IN BRIEF

ANTICANCER DRUGS

A high-affinity conformation of Hsp90 confers tumour selectivity on Hsp90 inhibitors.

Kamal, A. *et al. Nature* **425**, 407–410 (2003).

Inhibitors of heat-shock protein 90 (Hsp90) — which regulates the function and stability of key signalling proteins — have been shown to selectively kill cancer cells, despite the fact that Hsp90 is highly expressed in most cells. Kamal *et al.* now provide an explanation for this selectivity: Hsp90 in tumour cells exists in a functionally distinct molecular form that has a 100-fold higher affinity for the Hsp90 inhibitor 17-allylaminogeldanamycin (17-AAG; now in Phase I clinical trials) than Hsp90 from normal cells.

COMPUTATIONAL CHEMISTRY

Kinases, homology models, and high-throughput docking.

Diller, D. J. & Li, R. *J. Med. Chem.* 2003 Sep 20 (doi: 10.1021/jm020503a).

Homology models based on available representative protein structures could provide some compensation for the frequent lack of X-ray structural data for targets of interest early in drug discovery. Diller and Li assessed the current potential of such models of protein kinases, and found that known inhibitors could be successfully distinguished from random compounds, and that some important selectivity information could be obtained.

PROTEOLYSIS

The caspase-like sites of proteasomes, their substrate specificity, new inhibitors and substrates, and allosteric interactions with the trypsin-like sites.

Kisselev, A. F. *et al. J. Biol. Chem.* **278**, 35869–35877 (2003).

Inhibitors of proteasomes — the primary sites for protein degradation in mammalian cells — are creating great interest as a new class of treatments against cancer. However, the complex interactions between the chymotrypsin-like, trypsin-like and caspase-like sites of protease activity within the proteasome are not fully defined. Kisselev *et al.* designed inhibitors to elucidate the substrate preference for caspase-like sites, and showed how inhibitor binding can both activate and repress proteolytic activities of the other sites.

CARDIOVASCULAR DISEASE

A novel protective effect of erythropoietin in the infarcted heart.

Parsa, C. J. *et al. J. Clin. Invest.* **112**, 999–1007 (2003).

Recombinant forms of the cytokine erythropoietin (EPO), which stimulates the production of red blood cells, have been used for many years to treat anaemia. Parsa *et al.* now present evidence that EPO can protect the ischaemic and infarcted heart by inhibiting apoptosis of cardiomyocytes, and so could represent a novel treatment modality for myocardial ischaemia, reperfusion injury and infarction.

GPCRS

A solid view of GPCRs

G-protein-coupled receptors (GPCRs) are the largest class of targets for modern drug development. But the design of new GPCR-targeting compounds has been hampered by the dearth of direct structural information on interactions between GPCRs and their ligands. Fresh insights are now to hand, following the publication in the *Proceedings of the National Academy of Sciences* of a study that used solid-state NMR to probe the conformation of the peptide agonist neurotensin bound to one of its GPCRs, neurotensin type-1 receptor (NTS-1).

Neurotensin is a 13-amino-acid neuropeptide that modulates vascular and endocrine functions. Both the full-length peptide and its six-amino-acid C-terminus (NT(8–13)) bind with sub-nanomolar affinity to NTS-1. Such high-affinity binding precludes the use of solution-state NMR, so Marc Baldus and colleagues optimized solid-state NMR to conduct a comparative analysis of free and bound NT(8–13) at atomic resolution. Milligram quantities of high-quality receptor preparations were provided by Reinhard Grisshammer and co-workers.

To allow the NMR signals of the bound ligand to be detected unequivocally in the presence of large background signals from buffer components, detergents and lipids, NT(8–13) uniformly labelled with the NMR-active isotopes ^{13}C and ^{15}N was prepared by solid-phase peptide synthesis. Analysis of spectra from optimized two-dimensional ^{13}C NMR experiments with this labelled peptide revealed that free NT(8–13) remains essentially unstructured. However, in the presence of functional, lipid-reconstituted rat NTS-1 obtained from an *Escherichia coli* expression system, the NT(8–13) backbone assumes a defined β-strand conformation.

This structural model of the receptor-bound peptide could represent a viable template for three-dimensional pharmacophore-based searches of chemical libraries for non-peptide ligands, which might be therapeutically applicable. More generally, these data highlight the potential of solid-state NMR as a useful tool in unravelling the structural complexity of high-affinity GPCR–ligand interactions.

Suzanne Farley

References and links

ORIGINAL RESEARCH PAPER Luca, S. *et al.* The conformation of neurotensin bound to its G protein-coupled receptor. *Proc. Natl Acad. Sci. USA* **100**, 10706–10711 (2003)
FURTHER READING Special issue: Overexpression of integral membrane proteins. *Biochim. Biophys. Acta* **1610**, 1–153 (2003) | Luca, S., Heise, H. & Baldus, M. High-resolution solid-state NMR applied to polypeptides and membrane proteins. *Acc. Chem. Res.* (in the press)
WEB SITE
Encyclopedia of Life Sciences: http://www.els.net/
G-protein-coupled receptors | nuclear magnetic resonance (NMR): solid state