LEUKAEMIA

Fusion cooking

The mixed lineage leukaemia (*MLL*) gene can be fused to one of 30 different gene partners as a result of translocations involving the long arm of chromosome 11, but it is unclear whether this mutation alone can induce acute myeloid leukaemia (AML). Ono and colleagues now suggest that the leukaemogenesis that is mediated by MLL fusion proteins is a multistep process.

MLL is a nuclear protein with domains that implicate it as a transcriptional regulator as well as being involved in chromatin-modifying supercomplexes. Although diverse, the MLL fusion proteins are all oncogenic, apparently promoting leukaemia through similar mechanisms — the aberrant activation of homeobox genes. The fusion partners of MLL are either transcriptional activators (such as ENL), making activation of MLL target genes independent of MLL homodimerization, or proteins with oligomerization domains (such as SEPT6), causing unregulated dimerization and constitutive activation of MLL. However, expression of MLL fusion proteins in animals does not induce AML with the rapidity that is seen in the human disease. So Ono and colleagues investigated the idea that secondary genetic events might be involved.

The authors focused on MLL–SEPT6. SEPT6 is one of the septins, cytoplasmic proteins that are required for cytokinesis. Expression of the retrovirally expressed MLL– SEPT6 in mouse haematopoietic progenitor cells *in vitro* resulted in immortalization through a block in cell differentiation and increased self-renewal. Transplantation of these cells into a mouse model induced, after a long latency, a lethal myeloproliferative disease, but not AML.

MLL–SEPT6-expressing cells isolated from these animals require interleukin-3 (IL-3) for survival. Given that IL-3 independence is associated with leukaemic progression, the authors reasoned that IL-3 independence might be a cooperating lesion. They co-infected the MLL–SEPT6-expressing cells with a retrovirus expressing the mutant form of FMS-like receptor tyrosine kinase 3 (FLT3), which has also been implicated in AML and might substitute for the tyrosine-kinase survival signal normally supplied by IL-3. Co-expression of this gene led to IL-3-independent growth *in vitro* and the induction of AML with short latency *in vivo*.

Given that mutant FLT3 also cooperated with MLL–ENL, the authors surmise that MLL fusion proteins impair differentiation and enhance the self-renewal capacity of haematopoietic progenitors, and activation of FLT3 confers a proliferative and/or survival capacity.

Nicola McCarthy

References and links

ORIGINAL RESEARCH PAPER Ono, R. *et al.* Dimerization of MLL fusion proteins and FLT3 activation synergize to induce multi-lineage leukemogenesis. *J. Clinical Invest.* 10 Mar 2005 (doi:10.1172/JCI200522725)

IN BRIEF

STEM CELLS

Skin carcinoma arising from donor cells in a kidney transplant recipient.

Aractingi, S. *et al. Cancer Res.* **65**, 1755–1760 (2005)

Cutaneous tumours arising in female patients who had received a male kidney were examined by quantitative polymerase chain reaction and fluorescence *in situ* hybridization. Male cells were detected in many cases. A particular carcinoma showed a pattern of male cells that seemed to have arisen from the clonal expansion of a single donor cell. So, stem cells from a grafted organ might migrate to the skin, differentiate into, or fuse with, keratinocytes and then, rarely, undergo neoplastic transformation.

CIRCADIAN RHYTHMS

Circadian sensitivity to the chemotherapeutic agent cyclophosphamide depends on the functional status of the CLOCK/BMAL1 transactivation complex.

Gorbacheva, V. Y. *et al. Proc. Natl Acad. Sci. USA* **102**, 3407–3412 (2005)

How does the time of day regulate the body's sensitivity to chemotherapeutic agents? Gorbacheva *et al.* showed that mice lacking functional copies of two main circadian-rhythm-regulating genes, *CLOCK* and *BMAL1*, are highly sensitive to treatment with cyclophosphamide at any time of day, unlike controls. This is due to a decrease in the recovery and survival rate of B cells after treatment.

LEUKAEMIA

A sumoylation site in PML/RARA is essential for leukemic transformation.

Zhu, J. *et al. Cancer Cell* **7**, 143–153 (2005)

The *PML–RARA* oncogene causes acute promyelocytic leukaemia (APL) by repressing myeloid differentiation. Zhu *et al.* find that sumoylation of PML is required for transformation *ex vivo*. Expression in mice of a PML–RARα mutant that cannot be sumoylated leads to myeloid hyperplasia, but not to leukaemia. The authors show that sumoylation allows recruitment of the potent transcriptional repressor DAXX, indicating a mechanism by which PML–RAR might initiate APL.

TUMORIGENESIS

The RET/PTC–RAS–BRAF linear signaling cascade mediates the motile and mitogenic phenotype of thyroid cancer cells.

Melillo, R. M. *et al. J. Clin. Invest.* 10 Mar 2005 (doi:10.1172/JCI200522758)

Activating mutations of the oncogenes *BRAF* or *RAS*, or fusions of the RET tyrosine receptor kinase are all found in papillary thyroid carcinomas, but never together. Melillo *et al.* reveal that this is because they function in a linear oncogenic signalling pathway, where RET fusions stimulate RAS-dependent activation of BRAF. This cascade initiates a transcriptional programme in thyroid cells that eventually stimulates proliferation and invasion.