Genetic basis of drug resistance in childhood ALL

Current drug treatments fail in about 20% of children with acute lymphoblastic leukemia (ALL). Holleman and colleagues have investigated the multiple pathways governing drug resistance in their recent gene-expression profiling study. Leukemia cells from 173 children were first tested for sensitivity in vitro to the drugs prednisolone, vincristine, asparaginase and daunorubicin. Genes that were differentially expressed in drug-resistant and drug-sensitive cells were then identified by means of an oligonucleotide microarray. Finally, gene-expression signatures associated with resistance or sensitivity to each of the four drugs were compared with treatment outcome in both the original cohort and a second cohort of 98 children.

A total of 124 genes, belonging to numerous functional groups, were differentially expressed in cells resistant or sensitive to prednisolone (33 genes), vincristine (40 genes), asparaginase (35 genes) or daunorubicin (20 genes). Of these genes, 121 had not previously been linked to resistance to these drugs. Multivariate analysis indicated that expression of genes associated with drug resistance had an independent influence on outcome of treatment in both the original 173 patients and the validation cohort, who were being treated at a different center.

Holleman et al. conclude that differential expression of relatively few genes is linked with treatment response in childhood ALL, and that these genes may provide targets for improved therapy.

Original article Holleman A et al. (2004) Gene-expression patterns in drug resistant acute lymphoblastic leukemia cells and response to treatment. New Engl J Med 351: 533–542

Health-related quality of life in breast cancer

Health-related quality of life (HRQOL) is a good prognostic indicator in breast cancer but has only recently been included as an outcomes measure in clinical trials. To investigate HRQOL and its associated factors in women treated for early stage breast cancer within the previous 4 years, Bardwell et al. have analyzed a subset of data from the Women’s Healthy Eating and Living (WHEL) Study.

Women (n = 2582) completed the RAND-36 Health Survey, which includes four mental and four physical subscales measured from 0–100. Comparisons were made with US population norms and results from other breast cancer studies.

HRQOL was generally similar to population norms. Clinically meaningful differences were seen, however, in the ‘role limitations—due to physical problems’ subscale (6.7 points worse for the study population than for norms) and for ‘social functioning’ (5.2 points better for the study population than for norms). Comparisons with two other breast cancer studies again showed similar HRQOL, except for ‘role limitations—due to emotional problems’, in which the WHEL study participants were 5.1 points healthier. Multivariate analysis revealed that better physical HRQOL was linked to fewer psychological symptoms, lower body mass index, better sleep quality and more physical activity (P ≤ 0.001). Better mental HRQOL was related to better sleep quality, fewer life events, less pain and fewer gastrointestinal symptoms.

The study demonstrates that HRQOL was influenced by several factors. Bardwell et al. suggest that clinical interventions targeting some of these variables may improve HRQOL in these patients.

Original article Bardwell WA et al. (2004) Health-related quality of life in women previously treated for early-stage breast cancer. Psycho-Oncology 13: 595–604

The blood–testis barrier in health and disease

Chemoresistance of metastatic testicular tumors is thought to be mediated partly by the blood–testis barrier (BTB), which impedes delivery to the testis of certain cytotoxic agents. Little is known, however, about the arrangement of drug-efflux pumps within this barrier. Bart et al. have studied the localization of the efflux pumps P-GP, BCRP, MRP1 and MRP2 to better understand the role of the BTB.

Immunohistochemical staining for the four efflux pumps was performed on normal testicular tissue (n = 12), non-pretreated nonseminoma (n = 10), seminoma (n = 10) and testicular lymphoma (n = 9) and expression was assessed semiquantitatively. Newly formed blood vessels were localized using factor VIII staining.
In normal testicular tissue, and in tissue in the proximity of a testicular tumor, the myoid cells and endothelial cells strongly expressed P-gp and BCRP; the Sertoli cells expressed MRPI; and the Leydig cells expressed P-gp and MRPI. In seminomas and nonseminomas, P-gp, BCRP or MRPI were expressed, either alone or together. Lymphomas strongly expressed P-gp or BCRP and showed little or no MRPI staining. Newly formed blood vessels of all tumors showed staining for P-gp and BCRP. Expression of MRPI2 in the BTB was negligible in all cells, except the myoid cell layer of normal testis.

Bart et al. suggest that the observed expression patterns indicate optimal protection of spermatogenesis in normal tissue and may explain the chemoresistance of germ cell tumors to P-gp, BCRP and MRPI substrates. This supports the practice of removing the affected testis in cases of primary germ cell tumors and testicular lymphomas, whether or not the patient has undergone chemotherapy.

Original article Bart J et al. (2004) The distribution of drug-efflux pumps, P-gp, BCRP, MRPI and MRPI2, in the normal blood–testis barrier and in primary testicular tumours. *Eur J Cancer* 40: 2064–2070

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**Early promise for esophageal cancer diagnosis**

Esophageal cancer is usually advanced by the time symptoms appear, and at this stage the prognosis is generally poor. Since combined surgery and chemotherapy are effective in early disease, there is a pressing need for a reliable screening test. A pilot study conducted at Addenbrooke’s Hospital in the UK offers a promising new approach.

Williams et al. have previously demonstrated that dysregulation of minichromosome maintenance (MCM) proteins is characteristic of early epithelial carcinogenesis, and they have used these biomarkers in diagnostic screening applications for cervical and genitourinary tract cancer. On the basis of this work, the authors have now devised an immunofluorometric assay to measure levels of minichromosome maintenance protein 5 (Mcm5) in gastric aspirates. Samples were analyzed from 40 patients with suspected or known esophageal carcinoma or symptoms of dyspepsia. Results were then compared to endoscopy and biopsy histology results.

Mcm5 levels in the samples from patients with esophageal cancer were shown to be significantly elevated. The test differentiated between patients with and without cancer with a high degree of sensitivity (85%, 95% confidence interval (CI) 62–97%) and specificity (85%, 95% CI 66–96%). Inflammatory conditions (including esophagitis and Barrett’s metaplastic esophagus) did not yield false-positive results. Ulcerative lesions did generate higher signals than seen in other patients without malignancy, but these were significantly lower than for cancer patients.

The authors conclude that the level of Mcm5 is an important marker of esophageal cancer, and they suggest that their method could be applied widely in diagnosis and screening.

Original article Williams GH et al. (2004) Diagnosis of oesophageal cancer by detection of minichromosome maintenance 5 protein in gastric aspirates. *Br J Cancer* 91: 714–719

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**Occult tumor cell detection in colorectal cancer**

Tumor recurrence is common after surgery for colorectal cancer (CRC) and early detection of residual cancer may improve the success rate of adjuvant chemotherapy. Öberg and colleagues from Sweden have described novel assays for the early detection of disseminated tumor cells in the lymph nodes of CRC patients.

CEA and CK20 are two epithelial cell markers whose expression is retained in CRC. Detection of these markers in locations outside epithelial compartments—for example in the lymph nodes—indicates that disseminated tumor cells are present. The investigators devised real-time, quantitative, reverse transcriptase polymerase chain reaction (qRT-PCR) assays for CEA and CK20 mRNAs. They then assessed the value of the assays in the detection of disseminated tumor cells in lymph node samples from 51 CRC patients.

Compared with noncancer controls, levels of CEA and CK20 mRNA were significantly elevated in the CRC samples, with those from Dukes’ Stage C and D patients showing the highest values. The CEA assay was superior in terms of specificity, although the CK20 assay may prove useful in detecting cells with low CEA expression.