To investigate the relevance of these findings to the behaviour of disease in humans, 63 primary breast cancers were examined for expression of 50 genes from the bone-metastasis gene set that are also present in the poor-prognosis signature. Hierarchical clustering did not distinguish between tumours that had metastasized to bone and those that had not. However, when the analysis was restricted to those tumours that were known to have metastasized, the 50-bone-metastasis gene set did distinguish a bone-metastasis cluster from a lung-metastasis cluster.

Confirmatory studies could lead to an accurate predicter of bone-metastasis tropism in primary breast cancers, which would be valuable in the effective management of breast cancer patients.

Ezzie Hutchinson

References and links

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WEB SITE

Joan Massagué's lab: http://www.hhmi.org/research/investigators/massague.html

THERAPEUTICS

On the TRAIL of death

Histone-deacetylase inhibitors (HDACIs) have successfully entered clinical trials, but the basis of their antitumour activity is not clear. Two papers published in the January issue of *Nature Medicine* indicate that HDACIs increase the expression of the death-receptor ligand TRAIL in cancer cells, leading to tumour-cell death.

Histone deacetylases (HDACs) regulate transcription by altering chromatin structure and can also modify individual protein function. Their activity is frequently altered in human tumours. The best-characterized example of this is evident in myeloid leukaemia cells, where the oncogenic, chromosomal translocation fusion protein products PML–RAR or AML1–ETO function to silence genes and transform cells by interacting with HDACs.

Insinga and colleagues treated mice with PML–RAR-induced acute promyelocytic leukaemia (APL) with the HDACI valproic acid and compared their response with standard therapy for APL, all-*trans* retinoic acid. Both drugs prolonged the survival of these mice, but through different mechanisms — all-*trans* retinoic acid primarily induced the terminal differentiation of the leukaemic blast cells, whereas valproic acid induced massive blast-cell apoptosis. The authors found that the pro-apoptotic activity of valproic acid is not due to the inhibition of the PML–RAR-induced degradation of the tumour-suppressor gene product p53, but that treatment with HDACIs induces the selective upregulation of the death receptors DR5 and FAS and their cognate ligands TRAIL and FASL. Blocking access of these ligands to their receptors through blocking antibodies prevented valproic-acid-triggered apoptosis *in vitro* and RNA-interference studies confirmed this result *in vivo*. These authors show further that the effect of HDACIs is reproduced in other mouse leukaemic models and in a subset of freshly isolated human leukaemic blasts.

Nebbioso and colleagues examined the action of three HDACIs — including the benzamide derivative MS275 — on a human leukaemic cell line and a large number of blasts from patients with acute myeloid leukaemia (AML). They found that TRAIL expression and resultant apoptosis were induced and, in addition, that MS275 induced cell-cycle arrest, upregulation of the cell-cycle inhibitor p21(WAF1) and differentiation of the leukaemic cells. To examine the contribution of p21 and TRAIL to HDACI antitumour activity, these authors used RNA interference to knockdown the expression of these proteins. Their results show that p21 specifically induces HDACI-mediated growth arrest and that TRAIL induces the acute apoptotic response through the death-receptor pathway. Moreover, irrespective of their genetic defects, most *ex vivo* cultured AML blasts from patients responded to HDACI exposure. Nebbioso and co-workers also showed that MS275 induces the expression of the TRAIL gene *TNFSF10* by inhibiting promoter-resident HDAC1 and HDAC2 and recruiting and acetylating the transcription factors SP1 and SP3, allowing formation of a transcriptionally active complex.

Significantly, both groups show that no apoptosis was evident in the normal myeloid progenitors tested, despite their intrinsically higher levels of TRAIL expression. Both conclude that the HDACI-mediated selective TRAIL expression and apoptosis seen in myeloid leukaemic cells warrants further investigation and has implications for the treatment of other human tumours.

Nicola McCarthy

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