ONCOGENES

Showing some cleavage

Acute promyelocytic leukaemia (APL) is characterized by the accumulation of promyelocytes, although no one knows for certain why this particular stage of haematopoiesis is affected. Andrew Lane and Timothy Ley report in *Cell* that promyelocytes express high levels of a protease that cleaves a protein that facilitates leukaemogenesis.

Over 90% of patients with APL possess the t(15;17) translocation that leads to expression of the PML–RARα fusion protein. To investigate the function of this protein, Lane and Ley transiently expressed it in various myeloid and non-myeloid cell types, and observed that it was rapidly cleaved only in a promyelocytic cell line. Further analysis of the cell-specific proteolysis revealed that PML–RARα is cleaved by neutrophil elastase (NE), which is encoded by the *ELA2* gene. *ELA2* transcription is activated in early myeloid development and maximally expressed at the early promyelocyte stage. The authors showed that human APL cells express *ELA2* and that both mouse and human forms of NE are able to cleave both forms of PML–RARα.

But is this protease important for leukaemogenesis? When mice were engineered that transgenically expressed Pml–Rarα in promyelocytes, they all developed APL within 350 days. When this fusion protein was expressed in promyelocytes of mice in an NE-null background, however, only 45% of mice developed APL within the same time period. So, NE is important for the ability of Pml–Rarα to initiate APL. The effect is also specific for NE-null mice, as Pml–Rarα expression in mice that were deficient for the serine protease cathepsin G did not affect APL penetrance.

Several lines of evidence have indicated that PML–RARα requires an interaction with a factor that is present in early myeloid cells to initiate disease, so NE could be the long-sought-after APL cofactor. The authors propose that PML–RARα cleavage creates a modified form of the protein that is important for initiation of this cancer. Further experiments are required to determine the subcellular location at which the cleavage occurs and the function of the cleavage products. NE inhibitors, however, might now be tested as APL therapeutic agents.

Kristine Novak

References and links

ORIGINAL RESEARCH PAPER Lane, A. A. & Ley, T. J. Neutrophil elastase cleaves PML–RARα and is important for the development of acute promyelocytic leukemia in mice. *Cell* **115**, 305–318 (2003)

FURTHER READING Melnick, A. & Licht, J. D. Deconstructing a disease: RARα, its fusion partners, and their roles in the pathogenesis of acute promyelocytic leukemia. *Blood* **93**, 3167–3215 (1999)

WEB SITE

Timothy J. Ley's lab:
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IN BRIEF

CANCER PREVENTION

Prostate carcinogenesis in *N*-methyl-*N*-nitrosourea (NMU)-testosterone-treated rats fed tomato powder, lycopene, or energy-restricted diets.

Boileau, T. W.-M. *et al. J. Natl Cancer Inst.* **95**, 1578–1586 (2003)

Increased consumption of tomato products is known to reduce the risk of prostate cancer. Lycopene — the principal carotenoid in tomatoes — is thought to be the active component that produces the antitumour effects. Boileau *et al.* show that consumption of tomato powder, but not lycopene alone, inhibits prostate carcinogenesis in rats, indicating that other phytochemicals in tomatoes are required to prevent tumour formation.

PROSTATE CANCER

Pten dose dictates cancer progression in the prostate.

Trotman, L. C. *et al.* PLoS Biology. 27 Oct 2003
(doi: 10.1371/journal.pbio.0000059)

Loss of one allele of the tumour-suppressor gene *Pten* is common in prostate tumours, so the authors studied the effects of *Pten* dose variations on cancer progression in mice. They found that the levels and extent of *Pten* inactivation dictates prostate cancer incidence, progression, latency and pathogenesis. So, *Pten* dose is a key determinant in cancer progression.

GENE THERAPY

LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1.

Hacein-Bey-Abina, S. *et al. Science* **302**, 415–419 (2003)

X-linked severe-combined immunodeficiency (SCID-X1) has been successfully corrected in 9 out of 10 patients by retroviral transfer of the γc gene into bone-marrow progenitor cells. However, two patients later developed leukaemia-like syndromes due to uncontrolled proliferation of mature T cells. Hacein-Bey-Abina *et al.* report that the syndromes were caused by activation of the *LMO2* oncogene, following insertion of the γc gene into the *LMO2* promoter.

EPIDEMIOLOGY

Breast and ovarian cancer risks due to inherited mutations in *BRCA1* and *BRCA2*.

King, M.-C., Marks, J. H. & Mandell, J. B. *Science* **302**, 643–646 (2003)

Germ-line *BRCA1* and *BRCA2* mutations account for most cases of familial breast and ovarian cancer. As a high population frequency of three ancient *BRCA1* and *BRCA2* mutations is found in Ashkenazi Jewish women, King *et al.* studied breast and ovarian cancer risks in a cohort of these women. A key finding from this study is that non-genetic factors, such as obesity and lack of exercise, seem to significantly influence the penetrance of these already highly penetrant mutations, as risk is higher for women born after 1940 than before 1940.