IN BRIEF

THERAPY

Death-receptor O-glycosylation controls tumour-cell sensitivity to the proapoptotic ligand Apo2L/TRAIL

Wagner, K. W. *et al. Nature Med.* 2 September 2007 (doi:10.1038/nm1627)

Tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) can induce apoptosis of cancer cells through its receptors death receptor 4 (DR4) and DR5. Although TRAIL is being developed as an anticancer therapy, it is not known why some cancers respond to this agent and others do not. Wagner *et al.* found that expression of the peptidyl O-glycosyltransferase GALNT14 correlated with TRAIL sensitivity in cancer cell lines, and about 30% of samples of various human tumour types had GALNT14 overexpression. Knockdown of GALNT14 in cell lines using small interfering RNA reduces TRAIL sensitivity, and O-glycosylation of DR4 and DR5 seems to be required for apoptotic signalling. These data indicate that O-glycosylation and GALNT14 expression could possibly serve as predictive biomarkers for the efficacy of TRAIL-based therapy.

LEUKAEMIA

Cytokine-dependent imatinib resistance in mouse BCR-ABL^{+}, *Arf*-null lymphoblastic leukemia

Williams, R. T., den Besten, W. & Sherr, C. J. *Genes Dev.* 30 August 2007 (doi:10.1101/gad.1588,607)

Williams *et al.* show that expression of the oncogenic fusion protein BCR-ABL in mouse pre-B cells lacking the tumour suppressor ARF causes highly aggressive acute lymphocytic leukaemia (ALL) when the cells are intravenously inoculated into healthy syngeneic mice. These leukaemias are resistant to therapy with the BCR-ABL tyrosine kinase inhibitor imatinib, but recovered cells are sensitive, indicating that the resistance is non-tumour-cell-autonomous. If the pre-B cells also lack the cytokine receptor common γ chain, which is required for signalling by multiple cytokine receptors, then imatinib sensitivity is restored, suggesting that microenvironmental cytokines can facilitate resistance to imatinib.

THERAPY

Improved tumour imaging and therapy via i.v. IgG-mediated time-sequential modulation of neonatal Fc receptor

Singh Jaggi, J. *et al. J. Clin. Invest.* **117**, 2422–2430 (2007)

The use of radiolabelled and toxin-conjugated monoclonal antibodies for cancer therapy and imaging is limited by the long plasma half-life of immunoglobulin G (IgG), which causes toxicities to normal tissues and increases background for imaging. The neonatal Fc receptor (FcRn) prevents IgG degradation, so Singh Jaggi *et al.* reasoned that administration of high doses of IgG after delivery of a conjugated antibody would compete for binding to FcRn, thus enhancing clearance of the conjugated antibody. This strategy was able to reduce the length of time that a radiolabelled antibody remained in the blood of mice, therefore enhancing image contrast and reducing the effects of radiation on normal tissue while tumour uptake and therapeutic response stayed the same. IgG infusion also increased clearance of radiolabelled antibodies in humans.