IN BRIEF

CHEMICAL GENOMICS

Gene expression-based high-throughput screening (GE-HTS) and application to leukemia differentiation.

Stegmaier, K. *et al. Nature Genet.* **36**, 257–263 (2004).

Chemical genomics, which involves generating large collections of small molecules and using them to modulate cellular states, is emerging as a powerful tool for probing biological function. However, the speed at which small-molecule probes that have a particular cellular effect can be found is often limited by lack of knowledge of the target proteins involved. In such cases, small molecules are typically screened for an effect using low-throughput assays; for example, assays based on cell morphology. The authors describe a general, high-throughput approach for addressing this issue in which a gene-expression signature is used as a surrogate for cellular states, the utility of which they demonstrate by identifying several compounds from a 1,739-member library that induce the differentiation of acute myeloid leukaemia cells.

ANTICANCER DRUGS

Inhibition of the insulin-like growth factor receptor-1 tyrosine kinase activity as a therapeutic strategy for multiple myeloma, other hematologic malignancies, and solid tumors.

Mitsiades, C. S. *et al. Cancer Cell* 26 Feb 2004 (doi:10.1016/S1535610804000509).

In vivo antitumor activity of NVP-AEW541 — a novel, potent, and selective inhibitor of the IGF-IR kinase.

García-Echeverría, C. *et al. Cancer Cell* 26 Feb 2004 (doi:10.1016/S153561080 4000510).

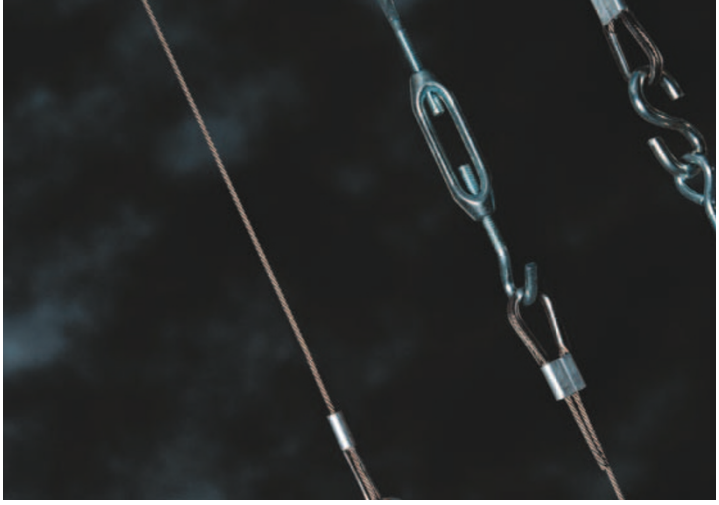
Insulin-like growth factors and their receptor, IGF-1R, have been linked to a wide range of cancers, but this pathway has not previously been viewed as a major therapeutic target, in part owing to the lack of clinically applicable small-molecule inhibitors of IGF-1R function. Using selective small-molecule inhibitors of the IGF-1R kinase, these two papers provide *in vivo* proof of concept for the use of such inhibitors as primary antitumour therapy or in combination with cytotoxic chemotherapy.

DRUG DELIVERY

Targeting angiogenesis with a conjugate of HPMA copolymer and TNP-470.

Fainaro-Satchi, R. *et al. Nature Med.* **10**, 255–261 (2004).

The small molecule TNP-470 inhibits tumour angiogenesis — the growth of new blood vessels necessary for tumour progression — and has shown activity in cancer patients. However, at the higher doses necessary for tumour regression, many patients experienced neurotoxicity. This paper shows that conjugating TNP-470 to a biocompatible copolymer prevents it crossing the blood–brain barrier, and also leads to its selective accumulation in tumour vessels, thereby minimizing toxicity.



NEURODEGENERATIVE DISEASE

Linking lipids to Alzheimer's

A new study in the *Proceedings of the National Academy of Sciences* establishes a link between amyloid β-peptide (Aβ), oxidative stress and perturbed lipid metabolism in the pathogenesis of Alzheimer's disease (AD).

AD-associated neurodegeneration is thought to be facilitated by deposition of toxic Aβ and by oxidative stress. There is also indirect evidence for the involvement of altered lipid metabolism, so Mark Mattson and colleagues set out to investigate how these factors might interact.

Elevated levels of long-chain ceramides — lipid mediators that are generated in response to oxidative stress — and free cholesterol were detected post-mortem in the middle frontal gyrus of AD patients, a brain region that contained extensive Aβ plaques and neurofibrillary tangles. Adducts of the lipid peroxidation product 4-hydroxynonenal (HNE) were also present at high concentrations in this area. By contrast, the concentrations of ceramides, cholesterol and HNE adducts in the cerebellum, which contained few plaques and tangles, did not differ between AD patients and controls.

Is there a causal link between these indicators of abnormal lipid metabolism and the deposition of Aβ? To test this hypothesis, the authors exposed cultured rat hippocampal cells to $A\beta_{1–42}$. Within six hours, levels of long-chain ceramides, cholesterol and HNE had increased significantly. Similar results were obtained for neuronal cultures exposed to the oxidative agent iron, indicating that lipid peroxidation is sufficient to induce the changes associated with $A\beta_{1–42}$ treatment.

In the experiments described above, neuronal death occurred six to eighteen hours after altered lipid metabolism was first detected. Pretreatment of cultures with the antioxidant α-tocopherol prevented the $A\beta_{1–42}$-induced alterations of lipid levels and neuronal death. Incubation with an inhibitor of serine palmitoyltransferase to reduce ceramide levels also attenuated the proportion of neurons killed by $A\beta_{1–42}$. Taken together, these data indicate that Aβ causes oxidative stress, which alters ceramide and cholesterol metabolism and in turn leads to the degeneration of neurons. Inhibitors of enzymes involved in ceramide production, such as serine palmitoyltransferase and sphingomyelinase, might therefore offer protection against AD-associated neurodegeneration.

Suzanne Farley

References and links

ORIGINAL RESEARCH PAPER Cutler, R. G. *et al.* Involvement of oxidative stress-induced abnormalities in ceramide and cholesterol metabolism in brain aging and Alzheimer's disease. *Proc. Natl Acad. Sci. USA* **101**, 2070–2075 (2004)

FURTHER READING Barnham, K. J., Masters, C. L. & Bush, A. I. Neurodegenerative diseases and oxidative stress. *Nature Rev. Drug Discov.* **3**, 205–214 (2004)