tumour-produced chemotactic factors. The authors examined a number of candidate chemokines and showed that CCL22, produced by both macrophages and tumour cells, attracts regulatory T cells, which express the CCL22 receptor CCR4. An antibody against CCL22 prevented trafficking of regulatory T cells to human ovarian tumours in the xenograft model.

Finally, Curiel and colleagues correlated regulatory T-cell numbers with patient prognosis — a review of 70 patients with ovarian cancer confirmed that the greater the number of tumour-associated regulatory T-cells, the more adverse the prognosis for all tumour stages. The authors conclude that inhibiting the function of regulatory T cells, or perhaps blocking tumour chemokine signalling to inhibit their migration, could improve the efficacy of many antitumour vaccines.

Nicola McCarthy

References and links

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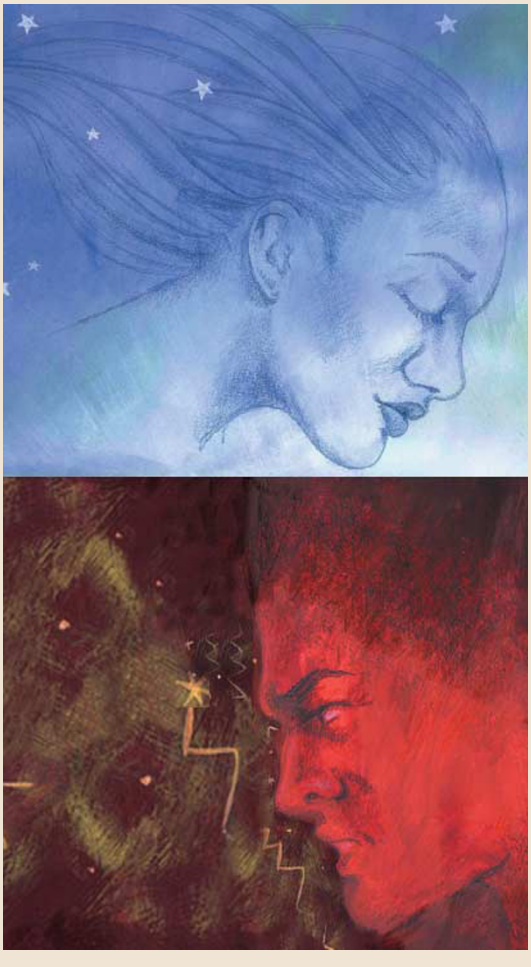

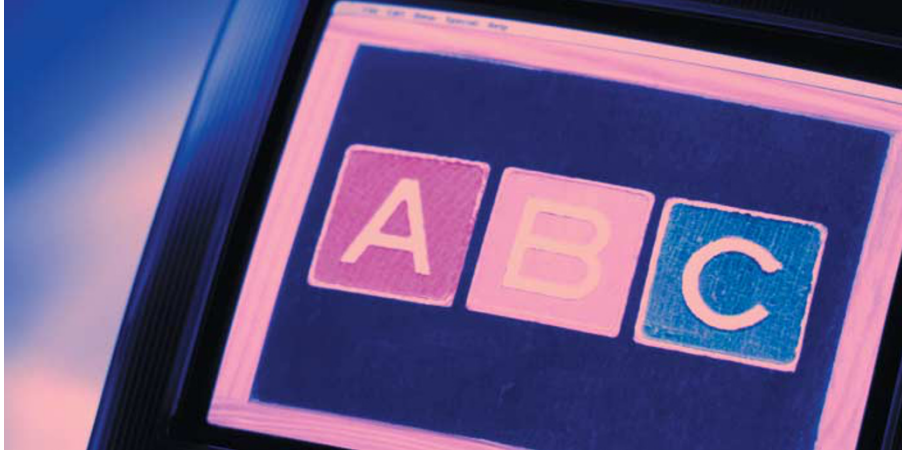

PHARMACOGENOMICS

ABCs of drug resistance

Multidrug resistance resulting from the activity of members of the ABC (ATP-binding cassette) family of membrane transporters, which actively pump many types of anticancer drugs out of cancer cells, is a significant barrier to effective cancer chemotherapy. However, efforts to overcome this problem have been hampered by limited knowledge of many members of the ABC transporter family. Now, as reported in *Cancer Cell*, Szakács *et al.* have coupled expression data for all human ABC transporters in cancer cells with information on the sensitivity of the cells to various anticancer drugs, providing a valuable tool for improving understanding of drug resistance mediated by these proteins.

Of the 48 human ABC transporters, only ~10 have been associated with cancer-drug resistance, such as the archetypal multidrug transporter ABCB1 (also known as MDR1 and P-glycoprotein). However, the high degree of sequence similarity between these ABC transporters indicated that further members might also export cancer drugs. So, Szakács *et al.* set out to explore this possibility by characterizing the expression of ABC transporters in a set of cancer cells whose responses to a large number of compounds are well-characterized: the panel of 60 cancer cell lines at the National Cancer Institute, which have been used to screen >100,000 compounds.

By using real-time PCR assays, which are more specific and sensitive than microarrays, to quantify the levels of messenger RNA of all 48 human ABC transporters, the authors obtained precise correlations between ABC-transporter expression and known patterns of drug activity for 1,429 compounds across the 60 cancer cell lines. As expected, good agreement was found between expression of ABCB1 and reduced cellular sensitivity to anticancer drugs that are known to be substrates for this transporter. Furthermore, using this method, several compounds that were not previously known to be substrates of ABCB1 were identified as potential substrates of this transporter, and these predictions were validated with follow-up experiments. And unexpectedly, some compounds were predicted — and subsequently confirmed — to have their anticancer activity potentiated by ABCB1, rather than antagonized; these compounds might serve as leads for drug development.

In total, the data revealed 131 drug–transporter pairs in which transporter expression correlated with resistance to the drug. As well as transporters known to be associated with drug resistance, several transporters that were not previously implicated in drug resistance were identified; again, follow-up experiments confirmed some of these predictions.

So, overall, the database created by the authors provides a resource for identifying transporters whose expression confers drug resistance, and compounds whose effects are antagonized, unaffected or even potentiated by transporter expression, which will be useful in developing strategies to address the problem of multidrug resistance. The database will also be valuable for future data mining to aid in studies of the function of the many ABC transporters that are not well characterized.

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References and links

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FURTHER READING Gottesman, M. M. *et al.* Multidrug resistance in cancer: role of ATP-dependent transporters. *Nature Rev. Cancer* **2**, 48–58 (2002)

WEB SITE

Database: http://discover.nci.nih.gov/abc/2004_cancercell_abstract.jsp