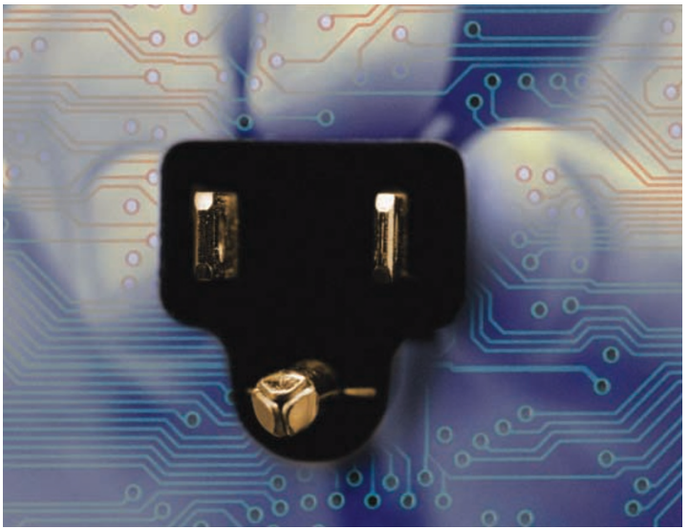
ANTICANCER DRUGS

# Pulling the plug on cancer



The characteristics of mitochondria — the ATP-synthesizing powerhouses of cells — can vary between normal and cancer cells, which could represent a promising opportunity for therapeutic intervention. Writing in *Cancer Cell*, Leder and colleagues provide support for this idea by identifying and characterizing the effects of a small molecule that can selectively inhibit the proliferation of a range of cancer cells, owing to its ability to target a difference in the properties of their mitochondria that is correlated with the overexpression of certain cancer-causing genes.

The authors began by screening a library of 16,000 small molecules for their effect on the proliferation of mouse mammary epithelial cells that overexpressed the gene *Neu*, the human counterpart of which — *ERBB2* — is overexpressed in 20–30% of breast cancers. Parallel comparison with control cells was used to discriminate selective inhibitors from generally cytotoxic/cytostatic compounds, and led to the identification of F16, a potent and selective inhibitor of the proliferation of cells that overexpress *Neu*.

Next, the authors investigated the mode of action of F16 by exploiting its natural fluorescence to monitor its fate inside cells. F16 was selectively concentrated in the mitochondria of several human breast-tumour and mouse-tumour cell lines that were sensitive to F16, but not in control cells or tumour cell lines that were insensitive to F16. Analysis of the effects of this accumulation of F16 showed that it induced mitochondrial damage, which was characterized by a failure to synthesize ATP, swelling and release of cytochrome *c*, a key trigger of apoptosis (programmed cell death).

So, how does the cell-selectivity arise? Mitochondria produce ATP by using energy accumulated in an electrochemical gradient across their inner membrane. The electrical portion of this gradient — the membrane potential, $\Delta\psi_m$ — can vary with cell type and metabolic status, and cancer cells often have a high $\Delta\psi_m$. F16 is a lipophilic molecule with a delocalized positive charge, which in theory should favour its accumulation in cells with a high $\Delta\psi_m$, and the authors provide strong evidence that this is the driving force behind selective F16 accumulation.

How the overexpression of some cancer-causing genes leads to changes in $\Delta\psi_m$ is not clear at present. But as high $\Delta\psi_m$ is a common characteristic of cancer cells, a drug that targets this could be expected to have a broad spectrum of activity. Moreover, given the pivotal role of mitochondria in the apoptotic signalling cascade, such a drug could prove particularly valuable in many cancers in which upstream components of the apoptotic cascade are defective, making the cells resistant to normal apoptotic stimuli.

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## References and links

**ORIGINAL RESEARCH PAPER** Fantin, V. R. *et al.* A novel mitochondriotoxic molecule that selectively inhibits cell growth. *Cancer Cell* **2**, 29–42 (2002)