MacLeod, Brown and Jones, epigenetic therapies are not just for cancer; they could be useful in any disorder where there is an underlying epigenetic problem, such as inherited syndromes in which genomic imprinting is faulty.

References

1 Cheng, J.C. *et al.* (2004) Preferential response of cancer cells to zebularine. *Cancer Cell* 6, 151–158

2 Egger, G. *et al.* (2004) Epigenetics in human disease and prospects for epigenetic therapy. *Nature* 429, 457–463

3 Brown, R. and Plumb, J.A. (2004) Demethylation of DNA by decitabine in cancer chemotherapy. *Expert Rev. Anticancer Ther.* 4, 501–510

4 Reid, G.K. *et al.* (2002) Selective inhibition of DNA methyltransferase enzymes as a novel strategy for cancer treatment. *Curr. Opin. Mol. Ther.* 4, 130–137

Stapled peptide induces cancer cell death

Jo Whelan, freelance writer

A new technique known as hydrocarbon stapling could allow peptides from the key domains of natural proteins to be used therapeutically. Using the technique on a peptide involved in apoptosis, researchers have succeeded in destroying cancer cells in a mouse model of leukemia.

Apoptosis (programmed cell death) is controlled by a complex web of protein–protein interactions involving so-called 'pro-death' and 'survival' proteins. Loren Walensky and colleagues at the Dana-Farber Cancer Institute (http://www.dfci.harvard.edu) report taking a 'death domain' from a class of pro-apoptosic molecules called BH3-only proteins and optimizing it to kill human leukemia cells in living mice.

Stabilizing BH3

BH3-only proteins contain a peptide subunit called BH3, which is a key initiator of cell death. BH3 is an α helix: a coiled, spring-like shape with amino acids on its surface that bind to and inhibit anti-death proteins such as BCL-2, as well as activating pro-death proteins under certain circumstances. However, when BH3 is produced synthetically without its parent protein, its shape is lost and its functionality impaired.

To stabilize the peptide, Walensky applied the hydrocarbon-stapling technique developed by chemist colleague Gregory Verdine. Some amino acids in the natural sequence are replaced with synthetic ones bearing hydrocarbon 'tethers'. These link to form chemical 'staples', which reinforce the α-helical structure. The new peptide retains its biological activity and actually binds more strongly to the BCL-2 target, the researchers report [1].

Therapeutic window

Importantly, it also passes across the cell membrane. Mice with established human leukemia given i.v. doses of the peptide for a week had a median survival time of 11 days, compared with five days for untreated leukemic controls. Tumor expansion was halted in most of the treated mice and many showed tumor regression. Post-mortem examination found no obvious signs of damage to normal tissues.

'There may be a therapeutic window for BH3 molecules in cancers that specifically exploit cell death pathways for survival,' says Walensky. 'If you can inhibit an anti-death protein distinctly required for the cancer but not singly necessary for a normal cell's survival, you may be able to trigger cell death in the cancer while leaving normal cells unharmed.'

Different BCL-2 proteins are implicated in different cancers, but all contain α-helical BH3 domains. The team hope to produce a panel of stapled BH3 peptides to explore and manipulate apoptotic pathways in various types of cancer cell.

Mimicking protein–protein interactions

'This is a proof of concept that you can turn on the death-promoting proteins with a peptidomimetic,' says Steve Dowdy of the Howard Hughes Medical Institute at the UCSD School of Medicine, La Jolla, USA (http://medicine.ucsd.edu) whose perspective article accompanied the Walensky paper [2]. 'More broadly it shows that mimicking protein–protein interactions can be therapeutically beneficial in preclinical models, and we should be able to apply this in other pathways too.' He adds that more work to investigate potential toxicity and solve the problem of delivery will be needed before the approach can be tried in humans.

The α-helix motif occurs frequently in biologically important protein interactions, so stapling might allow peptides to be used as drugs in many different applications. 'If we could target protein interactions at critical biological control points using the natural sequence for a protein target, we might have a whole new set of tools to study and manipulate protein interactions within cells', Walensky says.

References

1 Walensky, L.D. *et al.* (2004) Activation of apoptosis *in vivo* by a hydrocarbon-stapled BH3 helix. *Science* 305, 1466–1470

2 Denicourt, C. and Dowdy, S.F. (2004) Targeting apoptotic pathways in cancer cells. *Science* 305, 1411–1413

1359-6446/04/$ – see front matter PII: S1359-6446(04)03268-4