CANCER GENOMICS

Constructing a 'cancerpaedia'

Many of us have tried to explain our research projects to a friend or relative and ended up summarizing with the unsatisfactory phrase, "well, it's…complicated". That message is all too applicable in the translation of genomic findings in cancer cell lines to clinical therapies, but two recent papers in *Nature* aim to help by constructing encyclopaedias of cell lines and drug interactions.

The two groups of researchers each assembled a panel of hundreds of cancer cell lines and characterized multiple genomic features, gene expression and copy number variation. Each group then conducted a screen with anticancer drugs and used various bioinformatic analyses to correlate drug activity with changes in one or more genes: Barretina *et al.* profiled 24 drugs in 479 cell lines, and Garnett *et al.* profiled 130 drugs on 275–507 lines. The results showed a number of known interactions between gene mutations and drug sensitivities — such as changes in *BRAF* associated with RAF inhibitors — but several previously unseen connections emerged immediately.

For example, Barretina *et al.* showed that mutations in *NRAS* in some cell lines lead to sensitivity to MEK-inhibiting drugs through elevating expression of the aryl hydrocarbon receptor (*AHR*) gene. These findings could potentially be applied to the clinic by using expression levels of *AHR* as a biomarker for use of MEK inhibitors instead of *NRAS* mutations.

In addition to single-gene effects, Garnett *et al.* modelled interactions between drug response and multiple genes or transcripts at the same time. They found that general sensitivity to MEK inhibitors recurrently associated with 67 gene or transcript changes, and subsets of cancer cell lines had distinct patterns of biomarkers that should prove to be fruitful for further mechanistic research. Notably, in some cases, transcript levels were markers for drug sensitivity in cell lines without known sensitizing mutations.

An unexpected 'winner' from both efforts is the rare cancer Ewing's sarcoma. Garnett and colleagues found that Ewing's sarcoma cells were very sensitive to poly(ADP-ribose) polymerase (PARP) inhibitors, suggesting that these drugs could be explored as a treatment. Many current PARP inhibitor regimes use the drug with chemotherapy or radiation, but in Ewing's sarcoma cells, the PARP inhibitors were effective killers on their own. Barretina and colleagues found that, of the cell lines tested, Ewing's sarcoma cells were the most sensitive to several chemotherapy drugs. They also found that the expression level of schlafen family member 11 (*SLFN11*), which encodes a cell cycle control protein, is the top predictor of drug response across cell lines and that the Ewing's sarcoma lines were the cell lines that showed the highest expression of *SLFN11*. The authors suggest that expression levels of this gene might be useful in stratifying patients with Ewing's sarcoma (and other cancers) in ongoing trials of some conventional chemotherapy drugs.

Ultimately, of course, the real winners need to be patients with cancer. Both groups have posted their data sets online, in the hope that the community will treat these results as an open encyclopaedia.

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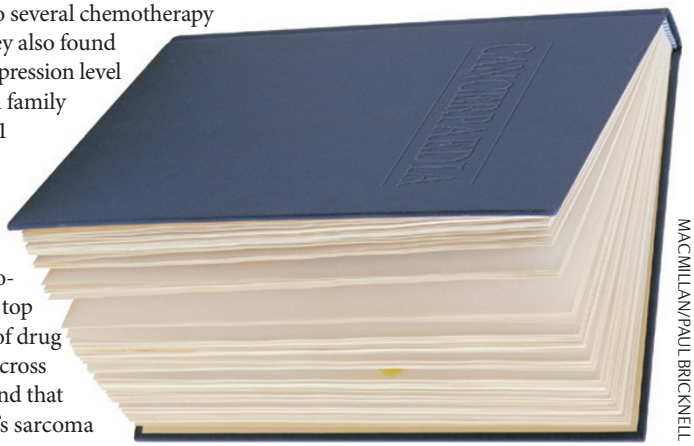
ORIGINAL RESEARCH PAPERS Barretina, J. *et al.* The Cancer Cell Line Encyclopedia enables predictive modelling of anticancer drug sensitivity. *Nature* **483**, 603–607 (2012) | Garnett, M. J. *et al.* Systematic identification of genomic markers of drug sensitivity in cancer cells. *Nature* **483**, 570–575 (2012)

FURTHER INFORMATION Genomics of Drug Sensitivity in Cancer project: http://www.cancerRxgene.org; Cancer Cell Line Encyclopedia: http://www.broadinstitute.org/ccle/home



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