APOPTOSIS

Invasive loss

Caspases are crucial components of the pro-apoptotic pathway, and although loss of expression of caspase 8 occurs in various cancer types, the functional significance of this has not been determined. Now, the Stupack, Lahti and Cheresh laboratories show that loss of caspase 8 in neuroblastoma facilitates the formation of metastases.

The authors used developing chick embryos to analyse the growth, invasion and spontaneous metastasis of implanted, patient-derived neuroblastoma cell lines. They noted that the more invasive neuroblastoma lines did not express caspase 8 and that those that did express the enzyme showed a much higher level of apoptosis when invading the surrounding tissues. Caspase-8 expression did not affect the size of the primary tumour, but it did limit the establishment of metastases in the lung and bone marrow. Moreover, the use of RNA interference to reduce the expression of the caspase-8 protein increased the ability of the caspase-8-expressing cells to establish metastases.

Caspase-8 activation can occur when cells are grown in an inappropriate extracellular matrix. This activation is triggered by unligated or antagonized integrins and is known as integrin-mediated cell death (IMD). Type 1 collagen is the principal matrix component in many stromal tissues, and the authors found that caspase-8-expressing neuroblastoma cells underwent apoptosis when plated in a three-dimensional type-1-collagen matrix. However, inhibition of the death-receptor pathway, which also recruits and activates caspase 8, did not prevent the death of these cells. This finding questions whether the death-receptor pathway has a function in limiting neuroblastoma metastases. The authors also showed that decreased expression of the $\alpha_3\beta_1$ integrin occurred in metastases isolated from patients and increased the survival of caspase-8-expressing cells in the type-1-collagen matrix. This indicates that unligated integrins might function similarly to dependence receptors and induce apoptosis when their ligand is absent.

So, it seems likely that caspase 8 is a metastasis suppressor and that overcoming IMD by suppressing caspase-8 expression, or through changes in integrin expression, facilitates tumour invasion by increasing cell survival.

Nicola McCarthy

ORIGINAL RESEARCH PAPER Stupack, D. G. *et al.* Potentiation of neuroblastoma metastasis by loss of caspase 8. *Nature* **439**, 95–99 (2006)

CHROMOSOMAL TRANSLOCATIONS

On the move

Although chromosomal translocations that involve the immunoglobulin heavy chain (*IgH*) locus are a defining feature of B-cell malignancies, little is known about how these translocations occur or what the mechanisms are that guard against these potentially tumorigenic events. Almudena Ramiro, Mila Jankovic and colleagues have unravelled some of these mechanisms in their recent *Nature* paper.

The authors examined the function of activation-induced cytidine deaminase (AID) — an enzyme that is essential for the switching of immunoglobulin class (for example, from IgM to IgG or IgA) during B-cell activation — in the production of translocations between *Myc* and *Igh* in primary mouse B cells. AID has previously been shown to be essential for the accumulation of *Myc–Igh* translocations, but the mechanism involved is unclear. Ramiro *et al.* compared the numbers of translocations produced in $Aid^{-/-}$ cells with those occurring in $Aid^{-/-}$ cells that were infected with a retroviral construct containing *Aid*.

Activation of the B cells resulted in the accumulation of *Myc–Igh* trans-

> “p53 mutation or loss is likely to contribute early on to the pathogenesis of lymphoma by facilitating AID-induced translocations”

BIOMARKERS

Different treatment

Localized oesophageal carcinoma is usually treated with pre-operative chemoradiotherapy, but the outcome of such intervention is hard to predict and there are often undesirable consequences. Now, Luthra *et al.* have used gene-expression profiling to discover potential biomarkers of therapeutic response.

Patients with localized oesophageal cancer have a 5-year survival rate of less than 20%. Despite a sharp increase in incidence in recent decades there has been no improvement in survival. This might be improved by being able