IN BRIEF

METHYLATION

Reduced rates of gene loss, gene silencing and gene mutation in Dnmt1-deficient embryonic stem cells.

Chan, M. F. *et al. Mol. Cell. Biol.* **21**, 7587–7600 (2001)

DNA methylation is an important way of inactivating tumour-suppressor genes, but what effect does it have on mutation rates? Using a model system in which loss of function for a transgene is selected for in the presence and absence of DNA methyltransferase 1 (*Dnmt1*), Chan and colleagues show that rates of both gene loss and missense mutation are reduced in *Dnmt1*-deficient cells, which might explain why reduced methyltransferase levels prevent polyposis in some mouse models of colorectal cancer.

EPIDEMIOLOGY

Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58 209 women with breast cancer and 101 986 women without the disease

Collaborative group on Hormonal Factors in Breast Cancer. *Lancet* **388**, 1389–1399 (2001)

This meta-analysis provides encouraging news for women with a family history of breast cancer: although the risk of developing breast cancer increases with the number of affected first-degree relatives, eight out of nine women who develop breast cancer don't have an affected relative, and most women with an affected relative will never develop the disease.

DIAGNOSTICS

BAALC, the human member of a novel mammalian neuroectoderm gene lineage, is implicated in hematopoiesis and acute leukemia

Tanner S. M. *et al. Proc. Natl Acad. Sci. USA* **98**, 13901–13906 (2001)

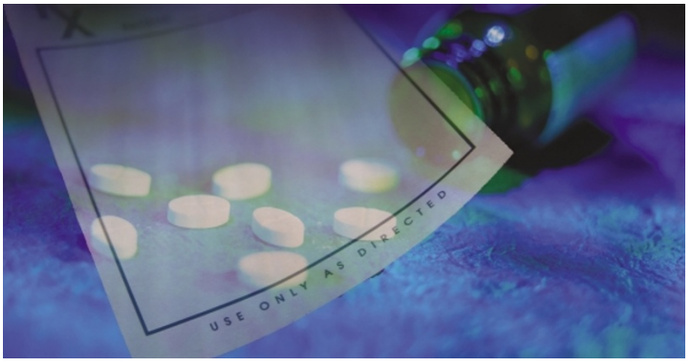
Tanner *et al.* have found that a highly conserved mammalian gene, *BAALC*, is overexpressed in the blast cells of patients with acute myelogenous leukaemia. In normal tissue, the gene is expressed in neuroectoderm-derived tissues, and the protein localizes to the cytoskeletal network. Although little is known about BAALC function, high levels of expression were associated with poor prognosis in leukaemia patients.

RADIATION RESISTANCE

Genes required for ionizing radiation resistance in yeast

Bennett, C. B. *et al. Nature Genet.* **29**, 426–434 (2001)

Resistance to radiotherapy has long been a major drawback for its treatment of cancer. But now, a new study in yeast has identified genes that could be involved in this resistance. Bennett *et al.* screened yeast that were homozygously deleted for nonessential genes, after exposure to γ-irradiation. They identified 107 new genes, many of which affect replication, recombination and checkpoint functions: 69 show some homology to human genes, and 17 are implicated in cancer. Further analysis of these genes could provide insight into the mechanisms of radiation resistance.



THERAPEUTIC STRATEGIES

Prescription for transcription

Acute promyelocytic leukaemia (APL) — a cancer that is characterized by the accumulation of promyelocytic cells in the bone marrow — is associated with translocations involving chromosome 17 that disrupt the gene for retinoic acid receptor-α (*RARα*). Binding to retinoic acid (RA) changes the function of RARα from a transcriptional repressor to a transcriptional activator, but these translocations create fusion proteins that are trapped in repressor mode. In the November issue of the *Journal of Clinical Investigation*, Li-Zhen He *et al.* describe a family of drugs that restore the ability of RARα fusion proteins to activate transcription and also induce remission in a mouse model of APL.

In the absence of RA, corepressors bind to RAR, recruiting histone deacetylases (HDACs) that modify chromatin and block transcription. In the presence of RA, the corepressor complex dissociates. RARα then upregulates genes — the products of which induce growth arrest and terminal differentiation in many cell types, including myeloid haematopoietic cells. In fact, RA is currently used to treat the most common type of APL.

APL-associated fusion proteins such as PML–RARα and PLZF–RARα form stable complexes with HDACs and can only repress transcription. But HDAC inhibitors had been previously shown to block repression of reporter genes by PLZF–RARα. So, could they be used to treat APL?

The authors examined the effects an HDAC inhibitor — known as suberoylanilide hydroxamic acid (SAHA) — on cells from an RA-responsive APL patient and on blasts from a transgenic mouse model of RA-resistant cancer. They found that SAHA treatment induced apoptosis and cell-cycle arrest in both cell types, and that RA-induced differentiation was potentiated by SAHA treatment. Treatment with both drugs also cleared leukaemic blasts from the peripheral blood of the transgenic mice, increasing survival time, whereas treatment with either drug alone did not lead to disease remission. The authors believe that SAHA might sensitize cells to the differentiating effects of RA.

SAHA treatment increased bulk histone acetylation in mice but, as Jonathan Licht points out in an accompanying commentary, the authors did not determine whether SAHA affected chromatin configuration near RAR target genes. SAHA did, however, potentiate RA-dependent transcriptional activation of known RAR target genes. Further research is required to see if SAHA acts directly on APL-associated fusion proteins, or through some other mechanism — such as acetylation of non-histone proteins involved in apoptosis signalling — to stop the spread of cancer cells.

Kristine Novak

References and links

ORIGINAL RESEARCH PAPER He, L.-Z., *et al*. Histone deacetylase inhibitors induce remission in transgenic models of therapy-resistant acute promyelocytic leukemia. *J.Clin. Invest*. **108**, 1321–1330 (2001)

FURTHER READING Licht, J. D.Targeting aberrant transcriptional repression in leukemia: a therapeutic reality? *J.Clin. Invest*.**108**,1277–1278 (2001) | Altucci, L. & Gronemeyer, H. The promise of retinoids to fight against cancer. *Nature Rev. Cancer* **1**, 181–193 (2001) | Marks, P. A. *et al*. Histone deacetylases and cancer: causes and therapies. *Nature Rev. Cancer* **1**, 194–202 (2001)

WEB SITE

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