs leukaemogenesis.

The authors first showed that SET — a known, potent inhibitor of PP2A — is a novel BCR-ABL

“activators of the PP2A tumour suppressor might be a useful approach to treat CML blast crisis...”

”

target (see figure). Expression of SET correlated with BCR-ABL activity and was highest in patient-derived CML blast crisis cells. Expression of PP2A was reduced by 52% in CD34⁺ CML chronic phase cells and by 94% in CD34⁺ CML blast crisis cells, compared with CD34⁺ normal bone marrow cells. Imatinib treatment reduced the expression of SET.

When SET was inhibited using short hairpin RNA in cell lines that expressed high levels of BCR-ABL, PP2A activity was restored to the levels seen in imatinib-treated cells and expression of BCR-ABL was suppressed. Overexpression of PP2A in the BCR-ABL⁺ CML cell lines also suppressed expression of BCR-ABL. In addition, exposure of BCR-ABL⁺ cell lines and CML blast crisis cells to the PP2A activator forskolin induced down-regulation of BCR-ABL in both imatinib-sensitive and -resistant cells. Conversely, increasing expression of SET in BCR-ABL⁺ CML cell lines decreased PP2A activity and increased the expression of BCR-ABL targets.

The authors also found that overexpressing PP2A or inhibiting SET markedly suppressed proliferation and survival of imatinib-sensitive and -resistant BCR-ABL⁺ CML cell lines and patient-derived CML blast crisis cells. This manipulation even had the same effects in a BCR-ABL-expressing cell line with the T3151

mutation in BCR-ABL — this is a clinically relevant mutation that confers potent resistance to imatinib.

So, what effect does PP2A expression have on BCR-ABL-induced leukaemogenesis? Severe combined immunodeficient (SCID) mice were injected with parental, SET-negative, or PP2A-overexpressing BCR-ABL-expressing cells. The parental cells formed tumours within 6–7 days and the SET-negative cells formed 75% smaller tumours within 10–12 days. By contrast, the PP2A-overexpressing cells produced ~90% smaller tumours by 15 days. When mice injected with imatinib-sensitive or -resistant BCR-ABL-expressing cells were treated with forskolin or 1,9-dideoxy forskolin, no evidence of leukaemogenesis was seen at 5 weeks post-injection. Furthermore, 50% of treated mice became BCR-ABL-negative by reverse transcription PCR and survived to 18 weeks. By contrast, mice injected with BCR-ABL-expressing cells that were not treated with forskolin died of leukaemia within 5 weeks.

So, activators of the PP2A tumour suppressor might be a useful approach to treat CML blast crisis, even if the patients have developed resistance to imatinib.

Ezzie Hutchinson

The role of PP2A in BCR-ABL-positive blast crisis of chronic myeloid leukaemia

ORIGINAL RESEARCH PAPER Neviani, P. *et al.*

The tumor suppressor PP2A is functionally inactivated in blast crisis CML through the inhibitory activity of the BCR-ABL-regulated SET protein. *Cancer Cell* **8**, 355–368 (2005)